ventricular salvos and cycle length of the VT, (2) maximum number of VAs during a 10-second period, and (3) VA score (1–4), which is defined as the severity of the worst VA during exercise as described previously.[18] 1 = no or isolated VA; 2 = bigeminal VA and/or frequent VA ($\geq$10 per minute); 3 = couplet; and 4 = VT ($\geq$3 successive VAs). The VA score of 1 was considered to indicate complete suppression of VAs. Less dramatic improvements in VA scores were considered to indicate partial suppression.

Follow-up

All patients were followed up at outpatient clinics every 1–3 months, and a 12-lead ECG was recorded. We investigated the incidence of arrhythmic events, defined as syncope, aborted cardiac arrest, or sudden cardiac death, and the side effects of flecainide through examination of medical history, physical findings, blood tests, 12-lead ECG, chest radiograph, and/or echocardiograph.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD or numbers and percentages, as appropriate. The Student t test was used to compare continuous variables, and the χ^2 test was used to compare categorical variables. A P value of <.05 was considered statistically significant.

Results

Patient characteristics

The study population consisted of 10 genotype-confirmed ATS probands who received oral flecainide from 6 Japanese institutes (Table 1). Seven patients were female probands. Their mean age at the beginning of flecainide therapy was 27 $\pm$ 11 years (range 9–47 years). Our cohort includes 5 patients (patients 3–6 and 8) with a family history of ATS, whose genotypes and phenotypes are presented in the Online Supplemental Figure. Eight patients (80%) showed

dysmorphic features, and 2 (20%) had a history of periodic paralysis. Two patients (20%) had both dysmorphic features and periodic paralysis.

No structural heart disease was observed by echocardiography in any patient. All patients had VAs documented by 12-lead ECG, Holter recording, and/or exercise testing. Bidirectional VT had been documented in all patients. Six patients were symptomatic, exhibiting syncope (n = 5), palpitations (n = 2), or dizziness (n = 2). There were no cases of aborted cardiac arrest or with family history of sudden cardiac death.

Nine patients were found to have missense mutations in 4 residues (R67G/Q/W, R218Q/W, G300V, and G301T), and 1 has an insertion (76insT) in the *KCNJ2* gene. All these are located in the N or C terminus, and 7 of these mutations have been previously reported.[19]

Medical therapy

A total of 7 patients had been treated with multiple drugs before flecainide. The drugs previously administered were β-blockers, namely, bisoprolol (n = 2), atenolol (n = 2), propranolol (n = 1), and propranolol + metoprolol (n = 1); sodium channel blockers, namely, disopyramide (n = 1), mexiletine (n = 1), and pilsicainide (n = 1); and the calcium channel blocker verapamil (n = 1). All of them failed to suppress VAs.

Flecainide was administered at a dose of 200 mg/d in 3 patients, at 150 mg/d in 2, and at 100 mg/d in 5 (mean dosage 140 $\pm$ 46 mg/d). In 4 patients, β-blockers were continued after flecainide.
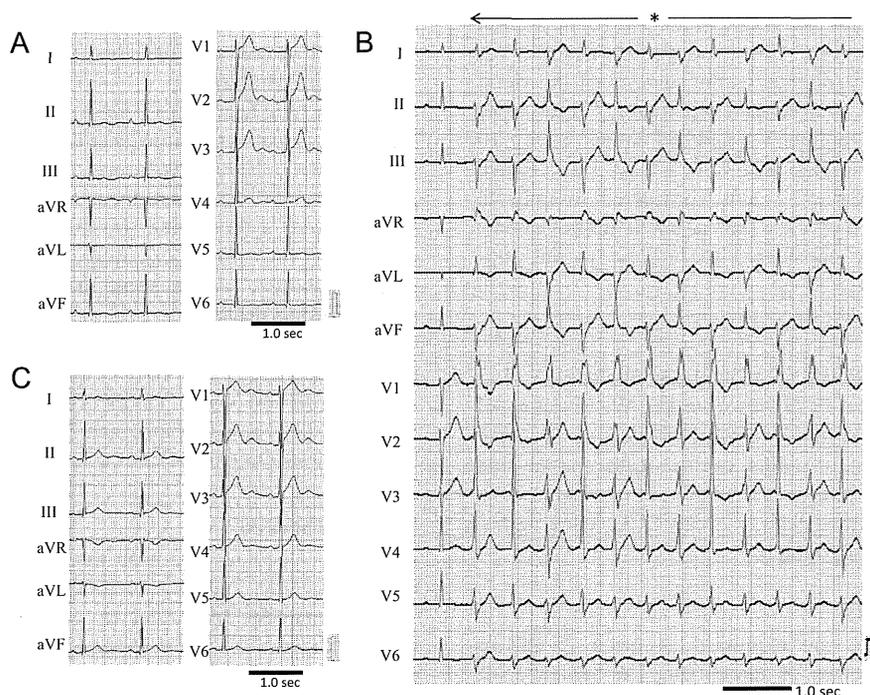
Twelve-lead ECG

Figure 1 shows representative 12-lead ECGs of a 24-year-old patient (patient 4) at baseline (Figures 1A and 1B) and after flecainide therapy (Figure 1C). Although this patient had been treated with propranolol (60 mg/d) and verapamil (240 mg/d), frequent VAs including bidirectional VT were still

Table 1   Clinical, mutational, and electrocardiographic characteristics of all probands with Andersen-Tawil syndrome

Patient no.	Mutation	Age/ sex	BW (kg)	Symptom	Syncope	FH	Dysmorphism/ periodic paralysis	Bi-VT and/or poly-VT	Flecainide dose (mg/d, mg/kg)	Flecainide concentration (ng/mL)	Medical treatment at baseline/concomitant with flecainide
1	M301T	27/F	42	+	−	−	+/−	+	150, 3.6	278	Bisoprolol/bisoprolol
2	R67W	41/F	57	+	+	−	+/−	+	200, 3.5	NA	Bisoprolol, disopyramide/ bisoprolol, nicorandil
3	G300V	29/F	47	+	+	+	+/−	+	200, 4.3	507	Atenolol/atenolol
4	G300V	24/M	61	+	+	+	+/−	+	200, 3.3	324	Propranolol, verapamil/ propranolol
5	R218W	13/M	35	−	−	+	+/+	+	100, 2.9	NA	Propranolol, metoprolol/ none
6	R67Q	23/M	53	−	−	+	−/−	+	100, 1.9	NA	Atenolol, mexiletine/ none
7	R218Q	27/F	46	−	−	−	−/−	+	100, 2.2	347	None/none
8	R218W	47/F	46	+	+	+	+/+	+	150, 3.3	532	Pilsicainide/none
9	76insT	9/F	26	−	−	−	+/−	+	100, 3.8	NA	None/none
10	R67G	25/F	45	+	+	−	+/−	+	100, 2.2	NA	None/none

Bi-VT = bidirectional ventricular tachycardia; BW = body weight; F = female; FH = family history; M = male; NA = not applicable; Poly-VT = polymorphic ventricular tachycardia; + = presence; − = absence.

Figure 1   Twelve-lead ECGs recorded from a 24-year-old male proband (patient 4) with *KCNJ2* mutations before (panels A and B) and after (panel C) flecainide therapy. **A:** Before flecainide therapy (propranolol 60 mg/d and verapamil 240 mg/d), the PR interval (280 ms) indicated first-degree atrioventricular block, the corrected QT interval was normal (<440 ms), and the U wave was widely distributed in leads II, aVF, and V_1-V_5. An enlarged U wave (wave amplitude $\geq$ 0.2 mV) was observed in leads V_2 and V_3, and the corrected QU interval was 663 ms. **B:** Bidirectional VT (cycle length 480 ms) in the 12-lead ECG at baseline (asterisk). The QRS complexes showed alternating polarities, and a right bundle branch block pattern was shown in VT beats. **C:** Twelve-lead ECG after the administration of flecainide (200 mg/d) in addition to propranolol (60 mg/d). Verapamil was discontinued after VA suppression by flecainide in this patient, and the PR interval was reduced. An enlarged U wave persists and remains widely distributed even after VA suppression by the administration of flecainide. ECG = electrocardiogram; VA = ventricular arrhythmia; VT = ventricular tachycardia.

observed (Figure 1B). After the administration of flecainide, the total number of VAs was remarkably reduced from 10,767 to 36 per day, although the U-wave amplitude and its distribution on the 12-lead ECG were unchanged.

Table 2 summarizes the changes in ECG parameters in all patients with ATS. Flecainide therapy caused no significant difference in heart rate, PQ interval, QRS duration, QTc interval, QUc interval, T- and U-wave amplitudes and durations, frequency of the enlarged U wave, or number of leads recording U waves. The U/T-wave ratio was also unchanged after flecainide therapy.

Holter recording

Twenty-four-hour Holter recordings demonstrated that flecainide therapy significantly and consistently reduced the total number of VAs (38,407 $\pm$ 19,956 to 11,196 $\pm$ 14,773 per day; $P = .03$; Figure 2A) and the number of the longest ventricular salvos (23 $\pm$ 19 to 5 $\pm$ 5 per day; $P = .01$; Figure 2B). Flecainide significantly reduced the number of VT episodes (1175 $\pm$ 1163 to 60 $\pm$ 167; $P = .008$): in 7 patients, the total number of VAs was reduced by more than 70% from the number at baseline; in 4 of these, flecainide completely eliminated VT. Flecainide therapy did not alter the cycle length of VAs (458 $\pm$ 72 to 488 $\pm$ 58 ms; $P = .35$).

Several Holter recordings or TMTs after flecainide and/or concomitant medication (β-blockers and verapamil) were performed in 6 patients (patients 1–5 and 8). As shown in the Online Supplemental Table, the total number of VAs per day and the longest ventricular salvos per day of each time were consistently reduced after flecainide therapy.

TMT

Exercise capacity (peak workload) was not different at baseline and after flecainide therapy (12.5 $\pm$ 4.2 METS vs 13.3 $\pm$ 4.1 METS; $P = .68$). The peak heart rate during exercise was also unchanged at baseline and after flecainide therapy (155 $\pm$ 19 beats/min vs 160 $\pm$ 23 beats/min; $P = .60$). Figure 3 shows a representative 12-lead ECG of patient 4 during the TMT before (baseline) (Figure 3A) and after (Figure 3B) flecainide therapy. In this case, flecainide therapy remarkably suppressed an exercise-induced bidirectional VT. In summary, the VA score during the TMT was improved in 9 of 10 patients after flecainide therapy. In particular, VA scores of 7 patients were improved by more than 2 levels (Figure 4A). Furthermore, the maximum number of VAs in any 10 seconds during the TMT was significantly reduced after flecainide therapy (Figure 4B). Several TMTs after flecainide therapy were also performed

Table 2 Electrocardiographic changes after flecainide therapy in patients with Andersen-Tawil syndrome

Variable	Baseline	Flecainide	P
Heart rate (beats/min)	68 ± 15	69 ± 17	.97
PQ interval (ms)	173 ± 41	178 ± 24	.74
QRS duration (ms)	93 ± 19	98 ± 18	.55
QTc interval (ms)	432 ± 26	448 ± 34	.26
QUc interval (ms)	667 ± 43	679 ± 35	.50
T-wave amplitude (mV)	0.55 ± 0.25	0.43 ± 0.20	.24
T-wave duration (ms)	290 ± 34	288 ± 43	.91
U-wave amplitude (mV)	0.21 ± 0.05	0.23 ± 0.05	.49
U-wave duration (ms)	215 ± 22	213 ± 25	.85
U/T-wave amplitude ratio at the highest amplitude U-wave lead	0.50 ± 0.18	0.62 ± 0.20	.17
Enlarged U-wave, no. of patients (%)	8 (80)	9 (90)	.53
U-wave distribution, no. of leads	4.6 ± 1.9	4.7 ± 1.9	.91

Values are presented as mean ± SD or as otherwise indicated.
QTc interval = corrected QT interval by Bazett's formula; QUc interval = corrected QU interval by Bazett's formula.

in 4 patients (patients 1–4), and VA scores and the maximum number of VAs during 10 seconds were reduced consistently in 3 patients except for patient 3 (see the Online Supplemental Table). These findings strongly suggested that flecainide may suppress exercise-induced lethal VAs in patients with ATS.

Follow-up
During a mean follow-up of 23 ± 11 months after starting oral flecainide therapy, no patients had arrhythmic events. No symptoms such as syncope or palpitations were observed in any patient. One patient experienced leg fatigue after the administration of flecainide at 200 mg/d; this symptom was improved after the dose was reduced to 150 mg/d. No other side effects were observed in any patient during follow-up.

Discussion
Main findings
There were several findings in this study. First, flecainide therapy decreased the number of VAs and the maximum number of VA salvos, although it caused no significant

changes in any ECG parameters. It was thus effective for the suppression of VAs in patients with ATS with KCNJ2 mutations. Second, flecainide therapy was safe in patients with ATS over a middle-term follow-up period. Therefore, flecainide may reduce the risk of sudden cardiac death in patients with ATS.

Medication for VAs in patients with ATS with KCNJ2 mutations
KCNJ2 encodes the α subunit of inward rectifier potassium channels (Kir2.1), which carry a critical component of the cardiac inward rectifying K^+ current (I_{K1}).[20,21] The I_{K1} regulates the terminal phase of repolarization and maintains the resting membrane potential in cardiomyocytes and skeletal muscle.[20,22,23] In this study, we observed 8 mutations (including 3 novel ones) in 5 residues of the KCNJ2 gene. Although we did not perform a functional analysis, most of these (R67Q, R67W, R218Q, R218W, and G300V) have been reported as loss-of-function mutations resulting in dominant-negative suppression of Kir2.1 channel function,[3–6] which prolongs the action potential duration (APD) across the ventricular wall and destabilizes the resting membrane
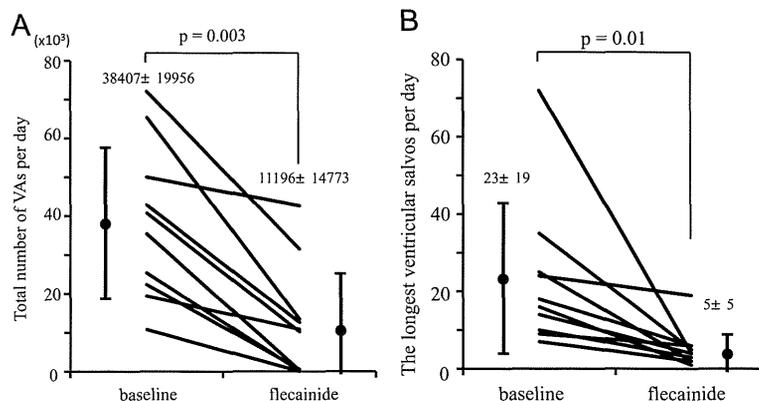
Figure 2 Total number of VAs and number of the longest ventricular salvos per day from a 24-hour Holter recording before (baseline) and after flecainide therapy. **A:** The total number of VAs per day was reduced after flecainide therapy in all patients, most notably in 7 patients whose VA counts were reduced by more than 70% from the baseline level. **B:** The number of the longest ventricular salvos per day was also reduced after flecainide therapy in all patients. Abbreviations as in Figure 1.
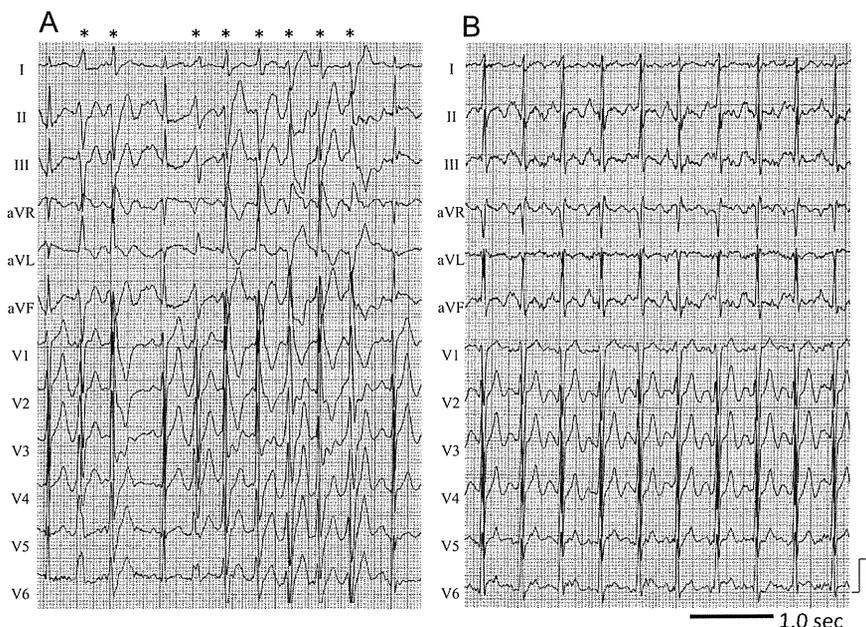
Figure 3   Twelve-lead ECG during the TMT before (baseline) (**A**) and after (**B**) flecainide therapy in a patient with ATS (patient 4). **A:** At baseline (propranolol 60 mg/d and verapamil 240 mg/d), frequent premature ventricular complexes and nonsustained VTs (the longest ventricular salvo was 6 beats) (asterisk) were observed during exercise. **B:** Flecainide (200 mg/d) in addition to propranolol (60 mg/d) suppressed exercise-induced VAs. TMT = treadmill exercise test; other abbreviations as in Figure 1.

potential.[4,24] APD prolongation also elicits an increase in calcium influx, leading to intracellular calcium overload. In addition, subsequent spontaneous calcium release may depolarize the membrane potential to the threshold of L-type calcium channel via transient inward currents carried by the Na^+-Ca^{2+}exchanger.[4,25,26] APD prolongation, instability of the resting membrane potential, and calcium overload result in the onset of delayed afterdepolarization.[4,24]

β-Blockers and calcium channel blockers had been regarded as the principal drugs for VAs in patients with ATS.[10,11,27] Studies on successful therapy using β-blockers and/or calcium channel blockers in patients with ATS were, however, limited to case reports, and the efficacy of these drugs were controversial. Bokenkamp et al[13] reported that β-blockers, the mainstay for other types of long QT syndrome, are ineffective for the suppression of VAs in patients with
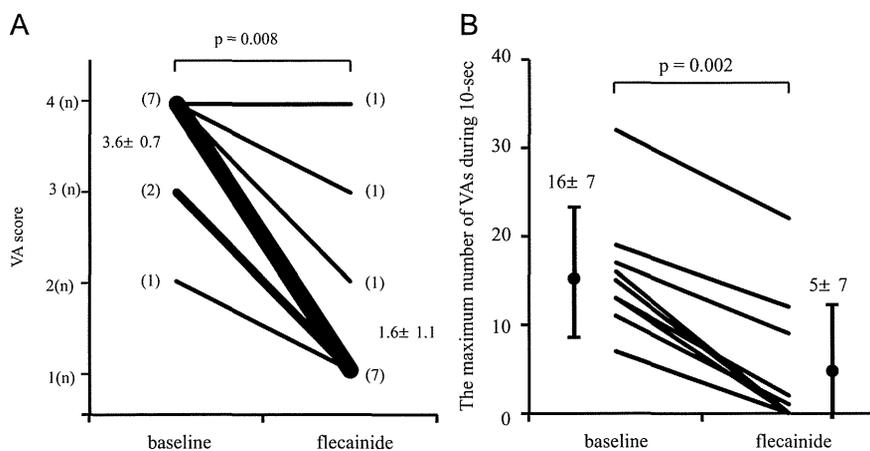
Figure 4   Effect of flecainide on exercise-induced VAs. **A:** VAs during the TMT are shown by VA scores: 1 = no or isolated VAs, 2 = bigeminal VAs and/or frequent VAs ($\geq$10 per minute), 3 = couplets, and 4 =VT ($\geq$3 successive VAs). VAs during the TMT are compared before (baseline) and after flecainide therapy in probands with ATS with *KCNJ2* mutations. The line thickness indicates the number of patients. The VA score was improved by flecainide therapy in 9 of 10 patients (90%). Flecainide therapy reduced the VA score from 3.6 $\pm$ 0.7 to 1.6 $\pm$ 1.1 (*P* = .008). **B:** The maximum number of VAs during any 10-second interval during the TMT at baseline and after flecainide therapy. Flecainide therapy reduced the maximum number of VAs from 16 $\pm$ 7 to 5 $\pm$ 7 (*P* = .002) during any 10-second interval. Abbreviations as in Figures 1 and 3.

ATS. Similarly, the efficacy of calcium channel blockers is uncertain; in addition, calcium channel blockers have risk of torsades de pointes and syncope in patients with ATS.[10,11,13] In this study, although β-blockers and/or calcium channel blockers were administered in 6 patients to prevent VAs, these drugs could not suppress VAs. Flecainide is a potent antiarrhythmic drug that can be used to suppress VAs in patients with ATS,[8,13] although a systematic evaluation of its efficacy and safety during follow-up remained unclear. Delannoy et al[7] retrospectively investigated cardiac characteristics and prognosis in patients with ATS, in which the prognosis in patients with ATS was relatively good, and the combination therapy of flecainide with β-blockers was efficient to prevent severe arrhythmic events. A recent case report[28] suggested that the combined use of verapamil and flecainide was effective for the suppression of VAs in patients with ATS.

Here, we prospectively demonstrated the efficacy of flecainide in detail by using 24-hour Holter recording and TMT as well as its safety over a middle-term follow-up period in patients with ATS. In patient 2, the combination therapy of flecainide and β-blockers may be more effective for the suppression of VAs in patients with ATS than was flecainide or β-blocker treatment alone (see the Online Supplemental Table). Although we showed that VAs were suppressed by flecainide treatment in patients with ATS, the reduction of VAs might not be sufficient in some patients. One possible explanation was that the dose of flecainide might be smaller in these patients because flecainide dose-dependently improved VAs in 3 (patients 1, 4, and 8) of 4 patients, although flecainide was less effective in 1 patient (patient 3) even at the higher dose (see the Online Supplemental Table).

Mechanisms of flecainide therapy

The mechanism underlying the suppression of VAs by flecainide in patients with ATS is not fully understood. One possible explanation is that the inhibition of the sodium channel may directly suppress a trigger of arrhythmia and/or indirectly inhibit the Na^+-Ca^{2+} exchange, resulting in reduced likelihood of intracellular calcium overload and decreased delayed afterdepolarization.[29] As an alternative explanation, Caballero et al[21] have reported that flecainide increases Kir2.1 channels, which increase I_{K1} as recorded in ventricular myocytes. In this study, however, as flecainide did not normalize the QU interval or the U-wave amplitude, the effect of flecainide on increasing I_{K1} seems to be not directly involved in the suppression of VAs.

Another possible mechanism underlying the antiarrhythmic effect of flecainide is a direct effect on ryanodine receptor 2 (RyR2). Some KCNJ2 mutation carriers lack the ATS phenotype but share the catecholaminergic polymorphic ventricular tachycardia (CPVT).[17,19,30] Although it is not clear whether exercise is a trigger of VAs in patients with ATS,[31] 5 of 10 patients had experienced syncope during exercise in this study.

Similar exercise-induced bidirectional VT is often observed in both patients with ATS and CPVT. Watanabe et al[32] reported that flecainide not only blocked cardiac sodium channels but also directly inhibited RyR2, thus preventing CPVT. These findings suggest that flecainide may affect calcium leakage from RyR2, resulting in the suppression of VAs in patient with ATS as well as the suppression in patients with CPVT.

Study limitations

First, this study have evaluated the efficacy of flecainide in the suppression of VAs using 24-hour Holter recording and TMT, but whether this short-term elimination of VAs contributes to suppress the subsequent cardiac events in this syndrome is still unclear. In addition, patients with ATS without flecainide therapy have not been included in this study, which might raise a bias of patient selection. Therefore, further investigations are necessary to show the long-term efficacy of flecainide for cardiac events in patients with ATS.

Second, our study population of KCNJ2-positive patients with ATS was relatively small because of the rarity. Larger numbers of patients with KCNJ2 mutations are needed to evaluate the efficacy and safety of flecainide therapy for VAs in patients with ATS. There appear to be several "hot spots" for pathogenic mutations, including, notably, the arginine amino acids at positions 67 and 218 in the N terminus and C terminus, respectively[19]; these were also included in this cohort study. Therefore, flecainide may be effective for the suppression of exercise-induced VAs in many patients with ATS with KCNJ2 mutations.

Third, approximately 40% of patients with the phenotypic features of ATS do not have KCNJ2 mutations,[31,33] suggesting the presence of other causative genes such as KCNJ5.[34] We did not assess the efficacy of flecainide therapy in clinical ATS cases without KCNJ2 mutations. Finally, a family with ATS and dilated cardiomyopathy has previously been reported,[35] but this study did not include such patients with left ventricular dysfunction. Therefore, we could not assess the efficacy and safety of flecainide in ATS with left ventricular dysfunction.

Conclusion

This multicenter study suggests that oral flecainide therapy is an effective and safe means of suppressing VAs in patients with ATS with KCNJ2 mutations, though the U-wave amplitude remained unchanged by flecainide. Flecainide with or without conventional drug therapy should be considered for VA suppression in patients with ATS.

Appendix
Supplementary data

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.hrthm.2014.12.009.

References

1. Andersen ED, Krasilnikoff PA, Overvad H. Intermittent muscular weakness, extrasystoles, and multiple developmental anomalies. A new syndrome? Acta Paediatr Scand 1971;60:559–564.

2. Tawil R, Ptacek LJ, Pavlakis SG, DeVivo DC, Penn AS, Ozdemir C, Griggs RC. Andersen's syndrome: potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Ann Neurol 1994;35:326–330.

3. Plaster NM, Tawil R, Tristani-Firouzi M, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 2001;105:511–519.

4. Tristani-Firouzi M, Jensen JL, Donaldson MR, et al. Functional and clinical characterization of *KCNJ2* mutations associated with LQT7 (Andersen syndrome). J Clin Invest 2002;110:381–388.

5. Ai T, Fujiwara Y, Tsuji K, Otani H, Nakano S, Kubo Y, Horie M. Novel *KCNJ2* mutation in familial periodic paralysis with ventricular dysrhythmia. Circulation 2002;105:2592–2594.

6. Zhang L, Benson DW, Tristani-Firouzi M, et al. Electrocardiographic features in Andersen-Tawil syndrome patients with *KCNJ2* mutations: characteristic T-U-wave patterns predict the *KCNJ2* genotype. Circulation 2005;111:2720–2726.

7. Delannoy E, Sacher F, Maury P, et al. Cardiac characteristics and long-term outcome in Andersen-Tawil syndrome patients related to *KCNJ2* mutation. Europace 2013;15:1805–1811.

8. Pellizzon OA, Kalaizich L, Ptacek LJ, Tristani-Firouzi M, Gonzalez MD. Flecainide suppresses bidirectional ventricular tachycardia and reverses tachycardia-induced cardiomyopathy in Andersen-Tawil syndrome. J Cardiovasc Electrophysiol 2008;19:95–97.

9. Peters S, Schulze-Bahr E, Etheridge SP, Tristani-Firouzi M. Sudden cardiac death in Andersen-Tawil syndrome. Europace 2007;9:162–166.

10. Kannankeril PJ, Roden DM, Fish FA. Suppression of bidirectional ventricular tachycardia and unmasking of prolonged QT interval with verapamil in Andersen's syndrome. J Cardiovasc Electrophysiol 2004;15:119.

11. Sumitomo N, Shimizu W, Taniguchi K, Hiraoka M. Calcium channel blocker and adenosine triphosphate terminate bidirectional ventricular tachycardia in a patient with Andersen-Tawil syndrome. Heart Rhythm 2008;5:498–499.

12. Erdogan O, Aksoy A, Turgut N, Durusoy E, Samsa M, Altun A. Oral verapamil effectively suppressed complex ventricular arrhythmias and unmasked U waves in a patient with Andersen-Tawil syndrome. J Electrocardiol 2008;41:325–328.

13. Bokenkamp R, Wilde AA, Schalij MJ, Blom NA. Flecainide for recurrent malignant ventricular arrhythmias in two siblings with Andersen-Tawil syndrome. Heart Rhythm 2007;4:508–511.

14. McManis PG, Lambert EH, Daube JR. The exercise test in periodic paralysis. Muscle Nerve 1986;9:704–710.

15. Surawicz B. U wave: facts, hypotheses, misconceptions, and misnomers. J Cardiovasc Electrophysiol 1998;9:1117–1128.

16. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002;106:69–74.

17. Kimura H, Zhou J, Kawamura M, et al. Phenotype variability in patients carrying *KCNJ2* mutations. Circ Cardiovasc Genet 2012;5:344–353.

18. Watanabe H, van der Werf C, et al. Effects of flecainide on exercise-induced ventricular arrhythmias and recurrences in genotype-negative patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2013;10:542–547.

19. Nguyen HL, Pieper GH, Wilders R. Andersen-Tawil syndrome: clinical and molecular aspects. Int J Cardiol 2013;170:1–16.

20. Lopatin AN, Nichols CG. Inward rectifiers in the heart: an update on I(K1). J Mol Cell Cardiol 2001;33:625–638.

21. Caballero R, Dolz-Gaiton P, Gomez R, et al. Flecainide increases Kir2.1 currents by interacting with cysteine 311, decreasing the polyamine-induced rectification. Proc Natl Acad Sci U S A 2010;107:15631–15636.

22. Dhamoon AS, Jalife J. The inward rectifier current (IK1) controls cardiac excitability and is involved in arrhythmogenesis. Heart Rhythm 2005;2:316–324.

23. Nichols CG, Makhina EN, Pearson WL, Sha Q, Lopatin AN. Inward rectification and implications for cardiac excitability. Circ Res 1996;78:1–7.

24. Silva J, Rudy Y. Mechanism of pacemaking in I(K1)-downregulated myocytes. Circ Res 2003;92:261–263.

25. Radwanski PB, Poelzing S. NCX is an important determinant for premature ventricular activity in a drug-induced model of Andersen-Tawil syndrome. Cardiovasc Res 2011;92:57–66.

26. Radwanski PB, Veeraraghavan R, Poelzing S. Cytosolic calcium accumulation and delayed repolarization associated with ventricular arrhythmias in a guinea pig model of Andersen-Tawil syndrome. Heart Rhythm 2010;7:1428–1435. (e1421).

27. Smith AH, Fish FA, Kannankeril PJ. Andersen-Tawil syndrome. Indian pacing Electrophysiol J 2006;6:32–43.

28. Janson CM, Poelzing S, Shah MJ. Combined inhibition of Na^+ and Ca^{2+} channels: a novel paradigm for the treatment of incessant ventricular arrhythmias in Andersen-Tawil syndrome. Heart Rhythm 2014;11:318–320.

29. Fox DJ, Klein GJ, Hahn A, Skanes AC, Gula LJ, Yee RK, Subbiah RN, Krahn AD. Reduction of complex ventricular ectopy and improvement in exercise capacity with flecainide therapy in Andersen-Tawil syndrome. Europace 2008;10:1006–1008.

30. Kawamura M, Ohno S, Naiki N, et al. Genetic background of catecholaminergic polymorphic ventricular tachycardia in Japan. Circ J 2013;77:1705–1713.

31. Tristani-Firouzi M, Etheridge SP. Kir 2.1 channelopathies: the Andersen-Tawil syndrome. Pflugers Arch 2010;460:289–294.

32. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med 2009;15:380–383.

33. Donaldson MR, Yoon G, Fu YH, Ptacek LJ. Andersen-Tawil syndrome: a model of clinical variability, pleiotropy, and genetic heterogeneity. Ann Med 2004;36:92–97.

34. Kokunai Y, Nakata T, Furuta M, et al. A Kir3.4 mutation causes Andersen-Tawil syndrome by an inhibitory effect on Kir2.1. Neurology 2014;82:1058–1064.

35. Schoonderwoerd BA, Wiesfeld AC, Wilde AA, van den Heuvel F, Van Tintelen JP, van den Berg MP, Van Veldhuisen DJ, Van Gelder IC. A family with Andersen-Tawil syndrome and dilated cardiomyopathy. Heart Rhythm 2006;3:1346–1350.

CLINICAL PERSPECTIVES

Andersen-Tawil syndrome (ATS) is a heterogeneous, autosomal dominant genetic or sporadic disorder characterized by ventricular arrhythmias (VAs), periodic paralyses, and dysmorphic features. VAs such as premature ventricular complex, polymorphic ventricular tachycardia (VT), and bidirectional VT in patients with ATS seem to be benign, but rarely lead to sudden cardiac death or tachy-induced cardiomyopathy. β-Blockers and calcium channel blockers have been used to treat VAs in patients with ATS; however, their efficacy is limited. Recently, the sodium channel blocker flecainide has been reported as an effective means for the suppression of VAs in patients with ATS. This multicenter study systematically evaluated the efficacy and safety of oral flecainide for VAs in patients with ATS with *KCNJ2* mutations. The electrocardiographic parameters (QT interval, QU interval, U-wave amplitude, and U/T-wave ratio) were not significantly altered after flecainide therapy, but parameters from the Holter recordings and treadmill exercise test can be used as a marker for the efficacy of flecainide. Moreover, the exercise-induced bidirectional VT or polymorphic VT is observed not only in patients with ATS but also in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). The clinical and electrocardiographic features including U wave is sometimes similar between ATS and CPVT. Flecainide therapy has also been useful for the suppression of VAs in patients with CPVT; thus, it should be available for the prediagnosed patients with ATS or CPVT. Finally, flecainide therapy is safe in patients with ATS without overt left ventricular dysfunction, although the patients in this study were not followed for a long-term period. Therefore, flecainide may reduce risk of sudden cardiac death in patients with ATS.

Electrocardiographic QRS Fragmentation as a Marker for Myocardial Fibrosis in Hypertrophic Cardiomyopathy

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fQRS Predicts Myocardial Fibrosis in HCM. *Introduction:* **Myocardial fibrosis in patients with hypertrophic cardiomyopathy (HCM) usually shows a patchy distribution, which may not be detected by pathological Q waves on 12-lead ECGs. Fragmented QRS complexes (fQRS) reflect intraventricular conduction delay and can be a marker of myocardial fibrosis. We assessed whether fQRS show better correlation with myocardial fibrosis than pathological Q waves in HCM.**

Methods and Results: **This cross-sectional study included 108 patients with HCM who underwent 12-lead ECG and cardiac magnetic resonance imaging with late gadolinium enhancement (LGE-CMR). The number of leads with pathological Q waves was not correlated with the extent of LGE measured at any different standard deviations (SDs) (2, 4, 6, 8, and 10 SD), whereas the number of leads with fQRS showed the best correlation with LGE at 6 SD (r = 0.32, P = 0.0008). Further, the number of leads with fQRS was an independent predictor for the extent of LGE at 6 SD. fQRS showed higher accuracy for detecting myocardial fibrosis defined by LGE at 6 SD than pathological Q waves; the overall sensitivity, specificity, and accuracy of fQRS were 40%, 80%, and 64%, respectively, whereas those of pathological Q waves were 7%, 97%, and 60%, respectively. fQRS in lateral leads showed the highest accuracy (75%), followed by inferior leads (59%) and anterior leads (57%), for detecting LGE at 6 SD in the corresponding left ventricular segment.**

Conclusions: **These findings suggest that fQRS may have a substantially higher sensitivity and diagnostic accuracy compared with pathological Q waves for detecting myocardial fibrosis in HCM.** *(J Cardiovasc Electrophysiol, Vol. 26, pp. 1081-1087, October 2015)*

cardiac magnetic resonance, fragmented QRS, fibrosis, hypertrophic cardiomyopathy, pathological Q waves

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder, often transmitted genetically, with a heterogeneous clinical expression.[1] The pathological hallmarks of HCM include myocardial fibrosis, which reflects expansion of the interstitial collagen and accumulation of foci of fibrotic tissue that arise after premature cardiomyocyte death.[2] Recent data demonstrate a correlation between myocardial fibrosis and unfavorable clinical manifestations such as fatal ventricular arrhythmias and the development of heart failure in HCM patients.[3-5]

Advances in cardiovascular magnetic resonance (CMR) have enabled noninvasive detection of myocardial fibrosis *in vivo* with the late gadolinium enhancement (LGE) technique in HCM and other cardiac diseases.[3-5] However, LGE-CMR may not be always available and involve significant cost. Furthermore, intravenous injection of the contrast agent is contraindicated in patients with renal failure. Therefore, clinically simple and cost-effective methods to screen for the presence of myocardial fibrosis in HCM are still required even when CMR is available. From this point of view, a simple and cost-effective 12-lead ECG can be used to detect myocardial fibrosis by the presence of pathological Q waves, although there are diagnostic limitations in HCM patients.[6] Even in patients with coronary artery disease, the overall sensitivity of pathological Q waves for prior myocardial infarction is limited, estimated to be as low as 25% for a lateral myocardial infarction.[7,8]

Fragmented QRS (fQRS) on 12-lead ECG reflects conduction delay caused by myocardial infarction.[8-10] Previous studies demonstrated that fQRS can be a more sensitive marker than pathological Q waves for detecting myocardial fibrosis that was determined by perfusion scintigraphy in

patients with coronary artery disease.[8] However, few data exist regarding the diagnostic value of fQRS for detecting myocardial fibrosis in HCM, which usually shows a patchy and nontransmural distribution. Therefore, we investigated whether fQRS can be used to detect myocardial fibrosis assessed by LGE-CMR, a technique that has been established as a sensitive modality to detect myocardial fibrosis.

Methods

Study Population

This study has been carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the Bioethical Committee on Medical Research, School of Medicine, Kanazawa University. Written informed consent was obtained from every patient for the administration of gadolinium-based contrast agents. The study population comprised 108 consecutive patients with HCM who underwent LGE-CMR at our institution between 2008 and 2015. Previously, we have published a study on CMR-determined right ventricular hypertrophy in 106 HCM patients who underwent LGE-CMR between 2008 and 2014.[11] The same 106 patients were included in this study population. HCM was diagnosed by the presence of a nondilated and hypertrophied left ventricle (LV) on 2-dimensional echocardiography (LV wall thickness ≥15 mm) in the absence of other disease that could account for the hypertrophy.[12]

Electrocardiography

A standard 12-lead ECG (0.5–150 Hz, 25 mm/s, 10 mm/mV) was recorded in the supine position during quiet respiration. The fQRS was defined as previously described,[8,9,13] as follows: in patients with QRS duration <120 milliseconds, (1) an additional R wave (R′ prime), (2) notching in nadir of the S wave, (3) notching of R wave, or (4) the presence of more than 1 R prime in 2 contiguous leads corresponding to the left ventricular (LV) segment; in patients with right or left bundle branch block (QRS duration ≥120 milliseconds), (1) various RsR′ pattern with >2 R′, (2) >2 notches in the R wave, or (3) >2 notches in the downstroke or upstroke of the S wave, in 2 contiguous leads corresponding to the LV segment. The criterion for pathological Q waves was defined as follows based on previous studies:[14] Q wave > 1/4 of the ensuing R wave in depth and/or >40 milliseconds in duration in at least 2 leads except aVR. The presence of fQRS or pathological Q waves in ≥2 contiguous anterior leads (V1–V5), lateral leads (I, aVL, and V6), or inferior leads (II, III, and aVF) was assigned to detect myocardial fibrosis in the anterior, lateral, or inferior segments, respectively.[8]

Echocardiography and CMR

Standard M-mode and 2-dimensional echocardiographic studies were performed to identify and quantify morphological features of the LV in accordance with the guideline of the American Society of Echocardiography.[15] Evaluation of LV outflow tract pressure gradient was performed by the continuous wave Doppler study. LV outflow tract obstruction (LVOTO) was defined as LVOT pressure gradient ≥30 mmHg.

CMR imaging was performed with a 1.5 Tesla scanner (GE). Delayed-enhancement images for detection of fibrosis were obtained 10 minutes after intravenous administration of gadolinium–DTPA (0.2 mmol/kg). Areas of LGE at different standard deviations (SDs) (2 SD, 4 SD, 6 SD, 8 SD, and 10 SD) above the normal myocardial signal were quantified as previously reported and presented as percentage of LV areas.[16-18]

Statistical Analysis

Values were expressed as the mean ± SD. Comparisons between continuous variables were made using the Student unpaired t-test for parametric variables and the Mann–Whitney test for nonparametric variables. Categorical data were compared using the chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were defined as previously reported.[6] Spearman rank correlation was used to assess the relationship between the extent of LGE at different threshold definitions and the number of leads with pathological Q waves or fQRS. Unadjusted and multivariate-adjusted logistic regression analyses were used to assess the associations between the clinical parameters and myocardial fibrosis. A P value of <0.05 was considered statistically significant, and all analyses were conducted using JMP software version 9.0.2 for Mac (SAS).

Results

Patients' Characteristics

Baseline characteristics of the 108 patients are presented in Table 1. Pathological Q waves in 2 contiguous leads were present in 11 (10%) patients, and fQRS in 2 contiguous leads was present in 61 (56%) patients. A representative 12-lead ECG with pathological Q waves and fQRS is presented in Figure 1. Patients with pathological Q waves showed the significantly increased extent of LGE measured at 6 SD and 8 SD compared with those without pathological Q waves (6 SD; 9.2 ± 11.4% vs. 17.3 ± 15.2%, P = 0.034, 8 SD; 13.7 ± 14.5% vs. 24.0 ± 19.7%, P = 0.034). The extent of LGE was significantly increased only at 6 SD in patients with fQRS compared with those without fQRS (11.3 ± 11.9% vs. 17.4 ± 17.2%, P = 0.039).

Distribution of Pathological Q Waves and fQRS in HCM

We first investigated the frequency of pathological Q waves and fQRS in the 108 HCM patients. fQRS was observed predominantly in the inferior leads, followed by the anterior, and lateral leads, whereas pathological Q waves were mainly found in lateral leads (Fig. 2A). fQRS was present more frequently than pathological Q waves in all segments. LGE was present predominantly in the anterior segments, followed by inferior and lateral segments (Fig. 2B).

Relationship Between LGE Measured at Different SDs and the Number of Leads With fQRS

We next examined which definition of LGE had the best correlation with the number of leads with pathological Q waves or fQRS in the 108 patients with HCM. The

TABLE 1

Comparison of Characteristics Between HCM Patients With and Without Pathological Q Waves, and Those With and Without fQRS

	No Pathological Q Waves n=97	Pathological Q Waves n=11	P Value	No fQRS Pattern n=47	fQRS Pattern n=61	P Value
Age (years)	62.3 ± 13.7	53.8 ± 18.1	0.062	62.3 ± 14.4	60.8 ± 14.3	0.58
Male gender, n (%)	62 (64)	8 (73)	0.55	43 (91)	27 (44)	0.16
AF, n (%)	19 (20)	2 (18)	0.91	8 (17)	13 (21)	0.57
QRS axis (degree)	26.4 ± 41.5	45.5 ± 76.3	0.19	28.9 ± 47.6	27.8 ± 45.2	0.9
LVOTO, n (%)	9 (9)	2 (19)	0.39	6 (13)	5 (8)	0.44
CMR measurements						
LVMWT (mm)	19.8 ± 4.5	20.0 ± 5.1	0.88	19.1 ± 4.5	20.4 ± 4.6	0.14
LVEDV (mL)	96.8 ± 31.0	129.5 ± 40.8	0.0018	97.9 ± 32.3	101.9 ± 34.3	0.54
LVEF (%)	72.9 ± 13.7	52.7 ± 23.7	<0.0001	74.0 ± 13.0	68.4 ± 17.8	0.069
LV mass (g)	145.8 ± 50.0	147.9 ± 39.0	0.89	135.3 ± 46.0	154.2 ± 49.9	0.046
LGE extent at 10 SD (%)	6.5 ± 9.1	11.8 ± 13.1	0.085	5.2 ± 7.4	8.5 ± 10.9	0.084
LGE extent at 8 SD (%)	9.2 ± 11.4	17.3 ± 15.2	0.034	7.5 ± 9.3	12.0 ± 13.5	0.058
LGE extent at 6 SD (%)	13.7 ± 14.5	24.0 ± 19.7	0.034	11.3 ± 11.9	17.4 ± 17.2	0.039
LGE extent at 4 SD (%)	21.7 ± 19.0	33.7 ± 24.6	0.057	18.9 ± 16.5	26.0 ± 21.7	0.064
LGE extent at 2 SD (%)	35.8 ± 23.3	46.8 ± 28.0	0.15	32.7 ± 21.5	40.2 ± 25.4	0.1
Conventional risk factors						
Family history of SCD, n (%)	20 (21)	6 (55)	0.023	11 (24)	15 (25)	0.9
Unexplained sycope, n (%)	8 (8)	1 (9)	0.94	3 (7)	6 (10)	0.52
History of VT/VF, n (%)	8 (8)	2 (18)	0.34	4 (9)	6 (10)	0.82
LVMWT >30 mm, n (%)	4 (4)	0 (0)	0.35	2 (4)	2 (3)	0.79
Medication						
Calcium antagonist	33 (34)	3 (27)	0.65	14 (30)	22 (36)	0.49
Beta blocker	49 (51)	7 (64)	0.41	24 (51)	32 (52)	0.89
Antiarrhythmics	13 (13)	3 (27)	0.26	5 (11)	11 (18)	0.28

AF = atrial fibrillation; CMR = cardiac magnetic resonance; fQRS = fragmented QRS; HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVMWT = left ventricular maximal wall thickness; LVOTO = left ventricular outflow tract obstruction; SCD = sudden cardiac death; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia.
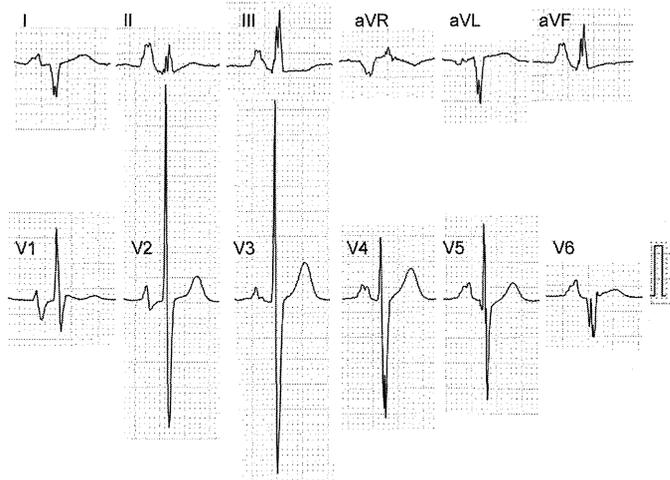

Figure 1. *A representative electrocardiogram with fQRS waves and pathological Q waves in an HCM patient. The different morphologies of fQRS are shown in this figure; notching of the R wave in leads II, III, and aVF, and notching in nadir of the S wave in leads I, aVL, V4, V5, and V6. Pathological Q waves are observed in leads I and V6.*

number of leads with pathological Q waves was not correlated with the extent of LGE at any threshold definitions (Table 2), whereas the number of leads with fQRS showed the best correlation with LGE measured at 6 SD (r = 0.32, P = 0.0008) (Table 2, Fig. 3). Multivariate adjusted regression analyses revealed that fQRS, LV ejection fraction, and maximal wall thickness of LV were independent predictors for the extent of LGE measured at 6 SD, even after adjustments for clinical cofounders (Table 3). In contrast, pathological Q waves did not independently predict the extent of LGE measured at 6 SD in HCM (Table 3).

Diagnostic Values of fQRS for Detecting the Presence of Myocardial Fibrosis in the HCM Hearts

Since LGE measured at 6 SD showed the best correlation with the number of leads with fQRS, we thought it prudent to assess the diagnostic values of fQRS in 2 contiguous leads for detecting myocardial fibrosis defined by LGE at 6 SD in the corresponding myocardial segments (Table 4, Fig. 4). The overall sensitivity, specificity, PPV, NPV, and accuracy of pathological Q waves for detecting myocardial fibrosis were 7%, 97%, 64%, 60%, and 60%, respectively,
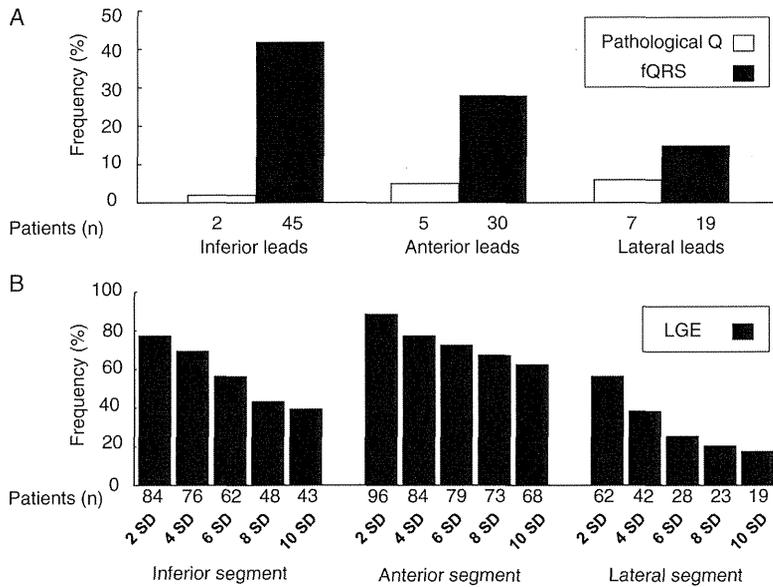
Figure 2. *Frequency of pathological Q waves, fQRS, and positive LGE in the 48 HCM patients. A: fQRS was found predominantly in the inferior leads, followed by the anterior, and lateral leads. Pathological Q waves were mainly found in the lateral leads. B: Frequency of positive LGE at different threshold definitions (2, 4, 6, 8, and 10 SD). LGE was present predominantly in the anterior segments, followed by inferior and lateral segments.*

TABLE 2

Correlation Between LGE Measured at Different Threshold Definitions and the Number of Leads With Pathological Q Waves or fQRS in the HCM Patients

	The Number of Leads with Pathological Q		The Number of Leads with fQRS	
	Spearman Correlation	P Value	Spearman Correlation	P Value
LGE at 2 SD	0.16	0.11	0.29	0.0025
LGE at 4 SD	0.15	0.11	0.29	0.0022
LGE at 6 SD	0.15	0.12	0.32	0.0008
LGE at 8 SD	0.17	0.07	0.31	0.0009
LGE at 10 SD	0.16	0.11	0.31	0.0012

fQRS, HCM, LGE, and SD definitions as in Table 1.

and those of fQRS were 40%, 80%, 58%, 66%, and 64%, respectively. Pathological Q waves in lateral leads showed the highest sensitivity (19%) for detecting myocardial fibrosis in the corresponding lateral LV segment, whereas fQRS in inferior leads showed the highest sensitivity (51%). The specificity of pathological Q waves was excellent for detecting myocardial fibrosis in each corresponding LV segment, whereas the specificity of fQRS in inferior leads was 64% for detecting myocardial fibrosis in the corresponding inferior LV segment. Examples of concordant fQRS and LGE findings in an HCM patient are shown in Figure 5.

Discussion

In this study, we demonstrated that the number of leads with fQRS showed the best correlation with LGE when measured at 6 SD and was an independent predictive factor for the extent of LGE in HCM. Further, fQRS showed a better sensitivity compared with pathological Q waves in HCM for detecting myocardial fibrosis defined by LGE at 6 SD.

Diagnostic Values of fQRS for Detecting Myocardial Fibrosis in HCM

Spiewak *et al.* reported that LGE measured at 6 SD provided the best agreement with visual assessment in HCM patients,[19] indicating that the number of leads with fQRS, which was best correlated with LGE at 6 SD in our study (Table 2, Fig. 3), may be associated with visually interpreted LGE in clinical practice of HCM. Interestingly, Moravsky *et al.* reported that LGE at 4 SD and 5 SD showed the closest approximation to the extent of total fibrosis (interstitial fibrosis and myocardial scarring), whereas LGE at 10 SD showed the best correlation with myocardial scarring measured by the histopathological standard of reference in HCM.[16] Together, these findings suggest that the number of leads with fQRS may reflect both interstitial fibrosis and myocardial scarring in HCM.

ECG abnormalities, such as pathological Q waves,[20] negative T waves,[21] right bundle branch block,[22] and deep-notched QRS in the absence of bundle branch block,[23] have been reported to correlate with myocardial fibrosis in HCM. Regarding fQRS, although Suwa *et al.* reported that the presence of fQRS may be associated with apical aneurysm in HCM,[24] it has been unclear whether fQRS can be used to detect myocardial fibrosis in the corresponding LV segment. In our study, fQRS showed a higher sensitivity than pathological Q waves for detecting myocardial fibrosis defined by LGE at 6 SD in the corresponding LV segment in HCM (Table 4, Fig. 4). However, there is a compromise in the specificity; fQRS in inferior leads was substantially less specific than pathological Q waves for detecting LGE at 6 SD. In
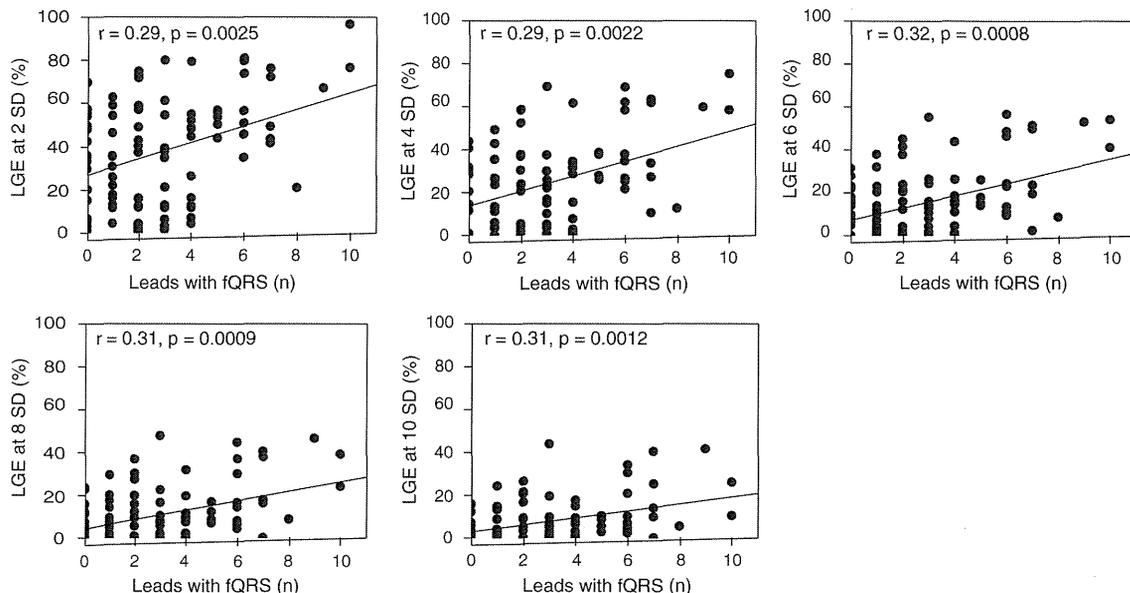
Figure 3. *Correlation between the number of leads with fQRS and LGE measured at different threshold definitions. The number of leads with fQRS showed a positive correlation with the extent of LGE measured at 2 SD, 4 SD, 6 SD, 8 SD, or 10 SD. The number of leads with fQRS was best correlated with the extent of LGE at 6 SD (r = 0.32, P = 0.0008).*

TABLE 3

Predictors of the Extent of LGE at 6 SD in the HCM Patients (Unadjusted and Multivariate-Adjusted Regression Analysis)

Variable	Univariate β ± SE	P Value	Adjusted (Model 1) β ± SE	P Value	Adjusted (Model 2) β ± SE	P Value	Adjusted (Model 3) β ± SE	P Value
Leads with fQRS	0.45 ± 0.040	<0.0001	0.45 ± 0.041	<0.0001	0.41 ± 0.043	<0.0001	0.27 ± 0.045	0.0015
Leads with pathological Q	0.23 ± 0.085	0.015			0.11 ± 0.090	0.22	0.031 ± 0.093	0.71
Male gender	−0.0063 ± 0.20	0.51	0.021 ± 0.021	0.82	−0.00043 ± 0.21	0.99	0.0019 ± 0.22	0.82
Age	−0.090 ± 0.0067	0.35	−0.045 ± 0.0069	0.62	−0.03 ± 0.0070	0.74	−0.0022 ± 0.0074	0.98
MWT	0.26 ± 0.021	0.007					0.30 ± 0.022	0.0002
LVEF	−0.50 ± 0.0060	<0.0001					−0.38 ± 0.0068	<0.0001
QRS axis	0.22 ± 0.0020	0.025					0.18 ± 0.0026	0.029

fQRS, HCM, LVEF, MWT, and SD definitions as in Table 1.

TABLE 4

Diagnostic Values of Pathological Q Waves or fQRS for Detecting LGE at 6 SD in Each Corresponding LV Segment

		Sensitivity	Specificity	PPV	NPV	Accuracy
Overall segments	Pathological Q	7%	97%	64%	60%	60%
	fQRS	40%	80%	58%	66%	64%
Inferior segments	Pathological Q	3%	99%	50%	64%	63%
	fQRS	51%	64%	44%	70%	59%
Anterior segments	Pathological Q	5%	95%	60%	39%	40%
	fQRS	38%	88%	83%	47%	57%
Lateral segments	Pathological Q	19%	98%	71%	78%	78%
	fQRS	30%	90%	50%	79%	75%

NPV = negative predictive value; PPV = positive predictive value. fQRS, HCM, and SD definitions as in Table 1.

this respect, both massive myocardial scarring and micro foci of fibrosis have been histologically demonstrated in HCM.[2] Micro foci of fibrosis are not identifiable by LGE-CMR or pathological Q waves; however, these small fibrotic tissues may cause conduction delay and thus result in fQRS,[9,10] presumably contributing to the lower specificity of fQRS than pathological Q waves in HCM.

Diagnostic values of fQRS for detecting myocardial fibrosis defined by LGE at 6 SD varied among different LV segments; fQRS in the inferior leads showed the highest sensitivity (51%) but the lowest specificity (64%), whereas fQRS in the lateral leads showed the lowest sensitivity (30%) but the highest specificity (90%) (Table 4, Fig. 4). Such differences in diagnostic values of fQRS were reported to be small
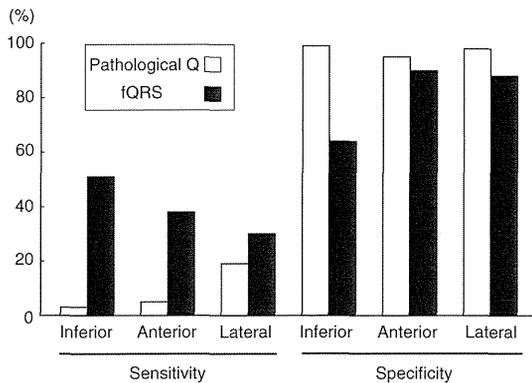
Figure 4. *Diagnostic values of pathological Q waves or QRS fragmentation for detecting myocardial fibrosis defined by LGE at 6 SD in HCM patients. The sensitivity of pathological Q waves was 3%, 5%, and 19% for inferior, anterior, and lateral segments, respectively; and that of fQRS was 51%, 38%, and 30% for inferior, anterior, and lateral segments, respectively. The specificity of pathological Q waves was 99%, 95%, and 98% for inferior, anterior, and lateral segments, respectively; and that of fQRS was 64%, 88%, and 90% for inferior, anterior, and lateral segments, respectively.*

in patients with coronary artery disease.[8] Because HCM characteristically exhibits a more heterogeneous and patchy appearance of myocardial fibrotic tissues[1-6] than coronary artery disease, we postulate that different diagnostic values of fQRS among LV segments in HCM may be attributed to differences in the amount of patchy myocardial fibrosis and micro foci of fibrosis in each of the inferior, anterior, and lateral segment.

Relationships Between the Number of Leads With fQRS and the Extent of Myocardial Fibrosis

Of note, our data demonstrated that the number of leads with fQRS was independently associated with the extent of

LGE at 6 SD in HCM patients (Table 3), indicating that fQRS can be used to both qualitatively and quantitatively detect myocardial fibrosis in HCM. Such correlations between fQRS and myocardial fibrosis raise important issues in terms of the pathophysiology of LV remodeling and arrhythmogenicity in HCM. Although the underlying mechanism by which myocardial fibrosis progresses in HCM remains unclear, it has been demonstrated that premature myocyte death due to regional ischemia and impaired myocardial metabolism[2] may lead to replacement fibrosis. Studies in HCM mouse models and in pressure overload models in mice have shown that fetal cardiac genes are re-expressed in the myocardium around replacement fibrosis,[2] which may further lead to myocyte death. Increased myocardial fibrosis not only results in LV systolic dysfunction and heart failure, but also may provide further structural substrates for arrhythmogenicity.[1-5] These considerations are consistent with recent studies which demonstrated associations between fQRS and heart failure progression[25] or the occurrence of arrhythmic events in HCM patients.[26-28] Indeed, Femenía et al. demonstrated that fQRS at implantable cardioverter defibrillator (ICD) implant can predict arrhythmic events using appropriate therapy delivered by the ICD as a surrogate.[26] Additionally, inclusion of fQRS in conventional risk factors[12] could improve the predictive value for sudden cardiac death in HCM patients.[27,28] Further study will be needed to clarify whether fQRS can be used in risk stratification in HCM.

Limitations

One limitation of this study was the small sample size. The significant correlations between fQRS and myocardial fibrosis observed in this study should be validated in a larger HCM patient cohort. Additionally, the study population was enrolled in a tertiary referral center, thus creating a selection bias regarding the stage of the disease.
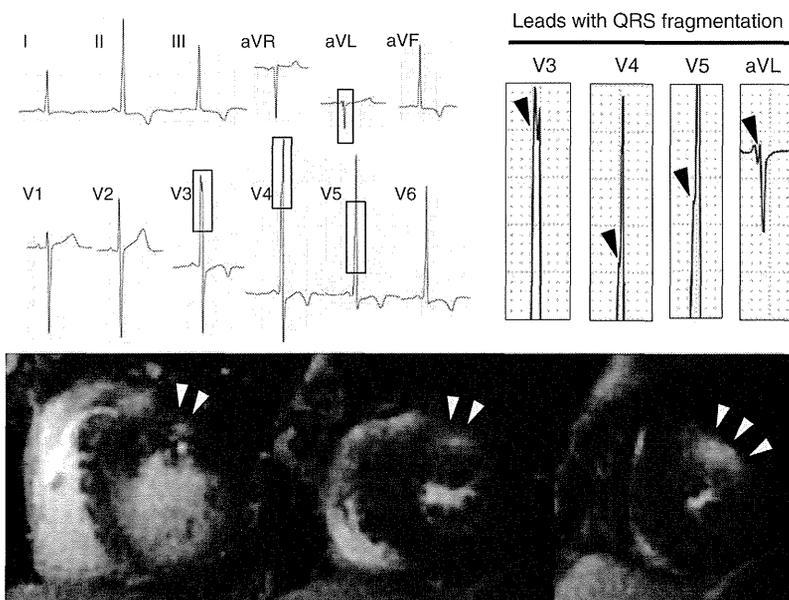
Figure 5. *Association of fQRS with ventricular LGE in an HCM patient. A 43-year-old female patient with HCM exhibited fQRS in anterior leads (V3, V4, and V5), and in a lateral lead (aVL). CMR demonstrated LGE on anterior to lateral segments of LV. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

Conclusion

The presence of fQRS on a 12-lead ECG showed a better sensitivity and diagnostic accuracy compared with pathological Q waves for detecting myocardial fibrosis determined by LGE at 6 SD in HCM. Even when CMR is available, the 12-lead ECG can be used as a screening modality for myocardial fibrosis in HCM because of its simplicity and cost-effectiveness.

References

1. Maron BJ, Maron MS: Hypertrophic cardiomyopathy. Lancet 2013;381:242-255.
2. Konno T, Chen D, Wang L, Wakimoto H, Teekakirikul P, Nayor M, Kawana M, Eminaga S, Gorham JM, Pandya K, Smithies O, Naya FJ, Olson EN, Seidman JG, Seidman CE: Heterogeneous myocyte enhancer factor-2 (Mef2) activation in myocytes predicts focal scarring in hypertrophic cardiomyopathy. Proc Natl Acad Sci U S A 2010;107:18097-18102.
3. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JA: Assessment of myocardial fibrosis with cardiovascular magnetic resonance. J Am Coll Cardiol 2011;57:891-903.
4. Todiere G, Aquaro GD, Piaggi P, Formisano F, Barison A, Masci PG, Strata E, Bacigalupo L, Marzilli M, Pingitore A, Lombardi M: Progression of myocardial fibrosis assessed with cardiac magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2012;60:922-929.
5. Moon J, Hong YJ, Kim YJ, Shim CY, Jang Y, Chung N, Cho SY, Ha JW: Extent of late gadolinium enhancement on cardiovascular magnetic resonance imaging and its relation to left ventricular longitudinal functional reserve during exercise in patients with hypertrophic cardiomyopathy. Circ J 2013;77:1742-1749.
6. Konno T, Shimizu M, Ino H, Yamaguchi M, Terai H, Uchiyama K, Oe K, Mabuchi T, Kaneda T, Mabuchi H: Diagnostic value of abnormal Q waves for identification of preclinical carriers of hypertrophic cardiomyopathy based on a molecular genetic diagnosis. Eur Heart J 2004;25:246-251.
7. Kosuge M, Ebina T, Hibi K, Iwahashi N, Tsukahara K, Endo M, Maejima N, Nagashima Z, Suzuki H, Morita S, Umemura S, Kimura K: Differences in negative T waves between takotsubo cardiomyopathy and reperfused anterior acute myocardial infarction. Circ J 2012;76:462-468.
8. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J: Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation 2006;113:2495-2501.
9. Das MK, Zipes DP: Fragmented QRS: A predictor of mortality and sudden cardiac death. Heart Rhythm 2009;6:S8-S14.
10. Flowers NC, Horan LG, Thomas JR, Tolleson WJ: The anatomic basis for high-frequency components in the electrocardiogram. Circulation 1969;39:531-539.
11. Nagata Y, Konno T, Fujino N, Hodatsu A, Nomura A, Hayashi K, Nakamura H, Kawashiri MA, Yamagishi M: Right ventricular hypertrophy is associated with cardiovascular events in hypertrophic cardiomyopathy: Evidence from study with magnetic resonance. Can J Cardiol 2015;31:702-708.
12. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:e212-60.
13. Hayashi T, Fukamizu S, Hojo R, Komiyama K, Tanabe Y, Tejima T, Nishizaki M, Hiraoka M, Ako J, Momomura S, Sakurada H: Fragmented QRS predicts cardiovascular death of patients with structural heart disease and inducible ventricular tachyarrhythmia. Circ J 2013;77:2889-2897.
14. Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, Dandamudi G, Mahenthiran J: Fragmented wide QRS on a 12-lead ECG. A sign of myocardial scar and poor prognosis. Circ Arrhythmia Electrophysiol 2008;1:258-268.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ: Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-1463.
16. Moravsky G, Ofek E, Rakowski H, Butany J, Williams L, Ralph-Edwards A, Wintersperger BJ, Crean A: Myocardial fibrosis in hypertrophic cardiomyopathy: Accurate reflection of histopathological findings by CMR. JACC Cardiovasc Imaging 2013;6:587-596.
17. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, Muthurangu V, Moon JC: Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovasc Imaging 2011;4:150-156.
18. Konno T, Hayashi K, Fujino N, Nagata Y, Hodatsu A, Masuta E, Sakata K, Nakamura H, Kawashiri MA, Yamagishi M: High sensitivity of late gadolinium enhancement for predicting microscopic myocardial scarring in biopsied specimens in hypertrophic cardiomyopathy. PLoS One 2014;9:e101465.
19. Spiewak M, Malek LA, Misko J, Chojnowska L, Milosz B, Klopotowski M, Petryka J, Dabrowski M, Kepka C, Ruzyllo W: Comparison of different quantification methods of late gadolinium enhancement in patients with hypertrophic cardiomyopathy. Eur J Radiol 2010;74:e149-e153.
20. Chen X, Zhao T, Lu M, Yin G, Xiangli W, Jiang S, Prasad S, Zhao S: The relationship between electrocardiographic changes and CMR features in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. Int J Cardiovasc Imaging 2014;30(Suppl 1):55-63.
21. Chen X, Zhao S, Zhao T, Lu M, Yin G, Jiang S, Prasad S: T-wave inversions related to left ventricular basal hypertrophy and myocardial fibrosis in non-apical hypertrophic cardiomyopathy: A cardiovascular magnetic resonance imaging study. Eur J Radiol 2014;83:297-302.
22. Harimoto K, Kawasaki T, Honda S, Miki S, Kamitani T: Right bundle branch block and ventricular septal fibrosis in patients with hypertrophic cardiomyopathy. J Electrocardiol 2014;47:636-641.
23. Kawasaki T, Harimoto K, Honda S, Sato Y, Yamano M, Miki S, Kamitani T: Notched QRS for the assessment of myocardial fibrosis in hypertrophic cardiomyopathy. Circ J 2015;79:847-853.
24. Suwa K, Satoh H, Sano M, Nobuhara M, Saitoh T, Saotome M, Urushida T, Katoh H, Tawarahara K, Ohtani H, Wakabayashi Y, Takase H, Terada H, Takehara Y, Sakahara H, Hayashi H: Functional, morphological and electrocardiographical abnormalities in patients with apical hypertrophic cardiomyopathy and apical aneurysm: Correlation with cardiac MR. Open Heart 2014;1:e000124.
25. Nomura A, Konno T, Fujita T, Tanaka Y, Nagata Y, Tsuda T, Hodatsu A, Sakata K, Nakamura H, Kawashiri MA, Fujino N, Yamagishi M, Hayashi K: Fragmented QRS predicts heart failure progression in patients with hypertrophic cardiomyopathy. Circ J 2015;79:136-143.
26. Femenía F, Arce M, VanGrieken J, Trucco E, Mont L, Abello M, Merino JL, Rivero-Ayerza M, Gorenek B, Rodriguez C, Hopman WM, Baranchuk A; Fragmented QRS in Hypertrophic Obstructive Cardiomyopathy (FHOCM) Study Investigators: Fragmented QRS as a predictor of arrhythmic events in patients with hypertrophic obstructive cardiomyopathy. J Interv Card Electrophysiol 2013;38:159-165.
27. Kang KW, Janardhan AH, Tae Jung K, Lee HS, Lee MH, Jin Hwang H: Fragmented QRS as a candidate marker for high risk assessment in hypertrophic cardiomyopathy. Heart Rhythm 2014;11:1433-1440.
28. Debonnaire P, Katsanos S, Joyce E, van den Brink OV, Atsma DE, Schalij MJ, Bax JJ, Delgado V, Marsan NA: QRS fragmentation and QTc duration relate to malignant ventricular tachyarrhythmias and sudden cardiac death in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol 2015;26:547-555.

Original Article

Evaluation of the Necessity for Cardioverter-Defibrillator Implantation in Elderly Patients With Brugada Syndrome

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Background—The clinical characteristics and prognosis of elderly patients with Brugada syndrome (BrS) are largely unknown. The purpose of this study was to evaluate the risks and benefits of implantable cardioverter defibrillator (ICD) in elderly patients with BrS based on a long follow-up.

Methods and Results—A total of 120 BrS patients with ICD (90 for aborted sudden cardiac arrest or syncope, mean age, 46.6±12.2 years; 50 with age ≥60 years at the last follow-up) were included in this study. During 102±68 months of follow-up, 31 patients (26%) experienced appropriate shocks. Age at the first attack of ventricular fibrillation (VF) was <70 years in all patients (mean, 45.0±12.1 years), the incidence of VF decreased with age, and VF did not recur after 70 years of age except in 2 patients with ischemic heart disease. Eleven of 28 patients with supraventricular tachycardia experienced inappropriate shocks. These inappropriate shocks increased with age and reached a peak in patients who were in their sixties. Lead failures occurred in later stages after implantation in 10 of 120 patients (8%).

Conclusions—Long-term follow-up of high-risk BrS patients with ICD showed a low incidence of VF in those aged >70 years. Considering the increasing risk of inappropriate shocks because of the relatively late onset of supraventricular tachycardia and lead failures, avoidance of ICD implantation, or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age. (***Circ Arrhythm Electrophysiol.*** 2015;8:785-791. DOI: 10.1161/CIRCEP.114.002705.)

Key Words: Brugada syndrome ■ death, sudden, cardiac ■ defibrillators, implantable ■ myocardial ischemia ■ syncope

Implantable cardioverter defibrillator (ICD) is considered to be the main therapy for prevention of sudden cardiac death in patients with Brugada syndrome (BrS). However, there have been several reports suggesting a higher prevalence of complications, such as inappropriate shocks, lead failure, and device infection compared with the incidence of lethal ventricular arrhythmia.[1] BrS is mainly diagnosed ≈40 years of age in men,[2,3] and sudden death is likely to be eliminated after ICD implantation. Meanwhile, the clinical characteristics and prognosis of elderly patients with BrS are largely unknown, and there are no reports on the incidence of ventricular fibrillation (VF) or the evaluations of the necessity for ICD in elderly patients. Provided that BrS is caused by depolarization abnormality,[4] ventricular arrhythmias may conceivably increase with age.

The purpose of this study was to investigate the incidence of appropriate shocks and ICD complications in patients with BrS during long-term follow-up after ICD implantation and to assess the risk and benefit of ICD implantation in elderly patients with BrS.

Methods

Study Population
The study population consisted of 120 consecutive BrS patients who were admitted to National Cerebral and Cardiovascular Center, Suita, Japan, between 1992 and 2013, and had undergone ICD implantation (115 men; mean age, 46.6±12.2 years). All patients except 1 were index cases. None of all the patients had structural heart disease, including arrhythmogenic right ventricular cardiomyopathy, which was confirmed by noninvasive studies (physical examination, 12-lead ECG, 87-lead body surface ECG, exercise stress test, signal-averaged electrocardiography, and cardiac magnetic resonance imaging or computed tomography), and invasive studies consisting of coronary angiography including ergonovine/acetylcholine injection and right or left ventricular cineangiography. This study was approved by the Institutional Research Board of National Cerebral and Cardiovascular Center.

Diagnosis of Brugada Syndrome
BrS was diagnosed when a type 1 ST-segment elevation was observed either spontaneously or after intravenous administration of a sodium channel blocking agent in at least 1 right precordial lead (V_1 and V_2), which was placed in a standard or a superior position (up to the

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WHAT IS KNOWN

- Brugada syndrome is mainly diagnosed around 40 years of age in men, and sudden death can be effectively prevented after implantable cardioverter defibrillator implantation.
- The clinical characteristics and prognosis of older patients with Brugada syndrome is largely unknown.

WHAT THE STUDY ADDS

- This study included 120 patients with Brugada syndrome after implantable cardioverter defibrillator implantation with a mean follow-up >8 years. Of the total, 90 had sudden death or syncope. The incidence of ventricular fibrillation (VF) decreased with age; the first VF did not occur after age of 70 years in all patients, and no VF recurrences occurred after age of 70 years in patients without ischemic heart disease.
- The inappropriate shocks because of supraventricular tachycardia increased with age, and the risk of lead failure also increased over time.
- Considering the risk of implantable cardioverter defibrillator–related complications and low risk of VF events associated with advancing age, avoidance of implantable cardioverter defibrillator implantation, or replacement may be considered in elderly Brugada syndrome patients who remain free from VF until 70 years of age.

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second intercostal space).[5] Type 1 ECG was defined as coved-type J-point or ST elevation ≥2 mm followed by a negative T-wave.[2] Drug provocation tests were conducted with pilsicainide (up to 1 mg/kg body weight injected at a rate of 5–10 mg/min), disopyramide (1.5 mg/kg, 10 mg/min), or flecainide (2 mg/kg, 10 mg/min) during standard and high costal (second and third) ECG recordings. All ECGs were recorded at 25 mm/s and 10 mm/mV and were analyzed by 2 independent cardiologists (T. Kamakura and S.K). Consensus was reached about the diagnosis.

Clinical Data, ECG, and Electrophysiological Testing

Clinical data including age at diagnosis, age at the first episode of VF, sex, family history of sudden cardiac death at <45 years of age, history of supraventricular tachycardia (SVT; atrial fibrillation [AF], atrial flutter, and atrial tachycardia) and ventricular tachyarrhythmia

(VF or ventricular tachycardia) lasting >30 s, indications for ICD implantation, and oral therapy were collected for all patients. Electrophysiological study (EPS) was conducted in 100 patients as previously described.[6] ICD was implanted in patients with an episode of VF or syncope judged to be likely caused by ventricular arrhythmias. ICD was also implanted in asymptomatic patients with induced VF at EPS or a family history of sudden death.[2] Vasovagal syncope was excluded by head-up tilt test using isoproterenol infusion and oral nitroglycerin. Genetic testing for mutations in *SCN5A* gene was performed in 80 patients (67%), as previously described.[7]

Follow-Up

All patients were followed up routinely every 3 to 6 months mainly for device interrogation. During follow-up, patients were considered to have an arrhythmic event if ICD interrogation revealed that appropriate shocks or antitachycardia pacing were delivered in response to VF or ventricular tachycardia. The beginning of the follow-up period was at the time of the first VF event in patients with a history of VF and at the time of admission in patients without VF. All the data about VF/ventricular tachycardia episodes, SVT, ICD shocks, and ICD complications were collected during follow-up periods. Electrical storm was defined as ≥3 episodes of VF within 24 hours. Lead failure was defined as a severe lead defect that required surgical correction, which did not include acute lead complications, such as lead perforations and lead dislodgements. Device programming was left to the individual physician's preference but was typically set with a single VF zone with shock only therapy. The medical therapy was decided by the patient's physician.

Statistical Analysis

Data were analyzed with JMP10 software (SAS Institute Inc, Cary, NC). Numeric values are presented as mean±SD or median (with interquartile range), depending on the normality of distribution. The χ^2 test, Student t test, 1-way ANOVA, or Mann–Whitney test was performed as appropriate to test for statistically significant differences. The incidence of VF was calculated on the basis of the age of incident cases at VF occurrence by a person-year method, stratified according to age, which was expressed as a number per 100 person-years of observation. Survival curves were constructed by the Kaplan–Meier method and compared using the log-rank test. A probability value of $P<0.05$ was considered statistically significant.

Results

Clinical Characteristics and Indication for ICD Implantation

The clinical characteristics of the 120 patients (115 men; mean age at diagnosis, 46.6±12.2 years) are shown in Table 1. Seventeen patients were ≥60 years at diagnosis. Before ICD implantation, 36 patients (30%) had a history of VF (VF group), 54 patients (45%) had an episode

Table 1.   Clinical Characteristics in Brugada Patients With VF, Syncope, and Without Symptoms

	VF (n=36)	Syncope (n=54)	Asymptomatic (n=30)	P Value Comparing 3 Groups	Total (n=120)
Age at diagnosis, y	42.5±11.1	49.5±13.4	46.1±10.3	0.02	46.6±12.2
Male (%)	35 (97)	51 (94)	29 (97)	0.78	115 (96)
FH of SCD (%)	3 (8)	13 (24)	12 (40)	0.01	28 (23)
SCN5A mutation	5/22 (23)	11/36 (31)	4/22 (18)	0.55	20/80 (25)
Spontaneous type 1 (%)	26 (72)	38 (70)	21 (70)	0.98	85 (71)
Induction of VF by EPS (%)	15/21 (71)	37/49 (76)	26/30 (87)	0.36	78/100 (78)

Numeric values are expressed as mean±SD. EPS indicates electrophysiological study; FH of SCD, family history of sudden cardiac death before 45 years of age; and VF, ventricular fibrillation.

of syncope (syncope group), and 30 patients (25%) were asymptomatic. Among the 30 asymptomatic patients, indications for ICD implantation included inducible VF at EPS and a family history of sudden death (n=12), inducible VF (n=14), no inducible ventricular arrhythmia but a family history of sudden death (n=2), and a spontaneous type 1 Brugada ECG pattern along with electrophysiologist or patient preference for ICD (n=2).

Clinical Outcome

Follow-up data are shown in Table 2. Mean follow-up period was 102±68 months. Seventeen patients were ≥70 years at the last follow-up. The mean follow-up period of these 17 patients aged >70 years at the last follow-up was 131.6±87.6 months. Their average age at the last follow-up was 74.8±4.4 years. After they reach 70 years, they were followed for 63.5±52.6 months on average. Two patients died by suicide. Thirty-one patients (26%) experienced appropriate shocks because of VF. There was no documentation of shocks by sustained monomorphic ventricular tachycardia. The incidence of VF during follow-up was significantly higher in the VF group (Figure 1). Among 50 patients who had VF before and during the follow-up period (VF group, 36; syncope group, 13; asymptomatic, 1), the peak age of VF onset was between 30 and 39 years, the age at the first VF was <70 years in all patients (mean age, 45.0±12.1 years; range, 27–69 years; Figure 2A and 2B), and the incidence of VF (VF events per 100 person-years) decreased with age (Figure 2C). Although no patients had new onset of VF after 70 years of age, 2 patients who were suspected to have myocardial ischemia experienced VF recurrence after 70 years of age. The first case was an 83-year-old man who was diagnosed with BrS and underwent ICD implantation because of a spontaneous type 1 ECG and a history of syncope during night at the age of 67 years. He developed new onset angina pectoris and underwent percutaneous coronary intervention at the age of

68. He experienced several VF recurrences after the first VF attack at the age of 69 years. However, no VF recurred after the age of 82, when he underwent coronary artery bypass graft surgery. The second case was an 80-year-old man who had undergone ICD implantation because of a spontaneous type 1 ECG and a history of syncope at the age of 63. The first VF attack occurred 8 months after ICD implantation, when he started to take nifedipine and quinidine because he was suspected to have vasospastic angina. However, VF recurred at the age of 80.

After ICD implantation, antiarrhythmic drugs were administered in 4 middle-aged patients in the VF group, and patients in the syncope and asymptomatic group were followed without drug at first. Although antiarrhythmic drugs (quinidine, 200–300 mg/d; denopamine, 15–30 mg/d; cilostazol, 100 mg/d, etc) were started in 5 patients in the VF group and 5 patients in the syncope group who experienced VF recurrence, 6 of 10 developed VF. Only 2 patients were treated with antiarrhythmic drugs (1: quinidine 200 mg/d and 1: quinidine 300 mg/d) during follow-up in the 17 patients who lived beyond 70 years of age. No patients underwent epicardial catheter ablation.

Twenty-eight patients (23%) experienced SVT (Table 2) including AF in 22 patients, atrial flutter in 5 patients, and atrial tachycardia in 1 patient as of the last follow-up. Mean age at the onset of SVT was 52.3±12.7 years.

Mutations of *SCN5A* gene were identified in 20 of 80 patients (25%). There were no statistically significant differences in the clinical parameters, including family history of sudden death, spontaneous type 1 ECG, history of AF, VF induction by EPS, and VF recurrence, between patients with and without a *SCN5A* mutation.

ICD Complications

Device-related complications occurred in 39 patients (33%) during the follow-up period (Table 2). The incidence of

Table 2. Clinical Outcomes and ICD Complications in the 3 Groups

	VF (n=36)	Syncope (n=54)	Asymptomatic (n=30)	P Value Comparing 3 Groups	Total (n=120)
Follow-up period, mo	116±76	98±69	92±53	0.45	102±68
Age at the last follow-up, y	52.4±12.8	57.7±14.8	53.9±11.0	0.08	55.2±13.3
Age ≥60 y at the last follow-up (%)	12 (33)	30 (56)	8 (27)	0.018	50 (42)
Age ≥70 y at the last follow-up (%)	4 (11)	11 (20)	2 (7)	0.19	17 (14)
VF recurrence (%)	17 (47)	13 (24)	1 (3)	0.0002	31 (26)
Electrical storm (%)	7 (19)	4 (7)	0 (0)	0.02	11 (9)
No. of appropriate shocks (total, median, IQR)	161, 0, 0–6.5	106, 0, 0–0.25	1, 0, 0–0	0.0002	268, 0, 0–1
Death (%)	1 (3)	1 (2)	0 (0)	0.67	2 (2)
Supraventricular tachycardia					
At the time of diagnosis (%)	3 (8)	5 (9)	3 (10)	0.97	11 (9)
At the last follow-up (%)	8 (22)	11 (20)	9 (30)	0.60	28 (23)
Atrial fibrillation (%)	8 (22)	8 (15)	6 (20)	0.65	22 (18)
Patients with ICD complications (%)	16 (44)	16 (30)	7 (23)	0.16	39 (33)
Patients with inappropriate shocks (%)	7 (19)	9 (17)	5 (17)	0.94	21 (18)
No. of inappropriate shocks (total, median, IQR)	8, 0, 0–0	27, 0, 0–0	8, 0, 0–0	0.98	43, 0, 0–0

Numeric values are expressed as mean±SD. ICD indicates implantable cardioverter defibrillator; IQR, interquartile range; and VF, ventricular fibrillation.
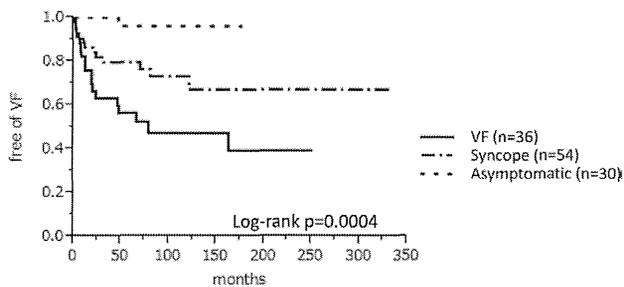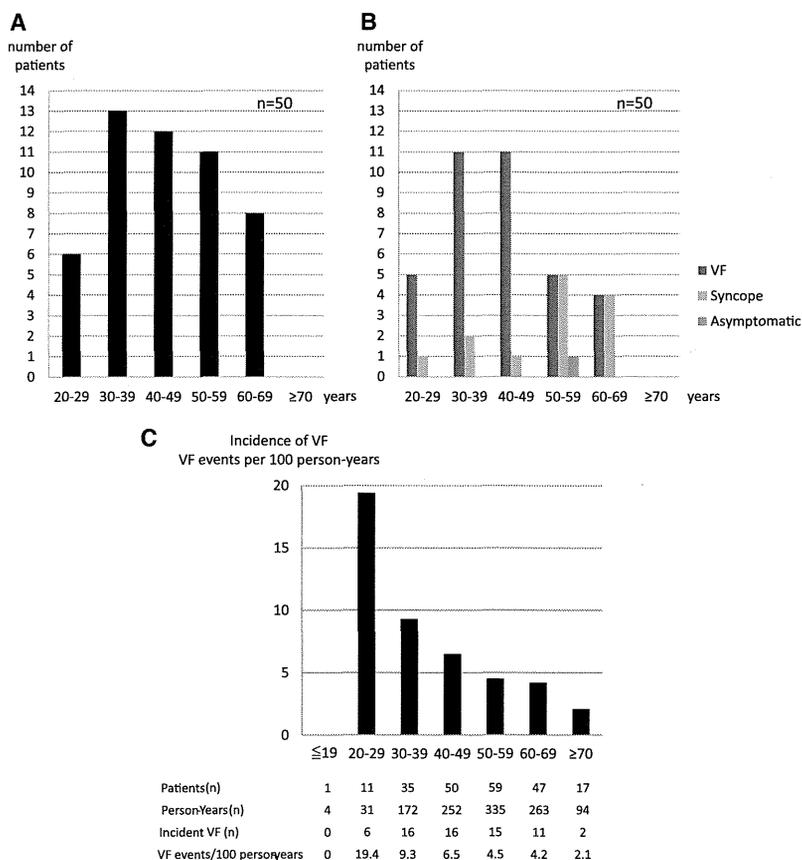
Figure 1. Kaplan–Meier analysis of freedom from lethal arrhythmic events (documented ventricular fibrillation [VF]) during follow-up in 3 groups (VF, sycope, and asymptomatic) of patients with Brugada syndrome. The incidence of VF during follow-up was significantly higher in the VF group than in the syncope and asymptomatic groups.

Number of patients

VF	36	17	9	7	3	2	0
Syncope	54	30	17	5	2	1	1
asymptomatic	30	25	14	5	0	0	0

complications among the 3 groups was not significantly different. A total of 43 inappropriate shocks occurred in 21 patients. The number of inappropriate shocks was higher than appropriate shocks in the asymptomatic group. Reasons for inappropriate shocks were SVT (n=26), sinus tachycardia (n=6), lead failure (n=5), T-wave oversensing (n=3), and others (n=3). Fifteen patients experienced trouble with a lead 98±41 months after ICD implantation: 10 patients with lead failure, 3 patients with

lead perforation, and 2 patients with lead dislodgement. The incidence of lead failure per 145 leads increased over time and reached 13% at the 10-year follow-up (Figure 3). Twenty-one leads (15%) were involved in a device recall or advisory (St. Jude Medical Riata or Medtronic Sprint Fidelis); however, the incidence of such lead failure was not statistically significantly different from ICD leads not involved in a recall process. New lead implantation was performed in all 10 patients including 2

Patients(n)	1	11	35	50	59	47	17
PersonYears(n)	4	31	172	252	335	263	94
Incident VF (n)	0	6	16	16	15	11	2
VF events/100 personyears	0	19.4	9.3	6.5	4.5	4.2	2.1

Figure 2. The age distribution of the first ventricular fibrillation (VF); in total (**A**), and according to the clinical subgroups (VF group, 36; syncope group, 13; and asymptomatic group, 1; **B**), and the incidence of VF depending on each age category (**C**). Among 50 patients who had VF before and during follow-up period, the peak age of VF onset was between 30 and 39 years, the age at the first VF was <70 years in all patients (range, 27–69 years), and the incidence of VF decreased with age after reaching a peak between 20 and 39 years of age.
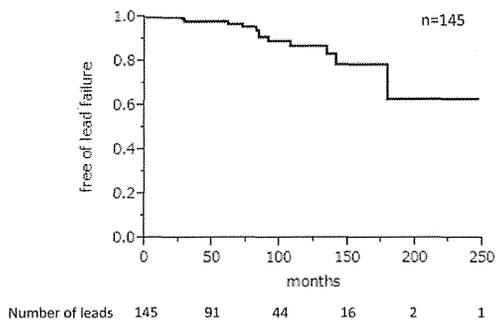
Figure 3. Kaplan–Meier analyses of lead failures during follow-up. The incidence of lead failure per 145 leads increased over time.

patients who required lead extraction. Another 10 patients had infection related to the ICD that required lead extraction in all patients including surgical approach in 3 patients. Three patients needed to change the location of generator because of pain.

Inappropriate shocks because of SVT occurred in 11 of 28 patients (39%) with SVT (10: AF and 1: atrial flutter). Eight cases of AF were newly detected when inappropriate shocks occurred. These shocks increased with age in accordance with increasing number of SVTs (Figure 4A) and reached a peak in patients who were in their sixties (Figure 4B).

Discussion

Main Findings

It is thought, albeit with uncertainty, that ICD implantation may provide less benefit to elderly patients with Brugada syndrome, although there is no definite evidence. This study, long-term (about 100 months) follow-up of 120 BrS patients with ICD including 90 high-risk patients, showed that the incidence of VF decreased with age, the first VF never occurred after age of 70 years in all patients, and no VF recurrences occurred after age of 70 years in patients without ischemic heart disease. The inappropriate shocks because of SVT increased with age, and the risk of lead failure also increased over time. Considering the higher risk of ICD complications with age, BrS patients who remain free from VF until 70 years of age might not benefit from an invasive procedure, such as ICD or lead implantation, and lead extraction after 70 years.

Prognosis of Elderly Patients With Brugada Syndrome

There is a considerable number of reports on the clinical characteristics and prognosis of the adult patients with BrS.[2,3,8,9] However, several case reports[10,11] and only 1 systemic study[12] exist about the clinical characteristics of the elderly patients with BrS. Conte et al[12] retrospectively analyzed 74 BrS patients aged >60 years, among whom 31 patients had ICD, and concluded that the BrS patients aged >70 years might be a lower risk category of patients compared with younger individuals because none of the elderly patients who were >70 years had aborted sudden death. However, the characteristics of their cohort were different from the previous reports of BrS,[3,8,9,13] that is, only 3% of the patients had a history of VF and only 13% of the patients had a spontaneous type 1 ECG. In addition, the mean follow-up period of their study was <55 months, and among 25 patients >70 years, no patients had a history of VF and only 9 patients had syncope. This means that their conclusion was drawn from the cohort consisting of a small number of high-risk patients who were followed for a shorter period than in this study. However, in this study, all the 120 patients including 50 patients who were aged ≥60 years had received ICD. Among them, 70% showed type 1 ECG spontaneously, 30% had a history of VF, and 45% had experienced an episode of syncope. The mean follow-up time was 102 months and 15 of 17 (88%) patients who were >70 years had a history of VF or syncope. Thus, the cohort in this study included a large number of patients not only with higher risk features but also with a much longer follow-up. Furthermore, contrary to the study by Conte et al, in which ventricular arrhythmias of elderly patients were incompletely tracked by a limited number of ICDs (31 patients with age ≥60 years, about 10 with age ≥70 years), this study showed the decennial VF incidence based on a more thorough arrhythmia tracking with a larger number of ICDs (50 patients with age ≥60 years, 17 with age ≥70 years). Although, every patient without a prior history of VF before 70 years of age and most patients with a history of VF experienced no VF after 70 years of age, whereas 2 patients >70 years were taking low-dose quinidine. In 2 elderly patients with VF recurrence, newly developed myocardial ischemia was suspected to trigger VF episodes although there was no ECG evidence showing acute coronary syndrome. This means that BrS patients aged >70 years without ischemic heart disease

A

B
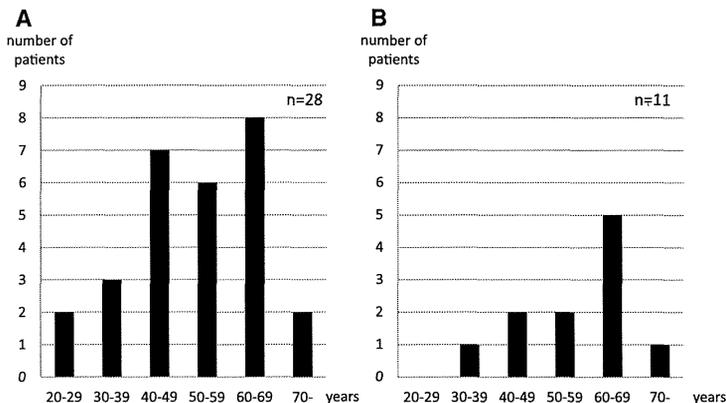
Figure 4. The age distribution of the first supraventricular tachycardia (SVT; **A**) and of the inappropriate shocks because of SVT (**B**). Inappropriate shocks because of SVT occurred in 11 of 28 patients (39%) with SVT. The number of SVT and inappropriate shocks increased with age.

might belong to a lower risk group of VF patients than younger BrS patients. Actually, as far as we know, there exist no reports of ECG documentation of new onset VF or electrical storm in patients with BrS after 70 years of age.

The decreasing incidence of VF with age in the middle-aged to elderly, which was first demonstrated using person-years analysis in this study, might give clues to the understanding of the mechanism of BrS (Figure 2C). Supposing that VF attack in BrS is caused by a depolarization abnormality only,[4] the number of ventricular arrhythmias would not decrease with age because structural changes would continue to contribute to arrhythmias. Yet the decreasing incidence of VF after reaching a peak between 20 and 39 years of age may indicate that the repolarization abnormality plays a major role in the pathogenesis of VF in patients with BrS. One of the possible background factors that influence ventricular repolarization is the level of sex hormone that can increase the outward potassium current or decrease the inward calcium current. There have been suggestions that Brugada phenotype has a relationship to the level of sex hormones,[14,15] and the decrease in blood level of testosterone with aging[16] might contribute to the low incidence of VF in elderly patients. Further studies will be needed to investigate the role of sex hormone in ventricular arrhythmias in BrS.

ICD Complications in Patients With Brugada Syndrome

This study showed a high incidence of inappropriate shocks, lead troubles, and ICD-related infections with increasing age of patients, some of which were reported by previous studies.[1,17–19] Moreover, as the second novel finding, we observed that the mean age at the onset of SVT was after middle age (52.3±12.7 years), and that inappropriate shocks because of SVT increased with age (Figure 4). This means optimal programming of ICD including single high-rate VF zone (210–220 beats per minute) and long VF detection interval, and the lead positioning with adequate R-wave discrimination might become essential for the prevention of inappropriate shocks in the elderly BrS patients. Furthermore, catheter ablation can also be effective to reduce inappropriate shocks in patients with AF.[20]

ICD generator/lead has been routinely implanted or exchanged in patients with a history of VF or syncope because they have been shown to have a poor prognosis.[1,3,8,9,17] However, it is difficult to decide not to implant an ICD in asymptomatic patients with multiple risk factors of sudden death (induced VF, strong family history, etc) because we still have no reliable data for predicting a future VF event. This study indicated that the BrS patients who had only syncope or remained asymptomatic until 70 years of age may be spared from a future VF event. In addition, given our data that none of the BrS patients without ischemic heart disease experienced further VF recurrence after 70 years of age, and the increasing risk of inappropriate shocks because of SVT or lead failure with aging, avoidance of an invasive procedure, such as new ICD implantation, or ICD generator/lead exchange may be advisable for such patients. Nevertheless, the device-guided management for patients with low or intermediate risk still remains controversial. Subcutaneous ICD[21] can be implanted as substitute for transvenous ICD for such patients.

Study Limitations

This was conducted at a single-center using retrospective analysis. The small number of patients might limit the interpretation of the results, yet, it should be pointed out that no other reports with a significant number of high-risk elderly BrS patients exist. In addition, the number of VF patients is larger, and the follow-up period in this study is much longer than that of the worldwide multicenter registry of BrS patients with ICD.[17] Furthermore, prospective multicenter studies with larger numbers of patients will be needed to confirm these results.

Conclusions

Long-term follow-up of high-risk BrS patients with ICD showed a low incidence of VF in the elderly patients. Considering the increasing risk of inappropriate shocks because of the relatively late onset of SVT and lead failures, avoidance of ICD implantation or replacement may be considered in elderly BrS patients who remain free from VF until 70 years of age.

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Disclosures

References

1. Sacher F, Probst V, Iesaka Y, Jacon P, Laborderie J, Mizon-Gérard F, Mabo P, Reuter S, Lamaison D, Takahashi Y, O'Neill MD, Garrigue S, Pierre B, Jaïs P, Pasquié JL, Hocini M, Salvador-Mazenq M, Nogami A, Amiel A, Defaye P, Bordachar P, Boveda S, Maury P, Klug D, Babuty D, Haïssaguerre M, Mansourati J, Clémenty J, Le Marec H. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation*. 2006;114:2317–2324. doi: 10.1161/CIRCULATIONAHA.106.628537.
2. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005;111:659–670. doi: 10.1161/01.CIR.0000152479.54298.51.
3. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635–643. doi: 10.1161/CIRCULATIONAHA.109.887026.
4. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. *J Mol Cell Cardiol*. 2010;49:543–553. doi: 10.1016/j.yjmcc.2010.07.012.
5. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963. doi: 10.1016/j.hrthm.2013.05.014.
6. Makimoto H, Kamakura S, Aihara N, Noda T, Nakajima I, Yokoyama T, Doi A, Kawata H, Yamada Y, Okamura H, Satomi K, Aiba T, Shimizu W. Clinical impact of the number of extrastimuli in programmed electrical

stimulation in patients with Brugada type 1 electrocardiogram. *Heart Rhythm*. 2012;9:242–248. doi: 10.1016/j.hrthm.2011.09.053.

7. Watanabe H, Nogami A, Ohkubo K, Kawata H, Hayashi Y, Ishikawa T, Makiyama T, Nagao S, Yagihara N, Takehara N, Kawamura Y, Sato A, Okamura K, Hosaka Y, Sato M, Fukae S, Chinushi M, Oda H, Okabe M, Kimura A, Maemura K, Watanabe I, Kamakura S, Horie M, Aizawa Y, Shimizu W, Makita N. Electrocardiographic characteristics and SCN5A mutations in idiopathic ventricular fibrillation associated with early repolarization. *Circ Arrhythm Electrophysiol*. 2011;4:874–881. doi: 10.1161/CIRCEP.111.963983.

8. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, Makita N, Hagiwara N, Inoue H, Atarashi H, Aihara N, Shimizu W, Kurita T, Suyama K, Noda T, Satomi K, Okamura H, Tomoike H; Brugada Syndrome Investigators in Japan. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. *Circ Arrhythm Electrophysiol*. 2009;2:495–503. doi: 10.1161/CIRCEP.108.816892.

9. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59:37–45. doi: 10.1016/j.jacc.2011.08.064.

10. Juang J.-M., Lai L.-P., Lin J.-L., Chiang F.-T. Brugada syndrome in the elderly in Taiwan: report of two cases. *Acta Cardiol Sin*. 2005;21:62–67.

11. Conte G, Levinstein M, Sarkozy A, Brugada P. Brugada syndrome in the elderly. *Eur Heart J*. 2013;34:319. doi: 10.1093/eurheartj/ehs415.

12. Conte G, DE Asmundis C, Sieira J, Levinstein M, Chierchia GB, DI Giovanni G, Baltogiannis G, Ciconte G, Saitoh Y, Casado-Arroyo R, Pappaert G, Brugada P. Clinical characteristics, management, and prognosis of elderly patients with Brugada syndrome. *J Cardiovasc Electrophysiol*. 2014;25:514–519. doi: 10.1111/jce.12359.

13. Delise P, Allocca G, Marras E, Giustetto C, Gaita F, Sciarra L, Calo L, Proclemer A, Marziali M, Rebellato L, Berton G, Coro L, Sitta N. Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach. *Eur Heart J*. 2011;32:169–176. doi: 10.1093/eurheartj/ehq381.

14. Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, Nagaya N, Suyama K, Aihara N, Kamakura S, Inamoto N, Akahoshi M, Tomoike H. Sex hormone and gender difference–role of testosterone on male predominance in Brugada syndrome. *J Cardiovasc Electrophysiol*. 2007;18:415–421. doi: 10.1111/j.1540-8167.2006.00743.x.

15. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing Clin Electrophysiol*. 2003;26(7 Pt 1):1551–1553.

16. Kells J, Dollbaum CM. Testosterone levels in an aging population: screen, measure, and restore. *Int J Pharm Compd*. 2011;15:102–112.

17. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A, Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A, Nogami A, Ritter P, Gourraud JB, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar P, Pierre B, Jaïs P, Pasquié JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P, Haïssaguerre M. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. *Circulation*. 2013;128:1739–1747. doi: 10.1161/CIRCULATIONAHA.113.001941.

18. Sarkozy A, Boussy T, Kourgiannides G, Chierchia GB, Richter S, De Potter T, Geelen P, Wellens F, Spreeuwenberg MD, Brugada P. Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. *Eur Heart J*. 2007;28:334–344. doi: 10.1093/eurheartj/ehl450.

19. Morrison TB, Friedman PA, Kallinen LM, Hodge DO, Crusan D, Kumar K, Hayes DL, Rea RF, Hauser RG. Impact of implanted recalled sprint Fidelis lead on patient mortality. *J Am Coll Cardiol*. 2011;58:278–283. doi: 10.1016/j.jacc.2011.03.027.

20. Conte G, Chierchia GB, Wauters K, De Asmundis C, Sarkozy A, Levinstein M, Sieira J, Baltogiannis G, Di Giovanni G, Ciconte G, Casado-Arroyo R, Saitoh Y, Brugada P. Pulmonary vein isolation in patients with Brugada syndrome and atrial fibrillation: a 2-year follow-up. *Europace*. 2014;16:528–532. doi: 10.1093/europace/eut309.

21. De Maria E, Cappelli S, Cappato R. Shock efficacy of the entirely subcutaneous defibrillator for termination of spontaneous ventricular fibrillation in Brugada syndrome. *Heart Rhythm*. 2013;10:1807–1809. doi: 10.1016/j.hrthm.2013.08.008.