Indian Heart Journal 69 (2017) 714–719

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Atrial electrical abnormality in patients with Brugada syndrome assessed by signal-averaged electrocardiography

Yasutsugu Nagamoto*, Yuto Fujii, Yuichi Morita, Yusuke Ueda, Yasuko Miyake, Kenichi Yamane, Mai Fujiwara, Shinji Mito, Yuichiro Watari, Hiromichi Tamekiyo, Tomokazu Okimoto, Yuji Muraoka, Yasuhiko Hayashi

Division of Cardiology, Tsuchiya General Hospital, Hiroshima, Japan

ARTICLE INFO

Article history:
Received 13 December 2016
Accepted 2 May 2017
Available online 23 May 2017

Keywords:
Atrial fibrillation
Brugada syndrome
Filtered P wave duration
Signal-averaged electrocardiography

ABSTRACT

Background: Ventricular fibrillation and atrial fibrillation are well-known arrhythmias in patients with Brugada syndrome. This study evaluated the characteristics of the atrial arrhythmogenic substrate using the signal-averaged electrogram (SAECG) in patients with Brugada syndrome.
Methods: SAECGs were performed during normal sinus rhythm in 23 normal volunteers (control group), 21 patients with paroxysmal atrial fibrillation (PAF; PAF group), and 21 with Brugada syndrome (Brugada group).
Results: The filtered P wave duration (fPd) in the control, Brugada, and PAF groups was 113.9 ± 12.9 ms, 125.3 ± 15.0 ms, and 137.1 ± 16.3 ms, respectively. The fPd in the PAF group was significantly longer compared to that in the control and Brugada groups ($p < 0.05$). The fPd in the Brugada group was significantly longer than that in the control group ($p < 0.05$) and significantly shorter than that in the PAF group ($p < 0.05$).
Conclusion: Patients with Brugada syndrome had abnormal P waves on the SAECG. The abnormal P waves on the SAECG in Brugada syndrome patients may have intermediate characteristics between control and PAF patients.

1. Introduction

Electrograms (ECGs) in Brugada syndrome are characterized by ST segment elevation in leads V_1–V_3 with a right bundle branch block pattern. These conduction abnormalities can cause nocturnal sudden cardiac death as a result of ventricular arrhythmias.[1,2] Mutations of the sodium channel gene have been reported in Brugada syndrome.[3–5] In cardiac sodium channel disease, electrical abnormalities may exist in the atrial myocardium as well as in the ventricular myocardium. Atrial fibrillation (AF) has been reported to frequently occur in patients with Brugada syndrome,[6,7] and atrial vulnerability is increased.[6,7] The signal-averaged ECG (SAECG) can detect subtle abnormalities of the intra-ventricular and intra-atrial conduction, identifying patients at risk for developing ventricular arrhythmias[8,9] and AF.[10–14] In Brugada syndrome, there is a high incidence of late potentials in the QRS segment, which is evaluated by the filtered QRS wave duration (fQRSd) on the SAECG and is well known.[15–18] Moreover, compared to patients without paroxysmal AF (PAF), the filtered P wave duration (fPd) is prolonged in patients with Brugada syndrome.[7] However, to date, the characteristics of the fPd in patients with Brugada syndrome compared that of the fPd in those with PAF remains unclear. We hypothesized that the atrial arrhythmogenic substrates in patients with Brugada syndrome were different from those in the control and PAF patients. To investigate this hypothesis, we used the SAECG to investigate the fPd.

2. Methods

2.1. Study population

Sixty-five subjects without organic heart disease were included in this retrospective study. The subjects were divided into three groups. Twenty-three normal volunteers without PAF served as the control group and 21 with documented symptomatic PAF were included in the PAF group. The duration of an AF history among the patients in the PAF group was 3.8 ± 2.1 years (1 to 8 years). All PAF patients had symptoms of palpitations only once or twice a year, and had no episodes of visiting a hospital. The AF duration was the estimated duration, which was not the interval from the first diagnosis of AF, but one from the first episode of palpitations.

* Corresponding author at: Division of Cardiology, Tsuchiya General Hospital, Hiroshima, 3-30, Nakajima town, Nakaku, Hiroshima, Japan.
E-mail address: sqopacificsouthern1978@yahoo.co.jp (Y. Nagamoto).

http://dx.doi.org/10.1016/j.ihj.2017.05.008

Therefore, the patients in the PAF group had no history of medications or AF ablation. The remaining 21 patients with Brugada syndrome were assigned to the Brugada group. Brugada syndrome was defined based on the typical ECG signs, which featured a right bundle branch block pattern and spontaneous documented ST segment elevation (coved- and/or saddle back-type) in the right precordial leads (V_1–V_3). A gene test for SCN5A mutations in the Brugada group was not performed in this study. Of the Brugada group patients, 10 had suffered from syncopal episodes and 11 had no symptoms. Two patients had a history of documented PAF. The Ethical Committee of Human Investigations at our institution approved the study protocol.

2.2. Clinical characteristics

The clinical characteristics are shown in Table 1. There were no significant differences among the three groups regarding the age, sex, cardiothoracic ratio on the chest X-ray, left atrial dimension, or ejection fraction measured by the two-dimensional ultrasound cardiography.

2.3. SAECG recording

Recordings were performed in a shielded room to minimize any noise. We used a multi-purpose ECG (VCM-3000, Fukuda Denshi CO., Tokyo, Japan) and micro-potential preamplifier (VL303, Fukuda Denshi CO., Tokyo, Japan) for the SAECG recordings using a modified X, Y, and Z lead system.[19] The X lead was placed between the shoulders, in a similar position to the standard lead I. The aVF lead was used as the Y lead. The Z lead was positioned on the precordial center line in the fifth intercostal space. The potential signals obtained through the X, Y, and Z leads were amplified by 1000 times. All signal data were identified using P wave template matching. The P wave-triggered signals of 250 beats during sinus rhythm, excluding any supraventricular or ventricular premature contractions, were integrated without filtering.[11,14] After integration, the noise level was $<1\ \mu V$.

Table 1
Clinical characteristics in the three groups.

	control group (n = 23)	PAF group (n = 21)	Brugada group (n = 21)	p value
Age (years)	54 ± 9	55 ± 10	54 ± 11	NS
Male (n)	17	18	20	NS
CTR (%)	45 ± 4	47 ± 5	45 ± 4	NS
LAD (mm)	34 ± 3	35 ± 3	34 ± 4	NS
LVEF (%)	72 ± 7	73 ± 7	73 ± 6	NS

The values are presented as the mean ± SD or n (%).
PAF, paroxysmal atrial fibrillation; CTR, cardiothoracic ratio.
LAD, left atrial dimension; LVEF, left ventricular ejection fraction.

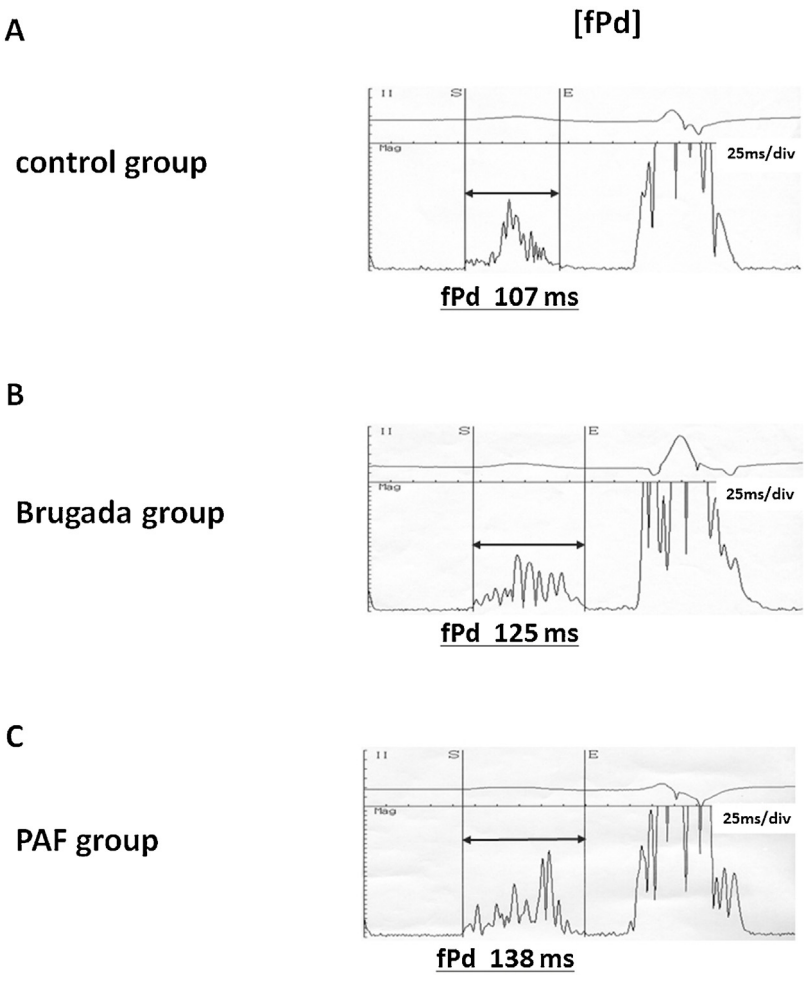

Fig. 1. Representative recordings of the P wave signal-averaged electrogram.
A. The fPd (107 ms) in a patient in the control group.
B. The fPd (125 ms) in a patient in the Brugada group.
C. The fPD (138 ms) in a patient in the PAF group.
fPD, filtered P wave duration; PAF, paroxysmal atrial fibrillation.

2.4. SAECG analysis

For the SAECG analysis, the averaged P wave-triggered signals were filtered through a Butterworth band pass filter at 40–300 Hz, according to the conventional method.[11,14] A spatial vector magnitude ECG was compiled with the X, Y, and Z leads. A computer cursor was used to identify the onset and offset of the P waves. The onset and offset of the P waves were defined as the point at which the voltage of the atrial signal exceeded 1 μV in the TP segment and the point at which the voltage returned to the 1 μV level, respectively. The fPd was measured for the analysis of the P waves.

2.5. Electrophysiological study

An electrophysiological study (EPS) was performed in 17 of the 21 patients in the Brugada group. Quadripolar catheters were placed at the high right atrium (HRA) and right ventricular (RV) apex or outflow tract through the right femoral vein. Programmed ventricular stimulation was performed with 1–3 extrastimuli from the right ventricular apex or outflow tract at basic cycle lengths of 600 or 500 and 400 ms. The S2, S3, and S4 were decremented to the effective refractory period (ERP) or 200 ms. Programmed atrial stimulation with a single extrastimulus from the HRA was also performed in 14 out of 17 patients at basic cycle lengths of 750 or 600 ms. The S2 was decremented to the ERP or 200 ms.

2.6. Statistical analysis

All data are expressed as the mean ± SD. Student's *t*-tests were used to compare the variables and a p value of < 0.05 was considered statistically significant.

3. Results

3.1. SAECGs in the three groups

Fig. 1 shows representative examples of the fPd in the three groups. The mean fPd in the control, Brugada, and PAF groups was 113.9 ± 12.9 ms, 125.3 ± 15.0 ms, and 137.1 ± 16.3 ms, respectively (Fig. 2). The fPd in the PAF group was significantly longer than that in the control ($p < 0.01$) and Brugada groups ($p < 0.05$). The fPd in the Brugada group was significantly longer than that in the control group ($p < 0.05$) and significantly shorter than that in the PAF group ($p < 0.05$).

3.2. SAECGs in the subgroups of the Brugada group

The fPd values for the subgroups in the Brugada group are shown in Fig. 3. Of the 21 patients in the Brugada group, 17 underwent an EPS. Eleven patients had induced ventricular fibrillation (VF), and an implantable cardioverter defibrillator (ICD) was implanted in those patients. In 11 patients with induced VF, five had a coved-type ST segment elevation and six a saddle-back type ST segment elevation. Four patients had no history of syncope while seven suffered from syncope. The fPd in the patients with and without a history of syncope was similar (122.7 ± 18.2 ms, 127.3 ± 12.3 ms; p = 0.5), and there was no significant difference in the fPd between the patients with and without induced VF (127.0 ± 16.7 ms, 122.4 ± 14.3 ms; p = 0.2) (Fig. 3A and B). Among the 11 patients without a history of syncope, five had a coved-type ST segment elevation and six a saddle-type ST segment elevation. On the other hand, two had a coved-type ST segment elevation and eight a saddle-back type ST segment elevation among 10 patients with syncope. The ECG in the patients with Brugada syndrome, which was performed at the same time as the SAECG, exhibited a coved-type ST segment elevation in seven and a saddle back-type ST segment elevation in 14 patients. There was no significant difference in the fPd between the patients with a coved-type or saddle back-type ST segment elevation (127.9 ± 17.5 ms, 123.7 ± 14.4 ms; p = 0.6) as shown in Fig. 3C.

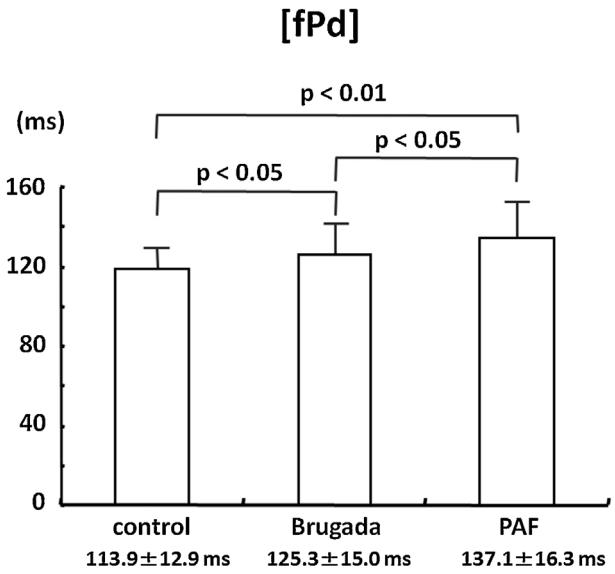

Fig. 2. The mean fPd of the control, Brugada, and PAF groups was 113.9 ± 12.9 ms, 125.3 ± 15.0 ms, and 137.1 ± 16.3 ms, respectively. The fPd in the PAF group was significantly longer than that in the control group ($p < 0.01$) and Brugada group ($p < 0.05$). The fPd in the Brugada group was significantly longer than that in the control group ($p < 0.05$) and shorter than that in the PAF group ($p < 0.05$). The abbreviations are the same as those in Fig. 1.

AF was induced in 4 of 14 patients (29%). There was no significant difference in the fPd (114.5 ± 7.6 ms vs 124.9 ± 16.8 ms; p = 0.2) between the patients with and without induced AF (Fig. 3D). All four patients with induced AF had a saddle back-type ST segment elevation while four had a coved-type ST segment elevation and six a saddle back-type ST segment elevation among the 10 patients without induced AF.

4. Discussion

4.1. Atrial arrhythmogenic substrate of paroxysmal atrial fibrillation

It has been reported that patients with PAF have atrial vulnerability. Tai et al.[20] reported increased delays in the individual potentials of fractionated atrial electrograms during the EPS. Pytkowski et al.[21] reported that the intra-atrial conduction delay after atrial extrastimulus pacing started earlier and the extent of the intra-atrial conduction delay is longer in PAF patients than the control. The P wave on the SAECG can detect subtle abnormalities of the intra-atrial conduction. Previous clinical studies have demonstrated a prolonged fPd in patients with PAF.[10–14] The mean fPd in patients with PAF was 137 ± 16 ms in the present study, which was similar to the 137 ± 14 ms reported by Fukunami et al.[11] and 135 ± 8 ms reported by Stafford et al.[13] Thus, an atrial arrhythmogenic substrate has been demonstrated in patients with PAF.

4.2. Ventricular arrhythmogenic substrate in Brugada syndrome

Mutations in the SCN5A gene, which is the gene encoding for the α subunit of the sodium channels, have been discovered in patients with Brugada syndrome.[5] SCN5A causes slow recovery of the sodium channels from an inactive state, which contributes to a conduction delay at the ventricular level. Late potentials in the QRS segment on the SAECG are known to reflect a ventricular arrhythmogenic substrate in Brugada syndrome.[15–18,22] The

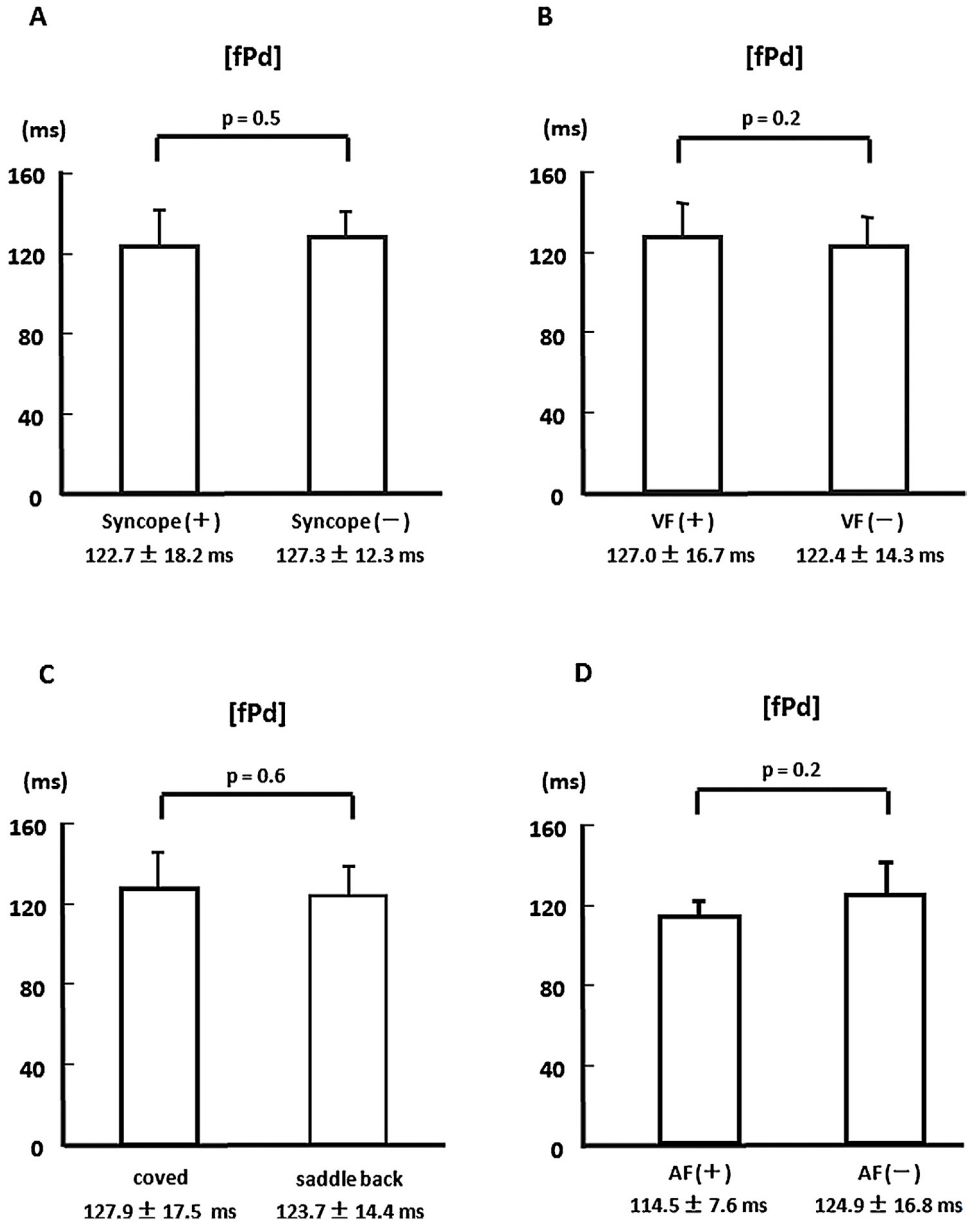

Fig. 3. The fPd in the subgroups of the Brugada group.
A. There was no significant difference in the fPd between the patients with and without a history of syncope (122.7 ± 18.2 ms, 127.3 ± 12.3 ms; p = 0.5).
B. There was no significant difference in the fPd between the patients with and without induced VF in the EPS (127.0 ± 16.7 ms, 122.4 ± 14.3 ms; p = 0.2).
C. There was no significant difference in the fPd between the patients with a coved- and saddle back-type ST segment elevation (127.9 ± 17.5 ms, 123.7 ± 14.4 ms; p = 0.6).
D. There was no significant difference in the fPd between the patients with and without induced AF in the EPS (114.5 ± 7.6 ms, 124.9 ± 16.8 ms; p = 0.2).
AF, atrial fibrillation; VF, ventricular fibrillation
Other abbreviations are the same as those in Fig. 1.

mechanism of the late potentials and fractionated potentials is estimated to be abnormal repolarization within the anterior aspect of the RV epicardium in experimental models of Brugada syndrome,[23] which causes ventricular arrhythmias.

4.3. Atrial arrhythmias in Brugada syndrome

A high incidence of AF (6%–39%) in patients with Brugada syndrome has been reported in previous studies.[24–28] Sacher et al.[26] found that 32 of 220 patients with Brugada syndrome and an ICD had supraventricular arrhythmias, and AF was observed in 23 patients (10%). Itoh et al.[27] reported that PAF occurred in nine of 30 patients (30%) with Brugada syndrome. Bordachar et al.[28] reported that the incidence of atrial arrhythmias in patients with Brugada syndrome was 20% (12 of 59 patients); during a median follow-up term of 32 months 10 patients presented with PAF, one with atrial flutter, and one with both PAF and atrial flutter. In the present study, two of 21 patients (10%) had a history of PAF.

4.4. Atrial vulnerability of Brugada syndrome

It has been reported that mutations of SCN5A increase the atrial vulnerability in Brugada patients without PAF, and was demonstrated using an EPS. Morita et al.[6] found a more increased

interatrial conduction time, increased repetitive atrial firing and AF inducibility, and prolonged duration of the atrial potentials in Brugada syndrome patients than that in the control patients. EPSs in other patients with Brugada syndrome demonstrated an atrial vulnerability, including an AF inducibility,[7,29] increased intra-atrial conduction time[30] and increased dispersion of the atrial potentials.[29]

In this study, AF was induced in 4 of 14 patients (29%) and the AF induction rate was lower than that in the previous studies. Some studies have reported AF inducibility in half of the patients with Brugada syndrome.[6,7,29] Programmed atrial stimulation with single extrastimuli from the HRA was performed at a basic cycle length of 600 ms or 750 ms. Other previous studies performed atrial extrastimulation at basic cycle lengths of 400 or 500 ms in addition to 600 ms,[7,29] which might be the reason for the higher AF induction rate compared to that in our study. The same basic cycle length of 600 ms in Norihisa et al.'s report[30] showed a lower AF induction rate (35%), which was similar to that in our study.

4.5. The fPD in Brugada syndrome

The fPD in Brugada syndrome has been reported to be longer than that in control patients.[7] However, the relationship of the fPD between the Brugada and PAF groups remains unclear. In the present study, the relationship of the fPd between the control, Brugada, and PAF groups was demonstrated. To the best of our knowledge, this is the first study to clarify this relationship.

The mechanism of the longer fPd in Brugada syndrome has not been accurately elucidated. A previous study reported that one of the factors affecting the P wave Duration was the intra-atrial conduction time.[31] The intra-atrial conduction delay in patients with Brugada syndrome was longer than that in the control patients.[32] The incidence of AF in this syndrome has been reported to be 6% to 39%.[24–28] Therefore, the presumption that a sodium channel dysfunction might exist in the atrium as well as the ventricle was based on the results of the longer fPD on the SEACG, intra-atrial conduction delay, and high incidence of AF described above.

4.6. The characteristics of the subgroups of Brugada syndrome

Previous studies have shown that spontaneous AF is closely linked to documented VF.[28,33,34] These findings suggest that the electrophysiological vulnerability increases with the progression of the disease. Moreover, atrial structural remodeling occurs in patients with Brugada syndrome, even in the absence of spontaneous AF.[30] In the present study there was no significant difference in the fPd in the Brugada patients with and without a history of syncope, induced AF or VF in the EPS. Furthermore, there was no difference in the fPd in the Brugada syndrome patients with a coved- or saddle back-type ST segment elevation. Furukawa at el.[35] also demonstrated a prolonged fPd in Brugada patients. However, there was no significant difference in the fPd of the patients with and without a history of syncope, or a coved- and saddle back-type ST segment elevation. Those findings are similar to those of the present study.

Based on the results of the previous studies and present study, the following mechanism is proposed in patients with Brugada syndrome. First, an atrial and ventricular conduction delay may occur, as was demonstrated by the prolonged fPd and fQRSd on the SAECG, and prolonged intra-atrial conduction or intra-ventricular conduction time in the EPS. Second, AF or VF induced by the EPS may occur in the absence of spontaneous AF or VF. The spontaneous occurrence of AF or VF may be the final step in Brugada syndrome. Therefore, an atrial conduction delay, demonstrated using the SAECG or an EPS, may already exist, even in patients without a history of syncope or induced AF or VF in the EPS.

5. Limitations

This study had two limitations. First, although there is a well known potential correlation with a susceptibility to AF in Brugada patients, the abnormal fPD on the SAECG was not correlated with the development of AF in this study as only two patients had a history of AF. The patient number in the Brugada group was rather small with 21 patients, which might have affected our results. Moreover, this study was a retrospective analysis, therefore, a prospective analysis should be needed to evaluate the development of AF in Brugada patients with an abnormal fPD. Second, a coved- or saddle back-type ST segment elevation was determined by the ECG at the time of the SAECG. There is some temporal variability in the ECGs in Brugada syndrome patients. Therefore, this timing issue could explain the lack of a difference in the fPd between the patients in the Brugada group with the two types of ST segment elevation.

6. Conclusion

Brugada syndrome is associated with an abnormal P wave on the SAECG. The abnormal P wave identified on the SAECG in patients with Brugada syndrome may have intermediate characteristics between the control and PAF patients.

Conflict of interest disclosures

None.

What is already known?

Late potentials in the QRS segment evaluated by the filtered QRS wave duration (fQRSd) on the signal-averaged electrocardiogram (SAECG) is well known in patients with Brugada syndrome.

What this study adds?

Patients with Brugada syndrome exhibit abnormal P waves on the SAECG and have intermediate characteristics between the control and paroxysmal atrial fibrillation patients.

Acknowledgment

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol*. 1992;20:1391–1396.
2. Alings M, Wilde A. Brugada syndrome: clinical data and suggested pathophysiological mechanism. *Circulation*. 1999;99:666–673.
3. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation*. 2000;101:510–515.
4. Rook MB, Bezzina Alshinawi C, Groenewegen WA, et al. Human SCN5A gene mutations alter cardiac sodium channel kinetics and are associated with the Brugada syndrome. *Cardiovasc Res*. 1999;44:507–517.
5. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998;392:293–296.
6. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol*. 2002;40:1437–1444.
7. Yamada T, Watanabe I, Okumura Y, et al. Atrial electrophysiological abnormality in patients with Brugada syndrome assessed by P-wave signal-averaged ECG and programmed atrial stimulation. *Circ J*. 2006;70:1574–1579.

8. Kanovsky MS, Falcone RA, Dresden CA, Josephson ME, Simson MB. Identification of patients with ventricular tachycardia after myocardial infarction: signal-averaged electrocardiogram, Holter monitoring, and cardiac catheterization. *Circulation*. 1984;70:264–270.
9. Savard P, Rouleau JL, Ferguson J, et al. Risk stratification after myocardial infarction using signal-averaged electrocardiographic criteria adjusted for sex, age, and myocardial infarction location. *Circulation*. 1997;96:202–213.
10. Rosenheck S. Signal-averaged P wave in patients with paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol*. 1997;20:2577–2586.
11. Fukunami M, Yamada T, Ohmori M, et al. Detection of patients at risk for paroxysmal atrial fibrillation during sinus rhythm by P wave-triggered signal-averaged electrocardiogram. *Circulation*. 1991;83:162–169.
12. Yoshida T, Ikeda H, Hiraki T, Kubara I, Ohga M, Imaizumi T. Detection of concealed left sided accessory atrioventricular pathway by P wave signal averaged electrocardiogram. *J Am Coll Cardiol*. 1999;33:55–62.
13. Stafford PJ, Turner I, Vincent R. Quantitative analysis of signal-averaged P waves in idiopathic paroxysmal atrial fibrillation. *Am J Cardiol*. 1991;68:751–755.
14. Hiraki T, Ikeda H, Ohga M, et al. Frequency- and time-domain analysis of P wave in patients with paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol*. 1998;21:56–64.
15. Ikeda T, Sakurada H, Sakabe K, et al. Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. *J Am Coll Cardiol*. 2001;37:1628–1634.
16. Masaki R, Watanabe I, Nakai T, et al. Role of signal-averaged electrocardiograms for predicting the inducibility of ventricular fibrillation in the syndrome consisting of right bundle branch block and ST segment elevation in leads V1-V3. *Jpn Heart J*. 2002;43:367–378.
17. Takami M, Ikeda T, Enjoji Y, Sugi K. Relationship between ST-segment morphology and conduction disturbances detected by signal-averaged electrocardiography in Brugada syndrome. *Ann Noninvasive Electrocardiol*. 2003;8:30–36.
18. Takagi A, Nakazawa K, Sakurai T, Nanke T, Miyake F. Prolongation of LAS40 (duration of the low amplitude electric potential component ($<$ 40 microV) of the terminal portion of the QRS) induced by isoproterenol in 11 patients with Brugada syndrome. *Circ J*. 2002;66:1101–1104.
19. Simson MB, Euler D, Michelson EL, Falcone RA, Spear JF. Moore EN: Detection of delayed ventricular activation on the body surface in dogs. *Am J Physiol*. 1981;241:H363–369.
20. Tai CT, Chen SA, Tzeng JW, et al. Prolonged fractionation of paced right atrial electrograms in patients with atrial flutter and fibrillation. *J Am Coll Cardiol*. 2001;37:1651–1657.
21. Pytkowski M, Jankowska A, Maciag A, et al. Paroxysmal atrial fibrillation is associated with increased intra-atrial conduction delay. *Europace*. 2008;10:1415–1420.
22. Ikeda T, Sakurada H, Sakabe K, et al. Assessment of noninvasive markers in identifying patients at risk in the Brugada syndrome: insight into risk stratification. *J Am Coll Cardiol*. 2001;37:1628–1634.
23. Szel T, Antzelevitch C. Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. *J Am Coll Cardiol*. 2014;63:2037–2045.
24. Eckardt L, Kirchhof P, Loh P, et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J Cardiovasc Electrophysiol*. 2001;12:680–685.
25. Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with brugada syndrome: multicenter study in Japan. *J Cardiovasc Electrophysiol*. 2007;18:1244–1251.
26. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation*. 2006;114:2317–2324.
27. Itoh H, Shimizu M, Ino H, et al. Arrhythmias in patients with Brugada-type electrocardiographic findings. *Jpn Circ J*. 2001;65:483–486.
28. Bordachar P, Reuter S, Garrigue S, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J*. 2004;25:879–884.
29. Choi KJ, Kim J, Kim SH, Nam GB, Kim YH. Increased dispersion of atrial repolarization in Brugada syndrome. *Europace*. 2011;13:1619–1624.
30. Toh N, Morita H, Nagase S, et al. Atrial electrophysiological and structural remodeling in high-risk patients with Brugada syndrome: assessment with electrophysiology and echocardiography. *Heart Rhythm*. 2010;7:218–224.
31. Darbar D, Jahangir A, Hammill SC, Gersh BJP. wave signal-averaged electrocardiography to identify risk for atrial fibrillation. *Pacing Clin Electrophysiol: PACE*. 2002;25:1447–1453.
32. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol*. 2002;40:1437–1444.
33. Kusano KF, Taniyama M, Nakamura K, et al. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol*. 2008;51:1169–1175.
34. Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. *Europace*. 2007;9:947–950.
35. Furukawa Y, Yamada T, Okuyama Y, et al. Increased intraatrial conduction abnormality assessed by P-wave signal-averaged electrocardiogram in patients with Brugada syndrome. *Pacing Clin Electrophysiol*. 2011;34:1138–1146.