

*The Prognostic Value of Electrophysiologic Investigations
in Symptomatic Patients with Brugada Syndrome*

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Key Words: Brugada Syndrome, Electrophysiologic Study, Ventricular Fibrillation, Syncope, Sudden Cardiac Death, Implantable Cardiac Defibrillator

ABSTRACT

Background: Brugada syndrome is characterized by ST segment elevation in the right precordial leads (V1-V3) and an episode of ventricular fibrillation (VF) in the absence of any structural heart diseases. In the present study, we examined the relationship between the electrocardiographic, electrophysiologic characteristics and the induction of VF by programmed ventricular stimulation (PVS) in patients with symptomatic Brugada syndrome. The implication of PVS-induced VF on the recurrence of cardiac events was also examined. **Methods:** Thirty-four patients with symptomatic Brugada syndrome were entered in this study. We divided the patients into 2 groups by the presence and the absence of VF induction; 22 patients with induced VF requiring direct cardioversion for termination (Induced VF group) and 12 patients without induced VF (Non induced VF group). **Results:** The QRS duration and the HV interval were longer, the incidence of right bundle branch block and late potentials detected by signal averaged electrocardiogram were higher, and the conduction time from the right ventricular outflow tract to the left ventricle at extrastimulation was longer in the Induced VF group than in the Non induced VF group. No significant difference in the recurrence of cardiac events (VF documented by an implantable cardioverter defibrillator and sudden cardiac death) was observed between the 2 groups during long-term follow-up (mean 38 months). **Conclusion:** The PVS-induced VF was related to the depolarization abnormalities, however it does not predict the recurrence of cardiac events in symptomatic patients with Brugada syndrome. These data suggest that depolarization abnormalities do not primarily contribute to spontaneous occurrence of VF in Brugada syndrome.

INTRODUCTION

The Brugada Syndrome, first described by Brugada and Brugada in 1992, is characterized by a distinct electrocardiographic (ECG) pattern consisting of right bundle branch block (RBBB) and ST segment elevation in the right precordial leads (V1-V3) and an episode of ventricular fibrillation (VF), which is unrelated to acute ischemia, electrolyte abnormalities or structural heart disease.¹⁻⁷ The incidence of the Brugada syndrome is higher in Asian countries, including Thailand and Japan than in the U.S. and European countries, in which more than 80% of those afflicted are adult males (44±22 years of age).⁸⁻²¹ Genetic studies have identified the first gene mutation linked to the Brugada syndrome on *SCN5A*, the gene that encodes for the α subunit of the Na^+ channel.²² Both experimental and clinical studies have suggested that heterogeneous repolarization across the ventricular wall of the right ventricular outflow tract (RVOT) was responsible for the ST segment elevation and the genesis of VF.²³⁻²⁵ A prominent transient outward current (I_{to})-mediated action potential (AP) notch and a subsequent loss of AP dome in the epicardial cell but not the endocardial cell of the RVOT are believed to result in the ST segment elevation and the induction of subsequent VF due to the mechanism of phase 2 reentry.²⁶ On the other hand, some clinical studies have reported the presence of depolarization abnormalities, such as prolonged His-Ventricular (HV) interval and the relatively high incidence of complete or incomplete RBBB and late potential (LP) detected by signal averaged electrocardiogram (SAECG) in patients with Brugada syndrome.^{1-3,10,27,28} Although Brugada syndrome is primarily an electrical disease due to repolarization abnormalities, it is unclear how depolarization abnormalities interact and contribute to the pathogenesis in Brugada syndrome. Moreover, the electrophysiologic characteristics and the implication of programmed ventricular stimulation (PVS)-induced VF are not fully evaluated in patients with Brugada syndrome. In the present study, we examined 1) the relationship between the electrocardiographic, electrophysiologic characteristics and the PVS-induced VF, and 2) the implication of PVS-induced VF on the recurrence of cardiac events during long-term follow-up in symptomatic patients with Brugada syndrome.

METHODS

Study population

We systematically studied 34 consecutive patients with symptomatic Brugada syndrome who were admitted to the National Cardiovascular center, Osaka, Japan (Figure 1). Symptomatic Brugada syndrome was diagnosed if the following criteria were fulfilled:²⁰ 1) a history of apparent syncope, or aborted cardiac arrest with or without documentation of VF, 2) spontaneously-documented persistent or transient ST segment elevation (a coved and or saddle-back type) in the right precordial leads (V1 to V3) with or without some degree of RBBB, 3) normal findings on physical examination and laboratory values, and 4) no evidence of structural heart diseases demonstrated by cardiac echocardiogram, coronary angiogram, right and left ventriculogram, radionucleogram, and magnetic resonance imaging. They were 33 males and one female, ranging in age from 19 to 68 years (mean: 44±12 years). All 34 patients had episodes of syncope and 23 patients had a history of aborted cardiac arrest before diagnosis. VF was documented in 22 patients, and 4 patients had family history of sudden cardiac death.

We divided the 34 patients into 2 groups according to the presence and the absence of PVS-induced VF. VF (≥ 300 bpm) was induced by up to triple extrastimuli from the right ventricular apex (RVA) or the RVOT and was terminated by direct cardioversion in 22 patients (Induced VF group). VF was not induced in the remaining 12 patients (Noninduced

VF group), in whom non-sustained polymorphic ventricular tachycardia (≥ 5 beats) was induced (8 patients), or no ventricular arrhythmias were induced (4 patients). We compared the electrocardiographic and electrophysiologic parameters, and the recurrence of cardiac events during follow-up between the 2 groups.

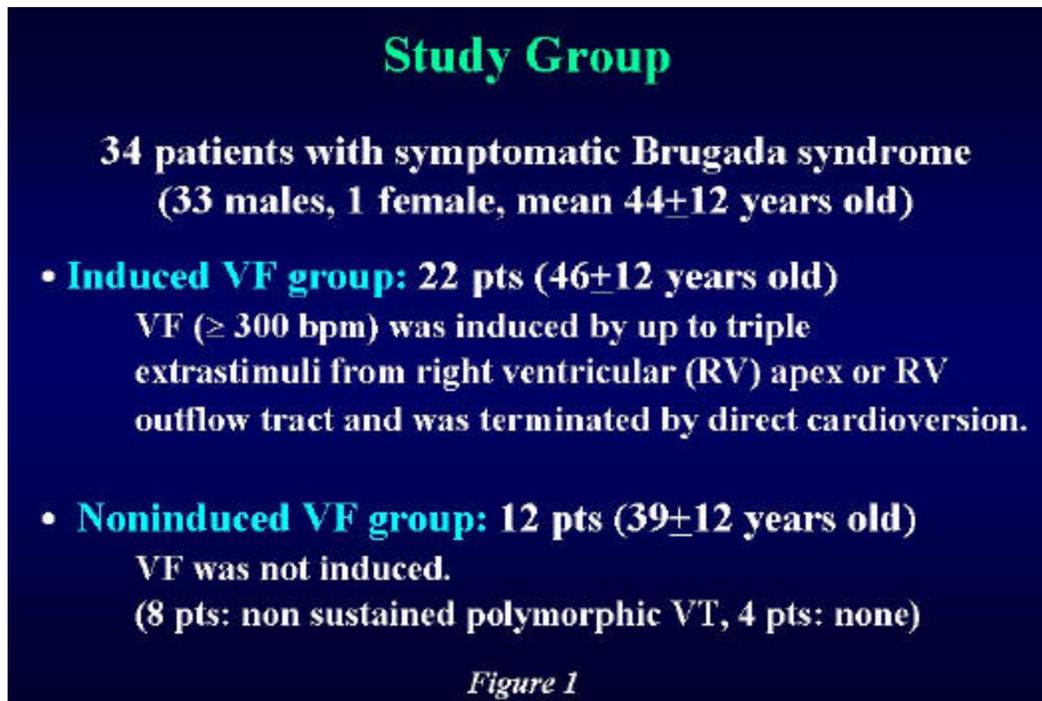


Figure 1. Study group.

12-leads ECG

A 12-leads ECG was recorded during sinus rhythm in the absence of any antiarrhythmic drugs. The RR interval, PQ interval, QRS duration and corrected QT (QTc) interval were measured in lead V5 or V6. RBBB was defined when the patient had a widened S wave in lead V6 and a QRS duration ≥ 100 ms; incomplete RBBB was defined if the QRS duration was < 120 ms, complete RBBB if it was ≥ 120 ms.

SAECG

The LP was analyzed using a SAECG system (Arrhythmia Research Technology LVP 1200EPX). The analysis of the signal-averaged ECG was based on the quantitative time domain measurements of the filtered vector magnitude of the orthogonal Frank X, Y, and Z leads. The QRS complexes were amplified, digitized, averaged (350 – 400 beats), and filtered with a high pass filter (40 Hz). Three parameters were assessed via a computer algorithm: 1) the total filtered QRS duration; 2) the root mean square voltage of the terminal 40 ms of the filtered QRS complexes (V40); and the duration of low-amplitude signals < 40 μ V of the filtered QRS complex (T40). The positive SAECG was defined when two criteria (V40 < 18 μ V and T40 > 38 ms) were fulfilled.

Electrophysiologic study

An electrophysiologic study was performed in all patients without any antiarrhythmic drugs after informed consent was obtained. The Atrio-His (AH) interval and the HV interval were measured during constant right atrial pacing at a

cycle length of 600 ms. PVS was performed at 2-msec and a twice-diastolic threshold current from the RVA and the RVOT, using two basic cycle lengths (500 and 600 ms) and a maximum of triple extrastimuli. Inducibility of ventricular arrhythmias was tested first at the RVA using single and double extrastimuli and, in case of noninducibility, it was tested at the RVOT using single and double extrastimuli. If ventricular arrhythmias were not induced using up to double extrastimuli, triple extrastimuli were introduced from the RVA first, and then from the RVOT. End points of the PVS were induction of VF associated with hemodynamic collapse or completion of the PVS protocol. If VF was not induced during PVS using up to double extrastimuli at the RVOT, we measured the conduction time from the RVOT to the lateral wall of the left ventricle during the double extrastimuli from the RVOT. The longest conduction time between the stimulus artifact at the RVOT and the ventricular electrogram at the distal coronary sinus was used as a parameter of conduction delay via the ventricular septum at a basic cycle length of 500 ms (S1V1), at a first extrastimulus (S2V2), and at a second extrastimulus (S3V3), respectively.

Therapy and follow-up

All patients were followed in the outpatient clinics of the National Cardiovascular Center. Implantation of an implantable cardioverter defibrillation (ICD) was recommended in all patients, because all patients were symptomatic. Some earlier cases refused to ICD implantation and were treated with antiarrhythmic drugs (disopyramide or amiodarone). Propranolol, a β -blocker was added in patients with ICD implantation in whom an inappropriate cardioversion was documented due to sinus tachycardia or atrial fibrillation. The end points were apparent syncope, sudden cardiac death, or VF documented by a storage memory of ICD. All patients could be followed up for more than 1 year in case of no recurrences of cardiac events.

Statistical analysis

Quantitative data are presented as means \pm SD, and were analyzed by a two-tailed Student's test. Categorical data are presented as absolute and were analyzed by the chi-square test. Kaplan-Meier life-table analysis was used to determine the differences in event-free survival rates between the 2 groups. A p value less than 0.05 was regarded as significant.

RESULTS

12-leads ECG

The QRS duration was longer in the Induced VF group than in the Noninduced VF group (110 ± 13 vs. 96 ± 10 ms; $P < 0.01$), whereas the PQ interval and the QTc interval were not different between the 2 groups (Figure 2). The incidence of complete or incomplete RBBB was higher in the Induced VF group than in the Noninduced VF group (20/22 patients (91 %) vs. 4/12 patients (33 %); relative risk, 2.72; $P < 0.01$) (Figure 3, left). The incidence of positive SAECG was also higher in the Induced VF group than in the Noninduced VF group (19/22 patients (86 %) vs. 6/12 patients (50 %); relative risk, 1.73; $P < 0.05$) (Figure 3, right).

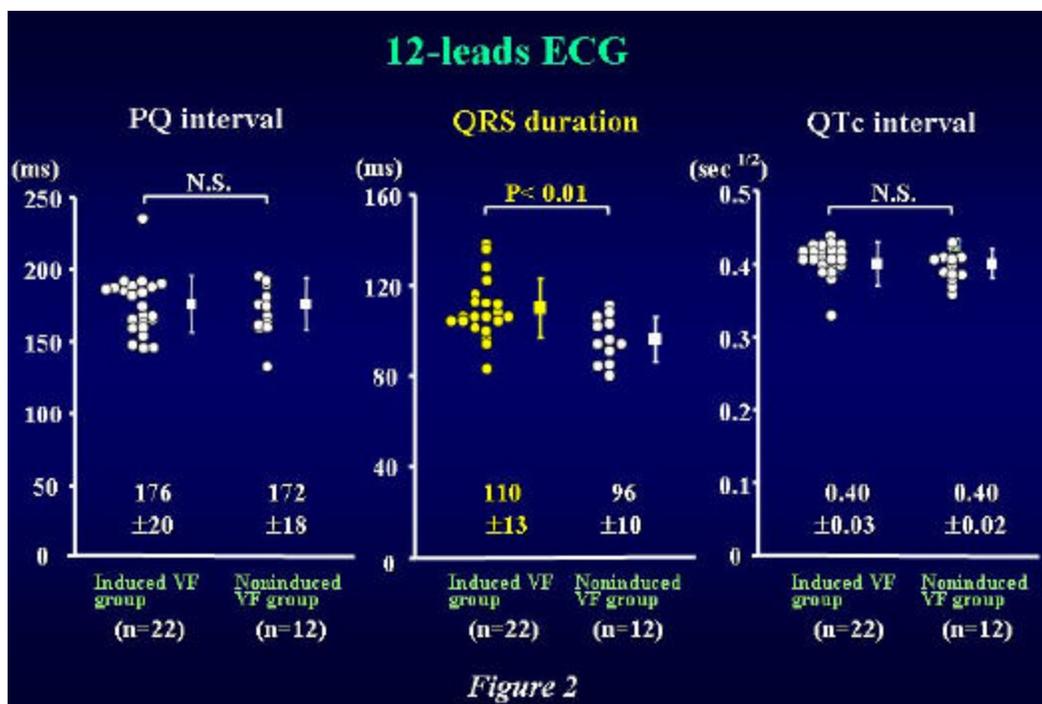


Figure 2. Comparison of PQ interval, QRS duration, corrected QT (QTc) interval between Induced VF group and Noninduced VF group.

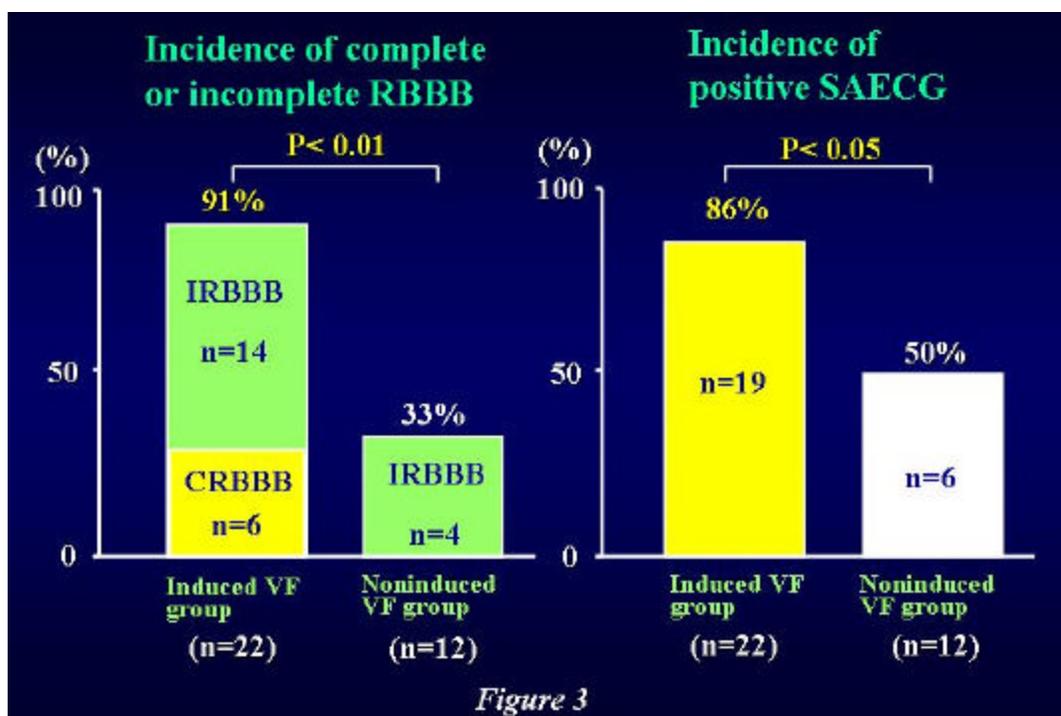


Figure 3. Comparison of incidence of complete or incomplete right bundle branch block (RBBB) and positive signal averaged electrocardiogram (SAECG) between Induced VF group and Noninduced VF group.

Electrophysiologic study

The HV interval was longer in the Induced VF group than in the Noninduced VF group (49 ± 9 vs. 41 ± 7 ms; $P < 0.05$), whereas the AH interval was no different between the 2 groups. There were no significant differences in the effective refractory period (ERP) at a basic cycle length of 500 ms at either RVOT or RVA between the 2 groups (Figure 4). The longest conduction time via the ventricular septum at the first extrastimulus (S2V2) and second extrastimulus (S3V3) were longer in the Induced VF group than in the Noninduced VF group (S2V2, 176 ± 39 vs. 142 ± 26 ms; $P < 0.05$, S3V3, 208 ± 35 vs. 176 ± 27 ms; $P < 0.05$) (Figure 5). VF was induced with a single extrastimulus (1 patient from the RVOT), double extrastimuli (12 patients; 8 from the RVOT and 4 from the RVA) and triple extrastimuli (9 patients; 6 from the RVOT and 3 from the RVA) in the Induced VF group. Non-sustained polymorphic ventricular tachycardia was induced with double extrastimuli (1 patient from the RVOT) and triple extrastimuli (7 patients from the RVOT) in the Noninduced VF group.

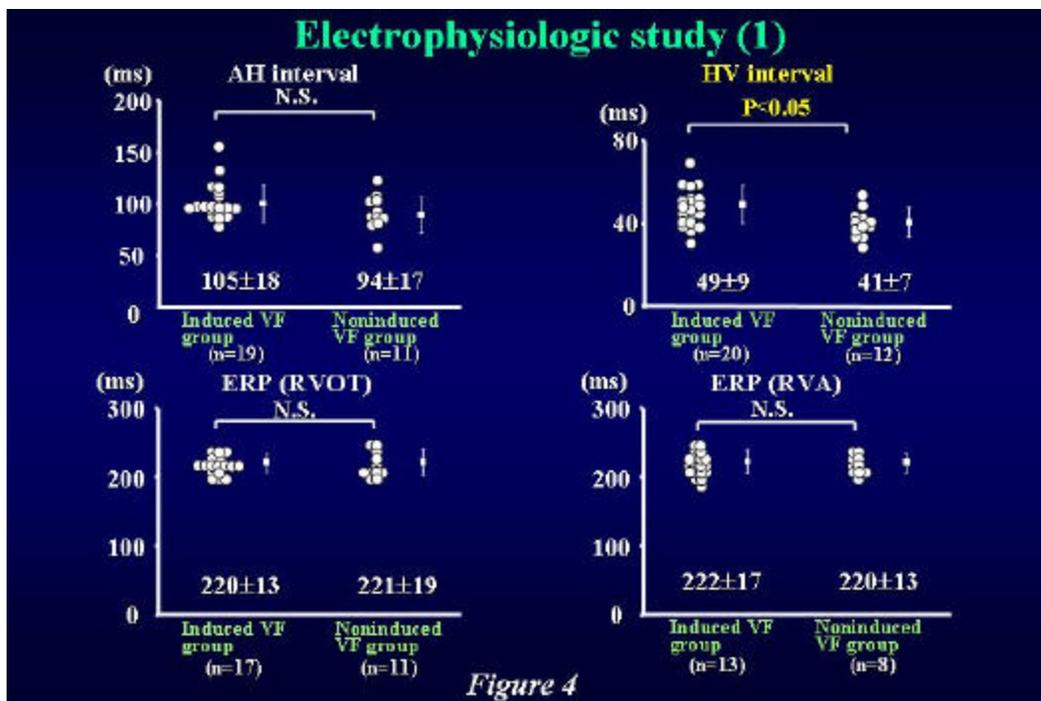


Figure 4

Figure 4. Comparison of Atrio-His (AH) interval, His-Ventricular (HV) interval, effective refractory period (ERP) at the right ventricular outflow tract (RVOT) and the right ventricular apex (RVA) between Induced VF group and Noninduced VF group.

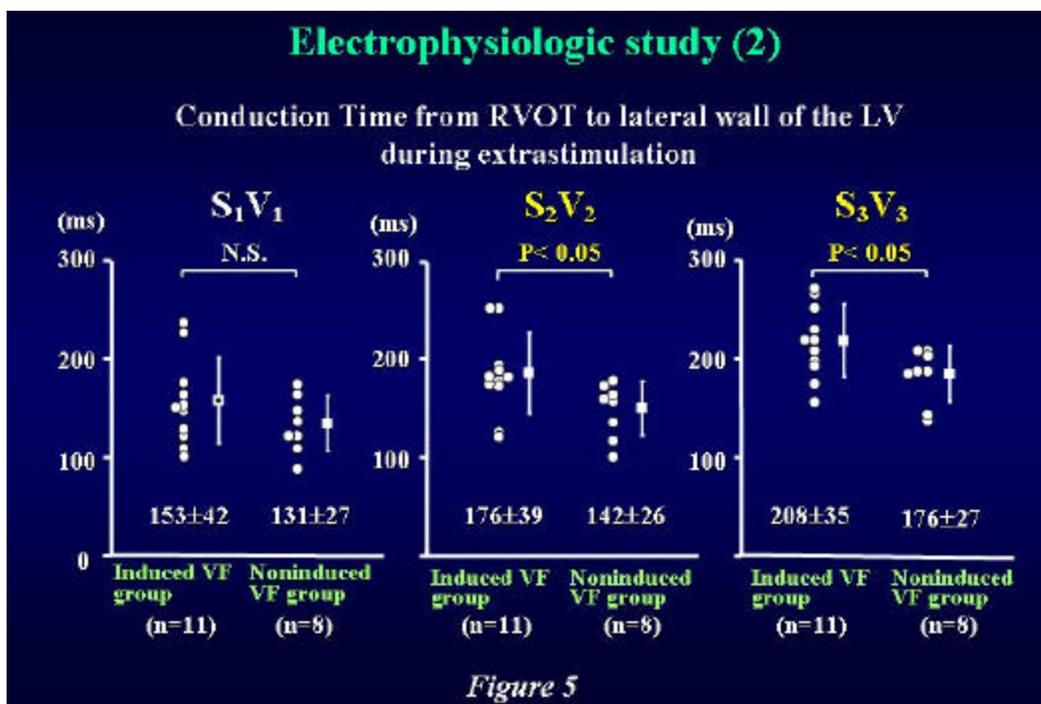


Figure 5

Figure 5. Comparison of conduction time from right ventricular outflow tract (RVOT) to lateral wall of the left ventricle (LV) during extrastimulation between Induced VF group and Noninduced VF group.

Therapy

ICD was implanted in 19 of 22 patients in the Induced VF group and in 9 of 12 patients in the Noninduced VF group (Figure 6). Propranolol was added in one patient with the Induced VF group and in 3 patients with the Noninduced VF group. One patient in the Noninduced VF group continued to have disopyramide after implantation of ICD. Three patients in the Induced VF group and 3 patients in the Noninduced VF group were treated with only antiarrhythmic drugs (disopyramide, amiodarone or pindolol).

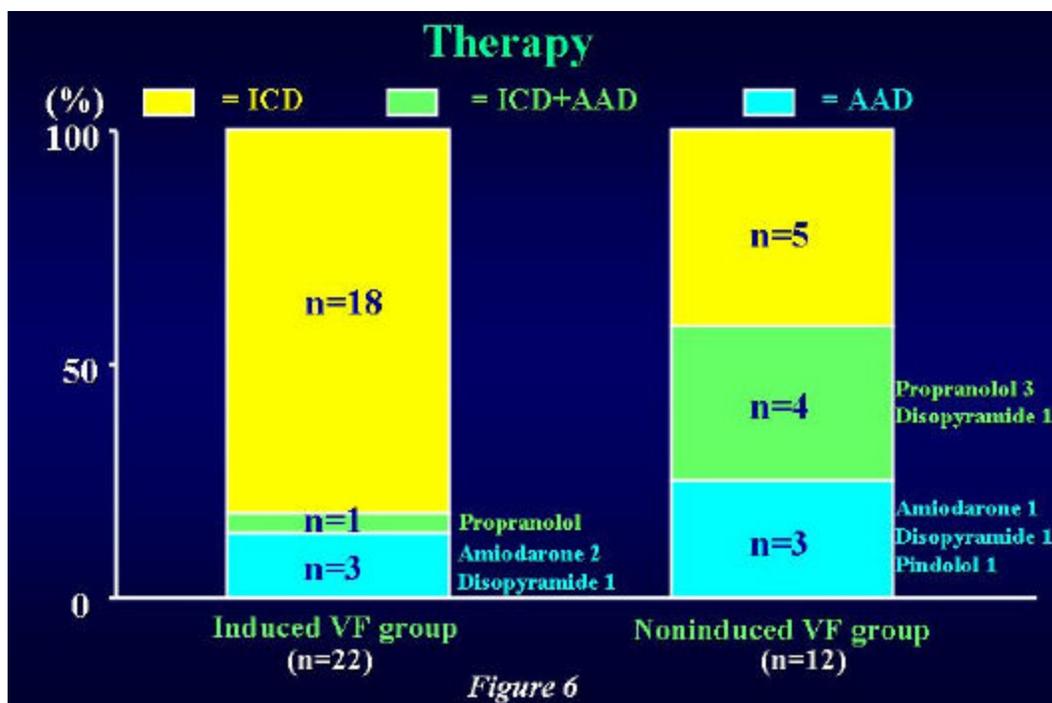


Figure 6. Comparison of therapy between Induced VF group and Noninduced VF group. ICD, implantable cardioverter defibrillator; AAD, antiarrhythmic drug.

Follow-up

The average follow-up periods were 36±32 months in the Induced VF group and 46±45 months in the Noninduced VF group, respectively. There was no significant difference in the recurrence of cardiac events (sudden cardiac death and VF documented by ICD) between the 2 groups (8/22 patients (36 %) vs. 7/12 patients (58 %)) during long-term follow-up. Two patients (One Induced VF group and one Noninduced VF group), who were treated with disopyramide, died suddenly. The ICD effectively terminated all episodes of VF, and prevented sudden cardiac death. A life-table analysis showing a comparison of the cumulative proportion of either VF or sudden cardiac death between the 2 groups demonstrated that there was no significant difference in the frequency of the recurrence of cardiac events between the 2 groups (Figure 7). The first recurrence of cardiac events was observed within 2 years in all but 3 patients.

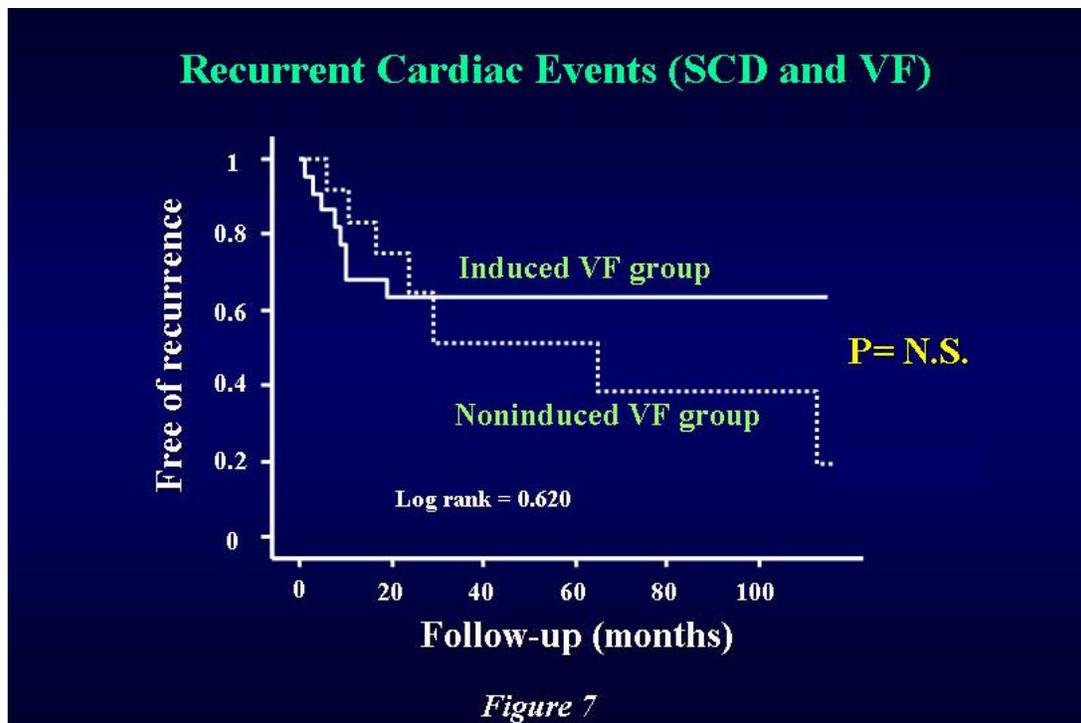


Figure 7. Kaplan-Meier curves of recurrent cardiac events (sudden cardiac death (SCD) and ventricular fibrillation (VF) documented by an implantable cardioverter defibrillator) in 22 patients with programmed ventricular stimulation (PVS)-induced VF (**solid line**) and in 12 patients without PVS-induced VF (**dotted line**).

DISCUSSION

The present study demonstrated that symptomatic Brugada patients with PVS-induced VF showed depolarization abnormalities more than those without PVS-induced VF. However, there was not significant difference in the recurrence of cardiac events during long term follow-up between patients with and without PVS-induced VF.

Cellular mechanism of ST segment elevation, and electrocardiographic and electrophysiologic characteristics

In 1992, Brugada and Brugada described 8 patients with a history of aborted sudden cardiac death due to VF and a distinct ECG pattern, consisting of RBBB and ST segment elevation in leads V1-V3 in the absence of any structural heart disease.¹⁻⁷ Yan and Antzelevitch used arterially-perfused canine right ventricular wedge preparations to develop an experimental model of Brugada syndrome.²⁴ They suggested that heterogeneous repolarization across the ventricular wall of the RVOT was responsible for the ST segment elevation and genesis of VF in Brugada syndrome. A prominent I_{to} -mediated AP notch during phase 1 depolarization and a sudden abbreviation of the APD due to loss of the AP dome in the epicardium but not in the endocardium gives rise to a transmural voltage gradient, which is responsible for a prominent ST segment elevation in this syndrome. We recently reported an asymptomatic Brugada patient in whom epicardial activation recovery interval (ARI) in the RVOT through the great cardiac vein as well as endocardial ARI from the multielectrode basket catheter located in the RVOT could be recorded during augmentation of Brugada-type ST segment elevation.²⁹ The epicardial ARI in the RVOT was observed to abbreviate dramatically at the beat of augmented ST segment elevation after a long pause or after the administration of sodium channel blocker, while the endocardial ARI in the RVOT were prolonged or not changed. More recently, Kurita et al. directly recorded epicardial and endocardial

monophasic action potential at the RVOT in 3 Brugada patients, and clearly showed the presence of a deeply notched action potential in only the epicardium but not in the endocardium.³⁰ These data directly and strongly support the hypothesis that transmural voltage gradient secondary due to accentuation of the epicardial notch and loss of the AP dome in the RVOT is responsible for the ST segment elevation in Brugada syndrome.

On the other hand, some clinical studies have reported prolongation of HV interval during electrophysiologic testing,¹⁻³ and a relatively high incidence of RBBB and LP detected by SAECG in patients with Brugada syndrome.^{10,28} More recently, Nagase et al. observed delayed potential (DP; average duration, 38 ± 10 ms) at the epicardium but not at the endocardium in the RVOT, corresponding to the LP in the SAECG.³¹ Similarly, in our 34 symptomatic Brugada patients, both the QRS duration and HV interval were moderately prolonged (QRS, 105 ± 14 ms; HV interval, 45 ± 9 ms). Moreover, 24 patients (71 %) showed incomplete (18 patients) or complete (6 patients) RBBB patterns, and 25 patients (74 %) had an abnormal SAECG. These findings suggested the presence of subtle depolarization abnormalities that cannot be reflected as structural abnormalities in symptomatic Brugada syndrome. However, the duration of the DP or LP outside the end of QRS is short (67 ± 24 ms even after sodium channel blocker), suggesting that these potentials did not primarily contribute to marked and extended (> 100 ms) ST segment elevation observed in Brugada syndrome.

Prognostic value of induced VF in electrophysiologic testing

Several previous reports have demonstrated a high inducibility of VF by less extrastimuli during the electrophysiologic testing in Brugada syndrome.³²⁻³⁴ VF requiring direct cardioversion for termination was induced in 22 of the 34 patients (65 %) in the present study. Moreover, the VF was induced by a single extrastimulus or double extrastimuli in 13 of the 22 patients. However, there was no significant difference in the recurrence of cardiac events between patients with and without PVS-induced VF, suggesting that the induction of VF with PVS is not able to predict the recurrence of cardiac events in symptomatic patients with Brugada syndrome. Recent two multicenter studies have reported the clinical course of both symptomatic and asymptomatic patients with Brugada syndrome during moderate to long term follow-up,^{33,34} but the prognostic value of the electrophysiologic testing in identifying high risk patients are still controversial. Although the inducibility of VF and the recurrence of VF in the present study were quite similar to those in the two previous studies, our data showing the limited value of electrophysiologic testing supports the data by Priori et al.³³ rather than that by Brugada et al..³⁴ One of major weakness of the present study was the small number of study population as well as the enrollment of only symptomatic patients, however, all 34 patients were probands from different families and underwent the electrophysiologic study using a uniform protocol in a single center. Further prospective study using a uniform protocol in a large population will be needed to conclude the true prognostic value of the electrophysiologic testing in both symptomatic and asymptomatic patients with Brugada syndrome.

In the present study, the inducibility of VF in the electrophysiologic testing was depending on the severity of depolarization abnormalities. However, PVS-induced VF did not predict the recurrence of VF and sudden cardiac death during long term follow-up periods. Once again, this finding suggests that depolarization abnormalities do not primarily contribute to spontaneous occurrence of VF in Brugada syndrome and that repolarization abnormalities are necessary in the generation of VF by modulating ST segment elevation and providing the initiating beat to induce VF as a result of phase 2 reentry.

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