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ORIGINAL ARTICLE

Utility of 12-lead and signal-averaged Holter electrocardiograms after pilsicainide provocation for risk stratification in Brugada syndrome

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Abstract Non-invasive risk stratification for ventricular fibrillation (VF) in Brugada syndrome (BrS) has not been fully evaluated. The aim of this study was to assess the utility of signal-averaged Holter electrocardiogram (Holter SAECG) and 12-lead Holter electrocardiogram (Holter ECG) after a pilsicainide provocation test for non-invasive risk stratification in BrS. We enrolled 30 consecutive patients with BrS [divided into 2 groups: the VF group, those with a previous history of VF ($n=10$); and the non-VF group, those without a history of VF ($n=20$)] and 10 control subjects without type 1 ECG. We evaluated late potentials [LP: filtered QRS (f-QRS), RMS40, and LAS40] on the Holter SAECG for 4 h after the pilsicainide provocation and in the same patients on another day without performing the pilsicainide provocation. Furthermore, we measured QRS duration and QTc interval in leads V2 and V5, and J amplitude in lead V2 on the Holter ECG after the pilsicainide provocation. On the Holter SAECG, the f-QRS at 1 h and LAS40 at 3 h after the pilsicainide provocation were significantly larger in the VF group than in the non-VF group (f-QRS at 1 h: 113.9 ± 8.9 vs. 104.9 ± 8 ms; $p=0.01$, LAS40 at 3 h: 45.4 ± 5.9 vs. 35.5 ± 7.4 ms; $p<0.001$). The receiver-operating characteristic curve analysis for a single parameter of VF occurrence was determined [f-QRS at 1 h: area under the curve (AUC) 0.8, with sensitivity 80% and specificity 80%; and LAS40 at 3 h: AUC 0.87, with sensitivity 90% and specificity 75%]. On the Holter ECG, there were no significant differences in these parameters between the VF and non-VF groups. In conclusion, the LP after the pilsicainide provocation using Holter SAECG may be useful for risk stratification of VF episodes in patients with BrS.

Keywords Brugada syndrome · Signal-averaged Holter electrocardiogram · Ventricular fibrillation · Late potential · Pilsicainide

Introduction

Brugada syndrome (BrS) is an inherited arrhythmogenic disease characterized by an ST segment elevation in the right precordial electrocardiogram (ECG) leads. It is associated with a risk of sudden cardiac death (SCD) due to ventricular fibrillation (VF) [1, 2]. A recent large study of patients with BrS reported that the incidence of cardiac events in patients with the previous VF episodes was higher (7.7–8.4%/year) than in patients with a history of syncope or those without symptoms [3, 4]. Little controversy exists regarding the high risk of cardiac event recurrence among patients with documented VF or SCD. Recently, the non-invasive risk stratification for VF in BrS was reported in several studies, but that remains controversial and needs to be confirmed.

It has been reported that BrS is caused by repolarization and depolarization abnormalities [5]. The repolarization abnormality in BrS is reflected by T-wave alternans (TWA) and T-wave variability. A recent study reported that elevated TWA confirms arrhythmia risk in symptomatic BrS patients [6–8]. On the other hand, the depolarization abnormality is reflected in the late potential (LP) detected by signal-averaged ECG (SAECG). Several studies reported time-to-time or day-to-day LP fluctuations in BrS, and

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single examination assessment of SAECG could underestimate differences in parameters between high-risk and low-risk patients. Recently, 24-h consecutive recordings have been used to assess continuous LPs, and the efficacy of LPs on signal-averaged Holter ECG (Holter SAECG) for risk stratification has been reported [9].

It has been reported that sodium channel dysfunction has an important role in ST elevation and occurrence of VF in patients with BrS, and sodium channel blockers are useful for unmasking intermittent or concealed BrS [10, 11]. A previous study reported that macroscopic TWA after a pilsicainide provocation was associated with a high risk of VF occurrence in patients with BrS [12]. However, the prognostic value of LPs on SAECG after the pilsicainide provocation in patients with BrS is still unknown. In this study, we assessed the utility of Holter SAECG and 12-lead Holter ECG (Holter ECG) after the pilsicainide provocation for the non-invasive risk stratification in patients with BrS.

Methods

Study population

From June 2010 to April 2016, we enrolled 30 consecutive patients with BrS (30 men, mean age 49 ± 4 years) and 10 control subjects without type1 ECG (9 men, mean age 48 ± 18 years) in this study. BrS was diagnosed on the basis of the following criteria: (1) J point elevation with type I morphology in ≥1 lead among the right precordial leads positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after the pilsicainide provocation; (2) normal findings on physical examination; (3) not taking antiarrhythmic drugs; and (4) no abnormality in either the right or left ventricular morphology and/or function as demonstrated by chest radiography and echocardiography. The patients with complete right bundle branch block (CRBBB) were excluded from analysis. We divided the patients with BrS into the 2 groups according to their past history: the VF group ($n = 10$), patients with documented VF episodes; and the non-VF group ($n = 20$), patients with unknown syncope episodes or no symptoms. This study was approved by the ethics review board of Osaka City University Graduate School of Medicine. The individuals who performed the SAECG and ECG analysis were blinded regarding patient status. Written informed consent was obtained from all patients and control subjects.

Study protocol

All patients underwent a pilsicainide provocation up to a dose of 1 mg/kg in 10 min at 1 p.m. All patients simultaneously underwent Holter SAECG after the pilsicainide provocation and at baseline on another day and Holter ECG after the pilsicainide provocation.

Analysis of parameters in Holter SAECG

LPs were analyzed using a Holter SAECG system (Spiderview, SorinGroup, Italia) that provided signals at a 1000-Hz sampling frequency with 2.5-μV resolution. The ECG was recorded during sinus rhythm using Frank X, Y, Z corrected orthogonal leads in all patients. Signals of 250 beats were amplified, digitized, averaged, and then filtered with a 4-pole band pass filter with 40–250 Hz. The following three parameters were calculated using a computer algorithm: the total filtered QRS duration (f-QRS), the root-mean-square voltage of the 40-ms terminal portion of the QRS (RMS40), and duration of the low-amplitude electric potential component (40 μV) of the terminal portion (LAS40) in a noise level <0.7 μV. LPs were considered positive when 2 of the following 3 parameters were met: f-QRS >114 ms, RMS40 <20 μV, and LAS40 >38 ms [13].

Frequency domain variables of the heart rate variability (HRV) were obtained using Fourier transformation of the Holter SAECG recordings. In considering circadian variations, we calculated the power with 2 frequency bands: the low-frequency (LF) band, 0.14–0.15 Hz; and the high-frequency (HF) band, 0.15–0.4 Hz, and the ratio of the LF/HF. In addition, heart rate (bpm) was measured every hour at baseline and after pilsicainide provocation.

We measured these parameters every hour for total of 4 h after the pilsicainide provocation and also measured them at the same time points at baseline (without the pilsicainide provocation) in the same patients.

Measurement of parameters in Holter ECG

The Holter ECG was recorded during sinus rhythm using the MARS PC Holter Monitoring and Review System software (Version 8, GE Healthcare). We measured the following parameters: (1) QRS duration in leads V2 and V5; the interval from QRS onset, defined as the earliest deflection of the QRS complex, to the J point; (2) QTc intervals in leads V2 and V5; the interval from QRS onset to the end of the T wave, calculated by Bazett's method; and (3) J point amplitude in lead V2. These measurements were made by 3 cardiologists who were unaware of the individuals' clinical findings. We evaluated these parameters every hour for total of 4 h after the pilsicainide provocation.

Reproducibility of SAECG parameters

Intra-observer and inter-observer variabilities were assessed in 10 randomly chosen subjects on SAECG. To

test intra-observer variability, a single observer analyzed the LP parameters twice on occasions separated by a 1-month interval. To test inter-observer variability, second observer analyzed the LP parameters without knowledge of the first observer's measurements.

Statistical analysis

The values are expressed as mean ± SD. The Tukey–Kramer's HSD was used to compare each parameter among the three groups. Analysis of receiver-operating characteristics curves (ROC) was performed to determine the risk factors and the best cut-off values. Intra-observer reproducibility and inter-observer reproducibility were assessed using the Bland and Altman method. All data were analyzed using JMP software, Version 10 (SAS, Cary, NC, USA); p values <0.05 were considered significant.

Results

Clinical profile of patients

Clinical profiles of patients with BrS and control subjects are shown in Table 1. There were no significant differences in age, height, body weight, the prevalence of spontaneous type 1 ECG, a family history of SCD, and a history of syncope, estimated glomerular filtration rate, or serum creatinine among the three groups. The prevalence of positive LP was significantly higher in the VF group than in control subjects. The number of patients requiring implanted ICDs was significantly higher in the VF group than in the non-VF group. In the present study, adverse effects of pilsicainide provocation, including VT/VF, did not occur.

LP parameters on Holter SAECG

Representative LP parameters on Holter SAECG at 1 h after pilsicainide provocation and at baseline in patient with BrS are shown in Fig. 1. There were no significant differences in heart rate at each hour at baseline or after pilsicainide provocation among the 3 groups (Figs. 2, 3). In patient with VF, f-QRS and LAS40 tended to be larger and RMS40 tended to be smaller after pilsicainide provocation than at baseline. On the other hand, in non-VF patient, f-QRS and LAS40 tended to be larger and RMS40 tended to be smaller after pilsicainide provocation than at baseline, but there were no significant differences between with and without pilsicainide provocation compared to patient with VF.

At baseline, the RMS40 at evening in the VF and non-VF groups was significantly smaller than those in control group, but there were no significant differences in the other LP parameters and heart rate at each hour among the 3 groups (Fig. 2). The f-QRS at early hours, the LAS40 at each hour, and RMS40 at each hour after pilsicainide provocation were significantly larger and smaller in the VF group than those in control group. The f-QRS at 1 h and LAS40 at 3 h after pilsicainide provocation in the VF group were significantly larger than those in the non-VF group (f-QRS at 1 h; 113.9 ± 8.9 vs. 104.9 ± 8 ms; $p = 0.01$, LAS40 at 3 h; 45.4 ± 5.9 vs. 35.5 ± 7.4 ms; $p < 0.001$) (Fig. 3). There was no significant difference in RMS40 between the VF and non-VF group.

We performed an ROC curve analysis to determine the cut-off values for f-QRS at 1 h and LAS40 at 3 h based on VF occurrence. The cut-off value for f-QRS at 1 h was determined to be 112 ms [area under the ROC curve (AUC) = 0.8; sensitivity 80%; specificity 80%; $p = 0.02$, and odds ratio (OR): 1.16, 95% confidence interval (CI): 1.03–1.36], and the cut-off value for LAS40 at 3 h was

Table 1 Demographics of the clinical profiles of patients

	VF ($n = 10$)	Non-VF ($n = 20$)	Control ($n = 10$)	p value
Mean age (year)	51.9 ± 8.7	47.9 ± 11.7	48.2 ± 14.4	NS
Men [n (%)]	10 (100%)	20 (100%)	9 (90%)	NS
Height (cm)	169.0 ± 5.5	171.9 ± 1.1	172.0 ± 5.0	NS
Body weight (kg)	62.8 ± 10.0	64.9 ± 10.9	62.1 ± 6.9	NS
Spontaneous type 1 [n (%)]	5 (50%)	6 (30%)		NS
Family history of SCD [n (%)]	3 (30%)	7 (35%)		NS
ICD implantation [n (%)]	10 (100%)	5 (25%)		<0.001
History of syncope [n (%)]	2 (20%)	3 (15%)		NS
LP positive [n (%)]	9 (90%)	15 (75%)	4 (40%)	0.01*
eGFR (mg/dl)	76.3 ± 7.5	87 ± 20.1	93.7 ± 16.9	NS
Scr (mg/dl)	0.85 ± 0.1	0.79 ± 0.2	0.73 ± 0.1	NS

VF ventricular fibrillation, *SCD* sudden cardiac death, *ICD* implantable cardioverter defibrillator, *LP* late potential, *eGFR* estimated glomerular filtration rate, *Scr* serum creatinine, VF vs. control*

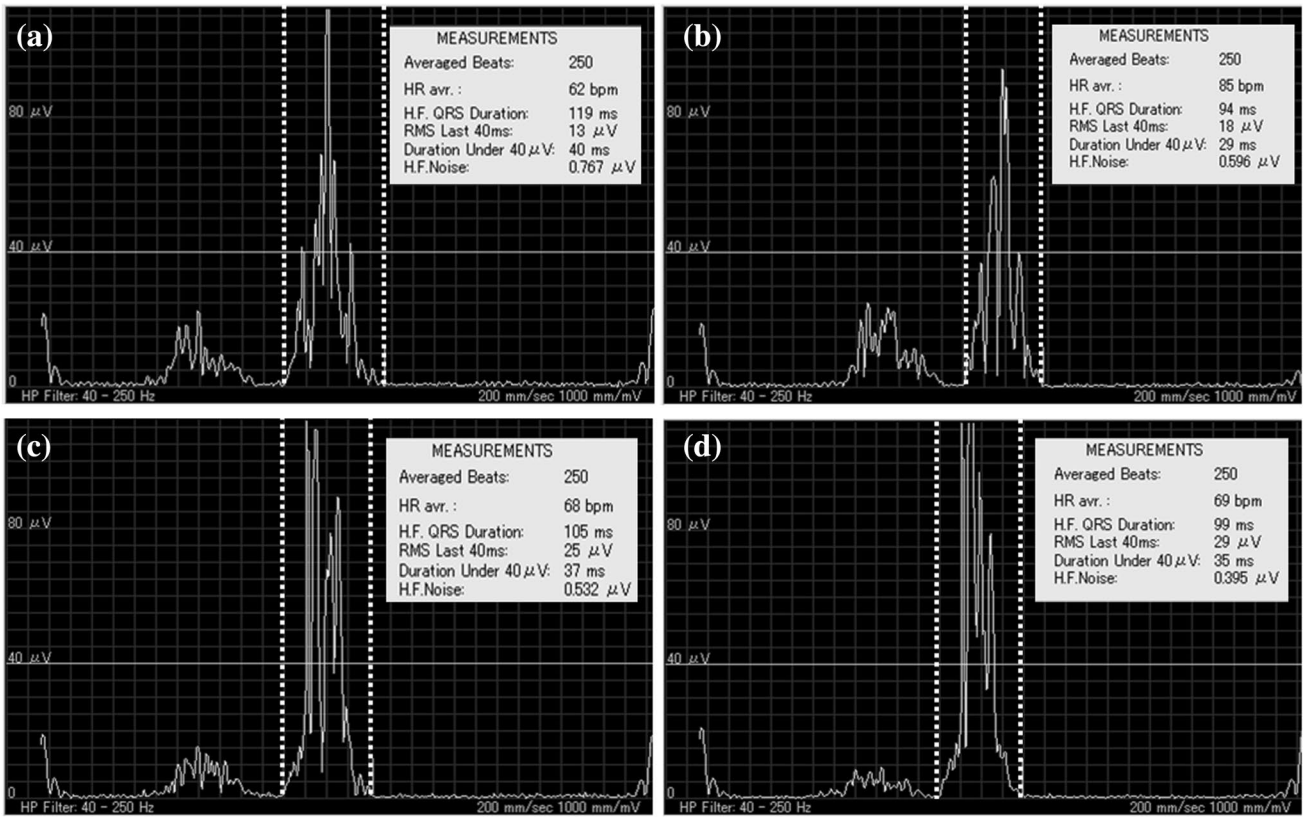

Fig. 1 Representative LPs on Holter SAECG at 1 h after pilsicainide provocation and at baseline in patients with BrS. **a** After pilsicainide provocation in the VF patient. **b** Baseline in the VF patient (same patient with **a**). **c** After pilsicainide provocation in the non-VF patient. **d** Baseline in the non-VF patient (same patient with **c**). In the VF group, f-QRS and LAS40 were significantly larger and RMS40 was smaller after pilsicainide provocation than those at baseline in comparison with non-VF patient

determined to be 41 ms (AUC = 0.87; sensitivity 90%; specificity 75%; $p = 0.01$, OR: 1.34, 95% CI 1.11–1.78) (Table 2; Fig. 4).

HRV findings on Holter SAECG

There were no significant differences in HF and LF/HF on Holter SAECG at each hour at baseline and after pilsicainide provocation among the three groups.

Reproducibility of SAECG parameters

There were no significant differences in intra- or inter-observer variabilities on analyzing SAECG parameters.

Parameters on Holter ECG

Comparisons of QRS durations in leads V2 and V5, J amplitude in lead V2, and QTc intervals in leads V2 and V5 at each hour after pilsicainide provocation between the VF and non-VF group are shown in Table 3. There were no significant differences in these parameters between the two groups.

Discussion

The major findings in this study were as follows: (1) the f-QRS at 1 h and LAS40 at 3 h after pilsicainide provocation in the VF group were significantly larger than those in the non-VF group; (2) f-QRS of ≥112 ms at 1 h and LAS40 of ≥41 ms at 3 h after pilsicainide provocation were useful parameters to discriminate high-risk patients with BrS. To the best of our knowledge, this is the first study to show fluctuation in LP parameters on Holter SAECG after a pilsicainide provocation and the efficacy of the f-QRS 1 h and LAS40 3 h after a pilsicainide provocation for non-invasive risk assessment in patients with BrS.

Depolarization abnormalities are reflected in LPs detected by SAECG, and there have been several reports evaluating the LPs in patients with BrS. Ikeda et al. reported that the occurrence of VF during follow-up was significantly higher in patients with positive LPs by

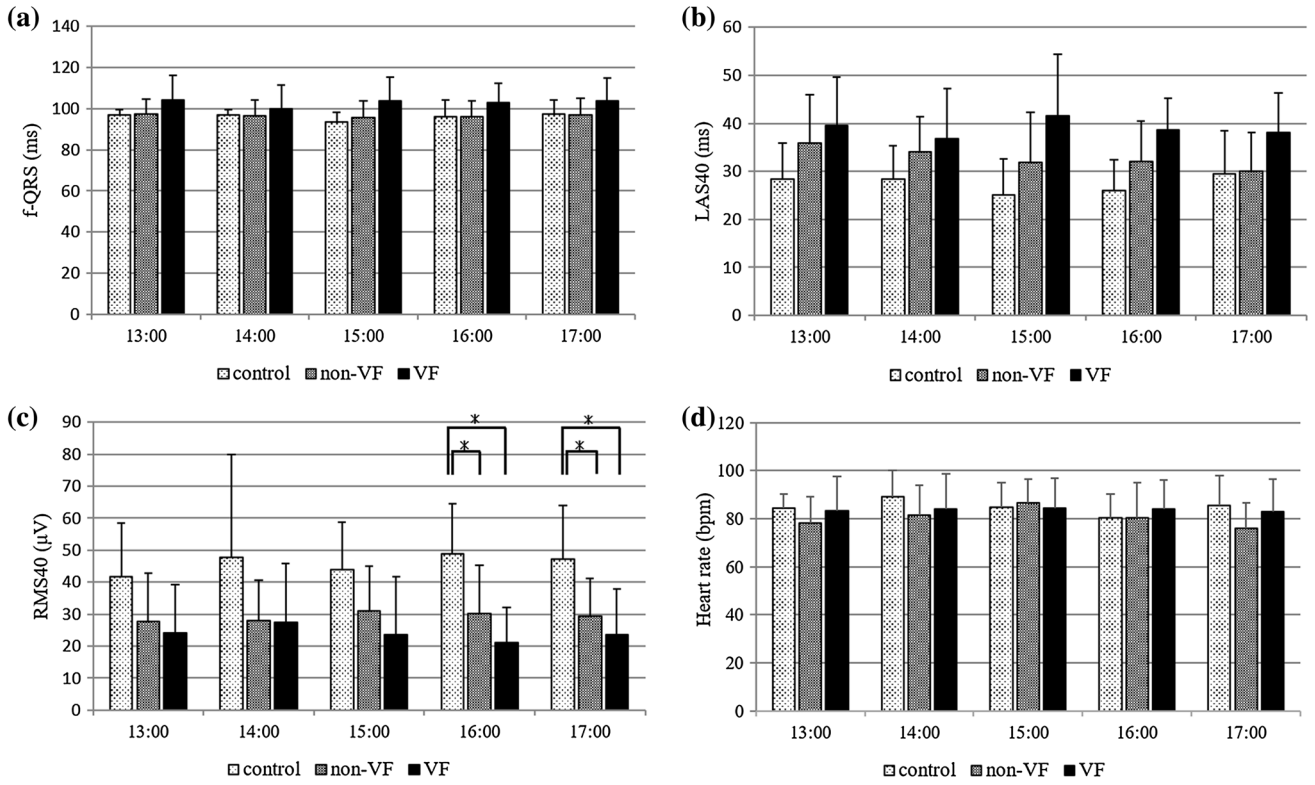

Fig. 2 LPs on Holter SAECG for 4 h at baseline among the 3 groups. **a** f-QRS. **b** LAS40. **c** RMS40. **d** Heart rate. There were no significant differences between the VF and non-VF group

SAECG than in those with negative LPs [14]. Ajiro et al. also reported that the RMS40 value was associated with a history of life-threatening arrhythmic events and VF recurrence [15]. On the contrary, another Japanese multicenter study demonstrated that there was no significant difference in the incidence of positive LPs between patients with documented VF and those with syncope or without symptoms [16]. Several studies revealed that the abnormal 12-lead ECG pattern of BrS showed circadian and daily fluctuations. Tatsumi et al. also reported that daily fluctuations in f-QRS duration and LAS40 were significantly more pronounced in patients with BrS and documented VF or a history of syncope than in patients without symptoms [17]. These findings suggest that a single examination assessment of SAECG could underestimate differences in parameters between high-risk and low-risk patients. A previous report using Holter SAECG for BrS over 24 h showed that high-risk patients had inherent daily LP fluctuations and increased positive LPs at nighttime [9]. In this study, in considering change in autonomic tone, we evaluated HF and LF/HF instead of these parameters, because we have not performed examination at nighttime, and there were no significant differences at each hour at baseline or after pilsicainide provocation among the three groups. In the present study, we simultaneously recorded the LP and ECG parameters in daytime using Holter SAECG and Holter ECG after the pilsicainide provocation in patients with BrS, and demonstrated that the f-QRS of ≥112 ms at 1 h and LAS40 of ≥41 ms at 3 h were useful parameters to identify high-risk patients.

A previous study reported that sodium channel dysfunction has an important role in ST elevation and occurrence of VF in patients with BrS [10]. The intravenous administration of pilsicainide, which is a pure sodium channel blocker, unmasks type 1 ECG and frequently induces fatal ventricular arrhythmias [18]. There were few reports investigating the depolarization abnormality after pilsicainide provocation for risk stratification in BrS. Doi et al. indicated that a conduction delay in the right ventricle (RV) was most prominent in patients with documented VF, and the conduction delay in the RV increased after the pilsicainide provocation and was related to the depolarization abnormality associated with the cardiac sodium channel [19]. Nademanee et al. also identified low voltage areas with fractionated electrograms and severe activation delay at the anterior epicardial aspect of the RV outflow tract (RVOT) and showed an area of fractionation increased after sodium channel blockade administration [20]. Furthermore, Yamasaki et al. reported that pilsicainide provocation produces further accentuation of depolarization abnormality

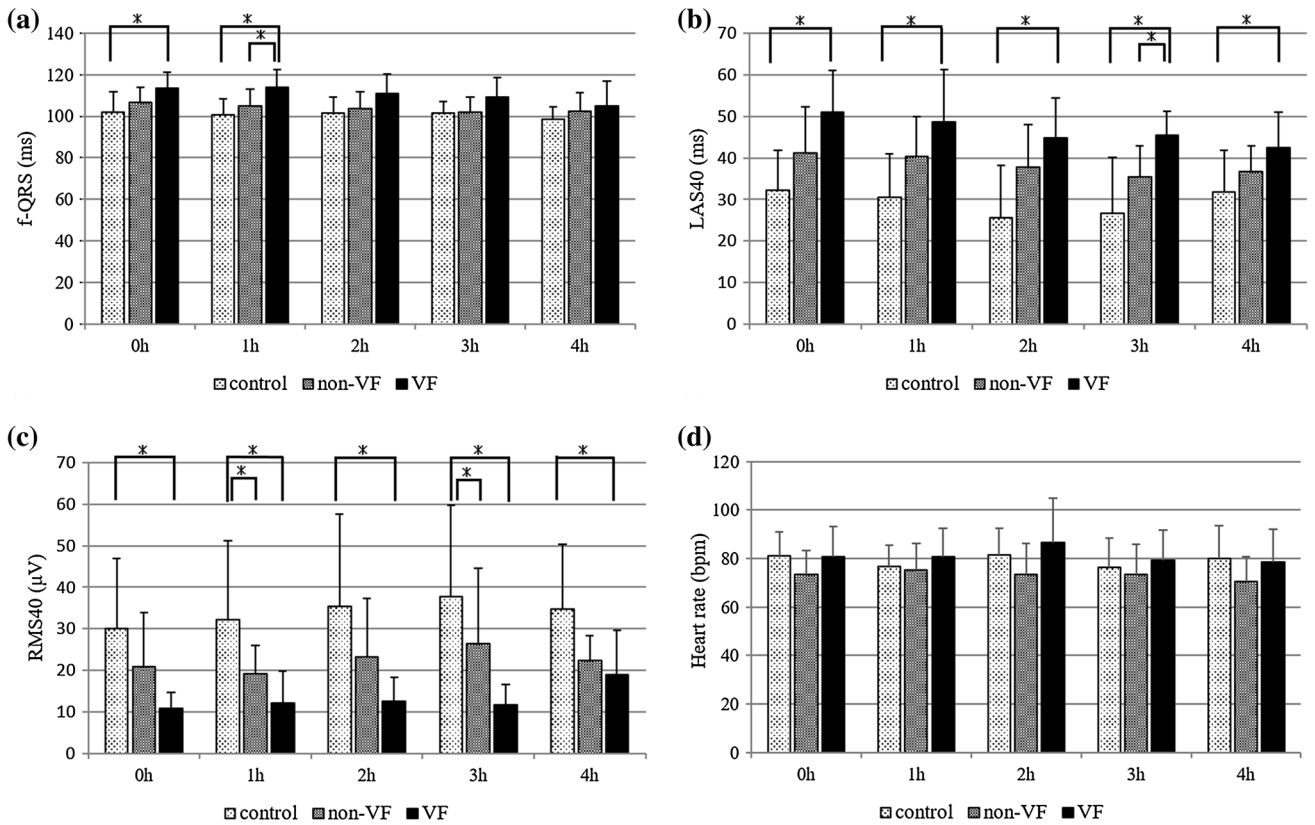

Fig. 3 LPs on Holter SAECG for 4 h after pilsicainide provocation among the 3 groups. **a** f-QRS. **b** LAS40. **c** RMS40. **d** Heart rate. f-QRS at 1 h and LAS 40 at 3 h after pilsicainide provocation were significantly larger in the VF group than those in the non-VF group

Table 2 ROC analysis of f-QRS at 1 h and LAS40 at 3 h after pilsicainide provocation

	Sensitivity (%)	Specificity (%)	OR	95% CI	CF (ms)	AUC	*p* value
f-QRS 1 h	80	80	1.16	1.03–1.36	112	0.80	0.02
LAS 40 3 h	90	75	1.34	1.11–1.78	41	0.87	0.01

ROC receiver-operating characteristic, *f-QRS* filtered QRS, *OR* odds ratio, *CI* confidence interval, *CF* cut-off, *AUC* area under the curve

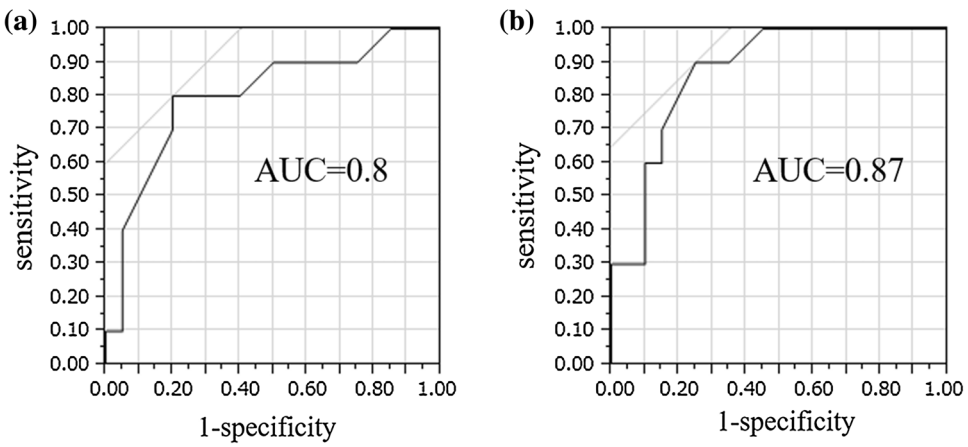

Fig. 4 Receiver-operating characteristic analysis of f-QRS at 1 h after pilsicainide provocation and LAS40 at 3 h after pilsicainide provocation. **a** f-QRS at 1 h after pilsicainide provocation. **b** LAS40 at 3 h after pilsicainide provocation

Table 3 Comparison of parameters on Holter ECG after pilsicainide provocation between the VF and non-VF group

	VF ($n=10$)	Non-VF ($n=20$)	p value
QRS duration (ms)			
V2 in 0 h	120.6 ± 8.6	118.5 ± 1.5	0.43
V5 in 0 h	106.6 ± 3.5	100.6 ± 2.5	0.17
V2 in 1 h	119.8 ± 2.2	117.7 ± 1.6	0.45
V5 in 1 h	101.3 ± 11.8	101 ± 11.0	0.95
V2 in 2 h	117.5 ± 8.9	116 ± 6.4	0.61
V5 in 2 h	101.1 ± 11.8	101.4 ± 7.5	0.91
V2 in 3 h	113.4 ± 8.9	114.2 ± 9.0	0.83
V5 in 3 h	100.2 ± 11.2	97.1 ± 7.9	0.38
V2 in 4 h	114.2 ± 9.0	110.8 ± 7.6	0.28
V5 in 4 h	100.3 ± 7.3	98.1 ± 11.4	0.57
J amplitude (mV)			
V2 in 0 h	0.26 ± 0.1	0.3 ± 0.1	0.33
V2 in 1 h	0.25 ± 0.1	0.25 ± 0.1	0.95
V2 in 2 h	0.23 ± 0.1	0.24 ± 0.1	0.81
V2 in 3 h	0.23 ± 0.1	0.23 ± 0.1	0.90
V2 in 4 h	0.23 ± 0.1	0.23 ± 0.1	0.95
QTc interval			
V2 in 0 h	406.4 ± 31	415.5 ± 49	0.59
V5 in 0 h	390.5 ± 14.8	396.7 ± 29.6	0.54
V2 in 1 h	393.5 ± 40	418 ± 39	0.11
V5 in 1 h	392.9 ± 28.1	402 ± 27.1	0.36
V2 in 2 h	409.5 ± 55.8	407.2 ± 40.4	0.89
V5 in 2 h	388.5 ± 23.7	404.5 ± 24	0.10
V2 in 3 h	389.1 ± 20.1	408.4 ± 41.2	0.17
V5 in 3 h	387.3 ± 27.3	392.8 ± 30.3	0.63
V2 in 4 h	385.6 ± 24.4	386.1 ± 32.3	0.96
V5 in 4 h	392.8 ± 18	387.7 ± 22.4	0.54

in RVOT epicardium, and ventricular premature contractions (VPCs) provoked by a low-dose of pisicainide in BrS patients [21]. We believe that pilsicainide provocation could accentuate the electrical vulnerability of arrhythmogenic substrate associated with the depolarization abnormality in BrS. In this study, we showed that the LP parameters of f-QRS at 1 h and LAS40 at 3 h after pilsicainide provocation were determined to be risk factors that can identify high-risk patients. Yokokawa et al. reported that the QRS duration in 87-leads body surface potential mapping ECG increased with a sodium channel blocker, pilsicainide, and this was observed homogeneously throughout the ventricular wall [22]. Because we evaluated the LP parameters of whole heart using Frank X, Y, Z corrected orthogonal leads, we thought that the drastic increase in the blood concentration of pilsicainide immediately after the provocation may produce a conduction delay on the entire right and left ventricles, and a depolarization abnormality in RVOT might be inconspicuous even in high-risk patients with BrS. Therefore, we speculated that abnormal f-QRS at 1 h after pilsicainide provocation might be more prominent with decreased effect on depolarization in left ventricle due to the decline of blood concentration of pilsicainide in high-risk patients with BrS, and that there might be no significant difference in f-QRS after 2 h because of decreased effect on depolarization in entire ventricles. LAS40 is the duration of the low-amplitude electric potential component (40 μV) of the terminal portion. We speculated that the LAS40 at 1–2 h after pilsicainide administration was masked by prolonged f-QRS duration because of low voltage (40 μV), and that abnormal LAS40 at 3 h might be manifest by decreasing the effect on depolarization of normal myocardium due to the further decline of blood concentration of pilsicainide in high-risk patients with BrS.

Pilsicainide exhibits very slow kinetics, and generally, the t1/2β of pilsicainide after intravenous infusion is 4.34 ± 1.98 (0.25 mg/kg), 5.74 ± 0.85 (0.5 mg/kg), and 4.37 ± 0.48 h (0.75 mg/kg). Therefore, we evaluated each parameter for 4 h after the pilsicainide provocation to take into consideration this half-life in blood. After intravenous administration of pilsicainide, >90% of the dose is eliminated primarily via the kidneys into the urine in an unchanged form in young healthy subjects [23, 24]. In this study, there were no significant differences in estimated glomerular filtration rate or serum creatinine among the three groups, and the blood concentration of pilsicainide was thought to be nearly equivalent among the three groups.

Study limitations

There were several limitations to this study. First, as the number of patients in the present study was quite small, further data are needed to improve the usefulness of the markers for identifying high-risk patients with BrS. Second, the Holter ECG parameters can be affected by many factors, such as body motion, posture, and changes in autonomic tone. Yoshioka et al. reported that LP variance by postural changes should be considered [9]. It is necessary to evaluate the parameters on Holter SAECG and ECG to take into consideration this fluctuation in the future. Third, we performed Holter SAECG and ECG only in the daytime. In BrS, it is well known that VF often occurs in the nighttime. Further assessments including Holter SAECG, ECG, and TWA after pilsicainide provocation in the nighttime would be necessary in future study. Forth, we did not assess the blood concentration of pilsicainide. We think that a future study is needed to evaluate both LP parameters and the concentration of pilsicainide after the provocation. Fifth, we excluded Brugada patients with CRBBB from this study. Therefore, a further assessment of the cut-off values of f-QRS for VF episode in Brugada patients with CRBBB

would be necessary in future study. Finally, this study was a retrospective study. It will be necessary to design a prospective study to confirm our results.

Conclusion

The f-QRS and the LAS40 after pilsicainide provocation using Holter SAECG may be useful for risk stratification for high-risk BrS. The prominent depolarization abnormality by sodium channel blocker provocation might be associated with electrical arrhythmogenic substrate in high-risk patients with BrS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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