Atrial tachyarrhythmias and heart failure events in patients with arrhythmogenic right ventricular cardiomyopathy

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A B S T R A C T

Background: Atrial tachyarrhythmias (ATAs) are associated with an increased risk of incident heart failure (HF). The aim of this study was to evaluate the incidence of ATAs and time of ATA development during disease progression as well as the influence of ATAs on HF-related events in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).
Methods: We retrospectively studied 90 ARVC patients who met the definitive diagnosis of the 2010 Task Force Criteria and were diagnosed with ARVC at our institutions between 1974 and 2012. The main outcomes were death due to HF and hospitalization due to worsening HF.
Results: Eleven patients had a history of ATAs at the time of ARVC diagnosis. Of 79 patients without a pre-diagnosis history of ATAs, 21 (27%) newly experienced ATAs during a median follow-up period of 11.4 (range, 0.1–29.6) years. Among them, 15 patients experienced their first hospitalization due to worsening HF a median of 1.7 (range, 0.0–9.8) years after the occurrence of ATAs. Patients with ATAs were more likely to experience death due to HF and hospitalization due to worsening HF than patients without ATAs (odds ratio 19.2, 95% confidence interval 2.0–92.3, P < 0.01 and odds ratio 29.7, 95% confidence interval 8.4–104.8, P < 0.01, respectively). Multivariable analysis revealed that ATAs were associated with an increased risk of hospitalization due to worsening HF (hazard ratio 15.55, 95% confidence interval 4.82–50.17, P < 0.01).
Conclusions: Our study suggests that the occurrence of ATAs is associated with an increased risk of HF-related events and worsens the prognosis of ARVC patients.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by ventricular arrhythmias and fibrofatty replacement of the right ventricular (RV) and/or left ventricular (LV) myocardium [1,2]. The classic ARVC phenotype is characterized by isolated RV involvement, and LV involvement has been recognized to occur in the late phase of the disease [2,3]. Because of the recent recognition of LV involvement as a characteristic feature of ARVC, the current classification of ARVC includes biventricular disease variants and a phenotype characterized by isolated LV involvement [3]. ARVC slowly pro-

gresses to more diffuse RV and LV dysfunction [2,3]. In the early and overt phases, symptomatic ventricular tachycardia (VT) or ventricular fibrillation (VF) predominantly occur; however, right or biventricular heart failure (HF) with or without the presence of ventricular arrhythmia appears, although less common, in the later phase [2].

Recently, atrial tachyarrhythmias (ATAs), including atrial fibrillation (AF), atrial flutter (AFL) and atrial tachycardia (AT), have been reported to be relatively frequently observed in ARVC patients [4,5], and some reports have suggested that the appearance of AF is linked to atrial remodeling associated with structural ventricular remodeling and the severity of ARVC [6–9]. A high ARVC diagnostic score based on the 2010 Task Force Criteria (TFC), which may be useful for predicting major adverse cardiovascular events, was also reported to be related to the occurrence of AF [9].

ATAs, including AF, can lead to hemodynamic deterioration and can also occur as a consequence of HF [10]. AF is associated with an increased risk of incident HF [11,12]. However, the role of ATAs,

including AF, in the clinical course and the HF-related events in ARVC patients is not fully understood. The aim of this study was to evaluate the time at which ATAs appear during disease progression and the impact of new-onset ATAs on the development of HF-related events in patients with ARVC.

2. Methods

2.1. Subjects

Individual pooled patient data were obtained from the Tokyo Women's Medical University ARVC cohort. The cohort is described in detail elsewhere [13]. Briefly, we retrospectively studied 90 consecutive ARVC patients who met the definitive diagnosis of the disease according to the 2010 TFC [14]. All patients admitted to the Department of Cardiology, Tokyo Women's Medical University Hospital for the evaluation of sustained VT/VF and/or cardiomyopathy between 1974 and 2012 and with available follow-up data (until December 31, 2013) were included in this cohort. Implanted cardioverter-defibrillators (ICDs) were found in 33 (37%) patients through the end of the follow-up period. The patients were divided into three subgroups: (1) patients with a prediagnosis history of ATAs at ARVC diagnosis, (2) patients who had experienced newly occurring ATAs after an ARVC diagnosis and (3) patients who did not experience ATAs during the follow-up period (Fig. 1). Left ventricular ejection fraction (LVEF) was measured by LV angiography, echocardiography, magnetic resonance imaging or radionuclide angiography. Right ventricular ejection fraction (RVEF) was measured using RV angiography, cardiovascular magnetic resonance imaging or radionuclide angiography.

The protocol was approved by the Institutional Review Board of Tokyo Women's Medical University.

2.2. ARVC diagnostic score

The ARVC diagnostic score was calculated as the sum of the major and minor criteria in all 6 subcategories of the 2010 TFC according to the structure of the RV structure and function, histology, electrocardiography, arrhythmia, and family history, with major criteria given 2 points and minor criteria given one point [13]. A definite diagnosis of ARVC according to the 2010 TFC was fulfilled by the presence of 2 major criteria, 1 major plus 2 minor criteria or 4 minor criteria from different categories. Thus, the ARVC diagnostic score ranged between 4 and 12. We divided the scores into 3 groups according to a previous report: 4–6 points, 7–9 points and 10–12 points [13].

2.3. ATA diagnosis

ATAs were confirmed from medical records, including electrocardiograms and records of ICD interrogations. We identified patients with persistent ATAs who required pharmacological management for rate and rhythm control, electric or pharmacological cardioversion, or catheter ablation to restore sinus rhythm. We also identified patients with self-terminating ATAs and lasted >30 s on ICD interrogation. ATAs were classified as ATs if regular atrial waves of 100–250 bpm with a regular ventricular rhythm (variable ventricular rate) were observed, as AFLs if the regular baseline atrial rhythm was observed as flutter waves of 250–350 bpm with a regular ventricular rhythm (usually with an atrioventricular block) or as AFs if an irregular baseline atrial rhythm was observed as fibrillation waves with an irregular ventricular rhythm [15]. ATAs appearing only during electrophysiologic studies, atrioventricular nodal reentrant tachycardia or atrioventricular reentrant tachycardia were excluded. Two investigators (N.K. and
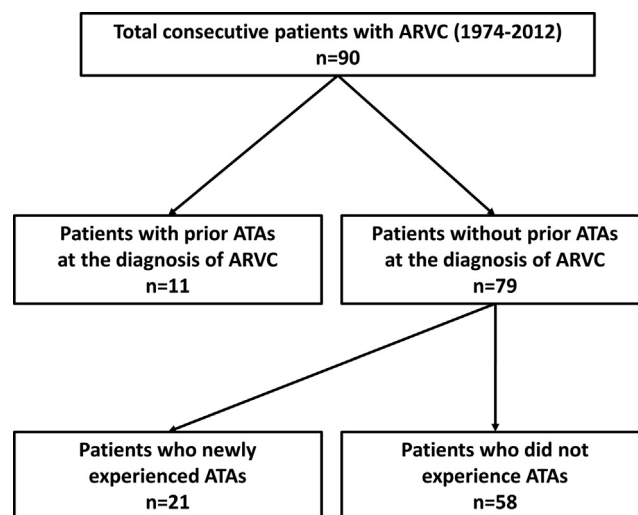

Fig. 1. Flowchart for arrhythmogenic right ventricular cardiomyopathy (ARVC) patients. ATAs: atrial tachyarrhythmias.

A.S.) reviewed the electrocardiograms and clinical notes of the entire patient cohort as well as the ICD data of the 33 patients with ICDs.

2.4. Outcomes

The main clinical outcomes were death due to HF and hospitalization due to worsening HF as HF-related events. Other outcomes were all-cause death and sudden death. Worsening HF was defined as new or progressive symptoms and signs of HF, such as dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, lower extremity edema, abdominal swelling/ascites, S3 gallop, jugular venous distention, and rales (Table 2), as well as the unplanned addition of oral or intravenous loop diuretic drugs, an increased dose of oral loop diuretics, the addition of a thiazide diuretic drug to loop diuretics or the need for treatment with intravenous vasodilators, intravenous inotropes or intra-aortic balloon pumping. The detailed causes of death were based on the clinical history obtained from the medical charts or information from other hospitals. Death due to HF was defined as death in the context of clinically worsening signs and symptoms of HF with no other apparent cause. Sudden death was defined as unexpected endogenous death within 24 h after last having been observed alive, unrelated to a specific cause of circulatory failure. The definition of worsening HF and the occurrence of events were validated through a medical record review by 2 investigators (N.K. and A.S.).

2.5. Statistical analysis

Summary data are presented either as the number of patients or as the median and range. Baseline clinical data were compared between the groups using one-way analysis of variance (ANOVA). Categorical variables were subjected to a chi-square analysis. The cumulative probabilities of first hospitalization due to worsening HF after diagnosis were estimated with the Kaplan-Meier method, and a comparison of cumulative events was performed with the log-rank test. Multivariable Cox proportional hazards regression analysis was used to estimate the relationship between clinical variables and new-onset ATAs as well as the relationship between clinical variables and hospitalization due to worsening HF. The frequencies of outcomes with odds ratios and 95% confidence intervals were calculated. P values < 0.05 were considered significant.

Table 1
Clinical characteristics of patients at diagnosis of ARVC.

	With a prediagnosis history of ATAs n = 11	Without a prediagnosis history of ATAs		p value
		Newly occurring ATAs n = 21	No ATAs n = 58	
Sex (Male)	9 (82)	16 (76)	44 (76)	0.91
Age at diagnosis (years)	52 (25–71)	48 (15–77)	42 (11–65)	0.07
Family history of ARVC	1 (9)	4 (19)	4 (7)	0.28
Previous sustained VT/VF/cardiac arrest	4 (36)	17 (81)	43 (74)	0.02
LVEF (%)	40 (13–62)	53 (22–75)	55 (14–85)	<0.01
RVEF (%)	25 (5–45)	23 (11–36)	34 (8–60)	<0.01
NYHA class at diagnosis				0.04
I	6 (55)	17 (81)	51 (88)	
II	3 (27)	4 (19)	5 (9)	
III/IV	2 (18)	0	2 (3)	
ARVC diagnostic score*				<0.01
4–6 points	3 (27)	1 (5)	21 (36)	
7–9 points	8 (73)	12 (57)	29 (50)	
10–12 points	0	8 (38)	8 (14)	
ICD implantation	3 (27)	3 (14)	10 (17)	0.65
Catheter ablation for VT	3 (27)	6 (29)	22 (38)	0.64
Medications				
Beta blockers	4 (36)	4 (19)	14 (24)	0.55
ACE inhibitors/ARBs	6 (55)	5 (24)	17 (29)	0.18
Amiodarone	6 (55)	7 (33)	25 (43)	0.50
Sotalol	1 (9)	0	1 (2)	0.23
Other antiarrhythmics	0	5 (24)	12 (21)	0.22
Diuretics	4 (36)	3 (14)	6 (10)	0.08
Anticoagulants	7 (64)	2 (10)	5 (9)	<0.01

Values are shown as the number (%) or median (range).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; ATA, atrial tachyarrhythmia; ECG, electrocardiography; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death; TFC. Task Force Criteria; VF, ventricular fibrillation; VT, ventricular tachycardia.
* The ARVC/D diagnostic score was calculated as the sum of major and minor criteria in all 6 subdivided categories of the 2010 TFC [14], with major criteria given 2 points and minor criteria given 1 point [13].

Table 2
Frequency of symptoms/signs of heart failure in 25 patients with ARVC.

Frequency of signs/symptoms	
Fatigue	23 (92)
Dyspnea on exertion	22 (88)
Lower extremity swelling	21 (84)
Jugular vein distention	15 (60)
Abdminal swelling/ascitis	11 (44)
Rales	5 (20)
S3 gallop	4 (16)
Paroxysmal nocturnal dyspnea	3 (12)
Orthopnea	2 (8)
Frequency of total number signs/symptoms per patient	
≥2	25 (100)
≥3	22 (88)
≥4	17 (68)
≥5	11 (44)
6	3 (12)

Values are shown as the number (%).

Data analyses were performed with SPSS statistical software (version 22.0, SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Patient characteristics

This study consisted of patients with relatively severe ARVC; the mean RVEF was 30 ± 12%, and 71% had sustained VT/VF/cardiac arrest prior to the diagnosis of ARVC.

Eleven patients had a prediagnosis history of ATAs at ARVC diagnosis: AF (n = 4), AFL (n = 6), and AT (n = 4). Among 79 patients without a prediagnosis history of ATAs at ARVC diagnosis, 21 (27%) newly experienced ATAs during a median follow-up period of 11.4 [0.1–29.6] years. Twenty patients showed persistent ATAs, and one patient showed AF of approximately 90 min duration on the ICD monitoring. The baseline characteristics of the patients at the time of ARVC diagnosis are shown in Table 1. Patients with a prediagnosis history of ATAs tended to be older than those without. The proportion of previous sustained VT/VF/cardiac arrest was lower in patients with a prediagnosis history of ATAs than in those without. The New York Heart Association (NYHA) functional class was higher and the LVEF was lower in patients with a prediagnosis history of ATAs than in those without.

3.2. Prediagnosis history of ATAs and HF-related events

Kaplan-Meier curves for death due to HF or first hospitalization due to worsening HF after an ARVC diagnosis are shown in Fig. 2. There were significantly higher incidences of death due to HF or hospitalization due to worsening HF in patients with a prediagnosis history of ATA than in patients without a prediagnosis history of ATA after ARVC diagnosis (both log-rank P < 0.01).

3.3. Newly occurring ATAs and HF-related events

There was no remarkable change in the left atrial dimension in patients who newly experienced ATAs during a median period of 9.9 [2.4–19.4] years from ARVC diagnosis to the first occurrence of ATAs (median 32 [19–50] mm vs 34 [20–50] mm). Multivariable analysis showed that an RVEF <30% at baseline was significantly associated with the occurrence of ATAs, which was independent of an age ≥65 years but not preexisting HF (NYHA class ≥ II) (Table 3). Regarding the ARVC diagnostic score, patients with newly occurring ATAs had higher scores than those without ATAs

A. Death due to HF
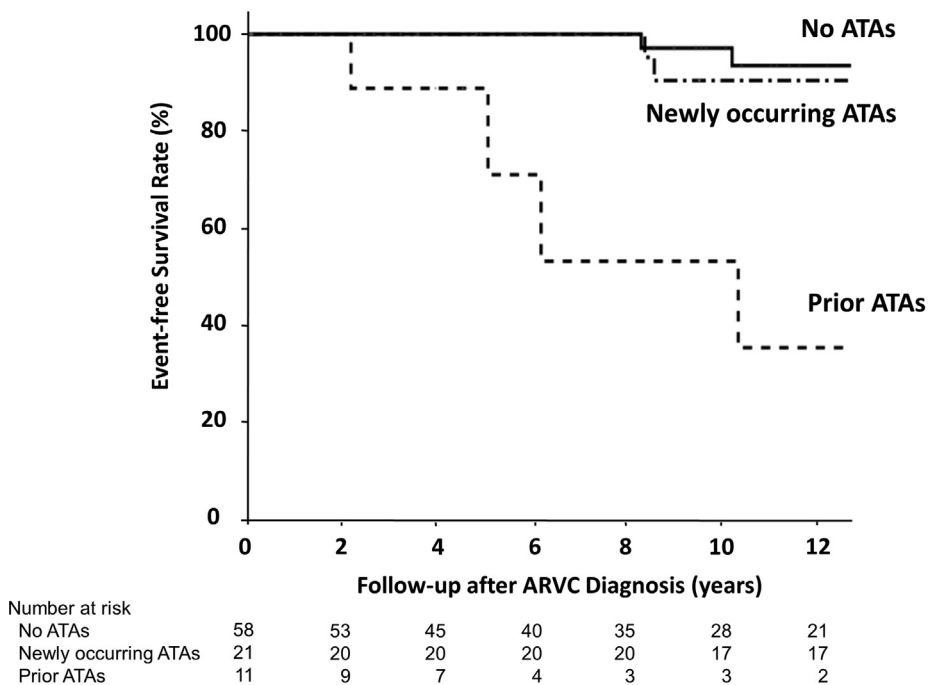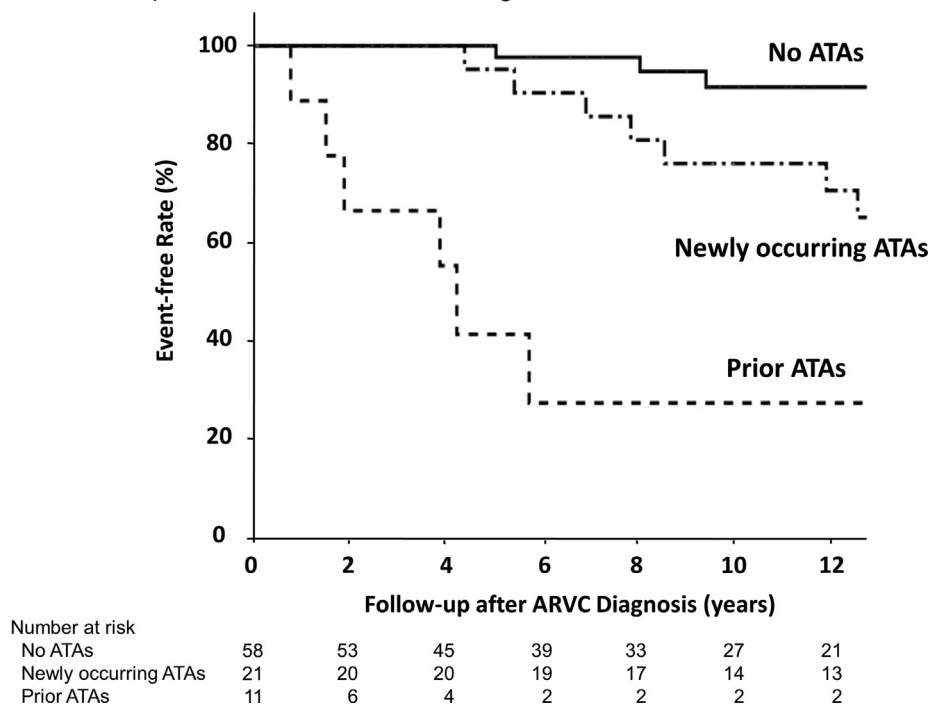

B. Hospitalization due to worsening HF

Fig. 2. Kaplan-Meier analysis of death due to heart failure (HF) (A) and hospitalization due to worsening HF (B) in arrhythmogenic right ventricular cardiomyopathy patients with prior atrial tachyarrhythmias (ATAs) at diagnosis, those with newly occurring ATAs after diagnosis and those with no ATAs.

(4–6 points: 1 vs 21; 7–9 points: 12 vs 29; and 10–12 points: 8 vs 8, P < 0.01).

The clinical courses of all patients with newly occurring ATAs are shown in Fig. 3. Although 2 patients were hospitalized due to worsening HF prior to the occurrence of ATAs, 15 patients experienced their first hospitalization due to worsening HF a median of

1.7 [0.0–9.8] years after the occurrence of ATAs. A patient with self-terminated AF on ICD recording was not subsequently hospitalized for worsening HF. There were significantly higher incidences of death due to HF or hospitalization due to worsening HF among patients who experienced newly occurring ATAs than among those who did not (both log-rank P < 0.01) (Fig. 2).

Table 3

Clinical predictors of newly occurring atrial tachyarrhythmias in patients without a prediagnosis history of ATAs.

Valable	Number of patients (%)	HR (95% CI)	p value
Age (≥65 years vs <65 years)	2/4 (50) vs 19/75 (25)	10.59 (1.44–77.73)	0.02
Gender (male vs. female)	16/60 (27) vs 5/19 (26)	0.25 (0.07–0.97)	0.05
Family history of ARVC (yes vs. no)	4/8 (50) vs 17/71 (24)	2.74 (0.78–9.59)	0.12
NYHA class at ARVC diagnosis (II-IV vs. I)	4/11 (36) vs 17/68 (25)	2.14 (0.45–10.27)	0.34
LA dimension (≥45 mm vs. <45 mm)	1/2 (50) vs 17/69 (25)	0.57 (0.04–8.73)	0.69
LVEF (<40% vs. ≥40%)	2/9 (22) vs 19/70 (27)	2.00 (0.35–11.52)	0.44
RVEF (<30% vs. ≥30%)	14/33 (42) vs 7/44 (16)	5.17 (1.65–16.20)	<0.01
Amiodarone (no vs. yes)	7/32 (22) vs 14/47 (30)	0.53 (0.16–1.82)	0.31

ARVC, arrhythmogenic right ventricular cardiomyopathy; ATA, atrial tachyarrhythmia; CI, confidence interval; HR, hazard ratio; LA, left atrium; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction.
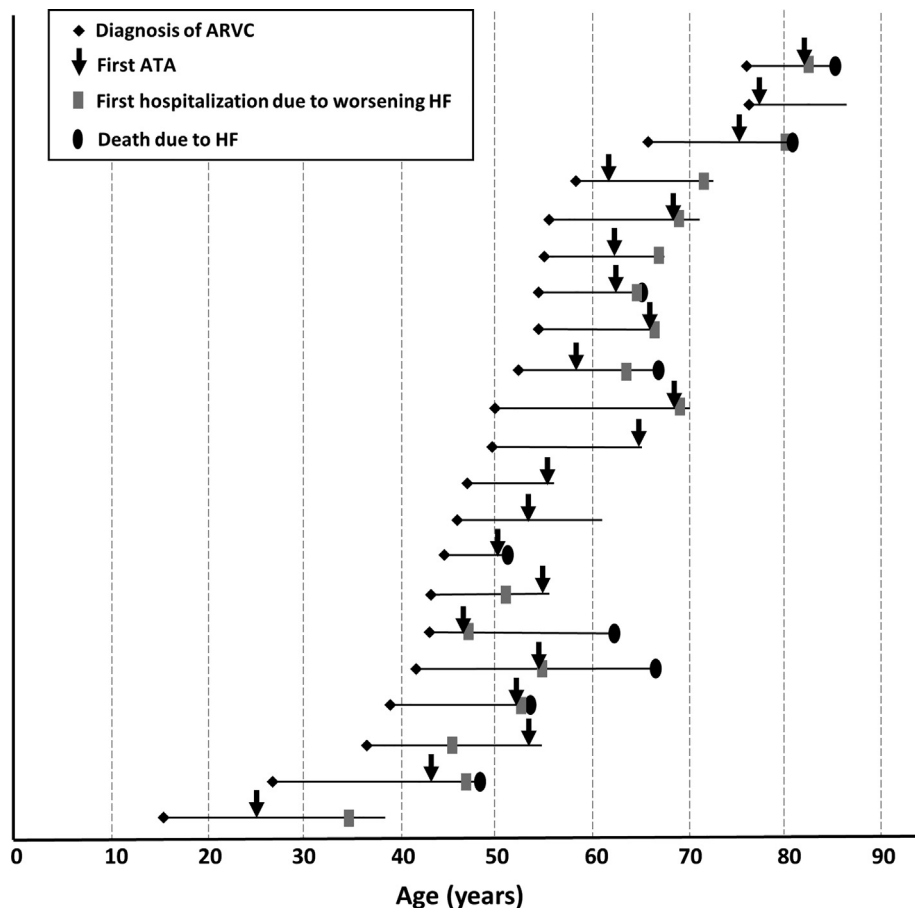

Fig. 3. Hospitalization due to worsening heart failure (HF) and death due to HF in each of 21 patients with a first occurring atrial tachyarrhythmia (ATA) after the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC).

3.4. ATAs and clinical outcomes

The differences in death and hospitalizations due to worsening HF between patients with and without ATAs are shown in Table 4. Patients with ATAs were more likely to experience all-cause death, especially death due to HF, which was a major cause of death, than patients without ATAs. Patients with ATAs were more likely to be hospitalized due to worsening HF than patients without ATAs. Multivariable analysis revealed that ATAs were associated with an increased risk of hospitalization due to worsening HF as well as a low LVEF among patients with severe ARVC (Table 5). Additionally, 12 patients underwent genetic testing in this study. Five patients with ATAs who were hospitalized due to worsening HF showed the following gene mutations: desmoplakin (n = 3), plakophilin-2 (n = 1), desmoglein-2 (n = 1) and desmocollin-2 (n = 1).

3.5. Type and treatment of ATAs

Among the 21 patients with newly occurring ATAs, 3 had AF, 12 had AFL, and 7 had AT. We used antiarrhythmic drugs, including amiodarone (n = 9), sotalol (n = 1), procainamide (n = 2), flecainide (n = 1) and bepridil (n = 1), for the patients who experienced ATAs. Among the 12 patients who experienced AFLs, 8 had typical AFLs, and 4 had atypical AFLs. We defined atypical AFLs as AFLs that were not dependent on the cavotricuspid isthmus. Among the 9 patients who underwent ATA ablation, 6 of 8 patients with typical AFLs experienced recurrence during the follow-up, and 1 patient with right-sided atypical AFL did not experience recurrence. There were no procedural complications.

During the median follow-up period of 4.0 [0.1–15.3] years after the development of ATAs, 16 patients experienced recurrence, and

Table 4
Odds ratio of heart failure-related events associated with atrial tachyarrhythmias.

Event	Patients with ATAs(n = 32)	Patients without ATAs(n = 58)	Odds ratio (95%CI)	p value
	Number of patients (%)			
All-cause death	14 (44)	7 (12)	5.7 (2.0–16.3)	<0.01
Death due to heart failure	13 (41)	2 (3)	19.2 (4.0–92.3)	<0.01
Sudden death	1 (3)	3 (5)	0.6 (0.1–5.9)	0.65
Non-cardiac death	0	2 (3)	0.4 (0.0–7.5)	0.29
Hospitalization due to worsening heart failure*	22 (69)	4 (7)	29.7 (8.4–104.8)	<0.01

ATA, atrial tachyarrhytmia; CI, confidence interval.
* Fisrt event after the occuence of ATAs.

Table 5
Multivariate analyses for hospitalization for worsening heart failure.

Variable	Number of patients (%)	HR (95% CI)	p value
Age (≥65 years vs <65 years)	2/6 (33) vs 26/84 (31)	0.97 (0.14–6.65)	0.97
Gender (male vs. female)	23/69 (33) vs 5/21 (24)	1.33 (0.46–3.84)	0.60
Family history of ARVC (yes vs. no)	5/9 (56) vs 23/81 (28)	2.19 (0.60–7.99)	0.88
NYHA class (II-IV vs. I)	7/16 (44) vs 21/74 (28)	2.19 (0.60–7.99)	0.23
Prior VT/VF/cardiac arrest (yes vs. no)	20/64 (31) vs 8/26 (31)	0.34 (0.11–1.03)	0.06
LVEF (<40% vs. ≥40%)	6/13 (46) vs 22/77 (29)	6.10 (1.68–22.21)	<0.01
ATAs (yes vs. no)	24/31 (77) vs 4/59 (7)	15.55 (4.82–50.17)	<0.01

ARVC, arrhythmogenic right ventricular cardiomyopathy; ATA, atrial tachyarrhythmia; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

9 of these patients died, while all 5 patients who did not experience recurrence survived (Fig. 4).

4. Discussion

Our study on patients with severe ARVC revealed the following results. 1) Patients with a prediagnosis history of ATAs at ARVC diagnosis were older and showed a reduced LVEF and a higher NYHA functional class than patients without a prediagnosis history of ATAs. 2) Patients with a prediagnosis history of ATAs experienced more HF-related events after ARVC diagnosis than patients without a prediagnosis history of ATAs. 3) New ATAs developed after ARVC diagnosis in a quarter of patients without a prediagnosis history of ATAs during the long follow-up period. 4) Patients

with ATAs were more likely to be hospitalized due to worsening HF or to experience death due to HF than patients without ATAs.

4.1. Diagnosis of ARVC and prior ATAs

The patients in our study were older at diagnosis, and there was a higher proportion of males and of patients with prior sustained VT/VF/cardiac arrest than in other studies [5–7,9]. Therefore, most patients in our study were in advanced ARVC stages, such as overt and later phases, and exhibited RV and/or LV structural abnormalities. In our study, patients with a prediagnosis history of ATAs showed a lower RVEF at ARVC diagnosis than patients without a prediagnosis history of ATAs. A low RVEF (<30%) at diagnosis and older age (≥65 years) were independent predictors of newly occurring ATAs. In general, the incidence of AF increases with age [16].
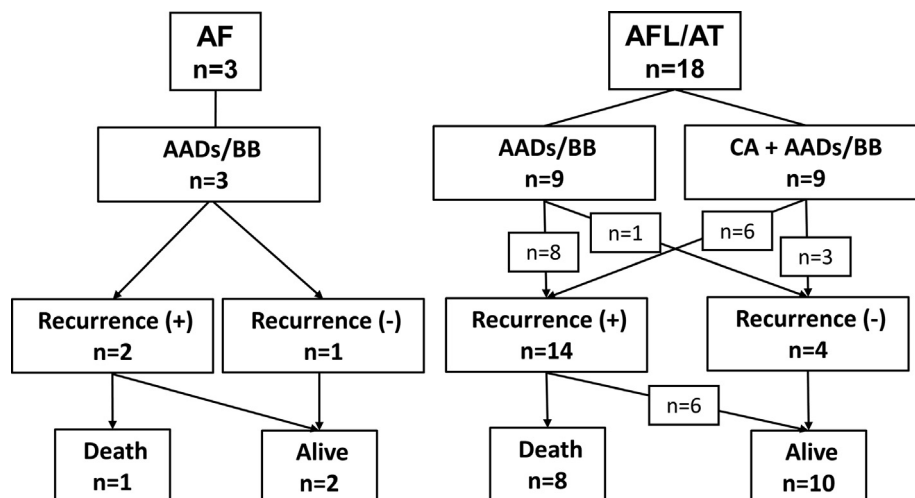

Fig. 4. Treatments for patients with atrial tachyarrhythmias (atrial fibrillation (AF), atrial flutter (AFL) and atrial tachycardia (AT)) and their prognoses. AADs, antiarrhythmic drugs; BB, beta blocker; CA, catheter ablation.

Older age itself is a contributing factor to the development of ATAs. The use of antiarrhythmics for ventricular arrhythmias might partially contribute to inhibiting the occurrence of ATAs. Some studies have also suggested that RV structural abnormalities are related to ATAs in patients with ARVC [4,6,9]. Moreover, a high ARVC diagnostic score is related to the occurrence of AF, as previously reported [9]. Because there are several categories of TFC, such as structural, functional and histological abnormalities [14], a higher ARVC diagnostic score indicates a more advanced disease status [13]. In patients with ARVC, ATAs can occur in advanced stages with RV and/or LV structural abnormalities.

4.2. Development of ATAs and their mechanism

In our study, 11 patients had a prediagnosis history of ATAs at the time of ARVC diagnosis, and 21 developed new ATAs during long-term treatment after ARVC diagnosis. Therefore, in total, 32 (36%) of the 90 enrolled patients experienced ATAs. Previous studies have reported that the prevalence of ATAs varies from 13% to 42% [4–9,17]. Chu et al reported a high proportion of ATAs (44%) in patients with severe ARVC and sustained VT, among whom 97% received an ICD and had a mean age of 47 years old [4]. However, a relatively lower frequency of ATAs has been observed in studies including family members (gene carriers) [5,9,17]. The difference in the prevalence of ATAs might be due to the severity of ARVC. Although the frequency of ATAs in our study cannot be generalized, the occurrence of ATAs is not uncommon in patients with severe ARVC [4,6,8,9]. In our study, the frequency of newly occurring ATAs was higher in patients with preexisting HF (NYHA class ≥ II) than in those without preexisting HF, but the presence of preexisting HF was not statistically significant because the number of patients who had preexisting HF was small.

In addition, the proportion of patients who experienced AFL/AT was higher than that of patients who experienced AF. Although the reason for this finding is not clear, remodeling of the right atrium secondary to RV overload might pathophysiologically contribute to the development of right-sided ATAs in ARVC patients. Among 9 patients who underwent catheter ablation, all AFLs were due to macroreentry in the right atrium. In our study, the left atrial dimension when ATAs occurred was not enlarged, and the proportion of patients who experienced AF among those who experienced ATAs was low.

4.3. ATAs and HF

In this study, hospitalization due to worsening HF occurred for patients with prior ATAs after ARVC diagnosis and for patients who experienced newly occurring ATAs after ATAs development. Because patients experience ATAs at an older age, ATAs are also related to disease progression. In ARVC patients, ATAs may be clinical signs of subsequent right HF following RV dysfunction and right heart overload in advanced stages. Camm et al suggested that ATAs may be associated with the severity of ARVC because both death and HF are prevalent in patients with ATAs [5]. Worsening HF in the later phase of ARVC, though rare, is an important outcome [18]. The results of this study suggest that the occurrence of ATAs may be a predictive marker of HF associated with disease progression in patients with longstanding ARVC.

Although genetic information was available from only a very limited number of patients in our study, desmoplakin mutations were observed in half of the patients with ATAs and HF-related events. Previous studies reported that plakophilin-2 mutations were predominant in patients with ARVC who developed HF symptoms/signs or HF events [18–20]. Other studies reported that

desmoplakin mutation carriers were at high risk of LV dysfunction and HF or that desmoglein-2 mutation carriers were at high risk of transplantation/death due to HF [21,22]. However, the definitions of HF among studies were not identical, and the patient sampling methods were different among the studies (number of study patients, single-center or multicenter registry, inclusion of family members/gene carriers). Since disease phenotypes in patients with ARVC may be affected by genetic backgrounds and nongenetic modifiers, further studies regarding the prognostic value of genotyping are required.

4.4. Treatment of ATAs and prognosis

Patients with AF received antiarrhythmic drugs, and those with AFL/AT received catheter ablation and/or antiarrhythmic drugs to prevent recurrence. Previous studies have described the use of catheter ablation for AFL and the use of antiarrhythmic drugs, such as amiodarone, sotalol and beta blockers, for ATAs, but their efficacies have not been evaluated [4,6,8]. Sixteen of 21 patients experienced recurrence, and half of them died thereafter. It is unclear whether antiarrhythmic drugs/catheter ablation prevented HF-related events because of the small number of patients or the lack of a control arm. Otherwise, the recurrence of ATAs might have been due to disease progression rather than an ineffective treatment. However, it is worth attempting to prevent the recurrence of ATAs in patients with ARVC since all patients without recurrence survived.

5. Limitations

There were some limitations to this study. First, this was a retrospective observational study performed at a single center. Some patients were lost to follow-up. Data concerning the clinical condition at the time of events were not fully available. In addition, there was a treatment bias. The treatment strategies used for each patient changed during the follow-up period. In Japan, ICDs were approved in 1996. Additionally, guidelines that first recommended ICD implantation as an indication for ARVC patients were published in 2012: only ARVC patients with a history of cardiac arrest, VF, and hemodynamically unstable sustained VT were indicated [23]. Therefore, the number of patients with an ICD was low in this long-term study. The potential confounding factors associated with time and era effects could not be completely excluded. Second, we could not assess ARVC patients whose first presentation of the disease was SCD. Our study did not include family members (gene carriers) without a definite ARVC phenotype. Third, a genetic evaluation was performed for only 12 patients in this study. We could not evaluate the effect of mutations in desmosomal genes or other genetic backgrounds on the occurrence of ATAs or HF-related events in this study. Fourth, our study population was limited to relatively severe high-risk ARVC patients and those who showed a high incidence of HF-related events. Therefore, we have not yet clearly determined whether our findings are generalizable to all ARVC patients. Additionally, the number of patients included in our study was small, and therefore, subgroup analysis was not feasible.

6. Conclusions

Our long-term observational study suggests that the occurrence of ATAs is associated with an increased risk of HF-related events and worsens the prognosis of ARVC patients.

Funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

References

[1] F.I. Marcus, G.H. Fontaine, G. Guiraudon, R. Frank, J.L. Laurenceau, C. Malergue, et al., Right ventricular dysplasia: a report of 24 adult cases, Circulation 65 (1982) 384–398.

[2] C. Basso, D. Corrado, F.I. Marcus, A. Nava, G. Thiene, Arrhythmogenic right ventricular cardiomyopathy, Lancet 373 (2009) 1289–1300.

[3] D. Corrado, C. Basso, G. Thiene, W.J. McKenna, M.J. Davies, F. Fontaliran, A. Nava, F. Silvestri, C. Blomstrom-Lundqvist, E.K. Wlodarska, G. Fontaine, F. Camerini, Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study, J. Am. Coll. Cardiol. 30 (6) (1997) 1512–1520.

[4] A.F. Chu, E. Zado, F.E. Marchlinski, Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia, Am J Cardiol. 106 (2010) 720–722.

[5] C.F. Camm, C.A. James, C. Tichnell, B. Murray, A. Bhonsale, A.S. te Riele, et al., Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy, Heart Rhythm. 10 (2013) 1661–1668.

[6] A.M. Saguner, S. Ganahl, A. Kraus, S.H. Baldinger, A. Medeiros-Domingo, A.R. Saguner, et al., Clinical role of atrial arrhythmias in patients with arrhythmogenic right ventricular dysplasia, Circ. J. 78 (2014) 2854–2861.

[7] L. Wu, J. Guo, L. Zheng, G. Chen, L. Ding, Y. Qiao, et al., Atrial remodeling and atrial tachyarrhythmias in arrhythmogenic right ventricular cardiomyopathy, Am. J. Cardiol. 118 (2016) 750–753.

[8] R. Cardona-Guarache, M. Åström-Aneq, A. Oesterle, R. Asirvatham, J. Svetlichnaya, G.M. Marcus, E.P. Gerstenfeld, L. Klein, M.M. Scheinman, Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy: Prevalence, echocardiographic predictors, and treatment, J. Cardiovasc. Electrophysiol. 30 (10) (2019) 1801–1810.

[9] M.A. Baturova, K.H. Haugaa, H.K. Jensen, A. Svensson, T. Gilljam, H. Bundgaard, et al., Atrial fibrillation as a clinical characteristic of arrhythmogenic right ventricular cardiomyopathy: experience from the Nordic ARVC Registry, Int. J. Cardiol. 298 (2020) 39–43.

[10] D. Kotecha, J.P. Piccini, Atrial fibrillation in heart failure: what should we do?, Eur. Heart J. 36 (2015) 3250–3257.

[11] S. Stewart, C.L. Hart, D.J. Hole, J.J.V. McMurray, A population-based study of the longterm risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study, Am. J. Med. 113 (2002) 359–364.

[12] T.J. Wang, M.G. Larson, D. Levy, R.S. Vasan, E.P. Leip, P.A. Wolf, R.B. D'Agostino, J.M. Murabito, W.B. Kannel, E.J. Benjamin, Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study, Circulation 107 (23) (2003) 2920–2925.

[13] N. Kikuchi, D. Yumino, T. Shiga, A. Suzuki, N. Hagiwara, Long-Term prognostic role of the diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia, JACC Clin. Electrophysiol. 2 (2016) 107–115.

[14] F.I. Marcus, W.J. McKenna, D. Sherrill, C. Basso, B. Bauce, D.A. Bluemke, et al., Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria, Circulation 121 (2010) 1533–1541.

[15] S. Goodacre, R. Irons, ABC of clinical electrocardiography: atrial arrhythmias, BMJ 324 (2002) 594–597.

[16] W.M. Feinberg, J.L. Blackshear, A. Laupacis, R. Kronmal, R.G. Hart, Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications, Arch. Intern. Med. 155 (1995) 469–473.

[17] M. Bourfiss, A.S. Te Riele, T.P. Mast, M.J. Cramer, J.F. van der Heijden, T.A. van Veen, et al., Influence of genotype on structural atrial abnormalities and atrial fibrillation or flutter in arrhythmogenic right ventricular dysplasia/cardiomyopathy, J. Cardiovasc. Electrophysiol. 27 (2016) 1420–1428.

[18] A.S. Vischer, S. Castelletti, P. Syrris, W.J. McKenna, A. Pantazis, Heart failure in patients with arrhythmogenic right ventricular cardiomyopathy: genetic characteristics, Int. J. Cardiol. 286 (2019) 99–103.

[19] N.A. Gilotra, A. Bhonsale, C.A. James, A.S.J. te Riele, B. Murray, C. Tichnell, A. Sawant, C.S. Ong, D.P. Judge, S.D. Russell, H. Calkins, R.J. Tedford, Heart failure is common and under-recognized in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia, Circ. Heart Fail 10 (9) (2017), https://doi.org/10.1161/CIRCHEARTFAILURE.116.003819.

[20] T. Gilljam, K.H. Haugaa, H.K. Jensen, A. Svensson, H. Bundgaard, J. Hansen, et al., Heart transplantation in arrhythmogenic right ventricular cardiomyopathy - experience from the Nordic ARVC Registry, Int. J. Cardiol. 250 (2018) 201–206.

[21] A. Bhonsale, J.A. Groeneweg, C.A. James, D. Dooijes, C. Tichnell, J.D. Jongbloed, et al., Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers, Eur. Heart J. 36 (2015) 847–855.

[22] A. Hermida, V. Fressart, F. Hidden-Lucet, E. Donal, V. Probst, J.C. Deharo, et al., High risk of heart failure associated with desmoglein-2 mutations compared to plakophilin-2 mutations in arrhythmogenic right ventricular cardiomyopathy/dysplasia, Eur. J. Heart Fail. 21 (2019) 792–800.

[23] JCS Joint Working Group, Guidelines for non-pharmacotherapy of cardiac arrhythmias (JCS 2011), Circ. J. 77 (2013) 249–274.