International Journal of Cardiology 241 (2017) 288–294

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Heart failure in patients with arrhythmogenic right ventricular cardiomyopathy: What are the risk factors?

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ARTICLE INFO

Article history:
Received 10 January 2017
Accepted 19 April 2017
Available online 21 April 2017

Keywords:
Arrhythmogenic right ventricular cardiomyopathy
First-degree atrioventricular block
Heart failure
Atrial arrhythmias

ABSTRACT

Background: We previously demonstrated that heart failure (HF) was one of the major causes of death in arrhythmogenic right ventricular cardiomyopathy (ARVC). The purpose of this study was to elucidate the clinical impact and risk factors of HF in patients with ARVC.

Methods and results: We evaluated cardiac adverse outcomes including HF in 113 consecutive patients with ARVC (85 men, mean age: 44 ± 15 years). During a median follow-up of 10.0 years (interquartile range: 5.2 to 15.7 years), 29 patients (26%) were hospitalized for progressive HF. The patients with one or more episodes of HF hospitalization had about a 10-fold increased incidence of cardiac death (14/29 [48%] vs. 4/84 [4.7%], $p < 0.0001$). Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) were significantly lower in the patients with HF hospitalization compared to the patients without HF hospitalization (LVEF, 45 ± 15 vs. 54 ± 13%, $p = 0.001$; RVEF, 26 ± 10 vs. 33 ± 11%, $p = 0.003$, respectively). Regarding the ECG findings, the prevalence of first-degree atrioventricular block (AVB, PR interval >200 ms) and epsilon waves were significantly higher in patients with HF hospitalization than those without HF hospitalization (first-degree AVB, 14/29 [48%] vs. 11/84 [13%], $p < 0.0001$; epsilon waves, 10/29 [34%] vs. 12/84 [14%], $p = 0.02$). In multivariate analysis, first-degree AVB at baseline was the strongest independent risk factor for HF hospitalization in patients with ARVC (hazard ratio 4.24, 95% confidence interval 1.79–10.47, $p = 0.0011$).

Conclusion: HF hospitalization has a significant relation with malignant clinical course in ARVC patients. First-degree AVB was an independent determinant for increased risk of HF hospitalization.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy that is characterized clinically by right ventricular (RV) dysfunction and ventricular arrhythmias [1–3]. The pathological hallmark of ARVC is fibrofatty replacement of the RV myocardium. The clinical course of ARVC is variable and marked by ventricular arrhythmias, sudden death, and heart failure (HF).

Recent developments in antiarrhythmic therapies including combination of medication, catheter ablation, and implantable cardioverter defibrillator, should contribute to better prognosis and even freedom from potentially lethal ventricular arrhythmic events in patients with ARVC [4–6]. In contrast, HF is an important determinant of clinical prognosis in ARVC patients. Although ARVC is typified by ventricular arrhythmias, HF incidence as high as 20% has been reported [7]. Importantly, about 60% of deaths were related to progressive HF in the previous study of the natural history of patients with

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; AVB, atrioventricular block; CMR, cardiac magnetic resonance; CRTD, cardiac resynchronization therapy defibrillator; ECG, electrocardiogram; EF, ejection fraction; EPS, electrophysiological study; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LV, left ventricle; RBBB, right bundle branch block; rTFC, revised Task Force criteria; SAECG, signal-averaged electrocardiogram; SCD, sudden cardiac death; VT, ventricular tachycardia; VF, ventricular fibrillation.

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http://dx.doi.org/10.1016/j.ijcard.2017.04.061
0167-5273/

Table 1
Baseline characteristics in patients with and without HF hospitalization during the follow-up.

	Overall	HF hospitalization (+)	HF hospitalization (−)	*p* value
n	113	29 (26%)	84 (74%)	
Gender (male)	85 (75%)	19 (66%)	66 (79%)	0.16
Age at diagnosis (yrs)	44 ± 15	46 ± 14	43 ± 15	0.37
Age at enrollment (yrs)	46 ± 15	48 ± 14	45 ± 15	0.32
BSA	1.65 ± 0.17	1.63 ± 0.22	1.66 ± 0.15	0.32
Family history of ARVC/SD	18 (16%)	3 (10%)	15 (18%)	0.56
Previous VT/VF	75 (66%)	15 (52%)	60 (71%)	0.07
Diagnosis based on the rTFC				0.82
Definite	100 (88%)	26 (90%)	74 (88%)	
Borderline	13 (12%)	3 (10%)	10 (12%)	
NYHA functional class				0.0001
I	87 (77%)	14 (48%)	73 (87%)	
II	23 (20%)	13 (45%)	10 (12%)	
III	3 (3%)	2 (7%)	1 (1%)	
Symptoms				
Asymptomatic	7 (6%)	2 (7%)	5 (6%)	0.86
Palpitation	73 (65%)	12 (41%)	61 (73%)	0.003
Syncope	41 (36%)	11 (38%)	30 (36%)	0.83
Atypical chest pain	21 (19%)	1 (3%)	20 (24%)	0.02
Leg edema	16 (14%)	12 (41%)	4 (5%)	<0.0001
Dyspnea	14 (12%)	9 (31%)	5 (6%)	0.0004
ECG findings				
First-degree AVB	25 (24%)	14 (48%)	11 (13%)	<0.0001
QRS (ms)	105 ± 25	110 ± 30	103 ± 24	0.23
CRBBB	26 (23%)	8 (28%)	18 (21%)	0.61
Epsilon waves	22 (19%)	10 (34%)	12 (14%)	0.02
Prolonged TAD ($n = 87$)*	75 (86%)	18 (86%)	57 (86%)	0.94
T wave inversion in precordial leads	73 (65%)	20 (69%)	53 (63%)	0.66
SAECG ($n = 74$)**				
LP positive	68 (92%)	16 (94%)	52 (91%)	1.00
TTE				
LVDd (mm)	48 ± 6	49 ± 8	47 ± 5	0.25
LVDd/BSA (mm/m^2)	29 ± 4	30 ± 5	29 ± 4	0.06
LVDs (mm)	33 ± 8	36 ± 10	32 ± 7	0.03
LVDd/BSA (mm/m^2)	20 ± 5	22 ± 5	20 ± 5	0.01
LVEF (%)	52 ± 14	45 ± 15	54 ± 13	0.001
LV involvement	30 (27%)	13 (45%)	17 (20%)	0.01
Moderate to severe TR	23 (20%)	9 (31%)	14 (17%)	0.11
IVC diameter (mm)	18.7 ± 6.0	20.0 ± 6.7	18.1 ± 5.6	0.23
CMR ($n = 58$)/radionuclide scanning ($n = 50$)				
RVEF (%)	31 ± 11	26 ± 10	33 ± 11	0.003
RV angiography ($n = 106$)				
RV akinesia, dyskinesia, or aneurysm	76 (72%)	21 (78%)	55 (71%)	0.62

BSA = body surface area; CMR = cardiac magnetic resonance; CRBBB = complete right bundle branch block; ECG = electrocardiogram; EF = ejection fraction; IVC = inferior vena cava; LP = late potential; LV = left ventricle; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; NYHA = New York Heart Association; rTFC = revised Task Force Criteria; RV = right ventricle; SAECG = signal averaged electrocardiogram; SD = sudden death; TAD = terminal activation duration; TR = tricuspid valve regurgitation; VF = ventricular fibrillation; VT = ventricular tachycardia. (*) Cases with CRBBB were excluded. (**) Cases with QRS duration ≥110 ms were excluded.

ARVC [7]. We also demonstrated HF was the most major cause of cardiac death in Asian patients with ARVC [8]. However, clinical characteristics and risk factors of HF in ARVC have not been well reported. This study evaluated the long-term outcome and risk factors of HF in patients with ARVC.

2. Methods

2.1. Study population

The study population consisted of 114 consecutive patients with ARVC followed by our institution, the National Cerebral and Cardiovascular Center in Osaka, Japan. All patients were probands or sporadic cases. No family members were included. For patients enrolled before 2010, medical records were reviewed retrospectively and the ARVC diagnosis was re-established according to the revised Task Force criteria (rTFC) [9], which defines "definite" ARVC as 1) the presence of two major criteria, 2) one major criterion plus two minor criteria, or 3) four or more minor criteria from different categories. Borderline ARVC is defined as the presence of one major criterion plus one minor criterion, or three minor criteria. Finally, possible ARVC is defined as the presence of only one major criterion or two minor criteria. In the present study, 100 patients (88%) were categorized as definite, 13 patients (11%) as borderline and only one patient (1%) as possible. For the purpose of this study, we excluded the patient considered to have possible ARVC ($n = 1$) from this study.

2.2. Clinical evaluation

Clinical evaluation included a detailed patient history, family history of sudden cardiac death (SCD), physical examination, resting 12-lead electrocardiogram (ECG), 24-h Holter monitoring and two-dimensional transthoracic echocardiogram (TTE) with Doppler screening. Durations of the P wave and PR interval were measured in lead II, and the PR interval was defined as the interval from the onset of the P wave (junction between the T-P isoelectric line and the beginning of the P-wave deflection) to the end of the PR segment (junction with the QRS complex) [10]. The QRS complex was measured in lead V6 to avoid including the partial conduction block. First-degree atrioventricular block (AVB) was defined as a PR interval >200 ms. The presence of intraventricular conduction disturbances was defined according to modified criteria drawn from the current guidelines for electrocardiographic interpretation [9]. Epsilon waves were defined as distinct waves of small amplitude that occupy the ST segment in the right precordial leads and are distinct from the QRS complex [11].

Signal-averaged ECG (SAECG) (Arrhythmia Research Technology model 1200 EPX, Austin, Texas) was also performed in all patients. The SAECG system measured vector magnitude using a bidirectional bandpass filter that permits frequencies between 40 and 250 Hz to be recorded as well as standard bipolar orthogonal (X, Y, Z) leads. The rTFC considers SAECG results to indicate ARVC if they fulfill one of the following three criteria [1]: filtered QRS duration ≥114 ms [2]; duration of the terminal QRS low-amplitude signals ≥38 ms; and [3] root-mean-square voltage of the last 40 ms of the QRS complex ≤20 μV [9].

All patients underwent at least one imaging study such as contrast-enhanced cardiac magnetic resonance (CMR) imaging ($n = 54$), radionuclide scanning ($n = 46$), or RV angiography ($n = 96$). The LV function was assessed by TTE, and LV involvement was

Table 2
Relation between clinical variables and HF hospitalization.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Clinical characteristics						
Age at diagnosis (1 year increase)	1.03	0.99–1.06	0.089			
Female gender	2.05	0.91–4.35	0.081			
BSA (0.01 decrease)	1.02	0.99–1.05	0.117			
ECG findings						
First-degree AVB	4.01	1.74–9.72	0.001	4.24	1.79–10.47	0.0011
QRS (1 ms increase)	1.01	0.99–1.02	0.438			
CRBBB	1.19	0.49–2.59	0.684			
Epsilon waves	1.73	0.77–3.67	0.176			
Prolonged TAD	0.77	0.25–3.35	0.694			
TWI in precordial leads	1.37	0.64–3.18	0.427			
Structural assessment						
LVEF (1% decrease)	1.04	1.01–1.06	0.004	1.03	0.99–1.06	0.052
RVEF (1% decrease)	1.09	1.04–1.12	0.001	1.07	1.02–1.11	0.003
Moderate to severe TR	2.22	0.95–4.82	0.065			
IVC diameter (1 mm increase)	1.02	0.95–1.10	0.501			

CI = confidence interval; CRBBB = complete right bundle branch block; ECG = electrocardiogram; HF = heart failure; HR = hazard ratio; IVC = inferior vena cava; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; TAD = terminal activation duration; TR = tricuspid valve regurgitation; TWI = T wave inversion.

defined as when LVEF by TTE was lower than 45%. Regional RV wall motion abnormalities (RV regional akinesia, dyskinesia, or aneurysm) were assessed by CMR or RV angiography, and RVEF by CMR imaging or radionuclide scanning. We were not able to evaluate the RVEF of the remaining four patients (4%). CMR images were obtained using a 1.5-T system (Magnetom Sonata, Siemens, Erlangen, Germany). The procedures used to acquire the MR images in this study have been previously described [12]. The RVEF obtained by radionuclide angiography was calculated from the background-corrected end-diastolic and end-systolic counts of the first-pass angiogram [13]. First-pass radionuclide angiography was performed using a MultiSPECT3 (Siemens, Germany). Ninety-two patients (88%) underwent an electrophysiological study (EPS) including programmed ventricular stimulation.

Myocardial biopsy from the RV was performed in 74 patients. Biopsy samples were obtained from the endocardium at the right interventricular septum by the transvenous approach via the femoral vein or the right jugular vein, and samples were histologically analyzed. The extent of residual myocytes was calculated by the area of myocytes (%) in the total area of the Masson's trichrome sample using a digital microscope (Aperio Scanscope, Aperio Technology, Vista, CA, USA) [14]. A representative case is shown in Fig. S1.

Genetic analysis for ARVC genes was performed in 13 patients. The detailed methods of genetic analysis are described in Supplementary Material.

2.3. Endpoints

Lethal ventricular arrhythmias were defined as composite major arrhythmic events, such as VF, sustained VT, or necessary intervention with an implantable cardioverter-defibrillator (ICD) occurring at any time during follow-up. An appropriate ICD intervention was defined as an ICD shock or anti-tachycardia pacing delivered in response to VT or VF. In addition, the stored EGMs were evaluated by the experts at that time and the events were determined to be appropriate ICD interventions. Hospitalization for HF was defined as the sudden or gradual onset of the signs or symptoms of NYHA class 3 or 4 heart failure requiring unplanned hospitalization without following VT/VF episodes. Sudden cardiac death was defined as any natural death occurring instantaneously or within 1 h from symptom onset. Cardiac death included SCD, heart failure-related death, and heart transplantation. Atrial arrhythmias were defined as the first composite atrial arrhythmic event such as atrial fibrillation, atrial tachycardia, or atrial standstill during the follow-up period.

2.4. Statistical analysis

Results are summarized as means and as n (%) for continuous and categorical variables, respectively. Categorical differences between groups were evaluated by the $\chi 2$ test or Fisher exact test as appropriate. Continuous variables were expressed as medians (25th to 75th percentiles) and compared using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Subjects were censored at the time of their first event or the time of their last clinical follow-up. Survival distribution during the follow-up was calculated using Kaplan-Meier curves and using lethal ventricular arrhythmia, hospitalization for HF, atrial arrhythmias, or cardiac death as the endpoints. The effects of covariates on the time to each endpoint were investigated using a Cox proportional hazards model. The hazard ratio and 95% confidential intervals (CIs) are always shown. A significance of 0.05 was required for variables to be candidates for the model. A value of $p < 0.05$ was taken as a threshold for statistical significance. All analyses were performed using JMP9.0 (SAS Institute Japan, Tokyo, Japan) or R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline clinical characteristics

The clinical characteristics of the 113 ARVC patients at the time of enrollment are shown in Table 1. There was a predominance of male patients ($n = 85$; 75%). Mean age at the diagnosis was 44 ± 15 years and more than sixty present of the patients had one or more previous VT episodes. Mean LVEF and RVEF was 52 ± 14% and 31 ± 11%, respectively. All the rTFC and the results of genetic testings were shown in Tables S1 and S2.

3.2. Clinical outcome during the follow-up

During the median follow-up of 10.0 years (interquartile range [IQR]: 5.2–15.7 years), there were 18 (16%) cardiac deaths: seven patients died suddenly, eight died due to worsening HF, one died of myocardial infarction, and two underwent heart transplantation because of decompensated HF.

Twenty-nine patients (26%) were hospitalized for HF (Fig. S2). All patients with HF hospitalization had clinical symptoms of right-side-dominant or biventricular HF. Importantly, patients with one or more episodes of HF hospitalization had about a 10-fold increased incidence of cardiac death (14/29 [48%] vs. 4/84 [4.7%], $p < 0.0001$). Baseline clinical characteristics of patients with HF hospitalization are shown in Table 1. All three patients with a "borderline" diagnosis at enrollment fulfilled the "definite" diagnosis when they were hospitalized due to HF. In the ECG findings, the prevalence of first-degree AVB and epsilon waves were higher in patients with HF hospitalization than those without (first-degree AVB, 14/29 [48%] vs. 11/84 [13%], $p < 0.0001$; epsilon waves, 10/29 [34%] vs. 12/84 [14%], $p = 0.02$). LVEF and RVEF were significantly lower in patients with HF hospitalization (LVEF, 45 ± 15 vs. 54 ± 13%, $p = 0.001$; RVEF, 26 ± 10 vs. 33 ± 11%, $p = 0.003$). Moreover, first-degree AVB was the strongest risk factor for admission due to worsening HF based on multivariate Cox regression analysis (hazard ratio 4.24, 95% confidence interval 1.79–10.47, $p = 0.0011$, Table 2). All explanatory variables in the multivariate model satisfied the assumption of proportional hazard.

3.3. Clinical characteristics in patients with ARVC and first-degree AVB

We conducted an additional analysis about the relationship between cardiac adverse outcomes and the presence of first-degree AVB. First-degree AVB was recognized in 25 patients (24%) at enrollment. Nine patients without normal sinus rhythm (atrial fibrillation 5, atrial tachycardia 2, atrial standstill 2) at the initial evaluation were excluded. In the remaining 104 patients, no significant differences were shown in age at ARVC diagnosis or in age at initial evaluation, family history of sudden death, and prior VT and/or VF episodes between patients with first-degree AVB and those without (Table 3). In the ECG findings, the QRS duration was significant longer (119 ± 29 vs. 100 ± 22 ms, $p < 0.0005$), and the prevalence of complete right bundle branch block (CRBBB) and epsilon waves were higher in patients with first-degree AVB than those without (CRBBB, 13/25 [52%] vs. 12/79 [15%], $p = 0.0003$; epsilon waves, 10/25 [40%] vs. 10/79 [13%], $p = 0.007$). LVEF and RVEF were comparable between groups. In invasive electrophysiological study, the HV interval was longer in patients with first-degree AVB compared to those without (47 ± 6 vs. 40 ± 6 ms, $p < 0.01$). The AH interval was comparable between the groups. Notably, histological

analysis ($n = 69$) revealed that the extent of residual myocytes was significantly lower in patients with first-degree AVB than those without (45 ± 24 vs. $56 \pm 17\%$, $p = 0.042$).

Table 3
Baseline characteristics and treatments during the follow-up in patients with and without first-degree AV block.

	Baseline PR interval		*p* value
	>200 ms	≤200 ms	
n	25 (24%)	79 (76%)	
Gender (male)	20 (80%)	57 (72%)	0.43
Age at diagnosis (yrs)	47 ± 14	42 ± 15	0.14
Age at enrollment (yrs)	49 ± 14	44 ± 15	0.08
Initial evaluation			
BSA	1.68 ± 0.19	1.65 ± 0.16	0.32
Family history of ARVC/SD	4 (16%)	12 (15%)	0.92
Previous VT/VF	19 (76%)	51 (65%)	0.28
Diagnosis based on the rTFC			
Definite/borderline	22 (88%)/3 (12%)	71 (90%)/8 (10%)	0.79
NYHA functional class			0.007
I	15 (60%)	68 (86%)	
II	10 (40%)	9 (11%)	
III	0 (0%)	2 (3%)	
Symptoms			
Asymptomatic	1 (4%)	6 (8%)	0.51
Palpitation	16 (64%)	53 (67%)	0.78
Syncope	8 (32%)	28 (35%)	0.75
Atypical chest pain	7 (28%)	13 (16%)	0.22
Leg edema	4 (16%)	8 (10%)	0.44
Dyspnea	5 (20%)	5 (6%)	0.06
ECG findings			
P (ms)	130 ± 15	107 ± 14	<0.0001
PR (ms)	234 ± 32	169 ± 21	<0.0001
QRS (ms)	119 ± 29	100 ± 22	<0.0005
CRBBB	13 (52%)	12 (15%)	0.0003
IRBBB	1 (4%)	3 (4%)	0.96
Epsilon waves	10 (40%)	10 (13%)	0.007
Prolonged TAD ($n = 79$)*	12 (100%)	56 (84%)	0.34
T wave inversion in precordial leads	17 (68%)	50 (63%)	0.67
SAECG ($n = 69$)**			
LP positive	9 (100%)	54 (90%)	1.00
TTE			
LVDd (mm)	48 ± 7	47 ± 6	0.47
LVDd/BSA (mm/m^2)	29 ± 4	29 ± 4	0.98
LVDs (mm)	33 ± 8	33 ± 8	0.66
LVDd/BSA (mm/m^2)	20 ± 5	20 ± 5	0.99
LVEF (%)	52 ± 15	51 ± 14	0.91
LV involvement	6 (24%)	22 (28%)	0.70
Moderate to severe TR	1 (4%)	17 (22%)	0.07
IVC diameter (mm)	17.4 ± 6.3	18.5 ± 5.8	0.45
CMR ($n = 54$)/radionuclide scanning ($n = 46$)			
RVEF (%)	31 ± 11	31 ± 11	0.95
RV angiography ($n = 96$)			
RV akinesia, dyskinesia, or aneurysm	17 (74%)	51 (70%)	0.71
EPS ($n = 92$)			
AA interval (ms)	868 ± 156	922 ± 180	0.27
AH interval (ms)	104 ± 27	93 ± 29	0.17
HV interval (ms)	47 ± 6	40 ± 6	<0.01
Inducible VT	16 (70%)	45 (65%)	0.70
Histological analysis ($n = 69$)			
Residual myocytes (%)	45 ± 24	56 ± 17	0.042
Final evaluation			
Medication			
β-blocker	12 (48%)	50 (63%)	0.18
ACE inhibitor/ARB	12 (48%)	26 (33%)	0.18
Diuretics	10 (40%)	22 (28%)	0.27
Amiodarone	12 (48%)	25 (32%)	0.14
Sotalol	5 (20%)	19 (24%)	0.67
Catheter ablation of VT	14 (56%)	36 (46%)	0.36
Device implantation			
PM	1 (4%)	2 (3%)	0.70
ICD	8 (32%)	31 (39%)	0.51
CRTD	1 (4%)	2 (3%)	0.71

3.4. Outcome in patients with ARVC and first-degree AVB

Approximately half of the patients underwent catheter ablation (48%) and/or received a cardiac rhythm device (44%, Table 3). The median duration between the initial diagnosis and the implantation of an ICD was 2.4 months (IQR 0.6–51.2). An ICD was implanted for primary prevention in nine patients. There were no significant differences between groups in terms of the proportion of patients who underwent catheter ablation of VT, received a cardiac rhythm management device, or were treated with amiodarone or a beta-blocker. Seventeen out of seventy-nine patients (22%) without first-degree AVB at baseline were newly diagnosed during the follow-up. Meanwhile, no patients developed complete AVB in either group.

We also evaluated ventricular pacing rate at the latest follow-up in patients with cardiac rhythm device. Ventricular pacing rate in 36 out of 45 patients with cardiac rhythm device was <1%, and over 50% of ventricular pacing rate was noted in only 4 patients (2 RV pacing and 2 biventricular pacing).

Kaplan-Meier analysis revealed that there were no significant differences in the cumulative probability of cardiac death, VT/VF events, and atrial arrhythmias between the groups, respectively (Fig. 1A, B, and C). In contrast, a higher predisposition to heart failure in patients with first-degree AVB was, however, recognized (14/25 [56%] vs. 9/79 [11%], $p = 0.0006$, Fig. 1D). Moreover, an additional subgroup analysis was conducted even in 23 patients whose RVEF was preserved or mildly reduced (RVEF ≥40%). Kaplan-Meier event-free analysis regarding HF hospitalization, revealed a significant difference between patients with and those without first-degree AVB (log-rank test, $p = 0.034$).

4. Discussion

To the best of our knowledge, this is the first study to demonstrate the HF-related outcome and its risk factors in patients with ARVC. Clinical characteristics in ARVC change significantly during long follow-up unlike other diseases. We concluded that HF hospitalization was noted in about quarter of the study subjects of ARVC and the presence of first-degree AVB at baseline was associated with a greater risk of hospitalization due to HF in ARVC patients. These findings provide a new approach to estimating the prognosis of ARVC patients.

4.1. Prevalence of first-degree AVB

The prevalence and prognostic impact of first-degree AVB were different in various reports. In the Framingham Heart Study, investigators identified that PR interval prolongation was associated with increased risk of AF, pacemaker implantation, and all-cause mortality in an over 7000 patient community-based cohort [10]. In this study, a PR interval >200 ms was observed in 1.6% of the cohort. Moreover, the mean age at enrollment was approximately 10 years older in subjects with a PR interval >200 ms than those without (55 ± 16 years old, vs. 46 ± 15 years old). In a Health ABC study on elderly subjects, first-degree AVB was recognized in approximately 12% of subjects, and investigators reported that a prolonged PR interval was related to HF and AF in elderly patients [15]. In terms of the different underlying diseases, several authors reported that PR prolongation was associated with adverse

Notes to Table 3:
ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; BSA = body surface area; CMR = cardiac magnetic resonance; CRBBB = complete right bundle branch block; CRTD = cardiac resynchronization therapy defibrillator; ECG = electrocardiogram; EF = ejection fraction; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; IVC = inferior vena cava; LP = late potential; LV = left ventricle; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; NYHA = New York Heart Association; PM = pacemaker; rTFC = revised Task Force Criteria; RV = right ventricle; SAECG = signal averaged electrocardiogram; SD = sudden death; TAD = terminal activation duration; TR = tricuspid valve regurgitation; VF = ventricular fibrillation; VT = ventricular tachycardia. (*) Cases with CRBBB were excluded. (**) Cases with QRS duration ≥110 ms were excluded.

outcomes in patients with hypertension [16], coronary disease [17], and HF [18]. Moreover, Maury et al. reported that the presence of first-degree AVB was significantly and independently linked to the occurrence of malignant arrhythmias in Brugada syndrome [19].

In patients with ARVC, the prevalence of first-degree AVB was not sufficiently elucidated. In 24 cases of the first report of ARVC, 2 cases with PR interval >200 ms and 5 cases with a PR interval equal to 200 ms were documented [1]. Moreover, in Steriotis's report, first-degree AVB was associated with disease progression [20]. Philips et al. reported that first-degree AVB was, however, not observed in any of the 42 ARVC patients although it was present in 53% of the patients with cardiac sarcoidosis [21]. Thus, the prevalence of first-degree AVB differs among reports. These discrepancies may be explained by the differences in patient backgrounds, such as if family members are included or not. In the present study, first-degree AVB was recognized in 24% of the patients. This may be explained by the background that all patients had proband status and 89% of the cohort had a definite diagnosis.

4.2. Clinical impact of first-degree AVB on patients with ARVC

There are several possible explanations for the close association between the presence of first-degree AVB and HF hospitalization in patients with ARVC. First, both QRS widening and PR prolongation may cause negative hemodynamic effects [22–24]. In a subset of patients, the onset of atrial depolarization occurs immediately after the previous ventricular contraction, which results in blood being forced against a closed tricuspid valve and pulsing retrogradely into the vena cava. This could adversely affect RV filling pressure, contributing to the clinical exacerbation of right-side-dominant HF.

Second, the potential of the reduced use of beta-blockers and the increased propensity for RV pacing may play an essential role in the progression of ventricular dysfunction. However, in our study, there were no significant differences between the groups in terms of the proportion of patients who were treated with a beta-blocker and who received a cardiac rhythm management device (Table 3). Moreover, almost all patients with a pacemaker or ICD maintained their own QRS, since no one developed complete AVB.

Third, first-degree AVB in patients with ARVC may reflect the more diffuse distribution of fibrofatty replacement. First-degree AVB results from conduction delay in any site of the right atrium, AV node, His bundle or Purkinje network. In the present study, the P wave duration and the HV interval were significantly longer, and the prevalence of CRBBB and epsilon waves were higher in patients with first-degree AVB than in those without. Importantly, histological analysis revealed that the extent of residual myocytes was significantly lower in patients with first-degree AVB than in those without. Thus, first-degree AV block may be a general marker of a more severe phenotype.

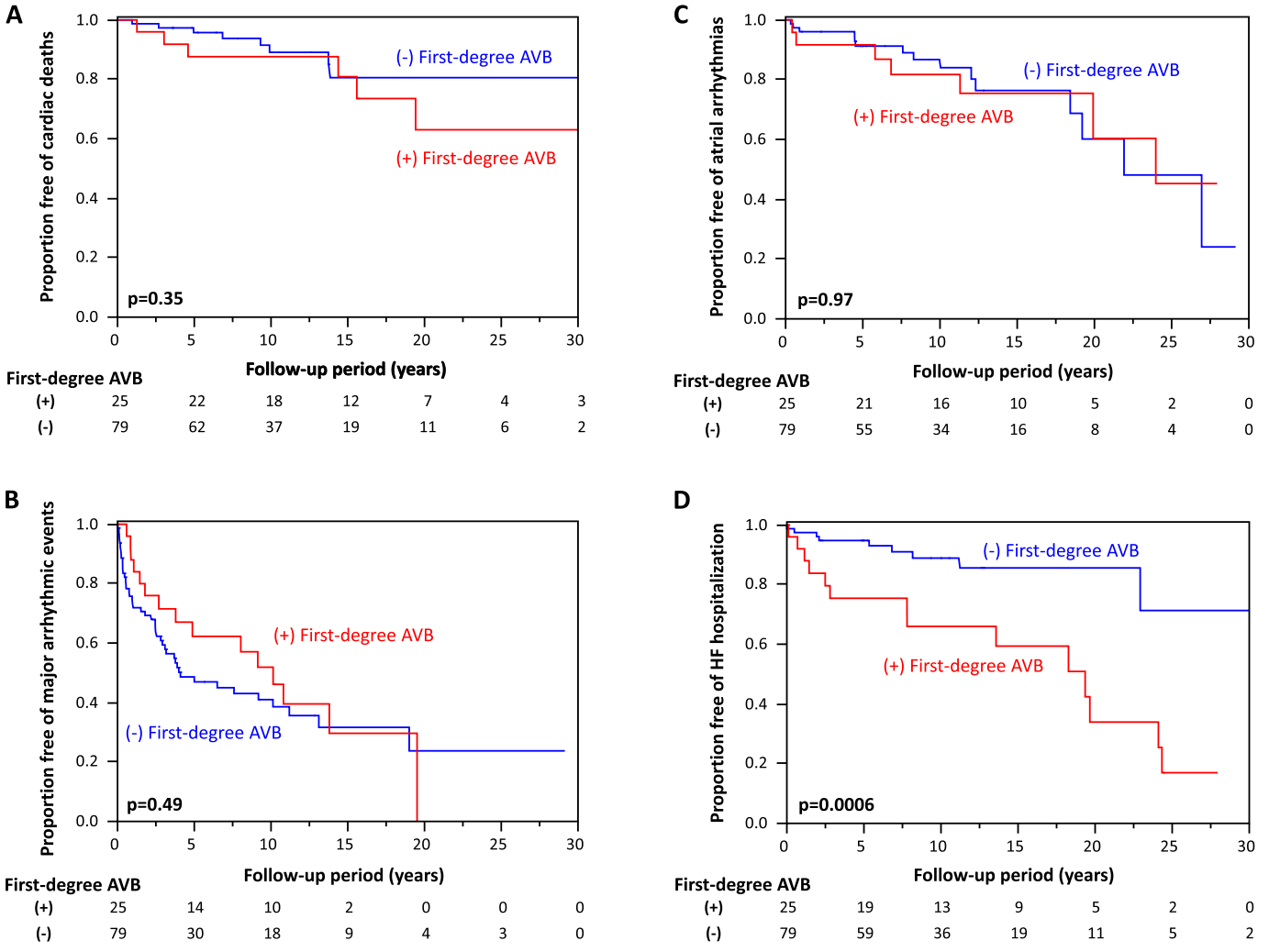

Fig. 1. Kaplan-Meier analysis of cardiac events in terms of the presence or absence of first-degree atrioventricular block. Kaplan-Meier analysis revealed that there were no significant differences in the cumulative probability of cardiac death (A), VT/VF events (B), and atrial arrhythmias (C) between the groups, respectively. In contrast, a higher predisposition to heart failure in patients with first-degree AVB was recognized (D). AVB = atrioventricular block, HF = heart failure.

It remained unclear why there were no significant difference in the cumulative probability of cardiac death and VT/VF events between the groups. One possible reason was the wide variety of mechanisms of ventricular tachyarrhythmias in ARVC. Both scar-related monomorphic VT and polymorphic VT was induced by isoproterenol, especially in the early phase [25]. Moreover, almost half of the patients were prescribed class III anti-arrhythmic agents, 59% were treated by beta-blockers, and 49% of patients underwent catheter ablation for VT. We consider that these combination therapies modified the arrhythmic outcome in patients with first-degree AVB and those without.

4.3. Study limitations

First, our cohort was recruited from a monocentric tertiary center, and our study is a retrospective cohort study. The patient characteristics and indications for catheter ablation and ICD implantation may reflect referral bias and institutional preferences. In addition, many changes of therapy occurred for each patient during the >10 year follow-up.

Second, in our cohort of probands of ARVC, a family history of sudden death was found to be present in approximately 15% of all patients. We did not have complete information on the causes of these events, and they may include undiagnosed cases of ARVC. However, it is unlikely that any undetected family history of ARVC would substantially change the overall results because there were no significant differences related to family history of sudden death.

Third, although a genetic study in ARVC patients would be clinically significant, only 13 patients in the study population underwent genetic testing of ARVC. Since many of the patients were registered more than several years before when the genetic analysis for ARVC genes was not always available, we could not determine the relationship between the genotype and first-degree AVB.

Fourth, almost all myocardial biopsy samples were obtained from the RV septum. Thus, the extent of tissue fibrosis may be underestimated [26].

5. Conclusions

This study reports that HF hospitalization has a significant relation with malignant clinical course in ARVC patients, and first-degree AVB at baseline is strongly associated with HF hospitalization. First-degree AV block may be a general marker of a more severe phenotype. Recent developments in early diagnosis, risk stratification, and antiarrhythmic therapies should contribute to better arrhythmic prognosis and freedom from sudden cardiac death in patients with ARVC. However, intervention in the malignant progress of ARVC remains a challenging issue. In patients with ARVC, the presence of first-degree AVB may identify those at higher risk for HF and may warrant more intense surveillance, follow-up, and preventive measures.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.04.061.

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