Natural History of Brugada Syndrome
Insights for Risk Stratification and Management

Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD; Maurizio Gasparini, MD; Carlo Pappone, MD; Paolo Della Bella, MD; Umberto Giordano, MD; Raffaella Bloise, MD; Carla Giustetto, MD; Roberto De Nardis, MD; Massimiliano Grillo, MD; Elena Ronchetti, PhD; Giovanna Faggiano, MD; Janni Nastoli, BS

Background—Treatment of patients with Brugada syndrome is complicated by the incomplete information on the natural history of the disease related to the small number of cases reported. Furthermore, the value of programmed electrical stimulation (PES) for risk stratification is highly debated. The objective of this study was to search for novel parameters to identify patients at risk of sudden death.

Methods and Results—Clinical data were collected for 200 patients (152 men, 48 women; age, 41 ± 18 years) and stored in a dedicated database. Genetic analysis was performed, and mutations on the SCN5A gene were identified in 28 of 130 probands and in 56 of 121 family members. The life-table method of Kaplan-Meier used to define the cardiac arrest–free interval in patients undergoing PES failed to demonstrate an association between PES inducibility and spontaneous occurrence of ventricular fibrillation. Multivariate Cox regression analysis showed that after adjusting for sex, family history of sudden death, and SCN5A mutations, the combined presence of a spontaneous ST-segment elevation in leads V1 through V3 and the history of syncope identifies subjects at risk of cardiac arrest (HR, 6.4; 95% CI, 1.9 to 21; P = 0.002).

Conclusions—The information on the natural history of patients obtained in this study allowed elaboration of a risk-stratification scheme to quantify the risk for sudden cardiac death and to target the use of the implantable cardioverter-defibrillator.

(Circulation. 2002;105:1342-1347.)

Key Words: death, sudden tachyarrhythmias risk factors genetics fibrillation

Brugada syndrome (BS) is an inherited arrhythmogenic disease characterized by the typical ECG pattern of ST-segment elevation in leads V1 through V3, incomplete right bundle-branch block, and an increased risk of sudden cardiac death as the result of ventricular fibrillation (VF). This disease was initially described in 1992 by Brugada and Brugada; in 1998, the same authors reported data on 63 patients, suggesting that irrespective of clinical manifestations, patients with BS have a 30% risk of cardiac arrest at 3-year follow-up and that inducibility at programmed electrical stimulation (PES) identifies high-risk subjects who should receive an implantable cardioverter-defibrillator (ICD). Because 60% to 90% of all patients with BS are inducible at PES, this approach resulted in the implantation of an ICD in a large number of asymptomatic individuals. We reported data on 60 patients confirming the adverse prognosis of patients with history of syncope or cardiac arrest and showing that asymptomatic patients are at lower risk of events than previously reported. These data were confirmed by Atarashi et al. Our data failed to confirm the predictive value of PES in BS, pointing to the lack of clinical parameters for risk stratification. Here we describe the natural history of 200 patients with BS and propose a scheme for risk stratification. Furthermore, we present data on 84 genotyped patients with BS representing the largest series of carriers of SCN5A mutations reported in the literature.

Methods

Study Population and Clinical Evaluation
Clinical diagnosis of BS was established in 130 white probands, based on the presence of ST-segment elevation ≥ 2 mm in leads V1 through V3 at baseline or after administration of intravenous sodium channel blockers (2 mg/kg flecainide or 1 mg/kg ajmaline). Identification of a proband prompted clinical evaluation of family members. Individuals with a clinical diagnosis of BS underwent genetic
counseling and were offered genetic testing. The presence of right ventricular cardiomyopathy was excluded in all patients by echocardiography, with careful evaluation of the right ventricle; 37 of 130 probands also underwent nuclear MRI, which was negative in all of them.

Electrophysiological study and PES were recommended in all patients and accepted by 86. Patient treatment was based on clinical judgment of referring clinicians: No patient received antiarrhythmic drugs, and 52 received an ICD. Patients were referred to the Inherited Arrhythmic Disorders Clinic of the Maugeri Foundation for family evaluation, genetic screening, and counseling.

Definitions
A “positive ECG” (ie, diagnostic for BS) is considered an ECG with or without right bundle-branch block presenting ST-segment elevation ≥2 mm in the right precordial leads (V1 to V3). A “spontaneous pattern” is defined as an ECG showing the pattern described above at baseline, for example, before pharmacological challenge with sodium channel blockers. “Proband” is defined as the first individual with clinical diagnosis within a family. “Mutation carrier” is defined as any individual with an SCN5A mutation. “Silent mutation carrier” is defined as any asymptomatic individual with an SCN5A mutation and normal ECG both at baseline and after pharmacological challenge. A “cardiac arrest” is defined as documented VF leading to syncope or sudden death. “Sudden cardiac death” is defined as a sudden and unexpected death occurring within 1 hour from the onset of symptoms.

Molecular Analysis
DNA was extracted by means of standard procedures. Primer pairs for SCN5A amplification were used. Single-strand conformational polymorphism analysis and/or denaturing high-performance liquid chromatography analysis were performed on amplified genomic DNA (Transgenomic). Abnormal patterns were directly sequenced or subcloned and sequenced on both strands with an automated DNA analyzer (ABI Prism 310, Perkin Elmer). A panel of 400 healthy white individuals (800 alleles) was used as control.

Statistical Analysis
Data are presented as mean±SD. A χ2 test was used to assess statistical difference among frequency of events or of results of clinical tests. A value of P<0.05 was considered statistically significant.

Survival from cardiac arrest was determined by means of the life-table method of Kaplan-Meier, and results were compared by means of the log-rank test. Cox multivariate survivorship analyses were performed to evaluate the significance and independence of the presence of the spontaneous ST-segment elevation and history of syncope as a predictor of cardiac arrest after adjustment for sex, family history of sudden cardiac death (SCD), and SCN5A mutations.

Results
Demographic and Clinical Profile of Patients
We have identified 130 probands (110 men, 20 women; mean age, 43±16 years; median, 42 years) with diagnosis of BS. Clinical and/or genetic evaluation of family members identified additional 70 affected subjects (42 men). Overall, the population of patients with BS reported includes 200 individuals (152 men, 48 women; mean age, 41±18 years; Table 1). Evaluation of cardiac events that occurred between birth and the last follow-up in the 200 individuals (ie, a mean observation time of 41 years) documented cardiac arrest in 22 individuals (20 men, 2 women) (Figure 1A). The mean age at cardiac arrest was 33±13 years (range, 2 months to 55 years); 5 of 22 (23%) of these patients had multiple cardiac arrests. A history of syncope was present in 34 of 200 patients (17%), and 8 of 34 (23.5%) had cardiac arrest, that is, 85% specificity and 36% sensitivity to identify cardiac arrest victims (Table 2).

A family history of unexplained sudden death was present in 26 of 130 (20%) probands: in their families there were 32 sudden death victims (25 men, 7 women; mean age, 37±20). Autopsy available for 11 of them failed to demonstrate structural heart disease in all. The presence of a family history of sudden death had 22% sensitivity and 65% specificity to identify individuals with cardiac arrest (Table 2).

ECG Pattern
Analysis of the morphology of the ST-segment elevation pattern on multiple ECGs (at least 3 ECGs taken on separate weeks) was performed in 176 individuals (mean age, 43±16 years; 125 men, 51 women). A spontaneous pattern was present in at least one of the ECGs recorded in 90 of 176 (51%) individuals: the presence of a spontaneous pattern presented a sensitivity of 77% and a specificity of 53% to identify patients with cardiac arrest (Table 2). The mean ST-segment elevation was 2.4±1.3 mm in patients with cardiac arrest and 2.6±1.8 mm in the remaining patients (P>0.05; NS). The morphology of the ST-segment elevation (coved versus saddle-back type) was similarly distributed between cardiac arrest victims and the other patients (Table 2).

Programmed Electrical Stimulation
PES was performed in 86 patients who provided informed consent. In analogy with the previous reports,2,4 patients were studied at different centers; therefore, the stimulation protocols were not identical: a maximum of 3 ventricular extrastimuli were delivered unless VF was elicited at a previous step. Data are presented in Table 3. In 57 of 86 patients (66%), VF or sustained polymorphic ventricular tachycardia was induced. Among the 29 of 86 noninducible patients (20

<table>
<thead>
<tr>
<th>TABLE 1. Breakdown of Clinically and Genetically Affected Subjects and of Screened Family Members</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Subjects</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Proband</td>
</tr>
<tr>
<td>Family members</td>
</tr>
<tr>
<td>Screened</td>
</tr>
<tr>
<td>Affected family members</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
men, 9 women; mean age, 37±15 years) 4 of 29 had cardiac arrest (false-negatives at PES). Overall, in this cohort of patients, the sensitivity of PES was 66% and specificity was 34% (Table 2 and Figure 1B).

When data were analyzed on the basis of the number of premature stimuli used during PES, we observed a sensitivity of 75% and a specificity of 36% when using 2 premature stimuli. When the PES protocol included 3 premature stimuli, the sensitivity was 50% and the specificity was 33%.

Genetic Analysis and Characteristics of Genotyped Patients

SCN5A mutations were identified in 28 of 130 probands (22%; 21 men, 8 women; mean age, 36±16 years; range, 2 to 65 years) (Table 1). None of 400 control subjects and of 200 LQTS probands carried the same DNA alterations. The 28 mutations included 22 single missense mutations, 4 deletions (2 in frame and 2 frameshifts), 1 nonsense mutation, and 1 splice error. These mutations were distributed along the entire predicted topology of the SCN5A protein: one in the N-terminus region, 3 in the C-terminus, 8 in the transmembrane spanning segments, and 16 in the intracellular (n=6) and extracellular (n=10) loops (Figure 2). Among the 28 probands presenting a genetic defect on SCN5A, family history of SCD was present in 46% (13 of 28).

One hundred twenty-one family members of the genotyped probands accepted genetic screening and 56 of 121 (46%) carried the mutation identified in the proband (Table 1). Overall data on 84 patients (28 probands and 56 family members) with a SCN5A mutation are reported. At the time of genetic diagnosis, 18 of 84 (21%) patients were symptomatic for syncope (n=11) or cardiac arrest (n=7). Among the 84 genotyped patients, 46 accepted to undergo pharmacological provocative testing, which was positive (exacerbation of ST-segment elevation ≥2 mm or unmasking of ST-segment elevation ≥2 mm) in 33 of 46 (71%). Thirteen mutation carriers (3 men, 10 women; mean age, 39±21 years) had a negative ECG at baseline and a negative flecainide test (silent mutation carriers). Interestingly, none had syncope or cardiac arrest. The presence of an SCN5A mutation showed 32% sensitivity and 57% specificity to identify patients with cardiac arrest (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Performance of Clinical and Genetic Variables in Predicting the Occurrence of Cardiac Arrest in Brugada Syndrome Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Predictive Value, %</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Family history of SCD</td>
</tr>
<tr>
<td>Positive pharmacological test</td>
</tr>
<tr>
<td>SCN5A mutation</td>
</tr>
<tr>
<td>Outcome at PES (global)</td>
</tr>
<tr>
<td>PES (2 premature stimuli)</td>
</tr>
<tr>
<td>PES (3 premature stimuli)</td>
</tr>
<tr>
<td>Coved-type ST elevation</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Spontaneous ST elevation</td>
</tr>
<tr>
<td>Syncope and spontaneous ST elevation</td>
</tr>
</tbody>
</table>
Predictors of Outcome

The life-tables method of Kaplan-Meier demonstrated that patients inducible at PES do not have increased risk of cardiac arrest (Figure 1B) as compared with noninducible individuals. A difference in the cardiac arrest-free survival curves was observed in a comparison of patients with ST-segment elevation at baseline (with or without history of syncope) with patients without spontaneous ECG pattern (log-rank test, \( P < 0.001 \)). We evaluated by multivariate Cox regression analysis the significance and independence of the history of syncope, the presence of a spontaneous ECG pattern of ST-segment elevation, and the combination of the two parameters to identify patients with an increased risk of cardiac arrest (Figure 3). The presence of syncope in the absence of spontaneous ST-segment elevation was not a marker of risk because none of the 16 individuals in this group had cardiac arrest. The spontaneous presence of ST-segment elevation was associated with a trend toward an excessive risk that was not statistically significant (hazard ratio \([HR]\), 2.1; 95% CI, 0.7 to 6.9; \( P = 0.05, \text{NS} \)). However, the association of the history of syncope with the presence of a spontaneous ST-segment elevation demonstrated a major statistically significant increase of the risk of death, even after adjustment for sex, history of sudden death in the family, and presence of a mutation in the SCN5A gene (HR, 6.4; 95% CI, 1.9 to 21; \( P < 0.002 \)) (Figure 3). Patients with cardiac arrest as the first manifestation were not included in this group. Therefore, the history of syncope in patients with BS is not an independent predictor of risk, but the association between syncope and spontaneous ST-segment elevation is the strongest factor to identify individuals with cardiac events (Figure 4).

When cardiac life-table analysis was performed on the events occurring at follow up (mean follow up of 34 ± 44 months), the patients in the high-risk category (ie, “the top section” of the risk stratification scheme in Figure 4) had a higher number of events than the patients in the low-risk groups (the middle and the lower sections of the risk stratification scheme in Figure 4; log-rank test, \( P < 0.02 \)). Figure 5 illustrates the difference in cumulative survival in the lower- versus the higher-risk group.

### Table 3. Programmed Electrical Stimulation in Brugada Syndrome

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. of Premature Stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
</tr>
<tr>
<td>Noninducible</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>4</td>
</tr>
<tr>
<td>No cardiac arrest</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
</tr>
<tr>
<td>Inducible</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>8</td>
</tr>
<tr>
<td>No cardiac arrest</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
</tr>
</tbody>
</table>

**Figure 2.** SCN5A mutations identified in patients with BS. Diagram shows predicted topology of SCN5A protein. Each circle represents a mutation. Table shows nucleotide change and coding effect of each mutation. del indicates deletion; s.e., splice error; and fs, frameshift. Codons numbering based on Gene Bank sequence No. NM_000335.

**Figure 3.** Cox regression analysis of cumulative survival from cardiac arrest according to the presence of positive ECG at baseline plus history of syncope (continuous line), positive ECG at baseline only (hatched line), history of syncope (dotted line), and history of syncope with negative ECG pattern at baseline (dotted-hatched line).

**Figure 4.** Risk stratification according to distribution of clinical variables in BS. Spont. Pattern indicates spontaneous positive ECG (see text for details).
We have assessed in our population the validity of the stratification scheme proposed by Brugada et al, who divided patients into 4 groups, based on clinical features and inducibility at PES (categories A to D). We observed 1 of 14 events in category D (7% of cardiac arrest) and 3 of 35 events in category C (8% of cardiac arrest); Brugada et al recommend no ICD in category D and ICD implantation in category C; obviously, our data cannot endorse this recommendation. When category A and category B are compared, no differences are observed (33% of events in category B and 30% of events in category A).

We therefore explored the value of several clinical parameters to differentiate between patients with and without cardiac arrest (Table 2). We applied the life-table method of Kaplan-Meier to assess the cumulative probability of cardiac arrest, based on PES. Our data confirm the view that PES is not helpful in identifying individuals at higher risk of major arrhythmic events (Figure 1B).

When sensitivity and specificity of PES is analyzed on the basis of number of premature stimuli, the use of two premature beats improves the sensitivity of the test from 50% to 75%. We had no adequate sample size to analyze the value of PES in different subgroups of patients. Recent data reported by Brugada et al showed a low positive predictive value (13%) but a good negative predictive value of PES in asymptomatic noninducible individuals (99%). It should be noted, however, that asymptomatic patients had a shorter follow-up, which may overestimate the negative predictive value of PES. Before conclusive statements are made on the value of PES in BS, data on large numbers of patients studied with the same protocol and with a longer follow up are needed.

We did not observe any significant predictive information when survival in inducible versus noninducible patients without spontaneous ST-segment elevation was assessed.

We have evaluated if other clinical parameters identify high-risk individuals demonstrating that patients with spontaneous pattern and history of syncope are at higher risk of cardiac arrest (Figure 3). Cox multivariate analysis demonstrated that the simultaneous presence of syncope and ST-segment elevation at baseline is the strongest predictor of cardiac arrest. At variance with our expectations, neither the presence of a family history of SCD nor the morphology of the ST-segment elevation (saddle-back or coved) proved to be outcome predictors. A genetic defect on the SCN5A gene was also not associated with a higher risk of events, suggesting that genetic analysis is a most useful diagnostic parameter but it is not helpful for risk stratification.

The ECG pattern is frequently intermittent in patients with BS, but so far it is unknown if transient normalization of the ECG during follow-up bears prognostic information.

From Risk Stratification to Treatment Strategy
We developed a risk-stratification scheme, dividing patients with BS into 3 groups, based on the risk of cardiac arrest (Figure 4). High-risk patients present a baseline ST-segment elevation and have history of syncope (HR, 6.4). In our population, 10% of patients fell into this category and 44% had cardiac arrest. These patients should be regarded as candidates for an ICD. Patients with a spontaneous ST-segment elevation ≥2 mm without history of syncope present...
a strong trend toward an increased risk that fails to reach statistical significance (HR, 2.1; 95% CI, 0.68 to 6.9; NS). In our population, this group included 41% of patients, and 14% of them had cardiac arrest: they are a group at intermediate risk, and their treatment is undetermined.

Finally, patients with a negative phenotype (silent mutation carriers) or who have a diagnostic ECG only after provocative challenge are at lower risk of cardiac events: They represent 49% of the population under study, and only 5% of them had cardiac arrest in 4 decades of follow-up. They should be reassured and advised to report immediately any symptom such as syncope or palpitation that may occur in order to be promptly reevaluated. Sodium channel–blocking antiarrhythmic drugs and tricyclic antidepressants should be avoided.

Study Limitations
This study presents limitations that should be acknowledged. First, it provides data from a registry; therefore, patients enrolled are not evaluated with identical protocols, referral bias may be present, and treatment selection may be based on dissimilar criteria. In particular, although PES was offered to all patients, only a limited number accepted the procedure, thus creating a potential selection of the population. Finally, because risk assessment was based on individuals with a mean age of 40 years, it may not apply to older patients.

Conclusions
We report data on one of the largest populations of patients with BS, including the largest group of genotyped individuals. On the basis of evaluation of cardiac events that occurred in our patients, we demonstrate that the presence of a spontaneous ST-segment elevation in leads V1 through V3 combined with the history of syncope is a powerful marker to identify individuals who had cardiac arrest. Interestingly, we demonstrate that history of syncope per se is not an independent marker of major cardiac events. Our data confirm that combined with the history of syncope is a powerful marker to identify individuals who had cardiac arrest. Interestingly, we demonstrate that the presence of a spontaneous ST-segment elevation in leads V1 through V3 combined with the history of syncope is a powerful marker to identify individuals who had cardiac arrest. Interestingly, we demonstrate that the presence of a spontaneous ST-segment elevation in leads V1 through V3 combined with the history of syncope is a powerful marker to identify individuals who had cardiac arrest.

Acknowledgments
This study was supported by Leducq Foundation, BIOMED grant BMH4-CT98-3872, Telethon Grant GP0227/01, and by the “Ricerca Finalizzata” DG-RSVE-RF2001-1862. We acknowledge the contribution of Paola Baiardi, PhD, for performing statistical analysis. We thank Cristina Barbaro, MD, Giuseppe Trevisan, MD, and Massimo Mantica, MD, who contributed to data analysis and data entry.

References
Natural History of Brugada Syndrome: Insights for Risk Stratification and Management
Silvia G. Priori, Carlo Napolitano, Maurizio Gasparini, Carlo Pappone, Paolo Della Bella, Umberto Giordano, Raffaella Bloise, Carla Giustetto, Roberto De Nardis, Massimiliano Grillo, Elena Ronchetti, Giovanna Faggiano and Janni Nastoli

_Circulation_. 2002;105:1342-1347; originally published online February 25, 2002;
doi: 10.1161/hc1102.105288
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/11/1342

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/