Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing?

Patients With an Asymptomatic Brugada Electrocardiogram Should Undergo Pharmacological and Electrophysiological Testing

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Brugada syndrome presents in a certain number of patients as an inherited cardiac arrhythmia disorder caused by mutations in the cardiac sodium channel gene SCN5A. Carriers of the disease may develop a variety of cardiac arrhythmias, including supraventricular tachycardias, atioventricular conduction defects or block, sick sinus syndrome with atrial standstill, and ventricular tachycardia and ventricular fibrillation. The disease is characterized by the lack of structural heart disease and an ECG with a characteristic coved-type ST-segment elevation in leads V1, V2, and V3. Syncopal episodes and paroxysmal palpitations are the only symptoms attributable to the disease that may warn before (aborted) sudden arrhythmic death occurs. General agreement exists that an implantable cardioverter defibrillator must be given to patients with Brugada syndrome resuscitated from ventricular fibrillation. However, controversy exists on how to approach the individual with a Brugada-like ECG who has never developed ventricular fibrillation.

For the past 12 years, we have maintained a large database of individuals and patients with a characteristic Brugada-like ECG (all coved type). At the last follow-up (January 2004), we analyzed the status of 724 individuals of whom 547 (75%) had no previous cardiac arrest. A subgroup of 167 asymptomatic individuals was also identified who had no family history of sudden death or Brugada syndrome and were considered fortuitous, isolated cases. The abnormal ECG was identified during the investigation of syncope in 124 individuals, during routine ECG screening in 170 individuals, and during study of family members of patients with the syndrome in 253 individuals. The characteristic ECG was present spontaneously in 391 cases and after pharmacological testing with a sodium channel blocker (usually ajmaline) in 156. Mean age of the 547 individuals was 41 ± 15 years, and 408 were male. During a mean follow-up of 28 ± 24 months, 45 (8%) individuals without previous cardiac arrest developed their first (aborted) sudden death. Multivariate analysis showed that inducibility of a sustained ventricular arrhythmia during programmed ventricular stimulation (P < 0.0001) and a history of syncope (P < 0.01) were the main predictors of arrhythmic events during follow-up. A family history of...
Brugada syndrome or sudden death was not predictive of outcome.

Of the 167 fortuitous cases with a Brugada-like ECG, 11 (6.5%) developed (aborted) sudden death. In these nonfamilial asymptomatic individuals, the best predictor of spontaneous ventricular fibrillation was the inducibility of a sustained arrhythmia during programmed ventricular stimulation ($P<0.008$). Fortuitous cases studied by programmed ventricular stimulation and inducible usually received an implantable defibrillator and survived when ventricular fibrillation occurred (6 individuals). There were 5 effective sudden deaths in the 167 fortuitous cases. None of the 5 had an electrophysiological study done, and none had a defibrillator implanted. For the whole group without previous cardiac arrest, logistic regression analysis showed that a previous history of syncope carries a sufficient risk of (aborted) sudden death (1.2% to 27.2% at 3-year follow-up) to recommend an implantable defibrillator independently from the results of programmed ventricular stimulation. In asymptomatic individuals (including the fortuitous, nonfamilial cases) programmed ventricular stimulation helps to stratify the risk of (aborted) sudden death and to identify candidates for prophylactic treatment, the hazard ratio of inducible individuals being 8.33 (95% confidence intervals 2.8 to 25.0) as compared with the noninducible ones.

The asymptomatic individual with a Brugada-like ECG requires further pharmacological and electrophysiological investigation to (1) confirm the diagnosis; (2) stratify the risk for ventricular arrhythmias; (3) provide, if needed, appropriate protection with an implantable defibrillator; and (4) generate sufficient clinical, pathophysiological, and genetic scientific data to cure the disease in the future. The lack of further investigations in a patient with a “coved-type” Brugada ECG may represent a risk of effective sudden arrhythmic death.

“The Right to Know”

From what was initially understood to be a medical curiosity, Brugada syndrome has emerged as a medical reality, with incidences in the general population surpassing any previous estimates. The syndrome reaches endemic characteristics in some areas such as southern Asia, where it has been reported to be the most common cause of natural death in men <50 years old. The diagnosis of the syndrome is based on a combination of electrocardiographic features (Figure 1) and symptoms of syncope or (aborted) sudden arrhythmic death caused by rapid polymorphic ventricular arrhythmias. Data from our group and from other institutions have confirmed the need for secondary prevention treatment in individual carriers of the disease who have already experienced near-sudden cardiac death. The approach to the asymptomatic individual with an ECG characteristic of Brugada syndrome remains controversial. Although our data strongly support the need for pharmacological and electrophysiological investigation of these individuals, other authors failed to confirm the value of these tests, particularly of programmed ventricular stimulation. To further analyze the value of these tests, a subgroup analysis of our database was performed. We specifically analyzed a group of 547 individuals who had not experienced a previous cardiac arrest at the time of diagnosis.
containing a subgroup of 167 individuals who were totally asymptomatic and had no family history of sudden death or Brugada syndrome (supposedly the subgroup with the best prognosis, ie, fortuitous cases. Some of these data have been reported previously.8

For the past 12 years, our group has maintained a large database of individuals with an ECG characteristic of Brugada syndrome (see the Appendix in the online-only Data Supplement). At the last follow-up (January 2004), the status of 724 phenotype carriers was analyzed. Of these patients, 547 had no previous cardiac arrest before diagnosis of the syndrome, with a subgroup of 167 individuals who were totally asymptomatic and in whom there was no family history of sudden cardiac death or of Brugada syndrome (fortuitous cases). In 161 of the 167 individuals, first-degree relatives were electrocardiographically tested and found to be negative.

Diagnosis
The diagnosis of Brugada syndrome was based on the ECG characteristics that define the phenotype of the disease following recently proposed criteria.11 The ECG was considered characteristic if a terminal r wave with a J point elevation ≥0.2 mV with a slowly descending ST segment in continuation with a flat or negative T wave appeared spontaneously in leads V1, V2, and sometimes in V3 (Figure 1). This type of ECG is known as the “coved-type” ECG and is the only one that we consider characteristic of the syndrome. The 2 varieties of the “saddleback-type” ECG11 are suspicious but not characteristic. The ECG was also considered characteristic when a suspicious or normal ECG changed into a typical coved-type ECG after administration of a sodium channel blocker such as ajmaline, procanamide, flecainide, propafenone, or pilsicainide.11 The ECG was spontaneously abnormal in 391 cases and after pharmacological testing in 156. It was identified during the investigation of syncope in 124 individuals, during routine ECG screening in 170, and during a study of family members of patients with the syndrome in 253 individuals. It is important to stress that in all of the individuals included in our database, a coved-type ECG was available. As discussed later in the article, the differences in prognosis in different databases may come from overdiagnosis of Brugada syndrome in individuals with a “saddleback-type” ECG in whom a “coved-type” ECG was never present. Structural heart disease was excluded by clinical history, physical examination, noninvasive methods (echocardiogram, exercise test, nuclear magnetic resonance), and invasive methods (coronary angiography, right and left heart catheterization and angiography, and myocardial biopsies) used at the discretion of the treating physician. Patients with systemic diseases and other conditions known to simulate Brugada syndrome were excluded.

Electrophysiological Study
The electrophysiological study included measurement of conduction intervals and programmed ventricular stimulation from the right ventricular apex with a maximum of 3 ventricular premature beats given at 3 different basic pacing rates. The shortest coupling interval of the premature beats was limited to 200 ms. A patient was considered inducible when a sustained ventricular arrhythmia (defined as one lasting >30 s or requiring intervention to terminate) was induced.

The individuals were studied prospectively for a mean of 28±42 months (range of 1 to 168) after the diagnosis was made. The clinical characteristics are shown in Table 1 for the whole group and for the fortuitous cases.

Whole-Group Analysis
There were 45 events (8.2%) during the follow-up (Figure 2). Sixteen events were sudden cardiac death and 29 resuscitated ventricular fibrillation. Multivariate analysis showed that there were 2 predictors of events during follow-up: inducibility during programmed ventricular stimulation (P=0.0001, hazard ratio [HR] of inducible individuals 5.88, 95% confi-
Asymptomatic Syncope

Fortuitous Individuals With Brugada Syndrome

TABLE 3. Analysis of Predictors of an Arrhythmic Event in 167 Fortuitous Individuals With Brugada Syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arrhythmic Event (n=11)</th>
<th>No Arrhythmic Event (n=156)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>10/1</td>
<td>128/28</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>43±13</td>
<td>45±13</td>
<td>NS</td>
</tr>
<tr>
<td>HV, ms</td>
<td>52±4</td>
<td>46±8</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>42±42</td>
<td>27±42</td>
<td>NS</td>
</tr>
<tr>
<td>ICD, yes/no</td>
<td>6/5</td>
<td>30/124</td>
<td>NS</td>
</tr>
<tr>
<td>Inducible</td>
<td>5</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Not inducible</td>
<td>1</td>
<td>88</td>
<td>0.008</td>
</tr>
<tr>
<td>No EPS</td>
<td>5</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

EPS indicates electrophysiological study.

TABLE 4. Final Outcome in 11 Fortuitous Patients With an Arrhythmic Event Depending on EPS

<table>
<thead>
<tr>
<th>EPS done</th>
<th>No EPS done</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>No Death</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Arrhythmic event defined as sudden cardiac death or documented ventricular fibrillation. EPS indicates electrophysiological study.

appropriately risk stratified and did not receive an implantable cardioverter-defibrillator (ICD). Therefore, when ventricular fibrillation developed, these patients died.

Discussion

Our data show that individuals with an ECG characteristic of Brugada syndrome and no previous cardiac arrest have a high risk of sudden cardiac death during a short follow-up period of 3 years. If the annual risk of sudden death in the general population with a mean age of 40 years (<1/10 000 per year) is considered, then the risk of these individuals is >300 times the risk of the matched population. It is obvious that careful stratification is required, not only because of this risk but also because of the young age of these individuals and because effective protection can be given with an ICD. The most important issue becomes how to perform the most optimal risk stratification to achieve the best cost–benefit and risk–benefit ratios. Ultimately, as physicians we attempt, on the one hand, to avoid unnecessary treatments and, on the other hand, to protect all of the individuals who have an unacceptable risk of sudden cardiac death. The analysis that we have done in this study shows that in the absence of a previous cardiac arrest, a history of syncope and inducibility during programmed ventricular stimulation are predictive of outcome in individuals with an ECG diagnostic of Brugada syndrome. Using these data, an algorithm for risk stratification (Table 5) can be constructed. Before discussing this algorithm, some important aspects deserve consideration to understand the possible discrepancies in the outcome of the different series of individuals with Brugada syndrome. These aspects include the diagnosis, follow-up, and general approach to risk stratification and treatment of individuals (and family members) suspected of having Brugada syndrome.

Diagnosis

We and others reported 3 different ECG patterns in individuals with proven Brugada syndrome. The type 1 ECG (Figure 1A) is the classic characteristic ECG of Brugada syndrome (coved-type). The 2 other patterns (types 2 and 3; Figure 1B and C) concern the saddleback-type ECG, which are suspicious but not characteristic of Brugada syndrome. Type 2 and 3 patterns are frequently seen in individuals with true Brugada syndrome at the time of (near) normalization of the ECG. We believe that this illustration has provoked diagnostic mistakes. Individuals have been diagnosed as having Brugada syndrome based on a type 2 and 3 pattern without ever showing a coved-type ECG. As shown in the
The present study, an spontaneous abnormal coved-type ECG (type 1) is associated with a poorer prognosis as compared with individuals with Brugada syndrome who show the characteristic ECG coved-type pattern only after pharmacological challenge. Therefore, there can be 2 reasons why other series report a better prognosis in individuals with Brugada syndrome while including individuals with only a saddleback-type ECG: (1) Either these individuals do not have Brugada syndrome, or (2) they do have Brugada syndrome and fall in the good prognosis group. Whatever the clinical presentation (resuscitated ventricular fibrillation, syncope, asymptomatic seen during screening with or without a family history of Brugada syndrome), all individuals with the suspicion of Brugada syndrome and a type 2 or 3 ECG need pharmacological challenge to prove the diagnosis.

Follow-Up

It is evident that the follow-up in all series of individuals with proven or suspected Brugada syndrome is much too short. In some patients, Brugada syndrome is caused by mutations in the cardiac sodium channel gene \(SCN5A\) that have been present since conception; however, symptoms and sudden cardiac death develop later in life (age \(\approx 40\) years). Brugada syndrome is not the only inherited disease that challenges our knowledge and imagination. Huntington chorea is a neurological inherited disease. The mutations are carried from the moment of conception. For 40 years, the carriers live a normal life without any symptoms. At 40 years of age the first neurological symptoms start, and 5 years later most patients die. Why these diseases become phenotypically manifest at a later stage is not clear, but what is clear is that classifications such as symptomatic and asymptomatic Brugada syndrome are totally artificial and irrelevant. Every individual with Brugada syndrome who developed ventricular fibrillation was asymptomatic the day before. The present follow-up data are limited and events during further follow-up can only increase.

Lack of Events During Follow-Up

The limited follow-up period in all series and the overdiagnosis of Brugada syndrome because of a saddleback-type ECG without a coved-type ECG may explain the lack of events during follow-up in other series.\(^{13,14}\) Our database includes only individuals with a coved-type ECG. During follow-up, there were events sufficient to reject the null hypothesis for the predictive value of syncope and inducibility during programmed ventricular stimulation. That a history of syncope is predictive of a poor outcome in Brugada syndrome has been confirmed by other series.\(^9,10\) The major discrepancies have been at the level of the positive predictive value of programmed ventricular stimulation in asymptomatic individuals.\(^15\) All series agree in the good negative predictive value, but this is simply because of the lack of events in noninducible individuals. The poor positive predictive value of inducibility in other series is also the result of the lack of events. Longer follow-ups may change this picture completely. With more events, the positive predictive value can only increase, whereas the negative predictive value can only decrease.

General Approach to Diagnosis and Treatment of Individuals With Proven or Suspected Brugada Syndrome

Dealing with families with inherited cardiac diseases is a major challenge. Genetic and therapeutic counseling are delicate, particularly when mutations are not found in all families studied and physicians must consider the possibility of false-positive and false-negative results. Brugada syndrome is not an invalidating disease. Individuals can live a normal life with only a few limitations related to drug intake,
the appropriate treatment of fever, and (the most important limitation) the eventual need for an ICD. (We do not discuss quinidine, which may be an alternative to the defibrillator.) Because of that, we believe the approach to these individuals must come under the motto “the right to know.” It is of no value to record an ECG to exclude Brugada syndrome and, if normal, not to proceed with pharmacological challenge; that is simply not answering the question our patient is asking us. Similarly, it is not appropriate that after a diagnosis of Brugada syndrome has been made no further risk stratification is done by means of the only available test—programmed ventricular stimulation. We believe that the responsibility of physicians dealing with these new diseases goes even further than that; they should direct all of their efforts to quickly generate sufficient clinical, genetic, and pathophysiological scientific data that lead to a cure. That means that treatment of this type of patient should be limited to centers willing to take the full responsibility of dealing with the consequences of a diagnosis. That is particularly difficult for physicians who are confronted with children with proven or suspected Brugada syndrome.

An Algorithm to Approach Individuals With Proven or Suspected Brugada Syndrome

There are many possible ways to approach individuals with proven or suspected Brugada syndrome because the diagnosis may be suspected or become obvious in a variety of ways. Despite all of the possible limitations, the algorithm we propose is a rational approach based on current scientific data. Four categories of clinical presentation are defined in Table 5.

The first category of patients concerns patients resuscitated from ventricular fibrillation with a structurally normal heart. Although we do not discuss the need to provide these patients with an ICD, the exact cause of the arrhythmia must be defined. The differential diagnosis includes the long QT syndrome, the short QT syndrome, catecholamine-induced polymorphic ventricular tachycardia, truly idiopathic ventricular fibrillation, and Brugada syndrome. The long QT and short QT syndromes are diagnoses based on ECG criteria. Idiopathic ventricular fibrillation is a diagnosis by exclusion, when other diagnoses cannot be confirmed. The exclusion of Brugada syndrome requires pharmacological challenge with a sodium channel blocker if the ECG is normal. Although electrophysiological investigations are not required for further risk stratification and to decide on the implantation of a defibrillator, we believe that programmed ventricular stimulation should be performed to better understand the sensitivity and specificity of the test to predict outcome.

The second category of individuals is those investigated because of syncope. Some patients have an ECG characteristic of Brugada syndrome and require no electrophysiological study for further stratification and implantation of a defibrillator. Others have a suspicious or normal ECG, and a pharmacological challenge should be performed to prove Brugada syndrome. If this is the case, then a defibrillator should be implanted irrespective of the results of programmed ventricular stimulation. Again, programmed stimulation should be performed to further characterize the sensitivity and specificity of the test.

The third category deals with individuals who are screened because they are asymptomatic members of a family with Brugada syndrome. The ECG may be spontaneously positive or normal. If it is normal, then a pharmacological test should be done to identify carriers of the disease. Those individuals with a characteristic ECG (spontaneously or after drug challenge) should undergo programmed ventricular stimulation. If the individual is inducible, then an ICD should be recommended.

Finally, the fourth category relates to individuals found by chance to have a spontaneously abnormal ECG during screening for whatever reason. This is the category of patient that better fits with our group of fortuitous cases. These individuals should undergo programmed ventricular stimulation for appropriate risk stratification. If inducible, then we recommend the implantation of an ICD. If noninducible, then our data indicate a low event rate during follow-up not justifying an aggressive approach. Because the follow-up time is probably too short at present, however, the situation may change when longer follow-up times become available.

Limitations

There are many limitations to our knowledge of this disease. Although the brilliant studies by Antzelevitch’s group have helped us to understand the pathophysiology of the disease, we still have the problem of genetic analysis. Mutations are not found in more than 30% of the familial cases, and we know that the disease is heterogeneous. We also do not have cellular electrophysiological studies of all the mutations thus far reported. This genetic heterogeneity may also explain differences in prognosis as well as in the response to drugs such as cilostazol and quinidine. It is specifically because of the limitations in our knowledge that a full investigation of these patients is required.

References

Risk Stratification in Brugada Syndrome

Management of Patients With Brugada Syndrome Should Not Be Based on Programmed Electrical Stimulation

Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD

In 1992, Brugada et al.1 suggested that the presence of right bundle-branch block and ST-segment elevation in leads V1 to V3, in the absence of structural heart disease is a marker of susceptibility to ventricular fibrillation and represents the diagnostic feature of a novel syndrome that rapidly became known as “Brugada syndrome.” A few years later, mutations in the human cardiac sodium channel gene (SCN5A) were identified in 3 families affected by the syn-
drome and was therefore classified among the inherited arrhythmogenic diseases.2

In the past 12 years, Brugada syndrome has become the focus of active investigations, and it has generated strong scientific debate concerning its diagnosis, risk stratification, and treatment. In this article, we present our view on the diagnosis and management of Brugada syndrome, with a specific focus on asymptomatic patients.

Diagnosis of Brugada Syndrome and Role of Pharmacological Testing

Morphology of ST-Segment Elevation

The diagnosis of Brugada syndrome is less obvious than initially anticipated for a variety of reasons. First, ST-segment elevation in right precordial leads is not the exclusive and distinguishing feature of this syndrome, and therefore, in the presence of this ECG pattern, differential diagnosis with a variety of other clinical conditions should be considered (Table).3–25

The morphology of the ST-segment elevation is frequently advocated as a robust parameter to divide patients with ST-segment elevation into “definitely affected” versus “possibly affected” by the Brugada syndrome. Three different morphologies of ST-segment elevation in the right precordial leads have been identified and are usually referred to as type 1, type 2, and type 3 ECGs (Figure 1). Recently, a panel of experts proposed that only the presence of an ST-segment elevation ≥2 mm with a “coved morphology” (ie, type 1) in at least 2 of the 3 right precordial leads should be considered as diagnostic for the syndrome.26 As is often the case, the diversity of scenarios identified in the clinical arena limits the practical use of recommendations: Even in patients with a genetically proven diagnosis of Brugada syndrome, the morphology of the ST-segment elevation varies considerably from day to day, and therefore the probability of encountering a typical “coved pattern” in the ECG increases with more frequent ECG recordings and even more if 12-lead Holter recording is used to monitor ST-segment morphology during a 24-hour period.

Recently, we tested the validity of the new recommendations for the electrocardiographic diagnosis of the syndrome26 in our genotyped families (ie, patients with proven diagnosis in whom a type 1 ECG is expected). Surprisingly, out of 115 genetically affected individuals, a type 1 ECG (spontaneous or induced by flecainide challenge) was lacking in 29 (25%) patients; these individuals were defined as “incompletely penetrant” cases of Brugada syndrome. Concealed forms of the disease are known to occur in the long-QT syndrome, in which 20% to 30% of mutation carriers have a normal QT interval.27 When we looked at symptoms in genotyped patients with Brugada syndrome we did not observe a difference in clinical manifestations between patients based on the ECG morphology. Cardiac arrest occurred in 11 of 86
Positioning of the EGC Leads

Positioning of the right precordial leads is known to affect the morphology of the ST-segment elevation. There is concordant opinion among different investigators that upward displacement of V1, V2, and V3 leads increases the number of ECGs that are diagnostic for the syndrome. Several authors have recommended the use of these “modified leads positioning” to increase the “yield” of diagnosis, but before doing so, we should question whether our patients will benefit from this approach. At present, there are no data that prove whether this maneuver increases the sensitivity of the diagnosis without affecting its specificity. We have observed 1 family referred elsewhere for clinical evaluation after the diagnosis of Brugada syndrome had been established in a relative who died suddenly. Sixty-three members of this family were evaluated and ECG recordings were performed with upward displacement of precordial leads and flecainide challenge; a type 1 ECG was identified in 25 of 63 (40%) individuals. DNA samples were then sent to our institution for genetic analysis that allowed the identification of an SCN5A mutation causing protein dysfunction. When we compared the results of clinical evaluation and those of genetic screening, we observed that the mutation was present in only 6 of the 25 individuals that had been diagnosed as affected on the basis of clinical findings. We concluded that modified upward positioning of right precordial leads may inappropriately overdiagnose the syndrome. Being aware that neither premature enthusiasm nor anecdotes should guide medicine, we have taken a conservative approach and it is our practice to use for diagnostic purposes only ECG recordings obtained via conventional positioning of the right precordial leads. We believe that upward displacement of right precordial leads should not be adopted until its sensitivity and specificity are defined in a large number of genetically characterized individuals.

Use of Pharmacological Testing

Administration of sodium channel blockers (flecainide, ajmaline, or procainamide) is largely used to exacerbate ST-segment elevation in patients with type 2 or type 3 ST-segment elevation. The test is performed under the assumption that the number of false positives (ie, patients developing a type 1 ECG without being affected by the disease) is extremely low. At present, no data derived from systematic studies support or disprove the concept that sodium channel blockers provide an accurate diagnosis of the syndrome. In fact, as long as every single patient developing a type 1 ECG is defined as affected by Brugada syndrome, it will be impossible to find anyone who is a defined as a false positive, thus perpetuating the perception that the pharmacological test is 100% accurate. The sensitivity and the specificity of the sodium channel blockers test remain to be defined with a systematic evaluation of members of genotyped families.

Evidence has been reported that false positive responses to sodium channel blockers may occur. For example, Peters et al reported that 16% of patients with right ventricular cardiomyopathy respond with an ST-segment elevation to intravenous sodium channel provocative test. These data show that development of ST-segment elevation in response to class IC sodium channel blockers is not unique to Brugada syndrome and suggest that the presence of structural abnormalities compatible with the diagnosis of arrhythmogenic right ventricular cardiomyopathy should be excluded in patients with positive pharmacological challenge before considering the Brugada syndrome.

We demonstrated that false negative responses to flecainide can be observed in patients with intermittent type 1 ECG. When flecainide challenge was performed in patients presenting with a normal ECG but with a previously documented type 1 ECG, not all of the patients converted to type 1 ECG, thus demonstrating that sensitivity of the test is <100% and that its reproducibility is not 100% (Figure 2). Unfortunately, a more systematic evaluation of the accuracy and reproducibility of sodium channel blocker provocative test has not been reported in the medical literature nor it is known to which extent the use of the different class IC sodium channel blockers may influence sensitivity and specificity of the results. While waiting for studies that will clarify these aspects, pharmacological challenge with sodium channel blockers is largely used in the clinics for diagnostic purposes. At our center we perform flecainide challenge (2 mg/kg in 10 minutes) whenever we suspect the diagnosis of

![Figure 2](image-url)
Brugada syndrome on an ECG that is not conclusively diagnostic both in symptomatic and asymptomatic individuals. The issue has been raised whether it is appropriate to use a provocative challenge in asymptomatic individuals to achieve an early diagnosis of the disease and the issue is not of marginal relevance. The psychological impact of the diagnosis of Brugada syndrome is major; in our experience it is much more dramatic than, for example, the diagnosis of long-QT syndrome. There are 2 reasons why patients have difficulty coping with this diagnosis: (1) Given the absence of pharmacological treatment for this disease, patients cannot benefit from the psychological support of feeling protected by medications; (2) the nocturnal occurrence of events has a major psychological impact because both patients and their relatives feel more vulnerable to an arrhythmic event that may occur during sleep.

It is our practice to recommend provocative drug challenge in asymptomatic individuals when they belong to families in which Brugada syndrome has been diagnosed and/or when the ECG raises a suspicion of Brugada syndrome that is not conclusively diagnostic. Before performing the test we explain to the patients that if the ECG becomes diagnostic during the provocative test, they will be asked to remain under periodic medical follow-up to detect a progression of the disease such as the development of a spontaneously diagnostic ECG pattern. Taking into consideration the low risk of events in the first 2 decades of life, we tend to discourage flecainide challenge in asymptomatic children.

**Risk Stratification in Brugada Syndrome**

The mainstay in the treatment of patients with Brugada syndrome is the implantable cardioverter-defibrillator (ICD) that is used both for primary and secondary prevention of cardiac arrest. To target the use of the device it would be extremely valuable to have a solid estimate of the risk of experiencing cardiac arrest in different patient groups, so that only high-risk individuals would receive an ICD. Unfortunately, the experience gathered from the study of highly prevalent acquired cardiac diseases has shown that risk stratification to predict sudden cardiac death has been largely unsuccessful. Several invasive and noninvasive parameters have been proposed in the past 20 years to identify postmyocardial infarction patients at risk of sudden death; however, they have failed to have a high positive predictive value that could identify candidates for ICD. A similar scenario is also present in genetic disorders such as hypertrophic cardiomyopathy or long-QT syndrome, in which prediction of cardiac arrest is particularly difficult and even invasive methods, such as programmed electrical stimulation (PES), have failed. The issue is particularly complex in the identification of individuals who will experience a first cardiac event (primary prevention). In all diseases, there is in fact consensus that survivors of cardiac arrest should be protected by an ICD. As a general rule for risk stratification in arrhythmogenic diseases, the occurrence of syncope is a strong risk predictor of cardiac arrest and the presence of a severe risk factor affecting survival. It seems logical that Brugada syndrome would follow the same principles; unfortunately, the issue is more controversial, and conflicting evidence exists, leaving practicing cardiologists and arrhythmia specialists in a delicate situation. In the next section we will review the scientific debate surrounding risk stratification in Brugada syndrome.

Before aiming at risk stratification in any disease it is important to know the percentage of patients who will experience cardiac arrest throughout their lifetime (ie, the natural history of the disease). On the basis of the lethality of the disease it is rational to choose between conservative or aggressive treatment strategies. This apparently logical task of defining the severity of a disease is not so straightforward to achieve in uncommon diseases. Collection of data on genetic disorders is usually achieved through international registries that collect self-reported nonconsecutive cases. An inherent bias of these registries is given by the fact that "symptomatic" cases are most likely referred to the registry than are "asymptomatic" cases, either because the latter escape clinical diagnosis or because physicians are more inclined to remember and to report complex cases than uneventful ones. As a consequence, in the initial description of novel diseases, there is often an overestimation of its mortality and morbidity. Over time, however, more asymptomatic cases are identified and a more realistic perception of the severity of the disease is obtained. The early reports on Brugada syndrome estimated an extremely high rate of occurrence of cardiac arrest. In a 1998 *Circulation* article, over 34 months of follow-up, 27% of the previously asymptomatic patients were reported as having experienced a first ventricular fibrillation or sudden cardiac death. This figure corresponds to an occurrence of life-threatening events of 10%/year. In 2002, in another *Circulation* article by the same authors, 8% of the previously asymptomatic patients had become symptomatic, corresponding to an occurrence of a life-threatening event of 3.5%/year. A similar figure is reported in a 2003 study in which asymptomatic patients have a yearly rate of cardiac arrest in the range of 4% (eg, Figure 3 of the referenced article). Despite that the rate of cardiac events among asymptomatic patients reported by Brugada et al has decreased over time, it remains unclear why asymptomatic patients with a fortuitous identification of ST-segment elevation during routine screening have a 4%/year rate of sudden cardiac death after the diagnosis. The remarkably high rate of sudden cardiac death within a few months from the detection of the first abnormal ECG is particularly difficult to understand, considering that patients were diagnosed during "routine" evaluation and not during investigations prompted by clinical symptoms that could indicate the onset of an "active phase" of the disease. It is tempting to speculate that the stress related to the medical
investigations prompted by the identification of the abnormal ECG may play a role in triggering ventricular fibrillation in these patients.

In the population of patients studied at our Center, the rate of events after diagnosis among asymptomatic patients is significantly lower than that reported by Brugada and Brugada. We showed that asymptomatic patients have a cumulative probability of 14% experiencing a cardiac arrest by age 40, corresponding to an incidence of cardiac arrest of 0.35%/year.35 This figure is similar to the incidence of cardiac arrest among untreated long QT1 (0.3%/year) and long QT2 patients (0.6%/year).36 Recently, in 300 patients with a type 1 ECG, we observed 42 episodes of ventricular fibrillation (14%), corresponding to an annual incidence of 0.3%. The reasons underlying the markedly different occurrences of cardiac arrest in the 2 populations is unknown, but obviously it influences the treatment approach recommended by the 2 groups of investigators.

In 2002, we35 showed that the presence of a spontaneous ST-segment elevation in leads V1, V2, and/or V3 was one of the most robust indicators of risk of cardiac events at follow-up. Patients with a spontaneously diagnostic pattern have a 2-fold greater risk of cardiac events than do patients with a pattern induced only by provocative test. Interestingly, our database now includes >500 patients, and the presence of a spontaneous pattern remains associated with a 2-fold risk of cardiac events. In the same study, patients with a spontaneous ECG pattern who have experienced syncope showed a 6-fold higher risk of cardiac arrest (Figure 3). On the basis of this observation, we proposed a risk stratification scheme (Figure 4) that suggested that patients resuscitated from cardiac arrest and patients with a spontaneous ECG pattern and history of syncope receive an ICD. Brugada et al came to identical recommendations for survivors of cardiac arrest and for patients with spontaneous ECG pattern and history of syncope.34 Agreement therefore exists that the treatment of these 2 groups of patients is not guided by PES.

The treatment of asymptomatic patients is more controversial, and of course, it reflects the difference in the perceived risk of sudden cardiac death. The data from Brugada et al34,37,38 have shown that PES is highly predictive of cardiac events at follow-up. Our own data are completely different, mainly because in our population we do not even come close to the figure of lethality of the disease reported by Brugada et al. As a consequence, our patients, irrespective of whether they are inducible, do not experience such a dramatic occurrence of events in the 2 years after PES. On the basis of the data published in 2003 by Brugada et al,38 we compared the performance of PES to that of the noninvasive risk stratification algorithm that we use39 (Figure 5). With PES as risk stratification parameter, 91 patients would be implanted to save 11 lives; therefore, 80 asymptomatic individuals would receive an ICD without any proven benefit during the follow-up period.

In our database, we have 132 patients who never experienced cardiac arrest and were studied with PES. At a mean follow-up of 31 months, 4 of 132 (ie, 3%) experienced a cardiac arrest or an appropriate shock of the ICD. This corresponds to a cardiac arrest rate of 1%/year, which of course is too low to demonstrate the value of risk stratification based on PES inducibility (cardiac arrest in inducible versus noninducible P=0.62). In this group of 132 asymptomatic patients, 61 were inducible, including 3 of the 4 patients who experienced cardiac arrest at follow-up. Had we used PES for risk stratification we would have implanted 61 patients and saved 3 lives. This corresponds to a number needed to treat (NNT) of 20 (ie, higher than that of the
Sudden Cardiac Death Heart Failure Trial and the Multicenter Automatic Defibrillator Implantation Trial II, which represent the forefront indications for the use of the ICD in primary prevention of cardiac arrest. More important, the NNT of 20 in the Brugada syndrome population would apply to a population implanted at a mean age of 40 years—in other words, 20 years earlier than in patients enrolled in heart failure trials. On the basis of these data, we remain in favor of the risk stratification scheme that we proposed in 2002 and await results from the large prospective PRogrammed Electrical stimUlation preDictivE value in Brugada syndrome (PRELUDE) study, initiated by the Italian Association of Electrophysiology, which will determine the role of PES in risk stratification.

Conclusions
Knowledge about Brugada syndrome is progressing. There is consensus that the severity of the clinical manifestation is the most powerful indicator of outcome and that survivors of cardiac arrest and patients with a spontaneous diagnostic pattern with a history of syncope are at higher risk of cardiac events and should receive an ICD without undergoing PES. Asymptomatic individuals and patients with a diagnostic pattern that can be observed only after flecainide administration are at lower risk of cardiac events. Data from different databases rank the risk of events among asymptomatic patients quite differently, ranging from <0.5% to 4%/year. Obviously, all registries are affected by referral biases and still have a short follow-up to provide conclusive data. To fill the gap of knowledge, it will be important to strengthen scientific collaboration and enrollment of patients in registries to reduce the time required to collect data that will guide the treatment of asymptomatic patients with Brugada syndrome.

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Response to Priori and Napolitano
Pedro Brugada, MD, PhD, FESC; Ramon Brugada, MD; Josep Brugada, MD, PhD

Priori and Napolitano correctly state that knowledge about Brugada syndrome is steadily progressing. Indeed, much has been learned in the past 13 years, particularly in terms of diagnosis and prognosis. In terms of diagnosis, the most recent advances have come from realizing that only a coved-type ECG is diagnostic of Brugada syndrome. Unfortunately, many series include individuals with a saddleback-type ECG who probably do not have Brugada syndrome. That may explain the differences in prognosis. Biases exist in all databases; however, there is a major bias when one goes in the direction of genetic samples to clinical data rather than clinical diagnosis to prognosis and genetics (our method). We may have a bias toward a more diseased population; however, it is because of having events during follow-up that we are able to assess the value of the tests employed. Our risk stratification, when applied to the series of Priori and Napolitano, shows that implanting 91 ICDs saves the lives of 11 individuals at a mean age of 40 years. We believe that this is as acceptable as the results of any published primary or secondary trial of prevention of sudden cardiac death with the ICD. The alternative is medically unacceptable: Not implanting any ICDs, as in the series of Priori and Napolitano, would result in 11 individuals dying suddenly at a mean age of 40 years.

Response to Brugada et al
Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD

Brugada et al once more strongly support PES for risk stratification in the Brugada syndrome. It is our opinion that the authors present incomplete and biased evidence to readers. They portray our work1,2 as the only one showing a lack of prognostic value for PES in Brugada syndrome. This is not true. Eckardt et al3 presented interesting data that questioned the value of PES and pointed to the fact that the stimulation protocol is a major determinant of inducibility. Even clearer is the message provided by Eckhardt and coworkers4 in a recent issue of Circulation. The authors presented a novel multicenter study that confirms all of the findings that we reported in 20001 and 2002,2 with survival curves that are almost identical to ours. The central statement of this article is the following: “We assessed the value of inducibility and confirmed previous reports of limited accuracy.” In light of a fair evaluation of the literature, the clear discordance on the predictive value of inducibility mandates a consideration of PES as an investigatory tool of uncertain value (Class IIb). We await revision of the consensus document5 that inappropriately attributed to PES a Class IIa recommendation.

References
Patients With an Asymptomatic Brugada Electrocardiogram Should Undergo Pharmacological and Electrophysiological Testing
Pedro Brugada, Ramon Brugada and Josep Brugada

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