Predictive Impact of the Inducibility of Ventricular Fibrillation in Patients With Brugada-Type ECG

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SUMMARY

The natural history of asymptomatic individuals with a Brugada-type electrocardiogram (ECG) is still controversial. In this study, we evaluated ventricular fibrillation (VF) inducibility in Brugada-type ECG patients and compared it with other risk factors to clarify the significance of these data on their prognosis.

The study population consisted of 38 patients who presented with a typical ST-segment elevation in the precordial leads and underwent an electrophysiological study (EPS). The patients were divided into 3 groups; group A: patients with spontaneous ventricular fibrillation (VF) \((n = 5)\), group B: patients without clinical VF but with inducible VF in EPS \((n = 16)\), and group C: patients with neither clinical nor inducible VF \((n = 17)\). The clinical features, diagnostic results, and prognosis were compared among these groups.

During the follow-up period of 26 ± 19 months, 2/5 (group A), 1/16 (group B), and 0/17 (group C) patients suffered fatal arrhythmic events. None of the clinical features showed any significant difference, although the incidence of positive results in a drug challenge test was higher in groups A and B than in group C \((P < 0.05)\). On the other hand, VF inducibility was higher in patients with positive results in the drug challenge test than in patients with negative results \((59\% \text{ versus } 13\%; P < 0.05)\).

No VF episodes were observed in patients without VF induction, although one was observed in 1 of 16 patients with VF induction in asymptomatic Brugada syndrome. The drug challenge test appears to be useful for predicting VF inducibility even though it is a noninvasive test. (Int Heart J 2006; 47: 229-236)

Key words: Brugada syndrome, Sudden death, Ventricular fibrillation, Electrophysiological study

SINCE the first report from Brugada and Brugada about idiopathic ventricular fibrillation (VF) with specific ST elevation in precordial leads,1) many reports concerning Brugada syndrome have been published, and a consensus report about
its diagnosis has recently been established. Because of the extremely high recurrence rate of VF in symptomatic Brugada syndrome, ie, a patient with previous spontaneous VF, the prevention of sudden cardiac death with an implantable cardioverter defibrillator (ICD) is recommended as the primary therapy in Brugada syndrome with VF history. However, the biggest question is the indication of ICD therapy for patients with asymptomatic Brugada syndrome as a prophylactic therapy for sudden cardiac death because the mortality for asymptomatic Brugada syndrome has been reported to be less than 2-10%, which is considerably less than that of symptomatic Brugada syndrome, but much more frequent than that in the normal population. Recently, it has been reported that the inducibility of VF in an electrophysiologic study (EPS) might be a useful predictor for the clinical occurrence of VF. In the present study, the clinical characteristics and electrophysiological properties in an EPS, especially the inducibility of VF, were evaluated in Brugada-type ECG patients, who were followed-up relatively long-term to clarify the significance of the findings as a predictor of future spontaneous VF.

**METHODS**

**Patient population:** The study population consisted of 38 consecutive patients who presented with typical coved or saddle-back type ST-segment elevation in the precordial leads (V_1-V_3) and underwent EPS at our institute. The patients underwent the clinical evaluations listed below, including a drug-challenge test and EPS, and were followed-up under close observation or with prophylactic ICD implantation when it was considered necessary. All study protocols were performed with the permission of the ethics committee of Kitasato University and written informed consent was obtained from each subject before their enrolment in the study.

**Clinical characteristics, ECG pattern, and drug challenge test:** Clinical information, including age at diagnosis, gender, prior syncope (unexplained cause), and family history of sudden cardiac death (at < 45 years old) was obtained and the pattern of ST segment elevation was classified in accordance with a consensus report published in 2002, ie, coved type as type 1 and saddle-back type as type 2. A drug challenge test using pilsicainide was performed in patients with type 2 ECG changes because this test has been reported to exaggerate the ST elevation specifically in Brugada syndrome. Pilsicainide at a dose of 1 mg/kg body weight was intravenously infused for 3 minutes followed by observation for 10 minutes. A 12-lead ECG was recorded every minute and the change in the ST segment was evaluated. This provocation test was considered positive when a type 2 ECG changed to a type 1 ECG.

**Electrophysiologic study and induction of VF:** Cardiac catheterization was per-
formed to exclude underlying structural heart diseases. After the basic measurement of intracardiac pressure, coronary angiography, including a provocation test of coronary spasm using acetylcholine (ACh), was performed because complications with coronary spasm and VF in Brugada syndrome have been reported.5,6) After excluding structural stenosis in the coronary artery, 20 and 50 µg ACh was infused into the right coronary artery and 20, 50, and 100 µg into the left coronary artery followed by observation for 5 minutes for each infusion. This provocation test was considered positive when the case met more than 2 of the following 3 criteria: 1) appearance of coronary stenosis (> 99%), 2) ST segment change in ECG, and 3) chest pain.

Programmed electrical stimulation was performed to evaluate the inducibility of VF. The induction protocol employed a maximum of 3 ventricular extrastimuli with 2 different paced cycle lengths (600 and 400 ms) at 2 right ventricular sites (the apex and the outflow tract). Premature beats were started in

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, y ±</th>
<th>Follow-up, mo ±</th>
<th>Male/female</th>
<th>History of clinicalVF</th>
<th>Inducibility ofVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>5</td>
<td>42 ± 17</td>
<td>36 ± 32</td>
<td>5/0</td>
<td>Yes</td>
</tr>
<tr>
<td>Group B</td>
<td>16</td>
<td>52 ± 13</td>
<td>23 ± 14</td>
<td>15/1</td>
<td>No</td>
</tr>
<tr>
<td>Group C</td>
<td>17</td>
<td>53 ± 16</td>
<td>30 ± 16</td>
<td>15/2</td>
<td>No</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier analysis of arrhythmic events (sudden cardiac death or documented ventricular fibrillation) during follow-up. Two of 5 patients in group A and one of 16 patients in group B had an arrhythmic event. No cardiac events were observed in group C. See text for discussion. SCD indicates sudden cardiac death; VF, ventricular fibrillation; and NS, not significant.
late diastole, and coupling intervals were shortened by 10 ms steps until refractoriness or a coupling interval of 180 ms was reached. Patients were classified as VF inducible when hemodynamically unstable rapid sustained ventricular rhythm (VF or rapid ventricular tachycardia) was induced. No patients received antiarrhythmic drugs.

123I-MIBG study: Patients underwent [123I] m-iodobenzylguanidine (123I-MIBG)-single-photon emission CT imaging to assess cardiac autonomic dysfunction. The result was considered abnormal if there was a massive reduction in 123I-MIBG uptake in the segmental portion of the ventricle.

Grouping: The patients were divided into the following 3 groups; group A: patients with a history of spontaneous VF (symptomatic Brugada syndrome: \(n = 5\)), group B: patients without clinical spontaneous VF, but with inducible VF in EPS (\(n = 16\)), and group C: patients with neither clinical VF nor inducible VF in EPS (\(n = 17\)). The clinical characteristics of the 3 groups are summarized in the Table. The other clinical data and prognosis were compared among the groups.

Statistical analysis: Statistical analysis was performed using JMP statistical software (SAS Institute, Cary, NC, USA). A comparison of categorical data between the groups was analyzed using Fisher's exact test. The event-free analysis was estimated with the Kaplan-Meier method. The statistical significance of each comparison was calculated with the log-rank test. A value of \(P < 0.05\) was considered statistically significant.

RESULTS

Prognosis of the patients: The patients were followed-up for 26 ± 19 months. During this follow-up period, 2 of 5 group A patients, 1 of 16 group B patients, and 0 of 17 group C patients suffered spontaneous VF episodes (Figure 1). Although there was no significant difference among the groups, it is important to note that the group B patient experienced a new VF episode during clinical follow-up. He was rescued from VF because prophylactic ICD implantation was indicated.

Comparison of clinical data: Figure 2 summarizes the comparison of clinical data among the 3 groups. The history of syncope, family history of sudden cardiac death, and the existence of type 1 ECG in the basal state did not exhibit any significant differences among the groups (Figure 2A-C). A positive result in the drug challenge test with pilsicainide was observed in 50% of the patients in group C, which was significantly lower than in the other 2 groups (group A: 100%, group B: 92%, Figure 2D). There were no significant differences in the inducibility of coronary spasm by ACh (Figure 2E) or abnormality in the 123I-MIBG scintigram (Figure 2F) among the 3 groups.
Since there was a significant difference in the drug challenge test with pil-secainide, the inducibility of VF was compared between patients with and without a positive result in this provocation test (Figure 3). The results showed that VF inducibility was significantly higher in patients with a positive result (59%) than in patients with a negative result (13%).
DISCUSSION

Importance of VF inducibility as a clinical predictor for VF: Brugada, et al reported on a large number of individuals diagnosed with Brugada syndrome based on ECG findings, but without a previous episode of cardiac arrest.\(^7\) In their report, patients had a relatively high risk for sudden arrhythmic death, even in the absence of a history of cardiac arrest: ie, 8.2% experienced sudden death or at least one documented episode of VF during a mean follow-up of 24 ± 33 months. However, this extremely poor outcome was not supported by other reports by Priori,\(^8\) Atarashi,\(^9\) and Eckardt.\(^10\) Although the second consensus report from Antzelevitch, et al focused on further diagnostic criteria, the risk stratification for patients without a previous VF episode was not established.\(^11\) Brugada, et al summarized these reports and suggested that among asymptomatic patients, the inducibility of VF during EPS may predict the risk, but Priori, et al could not find any association. Even in the latest report published by Brugada, et al, the authors still did not have the same opinion for asymptomatic patients.\(^12\)

In the present study, we focused on VF inducibility in patients with Brugada syndrome, and found that a clinical episode of VF was observed only in patients with inducible VF, but not in patients without inducible VF. Although this difference was not statistically significant, most likely because of the relatively small number of patients, the clinical importance of VF inducibility in EPS was suggested. The original important point of our report is that clinical VF occurred in 1 of 16 patients during a relatively short-term follow-up period. This single patient was rescued by ICD which was recommended because of VF inducibility.

Figure 3. The inducibility of VF was compared between patients with and without a positive result in this provocation test. VF inducibility was significantly higher in patients with a positive result than in patients with a negative result.
in EPS by an extrastimulus with a relatively short coupling interval. In other words, this patient could not be rescued without focusing on VF inducibility by a stimulus with a shorter coupling interval. Although the importance of VF inducibility and the protocol for VF induction itself are still controversial, our report seems to support the opinion of Brugada. However, we should clarify the importance of VF inducibility in asymptomatic Brugada syndrome in a larger population in a future study.

**Importance of the other clinical data:** In our study, other clinical data such as clinical background, inducibility of coronary spasm, $^{123}$I-MIBG abnormality, and the result of a drug challenge test with pilsicainide were compared among the 3 groups classified in accordance with inducibility or a history of VF. Only the drug challenge test showed a significant difference among the groups. Although VF inducibility might be an important predictor for clinical VF in the future, it can be evaluated only in EPS, which is an invasive technique. However, from the results of our study, VF inducibility in EPS was significantly higher in patients with a positive result in this provocation test than in those with a negative result. This indicates that the drug challenge test with pilsicainide might be a noninvasive predictor for VF inducibility, and it could become an alternative predictor for clinical VF. Although not evaluated in this study, other diagnostic data such as the detection of ventricular late potentials and abnormality in genetic testing might also help the risk stratification in Brugada syndrome. This should be also evaluated in a larger population in a future study.

**Prognosis and possible clinical management:** In our study, only one asymptomatic patient, a 59 year-old male who suffered spontaneous VF during follow-up, was classified as a patient with inducible VF and type 1 ECG unmasked by pilsicainide administration. The spontaneous VF was successfully terminated by the action of a prophylactic ICD. Although this patient was saved by selecting VF inducibility as a predictive index for the occurrence of VF, we are unable to strongly emphasize the importance of VF inducibility because this was only a single case. However, prophylactic ICD implantation might be indicated for patients with inducible VF, a family history of sudden death, or prior history of syncope especially in patients with type 1 ST elevation (spontaneous or unmasked by pilsicainide). To evaluate the usefulness of clinical predictors for sudden death, observations in a larger population are needed.

**Study limitations:** The study has a few limitations. First, the study population was relatively small. Second, the follow-up period was relatively short. To confirm the importance of clinical predictors for VF, similar observations should be continued in a larger number of patients for a longer period of follow-up.

**Conclusion:** Clinical VF occurred in 1 of 16 patients with inducible VF in EPS in asymptomatic Brugada syndrome and he was rescued by ICD implantation,
suggesting the importance of VF inducibility as a clinical predictor. Because the VF inducibility was significantly different in a drug challenge test with pilsicainide, a pilsicainide provocation test might be an alternative clinical predictor for VF in Brugada syndrome.

REFERENCES