Clinical Role of Atrial Arrhythmias in Patients With Arrhythmogenic Right Ventricular Dysplasia

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Background: The clinical role of atrial fibrillation/atrial flutter (AF-AFI) and variables predicting these arrhythmias are not well defined in patients with arrhythmogenic right ventricular dysplasia (ARVD). We hypothesized that transthoracic echocardiography (TTE) and 12-lead electrocardiography (ECG) would be helpful in predicting AF-AFI in these patients.

Methods and Results: ECGs and TTEs of 90 patients diagnosed with definite or borderline ARVD (2010 Task Force Criteria) were analyzed. Data were compared in (1) patients with AF-AFI and (2) all other patients. A total of 18 (20%) patients experienced AF-AFI during a median follow-up of 5.8 years (interquartile range 2.0–10.4). Kaplan-Meier analysis revealed reduced times to AF-AFI among patients with echocardiographic RV fractional area change <27% ($P<0.001$), left atrial diameter ≥ 24.4 mm/m² (parasternal long-axis, $P=0.001$), and right atrial short-axis diameter ≥ 22.1 mm/m² (apical 4-chamber view, $P=0.05$). From all ECG variables, P mitrale conferred the highest hazard ratio (3.37, 95% confidence interval 0.92–12.36, $P=0.067$). Five patients with AF-AFI experienced inappropriate implantable cardioverter-defibrillator (ICD) shocks compared with 4 without AF-AFI (36% vs. 9%, $P=0.03$). AF-AFI was more prevalent in heart-transplant patients and those who died of cardiac causes (56% vs. 16%, $P=0.014$).

Conclusions: AF-AFI is associated with inappropriate ICD shocks, heart transplantation, and cardiac death in patients with ARVD. Evidence of reduced RV function and atrial dilation helps to identify the ARVD patients at increased risk for AF-AFI. (*Circ J* 2014; **78**: 2854–2861)

Key Words: Arrhythmogenic right ventricular dysplasia; Atrial fibrillation; Atrial flutter; Cardiomyopathy

Arrhythmogenic right ventricular dysplasia (ARVD) is a hereditary cardiomyopathy characterized by fibrofatty infiltration of the right ventricle (RV).¹ Besides ventricular tachyarrhythmias and heart failure that may eventually lead to heart transplantation or cardiac death,^{2–4} spontaneous occurrence of sustained atrial arrhythmias has been recognized as a common clinical entity in ARVD, with up to 42% of patients being affected.⁵ Atrial fibrillation/atrial flutter (AF-AFI) have long been associated with an increased risk of morbidity and mortality in the general population,^{6,7} but the clinical role of these atrial arrhythmias, and the clinical variables predicting AF-AFI in particular, are not well defined in patients with ARVD.^{5,8–10} Other than the study by Camm et al,¹⁰ all previous studies have been constrained by small sam-

ple sizes and inclusion of patients with advanced ARVD.^{5,8,9} Moreover, atrial enlargement was not well defined in any of the studies, and none of them investigated the role of 12-lead surface ECG and RV function to predict AF-AFI. Thus, the purpose of the present study was to identify the electrocardiographic and echocardiographic variables that predict AF-AFI, and to investigate the clinical role of AF-AFI in a large cohort of patients with ARVD.

Methods

Study Population

The study population included 90 patients from 3 tertiary-care centers in Switzerland who had either a definite or a borderline

Received May 1, 2014; revised manuscript received September 3, 2014; accepted September 8, 2014; released online October 20, 2014
Time for primary review: 14 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0474

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Table 1. Definitions of the Electrocardiographic and Echocardiographic Parameters and Measurements

Variable	Definition
P wave duration (Pmax)	Longest interval between the earliest onset of the wave (positive deflection crossing the isoelectric line) and the latest off-set in any of 12 leads
P wave dispersion	Difference between Pmax and minimal P duration
Notched P wave	P wave “notched” if interpeak duration in the limb leads ≥ 40 ms
P mitrale	1) P wave in any lead >110 ms and 2) Notched P wave with interpeak duration ≥ 40 ms, 3) P wave axis $<30^\circ$, or 4) Positive P terminal force in aVL >0.5 mm
P pulmonale	P wave voltage ≥ 0.25 mV in any inferior lead or positive P wave in V1 >1.5 mm
RV FAC (%)	RV [Area D–Area S]/Area D measured in the apical 4CV
RA short axis (mm)	RA short-axis diameter measured in the apical 4CV All atrial diameters were measured at end-ventricular systole
RA long axis (mm)	RA long-axis diameter measured in the apical 4CV
RA dilation	RA short-axis diameter >25 mm/m ² or long-axis diameter ≥ 30 mm/m ²
LA long axis (mm)	LA diameter measured in the PLAX with M-mode (leading-edge to leading-edge)
LA dilation	LA diameter >23 mm/m ²
Significant TR	Moderate-to-severe TR ^{19,33}

Area D, right ventricular end-diastolic area; Area S, right ventricular end-systolic area; 4CV, 4-chamber view; FAC, fractional area change; LA, left atrial; PLAX, parasternal long axis; RA, right atrial; RV, right ventricular; TTE, transthoracic echocardiography; TR, tricuspid regurgitation.

Figure 1. (Left) Representative echocardiographic RV end-diastolic area (in green). (Middle) Representative echocardiographic RV end-systolic area (in blue), both taken from the apical four-chamber view in a patient with definite ARVD. RV end-diastolic area was 48.5 cm², and RV end-systolic area was 38.9 cm², resulting in an impaired RV fractional area change of 20%. (Right) M-mode measurement of LA dimension in ventricular end-systole in the parasternal long axis in the same patient (green line). The blue dashed line indicates the aortic root diameter. The LA was dilated at 54 mm (25.6 mm/m²). ARVD, arrhythmogenic right ventricular dysplasia; LA, left atrial; RV, right ventricular.

diagnosis of ARVD according to the 2010 Task Force Criteria,¹¹ who had an ECG recorded between February 1987 and April 2012, and for whom outcome data were available. The ECG constituted the earliest ECG available for analysis performed at one of the participating centers, and marked the starting point for study inclusion and follow-up analyses. None of the patients had had AF-AFI documented prior to study inclusion. In this observational study, patients were enrolled both prospectively (n=11) and retrospectively (n=79). All patients were participants in the multicenter Zurich ARVD Registry (www.arvc.ch). Clinical information regarding demographics and symptoms was obtained from hospital records. The study complied with the Declaration of Helsinki. Inclusion in this

registry was approved by the institutional review boards of each participating center.

Definitions of Electrocardiographic and Echocardiographic Parameters

The ECG and transthoracic echocardiographic (TTE) definitions and criteria used in this study are presented in [Table 1](#).

ECG Analysis

ECGs were recorded at rest (25 mm/s, 10 mm/mV amplitude) with standard lead positions, digitized with a high-resolution scanner, and analyzed with a digital caliper (Iconico; screen caliper version 4.0).¹² To increase the accuracy of measurements,

Table 2. Baseline Clinical Characteristics of Patients With Arrhythmogenic RV Dysplasia

Characteristic	All patients (n=90)	Atrial arrhythmia (n=18)	No atrial arrhythmia (n=72)	P value
Age at study inclusion (years)	44.2±14.6	47.8±13.4	43.3±14.9	0.24
Age at last follow-up (years)	49.7±14.6	54.1±3.3	48.7±1.7	0.16
Male	57 (63)	11 (61)	46 (64)	1.0
Systolic BP (mmHg)	120 (110–128)	118.5 (110–120.5)	120 (110–118)	0.15
Diastolic BP (mmHg)	76±9	75±8	77±9	0.51
Heart rate (beats/min)	65.2 (55.1–77.2)	67.2 (58.4–82.4)	65.2 (54.3–73.2)	0.19
BSA (m ²)	1.9 (1.7–2)	1.9 (1.8–2.0)	1.9 (1.7–2.0)	0.8
Body mass index (kg/m ²)	24.5 (22–26.5)	24.5 (21.8–27.3)	24.6 (22–26.3)	0.85
Previous sustained VT/VF/SCA	49 (54)	10 (56)	39 (54)	1.0
“Definite” ARVD	77 (86)	18 (100)	59 (82)	0.06
Amiodarone	14 (16)	3 (17)	11 (15)	1.0
β-blocker	43 (48)	10 (56)	33 (46)	0.6
Sotalolol	13 (14)	4 (22)	9 (13)	0.28
Other antiarrhythmic therapy	7 (8)	2 (11)	5 (7)	0.63

Values are mean±standard deviation, median with interquartile range and n (%).

Definite, a definite diagnosis of ARVD according to the 2010 Task Force Criteria.

BP, blood pressure; BSA, body surface area; RV, right ventricular; SCA, sudden cardiac arrest; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3. Electrocardiographic and Echocardiographic Data of Patients With Arrhythmogenic RV Dysplasia

Characteristic	All patients (n=90)	Atrial arrhythmia (n=18)	No atrial arrhythmia (n=72)	P value
RR interval (ms)	954±234	874±250	974±227	0.1
PQ interval (ms)	166 (147–184)	182 (158–198)	165 (147–182)	0.11
P max duration (ms)	108±19	104±20	108±18	0.46
P dispersion (ms)	38 (29–51)	36 (24–45)	40 (30–52)	0.35
Notched P wave	11 (12)	2 (11)	9 (13)	1.0
P pulmonale	5 (6)	0	5 (7)	0.58
P mitrale	8 (9)	3 (17)	5 (7)	0.2
QRS duration (ms)	111 (100–128)	122 (101–137)	110 (100–125)	0.18
RA short axis/BSA (mm/m ²)	22.1 (19.4–26.1)	23.9 (22.3–31.1)	21.4 (19.2–24.9)	0.016
RA long axis/BSA (mm/m ²)	27.6 (24–30.1)	29.5 (25.2–33.1)	27 (24–29.4)	0.05
RA dilation (short axis >25 mm/m ² or long axis ≥30 mm/m ²)	34 (38)	9 (50)	25 (35)	0.28
LA long axis/BSA (mm/m ²)	19.5±3.7	21.1±3.9	19.0±3.5	0.04
LA dilation (>23 mm/m ²)	12 (13)	6 (33)	6 (8)	0.012
RV FAC (%)	32 (22–42)	21.5 (20–25.8)	35 (27–42.5)	0.001
RV dysfunction (FAC <33%)	47 (52)	15 (83)	32 (44)	0.004
LVEF (%)	59 (52–64)	55 (49.8–60)	60 (52.8–65)	0.038
LV involvement (LVEF <50%)	14 (16)	4 (22)	10 (14)	0.47
Moderate/severe TR	11 (12)	5 (28)	6 (8)	0.04

Values are mean±standard deviation, median with interquartile range and n (%).

LV, left ventricular; LVEF, left ventricular ejection fraction. Other abbreviations as in Tables 1,2.

all ECGs were enlarged 4-fold. ECG intervals were measured in 2 consecutive sinus beats in each lead; the mean value of the 2 beats was used. If the difference between beats was >10 ms, then the mean of 3 beats was taken. Each ECG was independently analyzed by 2 experienced readers, each of whom was blinded to the clinical outcome data. Differences in the interpretation of the ECG parameters were adjudicated by a third cardiologist, and a final conclusion was made by consensus. ECG variables were measured according to current practice.^{13–18}

TTE

Conventional M-mode, 2-D, and color Doppler echocardiographic

images were obtained by an experienced cardiologist according to guidelines.¹⁹ Echocardiographic RV fractional area change (FAC) was calculated as previously reported (Figure 1, Table 1).²⁰ FAC <33% was considered abnormal. Left ventricular (LV) involvement was considered when LV regional wall motion abnormalities or a reduced ejection fraction (EF; <50% by Simpson's biplane method) were present and other causes had been excluded.²⁰ Atrial dimensions were measured as described in Table 1. RA short-axis dimension >25 mm/m² or RA long-axis dimension ≥30 mm/m², and LA dimension >23 mm/m² were considered abnormal in accordance with previous literature.^{19,21} The degree of tricuspid regurgitation was determined

as none, mild, moderate, or severe. Some of the echocardiographic data from 70 patients used in this study has been reported in a previous study from our group.²²

Outcome Measures

Follow-up for outcome data was performed by hospital chart review, including clinical visits, 12-lead ECGs, Holter ECGs, and implantable cardioverter-defibrillator (ICD) interrogations with stored electrograms (EGMs).²³ Inappropriate ICD therapy was defined as previously described.¹⁰ For the purpose of this study, atrial arrhythmia was defined as AF and/or AFL that lasted ≥30 s. Episodes lasting <30 s were only included if they were terminated by an ICD shock. AF-AFL only occurring during electrophysiological studies was excluded. When atrial arrhythmia was not diagnosed by 12-lead or Holter-ECG, discrimination between atrial arrhythmia and ventricular tachycardia was based on stored EGMs using standard diagnostic criteria, including regularity of ventricular arrhythmia, EGM morphology, and the relationship of atrial and ventricular EGMs.^{5,24} Cardiac death was defined as sudden cardiac death or death due to terminal heart failure. The influence of ECG and TTE parameters on long-term clinical outcome was compared in 2 patient groups: (1) those with atrial arrhythmia (composite of AF-AFL) and (2) all other patients. For Kaplan-Meier and Cox regression analyses, time from study inclusion to the occurrence of first episode of AF-AFL was the event of interest.

Statistical Analysis

Continuous variables are presented as mean±SD or median (with interquartile range, IQR), and compared using a 2-sided

t-test or Mann-Whitney U-test, as appropriate. Categorical variables are reported as frequency (percentage) and compared between groups by Fisher's exact test. Pearson's or Spearman's correlation was carried out to analyze correlations between TTE and cardiac magnetic resonance (CMR) parameters, as appropriate. Cut-off points for continuous variables that maximized the difference in survival free from AF-AFL were determined. This was done by minimizing the P-value of the log-rank test, and then correcting for multiple testing. Survival free from AF-AFL was estimated using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. Baseline variables associated with a significantly altered hazard for atrial arrhythmia were identified by univariable Cox regression analysis. The predictive discrimination of FAC, LA and RA dimensions was measured using Harrell's c-index, which accounts for censored measurements. We mainly focused on the electrocardiographic and echocardiographic data obtained during initial assessment of patients with ARVD that could be important for predicting AF-AFL during follow-up. To evaluate the effects of classical risk factors of AF-AFL in the general population, we included age, sex, arterial hypertension, coronary artery disease, and body mass index in our univariable model. The initial clinical assessment will guide the physician in choosing the appropriate therapy for each individual patient based on the risk for AF-AFL. As in most clinical situations, it is not appropriate to wait for an assessment of electrocardiographic and echocardiographic changes to evaluate the patient's risk for AF-AFL, so we have not used the change in parameters over time in predicting this endpoint. A 2-sided P-value ≤0.05 was considered significant. Statistical analysis was performed using R programming language

Table 4. Cox Regression Analysis of Clinical Variables Associated With AF/AFI in Patients With Arrhythmogenic RV Dysplasia

Variable	Univariable analysis	
	HR (95% CI)	P value
FAC $\geq 27\%$	0.099 (0.03–0.35)	<0.001
FAC $\geq 33\%$	0.26 (0.08–0.91)	0.036
FAC (%) per unit decrease	1.09 (1.03–1.14)	0.003
LA ≥ 24.4 mm/m ² (long axis)	7.03 (2.43–20.34)	<0.001
LA (mm/m ²) per unit increase (long axis)	1.15 (1.01–1.31)	0.031
RA ≥ 22.1 mm/m ² (short axis)	5.47 (1.55–19.37)	0.008
RA (mm/m ²) per unit increase (short axis)	1.08 (1.02–1.15)	0.013
P mitrale	3.37 (0.92–12.4)	0.067
Age at inclusion (per year increase)	1.02 (0.99–1.06)	0.13
Moderate/severe TR	2.07 (0.72–5.97)	0.18
LV involvement	1.95 (0.63–6.02)	0.25
β -blocker therapy	1.35 (0.53–3.44)	0.53
Female sex	1.32 (0.51–3.41)	0.57
Presence of CAD	2.03 (0.46–8.91)	0.35
Body mass index (kg/m ²)	0.99 (0.91–1.07)	0.76
Previous sustained VT/VF/SCA	0.89 (0.34–2.31)	0.81
Notched P wave	1.2 (0.27–5.44)	0.81
Amiodarone therapy	1.1 (0.31–3.95)	0.88
Presence of arterial hypertension	0.91 (0.26–3.17)	0.88

P values calculated by univariable Cox regression.

AF-AFI, atrial fibrillation and atrial flutter; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1–3.

(R Development Core Team, 2009) and GraphPad Prism 5 (GraphPad Software Inc, La Jolla, CA, USA).

Results

Study Population

Patient demographic data, baseline characteristics, and ECG and TTE variables are summarized in [Tables 2,3](#): 88 patients were index patients, and 2 were family members. ARVD was classified as definite in 77 (85%) patients, and borderline in 13 (15%) patients. In total, 57 (63%) patients had an ICD, 38 with a single-chamber device (VVI), 18 with a dual-chamber device (DDD), and 1 patient with a cardiac resynchronization device. Arterial hypertension was present in 17 (19%), and coronary artery disease in 6 (7%) patients.

Prevalence of AF-AFI

During a median follow-up of 5.8 years (IQR 2.0–10.4 years), 18 (20%) patients experienced the composite endpoint (AF $n=16/18$ [88%], AFI $n=2/18$ [12%]). Time from study inclusion to last patient contact was not significantly different between those with and without the composite endpoint (median 7.3, IQR 2.5–9.8 years vs. 5.3, IQR 1.7–10.6 years, $P=0.48$). Mean age at the time of the composite endpoint was 50 ± 13 years. Median time from study inclusion to atrial arrhythmia was 11.7 months (IQR 3.7–33 months). AF-AFI was paroxysmal in all but 1 patient; 12 patients with AF-AFI also suffered from sustained ventricular arrhythmia: in 7 of them, AF-AFI occurred prior to the first documented sustained ventricular event, while in 4 patients this occurred afterwards, and in 1 patient on the same day. The median CHA₂DS₂-VASc score of all patients with AF-AFI was 1 (range 0–4; mean 1.1), with 11 individuals recording a score ≥ 1 (61%). Oral anticoagulation

was prescribed in 9 patients and aspirin in 1 patient. No adverse events related to anticoagulation were recorded; 3 patients with AF suffered from stroke ($n=1$)/transitory ischemic attack (TIA, $n=1$)/other peripheral embolism ($n=1$) (CHA₂DS₂-VASc scores of 1, 4, and 3, respectively), and stroke ($n=1$)/TIA ($n=1$) was documented in 2 patients (CHA₂DS₂-VASc scores of 4 and 0) without AF-AFI (17% vs. 3%, $P=0.05$). Successful electrical cardioversion was performed in 1 patient with AF, and successful catheter ablation of the cavotricuspid isthmus was performed in 2 patients with AFI, one of whom later developed AF. Catheter ablation of AF was not performed in any of those 18 patients. Of the patients in whom the initial arrhythmia was AF ($n=16$), 2 also experienced AFI during follow-up.

Predictors of AF-AFI

Complete echocardiographic data sets were available for 77 (86%) patients in whom ECG analysis was performed ([Table 3](#)). Kaplan-Meier plots revealed that a reduced RV FAC and echocardiographic LA and RA dilation were significantly associated with lower survival free from atrial arrhythmia ([Figure 2](#)). For RV FAC, the best cut-off to predict atrial arrhythmias was $<27\%$, for LA dimension ≥ 24.4 mm/m² (measured in PLAX), and for RA dimension ≥ 22.1 mm/m² measured in the apical 4-chamber view (short axis). Consistent with this observation, the Harrell's c-index for FAC 27%, LA dimension 24.4 mm/m² and RA short-axis dimension 22.1 mm/m² equaled 0.75, 0.64 and 0.67, respectively. In line with these analyses, a reduced FAC, LA and RA dilation were identified as significant univariable predictors increasing the hazard ratio (HR) for the outcome event. In accordance with echocardiographic LA dilation, P mitrale more than tripled the hazard for atrial arrhythmias (HR 3.37, 95% confidence interval 0.92–12.36, [Table 4](#)). Other variables such as LV involvement, degree of

tricuspid regurgitation, use of antiarrhythmic medication and β -blockers, and a spontaneous episode of sustained ventricular tachycardia or ventricular fibrillation, and also the classical risk factors of AF-AFI in the general population such as arterial hypertension, coronary artery disease, sex, age, and BMI were not associated with a significantly altered hazard for AF-AFI on univariable analysis. CMR data were available and analyzed for 21 patients, showing a median RVEF of 45% (IQR 35–50.5), and a median RV end-diastolic volume index (RVEDVI) of 106.1 ml/m² (IQR 92–135.2). Atrial dimensions were measured in the CMR 4-chamber view, and yielded a median RA area of 23 cm² (IQR 18–36), and a median LA area of 22 cm² (IQR 17–24), respectively. Echocardiographic FAC and RV end-diastolic area index (RVEDAI) significantly correlated with RVEF and RVEDVI as determined by CMR, respectively ($r=0.48$, $P=0.028$ for FAC vs. RVEF; $r=0.67$, $P=0.001$ for RVEDAI vs. RVEDVI). Correlation between the echocardiographic RA short-axis dimension and RA area by CMR showed a trend towards significance ($r=0.6$, $P=0.07$).

Inappropriate ICD Shocks Related to AF-AFI

During follow-up, 5 patients (28%) with atrial arrhythmias suffered from inappropriate ICD shocks because of AF-AFI with rapid ventricular conduction. Of them, 3 patients ($n=3/5$, 60%) had a single-chamber ICD. In contrast, 4 patients without AF-AFI experienced inappropriate shocks during follow-up (36% vs. 9%, $P=0.03$). Distribution of single-chamber ($n=4$) and dual-chamber ($n=5$) ICDs was similar among the patients with AF-AFI who did not receive inappropriate shocks during follow-up.

Association of AF-AFI and Heart Transplantation/Cardiac Death

Of the 90 patients included in this study, 6 patients underwent heart transplantation, and 3 died of end-stage heart failure ($n=9/90$, 10%). AF-AFI was previously documented in 5 of these 9 patients, which was significantly more prevalent in this patient group with an adverse outcome compared with the remaining patients (56% vs. 16%, $P=0.014$).

Discussion

The results of this observational long-term study suggest that AF-AFI are common, and that their presence is associated with an adverse clinical outcome (inappropriate shocks, heart transplantation, cardiac death) in patients with ARVD. Echocardiographic evidence of reduced RV function and atrial dilation helps to identify ARVD patients at increased risk for the development of these atrial arrhythmias.

Supraventricular arrhythmias have been associated with ARVD since the initial description of this cardiomyopathy.²⁵ Previous groups have reported a prevalence rate between 4% and 42%.^{5,8–10,26} Early small-scale studies suggested that the presence of tricuspid regurgitation and atrial enlargement were associated with the development of atrial arrhythmias. A recent large-scale retrospective study has mainly confirmed those findings.¹⁰ However, atrial dilation was not well defined in any of these studies, and none of them has investigated the role of 12-lead ECG and RV function in predicting atrial arrhythmias.

Predictors of AF-AFI

There is limited data about the risk factors for AF-AFI in patients with ARVD.^{5,8–10} Except for the study by Camm et al,¹⁰ earlier studies were limited by small sample sizes and inclusion of patients with advanced ARVD.^{5,8,9} Although Chu et al demonstrated an association between RV dimensions and atrial

arrhythmias in ARVD,⁵ our study is the first to demonstrate an association between reduced RV function and AF-AFI in this patient population. Importantly, a cut-off of <27% for FAC, ≥ 24.4 mm/m² for LA dimensions measured with M-mode in the PLAX, and a RA short-axis dimension ≥ 22.1 mm/m² measured in the apical 4-chamber view best identified ARVD patients at increased risk for AF-AFI. In line with prior studies, the presence of moderate-to-severe tricuspid regurgitation increased the risk for AF-AFI in our cohort as well, although this association was not significant. Hence, our study extends those previous findings by demonstrating an association between RV function, a hallmark of ARVD, and AF-AFI, and by providing cut-off values for echocardiographic variables that may help to predict AF-AFI in these patients. Although in our cohort LVEF was generally lower in patients with AF-AFI, LV involvement was not associated with atrial arrhythmias in this our study, which corresponds well with the previous data from Chu et al,⁵ and could possibly be explained by the fact that LV involvement was rare (16% in our cohort), or that its current definition has a rather low sensitivity to detect early forms of LV involvement. We found that despite a rigid ECG analysis protocol, 12-lead ECG was generally less useful than TTE for predicting AF-AFI. The presence of P mitrale was associated with an increased risk for AF-AFI, with a trend towards statistical significance, in line with the finding that echocardiographic LA dilation constituted a significant predictor. Although the 12-lead surface ECG has been shown to be useful for predicting AF in patients without ARVD,^{13,27} ECG parameters of atrial dilation have generally been limited by poor sensitivity despite good specificity.²⁸ Although we used ECG definitions for atrial enlargement that have been validated by CMR, because of its high accuracy in volumetric assessment of cardiac chamber sizes,¹⁴ we were unable to identify any ECG variable that significantly predicted atrial arrhythmia in our ARVD cohort.

Classical Risk Factors of AF-AFI

Patients with AF-AFI were older than those without these arrhythmias.¹⁰ Accordingly, age increased the HR for AF-AFI, but was not a significant predictor in our univariable Cox model. The mean age of 50 years at last follow-up, with an AF-AFI prevalence of 20% in this cohort confirms a relatively high disease burden in an age group with a disease prevalence of usually around 0.5%.⁷ In contrast to the study by Camm et al¹⁰ and some population-based studies,²⁹ male sex did not increase the risk for AF-AFI in our cohort. Of note, other classical risk factors such as arterial hypertension, coronary artery disease, and BMI also did not predict AF-AFI. Our findings are in line with data from Chu et al⁵ and imply that reduced RV function, atrial dilation, and disease stage seem to be more important for assessing the risk of AF-AFI in ARVD patients rather than the classical risk factors.

Pathophysiology of Atrial Arrhythmias in ARVD

The causes of atrial arrhythmias in ARVD are not well understood. Although arterial hypertension and atrial dilation are known risk factors for AF in the general population,^{30,31} arterial hypertension was not significantly associated with AF-AFI in patients with ARVD in the current or previous studies. This may be related to the fact that AF-AFI manifests earlier in patients with ARVD. Furthermore, ARVD patients are often engaged in endurance sports and take blood pressure-lowering medication that may protect them from developing arterial hypertension.³² We have shown that biatrial dilation, and most importantly reduced RV function, are associated with AF-AFI.

To what extent our findings can explain the full pathophysiology of atrial arrhythmia in ARVD is unclear. Further research investigating the role of pathogenic mutations, fibrofatty infiltration, endurance training, and electrical propagation in the atria of these patients is certainly needed.

Arrhythmia Detection and Clinical Implications

AF-AFI in patients with ARVD is often not paid enough attention. We were able to show that AF is very common in this rather young population adverse outcomes. Only patients with definite ARVD experienced AF-AFI during follow-up. Of note, AF-AFI was not associated with the presence of sustained ventricular arrhythmias. However, our data are in line with previous data demonstrating that AF-AFI is associated with increased morbidity and adverse outcomes in this population. With regard to this, cardiac death and heart transplantation because of end-stage heart failure were more prevalent in the group with AF-AFI.¹⁰ Thus, it is very important to identify high-risk patients before AF-AFI occurs. The echocardiographic variables and cut-offs found in this study can help to identify such patients, and to adjust therapeutic interventions and individual arrhythmia monitoring. During follow-up, 36% of the present patients with AF-AFI suffered from inappropriate ICD shocks despite taking β -blockers or amiodarone, and the majority of these patients had a single-chamber ICD. Therefore, our results may help in the decision-making process of whether a patient should receive a single- or dual-chamber ICD (the latter preferentially in older patients and an increased risk for AF-AFI) and may affect ICD programming such as the enhancement of SVT detection algorithms in these patients. Serial ECGs, Holter ECGs and comprehensive ICD interrogations seem to be pivotal in detecting atrial arrhythmias in this population. Given the fact that AF-AFI was paroxysmal in 94% of patients, atrial arrhythmias may often go undetected. Moreover, based on our results therapeutic recommendations such as a higher degree of exercise restriction and enhanced control of other risk factors such as hypertension (eg, with angiotensin-converting enzyme inhibitors and potassium-sparing diuretics) and obesity may be warranted in individuals with ARVD and an increased risk for AF-AFI.

Study Limitations

This study is limited by its observational nature. All patients were recruited in tertiary-care centers, which may reflect a referral bias, and indicate the need for confirmation of our results in lower risk ARVD populations. However, these limitations are inherent to any orphan disease registry, and likely very well reflect the way these patients are managed in daily clinical practice. Because our ARVD program is emerging, we currently do not have sufficient genetic data, so we may have missed important genotype-phenotype correlations that could be associated with our findings.^{33,34}

Conclusions

This observational long-term study suggests that AF/AFI are common in patients with ARVD, and associated with inappropriate ICD shocks, heart transplantation, and cardiac death. Echocardiographic evidence of reduced RV function and atrial dilation helps to identify ARVD patients at increased risk of developing AF/AFI.

Acknowledgments

This work and the Zurich ARVC/D Program are supported by a grant from the Georg and Bertha Schwyzer-Winiker Foundation, Zurich, Switzerland.

Disclosures

Conflicts of Interest: Ardan M. Saguner received educational grants from Biotronik, Boston Scientific, St. Jude Medical and Sorin. Sabrina Ganahl: None. Andrea Kraus: None. Samuel H. Baldinger received educational grants from Boston Scientific. Argelia Medeiros-Domingo: None. Arhan R. Saguner: None. Stephan A. Mueller-Burri received educational grants from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical, and consultant speaker fees from Sorin. Thomas Wolber: None. Laurent M. Haegeli: None. Nazmi Krasniqi received consultant and/or speaker fees from Boston Scientific and educational grants from Biotronik, Medtronic and St. Jude Medical. Felix C. Tanner: None. Jan Steffel received consultant and/or speaker fees from Biotronik, Biosense Webster, Medtronic, Sorin and St. Jude Medical, and is co-director of CorXL LLC. Corinna Brunnhorst: None. Firat Duru received honoraria and grants from Biotronik, Medtronic, Sorin and St. Jude Medical.

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