Indication and Prognostic Significance of Programmed Ventricular Stimulation in Asymptomatic Patients with Brugada Syndrome

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Structured abstract

Aims) To establish the indication for programmed ventricular stimulation (PVS) for asymptomatic patients with Brugada syndrome (BrS), we evaluated the prognostic significance of PVS based on abnormal ECG markers.

Methods) One-hundred-twenty-five asymptomatic patients with BrS were included. We performed PVS at two sites of the right ventricle with up to 3 extrastimuli (2 pacing cycle lengths and minimum coupling interval (MCI) of 180 ms). We followed the patients for 133 months and evaluated ventricular fibrillation (VF) events. Fragmented QRS (fQRS) and Tpeak-Tend (Tpe) interval were evaluated as ECG markers for identifying high-risk patients.

Results) fQRS and long Tpe interval (≥100 ms) were observed in 66 and 37 patients, respectively. VF was induced by PVS in 60 patients. During follow-up, 10 patients experienced VF events. fQRS, long Tpe interval and PVS-induced VF with an MCI of 180 ms or up to 2 extrastimuli were associated with future VF events (fQRS: $p=0.015$, Tpe≥100 ms: $p=0.038$, VF induction: $p<0.001$). However, PVS-induced VF with an MCI of 200 ms was less specific ($p=0.049$). The frequencies of ventricular

tachyarrhythmia events during follow-up were 0%/year with no ECG markers and 0.1%/year with no VF induction. The existence of 2 ECG factors with induced VF was strongly associated with future VF events (event rate: 4.4%/year, $p < 0.001$), and the existence of 1 ECG factor with induced VF was also associated (event rate: 1.3%/year, $p=0.011$).

Conclusion) We propose PVS with a strict protocol for asymptomatic patients with fQRS and/or long Tpe interval to identify high-risk patients.

Keywords: Brugada syndrome; programed ventricular stimulation; ventricular fibrillation; fragmented QRS; Tpeak-Tend interval.

Introduction

Asymptomatic patients with Brugada syndrome (BrS) have a risk of sudden cardiac death (SCD)[1]. The incidence of ventricular fibrillation (VF) in asymptomatic patients has been shown to be about 0.5% in many recent studies[2, 3]. The risk of VF is low in asymptomatic patients compared to the risk in patients with syncope or VF[1, 2, 4-6], but it is not negligible[5, 7]. Appropriate risk stratification methods are necessary for asymptomatic patients.

Various risk markers including clinical and electrocardiogram (ECG) markers for identifying high-risk patients with BrS have been proposed. Clinical markers including age, gender and symptoms have been shown to be associated with future events[1, 7, 8]. Type 1 ECG is important for diagnosis of BrS, and many studies have shown that spontaneous type 1 ECG is a risk marker for VF[1, 5-8]. QRS and ST-T abnormalities have also been shown to be risk markers for VF events[2, 9-12], and we recently reported that fragmented QRS (fQRS) and the long interval between the peak and the end of the T wave (Tpe interval) are common risk markers for both initial VF episode in asymptomatic patients and recurrent VF episodes in

75 symptomatic patients[9].

76 An implantable cardioverter defibrillator (ICD) is required to prevent SCD in
77 high-risk patients, but it has not been established if prophylactic ICD implantation
78 can be determined only by ECG abnormalities in asymptomatic patients. According to
79 a recent expert consensus conference report, risk markers such as age, gender and
80 ECG characteristics should be taken into consideration and VF that is inducible by
81 less than 3 extrastimuli represents a class IIb indication of prophylactic ICD
82 implantation in asymptomatic patients[1]. However, it was not shown which patients
83 among asymptomatic patients with type 1 ECG are candidates for programmed
84 ventricular stimulation (PVS). The incidence of spontaneous type 1 ECG in the
85 general population has been reported to be 0.05% (1/2,000 persons)[13] and it is
86 difficult to perform PVS in all asymptomatic patients with type 1 ECG. Moreover,
87 PVS is invasive and appropriate selection of patients, especially asymptomatic
88 patients, is required.

89 The aim of this study was to clarify the clinical significance of PVS with a
90 uniform protocol in asymptomatic patients and to determine the appropriate
91 indication for PVS by ECG markers using data in our single-center database.

Methods

Subjects

The subjects of this study were 125 asymptomatic patients with BrS who had not experienced prior syncope or VF (age: 46 ± 12 years, 123 male patients). All of the patients underwent an electrophysiological study in our hospital during the period from March 1996 to February 2017. BrS was diagnosed according to the criteria of the Expert Consensus Statements[1]. There were no subjects from the same family. Echocardiography and coronary angiography showed no structural abnormality in any of the patients.

This study was approved by the Ethics Committee on Human Research and Epidemiology of Okayama University. Analysis of the *SCN5A* gene was performed in 79 patients in compliance with guidelines for human genome studies of the Ethics Committee of Okayama University.

ECG recording and measurement

We recorded standard 12-lead ECG and additional V1-3 leads at the 3rd intercostal space with a 0-150 Hz filter and evaluated ECG parameters at 400% size on a liquid crystal display. We retrospectively evaluated specific ECG markers that have been reported to be predictors of VF events: spontaneous type 1 ECG, fQRS, Tpe interval and inferolateral early repolarization (ER) (Figure 1). We defined fQRS as previously reported[14]: QRS complex with >2 positive spikes in the R or S wave in two contiguous leads of the right ventricular outflow tract (RVOT, leads V1 and V2 located at the 3rd intercostal space) and/or the inferior region (leads II, III and aVF) and/or the lateral region of the ventricle (leads I, aVL, V5 and V6). Inferolateral ER was defined as J point elevation with a slur or a notched J wave (≥ 0.1 mV) in at least two contiguous leads of the inferior leads (II, III, and aVF), lateral leads (I, aVL, and V4-6), or both[10]. Tpe interval was the measured interval from the peak or nadir of the T wave to the end of the T wave in lead V2, and Tpe ≥ 100 ms was considered abnormal[9, 11].

Electrophysiological study

We performed an electrophysiological study (EPS) in all patients. In asymptomatic patients, the main reasons for performing an EPS were typical type 1 ECG (n=64), family history of SCD (n=40), premature ventricular contractions (n=11), atrial fibrillation (n=3), paroxysmal supraventricular tachycardia (n=3), paroxysmal atrioventricular block (n=2), sick sinus syndrome (n=1) and palpitation (n=1). The risks were explained to each patient, and written informed consent was obtained before the study. Induction of ventricular arrhythmia was attempted by PVS without any antiarrhythmic drug administration. We performed PVS at an intensity of two times the threshold from the right ventricular apex (RVA) and the RVOT. The protocol included an 8-beat ventricular paced drive train at two basic cycle lengths (600 or 500 and 400 ms) followed by a decremental introduction of up to 3 extrastimuli. The coupling interval of the extrastimuli was not less than 180 ms. The endpoint was either induction of VF or completion of the protocol. If VF was induced at one site, we also performed PVS in the other site until completion of the protocol or induction of VF. When VF was induced during the PVS, cardioversion was initiated after 15 seconds of observation to confirm the absence of spontaneous

termination. If VF terminated spontaneously within 15 seconds, we defined it as non-sustained polymorphic ventricular tachycardia.

Statistical analysis

Continuous data are expressed as mean ± standard deviation values. Fisher's exact test or the χ^2 test was used for categorical variables. Continuous variables in the two groups were compared using Student's t-test for unpaired data. Ventricular tachyarrhythmia (VTA) events during follow-up were defined as the occurrence of sustained VTAs detected by appropriate therapy of an ICD or external defibrillator or ECG monitoring in an ambulance. Survival curves were plotted by the Kaplan-Meier method and analyzed by the log-rank test. Time from initial visit to the hospital to the first VTA event was analyzed using Cox's proportional hazards model. Hazard ratios (HRs) and confidence intervals (CIs) are presented for results of univariable analysis. A value of $p<0.05$ was defined as statistically significant and all tests were two-sided. All statistical analyses were performed using JMP 13.2.0 (SAS Institute, Cary, North Carolina). All authors had full access to and take full responsibility for the integrity of data.

Results

Clinical characteristics of asymptomatic patients

Baseline clinical and ECG characteristics of patients are presented in Table 1. As shown in the table, 76% of the patients had a spontaneous type 1 ECG, 28 patients (22%) had a family history of SCD, 6 out of 79 patients (8%) had *SCN5A* mutation, and fQRS, long Tpe interval (≥100 ms) and inferolateral ER were observed in 66 (53%), 37 (30%) and 28 patients (22%), respectively.

The results of EPS are also shown in Table 1. VF was induced by PVS with a minimum coupling interval (MCI) of 180 ms in 60 asymptomatic patients (48%) and with an MCI of 200 ms in 30 patients (24%). The average coupling interval that induced VF was 198 ms. VF was induced with a single extrastimulus, double extrastimuli and triple extrastimuli in 3 (5%), 36 (60%) and 21 patients (35%), respectively. VF was induced at the RVA, the RVOT and both sites in 13 (22%), 25 (41%) and 22 patients (37%), respectively.

176

177 *Risk markers for occurrence of VTA events during follow-up in asymptomatic*

178 *patients*

179 We implanted an ICD in 32 asymptomatic patients. VTA events occurred in

180 10 asymptomatic patients (VF events recorded by the ICD in 5 patients and by an

181 external defibrillator or ECG monitoring in 5 patients) during the follow-up period

182 (follow-up: 133 ± 60 months, incidence of VF: 0.72%/year).

183 There were no differences between clinical characteristics in patients with

184 and those without VTA events. Patients with VTA events had a longer Tpe interval

185 and more frequent fQRS than did patients without VTA events (Table 1). Incidences

186 of spontaneous type 1 ECG and inferolateral ER were not different between the two

187 groups. There were no differences in electrophysiological parameters between the two

188 groups. VF was more frequently induced with a shorter MCI and smaller number of

189 extrastimuli in patients with VTA events than in patients without VTA events during

190 follow-up (Table 1).

191 Univariable analysis of ECG markers showed that long Tpe interval (HR:

192 3.77, CI: 1.08-14.75, p=0.038) and fQRS (HR: 7.42, CI: 1.39-136.78, p=0.015) were

associated with future VTA events (Table 2, Figure 3A and 3B), whereas spontaneous type 1 ECG and inferolateral ER were not associated with VTA events in asymptomatic patients. The effective refractory period and HV interval could not predict VTA events (Table 2).

VF induced by PVS with an MCI of 180 ms was strongly associated with the occurrence of VTA events in asymptomatic patients (HR: 13.64, CI: 2.53-252.67, p=0.001) (Table 2, Figure 2). In contrast, VF induced by PVS with an MCI of 200 ms was significant but less specific compared to that with an MCI of 180 ms (HR: 3.64, CI: 1.00-13.25, p=0.049). The positive predictive value (PPV) of PVS with an MCI of 180 ms was 15% and the negative predictive value (NPV) was 98% in asymptomatic patients. VF induced by PVS with 1 extraxtimulus or 2 extrastimuli was associated with VTA events in asymptomatic patients (HR: 5.71, CI 1.58-26.59, p=0.008). The induction site of VF was not associated with VTA events.

Risk prediction of VF inducibility based on abnormal ECG markers

In an exploratory analysis, we examined whether the combination of abnormal ECG markers and inducibility of VF could narrow down high-risk

asymptomatic patients. fQRS and Tpe≥100 ms, which were associated with the occurrence of VTA events in asymptomatic patients, were used as abnormal ECG markers. Kaplan-Meier curves showed that the presence of both fQRS and long Tpe predicted a worse prognosis (log-rank test, p = 0.003, Figure 3C).

Based on the existence of abnormal ECG markers, VF induced by PVS appropriately identified high-risk patients: the frequencies of VTA events during follow-up were 0%/year with no ECG markers and 0.1%/year with no VF induction. The existence of 2 ECG markers with induced VF was strongly associated with the occurrence of VTA events (event rate: 4.4%/year, HR: 42.27, CI: 6.78-811.10, p <0.001), and the existence of 1 ECG marker with induced VF was also associated with the occurrence of VTA events (event rate: 1.3%/year, HR: 11.65, CI: 1.72-228.14, p=0.011) (Table 2, Figure 4 and Supplementary figure 1). Among asymptomatic patients with 2 ECG markers, the frequency of VTA events during follow-up was 0%/year when VF was not induced by PVS.

Discussion

227

228 *New observations*

229 In the present study, we first showed that fQRS and long Tpe interval

230 were risk markers for initial VF events in asymptomatic patients. We then

231 investigated the clinical significance of PVS with a uniform protocol in asymptomatic

232 patients. VF induced by PVS with an MCI of 180 ms and with 1 extrastimulus or 2

233 extrastimuli was associated with initial VTA events during follow-up. Next, we

234 investigated whether PVS-induced VF with the existence of abnormal ECG markers,

235 fQRS and long Tpe interval, could identify patients at high risk for VTA events

236 among asymptomatic patients. High-risk patients could be identified by the existence

237 of these ECG markers, and patients having both ECG markers should be indicated for

238 PVS.

239

240 *Risk stratification in asymptomatic patients*

241 How to assess the risk for asymptomatic patients with BrS is an unsolved

242 question. Various clinical risk factors including spontaneous type 1 ECG[2, 4, 6, 15], fQRS[2,

243 9, 10, 12], long Tpe interval[9, 11, 12] and family history of SCD[7, 16, 17] have been reported for

asymptomatic patients. Most of the clinical and ECG markers increase the risk of VF by approximately 2 to 6 times for asymptomatic patients or patients without previous VF. However, it is known that asymptomatic patients have a low arrhythmia event rate of about 0.5%/year[2, 3], and clinical risk factors might have a low PPV. For example, it was reported that type 1 ECG is associated with a 2.0-fold increased risk of VF for asymptomatic patients[7], so the risk of VF would be 1%/year in asymptomatic patients with type 1 ECG[18]. Patients who have the proposed risk markers will be at high risk for VF events. However, it seems to be difficult to determine the indication for prophylactic ICD implantation in asymptomatic patients by such a single clinical or ECG sign or by VF inducibility. ICD implantation at a young age has problems with ICD malfunction, life style restrictions, and risks such as infections due to repeated battery changes[16]. It is important to narrow down high-risk patients and determine indications for ICD implantation, especially in asymptomatic patients.

PVS for asymptomatic patients with BrS

The usefulness of PVS for risk stratification in BrS has also been long debated, but the issue has not yet been fully resolved[19]. The problems with PVS are that there is no established induction protocol and the level of prognostic accuracy is not high.

Regarding the induction protocol, when the MCI was set to 180 ms rather than 200 ms, VF inducibility and prognosis had a stronger correlation in this study. Eckardt et al. reported that coupling intervals shorter than 200 ms were required to induce sustained ventricular arrhythmias in the majority of VF-inducible asymptomatic patients with BrS[19]. Symptomatic patients should have more advanced arrhythmic substrates than those in asymptomatic patients, and it is therefore easier to induce VF with premature stimuli at long coupling intervals. However, it may be necessary to shorten the coupling interval to induce VF in asymptomatic patients. VF was induced for the first time by triplet extrastimuli with a coupling interval of 180 ms in only 1 out of 10 patients who had VTA events. VF in most of the patients was induced by double extrastimuli with a coupling interval of less than 200 ms. We consider that VF inducibility obtained by triplet extrastimuli with a short coupling interval was not negligible. It has been shown that VF induction with fewer

277 extrastimuli is associated with a high-risk for future VF events in asymptomatic
278 patients[6], being consistent with the results of our study.
279 Regarding the prognostic accuracy of PVS, the relationship between VF
280 inducibility and future arrhythmia risk has been investigated in recent large-scale
281 studies. VF induced by PVS was not significant in the PRELUDE study, but not all of
282 the patients in that study were asymptomatic patients. Sixty-four patients (21%) with
283 syncope were included in that study. Indeed, the FINGER registry showed that VF
284 inducibility was associated with arrhythmic events when restricted to VF inducibility
285 in asymptomatic patients[7]. When introduced in multivariable analysis, it lost statistical
286 association (p=0.09), but the number of events in the asymptomatic population was
287 10 and therefore a lack of statistical power might have been responsible for this result[3].
288 Using pooled data, Sroubek et al. showed that inducibility is associated with increased
289 risk of VF events during follow-up in both asymptomatic and symptomatic patients
290 with BrS[6]. However, the absolute difference between incidences of VF events in
291 asymptomatic patients with and those without induced VF was too small for confident
292 recommendation of different treatment policies; in asymptomatic patients with type 1
293 ECG, the incidences of VF events were 1.2–1.7%/year in patients with induced VF

294 and 0.57–0.78%/year in patients without induced VF[6, 7]. PVS is invasive and not a
295 feasible examination for all asymptomatic cases, and the prognostic information
296 provided by VF inducibility alone is not sufficient for clinical decision-making.
297
298 *Indication for PVS on the basis of abnormal ECG markers*
299 The use of a combination of risk markers to identify patients with a very high
300 risk for VF has been evaluated[10, 17]. Risk markers assessed in previous studies were
301 spontaneous type 1 ECG, syncope, inducible VF, family history of SCD, fQRS and
302 early repolarization[8, 10, 17]. However, many studies included patients with syncope or
303 VF, and the application of these combinations of markers to asymptomatic patients
304 was not fully evaluated.
305 We previously reported that fQRS and long Tpe interval were associated with
306 VF during follow-up in both asymptomatic and symptomatic patients[9]. In the present
307 study, both markers were also predictors of VF events in asymptomatic patients in
308 whom PVS was performed, and no patients without these markers had any VTA event
309 regardless of VF inducibility during EPS. Conversely, VF was induced in 16 patients
310 with no ECG markers. It has been reported that VF could be induced by a severe

311 protocol of PVS even in healthy people[20]. False positives of PVS should be reduced by
312 screening using the abnormal ECG markers. PVS is not recommended for patients
313 with neither fQRS nor long Tpe interval. If VF was induced on the basis of the
314 presence of 2 ECG markers, the VTA event rate is 4.4%/year, and the combination of
315 these makers could narrow down high-risk patients without previous symptoms. We
316 recently reported that fQRS and long Tpe abnormalities could develop in association
317 with initial VF events[12]. We will recommend PVS for patients in whom these two
318 indicators appear during follow-up. The addition of results of PVS to the combination
319 of these two ECG markers enabled high-risk patients to be identified, and
320 asymptomatic patients in whom VF was induced in the presence of two ECG markers
321 would be candidates for prophylactic ICD implantation.
322
323 *Limitations*
324 Some limitations exist in this study. First, we retrospectively investigated
325 asymptomatic BrS patients who received PVS in our hospital. These patients could
326 have a more advanced arrhythmogenic substrate than that in randomly selected BrS
327 patients without prior VF, which may lead to a selection bias. Second, we could not

validate ECG risk markers and the value of PVS since the statistical power would be reduced if the patients were divided into two groups. A prospective study with a large number of patients is required to confirm the indication for PVS on the basis of fQRS and/or long Tpe in asymptomatic BrS patients.

Conclusion

This study showed that abnormal ECG factors (fQRS and long Tpe interval) were risk markers for VF events and that VF inducibility with an MCI of 180 ms and with 1 extrastimulus or 2 extrastimuli was associated with initial VTA events during follow-up in asymptomatic patients. We recommend that PVS with a strict protocol be performed for asymptomatic patients when fQRS and/or long Tpe interval appear at the initial examination or during follow-up.

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Figure legends

Figure 1. ECG parameters.

The upper panel shows an example of type 1 ECG (arrow) with fragmented QRS (arrowheads). The interval between the peak and the end of the T wave (Tpe) was measured in lead V2. The end of the T wave was determined by crossing between a tangent of a later part of the T wave and the baseline. The lower panel shows an example of early repolarization in lead I, which was characterized by J-point elevation manifested as QRS slurring or notching (arrow).

Figure 2. Event-free survival according to ventricular fibrillation induced by programmed ventricular stimulation.

(A) Event-free survival according to ventricular fibrillation (VF) induced by programmed ventricular stimulation (PVS) with a minimum coupling interval (MCI) of 180 ms. Asymptomatic patients with induced VF had a shorter time to experience VTA events than did patients without induced VF. (B) Event-free

survival according to VF induced by PVS with an MCI of 200 ms. VF induced by this PVS protocol was less specific for VTA events than was PVS with an MCI of 180 ms. PVS-VF: patients with PVS-induced VF

Figure 3. Event-free survival according to abnormal ECG markers.

A. Event-free survival according to the existence of fragmented QRS (fQRS). Patients with fQRS had worse prognosis than did patients without fQRS. B. Event-free survival according to Tpe interval. Patients with a long Tpe interval (≥ 100 ms) had a shorter time to experience ventricular fibrillation (VF) than did patients with a short Tpe interval (<100 ms). C. Patients with both ECG markers had the shortest time to experience initial VF events, followed by patients with 1 ECG marker. No VF occurred in patients without any ECG markers.

Figure 4. Event-free survival stratified by ECG factors and ventricular fibrillation induced by programmed ventricular stimulation.

Ventricular fibrillation (VF) induction was attempted by programmed ventricular stimulation (PVS) with a minimum coupling interval of 180 ms in asymptomatic patients. Patients with 2 ECG markers and induced VF had the shortest time to experience initial VF events, followed by patients with 1 ECG marker and induced VF. To make the graph easier to see, we combined three groups with low event rates. No ECG marker and no PVS-induced VF, 1 ECG marker and no PVS-induced VF, and 2 ECG markers and no PVS-induced VF were grouped into 0-2 ECG marker + No PVS-VF. PVS-VF: patients with PVS-induced VF

Supplement figure 1. Event-free survival stratified by ECG factors and ventricular fibrillation induced by programmed ventricular stimulation.

Supplement figure 1 is a more detailed subgroup graph of the graph shown in Figure 4. Group 1 = No ECG marker + No PVS-VF, Group 2 = No ECG marker + PVS-VF, Group 3 = 1 ECG marker + No PVS-VF, Group 4 = 1 ECG marker + PVS-VF, Group 5 = 2 ECG markers + No PVS-VF, Group 6 = 2 ECG markers + PVS-VF. PVS-VF: patients with programmed ventricular stimulation-induced ventricular fibrillation.

465