Atrial fibrillation as a clinical characteristic of arrhythmogenic right ventricular cardiomyopathy:

Experience from the Nordic ARVC Registry

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Key words: atrial fibrillation, arrhythmogenic cardiomyopathy, diagnostic score.

Abstract

Aims: Recent studies in arrhythmogenic right ventricular cardiomyopathy (ARVC) patients have drawn attention to atrial fibrillation (AF) as an arrhythmic manifestation of ARVC and as an indicator of atrial involvement in the disease progression. We aimed to assess the prevalence of AF in the Scandinavian cohort of ARVC patients and to evaluate its association with disease clinical manifestations.

Methods: Study sample comprised of 293 definite ARVC patients by 2010 Task Force criteria (TFC2010) and 141 genotype-positive family members (total n=434, 43% females, median age at ARVC diagnosis 41 years [interquartile range (IQR) 28-52 years]). ARVC diagnostic score was calculated as the sum of major (2 points) and minor (1 point) criteria in all categories of the TFC2010.

Results: AF was diagnosed in 42 patients (10%): in 41 patients with definite ARVC diagnosis (14%) vs in one genotype-positive family member (1%), $p<0.001$. The median age at AF onset was 51 (IQR 38-58) years. The prevalence of AF was related to the ARVC diagnostic score: it significantly increased starting with the diagnostic score 4 (2% in those with score 3 vs 13% in those with score 4, $p=0.023$) and increased further with increased diagnostic score (Somer's d value is 0.074, $p<0.001$).

Conclusion: AF is seen in 14% of definite ARVC patients and is related to the severity of disease phenotype thus suggesting AF being an arrhythmic manifestation of this cardiomyopathy indicating atrial myocardial involvement in the disease progression.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibro-fatty replacement of the myocardium and a high degree of electric instability.[1] Right ventricular (RV) dysfunction and ventricular arrhythmias are common in ARVC patients, and there is an increased risk of sudden cardiac death.[2, 3] However, the phenotype of the disease is highly variable ranging from asymptomatic cases to those with life-threatening ventricular arrhythmias. While studies of arrhythmic substrate in ARVC has understandably been focused on the risk of life-threatening ventricular arrhythmias, recent studies have drawn attention to atrial fibrillation (AF) that appears to have high prevalence among ARVC patients.[4-6]

The underlying mechanisms behind AF development in ARVC remain unclear. Hemodynamic consequences of the RV contractile dysfunction may contribute to right atrial overload, increased stretch and development of fibrosis in the atrial walls.[7] Left ventricular (LV) involvement in the disease leading to systolic dysfunction may also be associated with complications such as AF and thromboembolic events.[2] On the other hand, it has been suggested that development of atrial myocardial substrate in ARVC may be driven by genetically determined desmosomal dysfunction.[8] It is possible that involvement of atrial myocardium leading to atrial dilatation[5] and AF is caused by the same mechanisms as fibrotic replacement of myocardium in the right ventricular walls and takes place in a parallel with involvement of ventricular myocardium.

We aimed to assess the prevalence of atrial fibrillation (AF) as an indicator of atrial involvement in the disease progression in a large contemporary cohort of patients with ARVC and to evaluate its association with clinical manifestations of the disease.

Material and methods

The Nordic ARVC Registry (www.arvc.dk) was launched in June 2010 and has been recruiting patients with ARVC previously diagnosed using 1994 TFC and followed in eight tertiary care centers in Denmark, Norway or Sweden, covering a population of approximately 14 million.[9, 10] The registry has also been prospectively including newly diagnosed patients after 2010 with definite ARVC according to 2010 Task Force Criteria (TFC2010),[11] and their genotype-positive family members. We included all patients who met TFC2010 criteria for definite ARVC diagnosis in this study. Genotype-positive family members with a borderline or possible ARVC phenotype were considered to be in the preclinical phase of the disease. We included them in the analysis in order to assess the association between AF prevalence and clinical characteristics at different stages of disease progression.

We extracted clinical registry data as previously described.[10] Registry captured baseline clinical characteristics and data specific for ARVC TFC2010 diagnostic criteria.[11]

Prospective follow-up information was available until November 2017 when data for the current study were retrieved. All analyses were performed using registry data by the time point of the last follow-up date.

AF diagnosis included in the registry was based on the data from patients' medical records as assessed by a principal investigator of the participating site or on AF documentation by ECG, Holter or implantable cardioverter-defibrillator (ICD) interrogation data. AF was defined when at least one episode lasting 30 seconds or longer was recorded.

Ventricular tachyarrhythmias were defined as either ECG-verified or captured by ICD device diagnostics ventricular tachycardia (VT) and ventricular fibrillation (VF). Historical information regarding VT/VF and syncope was retrieved from patients' medical records.

Data on hypertension, diabetes, ischemic heart disease, stroke and heart failure by New York

Heart Association (NYHA) classification were collected according to the registry protocol. All subjects underwent transthoracic echocardiography and parameters included in the TFC 2010 were recorded. Data on left atrial (LA) and right atrial (RA) measurements were extracted from the cardiac ultrasound reports from medical records. Cardiac magnetic resonance imaging (MRI) was performed in 286 patients (66%).

Biopsy and morphometric analyses were performed in 19% of patients.

For all patients we calculated an ARVC diagnostic score as previously proposed.[5, 12] The score is calculated as the sum of major and minor criteria in all categories of the 2010 TFC with each major criteria contributing with 2 points and minor criteria contributing 1 point. In each subgroup of patients categorized according to the ARVC diagnostic score we assessed the prevalence of AF.

Regional ethics committees approved the Registry. In Denmark, registry studies do not require approval from an ethics committee, but approval was obtained from the Danish Data Protection Agency. The study complies with the Declaration of Helsinki.

Statistical methods

We used Student's t-test, Wilcoxon rank sum test, Chi-square test, or Fischers exact test to compare differences between groups.

To assess the link between the ARVC diagnostic score and the prevalence of AF we performed in the standard fashion receiver operating characteristic (ROC) analysis with the estimation of the area under the curve (AUC). Model fit was assessed using Somers' d since there was an assumption of dependency (AF prevalence depending on the degree of phenotypical manifestations).

Univariate binary logistic regression analyses were performed to evaluate odds ratios (OR) and 95% confidence interval (CI) of the association between AF and demographic and

clinical characteristics including each component of the TFC2010. Variables associated with AF at a significant level in the univariate analyses were included in the multivariable model.

A two-sided P-value of <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics 25 (SPSS Inc, Chicago, Illinois, USA).

Results

Clinical and genetic assessment of patients.

We included 434 patients in the study, of which 293 had definite ARVC. Patients characteristics are presented in Table 1. Definite ARVC patients more often had heart failure, ischemic heart disease, greater LA volume index (LAVI) and RA volume index (RAVI), but did not differ in regard to the presence of hypertension, diabetes or stroke.

A total of 42 (10%) patients had had AF at any time by the date of the last follow-up. Of these patients 41 had definite ARVC, whereas one was a genotype-positive family member with borderline ARVC. Among definite ARVC patients, the prevalence of AF was 14 %. In patients with definite ARVC, 19 patients (6%) had AF prior to ARVC diagnosis and 22 (8%) developed AF during follow up after diagnosis. Median age at AF onset was 51 (IQR 38-58) years.

Definite ARVC patients with AF had higher prevalence of hypertension, diabetes, RV structural abnormalities, greater LAVI and RAVI than definite ARVC patients without AF. Two ARVC patients with AF had ischemic stroke, but none of ARVC patients without AF. We found no differences in regard to VT/VF, sustained VT and syncope.

Genetic testing was performed in 383 subjects: in 242 ARVC patients (83%) and in all 192 genotype-positive family members, (51 of them with definite ARVC and 141 with borderline or possible ARVC). The majority of mutation-positive patients (n=324) carried a mutation in the plakophillin-2 (*PKP2*) gene (n=214, 66%), followed by desmoglein-2 (*DSG2*, n=63,

19%), desmoplakin (*DSP*, n=38, 12%), desmocolin-2 (*DSC2*, n=20, 6%), transmembrane protein 43 (*TMEM43*, n=12, 4%) and plakoglobin (*JUP*, n=4, 1%); 28 patients had mutations in two genes (9%).

Biopsy was performed in 82 patients (19%); in 16 of them (20%) it was taken from the RV free wall and yielded findings consistent with major diagnostic criterion in 12 patients (75%). Due to the limited data availability, biopsy findings were not included in the statistical analysis.

Association of AF with ARVC phenotype and significant co-morbidities in definite ARVC patients

In the univariate logistic regression analysis (Table 2), age at ARVC diagnosis, male gender, hypertension, diabetes, heart failure greater than II class by New-York Heart Association classification, ventricular arrhythmias, RV structural abnormalities and LAVI were significantly associated with AF. In the multivariable analysis only LAVI and RV structural abnormalities remained independently associated with AF.

Among patients with definite ARVC, the prevalence of AF in patients with major imaging diagnostic criteria (n=201) was 17% (n=34) vs 8% (n=7) in those without (n=92), p=0.045. Major imaging criteria were found in 34 of 41 definite ARVC patients with AF (83%) vs 167 of 252 definite ARVC patients without AF (66%), p=0.045.

AF and ARVC diagnostic score.

The distribution of AF prevalence in patients according to the ARVC diagnostic score is presented in Figure 1. Starting with the diagnostic score 4, which is a threshold for definite ARVC diagnosis, the prevalence of AF increased concomitant with the increase in the diagnostic score. AUC in ROC analysis was 0.688, $p<0.001$. There was a positive significant correlation between AF and diagnostic score ($d = 0.074$, $p < 0.001$).

Discussion

Main finding

We assessed the prevalence of AF and its association with ARVC phenotype prominence in a large register-based Scandinavian cohort of patients with definite ARVC by TF2010 and their genotype-positive family members. We report that AF is observed in nearly one of seven patients with definite ARVC at 50-years of age. The risk of developing AF was significantly related to the severity of ARVC phenotype. AF prevalence was at least six-fold higher in patients with clinically manifest ARVC than in genotype-positive family members with less penetrant disease, which is a novel finding. In the genotype-positive family members without clinical signs of ARVC the prevalence of AF was low and corresponded to the prevalence reported for the general population at age under 50 years.

Study cohort

Most previous studies focusing on atrial arrhythmias in ARVC patients were modest in regard to the sample size (n=71)[4] or included highly selected symptomatic patients with VT with number of patients varying from 36[6] to 72.[13]

Our study sample size is comparable with the Johns Hopkins ARVC registry report which was the first large scale study focusing on atrial arrhythmias in the context of ARVC and included 248 patients with definite ARVC.[5] We performed our study on 293 definite ARVC patients, but, in contrast to the Johns Hopkins ARVC registry,[5] also included 141 genotype-positive family members without definite ARVC to assess whether AF was the early manifestation of the disease and to compare AF prevalence in them to the AF prevalence in patients with ascertained clinical diagnosis.

Prevalence of AF in ARVC

One of the most important findings of our study is the observed AF prevalence of 14% among definite ARVC patients of a relatively young age.

According to the epidemiological data from the same geographical region, such as the Malmo Diet and Cancer Study,[14] the prevalence of AF for the age 50-55 years is reported to be as low as 1%, or even lower for the age range 40-50 years, in which most of our patients were diagnosed with ARVC, that might be the cause of clearly premature AF. Notably, in our study the prevalence of AF in genotype-positive family members without prominent disease was 1 of 141 (0.7%), which is similar to the prevalence in the general population.

The higher age-specific prevalence of AF in ARVC patients than in the general population has been observed in previous ARVC studies on atrial arrhythmias. The prevalence of atrial arrhythmias ranged from 14% in definite ARVC patients [5] to 24% in ARVC patients with VT [13] and up to 42 % in ARVC patients who underwent ablation for VT.[6] The difference in the prevalence of atrial arrhythmias might be explained by the patient selection since the highest prevalence was observed among patients with VT representing patients with severe disease phenotype, though in our study we did not observe any relation between AF and VT. Our data from the unselected cohort of Scandinavian patients with ARVC are in line with the data from the Johns Hopkins ARVD/C registry.[5] An AF prevalence of 14-times higher than the reported prevalence in the general population of the same age indicates that AF might be considered as one of the arrhythmic manifestations of ARVC.

Pathophysiologic mechanisms of AF in ARVC patients.

The mechanisms underlying AF development in ARVC patients are not fully understood. Though we could not exclude the role of pulmonary vein triggers in the development of AF, mechanistically, two principal mechanisms leading to development of AF in ARVC can be considered.

According to the current pathophysiological paradigm, ARVC is considered to be a disease of the cardiac desmosome.[15] Desmosomes are found throughout the cardiac myocardium,

including atrial myocardium.[16] There are anecdotal reports documenting atrial myocardial involvement in ARVC patients based on postmortem case series[17] and supported by animal studies.[8],[18] The evidence of altered electrical conduction within the atria of ARVC patients has also previously been demonstrated.[19] It is therefore plausible to suggest that atrial involvement in the disease progression may be driven by the same desmosomal dysfunction leading to fibrotic transformation of atrial myocardium as in the ventricles, which is likely to be causally related to development of AF.

On the other hand, AF can develop as a result of hemodynamic consequences of RV dysfunction, that leads to RA enlargement in ARVC patients. The association between AF and RA enlargement has been reported previously,[7] however, we did not find any association of AF with RA enlargement in our study. Furthermore, the prevalence of AF reached 8% in patients with definite ARVC diagnosis without advanced RV or LV dysfunction which indirectly supports the notion of AF being a consequence of atrial structural remodeling not related to atrial overload caused by ventricular malfunction, but most likely due to atrial fibrosis.

In our study AF was associated with the LA size, the association which in ARVC patients is not fully understood. As LAVI did not express any significant association with LV dysfunction in our study, the relationship between the AF and LA enlargement in the context of ARVC resemble the one observed in patients with non-valvular AF suggesting that the arrhythmia in patients with ARVC maybe LA driven. On the other hand, LA enlargement may also be a result rather than a cause of AF, since LA enlargement is a known secondary effect of AF. [20] However, in our study ARVC patients with AF more often had arterial hypertension and diabetes than their non-arrhythmic counterparts. Both hypertension and diabetes are known to be associated with LA dilation. Although neither of these factors

remained an independent AF predictor in the multivariate analysis, their contribution to an increase LA size and as a consequence the occurrence of AF cannot be excluded.

Early onset AF observed in our ARVC cohort suggests that cardiomyopathy-associated structural remodeling of atrial myocardium may occur at young age and predispose to AF breakthrough.

AF and ARVC phenotype

To the best of our knowledge, we are the first to report the association between AF and phenotypical manifestations of ARVC. We used the diagnostic score in the same way as earlier reported,[5, 12] as a measure of ARVC phenotype severity, and found that AF prevalence was significantly associated with the score thus indicating that the more advanced is the disease phenotype, the higher is the prevalence of AF.

AF was strongly linked to disease severity and was found primarily among our patients with definite ARVC diagnosis. Among genotype-positive family members with borderline or possible ARVC only one had AF which indicates the possibility of atrial and ventricular expression taking place in a parallel. Furthermore, the described association of AF and RV structural abnormalities in our study population supports the hypothesis of AF being a phenotypical manifestation of the disease.

Clinical perspective

The high prevalence of AF in ARVC patients indicates a need for alertness among clinicians to rule out AF as not all palpitations in ARVC patients are VT. Furthermore, though ARVC patients are usually young and do not have cardiovascular comorbidities, the detection of AF may lead to prescription of anticoagulant therapy if additional cardiovascular risk factors are present. Notably, 2 of 41 (5%) ARVC patients with AF in our study had ischemic stroke at age 33 and 78 years respectively. Given the consistently reported high prevalence of AF in ARVC patients at young age and a possibility of under-diagnosis of AF in mildly

symptomatic patients, our data indicate the need for systematic screening for AF among ARVC patients.

Study limitation

Though Nordic ARVC Registry is a prospective observational study with AF as a prespecified reportable clinical event, information regarding AF prior to ARVC diagnosis and inclusion in the registry was collected retrospectively, which is a limitation of our study. Furthermore, due to the observational nature of our study, we did not perform a systematic screening for AF, which may have led to some asymptomatic AF cases being undiagnosed in genotype-positive family members without clinical signs of ARVC, in which follow-up could be less stringent and who did not have ICD. However, the majority of patients with definite ARVC were implanted with ICD and we had a possibility to detect asymptomatic AF episodes using implantable device diagnostics thus coming closer to the real AF prevalence among definite ARVC patients.

Conclusion

AF is common in patients with definite ARVC and is related to the disease severity thus suggesting AF being an arrhythmic manifestation of this cardiomyopathy. Out data suggest atrial myocardial involvement in the disease progression.

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Table 1. Clinical characteristics of patients from the Nordic Arrhythmogenic right ventricular cardiomyopathy (ARVC) Registry with Definite ARVC (TF2010) or genetic positive family members wih atrial fibrillation (AF) at any time and without AF.

				P value	Definite ARVC		
	All, n=434	Definite ARVC, n=293	Non-definite ARVC, n=141	Definite vs Non-definite ARVC	AF n=41	No AF n=252	P value AF vs No AF
Follow-up time in years, mean±std	9±6	10±7	7±3	0.003	11±7	10±7	0.131
Female gender, n (%)	186 (43)	102 (35)	84 (60)	<0.001	7 (17)	95 (38)	0.013
Probands, n (%)	226 (52)	213 (73)	13 (9)	<0.001	6 (15)	74 (29)	0.058
Mutation positive, n (%)	324 (75)	183 (63)	141 (100)	<0.001	25 (61)	158 (63)	0.863
Definite ARVC, n (%)	293 (68)	-	-	-	-	-	
Borderline ARVC, n (%)	58 (13)	-	-	-	-	-	
Possible ARVC, n (%)	83 (19)	-	-	-	-	-	
Age at ARVC diagnosis, median (IQR)	41 (28-52)	41 (30-52)	43 (25-52)	0.676	42 (35-57)	40 (29-51)	0.050
Any VT/VF, n (%)	223 (51)	212 (72)	11 (8)	<0.001	33 (81)	179 (71)	0.260
Sustained VT, n (%)	135 (31)	135 (46)	0 (0)	<0.001	24 (59)	111 (44)	0.093
Syncope, n (%)	28 (7)	24 (7)	4 (3)	0.037	4 (10)	20 (8)	0.757
ICD, n (%)	213 (49)	213 (73)	0 (0)	<0.001	34 (83)	179 (71)	0.132
Hypertension, n (%)	36 (8)	28 (10)	8 (6)	0.262	9 (23)	19 (8)	0.006
Ischemic stroke, n (%)	3 (0.7)	2 (0.7)	1 (0.7)	1.000	2 (5)	0 (0)	0.018
Diabetes, n (%)	13 (3)	9 (3)	4 (3)	1.000	4 (10)	5 (2)	0.023
Ischemic heart disease, n (%)	14 (3)	13 (5)	1 (0.7)	0.044	4 (10)	9 (4)	0.085
Heart failure >=NYHA II, n (%)	39 (9)	37 (13)	2 (1)	<0.001	8 (20)	29 (12)	0.201
Right ventricular structural abnormalities major, n (%)	201 (46)	201 (67)	0 (0)	<0.001	34 (83)	167 (66)	0.045
Right ventricular structural abnormalities minor, n (%)	20 (5)	20 (7)	0 (0)	<0.001	0 (0)	20 (8)	0.088

Left ventricular ejection fraction, mean±std	56±8	54±9	59±5	<0.001	54±9	56±9	0.260
Left atrial volume index, ml/m^2, mean±std	29±10	30±10	26±8	0.002	37±12	29±10	<0.001
Right atrial volume index, ml/m^2, mean±std	32±19	36±21	23±7	<0.001	35±18	36±21	0.811
Cardiac MRI performed	286 (66)	214 (73)	72 (51)	<0.001	29 (71)	185 (73)	0.708
Right ventricular ejection fraction (MRI), mean±std	45±12	42±12	54±7	<0.001	39±14	42±11	0.288
Repolarization abnormalities major, n (%)	153 (35)	153 (52)	0 (0)	<0.001	18 (44)	135 (54)	0.312
Repolarization abnormalities minor, n (%)	38 (9)	32 (11)	6 (4)	0.028	2 (5)	30 (12)	0.279
Depolarization abnormalities major, n (%)	21 (5)	21 (7)	0 (0)	<0.001	4 (10)	17 (7)	0.511
Depolarization abnormalities minor, n (%)	192 (44)	158 (54)	34 (24)	0.028	19 (46)	139 (55)	0.315
Arrhythmias major, n (%)	83 (19)	83 (28)	0 (0)	<0.001	13 (32)	70 (28)	0.581
Arrhythmias minor, n (%)	256 (59)	238 (81)	18 (13)	<0.001	34 (83)	204 (81)	1.000
Holter performed, n (%)	342 (79)	225 (77)	117 (83)	0.168	26 (63)	199 (70)	0.044
Ventricular extrasystoles, mean n ±std	2055±4542	3185±5431	557 ±2256	<0.001	1946 ±5622	3316±2923	0.408
Family history major, n (%)	335 (77)	194 (66)	141 (100)	<0.001	26 (63)	168 (67)	0.723
Family history minor, n (%)	9 (2)	9 (3)	0 (0)	0.035	0 (0)	9 (4)	0.618
ARVC diagnostic score, mean±std	5±2	6±2	2±1	<0.001	6±2	6±2	0.774

Std – standard deviation, IQR – interquartile range 25%-75%, VT – ventricular tachycardia, VF – ventricular fibrillation, ICD – implantable cardioverter-defibrillator, NYHA – New York Heart Association classification, MRI – magnetic resonance imaging.

Table 2. Logistic regression analysis showing the association clinical characteristics of definite ARVC patients and carriers of genetic mutation with atrial fibrillation.

	OR	**95% CI**	**p value**
Univariate logistic regression			
Age at diagnosis	**1.02**	**1.00-1.04**	**0.037**
VT/VF	**4.57**	**2.06-10.11**	**<0.001**
Sustained VT	3.37	1.76-6.46	<0.001
Syncope	1.91	0.40-9.02	0.414
Male gender	**4.20**	**1.82-9.69**	**0.001**
Hypertension	**3.81**	**1.65-8.681**	**0.002**
Diabetes	**4.59**	**1.35-15.66**	**0.015**
Ischemic heart disease	0.69	0.45-1.07	0.098
Heart failure >=NYHA II	**2.74**	**1.17-6.43**	**0.021**
Left atrial volume index	**1.08**	**1.04-1.13**	**<0.001**
Right atrial volume index	1.01	0.99-1.03	0.366
RV structural abnormalities major	**5.73**	**2.58-12.69**	**<0.001**
Repolarization abnormalities major	1.43	0.75-2.72	0.280
Repolarization abnormalities minor	0.49	0.12-2.13	0.345
Depolarization abnormalities major	2.32	0.74-7.25	0.147
Depolarization abnormalities minor	1.05	0.55-1.98	0.891
Arrhythmias major	2.06	1.02-4.17	0.044
Arrhythmias minor	1.14	0.48-2.73	0.764
Multivariate logistic regression (final model)			
Age at diagnosis	0.99	0.96-1.02	0.540
VT/VF	0.70	0.21-2.37	0.564
Male gender	2.86	0.95-8.65	0.063
Diabetes	0.93	0.08-11.51	0.955
Heart failure >=NYHA II	0.60	0.12-3.70	0.543
Hypertension	3.96	0.96-16.40	0.057

Left atrial volume index	**1.07**	**1.03-1.12**	**0.001**
RV structural abnormalities major	**4.47**	**1.02-19.53**	**0.047**

OR – odds ratio, CI – confidence interval, VT – ventricular tachycardia, VF – ventricular fibrillation, NYHA – New York Heart Association classification.

Figure. Prevalence of atrial fibrillation (AF) among patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis and carriers of disease-causing genetic variants according to the ARVC diagnostic score based on assignment of 1 point for a minor diagnostic criterion and 2 points for a major diagnostic criterion. The lowest score of 2 corresponds to mutation-carrying status without other disease manifestations (a major diagnostic criterion).