Tohoku J. Exp. Med., 2016, **240**, 191-198

Prognostic Significance of Late Potentials in Outpatients with Type 2 Brugada Electrocardiogram

Makoto Nakano,[1] Koji Fukuda,[1] Masateru Kondo,[1] Masato Segawa,[1] Michinori Hirano,[1] Takahiko Chiba,[1] Kyoshiro Fukasawa,[1] Keita Miki,[1] Susumu Morosawa[1] and Hiroaki Shimokawa[1]

[1]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan

Brugada syndrome is characterized by distinguishing electrocardiogram (ECG) patterns (coved and saddle-back types with day-to-day variation) and occurrence of lethal tachy-arrhythmias. The appearance of coved type ECG (type 1) is required for the diagnosis of Brugada syndrome, whereas the significance of saddle-back type ECG (type 2), which is inadequate for the diagnosis, has not been fully established. We enrolled 34 consecutive patients with type 2 ECG on outpatient-clinic. Among them, 7 patients were ventricular fibrillation (VF) survivors who were diagnosed as Brugada syndrome with transient appearance of type 1 ECG, and showed type 2 ECG on their first outpatient-clinic visit after the VF event (VF group). The remaining 27 were asymptomatic and never showed type 1 ECG on repeated ECG examinations (control group). The VF group showed significantly longer RJ intervals in leads V1 and V2 and QTc intervals in lead V2 compared with the control group ($P < 0.030$, $P < 0.017$, and $P < 0.030$, respectively). Late potentials, detected on the signal-averaged ECG (SA-ECG), reflect conduction abnormalities and are known as one of the risk markers of arrhythmic events. Among the 34 patients, late potentials were negative in 12 patients belonging to the control group. In conclusion, the SA-ECG could be helpful to identify high-risk patients for its high negative predictive value as the first step, and ECG parameters, including RJ intervals in leads V1 and V2 and QTc interval in lead V2, could be useful for further risk stratification in patients with type 2 Brugada ECG.

Keywords: Brugada Syndrome; electrocardiogram; late potentials; risk stratification; type 2 (saddle-back)
Tohoku J. Exp. Med., 2016 November, **240** (3), 191-198.

Introduction

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and sudden death due to fatal ventricular arrhythmia, such as ventricular fibrillation (VF) and polymorphic ventricular tachycardia, in spite of lack of structural heart disease (Antzelevitch 2006). Since some cases are presented with sudden cardiac death as their first manifestation, it is important to establish risk classification strategy for patients with Brugada syndrome. Coved type (type 1) electrocardiogram (ECG) is necessary for diagnosis of Brugada syndrome, and it has been demonstrated that spontaneous type 1 Brugada ECG and prolonged QRS duration in precordial leads could be one of the markers for high-risk patients with Brugada syndrome (Gehi et al. 2006; Takagi et al. 2007). However, it is also the fact that in clinical setting that a number of patients are presented with saddle-back type (type 2) Brugada ECG, which does not have enough power to diagnose Brugada syndrome, on their first visit (Sakabe et al. 2003). Indeed, the risk classification strategy for patients with type 2 Brugada ECG remains to be established. Drug challenge test with sodium channel blocking agents would be useful for unmasking type 1 ECG for patients with type 2 ECG, however, it does not play any role in risk stratification in asymptomatic patients with Brugada ECG (Zorzi et al. 2012; Dobbels et al. 2016). In addition, it would be impractical to perform drug challenge test for all the patients with type 2 ECG. Although inducibility of VF during electrophysiological study (EPS) is considered to be one of the risk stratification tools in patients with Brugada syndrome, its usefulness has been controversial (Brugada et al. 2002; Priori et al. 2002). Moreover, EPS is an invasive examination, which does not suit for the initial examination for risk classification at outpatient clinic, especially for those without type 1 Brugada ECG. Therefore, non-invasive examination would be needed to detect high-risk cases with type 2 ECG, who should receive further invasive examination.

Late potentials on the signal-averaged ECG (SA-ECG) are known as one of the risk markers of arrhythmic events in patients with organic heart disease (Kuchar et al. 1987; Ikeda et al. 2000). Late potentials are also frequently seen

Received April 18, 2016; revised and accepted October 6, 2016. Published online November 2, 2016; doi: 10.1620/tjem.240.191.
Correspondence: Makoto Nakano, M.D., Ph.D., Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
e-mail: vdm@cardio.med.tohoku.ac.jp

in patients with Brugada syndrome, especially among those with type 1 ECG, and they also could be associated with their arrhythmic risk stratification (Huang et al. 2009). However, their roles in patients with type 2 ECG remain to be elucidated. In the present study, we thus examined the ECG parameters and late potentials in order to identify high-risk cases among patients with type 2 Brugada ECG.

Methods

Study population

From January 2007 to February 2013, we retrospectively enrolled 34 consecutive patients who showed type 2 Brugada ECG at the fourth and third intercostal space and no structural heart disease on their first visit at our outpatient-clinic (male/female 33/1, mean age, 48.1±13.9 [SD] years old). ECGs were reviewed independently by two physicians according to the consensus report of ECG criteria for diagnosis of Brugada syndrome in 2005 (Antzelevitch et al. 2005). Structural heart diseases were diagnosed by transthoracic echocardiogram and if present, the cases were excluded from the present study. Among the 34 enrolled patients, 7 patients, categorized as VF group, were diagnosed as Brugada syndrome with documented type 1 ECG spontaneously or in response to drug challenge test during hospitalization for VF events. The patients in the VF group showed type 2 ECG on their first outpatient clinic visit after the VF event. The remaining 27 patients who were asymptomatic and never showed type 1 ECG on repeated ECG examinations belonged to the control group (Fig. 1).

In the present study, in order to develop rapid risk stratification, we analyzed 12-lead ECG and late potentials on SA-ECG examined on their first visit. This study was approved by ethical committee in Tohoku University of Graduate School of Medicine.

Twelve-lead ECG

12-lead ECG was recorded at a paper speed of 25 mm/sec and amplitude of 1 cm/mV. We measured PR, RJ and corrected QTc intervals (calculated by Bazett's method) in both groups **(**Fig. 2**)** (Tatsumi et al. 2006). All of these parameters were measured in V1, V2 and V6 leads at the fourth intercostal space. J points in V1 and V2 were measured by extrapolation from that in V6. These parameters were measured independently by two experienced cardiologists who did not know patient information. When the measured values

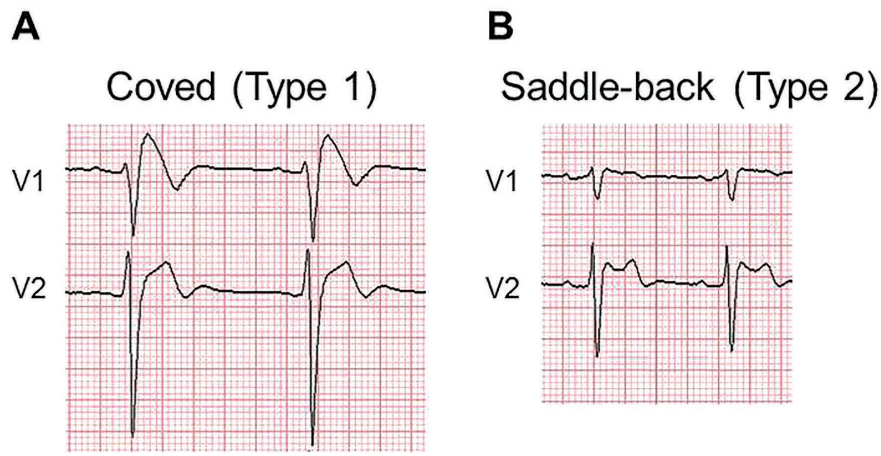

Fig. 1. Representative ECGs of coved (type 1) and saddle-back (type 2) Brugada ECG.
Coved type (type 1; A) ECG is necessary for diagnosis of Brugada syndrome. On the other hand, saddle-back type (type 2; B) ECG in itself does not have enough power to diagnose Brugada syndrome.

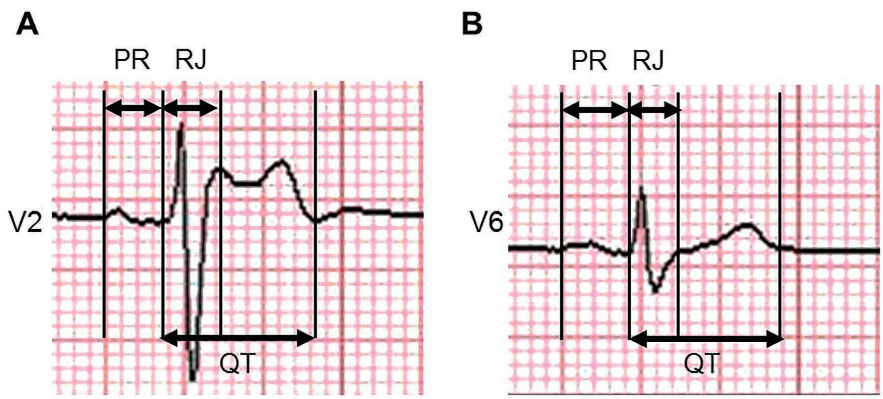

Fig. 2. Measurement points of 12-lead ECG.
The parameters were measured in lead V2 (A) and lead V6 (B). PR interval; interval from the onset of P wave to QRS onset. RJ interval; interval from QRS onset to J point, which is flexion point from S wave to T wave. QT interval; interval from QRS onset to the end of T wave.

were not identical, the mean values of the two measurements were used for analysis.

Signal-averaged ECG

Late potentials were analyzed using a SA-ECG system (FP-705LP System, Fukuda Denshi, Tokyo, Japan). The filtered QRS duration (fQRS), the root mean square voltage of the terminal 40 msec in the filtered QRS complex (RMS40), and the duration of low-amplitude signals (< 40 μV) in the terminal filtered QRS complex (LAS40) were measured using the SA-ECG system in both groups. Late potentials were considered as positive when two criteria were met (RMS40 < 20 μV and LAS40 > 38 msec) (Tatsumi et al. 2006; Huang et al. 2009).

Statistical analysis

Statistical analysis was performed using Mann-Whitney U-test to compare the ECG parameters between the two groups. All results are expressed as mean ± SD. To quantify the classification ability of the covariates, the area under the curve (AUC) of the receiver-operator characteristic (ROC) curve was used. The univariate and multivariate logistic regression models with forward selection/backward elimination stepwise variable selection were also applied to analyze the association between arrhythmic risks and the covariates. The P value < 0.05 was considered to be statistically significant.

Results

Patients characteristics

There was no significant difference in the prevalence of family history of Brugada syndrome or sudden cardiac death between the two groups. In the VF group, one patient (VF 7) had family history; a sister of the patient had been diagnosed as Brugada syndrome by coved-type ECG and family history of sudden death (Table 1). The control group had 4 patients with family history (control 8, 14, 15 and 17); all of them had relatives who died suddenly in their twenties. In the VF group, 5 patients (VF 1, 2, 3, 5 and 6) suffered from VF attacks during night, suggesting typical clinical situation of fatal arrhythmic attacks in patients with Brugada syndrome. The remaining 2 patients in the VF group (VF 4 and 7) had VF attacks during daytime. One patient in the control group (control 8) had history of syncope, which was diagnosed as neurally mediated syncope by detailed history taking (Table 1). All patients in the VF group underwent implantation of implantable cardioverter-defibrillator (ICD) after the first VF attack, whereas no patient in control group had ICD. During the mean follow-up period of 41.1 ± 16.1 months, three patients in the VF group (VF 1, 2 and 6) had recurrence of VF attacks, all of which were successfully terminated by ICD shocks. In contrast, all patients in the control group had no arrhythmic events in their clinical course.

12-lead ECG analysis

There was no difference in PR intervals in lead V1, V2 or V6 between the two groups in 12-lead ECG measurements. In the RJ interval measurement, patients in the VF group showed significantly longer duration in leads V1 and V2 compared with the control group (RJ in lead V1, 121 ± 18.6 vs. 106 ± 10.1 msec, P < 0.030; RJ in lead V2, 130 ± 27.7 vs. 105 ± 11.6 msec, P < 0.017) (Table 2), whereas there was no significant difference in RJ intervals in lead V6 between the two groups. Moreover, in the QTc interval measurement, patients in the VF group also demonstrated significantly longer duration in lead V2 compared with the control group (417 ± 30.9 vs. 398 ± 21.7 msec, P < 0.030) (Table 2), although we found no differences in QT interval in lead V1or V6 (Table 2). Next, we quantified the ability of useful variables (RJ intervals in lead V1 and V2 and QTc interval in lead V2) to detect patients with high arrhythmic risks using ROC curve analysis. Each value of area under the ROC curve of RJ intervals in lead V1 and V2 and QTc interval in lead V2 was 0.751, 0.783, and 0.772, respectively (Table 2).

Late potentials by signal-averaged ECG analysis

In SA-ECG analysis, averaged noise level of these data was 0.30 ± 0.14 μV. SA-ECG analysis showed that all 12 patients with negative late potentials belonged to the control group (Table 1). In contrast, voltage of RMS40 in patients in the VF group was lower compared with the control group (12.1 ± 4.9 vs. 17.6 ± 9.0, P = 0.187) (Fig. 3). In addition, duration of LAS40 in the VF group was also longer than in the control group (53.7 ± 14.1 vs. 42.5 ± 12.5, P = 0.061) (Fig. 3), whereas there was no significant difference in fQRS duration between the two groups (Fig. 3). Next, we examined the risk stratification ability of late potentials. RMS40 showed sensitivity of 100%, specificity of 40.7%, positive predictive value of 30.4%, and negative predictive value of 100%. LAS40 showed sensitivity of 100 %, specificity of 44.4%, positive predictive value of 31.8 %, and negative predictive value of 100% for detecting high-risk patients (Table 3). Finally, positive late potential (both RMS40 and LAS40 were positive) showed sensitivity of 100%, specificity of 44.4%, positive predictive value of 31.8%, and negative predictive value of 100% (Table 3).

Univariate regression analysis

Finally, the univariate and multivariate logistic regression models were analyzed. The multivariate model with all covariates failed to fit because probabilities 0 or 1 occurred. The best subset of the covariates was selected with only V2RJ by forward selection/backward elimination stepwise procedure (Table 4).

Representative cases

We demonstrated representative cases in Fig. 4. Although ECG of both cases appeared almost normal or type 2 changes on the fourth or third intercostal space, we were able to find the differences between the two cases on SA-ECG; the patient in the control group had negative late potentials and that in the VF group had positive late potential with lower voltage in RMS40 and longer duration of

Table 1. Clinical characteristics of the patients.

Group	Patient No.	Sex	Age	FH	Symptom (situation or diagnosis)	LPs
VF	1	M	60	-	VF (night, after dinner)	+
VF	2	M	44	-	VF (night, after dinner)	+
VF	3	M	38	-	VF (night, sleeping, after drinking alcohol)	+
VF	4	M	42	-	VF (morning, after breakfast)	+
VF	5	M	61	-	VF (night, sleeping)	+
VF	6	M	41	-	VF (night, sleeping, after drinking alcohol)	+
VF	7	F	60	+	VF (daytime, during activity)	+
control	1	M	64	-	-	-
control	2	M	38	-	-	+
control	3	M	38	-	-	-
control	4	M	34	-	-	+
control	5	M	39	-	-	+
control	6	M	54	-	-	-
control	7	M	70	-	-	-
control	8	M	24	+	Syncope (neurally mediated syncope)	-
control	9	M	59	-	-	+
control	10	M	64	-	-	+
control	11	M	38	-	-	+
control	12	M	36	-	-	+
control	13	M	42	-	-	+
control	14	M	22	+	-	-
control	15	M	64	+	-	+
control	16	M	37	-	-	+
control	17	M	33	+	-	-
control	18	M	35	-	-	+
control	19	M	63	-	-	+
control	20	M	76	-	-	-
control	21	M	44	-	-	+
control	22	M	52	-	-	-
control	23	M	40	-	-	+
control	24	M	56	-	-	+
control	25	M	40	-	-	-
control	26	M	60	-	-	-
control	27	M	68	-	-	-

Sex; M, male; F, female; FH, Family History; VF, ventricular fibrillation; LPs, late potentials.
In FH, symptom and LPs, +; positive, −; negative.

LAS40 than in the control group patient. Moreover, we were also able to detect the difference in RJ intervals in leads V1 and V2 and QTc interval in lead V2; the patient in the VF group showed longer duration in RJ intervals in leads V1 and V2, and QTc interval in lead V2 than in the patient in the control group.

Discussion

The novel findings of the present study are that (1) the patients in the VF group showed significantly longer duration in RJ intervals in leads V1 and V2, and in QTc interval in lead V2 compared with the control group (2) all patients with negative late potentials belonged to the control group and (3) the patients in the VF group showed lower tendency in voltage of RMS40 and longer tendency in duration of LAS40 compared with the control group. To our best knowledge, this is the first study that demonstrates the usefulness of ECG parameters and late potentials on SA-ECG for the risk stratification of patients with type 2 Brugada ECG.

Table 2. 12-lead ECG findings of the 2 groups.

	VF group (n = 7)	Control group (n = 27)	P value	AUC
PR (msec)	165 ± 16.1	155 ± 21.5	0.16	0.677
V1 RJ (msec)	121 ± 18.6	106 ± 10.1	0.03	0.751
V1 QT (msec.)	390 ± 22.4	391 ± 27.1	0.913	0.516
V1 QTc ($msec^{1/2}$)	424 ± 69.4	397 ± 27	0.371	0.614
V2 RJ (msec)	130 ± 27.7	105 ± 11.6	0.017	0.783
V2 QT (msec)	417 ± 30.9	398 ± 21.7	0.149	0.677
V2 QTc ($msec^{1/2}$)	457 ± 69.8	405 ± 23.1	0.03	0.772
V6 RJ (msec)	111 ± 22.7	101 ± 12.9	0.266	0.368
V6 QT (msec)	396 ± 27	393 ± 23.7	0.81	0.532
V6 QTc ($msec^{1/2}$)	429 ± 59.4	400 ± 26.3	0.335	0.624

AUC, area under the receiver-operator characteristic curve.
P values of interval of V1RJ, V2RJ and V6QTc were underlined because of their significant difference between patients in VF group and control group.

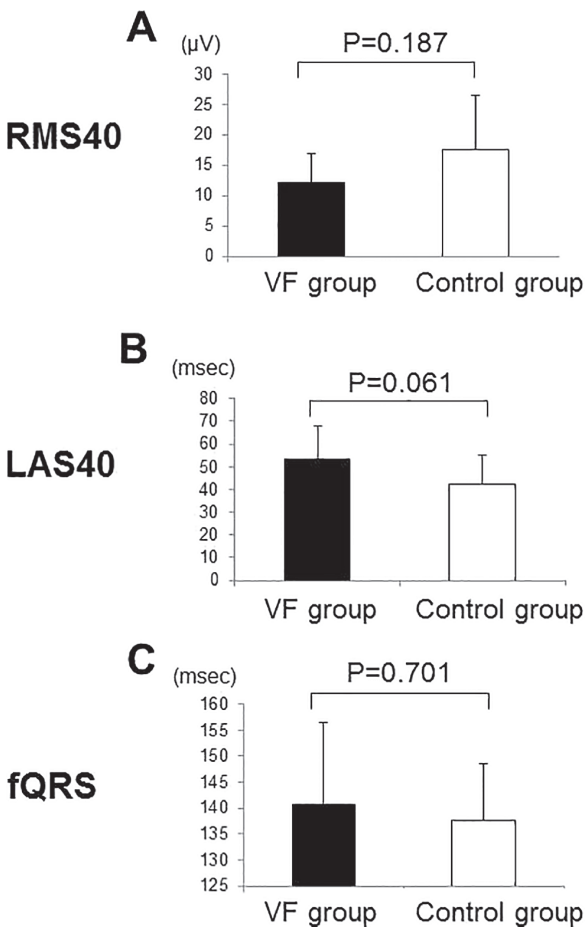

Fig. 3. Results of late potentials (RMS40, LAS40, fQRS) detected by signal-averaged ECG analysis in the VF and control groups.
A. Voltage of RMS40. B. Duration of LAS40. C. Duration of fQRS. Results are expressed as mean ± SD.
Voltage of RMS40 in patients in the VF group was lower compared with the control group (A). Duration of LAS40 in the VF group was also longer than in the control group (B). There was no significant difference in fQRS duration between the two groups (C).

Late potentials by SA-ECG

Since late potentials detected by SA-ECG reflect conduction abnormalities, they are considered to be a predictive marker of arrhythmic events in organic heart disease (Kuchar et al. 1987; Ikeda et al. 2000). On the other hand, the mechanisms of developing late potentials in Brugada syndrome are considered as being based on both repolarization and depolarization abnormality theory (Antzelevitch 2002; Huang et al. 2009). In general, it is known that action potential duration in endocardial cells is longer than that in epicardial cells and that epicardial cells show a notch on the first phase of action potential, which was not observed in endocardial cells (Antzelevitch 2006). Moreover, transient outward potassium channel, which is known to be expressed especially on myocardial cells in the right ventricular outflow tract (RVOT), mainly contribute to the deeper notch on epicardial cells, resulting in larger transmural dispersion between endocardial and epicardial cells on the RVOT (Antzelevitch 2006). Such distinct electrophysiological differences between endocardial and epicardial cells especially in the RVOT cause transmural dispersion of repolarization (Antzelevitch 2006). Recent reports showed abnormal potentials developed by such repolarization abnormality, including concealed phase 2 reentry, contributing to the generation of late potentials on SA-ECG (Antzelevitch 2002).

On the other hand, depolarization abnormality could also play a role in pathogenesis of Brugada syndrome. Recent studies demonstrated that in patients with Brugada syndrome who suffered from repetitive ICD discharges due to VF attacks, catheter ablation of fractionated potentials in the epicardial RVOT could eliminate VF attacks and normalize their type 1 ECG (Nademanee et al. 2011; Sunsaneewitayakul et al. 2012). Fractionated potentials are supposed to reflect conduction abnormality, which are caused by separation of myocardial fibers by scar or fat tissue (de Bakker et al. 1993; Corrado et al. 2005). Some

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of late potentials.

	sensitivity (%)	specificity (%)	positive predictive value (%)	negative predictive value (%)
RMS40	100	40.7	30.4	100
LAS40	100	44.4	31.8	100
Late potentials	100	44.4	31.8	100

RMS40; the root mean square voltage of the terminal 40 msec in the filtered QRS complex (RMS40 < 20 μV; positive).
LAS40; the duration of low-amplitude signals (< 40 μV) in the terminal filtered QRS complex (LAS40 > 38 msec; positive).
Late potentials were considered as positive when 2 criteria were met (RMS40 < 20 μV and LAS40 > 38 msec).

Table 4. Results of univariate analysis.

	Odds ratio	lower 95% CI	upper 95% CI	p-value
PR	0.977	0.935	1.017	0.257
V1RJ	0.914	0.829	0.978	0.025
V1QT	1.002	0.971	1.039	0.891
V1QTc	0.984	0.961	1.004	0.125
V2RJ	0.921	0.838	0.974	0.023
V2QT	0.969	0.933	1.002	0.077
V2QTc	0.968	0.926	0.992	0.052
V6RJ	0.960	0.904	1.013	0.142
V6QT	0.995	0.961	1.032	0.784
V6QTc	0.981	0.955	1.002	0.090
age	0.991	0.931	1.055	0.776
RMS40	1.106	0.984	1.300	0.142
LAS40	0.937	0.869	0.999	0.061
fQRSd	0.979	0.913	1.053	0.546

Abbreviations are the same as Tables 2 and 3.
fQRSd; the filtered QRS duration.

patients with type 1 ECG could show fractionated QRS as a result of conduction abnormality (Morita et al. 2008). A recent report showed that such fractionated QRS may have some relationship with their arrhythmic events in patients with type 1 ECG (Morita et al. 2008). Other study also showed that right ventricular conduction is delayed in patients with Brugada syndrome (Tukkie et al. 2004). Depolarization abnormalities noted in these studies may contribute to the development of late potentials in patients with Brugada syndrome. It was previously reported that late potentials detected by SA-ECG play some roles in risk stratification for patients with type 1 ECG, in whom especially measurement of RMS40 in late potentials is useful to predict their arrhythmic events (Kuchar et al. 1987; Ikeda et al. 2000; Ajiro et al. 2005; Huang et al. 2009). However, the risk stratification strategy for patients with type 2 ECG remains to be established (Ikeda et al. 2001; Ajiro et al. 2005; Huang et al. 2009).

Risk stratification strategy for patients with Type 2 Brugada ECG

In the present study, we were able to demonstrate that patients with negative late potentials were all asymptomatic in their first visit to our hospital and had no arrhythmic events in their clinical course. We also were able to demonstrate that patients in the VF group showed significant longer duration in RJ intervals in leads V1 and V2 and in QTc intervals in lead V2 compared with the control group. Furthermore, patients in the VF group tended to have low voltage of RMS40 and long duration of LAS40 compared with the control group. A recent study showed that prolonged QRS duration in precordial leads could be useful for risk stratification of patients with Brugada syndrome (Takagi et al. 2007). Although there were some differences in patient characteristics between the previous study (Takagi et al. 2007) and our present study, both studies showed that depolarization abnormality could play some roles in arrhythmogenesis in patients with Brugada ECG. In addition, the present results showed that QTc interval in lead V2

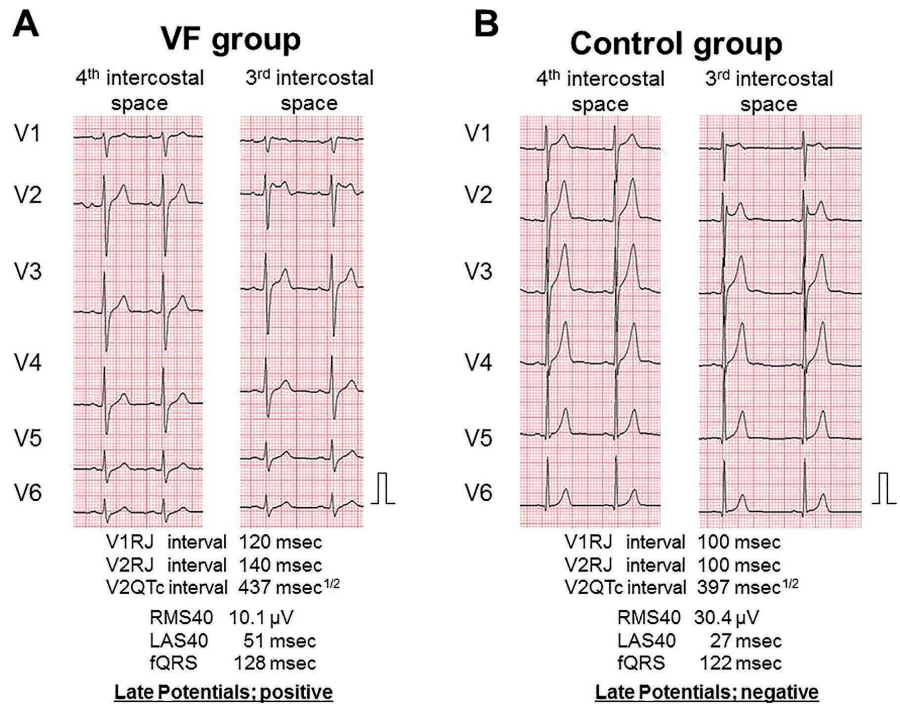

Fig. 4. Representative ECGs, ECG parameters and late potentials (RMS40, LAS40, fQRS) detected by signal-averaged ECG.
Representative ECGs, and their parameters and late potentials detected by signal-averaged ECG of a patient in the VF group (A) and that in the control group (B).
Although ECG of both cases appeared almost normal or saddle-back (type 2) changes on the fourth or third intercostal space, the patient in the control group (B) had negative late potentials and that in the VF group (A) had positive late potential with lower voltage in RMS40 and longer duration of LAS40 than in the control group patient. On 12-lead ECG Analysis, the patient in the VF group (A) showed longer duration in RJ intervals in lead V1 and V2, and QTc interval in lead V2 than in the patient in the control group (B).

is important as it reflects the repolarization abnormality related to type 2 ECG. This notion is supported by the present results of late potential analysis. Both depolarization and repolarization abnormalities could contribute to pathophysiology and electrophysiology of Brugada syndrome (Antzelevitch 2006), not only in type 1 ECG but also in type 2 ECG. The present study demonstrates that in clinical settings, first we are able to identify patients with type 2 Brugada ECG at high arrhythmic risks by checking late potentials, followed by checking RJ intervals in leads V1 and V2 and QTc interval in lead V2 as the markers of patients at high arrhythmic risks.

Study limitations

Several limitations should be mentioned for the present study. First, the number of patients examined in the present study was relatively small, and period of follow-up was also relatively short. Second, the present study was a retrospective study. Third, we analyzed 12-lead ECG and late potentials on SA-ECG examined on their first visit to develop simple risk stratification as a first step; however, parameters in patients with Brugada syndrome sometimes show daily fluctuation. Thus, the present findings need to be confirmed in future prospective studies with a large number of patients with type 2 Brugada ECG.

Conclusions

In the present study, we were able to demonstrate that diagnostic strategy based on the combination of ECG parameters and late potentials would be helpful among patients with type 2 Brugada ECG. The late potentials with high negative predictive value could be helpful to identify high-risk patients as the first step, and among them, RJ intervals in leads V1 and V2 and QTc interval in lead V2 could be the markers of patients with high arrhythmic risk as the second step. The present findings could be useful for risk stratification of patients with type 2 Brugada ECG, although they need to be confirmed in future prospective studies with a large number of patients.

Acknowledgments

The present study was partly presented in the 79th annual scientific meeting of Japanese Circulation Society.

We thank Satoshi Miyata, Ph.D. for his excellent statistical advice.

Funding

M.N. was supported in part by the Research Grant from Yamashita Taro Ikueikai, Japan.

Conflict of Interest

The authors declare no conflict of interest.

References

Ajiro, Y., Hagiwara, N. & Kasanuki, H. (2005) Assessment of markers for identifying patients at risk for life-threatening arrhythmic events in Brugada syndrome. *J. Cardiovasc. Electrophysiol.*, **16**, 45-51.

Antzelevitch, C. (2002) Late potentials and the Brugada syndrome. *J. Am. Coll. Cardiol.*, **39**, 1996-1999.

Antzelevitch, C. (2006) Brugada syndrome. *Pacing Clin. Electrophysiol.*, **29**, 1130-1159.

Antzelevitch, C., Brugada, P., Borggrefe, M., Brugada, J., Brugada, R., Corrado, D., Gussak, I., LeMarec, H., Nademanee, K., Perez Riera, A.R., Shimizu, W., Schulze-Bahr, E., Tan, H. & Wilde, A. (2005) Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*, **111**, 659-670.

Brugada, J., Brugada, R., Antzelevitch, C., Towbin, J., Nademanee, K. & Brugada, P. (2002) Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation*, **105**, 73-78.

Corrado, D., Basso, C., Leoni, L., Tokajuk, B., Bauce, B., Frigo, G., Tarantini, G., Napodano, M., Turrini, P., Ramondo, A., Daliento, L., Nava, A., Buja, G., Iliceto, S. & Thiene, G. (2005) Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation*, **111**, 3042-3050.

de Bakker, J.M., van Capelle, F.J., Janse, M.J., Tasseron, S., Vermeulen, J.T., de Jonge, N. & Lahpor, J.R. (1993) Slow conduction in the infarcted human heart. 'Zigzag' course of activation. *Circulation*, **88**, 915-926.

Dobbels, B., De Cleen, D. & Ector, J. (2016) Ventricular arrhythmia during ajmaline challenge for the Brugada syndrome. *Europace*, **18**, 1501-1506.

Gehi, A.K., Duong, T.D., Metz, L.D., Gomes, J.A. & Mehta, D. (2006) Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J. Cardiovasc. Electrophysiol.*, **17**, 577-583.

Huang, Z., Patel, C., Li, W., Xie, Q., Wu, R., Zhang, L., Tang, R., Wan, X., Ma, Y., Zhen, W., Gao, L. & Yan, G.X. (2009) Role of signal-averaged electrocardiograms in arrhythmic risk stratification of patients with Brugada syndrome: a prospective study. *Heart Rhythm*, **6**, 1156-1162.

Ikeda, T., Sakata, T., Takami, M., Kondo, N., Tezuka, N., Nakae, T., Noro, M., Enjoji, Y., Abe, R., Sugi, K. & Yamaguchi, T. (2000) Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. A prospective study. *J. Am. Coll. Cardiol.*, **35**, 722-730.

Ikeda, T., Sakurada, H., Sakabe, K., Sakata, T., Takami, M., Tezuka, N., Nakae, T., Noro, M., Enjoji, Y., Tejima, T., Sugi, K. & Yamaguchi, T. (2001) Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. *J. Am. Coll. Cardiol.*, **37**, 1628-1634.

Kuchar, D.L., Thorburn, C.W. & Sammel, N.L. (1987) Prediction of serious arrhythmic events after myocardial infarction: signal-averaged electrocardiogram, Holter monitoring and radionuclide ventriculography. *J. Am. Coll. Cardiol.*, **9**, 531-538.

Morita, H., Kusano, K.F., Miura, D., Nagase, S., Nakamura, K., Morita, S.T., Ohe, T., Zipes, D.P. & Wu, J. (2008) Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation*, **118**, 1697-1704.

Nademanee, K., Veerakul, G., Chandanamattha, P., Chaothawee, L., Ariyachaipanich, A., Jirasirirojanakorn, K., Likittanasombat, K., Bhuripanyo, K. & Ngarmukos, T. (2011) Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation*, **123**, 1270-1279.

Priori, S.G., Napolitano, C., Gasparini, M., Pappone, C., Della Bella, P., Giordano, U., Bloise, R., Giustetto, C., De Nardis, R., Grillo, M., Ronchetti, E., Faggiano, G. & Nastoli, J. (2002) Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation*, **105**, 1342-1347.

Sakabe, M., Fujiki, A., Tani, M., Nishida, K., Mizumaki, K. & Inoue, H. (2003) Proportion and prognosis of healthy people with coved or saddle-back type ST segment elevation in the right precordial leads during 10 years follow-up. *Eur. Heart J.*, **24**, 1488-1493.

Sunsaneewitayakul, B., Yao, Y., Thamaree, S. & Zhang, S. (2012) Endocardial mapping and catheter ablation for ventricular fibrillation prevention in Brugada syndrome. *J. Cardiovasc. Electrophysiol.*, **23** Suppl 1, S10-16.

Takagi, M., Yokoyama, Y., Aonuma, K., Aihara, N., Hiraoka, M. & Japan Idiopathic Ventricular Fibrillation Study, I. (2007) Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with brugada syndrome: multicenter study in Japan. *J. Cardiovasc. Electrophysiol.*, **18**, 1244-1251.

Tatsumi, H., Takagi, M., Nakagawa, E., Yamashita, H. & Yoshiyama, M. (2006) Risk stratification in patients with Brugada syndrome: analysis of daily fluctuations in 12-lead electrocardiogram (ECG) and signal-averaged electrocardiogram (SAECG). *J. Cardiovasc. Electrophysiol.*, **17**, 705-711.

Tukkie, R., Sogaard, P., Vleugels, J., de Groot, I.K., Wilde, A.A. & Tan, H.L. (2004) Delay in right ventricular activation contributes to Brugada syndrome. *Circulation*, **109**, 1272-1277.

Zorzi, A., Migliore, F., Marras, E., Marinelli, A., Baritussio, A., Allocca, G., Leoni, L., Perazzolo Marra, M., Basso, C., Buja, G., Thiene, G., Iliceto, S., Delise, P. & Corrado, D. (2012) Should all individuals with a nondiagnostic Brugada-electrocardiogram undergo sodium-channel blocker test? *Heart Rhythm*, **9**, 909-916.