Clinical Differences in Japanese Patients Between Brugada Syndrome and Arrhythmogenic Right Ventricular Cardiomyopathy With Long-Term Follow-Up

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Some Brugada syndrome (BrS) patients have been suspected of being in the initial state of arrhythmogenic right ventricular cardiomyopathy (ARVC). This study aimed to clarify the electrocardiographic (ECG) and clinical differences between BrS and ARVC in long-term follow-up (mean 11.9 ± 6.3 years). A total of 50 BrS and 65 ARVC patients with fatal ventricular tachyarrhythmia (VTA) were evaluated according to the revised Task Force Criteria for ARVC. Based on the current diagnostic criteria concerning electrocardiographic, repolarization abnormality was positive in 2.0% and 2.6% of BrS patients at baseline and follow-up, and depolarization abnormality was positive in 6.0% and 12.8% of BrS patients at baseline and follow-up, respectively. At baseline, none of the BrS patients were definitively diagnosed with ARVC. Considering patients' lives since birth, Kaplan-Meier analysis revealed that age at first VTA attack showed the same tendency between the groups (BrS: mean 42.2 ± 12.5 years old vs ARVC: mean 44.8 ± 13.7 years old, log-rank p = 0.123). Moreover, the incidence of VTA recurrence was similar between the groups during follow-up (log-rank p = 0.906). Incidence of sustained monomorphic ventricular tachycardia was significantly higher in ARVC than in BrS whereas the opposite was true for ventricular fibrillation (log-rank p <0.001 and p <0.001, respectively). None of the diagnoses of BrS patients were changed to ARVC during follow-up. During long-term follow-up, although age at first VTA attack and VTA recurrence were similar, BrS consistently exhibited features that differed from those of ARVC. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:715−722)**

Both arrhythmogenic right ventricular cardiomyopathy (ARVC) and Brugada syndrome (BrS) are inherited diseases in which a predisposition for fatal ventricular tachyarrhythmia originates from the right ventricle (RV).[1−4] BrS involves a myocardial disorder presenting as a structural abnormality on several imaging modalities and endomyocardial biopsy, similar to ARVC.[3−5] In both diseases, electrocardiograms (ECGs) show late r'/J wave with T-wave inversion and QRS fragmentation/epsilon wave in right precordial leads, and electrophysiologic studies show fractionated/delayed potential predominantly on the RV epicardium.[2,6−12] Genetic overlapping has also been reported.[13] Because of their similar manifestation, an overlapping pathogenetic link between the 2 syndromes and BrS as a first stage of ARVC has been proposed as a newly controversial topic.[1,2,12] The present study aimed to clarify the difference in phenotype and transition of diagnosis between BrS and ARVC with long-term follow-up.

Methods

The present study population consisted of 115 consecutive patients who visited our institution between 2001 and 2011 and were followed up. In general, BrS and ARVC involve patients with no episodes of fatal arrhythmia. To compare ARVC patients who appear similar to BrS patients, we analyzed both ARVC and BrS patients with fatal ventricular tachyarrhythmia. A diagnosis of BrS or ARVC was made according to the Shanghai Brugada Scoring System and the revised Task Force Criteria 2010, respectively.[14,15] In BrS, all patients presented with spontaneous or pilsicainide-induced type 1 ECG. None of the BrS patients were definitively diagnosed with ARVC at baseline. All of the ARVC patients were considered to have definite ARVC based on the current diagnostic criteria.[15] All subjects had

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experienced malignant ventricular arrhythmias, including sustained monomorphic ventricular tachycardia (SMVT) and/or ventricular fibrillation (VF). A malignant ventricular arrhythmias episode was defined as an episode of cardiopulmonary resuscitation or an event lasting over 30 seconds recorded on an implantable cardioverter defibrillator (ICD) or surface ECG. Electrical storm was defined as ≥3 episodes of VF within 24 hours. The present study was approved by the Institutional Research Board of the National Cerebral and Cardiovascular Center.

Clinical characteristics such as age at first visit to our institution, gender, height, body weight, co-morbidity (hypertension, coronary artery disease, and atrial flutter/fibrillation), episodes of syncope, family history of sudden cardiac death defined as any unexplained death before 45 years of age within the second degree of kinship, implantation of an ICD, time from first visit to an index cardiac event (malignant ventricular arrhythmias, congestive heart failure, cardiac transplantation, or cardiac death), echocardiography, age at first malignant ventricular arrhythmias attack, and several ECG parameters were collected.

Patients were followed for a mean of 11.9 ± 6.3 years until 2019. After a median follow-up time of 12.0 years, a re-examination of ECG was performed between 2008 and 2019. Comparisons were made between the electrophysiological features at the time of first visit (baseline) and those at the time of last visit (follow-up) for patients who were followed up over 5 years. Echocardiography was re-evaluated in 32 BrS patients who were followed up more than 5 years.

Detailed information related to methods of ECG, signal averaged ECG (SAECG), and statistical analysis is available in Supplementary Material. Depolarization and repolarization abnormalities were determined according to the current diagnostic criteria.[15] Briefly, depolarization abnormality was determined by SAECG, epsilon wave, or terminal activation duration of QRS and repolarization abnormality was determined by inverted T waves (ITW) in precordial leads (Figure 1).

Results

Clinical characteristics at baseline are described in Table 1. Incidence of SMVT episodes was significantly

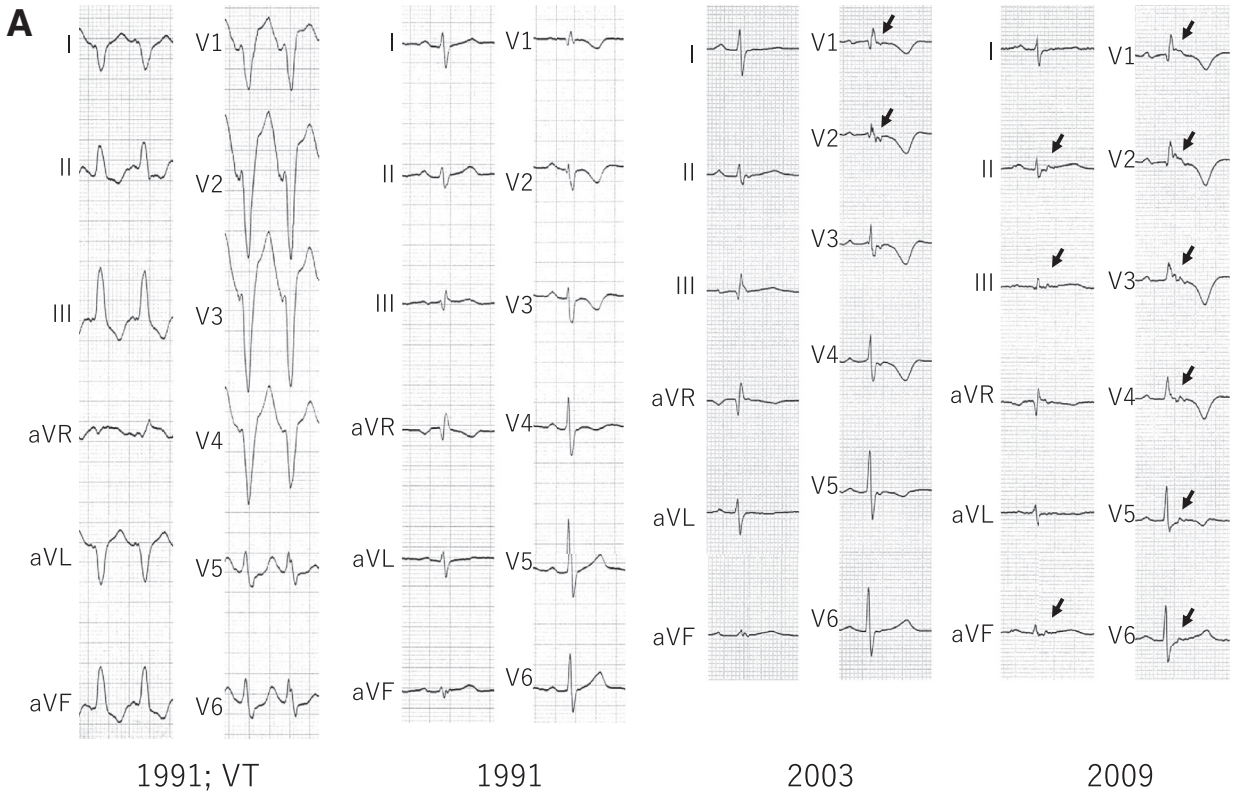

Figure 1. **A.** Representative ECGs in a patient with arrhythmogenic right ventricular cardiomyopathy. A 45-year-old male patient with arrhythmogenic right ventricular cardiomyopathy who had episodes of sustained monomorphic ventricular tachycardia (SMVT) in 1991. ECG at baseline exhibited inverted T waves (ITW) in leads V1 to V4. After 12 years, ITW extended to lead V5 and epsilon waves appeared in leads V1 and V2 (ECG in 2003). At follow-up (ECG in 2009), QRS fragmentation (epsilon waves) extended to all precordial leads and inferior leads; moreover, QRS amplitude decreased, especially in left precordial leads. B. Representative ECGs in a patient with arrhythmogenic right ventricular cardiomyopathy. A 43-year-old male patient with arrhythmogenic right ventricular cardiomyopathy. At baseline (ECG in 1993), the ECG exhibited inverted T waves (ITW) in leads V1 to V4 and inferior leads. Moreover, extended ITW to lead V5 decreased amplitude and widened duration of QRS waves in all leads, extended QRS fragmentation (epsilon waves) to lead V5, II, and aVF appeared at follow-up (ECG in 2006). C. Representative ECGs in a patient with Brugada syndrome. A 67-year-old male patient with Brugada syndrome who had episodes of ventricular fibrillation. At baseline (ECG in 2003), coved-type ECG presented in leads V1 and V2. In comparison with arrhythmogenic right ventricular cardiomyopathy, extension of ITW appearance, miniaturization of QRS amplitude, widening of QRS duration, and appearance of QRS fragmentation were not remarkable, even after more than 10 years (ECG in 2011 and 2017). Arrows in A and B indicate epsilon waves and QRS fragmentation.

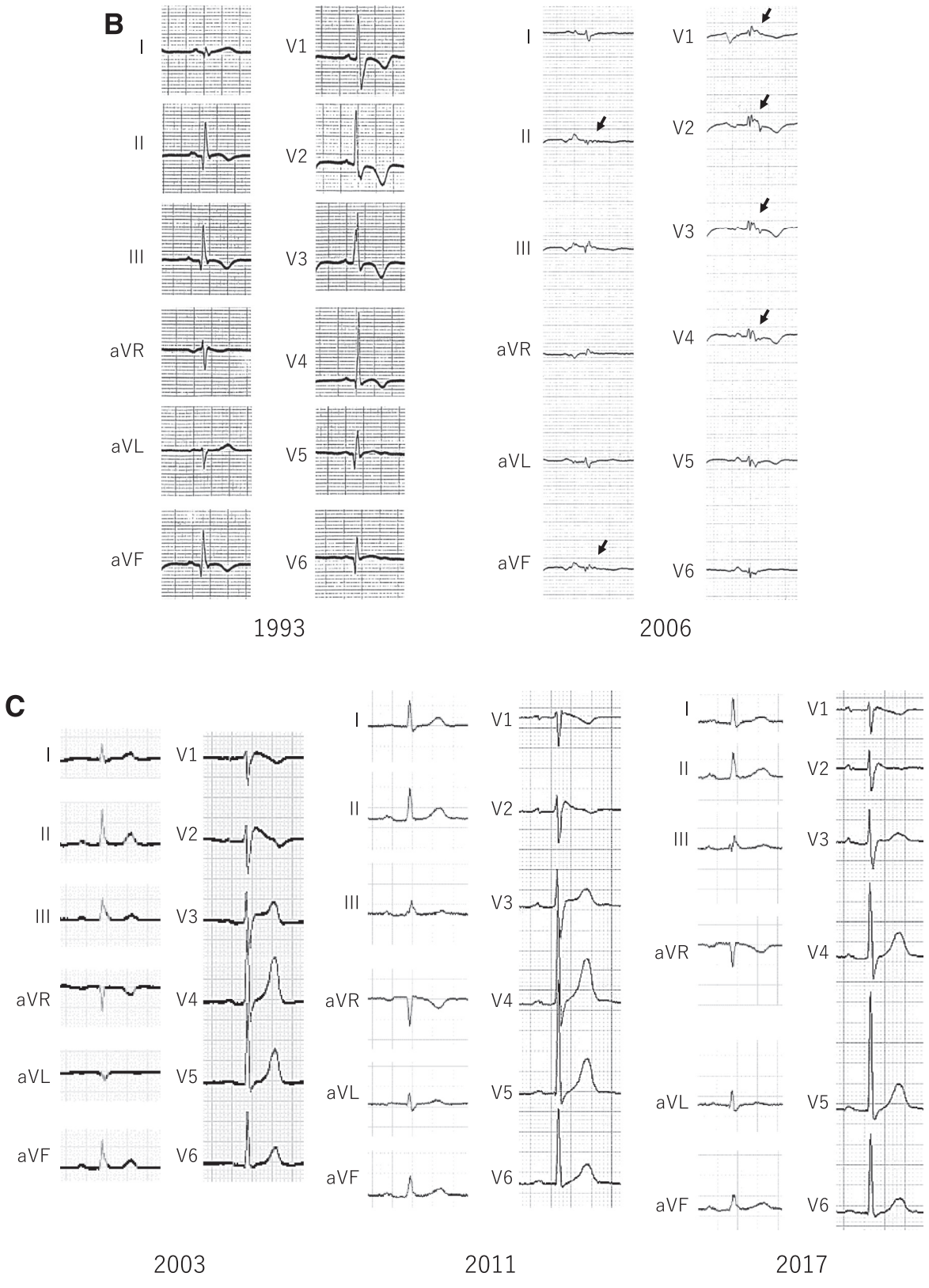

Figure 1. Continued.

Table 1
Clinical characteristics

Variable	BrS	ARVC	p Value
Number of patients	50	65	
Age at diagnosis (years)	46.4 ± 13.0	51.4 ± 15.3	0.068
Male	49 (98%)	50 (76%)	0.002
Height (cm)	170.3 ± 7.9	163.6 ± 8.2	<0.001
Weight (kg)	66.2 ± 9.5	62.4 ± 11.4	0.096
Body mass index (kg/m^2)	22.8 ± 2.4	23.2 ± 3.5	0.466
Echocardiography			
Left ventricular end diastolic dimension (mm)	47.4 ± 4.4	47.2 ± 4.8	0.764
Left ventricular end systolic dimension (mm)	30.7 ± 3.6	32.5 ± 5.5	0.049
Left ventricular ejection fraction (%)	58.9 ± 6.1	52.5 ± 12.5	0.001
Comorbidity			
Hypertension	4 (8%)	5 (8%)	0.790
Coronary artery disease	6 (12%)	5 (8%)	0.627
Atrial flutter/fibrillation	8 (16%)	19 (29%)	0.164
Syncope	21 (42%)	24 (36%)	0.537
Family history of sudden cardiac death	6 (12%)	3 (5%)	0.256
Usage of antiarrhythmic drugs	1 (2%)	43 (65%)	<0.001
Class I	1 (2%)	28 (42%)	<0.001
Class III	0	9 (14%)	0.005

higher in ARVC than in BrS; however, the opposite was true for VF. Usage of antiarrhythmic drugs (AADs) was significantly higher in ARVC than in BrS. No patients with BrS and 4 patients with ARVC received radiofrequency ablation for malignant ventricular arrhythmias before the baseline. The comparison of ECG and SAECG characteristics at baseline between BrS and ARVC is shown in Table 2. Epsilon waves (epsilon-like waves in BrS[17]) and QRS fragmentation could be detected more frequently in ARVC than in BrS. Incidence of positive late potential (LP) on SAECG was similar between the 2 groups. Incidence of ITW in precordial and inferior leads was higher in ARVC than in BrS, except for in lead V6 (Figure 2). ECG features in right precordial leads (leads V1 to V3) were compared for BrS and ARVC (Table 1 in Data Supplement).

Among 115 patients enrolled in the present study, 88 patients (39 patients with BrS and 49 patients with ARVC) could be followed up more than 5 years. ICDs were implanted

Table 2
Comparison of ECG parameters between BrS and ARVC

ECG parameters	Baseline			Follow-up		
	BrS	ARVC	*p* value	BrS	ARVC	p Value
Number of patients	50	65		39	49	
Heart rate (bpm)	63.7 ± 9.6	64.5 ± 11.3	0.714	68.3 ± 9.1	62.8 ± 13.4	0.001
PQ interval (ms)	188.3 ± 29.7	188.4 ± 42.4	0.987	199.5 ± 35.2	200.1 ± 47.3	0.608
First-degree AVB	14 (28%)	22 (34%)	0.433	13 (33%)	20 (41%)	0.513
QRS duration in lead II (ms)	110.3 ± 23.9	107.1 ± 27.1	0.586	114.6 ± 25.2	117.5 ± 29.2	0.637
CRBBB	8 (16%)	17 (26%)	0.255	9 (23%)	18 (37%)	0.245
Epsilon waves	3 (6%)	27 (42%)	< 0.001	6 (15%)	24 (49%)	0.001
QRS fragmentation	9 (18%)	30 (46%)	0.002	12 (31%)	27 (55%)	0.031
Positive LP/total number	28/35 (80%)	45/50 (90%)	0.219	14/22 (64%)	No data	
fQRS (ms)	123.0 ± 21.2	160.4 ± 52.3	< 0.001	124.8 ± 29.7		
RMS40 (μV)	12.4 ± 9.4	8.2 ± 11.6	0.081	15.5 ± 11.3		
LAS40 (ms)	50.6 ± 15.5	86.4 ± 49.9	< 0.001	50.7 ± 22.1		
S wave in lead I						
Amplitude (mV)	0.20 ± 0.14	0.24 ± 0.14	0.122	0.25 ± 0.14	0.25 ± 0.14	0.869
Duration (ms)	51.8 ± 23.7	60.1 ± 21.2	0.063	55.1 ± 30.3	63.5 ± 28.9	0.218
ER pattern						
In inferior leads	7 (14%)	7 (11%)	0.812	6 (15%)	4 (8%)	0.328
In lateral leads	7 (14%)	3 (5%)	0.151	0	3 (6%)	0.251
In leads I and aVL	4 (8%)	0	0.071	3 (8)	0	0.083
Depolarization abnormality						
Major criteria	3 (6%)	27 (42%)	< 0.001	5 (13%)	24 (49%)	< 0.001
Minor criteria	30 (60%)	28 (43%)	0.091	15 (38%)	12 (24%)	0.172
Repolarization abnormality						
Major criteria	1 (2%)	24 (37%)	< 0.001	1 (3%)	18 (37%)	< 0.001
Minor criteria	10 (20%)	16 (25%)	0.655	9 (23%)	17 (35%)	0.252

AVB = atrioventricular block; CRBBB = complete right bundle branch block; ER = early repolarization; LP = late potential on signal-averaged ECG.

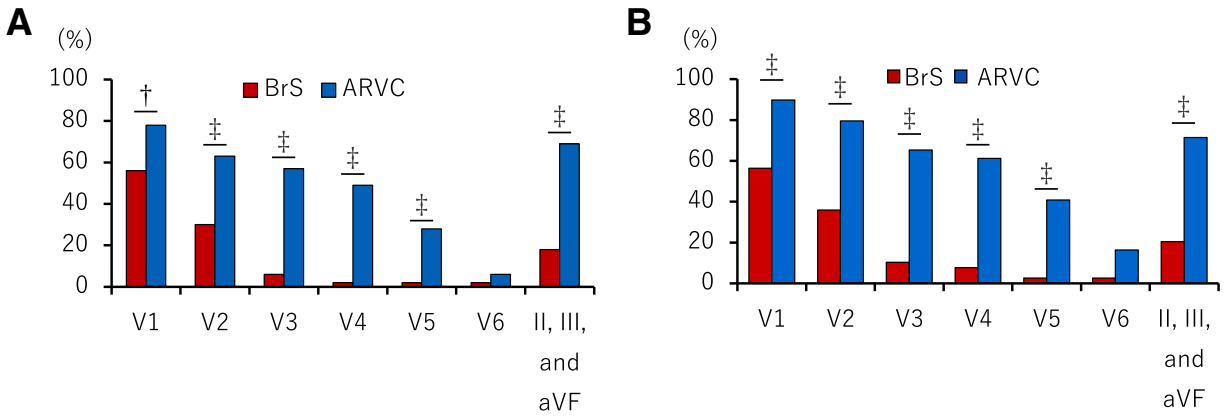

Figure 2. **A.** Incidence of inverted T wave in each lead at baseline. † $p < 0.01$ and ‡ $p < 0.001$. B. Incidence of inverted T wave in each lead at follow-up. ‡ $p < 0.001$.

in all BrS patients whereas only 50% patients of ARVC had ICDs. During follow-up, radiofrequency ablation for malignant ventricular arrhythmias was performed in 1 BrS patient and 4 ARVC patients. Usage of AADs was significantly higher in ARVC than in BrS, especially in class III AAD (28 [57%] vs 6 [15%], $p < 0.001$, respectively), but not in class I (13 [27%] vs 6 [15%], $p = 0.298$, respectively). ECG characteristics at follow-up were used to compare BrS with ARVC (Table 2). Epsilon waves, QRS fragmentation, S-wave amplitude and duration in lead I, incidence of early repolarization pattern, and incidence of ITW showed the same trends as those at baseline (Table 2 and Figure 2). ECG features in precordial leads were also compared for BrS and ARVC (Table 1 in Data Supplement). In right precordial leads, both depolarization and repolarization parameters showed the same trends as those at baseline, except for R-wave amplitude in lead V3. In left precordial leads, both depolarization and repolarization parameters showed the same trends as those at baseline, except for QRS duration, which was significantly longer in ARVC than in BrS. Based on the current diagnostic criteria, depolarization and repolarization abnormalities were evaluated at baseline and follow-up in both groups (Table 2). Even though other depolarization and repolarization parameters indicated similar changes with follow-up in precordial leads, QRS durations in leads V4 to V6 were significantly more prolonged in ARVC compared with BrS but not in leads V1 to V3 (Table 2 in Data Supplement).

In Kaplan-Meier analysis, age at first malignant ventricular arrhythmias attack showed the same tendency in both groups (log-rank $p = 0.123$, Figure 3). Onset occurred in the teens and ended at around 70, and average ages in both groups were in the middle-age range (BrS: 42.2 ± 12.5 years old vs ARVC: 44.8 ± 13.7 years old, $p = 0.308$). The mean follow-up period was 13.2 ± 7.8 years in BrS and 10.9 ± 4.6 years in ARVC ($p = 0.054$). Interestingly, incidence of malignant ventricular arrhythmias recurrence did not significantly differ between the 2 groups during follow-up (log-rank $p = 0.906$, Figure 3). Incidence of SMVT was significantly higher in ARVC than in BrS whereas the opposite was true for VF (log-rank $p < 0.001$ and $p < 0.001$, respectively, Figure 3). Patients with BrS demonstrated significantly favorable outcomes regarding all-cause mortality compared with the ARVC group (log-rank $p = 0.024$, Figure 3). Although 12.3% patients with ARVC died from cardiovascular disease or received transplantation during follow-up, this was absent in BrS patients (log-rank $p = 0.011$, Figure 3). Heart failure hospitalization was also significantly higher in ARVC and was absent in BrS (log-rank $p < 0.001$, Figure 3). Incidence of malignant ventricular arrhythmias storm was significantly higher in BrS compared with ARVC (log-rank $p = 0.048$, Figure 3).

All diagnoses in BrS patients were re-evaluated at follow-up using the current diagnostic criteria for analysis of the development from BrS to ARVC.[15] No patients with BrS were newly diagnosed with definite ARVC, however. Echocardiography did not reveal regional RV akinesia, dyskinesia, or aneurysm in any of the 32 BrS patients at follow-up. In BrS patients, 3 were borderline and 10 were possible at baseline, and 2 were borderline and 8 were possible at follow-up for a diagnosis of ARVC.

Discussion

The major findings of the present study are as follows. First, age at first episode and recurrence of malignant ventricular arrhythmias showed the same tendency in BrS and ARVC. However, none of the BrS patients with fatal ventricular tachyarrhythmias were definitively diagnosed with ARVC at baseline or after follow-up. Second, incidence of SMVT was higher in ARVC than in BrS whereas the opposite was true for VF. Cardiovascular death and heart failure hospitalization were frequent in ARVC and absent in BrS. Third, ECG abnormalities were more exacerbated in ARVC than in BrS at both baseline and follow-up.

Several papers have reported that conduction abnormalities could be characterized in ARVC. The abnormality of ventricular depolarization due to fibrosis is represented by epsilon waves, LPs, or QRS fragmentation.[18,19] BrS is also characterized by conduction abnormalities demonstrated by QRS fragmentation and LPs.[8,16,20] The present data indicate that depolarization abnormality is more prominent in ARVC than in BrS, and that this difference increases after long-term follow-up. Regarding repolarization abnormalities, differences in QT interval, JT interval, and ITW have not been described in previous papers.[2] Our results showed QTc and JTc intervals in all precordial leads were longer in ARVC than in BrS, and the expanse of ITW in precordial and inferior leads was larger in ARVC than in BrS. ITW in precordial leads, especially in leads V1 to V3, has been

recognized as an important diagnostic feature in ARVC, and ITW in inferior leads was reported to be associated with ventricular arrhythmia.[15,19] Our results suggested that the expanse of ITW was significantly different between BrS and ARVC at both baseline and follow-up. BrS has been reported to exhibit both depolarization and repolarization abnormalities.[21] ARVC exhibited more severe depolarization and repolarization abnormality than BrS at baseline and follow-up.

As described above, ECG evaluation revealed that ARVC is a more severe myocardial disorder concomitant with depolarization and repolarization abnormality than BrS, even after long-term follow-up. Consequently, the incidence of heart failure hospitalization increased to 26% in ARVC whereas it was absent in BrS. Cardiovascular death/transplantation was also significantly frequent in ARVC and absent in BrS. Age at first malignant ventricular arrhythmias attack did not differ between the 2 groups. Despite a similar incidence of malignant ventricular arrhythmias recurrence, ARVC patients demonstrated SMVT dominance whereas BrS patients demonstrated VF dominance even after long-term follow-up. Electrical storm was significantly frequent in BrS compared with ARVC. None of the diagnoses of the BrS patients were changed to ARVC. In previous studies, there has been no comparison regarding the natural history between BrS and ARVC.[2] The results may indicate that the 2 diseases involve a different pathogenesis of cardiac events, and the clinical phenotypes are apparently different, regardless of disease progression after long-term follow-up. Our investigation did not evaluate the pathophysiologic mechanism in each disease, which should be examined in future research. The hypothesis that BrS is the initial state of ARVC was not confirmed in our limited cohort.

This study has several limitations. First, the present study was assessed retrospectively. Second, the sample size is relatively modest because BrS and ARVC with ventricular tachyarrhythmias are rare diseases in a single center. However, because it was a single-center study and the subjects share the same ethnic background, we were able to compare patients with BrS and ARVC over time under the same conditions.

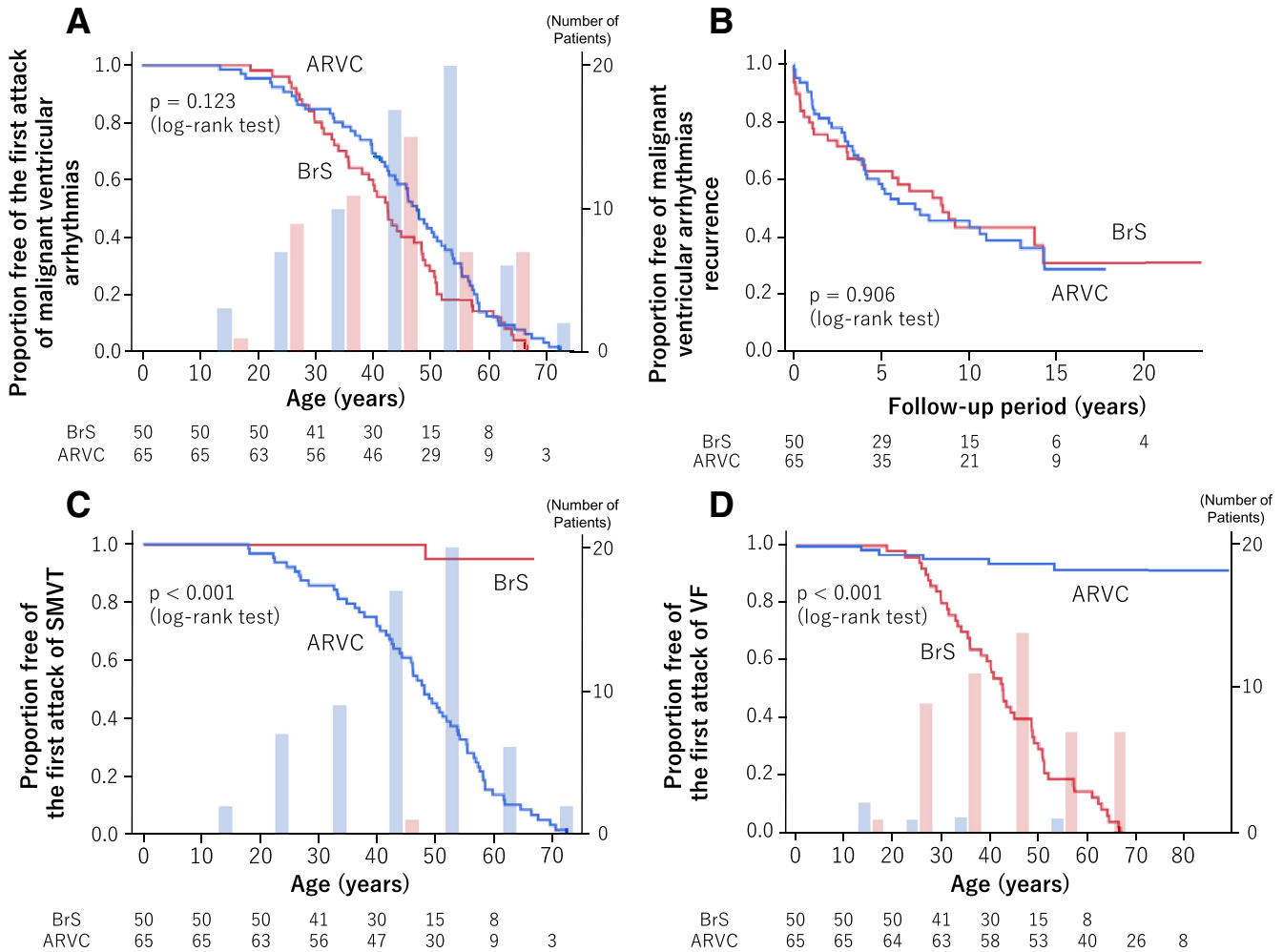

Figure 3. Kaplan-Meier analysis. Kaplan-Meier analysis regarding age at first malignant ventricular arrhythmias attack (A), incidence of malignant ventricular arrhythmias recurrence (B), age at first SMVT attack (C), age at first VF attack (D), all-cause death (E), cardiovascular death/transplantation (F), heart failure hospitalization (G), and malignant ventricular arrhythmias storm (H). Bar graphs in A, C, and D indicate the number of patients who developed malignant ventricular arrhythmias (A), SMVT (C), and VF (D) in each age decade, and the scale is displayed on the right-hand side. Red lines or bars indicate BrS; blue lines or bars, ARVC. (Color version of figure is available online.)

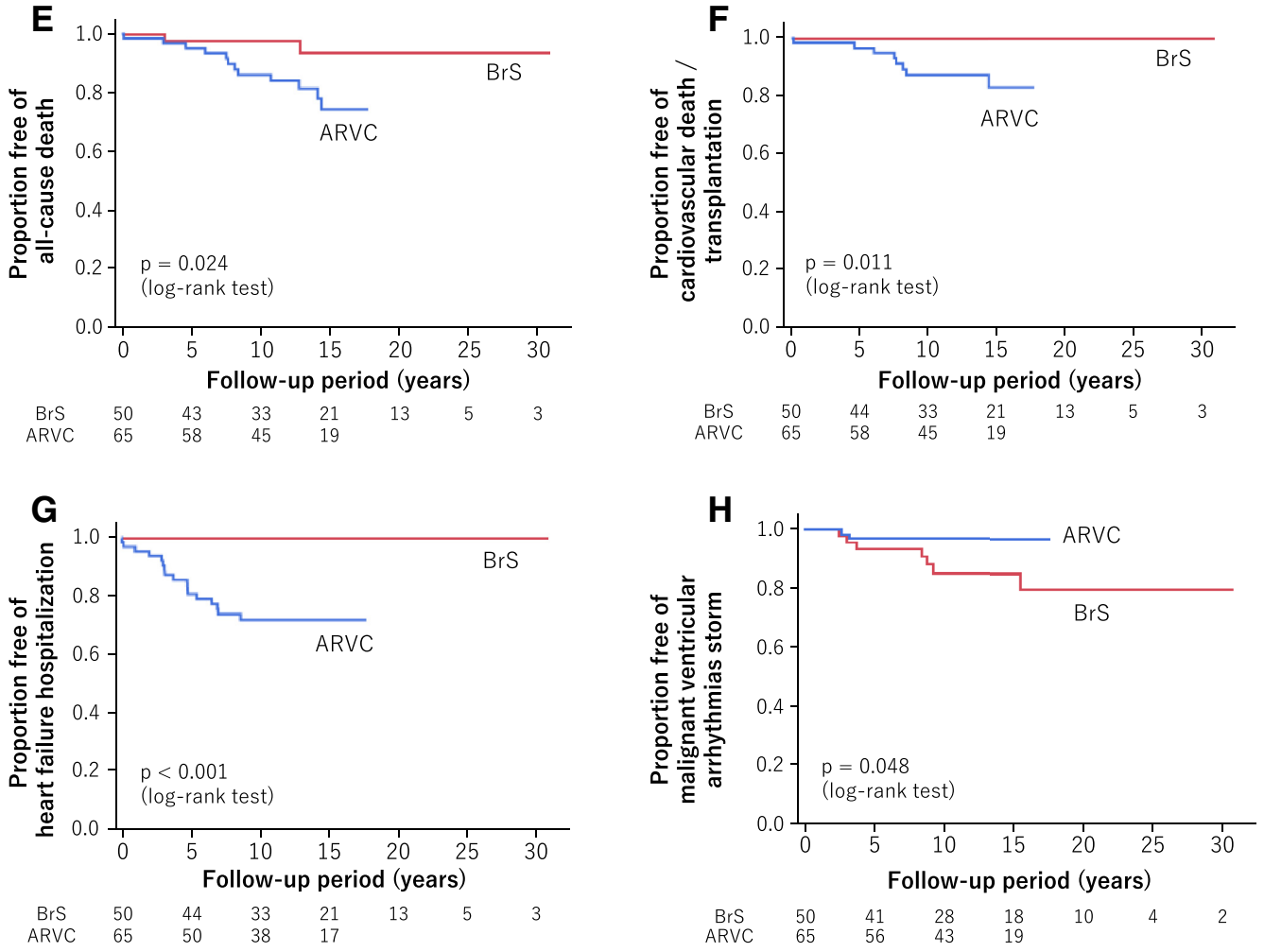

Figure 3. Continued.

Third, the difference of AADs, prevalence of atrial fibrillation, and left ventricular ejection fraction could affect ECG parameters and clinical prognoses. Fourth, adequate echocardiography data regarding right ventricular function and dimension might support the difference between the 2 diseases. Finally, no information on gene mutations and structural abnormalities related to the RV that can be found in cardiac magnetic resonance imaging, angiography, and endomyocardial biopsy were evaluated specifically at follow-up. These parameters may also be useful in verifying the homologies between BrS and ARVC.

In conclusion, both depolarization and repolarization parameters were more aggravated at baseline and further advanced at follow-up in ARVC compared with BrS. Although previous reports have noted the overlapping features between BrS and ARVC, in this limited cohort study, despite similar age at first event and recurrence rate of fatal ventricular tachyarrhythmia, all patients with BrS consistently exhibit features that differ from those of ARVC after long-term follow-up.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.067.

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