Evaluation of the Necessity for Cardioverter-Defibrillator Implantation in Elderly Patients With Brugada Syndrome

Tsukasa Kamakura, MD; Mitsuru Wada, MD; Ikutaro Nakajima, MD; Kohei Ishibashi, MD; Koji Miyamoto, MD; Hideo Okamura, MD; Takashi Noda, MD, PhD; Takeshi Aiba, MD, PhD; Hiroshi Takaki, MD, PhD; Satoshi Yasuda, MD, PhD; Hisao Ogawa, MD, PhD; Wataru Shimizu, MD, PhD; Takeru Makiyama, MD, PhD; Takeshi Kimura, MD, PhD; Shiro Kamakura, MD, PhD; Kengo Kusano, MD, PhD

**Background**—The clinical characteristics and prognosis of elderly patients with Brugada syndrome (BrS) are largely unknown. The purpose of this study was to evaluate the risks and benefits of implantable cardioverter defibrillator (ICD) in elderly patients with BrS based on a long follow-up.

**Methods and Results**—A total of 120 BrS patients with ICD (90 for aborted sudden cardiac arrest or syncope, mean age, 46.6±12.2 years; 50 with age ≥60 years at the last follow-up) were included in this study. During 102±68 months of follow-up, 31 patients (26%) experienced appropriate shocks. Age at the first attack of ventricular fibrillation (VF) was <70 years in all patients (mean, 45.0±12.1 years), the incidence of VF decreased with age, and VF did not recur after 70 years of age except in 2 patients with ischemic heart disease. Eleven of 28 patients with supraventricular tachycardia experienced inappropriate shocks. These inappropriate shocks increased with age and reached a peak in patients who were in their sixties. Lead failures occurred in later stages after implantation in 10 of 120 patients (8%).

**Conclusions**—Long-term follow-up of high-risk BrS patients with ICD showed a low incidence of VF in those aged >70 years. Considering the increasing risk of inappropriate shocks because of the relatively late onset of supraventricular tachycardia and lead failures, avoidance of ICD implantation, or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age. (Circ Arrhythm Electrophysiol. 2015;8:785-791. DOI: 10.1161/CIRCEP.114.002705.)

**Key Words:** Brugada syndrome ▪ death, sudden, cardiac ▪ defibrillators, implantable ▪ myocardial ischemia ▪ syncope

**Implantable cardioverter defibrillator (ICD) is considered to be the main therapy for prevention of sudden cardiac death in patients with Brugada syndrome (BrS). However, there have been several reports suggesting a higher prevalence of complications, such as inappropriate shocks, lead failure, and device infection compared with the incidence of lethal ventricular arrhythmia.** BrS is mainly diagnosed at 40 years of age in men, and sudden death is likely to be eliminated after ICD implantaion. Meanwhile, the clinical characteristics and prognosis of elderly patients with BrS are largely unknown, and there are no reports on the incidence of ventricular fibrillation (VF) or the evaluations of the necessity for ICD in elderly patients. Provided that BrS is caused by depolarization abnormality, ventricular arrhythmias may conceivably increase with age.

The purpose of this study was to investigate the incidence of appropriate shocks and ICD complications in patients with BrS during long-term follow-up after ICD implantation and to assess the risk and benefit of ICD implantation in elderly patients with BrS.

**Methods**

**Study Population**
The study population consisted of 120 consecutive BrS patients who were admitted to National Cerebral and Cardiovascular Center, Suita, Japan, between 1992 and 2013, and had undergone ICD implantation (115 men; mean age, 46.6±12.2 years). All patients except 1 were index cases. None of all the patients had structural heart disease, including arrhythmogenic right ventricular cardiomyopathy, which was confirmed by noninvasive studies (physical examination, 12-lead ECG, 87-lead body surface ECG, exercise stress test, signal-averaged electrocardiography, and cardiac magnetic resonance imaging or computed tomography), and invasive studies consisting of coronary angiography including ergonovine/acytcholine injection and right or left ventricular cineangiography. This study was approved by the Institutional Research Board of National Cerebral and Cardiovascular Center.

**Diagnosis of Brugada Syndrome**
BrS was diagnosed when a type 1 ST-segment elevation was observed either spontaneously or after intravenous administration of a sodium channel blocking agent in at least 1 right precordial lead (V1 and V3), which was placed in a standard or a superior position (up to the
WHAT IS KNOWN

- Brugada syndrome is mainly diagnosed around 40 years of age in men, and sudden death can be effectively prevented after implantable cardioverter defibrillator implantation.
- The clinical characteristics and prognosis of older patients with Brugada syndrome is largely unknown.

WHAT THE STUDY ADDS

- This study included 120 patients with Brugada syndrome after implantable cardioverter defibrillator implantation with a mean follow-up >8 years. Of the total, 90 had sudden death or syncope. The incidence of ventricular fibrillation (VF) decreased with age; the first VF did not occur after age of 70 years in all patients, and no VF recurrences occurred after age of 70 years in patients without ischemic heart disease.
- The inappropriate shocks because of supraventricular tachycardia increased with age, and the risk of lead failure also increased over time.
- Considering the risk of implantable cardioverter defibrillator–related complications and low risk of VF events associated with advancing age, avoidance of implantable cardioverter defibrillator implantation, or replacement may be considered in elderly Brugada syndrome patients who remain free from VF until 70 years of age.

Clinical Data, ECG, and Electrophysiological Testing

Clinical data including age at diagnosis, age at the first episode of VF, sex, family history of sudden cardiac death at <45 years of age, history of supraventricular tachycardia (SVT; atrial fibrillation [AF], atrial flutter, and atrial tachycardia) and ventricular tachyarrhythmia (VF or ventricular tachycardia) lasting >30 s, indications for ICD implantation, and oral therapy were collected for all patients. Electrophysiological study (EPS) was conducted in 100 patients as previously described. ICD was implanted in patients with an episode of VF or syncope judged to be likely caused by ventricular arrhythmias. ICD was also implanted in asymptomatic patients with induced VF at EPS or a family history of sudden death. Vasovagal syncope was excluded by head-up tilt test using isoproterenol infusion and oral nitroglycerin. Genetic testing for mutations in SCN5A gene was performed in 80 patients (67%), as previously described.

Follow-Up

All patients were followed up routinely every 3 to 6 months mainly for device interrogation. During follow-up, patients were considered to have an arrhythmic event if ICD interrogation revealed that appropriate shocks or antitachycardia pacing were delivered in response to VF or ventricular tachycardia. The beginning of the follow-up period was at the time of the first VF event in patients with a history of VF and at the time of admission in patients without VF. All the data about VF/ventricular tachycardia episodes, SVT, ICD shocks, and ICD complications were collected during follow-up periods. Electrical storm was defined as ≥3 episodes of VF within 24 hours. Lead failure was defined as a severe lead defect that required surgical correction, which did not include acute lead complications, such as lead perforations and lead dislodgements. Device programming was left to the individual physician’s preference but was typically set with a single VF zone with shock only therapy. The medical therapy was decided by the patient’s physician.

Statistical Analysis

Data were analyzed with JMP10 software (SAS Institute Inc, Cary, NC). Numeric values are presented as mean±SD or median (with interquartile range), depending on the normality of distribution. The data were analyzed with JMP10 software (SAS Institute Inc, Cary, NC). Numeric values are presented as mean±SD or median (with interquartile range), depending on the normality of distribution. The χ² test, Student t test, 1-way ANOVA, or Mann–Whitney test was performed as appropriate to test for statistically significant differences. The incidence of VF was calculated on the basis of the at the time of admission in patients without VF. All the data about VF/ventricular tachycardia episodes, SVT, ICD shocks, and ICD complications were collected during follow-up periods. Electrical storm was defined as ≥3 episodes of VF within 24 hours. Lead failure was defined as a severe lead defect that required surgical correction, which did not include acute lead complications, such as lead perforations and lead dislodgements. Device programming was left to the individual physician’s preference but was typically set with a single VF zone with shock only therapy. The medical therapy was decided by the patient’s physician.

Results

Clinical Characteristics and Indication for ICD Implantation

The clinical characteristics of the 120 patients (115 men; mean age at diagnosis, 46.6±12.2 years) are shown in Table 1. Seventeen patients were ≥60 years at diagnosis. Before ICD implantation, 36 patients (30%) had a history of VF (VF group), 54 patients (45%) had an episode

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics in Brugada Patients With VF, Syncope, and Without Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF (n=36)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>FH of SCD (%)</td>
</tr>
<tr>
<td>SCN5A mutation</td>
</tr>
<tr>
<td>Spontaneous type 1 (%)</td>
</tr>
<tr>
<td>Induction of VF by EPS (%)</td>
</tr>
</tbody>
</table>

Numeric values are expressed as mean±SD. EPS indicates electrophysiological study; FH of SCD, family history of sudden cardiac death before 45 years of age; and VF, ventricular fibrillation.
of syncope (syncope group), and 30 patients (25%) were asymptomatic. Among the 30 asymptomatic patients, indications for ICD implantation included inducible VF at EPS and a family history of sudden death (n=12), inducible VF (n=14), no inducible ventricular arrhythmia but a family history of sudden death (n=2), and a spontaneous type 1 Brugada ECG pattern along with electrophysiologist or patient preference for ICD (n=2).

**Clinical Outcome**

Follow-up data are shown in Table 2. Mean follow-up period was 102±68 months. Seventeen patients were ≥70 years at the last follow-up. The mean follow-up period of these 17 patients aged >70 years at the last follow-up was 131.6±87.6 months. Their average age at the last follow-up was 74.8±4.4 years. After they reach 70 years, they were followed for 63.5±2.6 months on average. Two patients died by suicide. Thirty-one patients (26%) experienced appropriate shocks because of VF. There was no documentation of shocks by sustained monomorphic ventricular tachycardia. The incidence of VF during follow-up was significantly higher in the VF group (Figure 1). Among 50 patients who had VF before and during the follow-up period (VF group, 36; syncope group, 13; asymptomatic, 1), the peak age of VF onset was between 30 and 39 years, the age at the first VF was <70 years in all patients (mean age, 45.0±12.1 years; range, 27–69 years; Figure 2A and 2B), and the incidence of VF (VF events per 100 person-years) decreased with age (Figure 2C). Although no patients had new onset of VF after 70 years of age, 2 patients who were suspected to have myocardial ischemia experienced VF recurrence after 70 years of age. The first case was an 83-year-old man who was diagnosed with BrS and underwent ICD implantation because of a spontaneous type 1 ECG and a history of syncope during night at the age of 67 years. He developed new onset angina pectoris and underwent percutaneous coronary intervention at the age of 68. He experienced several VF recurrences after the first VF attack at the age of 69 years. However, no VF recurred after the age of 82, when he underwent coronary artery bypass graft surgery. The second case was an 80-year-old man who had undergone ICD implantation because of a spontaneous type 1 ECG and a history of syncope at the age of 63. The first VF attack occurred 8 months after ICD implantation, when he started to take nifedipine and quinidine because he was suspected to have vasospastic angina. However, VF recurred at the age of 80.

After ICD implantation, antiarrhythmic drugs were administered in 4 middle-aged patients in the VF group, and patients in the syncope and asymptomatic group were followed without drug at first. Although antiarrhythmic drugs (quinidine, 200–300 mg/d; denopamine, 15–30 mg/d; cilostazol, 100 mg/d, etc) were started in 5 patients in the VF group and 5 patients in the syncope group who experienced VF recurrence, 6 of 10 developed VF. Only 2 patients were treated with antiarrhythmic drugs (1: quinidine 200 mg/d and 1: quinidine 300 mg/d) during follow-up in the 17 patients who lived beyond 70 years of age. No patients underwent epicardial catheter ablation.

Twenty-eight patients (23%) experienced SVT (Table 2) including AF in 22 patients, atrial flutter in 5 patients, and atrial tachycardia in 1 patient as of the last follow-up. Mean age at the onset of SVT was 52.3±12.7 years.

Mutations of SCN5A gene were identified in 20 of 80 patients (25%). There were no statistically significant differences in the clinical parameters, including family history of sudden death, spontaneous type 1 ECG, history of AF, VF induction by EPS, and VF recurrence, between patients with and without a SCN5A mutation.

**ICD Complications**

Device-related complications occurred in 39 patients (33%) during the follow-up period (Table 2). The incidence of

| Table 2. Clinical Outcomes and ICD Complications in the 3 Groups |
|------------------|-----------------|-----------------|-----------------|------------------|
|                  | VF (n=36)       | Syncope (n=54)  | Asymptomatic (n=30) | P Value Comparing 3 Groups |
| Follow-up period, mo | 116±76          | 98±69           | 92±53           | 0.45 |
| Age at the last follow-up, y | 52.4±12.8      | 57.7±14.8       | 53.9±11.0       | 0.08 |
| Age ≥60 y at the last follow-up (%) | 12 (33)        | 30 (56)         | 8 (27)          | 0.018 |
| VF recurrence (%) | 17 (47)         | 13 (24)         | 1 (3)           | 0.0002 |
| Electrical storm (%) | 7 (19)          | 4 (7)           | 0 (0)           | 0.02 |
| No. of appropriate shocks (total, median, IQR) | 161, 0, 0–6.5 | 106, 0, 0–0.25 | 1, 0, 0–0      | 0.0002 |
| Death (%) | 1 (3)           | 1 (2)           | 0 (0)           | 0.67 |
| Supraventricular tachycardia |                  |                  |                  |                      |
| At the time of diagnosis (%) | 3 (8)           | 5 (9)           | 3 (10)          | 0.97 |
| At the last follow-up (%) | 8 (22)          | 11 (20)         | 9 (30)          | 0.60 |
| Atrial fibrillation (%) | 8 (22)          | 8 (15)          | 6 (20)          | 0.65 |
| Patients with ICD complications (%) | 16 (44)         | 16 (30)         | 7 (23)          | 0.16 |
| Patients with inappropriate shocks (%) | 7 (19)          | 9 (17)          | 5 (17)          | 0.94 |
| No. of inappropriate shocks (total, median, IQR) | 8, 0, 0–0.0     | 27, 0, 0–0      | 8, 0, 0–0      | 0.98 |

Numeric values are expressed as mean±SD. ICD indicates implantable cardioverter defibrillator; IQR, interquartile range; and VF, ventricular fibrillation.
complications among the 3 groups was not significantly different. A total of 43 inappropriate shocks occurred in 21 patients. The number of inappropriate shocks was higher than appropriate shocks in the asymptomatic group. Reasons for inappropriate shocks were SVT (n=26), sinus tachycardia (n=6), lead failure (n=5), T-wave oversensing (n=3), and others (n=3). Fifteen patients experienced trouble with a lead 98±41 months after ICD implantation: 10 patients with lead failure, 3 patients with lead perforation, and 2 patients with lead dislodgement. The incidence of lead failure per 145 leads increased over time and reached 13% at the 10-year follow-up (Figure 3). Twenty-one leads (15%) were involved in a device recall or advisory (St. Jude Medical Riata or Medtronic Sprint Fidelis); however, the incidence of such lead failure was not statistically significantly different from ICD leads not involved in a recall process. New lead implantation was performed in all 10 patients including 2

Figure 1. Kaplan–Meier analysis of freedom from lethal arrhythmic events (documented ventricular fibrillation [VF]) during follow-up in 3 groups (VF, syncope, and asymptomatic) of patients with Brugada syndrome. The incidence of VF during follow-up was significantly higher in the VF group than in the syncope and asymptomatic groups.

Figure 2. The age distribution of the first ventricular fibrillation (VF); in total (A), and according to the clinical subgroups (VF group, 36; syncope group, 13; and asymptomatic group, 1; B), and the incidence of VF depending on each age category (C). Among 50 patients who had VF before and during follow-up period, the peak age of VF onset was between 30 and 39 years, the age at the first VF was <70 years in all patients (range, 27–69 years), and the incidence of VF decreased with age after reaching a peak between 20 and 39 years of age.
patients who required lead extraction. Another 10 patients had infection related to the ICD that required lead extraction in all patients including surgical approach in 3 patients. Three patients needed to change the location of generator because of pain.

Inappropriate shocks because of SVT occurred in 11 of 28 patients (39%) with SVT (10: AF and 1: atrial flutter). Eight cases of AF were newly detected when inappropriate shocks occurred. These shocks increased with age in accordance with increasing number of SVTs (Figure 4A) and reached a peak in patients who were in their sixties (Figure 4B).

Discussion

Main Findings

It is thought, albeit with uncertainty, that ICD implantation may provide less benefit to elderly patients with Brugada syndrome, although there is no definite evidence. This study, long-term (about 100 months) follow-up of 120 BrS patients with ICD including 90 high-risk patients, showed that the incidence of VF decreased with age, the first VF never occurred after age of 70 years in all patients, and no VF recurrences occurred after age of 70 years in patients without ischemic heart disease. The inappropriate shocks because of SVT increased with age, and the risk of lead failure also increased over time. Considering the higher risk of ICD complications with age, BrS patients who remain free from VF until 70 years of age might not benefit from an invasive procedure, such as ICD or lead implantation, and lead extraction after 70 years.

Prognosis of Elderly Patients With Brugada Syndrome

There is a considerable number of reports on the clinical characteristics and prognosis of the adult patients with BrS. However, several case reports and only 1 systemic study exist about the clinical characteristics of the elderly patients with BrS. Conte et al retrospectively analyzed 74 BrS patients aged >60 years, among whom 31 patients had ICD, and concluded that the BrS patients aged >70 years might be a lower risk category of patients compared with younger individuals because none of the elderly patients who were >70 years had aborted sudden death. However, the characteristics of their cohort were different from the previous reports of BrS that is, only 3% of the patients had a history of VF and only 13% of the patients had a spontaneous type I ECG. In addition, the mean follow-up period of their study was <55 months, and among 25 patients >70 years, no patients had a history of VF and only 9 patients had syncope. This means that their conclusion was drawn from the cohort consisting of a small number of high-risk patients who were followed for a shorter period than in this study. However, in this study, all the 120 patients including 50 patients who were aged ≥60 years had received ICD. Among them, 70% showed type 1 ECG spontaneously, 30% had a history of VF, and 45% had experienced an episode of syncope. The mean follow-up time was 102 months and 15 of 17 (88%) patients who were >70 years had a history of VF or syncope. Thus, the cohort in this study included a large number of patients not only with higher risk features but also with a much longer follow-up. Furthermore, contrary to the study by Conte et al, in which ventricular arrhythmias of elderly patients were incompletely tracked by a limited number of ICDs (31 patients with age ≥60 years, about 10 with age ≥70 years), this study showed the decennial VF incidence based on a more thorough arrhythmia tracking with a larger number of ICDs (50 patients with age ≥60 years, 17 with age ≥70 years). Although, every patient without a prior history of VF before 70 years of age and most patients with a history of VF experienced no VF after 70 years of age, whereas 2 patients >70 years were taking low-dose quinidine. In 2 elderly patients with VF recurrence, newly developed myocardial ischemia was suspected to trigger VF episodes although there was no ECG evidence showing acute coronary syndrome. This means that BrS patients aged >70 years without ischemic heart disease...
might belong to a lower risk group of VF patients than younger BrS patients. Actually, as far as we know, there exist no reports of ECG documentation of new onset VF or electrical storm in patients with BrS after 70 years of age.

The decreasing incidence of VF with age in the middle-aged to elderly, which was first demonstrated using person-years analysis in this study, might give clues to the understanding of the mechanism of BrS (Figure 2C). Supposing that VF attack in BrS is caused by a depolarization abnormality only, the number of ventricular arrhythmias would not decrease with age because structural changes would continue to contribute to arrhythmias. Yet the decreasing incidence of VF after reaching a peak between 20 and 39 years of age may indicate that the repolarization abnormality plays a major role in the pathogenesis of VF in patients with BrS. One of the possible background factors that influence ventricular repolarization is the level of sex hormone that can increase the outward potassium current or decrease the inward calcium current. There have been suggestions that Brugada phenotype has a relationship to the level of sex hormones, and the decrease in blood level of testosterone with aging might contribute to the low incidence of VF in elderly patients. Further studies will be needed to investigate the role of sex hormone in ventricular arrhythmias in BrS.

ICD Complications in Patients With Brugada Syndrome

This study showed a high incidence of inappropriate shocks, lead troubles, and ICD-related infections with increasing age of patients, some of which were reported by previous studies. Moreover, as the second novel finding, we observed that the mean age at the onset of SVT was after middle age (52.3±12.7 years), and that inappropriate shocks because of SVT increased with age (Figure 4). This means optimal programming of ICD including single high-rate VF zone (210–220 beats per minute) and long VF detection interval, and the lead positioning with adequate R-wave discrimination might become essential for the prevention of inappropriate shocks in the elderly BrS patients. Furthermore, catheter ablation can also be effective to reduce inappropriate shocks in patients with AP.

ICD generator/lead has been routinely implanted or exchanged in patients with a history of VF or syncope because they have been shown to have a poor prognosis. However, it is difficult to decide not to implant an ICD in asymptomatic patients with multiple risk factors of sudden death (induced VF, strong family history, etc) because we still have no reliable data for predicting a future VF event. This study indicated that the BrS patients who had only syncope or remained asymptomatic until 70 years of age may be spared from a future VF event. In addition, given our data that none of the BrS patients without ischemic heart disease experienced further VF recurrence after 70 years of age, and the increasing risk of inappropriate shocks because of SVT or lead failure with aging, avoidance of an invasive procedure, such as new ICD implantation, or ICD generator/lead exchange may be advisable for such patients. Nevertheless, the device-guided management for patients with low or intermediate risk still remains controversial. Subcutaneous ICD can be implanted as substitute for transvenous ICD for such patients.

Study Limitations

This was conducted at a single-center using retrospective analysis. The small number of patients might limit the interpretation of the results, yet, it should be pointed out that no other reports with a significant number of high-risk elderly BrS patients exist. In addition, the number of VF patients is larger, and the follow-up period in this study is much longer than that of the worldwide multicenter registry of BrS patients with ICD. Furthermore, prospective multicenter studies with larger numbers of patients will be needed to confirm these results.

Conclusions

Long-term follow-up of high-risk BrS patients with ICD showed a low incidence of VF in the elderly patients. Considering the increasing risk of inappropriate shocks because of the relatively late onset of VF and lead failures, avoidance of ICD implantation or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age.

Sources of Funding

This work was supported by a research grant for the cardiovascular diseases (grant number H26-040) from the Ministry of Health, Labor, and Welfare, Japan, and intramural research funds (M25-74) for cardiovascular disease from National Cerebral and Cardiovascular Center.

Disclosures

None.

References


Evaluation of the Necessity for Cardioverter-Defibrillator Implantation in Elderly Patients With Brugada Syndrome

Tsukasa Kamakura, Mitsuru Wada, Ikutaro Nakajima, Kohei Ishibashi, Koji Miyamoto, Hideo Okamura, Takashi Noda, Takeshi Aiba, Hiroshi Takaki, Satoshi Yasuda, Hisao Ogawa, Wataru Shimizu, Takeru Makiyama, Takeshi Kimura, Shiro Kamakura and Kengo Kusano

Circ Arrhythm Electrophysiol. 2015;8:785-791; originally published online June 11, 2015;
doi: 10.1161/CIRCEP.114.002705
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/8/4/785

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology 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: Arrhythmia and Electrophysiology is online at: http://circep.ahajournals.org//subscriptions/