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Sex differences in disease progression and arrhythmic risk in patients with arrhythmogenic cardiomyopathy

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Aims We aimed to assess sex-specific phenotypes and disease progression, and their relation to exercise, in arrhythmogenic cardiomyopathy (AC) patients.

Methods and results In this longitudinal cohort study, we included consecutive patients with AC from a referral centre. We performed echocardiography at baseline and repeatedly during follow-up. Patients' exercise dose at inclusion was expressed as metabolic equivalents of task (MET)-h/week. Ventricular arrhythmia (VA) was defined as aborted cardiac arrest, sustained ventricular tachycardia, or appropriate therapy by implantable cardioverter-defibrillator. We included 190 AC patients (45% female, 51% probands, age 41 ± 17 years). Ventricular arrhythmia had occurred at inclusion or occurred during follow-up in 85 patients (33% of females vs. 55% of males, $P = 0.002$). Exercise doses were higher in males compared with females [25 (interquartile range, IQR 14–51) vs. 12 (IQR 7–22) MET-h/week, $P < 0.001$]. Male sex was a marker of proband status [odds ratio (OR) 2.6, 95% confidence interval (CI) 1.4–5.0, $P = 0.003$] and a marker of VA (OR 2.6, 95% CI 1.4–5.0, $P = 0.003$), but not when adjusted for exercise dose and age (adjusted OR 1.8, 95% CI 0.9–3.6, $P = 0.12$ and 1.5, 95% CI 0.7–3.1, $P = 0.30$, by 5 MET-h/week increments). In all, 167 (88%) patients had ≥2 echocardiographic examinations during 6.9 (IQR 4.7–9.8) years of follow-up. We observed no sex differences in deterioration of right or left ventricular dimensions and functions.

Conclusion Male AC patients were more often probands and had higher prevalence of VA than female patients, but not when adjusting for exercise dose. Importantly, disease progression was similar between male and female patients.

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Graphical Abstract

190 patients with arrhythmogenic cardiomyopathy

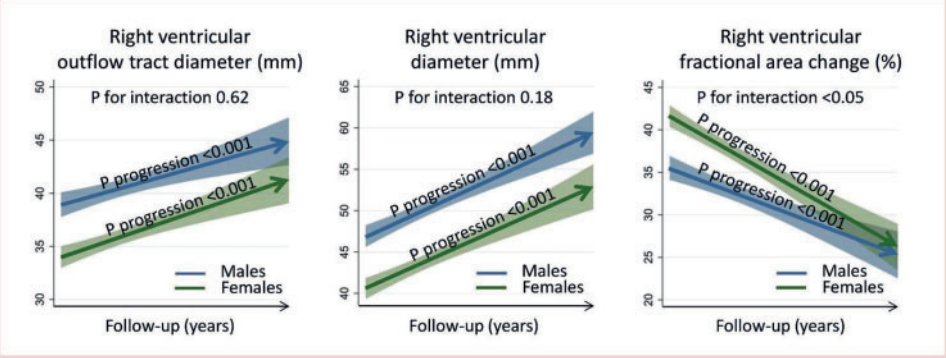
Previous exercise dose outperformed male sex as a risk marker of ventricular arrhythmias

Markers of life threatening arrhythmias by last clinical follow-up

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex, male	2.6 (1.4-5.0)	0.003	1.5 (0.7-3.1)	0.30
Age	1.0 (1.0-1.0)	0.24	1.0 (1.0-1.0)	0.12
Exercise dose	1.3 (1.2-1.4)	<0.001	1.3 (1.1-1.4)	<0.001

Males had worse disease at inclusion, but disease progression was similar during long-term follow-up

Right ventricular structural and functional deterioration by 713 echocardiographic assessments during 6.9 years follow-up



Keywords Arrhythmogenic cardiomyopathy • Sex • Disease penetrance • Disease progression • Ventricular arrhythmia

Introduction

Arrhythmogenic cardiomyopathy (AC), also known as arrhythmogenic right ventricular cardiomyopathy (ARVC), is an inheritable heart disease characterized by fibro-fatty replacement and subsequent structural and functional alterations of primarily the right ventricle (RV), but also the left ventricle (LV).[1] Pathogenic mutations are mainly found in genes encoding desmosomal proteins. The disease is characterized by high risk of life-threatening ventricular arrhythmia (VA), and variable disease penetrance and expressivity.[2]

Although an autosomal dominant inherited disease, several studies have reported higher disease penetrance and worse outcome in male than in female patients.[3–5] The reasons for this are not fully understood and possible explanations have included enhanced disease penetrance by testosterone[6] and sex differences in gene expression.[7] Exercise is known to accelerate and aggravate AC disease.[8–10] Population studies have reported that men generally do more exercise and participate in more competitive sports than women.[11] Different exercise habits may therefore contribute to variance in penetrance and adverse outcome between the sexes, but this is not explicitly studied. Furthermore, there are obvious physiological cardiac differences between males and females including size and hormonal factors, which may play a role in disease progression of AC patients.

We aimed to explore the sex-specific phenotype, disease progression and arrhythmic outcome in AC patients, and their relation to

What's new?

- We describe sex differences in arrhythmogenic cardiomyopathy phenotypes in a large cohort of patients with repeated measurements and long follow-up.
- Male sex was associated with more severe disease. However, exercise exposure was greater in males, and male sex was no longer a risk marker of ventricular arrhythmias after adjusting for exercise. Exercise exposure is an important marker of outcome that may have confounded previous reports.
- There were no sex differences in structural and functional disease progression during follow-up after the diagnosis was established and exercise restriction was recommended.
- The ability of imaging parameters to predict ventricular arrhythmias did not differ between male and female patients.

exercise. We hypothesized that the unfavourable effect of male sex in AC disease is confounded by exercise habits.

Methods

Study design and population

We evaluated patients diagnosed with AC at Oslo University Hospital, Rikshospitalet, Norway, between 1997 and 2019 for inclusion in a longitudinal study, expanding on a previously published dataset of follow-up consultations in AC patients.[12] Patients with previous myocardial infarction and congenital heart disease were excluded. Probands, defined as individuals without known family history of AC who sought medical attention due to clinical manifestations of the disease, underwent genetic testing. We performed cascade genetic screening in family members of mutation-positive probands. Mutation-positive family members were included regardless of fulfilling definite, borderline, or possible diagnosis at time of inclusion. Mutation-negative probands were only included if fulfilling a definite AC diagnosis by the revised Task Force Criteria,[13] and their family members were included only if fulfilling a definite AC diagnosis. The pathogenicity of mutations was evaluated according to the guidelines from the American College of Medical Genetics and Genomics (and the Association for Molecular Pathology),[14] but with focus on segregation analysis and, if needed, supplementing functional studies. Patients with pathogenic (P) and likely pathogenic (LP) genetic variants were considered mutation positive, and mutation pathogenicity was re-evaluated over time. In a recent re-evaluation of mutation pathogenicity, eight probands have had their mutation re-evaluated not being P/LP, while a P/LP genetic variant has been identified in three probands previously considered mutation negative. One family member in which the mutation has been re-evaluated not being P/LP, and clinically not fulfilling the 2010 Task Force Criteria, have been excluded from the cohort. All patients gave written informed consent. The study complied with the declaration of Helsinki and was approved by the Regional Ethical Committee of South-Eastern Norway.

The systematic collection of exercise data started in 2012. We recorded exercise habits during the 3 years prior to inclusion by standardized interviews. The patients disclosed their exercise activities and durations, and were assigned intensity levels on the basis of the Compendium of Physical Activity of 2011.[15] Exercise dose was calculated by multiplying exercise intensity and exercise duration per week and expressed as MET (metabolic equivalents of task) h/week. Exercise dose was also assessed dichotomized as below or above 12.5 MET h/week, based on the American Heart Association/American College of Sports Medicine recommendations[16] and a recent publication on exercise restriction in genotype-positive AC family members.[17] High-intensity exercise was defined as >6 METs.[16] Athletes were defined as exercise doses equivalent to ≥4 h of high-intensity exercise per week according to a previously used definition of athletic activity.[9] We advised all patients to abstain from vigorous exercise at first contact, and this was repeated at every patient interaction.

Life-threatening VA was defined as sustained ventricular tachycardia (VT, runs of consecutive ventricular beats ≥100 b.p.m. lasting longer than 30 s or requiring intervention earlier due to haemodynamic instability) documented on 12-lead electrocardiogram (ECG) or 24-h Holter recording, ventricular fibrillation (VF), aborted cardiac arrest or appropriate therapy from an implantable cardioverter-defibrillator (ICD). Appropriate ICD-therapy was defined as anti-tachycardia pacing or shock therapy for documented VT or VF. We assessed VA both retrospectively and prospectively in relation to study inclusion. VA before or at inclusion was reported as 'previous VA', and VA occurring during follow-up in patients without previous VA was reported as 'first time VA'. The combination of all events was reported as 'all VA'.

Electrocardiography

We obtained 12-lead ECG at first visit and noted presence and type of bundle branch block (BBB), epsilon waves, extent of T-wave inversions (TWI) and terminal activation duration (TAD). We assessed major and minor criteria according to revised Task Force Criteria.[13] Signal-averaged ECG (SAECG) was obtained at first visit as previously described.[10]

Echocardiography

All participants underwent a mandatory complete echocardiography with compatible hardware at study baseline (Vivid 7, E9 or E95, GE; Vingmed, Horten, Norway, offline data analysis, EchoPac 201, GE; Vingmed). Task Force Criteria of 2010 were assessed, in addition to supplementary parameters.[18] We measured LV end-diastolic diameter in 2D-mode, and LV ejection fraction (EF) by the biplane Simpson's method. The LV global longitudinal strain (GLS) was derived from speckle tracking analyses on 2D grey scale image loops with >50 frames/s from the three apical views, and expressed as the average peak-negative strain in a 16 segment LV model.

Right ventricular dimensions were quantified by proximal diameter of RV outflow tract (RVOT) from parasternal short axis view, and RV basal diameter [right ventricular diameter (RVD)] from an RV-focused apical four-chamber view. RV function was assessed by fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and RV longitudinal strain (RVLS), defined as the average peak-negative strain in three free-wall RV segments.

All subsequent echocardiographic examinations from baseline to last follow-up by 1 July 2019 were analysed for key parameters in AC. The interval of follow-up echocardiographic examinations was based on the clinical indication for each patient, and ranged from every 6 months to every second year depending on clinical status. The time intervals from baseline echocardiography to follow-up exams were precisely noted, and RVOT diameter, RVD, RV FAC, LV EF, and LV GLS were assessed at every time point. Examinations performed no more than 30 days prior to or after recorded VA were considered as performed at the time of arrhythmic event.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) imaging was performed on clinical indication at the time of inclusion in a 1.5 T unit (Magnetom Sonata, Magnetom Vision Plus or Avanto, Siemens, Erlangen, Germany) as previously described.[9] We included parameters from 2010 Task Force Criteria and corresponding cut-off values.[13]

Statistics

Statistical analyses were performed using IBM SPSS 25.0 (IBM Corp, Armonk, NY, USA) and Stata SE 15.1 (StataCorp LLC, TX, USA). Values were expressed as mean with standard deviations (SDs) and standard error (SE), frequencies with percentages or median with interquartile range (IQR), and were compared by Student's *t*-test, χ^2 test, Fisher's exact test, or Mann–Whitney *U* test as appropriate. We performed logistic regression analysis to assess the confounding impact of exercise habits on sex differences in risk of VA, adjusting for age at inclusion. We assessed sex differences in disease progression by linear mixed model analyses including key imaging parameters (RVOT, RVD, RV FAC, EF, and GLS) with exchangeable covariance structure and random individual intercept. Sex differences in disease trajectory were expressed by an interaction term between patient sex and time. We assessed odds of life-threatening VA during follow-up by a marginal logistic model with independent working

Table 1 Baseline characteristics of 190 AC patients, comparing female and male patients

	All, *n* = 190	Female, *n* = 86	Male, *n* = 104	*P*-value
Probands, *n* (%)	97 (51)	34 (40)	63 (61)	0.004
Definite AC by TFC, *n* (%)	117 (62)	44 (51)	73 (69)	0.007
Age (years)	41 ± 17	41 ± 16	41 ± 17	0.81
BSA (m^2)	1.9 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	<0.001
Exercise dose, MET-h/week (IQR)	17 (12–40)	12 (7–22)	25 (14–51)	<0.001
Exercise dose >12.5 MET-h/week, *n* (%)	96 (60)	29 (40)	67 (76)	<0.001
Exercise intensity >6 METs, *n* (%)	80 (50)	21 (29)	59 (67)	<0.001
Exercise duration >2.5 h/week, *n* (%)	78 (49)	23 (32)	55 (63)	<0.001
VA, *n* (%)	64 (34)	21 (24)	43 (41)	0.01
Age at VA (years)	41 ± 16	38 ± 12	43 ± 17	0.28
NSVT, *n* (%)	38 (20)	13 (15)	25 (24)	0.13
Medication, *n* (%)	89 (47)	37 (43)	52 (50)	0.28
β-Blocker, *n* (%)	80 (42)	34 (40)	46 (44)	0.41
Flecainide, *n* (%)	6 (3)	1 (1)	5 (5)	0.22
Amiodarone, *n* (%)	9 (5)	2 (2)	7 (7)	0.19
Major TWI, *n* (%)	63 (33)	29 (34)	34 (33)	0.88
Epsilon wave, *n* (%)	18 (9)	3 (3)	15 (14)	0.01
Prolonged TAD, *n* (%)	28 (15)	8 (9)	20 (19)	<0.05
SAECG	*n* = 152	*n* = 72	*n* = 80	
SAECG pathology, *n* (%)	89 (59)	30 (42)	59 (74)	<0.001
Filtered QRS duration (ms)	119 ± 20	113 ± 13	125 ± 22	<0.001
HFLA (ms)	41 ± 20	36 ± 13	46 ± 23	0.002
RMS (μV)	28 ± 18	34 ± 19	23 ± 16	<0.001

Values are mean ± SD if not stated otherwise. *P*-values by Mann–Whitney *U* test, Student's *t*-tests, χ^2, or Fisher's exact test as appropriate.
AC, arrhythmogenic cardiomyopathy; BSA, body surface area; ECG, electrocardiogram; HFLA, high-frequency low-amplitude; ICD, implantable cardioverter-defibrillator; IQR, inter-quartile range; MET, metabolic equivalents of task; NSVT, non-sustained ventricular tachycardia; RMS, root-mean square; SAECG, signal averaged electrocardiogram; TAD, terminal activation duration; TFC, revised 2010 Task Force Criteria; VA, ventricular arrhythmia; TWI, T-wave inversion.

correlation within our longitudinal data together with time of follow-up as co-variate, and key imaging parameters as time-varying co-variates. We performed subgroup analyses for risk markers of all VA in five subgroups: mutation-positive patients, mutation-negative patients, probands, patients with definite AC by 2010 TFC, and patients with first VA ≤30 days prior to inclusion. *P*-Values were two-sided, and values <0.05 were considered significant.

Results

Baseline characteristics

We included 190 patients (45% female, 51% probands, age 41 ± 17 years, *Table 1*), with follow-up time of 7.6 (IQR 5.5–10.9) years, of which 173 have been included in a previous publication from our research group.[12] Seven patients died during the study period, one from end-stage heart failure and the remaining from non-cardiac or unknown cause. Exercise data were available in 160 (84%) patients. Genetic analyses were performed in all except 4 non-consenting probands. 55% of tested probands were mutation- positive (66% of females vs. 49% of males, *P* = 0.13), and 93 mutation-positive family members were identified by cascade screening. Of the 144 mutation-positive patients, 118 (82%) had mutations in the plakophilin-2 (PKP2) gene, 8 (6%) in the desmoplakin (DSP) gene, 12 (8%) in the desmoglein-2 (DSG2) gene, 2 (1%) in the desmocollin-2 (DSC2) gene, 1 (1%) in the phospholamban (PLN) gene, and 1 (1%) in the transmembrane protein 43 (TMEM43) gene, while 2 (1%) patients had mutations in both the PKP2 and DSG2 gene. Supplementary material online, *Tables S1 and S2* show the classification of study participants in proband status, genotype and diagnosis according to 2010 Task Force Criteria.

Males had higher exercise doses than female patients (*P* < 0.001) (*Table 1*). The median exercise dose of males was 25 MET-h/week (equivalent to ≥4 h of high-intensity exercise per week defining athletes). The median exercise dose in females was 12 MET-h/week and 16 females fulfilled the athlete definition.

At inclusion, 117 patients were classified as having definite AC diagnosis by 2010 Task Force Criteria (70% of males vs. 51% of females, *P* = 0.007). Males were more frequently probands (40% of females vs. 61% of males, *P* = 0.004), but when adjusted for exercise dose and age, male sex was not associated with proband status [adjusted odds ratio (OR) 1.8, 95% confidence interval (CI) 0.9–3.6, *P* = 0.12, by 5 MET-h/week increments].

Sex differences in electrocardiogram

Resting 12-lead ECG was performed in all patients. SAECG was available in 158 patients, of which 8 with BBB were excluded from analysis. Male patients had more epsilon waves, prolonged TAD and SAECG pathology, but there were no differences in the prevalence

Table 2 Baseline echocardiographic and CMR characteristics in 190 AC patients, comparing female and male patients

Echocardiography	All, $n = 190$	Female, $n = 86$	Male, $n = 104$	*P*-value
LV EF (%)	56 ± 7	58 ± 5	55 ± 8	0.002
LVIDdi (mm)	27 ± 4	28 ± 3	27 ± 4	0.31
GLS (%)	−18.7 ± 3.3	−19.7 ± 2.8	−17.9 ± 3.5	<0.001
RVD (mm)	42 ± 8	39 ± 8	45 ± 8	<0.001
RVDi (mm/m^2)	22 ± 4	22 ± 5	22 ± 4	0.40
RVOT (mm)	36 ± 8	33 ± 7	39 ± 8	<0.001
RVOTi (mm/m^2)	19 ± 4	18 ± 5	19 ± 4	0.29
TAPSE (mm)	19 ± 5	21 ± 4	19 ± 6	0.005
RV FAC (%)	38 ± 11	42 ± 9	34 ± 11	<0.001
RVLS (%)	−22.4 ± 7.9	−23.9 ± 8.2	−21.2 ± 7.5	0.04
CMR	$n = 154$	$n = 69$	$n = 85$	
LV EF (%)	56 ± 10	58 ± 9	54 ± 10	0.05
LV EDVi (mL/m^2)	87 ± 20	82 ± 15	92 ± 22	0.02
RV EF (%)	46 ± 12	49 ± 13	44 ± 12	0.03
RV EDVi (mL/m^2)	108 ± 34	100 ± 40	116 ± 24	0.02
RV akinesia/dyskinesia ($n = 146$), *n* (%)	65 (45)	22 (34)	43 (66)	0.02
RV aneurysm ($n = 144$), *n* (%)	20 (14)	5 (8)	15 (19)	0.04
Fat infiltration ($n = 144$), *n* (%)	17 (12)	3 (5)	14 (18)	0.01
LGE ($n = 122$), *n* (%)	23 (19)	5 (9)	18 (27)	0.01

Values are mean ± SD if not stated otherwise. *P*-values by Student's *t*-tests, χ^2, or Fisher's exact test as appropriate.
AC, arrhythmogenic cardiomyopathy; CMR, cardiac magnetic resonance imaging; EF, ejection fraction; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LV EDVi, left ventricular end diastolic volume indexed; LVIDdi, LV internal diameter end diastole indexed; RV EDVi, right ventricular end diastolic volume indexed; RV FAC, RV fractional area change; RVDi, RV diameter indexed; RVLS, RV longitudinal strain; RVOTi, RV outflow tract indexed; TAPSE, tricuspid annular plane systolic excursion.

of major TWI by 2010 Task Force Criteria between the sexes (*Table 1*).

Sex differences in cardiac structure and function at baseline and progression

At inclusion, males had worse cardiac function than females for most parameters (*Table 2*). We included 713 echocardiographic assessments in 167 (88%) patients with ≥2 echocardiographic exams [2–10 exams, follow-up 6.9 (IQR 4.7–9.8) years]. RV structural deterioration during long-term follow-up was similar in female and male patients, while RV function decreased more in females (*Figure 1*). There was no difference in decline of LV function between the sexes [EF yearly progression rate 0.05 (SE 0.06) in males vs. –0.02 (SE 0.07) in females, *P* for interaction 0.44, and GLS yearly progression rate 0.06 (SE 0.03) in males vs. 0.11 (SE 0.03) in females, *P* for interaction 0.19).

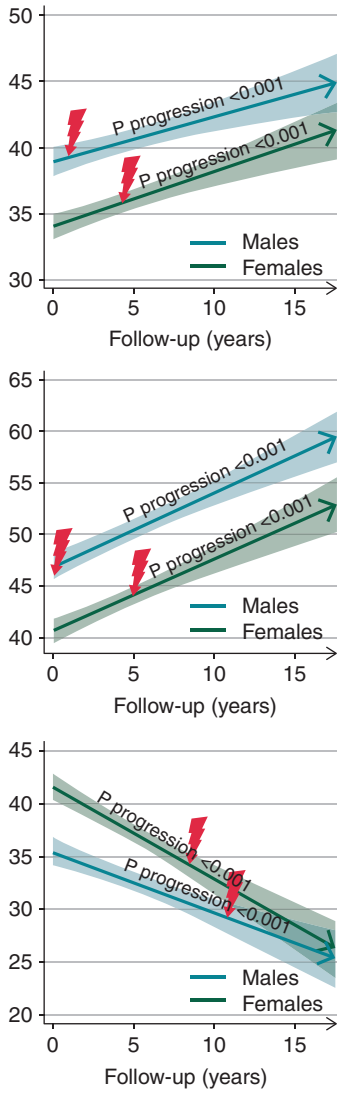
Sex differences in arrhythmic outcome

Eighty-five (45%) patients had experienced life-threatening arrhythmia by last clinical follow-up (33% of females vs. 55% of males, $P = 0.002$), of which 64 (34%) had experienced previous VA and 21 (12%) experienced first time VA during follow-up, after 1.9 (IQR 0.6–3.6) years. Compared with female patients, males had higher prevalence of previous VA (24% of females vs. 41% of males, $P = 0.01$) and a tendency of higher incidence of first time VA during follow-up (12% of females vs. 23% of males, $P = 0.07$). However, there was no difference in odds of neither previous, first time, nor all VA when adjusting for exercise dose (*Table 3*). Assessing exercise exposure as a categorical variable, as well as excluding age as a covariate, yielded similar results (Supplementary material online, *Table S3*). In separate analyses of female and male patients, exercise dose was a marker of all VA in both sexes (males: OR 1.3, 95% CI 1.2–1.5, $P < 0.001$ and females: OR 1.2, 95% CI 1.0–1.3, $P < 0.05$, by 5 MET-h/week increments, adjusted for age).

Subgroup analyses of mutation-positive patients, mutation-negative patients, probands, patients with definite AC by 2010 Task Force Criteria and patients with first VA ≤30 days prior to inclusion showed similar results as in the total population: exercise dose was a strong marker of all VA, while male sex was no longer a marker of VA after adjusting for exercise dose and age (Supplementary material online, *Table S4*).

Disease severity at first arrhythmic event and predictors of arrhythmia

Of the 85 patients with arrhythmic events, 39 (46%) patients had an echocardiographic examination within 30 days of their first VA. There was no difference in RVD or RV function in females and males at the time of first arrhythmic event (*Figure 1*). Similarly, LV function did not differ at first arrhythmic event (EF 54 ± 6% in males vs. 58 ± 6% in females, $P = 0.13$ and GLS −17.2 ± 2.2% in males vs. –18.8 ± 3.0% in females, $P = 0.12$). Increase in RVD, worsening of RV function, and worsening of LV function by GLS were all



Right ventricular outflow tract diameter (mm)

	At time of inclusion	At time of VA	At time of follow-up	Progression rate 1 year (SE)
	n=168	n=39	n=168	n=168
Males	38 ± 8	39 ± 7	42 ± 8	0.51 (0.04)
Females	33 ± 7	35 ± 7	37 ± 7	0.47 (0.05)
P-value	<0.001	0.16	<0.001	0.64

Right ventricular diameter (mm)

	At time of inclusion	At time of VA	At time of follow-up	Progression rate 1 year (SE)
	n=168	n=39	n=168	n=168
Males	44 ± 8	46 ± 6	50 ± 10	0.78 (0.06)
Females	39 ± 8	44 ± 10	44 ± 9	0.68 (0.05)
P-value	<0.001	0.43	<0.001	0.18

Right ventricular fractional area change (%)

	At time of inclusion	At time of VA	At time of follow-up	Progression rate 1 year (SE)
	n=168	n=39	n=168	n=168
Males	34 ± 11	29 ± 11	32 ± 10	-0.63 (0.05)
Females	43 ± 9	34 ± 9	36 ± 9	-0.79 (0.06)
P-value	<0.001	0.26	0.007	<0.05

Figure 1 Right ventricular functional and structural deterioration in female (green) and male (blue) patients with AC. Arrow-head of lightning represents mean value at first VA. Values are mean ± standard deviation if not stated otherwise. Yearly progression rates and interaction analyses by linear mixed model statistics of 713 echocardiographic assessments in 167 patients (exchangeable covariance structure and random intercept) during median follow-up time 6.9 (IQR 4.7–9.8) years. Mean values at time of first VA in 39 patients. AC, arrhythmogenic cardiomyopathy; IQR, interquartile range; RVD, right ventricular basal diameter; RVOT, right ventricular outflow tract diameter; RV FAC, right ventricular fractional area change; SE, standard error; VA, ventricular arrhythmia.

predictive of first arrhythmic event (*Table 4*). The prognostic ability of the parameters to predict events did not differ between male and female patients.

Discussion

This study showed apparently higher odds of proband status, more prevalent VA, and generally more severe AC disease in men compared with women. However, male patients had higher exercise doses, and when adjusted for exercise, odds of proband status and VA did not differ between the sexes. Exercise exposure may be an important confounder for the unfavourable effect of male sex on AC disease. Importantly, the disease progression during follow-up was not worse in men after introduction of exercise restrictions. These findings support similar risk in both sexes and indicate that women should not be regarded as low-risk patients simply based on their sex.

Influence of exercise dose on disease expression

Male sex has been considered a risk factor of VA in patients with AC in several studies.[3–5] This study showed for the first time that sex

Table 3 Male sex as risk marker and predictor of VA in 160 AC patients with reported exercise habits prior to study inclusion, unadjusted and adjusted for age and exercise habits at inclusion

	Univariate, OR (95% CI)	*P*-value	Multivariate, OR (95% CI)	*P*-value
Markers of previous VA (*n* = 55/160)				
Sex, male	2.2 (1.1–4.3)	0.03	1.5 (0.7–3.1)	0.32
Age	1.0 (1.0–1.0)	0.09	1.0 (1.0–1.0)	0.05
Exercise dose[a]	1.1 (1.1–1.2)	<0.001	1.1 (1.0–1.2)	0.002
Predictors of first time VA during follow-up (*n* = 19/105)				
Sex, male	2.7 (1.0–7.7)	0.06	1.8 (0.6–5.7)	0.32
Age	1.0 (1.0–1.0)	0.80	1.0 (1.0–1.0)	0.81
Exercise dose[a]	1.3 (1.1–1.4)	0.001	1.2 (1.1–1.4)	0.003
Markers of all VA (*n* = 74/160)				
Sex, male	2.6 (1.4–5.0)	0.003	1.5 (0.7–3.1)	0.30
Age	1.0 (1.0–1.0)	0.24	1.0 (1.0–1.0)	0.12
Exercise dose[a]	1.3 (1.2–1.4)	<0.001	1.3 (1.1–1.4)	<0.001

Values are OR for VA.
[a]Exercise dose at inclusion is expressed as average MET-h/week with 5-unit increments.
AC, arrhythmogenic cardiomyopathy; CI, confidence interval; MET, metabolic equivalents of task; OR, odds ratio; VA, ventricular arrhythmia.

Table 4 Structural and functional disease progression as predictors of first VA during 7.3 years follow-up by 445 echocardiographic assessments in 120 AC patients, subgrouped by sex

	Females		Males	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
RV FAC, −5%	5.4 (2.6–11.2)	<0.001	2.1 (1.3–3.4)	0.002
RVD (mm)	1.4 (1.2–1.7)	<0.001	1.1 (1.0–1.2)	0.002
RVOT (mm)	1.3 (1.1–1.5)	0.005	1.1 (1.0–1.2)	0.006
LV EF, −5%	1.5 (0.7–2.9)	0.29	1.5 (1.0–2.2)	0.06
GLS (%)	1.4 (1.0–1.9)	0.03	1.2 (1.1–1.6)	0.01

Values are OR for impending VA adjusted for time, calculated by marginal logistic models with independent covariance structure.
AC, arrhythmogenic cardiomyopathy; CIs, confidence intervals; GLS, global longitudinal strain; LV EF, left ventricular ejection fraction; OR, odds ratio; RV FAC, right ventricular fractional area change; RVD, right ventricular diameter; RVOT, right ventricular outflow tract diameter; VA, ventricular arrhythmia.

differences may, at least in part, be explained by higher exercise doses in male patients. Previous studies have indicated a strong relationship between exercise and AC outcome.[8–10] Our female patients reported exercise doses equivalent to 2 h of high-intensity exercise per week, compared with 4 h in males, matching weekly exercise doses previously associated with adverse outcome in AC.[9]

In this study, male sex was outperformed by exercise dose as a risk marker for VA. However, even though the association between male sex and VA was greatly reduced and no longer statistically significant after adjusting for exercise dose, it is possible that a larger sample size could reintroduce male sex as a significant marker of arrhythmic outcome.

We suggest that the observed worse phenotype in males were at least partly attributable to differences in exercise exposure. Other possible explanations include sex differences in cardiac physiology, hormonal, and intrinsic factors. One recent report showed that high levels of testosterone in men and low levels of estradiol in women were associated with arrhythmic events[6] while exercise history was not included. Sex-specific risk in AC is most likely multifactorial including genetic, hormonal, and behavioural factors of which exercise plays an important role.

All patients were recommended to avoid high-intensity exercise. Therefore, events occurring during follow-up may be more representative for general disease dynamics. The present study assessed disease trajectory and incident of life-threatening VA during the course of 713 observations. There were no signals indicating sex differences during follow-up. We did observe a slightly steeper decline in RV FAC in female than in male patients, but this may be explained by a regression to the sample mean phenomenon. We hypothesize that males presented with more prominent disease compared with females, possibly due to higher exercise exposure, while later disease progressed at similar rate due to implementation of exercise restrictions.

Importantly, this study illustrates that female AC patients should not be regarded as low-risk patients by default, and that high exercise dose is a strong predictor of adverse outcome also in female patients. This is in line with a recent study reporting a strong association between exercise dose and definite AC criteria and VA in mutation-positive family members, and this association was more prominent in females.[17]

Sex-specific markers of ventricular arrhythmia

A high proportion of patients with AC present with VA as first manifestation of disease,[1,19] making this population vulnerable for sudden cardiac death and in great need of precise and efficient risk stratification.[20] Only one study has previously assessed sex-specific risk stratification in AC, and interestingly, they did not find markers of VA in women when evaluating Task Force Criteria.[5] In contrast, we

observed several predictors of VA independent of patient sex by echocardiographic examination, possibly enabled by the larger sample size. Structural markers at time of first VA were not different between males and females. However, these findings may be limited by a relatively low number of observations. There is a need for larger studies to explore whether sex-specific cut-off values provide better risk stratification of AC patients.

Limitations

This was a longitudinal cohort study with inherent limitations. The national referral nature of our centre may have resulted in high disease prevalence and the single-centre design may have limited the external validity of the results. Due to the high prevalence of patients with mutations in the PKP2 gene, the generalizability to patient populations with other dominating mutations is uncertain. Exercise doses were self-reported, which may lead to reporting and recall bias, especially in patients with a long follow-up period prior to registration of exercise habits. We arbitrary chose to record exercise history 3 years before diagnosis to reduce recall bias. Other alternatives of reporting may be of interest in future studies. After diagnosis, patients were advised to restrict their exercise, and further exercise level was not recorded. The effect of detraining was therefore not assessed. Furthermore, advice may have differed according to time of diagnosis and the current knowledge and recommendations on exercise. All patients were continuously updated according to newest recommendations when available. Disease progression was assessed by echocardiography and not by CMR. Repeated CMR was performed for diagnostic purpose in a limited number of patients with mild disease.

Conclusions

Male AC patients were more likely to be probands and had higher prevalence of VA than female patients, but not when adjusting for exercise dose. Importantly, male and female patients had similar disease progression after implementation of exercise restrictions, suggesting less sex-specific impact on outcome than previously reported. Female AC patients should therefore not be regarded as low-risk patients based on their sex only.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will not be shared publicly.

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