Risk of cardioembolic ischemic events and relation to atrial fibrillation/flutter in patients with arrhythmogenic cardiomyopathy during a long-term follow-up

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ABSTRACT

Background: Arrhythmogenic cardiomyopathy (ACM) is an inherited heart disease characterized by fibro-fatty replacement of myocardium. Limited data is available concerning cardioembolic stroke. This study sought to determine the occurrence of cardioembolic ischemic events (CIEs) in ACM patients and to identify clinical and imaging predictors of CIEs.

Methods: Every consecutive ACM patient was enrolled. ECG, Holter monitoring or implantable cardiac devices were used to detect atrial arrhythmias (AAs). CIEs were defined according to TOAST classification.

Results: In our cohort of 111 patients, CIEs were observed in eleven (10%) over a 12.9-year median follow-up, with an incidence of 7.9 event/1000 patient-year (HR 4.12 compared to general population). Mean age at the event was 42 ± 9 years. Female sex (p = 0.03), T-wave inversion (p = 0.03), RVOT dilatation (p = 0.006) and lower LVEF (p = 0.006) were associated with CIEs. Among patients with AAs (23/111, 20.7%), 5 (21.7%) experienced CIEs.

CHA2DS2-VASc did not prove useful to define patients at higher risk of CIEs (p = 0.098). 60% of stroke suffering patients had a pre-event score between 0 and 1 (if female).

Conclusions: In ACM patients, CIEs are much more common than in general population and present a high burden at younger age. AAs relate to less than half of these events. In AAs patients, CHA2DS2-VASc is not useful to stratify those requiring oral anticoagulation. As a hypothesis-generating study, our research proposes the role of atrial myopathy, irrespective of AAs, as a pivotal factor in thrombogenesis risk, pointing out a definite unmet need in ACM therapeutic algorithm.

INTRODUCTION

Arrhythmogenic cardiomyopathy (ACM) is an inherited heart muscle disease characterized by progressive fibrofatty replacement of right and/or left ventricular myocardium, which predisposes to ventricular arrhythmias, sudden cardiac death and heart failure [1]. ACM was found to be caused by genetic defects and desmosomal genes' mutations were described in approximately 50% of patients [2]. The pathological hallmark of the disease, the myocardial fibrofatty replacement, which proceeds from the epicardium towards the endocardium, is usually present in the right ventricle (RV), but may also occur in the left ventricle (LV), and leads to wall thinning and aneurysm formation [3].

While most studies on the arrhythmic substrate in ACM has understandably been focused on the risk of life-threatening ventricular tachycardias, clinical implications of atrial arrhythmias (AAs) have been poorly investigated in these patients. A recent metanalysis encompassing 16 studies with 1986 ACM patients reported a pooled prevalence of AAs of 17.9% and a pooled prevalence of atrial fibrillation (AF) of 12.9% [4]. In the general population, AF increases the risk of stroke with varying degrees of risk depending on the presence of specific risk factors, commonly summarized in the CHA_2DS_2-$VASc$ score [5]. The 2020 European Society of

Cardiology Guidelines recommend the use of oral anticoagulants for stroke prevention in AF patients with CHA_2DS_2-VAS_C score ≥ 2 in men and ≥ 3 in women (class I, level of evidence A) and suggest that OACs should be used in men with a CHA_2DS_2-VAS_C score of 1 and in women with a CHA_2DS_2-VAS_C score of 2 (class IIa, level of evidence B) [6]. However, since cardio-embolic events can occur temporally disassociated from arrhythmic episodes in paroxysmal AF or even in patients without overt AF [7], the concept of atrial cardiopathy, describing atria with anatomic and physiological derangements, as a possible underlying cause of cryptogenic stroke, is emerging [8-10]. The development of atrial isolated cardiopathy in ACM is demonstrated by histopathological [11,12], electrocardiographic [13], electrophysiological [14] and imaging studies [15].

In current clinical practice, OAC therapy for stroke prevention in ACM patients with AF is recommended according to the CHA_2DS_2-VAS_C score, similarly to the general population of AF patients. However, the prognostic efficacy of this score in ACM patients might be questioned. This study sought to determine the incidence of ischemic stroke or transient ischemic attack in ACM patients and aimed to identify clinical and imaging parameters associated with increased risk of cardioembolic events.

METHODS

This ambispective (retrospective and prospective) observational study included consecutive adult (≥18 years) patients with definite ACM diagnosis according to the latest Task Force Criteria (TFC) at the time of enrollment referred to the "Città della Salute e della Scienza" Hospital (Turin, Italy) from 1982 to October 2022.

Patients with family history of ACM but without phenotypic expression of the disease and ACM mimics were excluded. ACM mimics were defined as RV dysfunctions not secondary to ischemic or postoperative conditions and included non-ischaemic dilated cardiomyopathy,

infiltrative diseases, myocarditis, Brugada syndrome, idiopathic right ventricular outflow tract ventricular tachycardias, congenital heart disease and pulmonary arterial hypertension.

Baseline and follow-up clinical, instrumental (including electrocardiograms, transthoracic echocardiograms and cardiac magnetic resonance images) and outcome data of the included patients were retrieved via dedicated electronic softwares used in each center and collected from outpatients' visits and telephonic follow-up.

All patients provided written informed consent for the inclusion in the present study, which was approved by the local Ethics committee and was conducted according to the principles of the latest version of the Declaration of Helsinki.

Study outcomes

The primary endpoint of the study was to determine the incidence of cardioembolic ischemic events (CIEs) in ACM patients; moreover, this study aimed to identify clinical and imaging predictors of CIEs. CIEs were defined according to the Trial of ORG 10172 in Acute Ischemic Stroke Treatment (TOAST) classification [16], which defines cardioembolism as an arterial occlusion presumably due to an embolus arising in the heart, in patients with at least one high-risk or medium-risk conditions. CIEs included both strokes and transient ischemic attacks; cardioembolic strokes were defined by the presence of clinical evidence of cortical or cerebellar dysfunction and imaging evidence of cortical, cerebellar, brain stem or subcortical infarcts > 1.5 cm, whereas transient ischemic attacks were defined as the presence of transient cerebral ischemia symptoms and signs with spontaneous regression (within 24 hours), associated with a negative cerebral imaging. For both conditions, any other etiology was systematically excluded using cervical carotid arteries and intracranial vessels imaging, according to the recommendations of the American Heart Association/American Stroke Association [17]. Furthermore, patients underwent in-hospital cardiac monitoring to screen for AAs,

transthoracic or transesophageal echocardiography to detect the presence of intra-cardiac thrombi or patent foramen ovale, and laboratory screening to exclude thrombophilic conditions.

Atrial arrhythmias

Every patient was screened for the occurrence of embolic AAs, namely AF or atrial flutter (AFL), with 12-lead surface electrocardiogram, 24-hour ECG Holter monitoring and/or implantable cardiac devices monitoring, when available, both at ACM diagnosis and during follow-up. AF was defined as a supraventricular tachycardia characterized by no discernible P waves and irregular RR intervals at the surface ECG. AFL was defined as a macro-reentrant supraventricular tachycardia, characterized by a regular and rapid atrial activation, from 250 to 330 bpm at surface ECG. Both AF and AFL diagnoses required the arrhythmia documentation at a standard 12-lead ECG or a single-lead ECG tracing of ≥ 30 seconds [7]. The CHA_2DS_2-VASc score was calculated at the time of first AAs occurrence.

Imaging data

Transthoracic echocardiographic data were collected. According to current guidelines, RV dilation was defined as RV basal diameter ≥ 42 mm or RV end-diastolic area ≥ 25 cm^2 in men or ≥ 21 cm^2 in women. RV outflow tract (RVOT) dilation was defined as RVOT diameter in parasternal long axis-view > 30 mm or RVOT proximal diameter in parasternal short axis-view > 35 mm or RVOT distal diameter in parasternal short axis-view > 27 mm [18]. Left ventricular involvement was defined by the presence of global LV dysfunction with or without LV dilatation, or of regional LV hypokinesia o akinesia [1]. Cardiac magnetic resonance (CMR) imaging data regarding chambers size and function and fibrofatty involvement were also gathered.

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (interquartile range), as appropriate, while categorical variables were reported as numbers and percentages. The prevalence and predictors of CIE were assessed both in the overall population and in ACM patients with AAs. Also, the characteristics of patients with AAs were compared to those of individuals without AAs. Comparisons between individual study groups were performed by means of Student t-test for continuous variables with normal distribution, Kruskal-Wallis non-parametric test for non-normally distributed continuous variables and Fisher's exact test for categorical variables. Significant p-value was set at 0.05. Statistical analysis was performed using SPSS 22 (IBM Corporation, Armonk, NY, USA).

RESULTS

One hundred and eleven ACM were ambispectively enrolled, with a median follow-up of 12.9 years; the retrospective section included 102 (91.9%) individuals and the prospective section 9 (8.1%). Baseline characteristics of the study population are reported in Table 1. Mean age at diagnosis was 38.6 ± 14.5 years, 35 (31.5%) patients were female and 109 (98.2%) patients were Caucasian. The main reason for clinical presentation was major ventricular arrhythmias (48 patients, 46.3%), followed by palpitations (14 patients, 12.6%), HF (7 patients, 6.3%), syncopal episodes (5 patients, 4.5%), AAs (5 patients, 4.5%), other clinical presentation (1 patient, 0.9%) and CIEs (1 patient, 0.9%); in 30 (27%) patients ACM was an occasional finding. Among patients with available data, the most common ECG finding was T wave inversion in precordial leads V1 to V3, occurring in 60 (60%) patients; terminal activation duration (TAD) of QRS ≥ 55 msec was found in 41 (42.3%) patients, epsilon wave in 26 (26.3%), and low QRS voltage in peripheral leads in 19 (19.4%); 16 (14.4%) patients had a QRS duration ≥ 120 msec, of whom 12 (75%) showed right bundle branch block morphology and 4 (25%) left bundle

branch block morphology. Sixty-nine (68.3%) patients showed RV dilation, 43 (52.4%) RV outflow tract dilatation, 46 (47.9%) right atrial dilatation and 41 (48.4%) had RV regional akinesia/dyskinesia. Thirty-nine (38.6%) patients had echocardiographic signs of left ventricular involvement at diagnosis and 31 (32%) individuals showed left atrial dilatation. Regarding cardiac magnetic resonance findings, 46 patients (50%) presented apical RV fibro-fatty infiltration, 51 patients (55.4%) RV free-wall fibro-fatty infiltration and 45 patients (48.9%) RV outflow tract fibro-fatty infiltration.

Thirty-five (32.1%) patients underwent genetic analysis, which resulted positive in 23 (65.7%). Twenty-one (91.3%) pathogenic sequence variations were found on desmosomal genes, and 3 (13.1%) on non-desmosomal genes.

Cardioembolic ischemic events

CIEs were observed in 11 (11%) patients over the median follow-up of 12.9 years, with an incidence of 7.9 events every 1000 patient-year, compared to the general population incidence of 1.9 events every 1000 patient-year (hazard ratio of 4.12) [19]. Mean age at the event was 42 ± 9 years. In one patient the CIE represented the reason for clinical presentation. Ischemic stroke accounted for 7 (63.6%) of the 11 CIEs and transient ischemic attack for 4 (36.3%). Five (45%) stroke patients experienced AFL or AF during the follow-up.

A comparison of the clinical, electrocardiographic and imaging features of ACM patients with vs. without CIEs is shown in Table 1. Compared to individuals without CIEs, patients with CIEs were more frequently female (54.5% vs 29%, respectively, p 0.03) and had higher prevalence of T wave inversion at basal ECG (90.9% vs 56.2%, respectively, p 0.027). Also, patients with CIEs more frequently had RV outflow tract dilatation (90.9% vs 46.5%, p 0.006) and lower left ventricular ejection fraction at diagnosis (50.1 ± 7.3 vs 57.5 ± 8.2, p 0.006) than those without CIEs.

Atrial arrhythmias

Among the 111 included patients, 23 (20.7%) experienced AAs over a median follow-up of 12.9 years, including 15 (65.2%) cases of AF and 8 (34.8%) cases of AFL. AAs were found on presentation in 5 (4.5%) patients. AF was paroxysmal in 12 (80%) subjects, persistent in 1 (6.7%) and permanent in 2 (13.3%). A comparison of the clinical, electrocardiographic and imaging features of ACM patients with vs. without AAs is shown in Table 3. Compared to patients without AAs, those with AAs had longer P wave duration at surface ECG (109.6 ± 13.6 msec vs 98 ± 17.5 msec, p 0.013), and more frequently had left atrial dilation on CMR (50% vs 11.1%, p 0.001) and right atrial dilatation on echocardiography (72.7% vs 40.5%, p 0.008) and CMR (75% vs 36.8%, p 0.003) , with no difference regarding demographic features, including age at diagnosis, sex, hypertension and diabetes, nor other ECG or imaging characteristics.

Among the 23 patients with AAs, 5 (23.8%) experienced ischemic stroke/TIA (Table 2). Among individuals with AAs, echocardiographic evidence of LV involvement was significantly more common in patients with CIEs compared those without CIEs (80.0% vs 27.8%, p 0.03), with no significant difference regarding the CHA_2DS_2-VASc score (1 [IQR 1, 2] vs. 0 [IQR 0, 1], p 0.098); moreover 3 (60%) patients with AAs and stroke had a pre-event CHA_2DS_2-VASc score of 0 or 1 (if female).

DISCUSSION

The main findings of this observational ambispective study can be summarized as follows: in ACM patients, CIEs are more common than in general population and present at a younger age; AAs are common in patients with ACM, but among ACM patients with AAs the CHA_2DS_2-VASc score does not prove useful to stratify those at higher cardioembolic risk and thus requiring anticoagulation; AAs, albeit more frequent in patients with CIEs, are associated with only less than half of cerebral ischemic events at long-term follow-up.

Currently, data on cardioembolic risk in ACM are limited. Patients with ACM are at risk of developing intracardiac thrombi, which have been reported to occur mostly in the setting of RV dilatation, aneurysms and wall motion abnormalities with a prevalence of 4% of ACM cases and an annual incidence of thromboembolic complications of 5/1000 patients [20]. Long-term OAC is recommended in ACM patients with documented intracardiac thrombi in terms of secondary prevention [21]. In the presence of AAs, atrial thrombi have been mostly described in ACM patients with extensive forms of the disease [22-24], but limited data are available concerning the cardioembolic risk of ACM overall. In current clinical practice, oral anticoagulation therapy in ACM patients with AAs is recommended according to the CHA_2DS_2-VASc score, similarly to the general population of AAs patients. Our study reported an incidence of CIEs in ACM patients of 7.9/1000 patient-year, with a 4.15-fold increase in relative risk compared to the general population [19]; furthermore, ACM patients often present CIEs at a younger age compared to the general population (mean age at the event of 42 ± 9 years vs. > 60 years, respectively). Interestingly, in patients with ACM and AAs, the CHA_2DS_2-VASc score did not prove useful to define patients at higher risk of cardioembolic events. Indeed, 60% of ACM patients with CIEs and AAs had a pre-event score between 0 and 1 (if female), which would normally estimate a very low embolic risk at 1 year (0.9-1.3%) [25]. However, the high number of embolic events which we found even in patients with low CHA_2DS_2-VASc score stresses the increased thromboembolic potential of ACM and highlights that cardioembolic risk stratification in ACM population with AAs may not rely on the same parameters used in the general population. This underscores a definite unmet need in the therapeutic algorithm of ACM, namely the identification of ACM patients with AAs at higher cardioembolic risk and thus requiring anticoagulation.

The prevalence and pathogenesis of AAs in the setting of ACM is debated. Our report on 111 ACM patients followed-up for a median of 12.9 years showed an incidence of AAs of 20.7%,

mostly represented by AF (65.2%). The incidence of AAs in our study is higher than that reported in previous works, likely due to the longer follow-up duration of the present study; in 2013, Camm and colleagues described an incidence of AAs of 14.1% in 248 patients with ACM over a shorter follow-up of 5.8 years [26]. A recent metanalysis reported a pooled prevalence of overall AAs of 17.9% among 1986 patients from 16 studies [4]. Two underlying mechanisms behind AAs have been suggested: 1) AAs may develop as a hemodynamic consequence of biventricular dysfunction contributing to atrial overload, increased stretch and subsequent development of atrial wall fibrosis [27-29]; 2) AAs may develop as a phenotypic expression of an isolated atrial disease, which proceeds regardless of the degree of ventricular dysfunction as a result of atrial structural remodeling induced by genetically determined desmosomal dysfunction [13-15]. Our study showed that ECG and imaging parameters of atrial cardiopathy (P wave duration at ECG, right atrial dilatation at transthoracic echocardiography and biatrial dilatation at CMR imaging) were significantly associated with AAs occurrence during follow-up, while RV ejection fraction, LV involvement or LVEF were not, thus supporting the hypothesis that AF is a phenotypic expression of ACM atrial involvement, which proceeds regardless of the severity of the disease.

Limitations

This study has some limitations. The observational nature of this study is subject to the limitations of such design, and its results must be considered hypothesis-generating rather than definite conclusions. The sample size was small, thus restricting the power of the analyses performed; however, ACM is a rare disease, and the long-term follow-up of the present work allowed to counterbalance, at least partially, the uncommonness of this condition. Implantable cardiac devices were not always available, and patients' follow-ups were at each physician's discretion; thus, asymptomatic paroxysmal episodes of AAs might have been missed.

CONCLUSIONS

In ACM patients, cardioembolic cerebral events are much more common than in general population and present a high burden even at a relatively young age; AAs relate to less than half of these events. In AAs patients, the CHA_2DS_2-VASc score may not help stratify those requiring oral anticoagulation. As a hypothesis-generating study, our research proposes the role of atrial dilation and atrial myopathy as a pivotal factor in the thrombogenesis risk of these patients, pointing out a definite unmet need in ACM anticoagulation therapeutic algorithm.

TABLES

Table 1. Baseline characteristics of the study population.

Variable	Whole population (N = 111)	CIEs (N = 11)	No CIEs (N = 100)	P-value
Age at diagnosis – years	38.62 ± 14.5	36.4 ± 9.1	38.9 ± 15	0.589
Female sex – no (%)	35 (31.5%)	6 (54.5%)	29 (29%)	**0.03**
Ethnicity – no. (%)				
Caucasian	109 (98.2%)			
Black	1 (0.9%)			
Asian	0 (0%)			
Hispanic	0 (0%)			
Others	1 (0.9%)			
Arterial hypertension – no. (%)	27 (24.3%)	3 (27.3%)	24 (24%)	0.81
Diabetes mellitus – no. (%)	3 (2.7%)	0 (0%)	3 (3%)	0.56
Main clinical presentation – no. (%)				
Heart failure	7 (6.3%)			
Major ventricular arrhythmias	48 (43.2%)			
AAs	5 (4.5%)			
CIEs	1 (0.9%)			
Syncope	5 (4.5%)			
Asymptomatic	30 (27%)			
Palpitations	14 (12.6%)			
Other clinical presentations	1 (0.9%)			
Epsilon wave – no. (%)	26 (26.3%)	4 (36%)	22 (25%)	0.419
TAD ≥ 55 msec – no. (%)	41 (42.3%)	7 (63.6%)	34 (39.5%)	0.128
T wave inversion V1-V3 – no. (%)	60 (60%)	10 (90.9%)	50 (56.2%)	**0.027**
Low QRS voltage in limb leads – no. (%)	19 (19.4%)	2 (18%)	17 (19.5%)	0.914
P wave duration – ms	99.7 ± 17.4	106.2 ± 9.2	99 ± 17.8	0.266
P wave voltage – mV	0.13 ± 0.04	0.13 ± 0.04	0.14 ± 0.04	0.502
Genetic test – no. (%)	35 (32.1%)	5 (45.5%)	30 (30%)	0.326
Pathogenic mutation – no. (%)	23/35 (65.7%)			
Desmosomal genes – no. (%)	21/23 (91.3%)	4 (36.4%)	17 (17%)	0.120

PKP-2	10/21 (47.6%)			
DSP	5/21 (23.8%)			
PKG	0/21 (0%)			
DSG 2	6/21 (28.6%)			
DSC 2	0/21 (0%)			
Non-desmosomal genes – no. (%)	3/23 (13%)	0 (0%)	3 (3%)	0.264
PLN	0/3 (0%)			
TMEM43	3/3 (100%)			
LVEF at diagnosis – %	56.5 ± 8.5	50.1 ± 7.3	57.5 ± 8.2	**0.006**
RA dilatation at echo – no. (%)	46 (47.9%)	5 (45.4%)	41 (48.2%)	0.862
RV dilatation at echo – no. (%)	69 (68.3%)	9 (81.8%)	60 (66.7%)	0.308
RVOT dilatation at echo – no. (%)	43 (52.4%)	10 (90.9%)	33 (46.5%)	**0.006**
RV akinesia/dyskinesia at echo – no. (%)	41 (48.2%)	7 (63.6%)	34 (45.9%)	0.273
LA dilatation at echo – no. (%)	31 (32.3%)	4 (36.3%)	27 (31.8%)	0.759
LV involvement at echo – no. (%)	39 (38.6%)	6 (54.5%)	33 (36.7%)	0.250
Fibrofatty infiltration at CMR – no. (%)				
Apical	46 (50%)	7 (63.6%)	39 (48.1%)	0.335
RV free wall	51 (55.4%)	7 (63.6%)	44 (54.3%)	0.560
RV outflow tract	45 (48.9%)	7 (63.6%)	38 (46.9%)	0.298
RA dilatation at CMR – no. (%)	40 (45.5%)	6 (54.5%)	34 (44.1%)	0.517
RV dilatation at CMR – no. (%)	70 (72.9%)	9 (81.8%)	61 (71.8%)	0.480
RVOT dilatation at CMR – no. (%)	34 (47.9%)	7 (63.6%)	27 (45%)	0.255
RV akinesia/dyskinesia at CMR – no. (%)	64 (70.3%)	9 (81.8%)	55 (68.7%)	0.374
LA dilatation at CMR – no. (%)	16 (21.6%)	4 (36.3%)	12 (19%)	0.198
LV involvement at CMR – no. (%)	44 (48.4%)	4 (36.3%)	40 (50%)	0.396
AAs – no. (%)	23 (20.7%)	5 (45.5%)	18 (18.0%)	**0.048**

Percentages were calculated on the total number of subjects with available data for each variable. Significant p-values are written in bold.

AAs, atrial arrythmias; CIEs, cardioembolic ischemic events; CMR, cardiac magnetic resonance; DSC 2, desmocollin-2; DSG 2, desmoglein-2; DSP, desmoplakin; IQR, interquartile range; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; PKG, plakoglobin; PKP 2, plakophilin-2; PLN-phospholamban; RA, right atrium; RV, right ventricle; RVOT, right ventricle outflow tract; TAD, terminal activation duration; TIA, transient ischemic attack; TMEM43, transmembrane protein 43.

Table 2. Baseline characteristics of patients with atrial arrhythmias divided according to the occurrence of cardioembolic ischemic events.

Variable	**AAs with CIEs (N = 5)**	**AAs without CIEs (N = 18)**	**P-value**
Age at diagnosis – years	39.6 ± 6.8	43.9 ± 15.3	0.549
Female sex – no. (%)	1 (20%)	3 (16.7%)	0.862
Arterial hypertension – no. (%)	2 (40%)	4 (22.2%)	0.423
Diabetes mellitus – no. (%)	0 (0%)	1 (5.5%)	0.59
CHA_2DS_2-VASc score	1 [IQR 1, 2]	0 [IQR 0, 1]	0.098
Epsilon wave – no. (%)	3 (60%)	5 (29.4%)	0.211
TAD ≥ 55 msec – no. (%)	2 (40%)	7 (41.2%)	0.962
T wave inversion V1-V3 – no. (%)	4 (80%)	10 (58.8%)	0.387
Low QRS voltage in limb leads – no. (%)	1 (20%)	3 (17.6%)	0.905
P wave duration – ms	110 ± 10	109 ± 15	0.954
P wave voltage – mV	0.12 ± 0.04	0.14 ± 0.03	0.307
LVEF at diagnosis – years	50 ± 6	56 ± 8	0.187
RA dilatation at echo – no. (%)	3 (60%)	13 (76.5%)	0.467
RV dilatation at echo – no. (%)	5 (100%)	14 (77.8%)	0.246
RVOT dilatation at echo – no. (%)	4 (80%)	8 (47%)	0.193
RV akinesia/dyskinesia at echo – no. (%)	3 (60%)	10 (58.8%)	0.962
LA dilatation at echo – no. (%)	2 (40%)	7 (41.2%)	0.962
LV involvement at echo – no. (%)	4 (80%)	5 (27.8%)	**0.034**
Fibrofatty infiltration at CMR – no. (%)			
Apical	3 (60%)	7 (43.7%)	0.525
RV free wall	2 (40%)	8 (50%)	0.696
RV outflow tract	3 (60%)	8 (50%)	0.696
RA dilatation at CMR – no (%)	4 (80%)	11 (73.3%)	0.766
RV dilatation at CMR – no (%)	4 (80%)	12 (75%)	0.819
RVOT dilatation at CMR – no (%)	3 (60%)	7 (46.7%)	0.606
RV akinesia/dyskinesia at CMR – no (%)	4 (80%)	13 (81.2%)	0.95
LA dilatation at CMR – no (%)	3 (60%)	7 (46.7%)	0.606
LV involvement at CMR – no (%)	3 (60%)	5 (31.2%)	0.248

Percentages were calculated on the total number of subjects with available data for each variable. Significant p-values are written in bold.

Abbreviations as in Table 1.

Table 3. Baseline characteristics of the study population divided according to the occurrence of atrial arrhythmias.

Variable	**AAs (N = 23)**	**No AAs (N = 88)**	**P-value**
Age at diagnosis - years	43 ± 13.9	37.5 ± 14.5	0.104
Female sex – no. (%)	4 (17.3%)	31 (35.2%)	0.10
Arterial hypertension – no. (%)	6 (28.6%)	21 (23.9%)	0.82
Diabetes mellitus – no. (%)	1 (4.3%)	2 (2.3%)	0.58
CHA2DS2-Vasc score	1 (IQR 0-1)	1 (IQR 0-1)	0.977
Epsilon wave – no. (%)	8 (36.3%)	18 (23.4%)	0.22
TAD ≥ 55 msec – no. (%)	9 (40.9%)	32 (42.7%)	0.885
T wave inversion V1-V3 – no. (%)	14 (63.6%)	46 (58.9%)	0.693
Low QRS voltage in limb leads – no. (%)	4 (18.1%)	15 (19.7%)	0.871
P wave duration – ms	109.58 ± 13.56	98.03 ± 17.5	**0.033**
P wave voltage – mV	0.13 ± 0.03	0.13 ± 0.04	0.902
LVEF at diagnosis – %	54.7 ± 8.6	57.1 ± 8.4	0.263
RA dilatation at echo – no. (%)	16 (72.7%)	30 (40.5%)	**0.008**
RV dilatation at echo – no. (%)	19 (82.6%)	50 (64.1%)	0.094
RVOT dilatation at echo – no. (%)	12 (54.5%)	31 (51.7%)	0.817
RV akinesia/dyskinesia at echo – no. (%)	13 (59%)	28 (44.4%)	0.237
LA dilatation at echo – no. (%)	9 (40.9%)	22 (29.7%)	0.325
LV involvement at echo – no. (%)	9 (39.1%)	30 (38.5%)	0.954
Fibrofatty infiltration at CMR – no. (%)			
Apical	10 (47.6%)	36 (50.7%)	0.804
RV free wall	10 (47.6%)	41 (57.7%)	0.412
RV outflow tract	11 (52.4%)	34 (47.9%)	0.717
RA dilatation at CMR – no. (%)	15 (75%)	25 (36.8%)	**0.003**
RV dilatation at CMR – no. (%)	16 (76.2%)	54 (72%)	0.703
RVOT dilatation at CMR – no. (%)	10 (50%)	24 (47%)	0.823
RV akinesia/dyskinesia at CMR – no. (%)	17 (80.9%)	47 (67.1%)	0.224
LA dilatation at CMR – no. (%)	10 (50%)	10 (11.1%)	**0.001**
LV involvement at CMR – no. (%)	8 (38.1%)	36 (51.4%)	0.284

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