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Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members

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Aims Exercise increases risk of ventricular arrhythmia in subjects with arrhythmogenic right ventricular cardiomyopathy (ARVC). We aimed to investigate the impact of exercise on myocardial function in ARVC subjects.

Methods and Results We included 110 subjects (age 42 ± 17 years), 65 ARVC patients and 45 mutation-positive family members. Athletes were defined as subjects with ≥4 h vigorous exercise/week [≥1440 metabolic equivalents (METs × minutes/week)] during a minimum of 6 years. Athlete definition was fulfilled in 37/110 (34%) subjects. We assessed right ventricular (RV) and left ventricular (LV) myocardial function by echocardiography, and by magnetic resonance imaging (MRI). The RV function by RV fractional area change (FAC), RV global longitudinal strain (GLS) by echocardiography, and RV ejection fraction (EF) by MRI was reduced in athletes compared with non-athletes (FAC 34 ± 9% vs. 40 ± 11%, RVGLS −18.3 ± 6.1% vs. −22.0 ± 4.8%, RVEF 32 ± 8% vs. 43 ± 10%, all P < 0.01). LV function by LVEF and LVGLS was reduced in athletes compared with non-athletes (LVEF by echocardiography 50 ± 10% vs. 57 ± 5%, LVEF by MRI 46 ± 6% vs. 53 ± 8%, and LVGLS −16.7 ± 4.2% vs. −19.4 ± 2.9%, all *P* < 0.01). The METs × minutes/week correlated with reduced RV and LV function by echocardiography and MRI (all *P* < 0.01). The LVEF by MRI was also reduced in subgroups of athlete index patients (46 ± 7% vs. 54 ± 10%, P = 0.02) and in athlete family members (47 ± 3% vs. 52 ± 6%, *P* < 0.05).

Conclusion Athletes showed reduced biventricular function compared with non-athletes in ARVC patients and in mutation-positive family members. The amount and intensity of exercise activity was associated with impaired LV and RV function. Exercise may aggravate and accelerate myocardial dysfunction in ARVC.

Keywords Arrhythmogenic cardiomyopathy • Heart failure • Exercise • Myocardial function • Ventricular arrhythmia

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiac cardiomyopathy predisposing to ventricular arrhythmia (VA) and sudden cardiac death in apparently previously healthy young individuals. Molecular genetic studies have revealed that pathomechanisms involve dysfunction in cardiac desmosomes. Desmosomal dysfunction ultimately leads to apoptosis and fibro-fatty replacement of the myocardium. The cardiac phenotype presents as a dilated right ventricle with wall thinning and

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aneurysms, and the occurrence of life-threatening VA. Pathology is not restricted to the right ventricle (RV) and left ventricular (LV) involvement is common.[1]

Although the benefit of physical activity on individual health is indisputable[2,3], exercise may have adverse effects in patients with underlying desmosomal dysfunction.[4] A high level of physical activity is reported to increase risk of VA in patients with ARVC[4,5] and these patients are recommended to refrain from competitive sports.[6] However, the impact of a high level of physical activity on myocardial function in patients with ARVC has not been fully investigated. Exercise increases wall stress by volume overload and sympathetic stimulation, which may trigger the disease,[7] and case reports indicate a high prevalence of ARVC in competitive athletes.[8] Furthermore, experimental studies support that vigorous exercise accelerates RV dysfunction in mice with ARVC-related mutations.[9] However, in humans, systematic data on exercise as a trigger of biventricular cardiomyopathy and data on how exercise affects mutation positive family members are sparse. Information about the effect of physical activity on a genetically altered myocardium is of upmost importance for patients with ARVC, and in particular for their mutation-positive family members in whom overt myocardial dysfunction has not yet been detected.

We aimed to investigate the impact of vigorous exercise on myocardial function in patients with ARVC and in their mutation positive family members. We hypothesized that myocardial function is more reduced in ARVC subjects with a history of athletic activity compared to those without athletic activity.

Methods

Study subjects

In this cross-sectional study, subjects were recruited from two university hospitals (Oslo University Hospital, Norway and Lund University Hospital, Sweden). We used the 2010 Task Force Criteria (2010 TFC) in the diagnostics of ARVC.[10] Index patients were genetically tested for ARVC related mutations. Family members positive for a truncation, frameshift or splice site mutation, or with an ARVC-related missense mutation that co-segregated with ARVC phenotype in the family were included.

The age of the ARVC subjects at echocardiographic examination, at implantable cardioverter defibrillator (ICD) implantation, and at cardiac transplantation was recorded. Ventricular arrhythmias were defined as syncopes with assumed arrhythmic origin, documented sustained ventricular tachycardias (VTs) and aborted cardiac arrests. Exercise induced VA were defined as VA occurring during physical activity. Any ARVC related medication received at time of echocardiographic examination was recorded.

Written informed consent was given by all study participants. The study complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics in Sweden and Norway.

Athlete definition

The study participants were asked about their history of and current amount of athletic activity by direct interview or by telephone calls. Amount of physical activity was expressed in metabolic equivalents (METs) × min/week. One MET represents an individual's energy expenditure while sitting quietly and is approximated to 3.5 mL O_2/kg.min or 1 kcal/kg.h.[11] Intensity of physical activity was graded as vigorous if ≥6 METs.[12] The duration of regularly performed exercise was expressed in years. Subjects with a history of physical activity with intensity ≥6 METs for ≥4 hours/week (≥1440 METs × min/week) during minimum 6 years were defined as athletes. Quartiles of METS × min/week were created to explore the relationship between activity level and cardiac function and volumes.

Echocardiographic study

All subjects underwent an echocardiographic study (Vivid 7 and Vivid E9, GE; Vingmed, Horten, Norway) and data were analysed off-line (EchoPac®, GE; Vingmed). We assessed the following RV parameters: diameter of RV outflow tract (RVOT) from parasternal short axis view (PSAX), RV basal diameter (RVD), RV fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE),[13,14] and evaluated for the presence of RV wall abnormalities by 2010 TFC.[10] From the LV we assessed end-diastolic diameter (LVEDD), end-diastolic (LVEDV) and end-systolic (LVESV) volume, ejection fraction (LVEF), and cardiac output.[13] Values were considered abnormal according to current guidelines.[10,14] Strain analyses were performed by two-dimensional (2D) speckle tracking echocardiography. The LV strain was traced from 2D images from the three apical views,[15] and RV strain was traced from the four-chamber view with focus on the right ventricle.[16] Peak systolic longitudinal strain was determined in 16 LV segments and averaged to LV global longitudinal strain (LVGLS). Peak systolic longitudinal strain from six RV segments was averaged to RVGLS. The LVEF was analyzed by two independent observers blinded to all clinical information and athlete status.

Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) was performed in a subset of patients using 1.5 Tesla scanner (Magnetom Vision Plus or Magnetom Sonata; Siemens, Erlangen, Germany) and a phased array body coil. The RV and LV were covered by axial and sagittal breath-hold T1-weighted turbo spin echo (TSE) images, and by multiple short axis cine images using a breath-hold segmented balanced gradient echo sequence (fast imaging with steady-state free precession, trueFISP). Two-chamber and four-chamber cine acquisitions were obtained. Calculations of RV and LV volumes were accomplished by summing the luminal areas on the short axis images at end-diastole and end-systole, including the RV and LV outflow tracts.[17] Only MRI studies including short axis images were defined as appropriate. Post-processing analyses were performed using Qmass® MR 6.1.6 software (Medis Medical Imaging Systems, Leiden, the Netherlands). Interobserver analyses for RV and LV volumes were performed in 10 patients.

Genetic analyses

Genomic DNA was isolated from peripheral blood. The individual exons with flanking intron sequences of the plakophilin-2 (PKP2), desmocollin-2 (DSC2), desmoglein-2 (DSG2), desmoplakin (DSP) genes and 29 of the 105 exons of the ryanodine receptor-2 (RYR2) gene were sequenced by polymerase chain reaction amplification in combination with direct sequencing. Genetic screening was performed in family members of patients with pathogenic mutations. Family members of patients with variants of uncertain significance (VUS)

Table 1 Clinical characteristics in 110 arrhythmogenic right ventricular cardiomyopathy (ARVC) subjects, 73 non-athletes and 37 athletes

Clinical characteristics	Total ($n = 110$)	Non-athletes ($n = 73$)	Athletes ($n = 37$)	*P*-value	Adjusted odds ratio (95% CI)	Adjusted *P*-value*
Index (*n*)	65 (59%)	37 (51%)	28 (76%)	<0.01		
Male gender (*n*)	64 (58%)	35 (48%)	29 (78%)	<0.01		
Index		22 (60%)	22 (79%)	0.10		
Non-index		13 (36%)	7 (78%)	0.06		
Age at baseline echocardiography (years)	42 ± 17	45 ± 18	36 ± 13	<0.01		
Index		50 ± 16	37 ± 13	<0.01		
Non-index		39 ± 18	32 ± 12	0.29		
Definite ARVC by TFC	78 (71%)	43 (59%)	35 (95%)	<0.001	22.92 (4.27–123.07)	<0.001
Index ($n = 59$)		32 (87%)	27 (96%)	0.22		
Non-index ($n = 19$)		11 (31%)	8 (89%)	<0.01		
Non-definite ARVC by TFC	32 (29%)	30 (41%)	2 (5%)	<0.001	0.04 (0.01–0.23)	<0.001
Index ($n = 6$)		5 (13%)	1 (4%)	0.22		
Non-index ($n = 26$)		25 (69%)	1 (11%)	<0.01		
Syncope (n)	40 (44%)	19 (33%)	21 (62%)	<0.01	3.35 (1.29–8.71)	0.01
Index		12 (50%)	17 (68%)	0.20		
Non-index		7 (21%)	4 (44%)	0.20		
VA (*n*)	66 (60%)	37 (51%)	29 (78%)	<0.01	4.53 (1.59–12.94)	<0.01
Index		34 (92%)	27 (96%)	0.63		
Non-index		3 (8%)	2 (22%)	0.26		
Exercised-induced VA (*n*)	41 (37%)	13 (18%)	28 (80%)	<0.001	16.54 (5.59–49.98)	<0.001
Index		11 (31%)	26 (100%)	<0.001		
Non-index		2 (6%)	2 (22%)	0.17		
ICD (*n*)	52 (47%)	29 (40%)	23 (62%)	0.03	2.58 (1.05–6.38)	0.04
Index		27 (73%)	21 (75%)	0.85		
Non-index		2 (6%)	2 (22%)	0.17		
Age at ICD implantation(years)	39 ± 16	45 ± 16	33 ± 13	<0.01		
Index		46 ± 16	34 ± 13	<0.01		
Non-index		29 ± 11	28 ± 16	0.95		
Heart transplantation (*n*)	5 (5%)	0 (0%)	5 (14%)	<0.01		
ARVC mutation positive (n)	75 (68%)	53 (79%)	22 (67%)	0.18		
Beta-blocker (*n*)	62 (56%)	33 (56%)	29 (78%)	0.03		
Amiodarone (*n*)	23 (21%)	8 (14%)	15 (41%)	<0.01		

ARVC, arrhythmogenic right ventricular cardiomyopathy; 2010 TFC, 2010 Task Force Criteria; VA, ventricular arrhythmia; ICD, implantable cardioverter–defibrillator; ECG, electrocardiogram.
*Adjusted for age and male gender

were included only if they had an ARVC phenotype and if a familial co-segregation of symptoms was present.

Statistical analyses

Data were presented as mean ± standard deviation or as median (range). Differences between groups were assessed by chi-square test and Fisher's exact test and Student's *t*-test (SPSS 20.0; SPSS Inc., Chicago, IL, USA). The subgroups of index and non-index subjects were analysed separately. Correlations between the amount of physical activity and RV and LV function were assessed by Pearson bivariate correlation. Kaplan–Meier curves were constructed and log-rank test was performed to assess cumulative lifetime cardiac transplantation free survival. The *C* statistic was calculated by receiver operating characteristic (ROC) curves for amount of physical activity that optimally detected those with arrhythmic events and those with RVFAC <35%. The value closest to the upper left corner of the ROC curve was defined as giving optimal sensitivity and specificity. Multivariate logistic regression was performed to adjust the outcome of athlete status for age and gender. Intra-observer and inter-observer variability was expressed as intraclass correlation coefficient. Two-sided *P*-values <0.05 were considered significant.

Results

Patients characteristics and athlete status

We included 110 subjects of which athlete status could be determined. Of the 110, 65 (59%) were consecutive ARVC index patients and 45 (41%) were mutation-positive family members (*Table 1*). The definition of athlete status was fulfilled in 37 (34%), while 73 (66%) were non-athletes (*Table 1*). Athletes had a history

Table 2 Echocardiographic parameters in 73 non-athletes and in 37 athletes

Parameters	Total	Non-athletes ($n = 73$) 37 index 36 non-index	Athletes ($n = 37$) 28 index 9 non-index	*P*-value	Adjusted odds ratio (95% CI)	Adjusted *P*-value*
Heart rate (beats per min)	63 ± 13	65 ± 13	59 ± 12	0.06	0.96 (0.92–1.00)	0.05
Index		61 ± 11	58 ± 11	0.24		
Non-index		68 ± 14	65 ± 13	0.62		
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	0.84	1.04 (0.91–1.18)	0.58
Index		26 ± 4	25 ± 4	0.64		
Non-index		24 ± 4	24 ± 3	0.99		
Right ventricular parameters						
RVOT PSAX (mm)	36 ± 9	34 ± 7	39 ± 10	<0.01	1.08 (1.02–1.15)	0.01
Index		36 ± 8	40 ± 11	0.11		
Non-index		32 ± 5	35 ± 6	0.18		
Right ventricular basal diameter (mm)	44 ± 9	42 ± 8	47 ± 9	<0.01	1.10 (1.03–1.16)	<0.01
Index		46 ± 8	49 ± 9	0.12		
Non-index		37 ± 4	41 ± 5	0.03		
RVTAPSE/displacement (mm)	18 ± 5	19 ± 4	16 ± 5	<0.01	0.88 (0.79–0.98)	0.02
Index		19 ± 5	15 ± 5	<0.01		
Non-index		19 ± 4	19 ± 3	0.67		
RVFAC (%)	38 ± 11	40 ± 11	34 ± 9	<0.01	0.93 (0.88–0.98)	<0.01
Index		36 ± 10	32 ± 9	0.14		
Non-index		45 ± 9	40 ± 8	0.08		
RVGLS (%)	20.7 ± 5.5	−22.0 ± 4.8	−18.3 ± 6.1	<0.01	1.18 (1.06–1.32)	<0.01
Index		−20.6 ± 5.4	−17.4 ± 6.5	0.04		
Non-index		−23.4. ± 3.8	−21.4 ± 3.1	0.15		
RV wall abnormalities by 2010 TFC	69 (63%)	38 (53%)	31 (84%)	<0.01	13.86 (4.35–44.09)	<0.001
Index		28 (76%)	25 (89%)	0.16		
Non-index		10 (29%)	6 (67%)	0.05		
Left ventricular parameters						
Cardiac output (L/min)	3.7 ± 1.2	3.8 ± 1.2	3.6 ± 1.3	0.53	0.71 (0.46–1.08)	0.11
Index		3.6 ± 1.1	3.3 ± 1.3	0.42		
Non-index		4.0 ± 1.2	4.6 ± 1.0	0.21		
LVEDV (mL)	113 ± 40	105 ± 25	128 ± 56	<0.01	1.01 (1.00–1.03)	0.11
Index		108 ± 27	129 ± 63	0.08		
Non-index		103 ± 23	125 ± 21	0.01		
LVESV (mL)	54 ± 31	47 ± 15	67 ± 47	<0.01	1.03 (1.00–1.06)	0.03
Index		49 ± 17	70 ± 53	0.03		
Non-index		44 ± 11	55 ± 12	0.02		
LVEF (%)	54 ± 8	57 ± 5	50 ± 10	<0.001	0.87 (0.80–0.95)	<0.01
Index		55 ± 6	48 ± 11	<0.01		
Non-index		58 ± 3	56 ± 3	0.04		
LVGLS (%)	18.5 ± 3.7	−19.4 ± 2.9	−16.7 ± 4.2	<0.001	1.25 (1.06–1.46)	<0.01
Index		−18.2 ± 2.8	−16.0 ± 4.4	0.03		
Non-index		−20.4 ± 2.7	−19.0 ± 2.5	0.20		

ARVC, arrhythmogenic right ventricular cardiomyopathy; RVOT PSAX, right ventricular outflow tract parasternal short-axis; RVTAPSE, right ventricular tricuspid annular plane systolic excursion; RVFAC, right ventricular fractional area change; RVGLS; right ventricular global longitudinal strain; 2010 TFC, 2010 Task Force Criteria; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global strain.
*Adjusted for age and gender.

of physical activity level of 3178 ± 886 METs × min/week and non-athletes of 669 ± 290 METs × min/week, ($P < 0.001$). In athletes, age at start of athletic activity was 11 ± 3 years and the duration of activity ≥1440 METs × min/week was 11 ± 4 years. According to the definition employed, all athletes had a history of athletic activity ≥6 years. Athletes were more frequently male, had more frequently definite ARVC by 2010 TFC and were more frequently index patients compared with non-athletes (all $P < 0.01$) (Table *1*). Therefore, all analyses were also performed for index patients separately and results were adjusted for gender in addition to age.

Echocardiographic and MRI findings

By echocardiography, the ARVC population had reduced RV function by RVFAC (38 ± 11%) and increased RV (44 ± 9 mm) and RVOT (36 ± 9 mm) diameters compared with established normal values in healthy subjects (*Table 2*).[13,14] Values for LV function and volumes by echocardiography were normal (*Table 2*).

Athletes were younger at the time of baseline echocardiography ($P < 0.01$), which in the majority of cases coincided with the time of diagnosis (*Table 1*). In addition, by separate analysis of index patients, athletes were younger at first echocardiographic examination. Resting heart rate was not lower in athletes vs. non-athletes ($P = 0.06$), or in index patients ($P = 0.24$), or in mutation positive family members ($P = 0.62$)(*Table 2*). Cardiac MRI was performed in 54 subjects, 20 athletes and 34 non-athletes.

RV function and diameters

Athletes had increased RV diameters compared with non-athletes and reduced RV function by RVFAC, TAPSE, and RVGLS (all $P < 0.01$) (*Table 2*) and reduced RVEF by MRI ($P < 0.001$) (*Table 3*). Athletes had a higher frequency of wall abnormalities by 2010 TFC (*Table 2*). Increased amount of physical activity in quartiles correlated with increased RVOT diameter ($R = 0.24$, $P = 0.02$) and with reduced RV strain ($R = 0.21$, $P = 0.03$) by echocardiography (*Figure 1*). Increasing amount of physical activity expressed as METs × min/week correlated with reduced RVEF by MRI ($R = -0.51$, $P < 0.001$) (*Figure 2*). By ROC analyses, 840 METs × min/week (=2.3 h vigorous exercise/week) during a minimum of 6 years optimally detected those with RVFAC <35% with a sensitivity of 69% [95% confidence interval (CI) 0.53–0.82], and specificity of 49% (95% CI 0.36–0.62).

LV function and volumes

The LVEF by echocardiography and MRI was lower in athletes compared with non-athletes in the total population (both $P < 0.01$), in the subgroups of index patients ($P < 0.01$ and $P = 0.02$, respectively) and in mutation-positive family members (both $P < 0.05$; *Tables 2* and *3*). Reduced LVEF and LVGLS by echocardiography correlated with increasing amount of physical activity expressed as METs × min/week during a minimum of 6 years ($R = -0.41$, $P < 0.001$ and $R = 0.32$, $P < 0.01$, respectively; *Figure 1*).

Intra- and inter-observer intraclass correlation for LVEF by echocardiography was 0.97 (95% CI 0.96–0.98) and 0.81 (95% CI 0.73–0.88), respectively, and 0.84 (95% CI 0.49–0.96) and 0.79 (95% CI 0.67–0.87), respectively, for RVEF by MRI.

Arrhythmias and outcome

In total, 66 (60%) of 110 subjects had experienced VA, and these events were more frequent in athletes compared with non-athletes ($P < 0.01$; *Table 1*) and occurred at younger age in athletes (36 ± 13 years vs. 50 ± 16 years, $P < 0.01$). Patients with VA had a history of higher amount of METs × min/week during a minimum of 6 years compared with those without (1739 ± 1434 METs × min/week vs.1177 ± 1056 METs × min/week, $P = 0.03$).

Table 3 Magnetic resonance imaging parameters in 54 arrhythmogenic right ventricular cardiomyopathy (ARVC) study participants

Parameters	Total population (33 index, 21 non-index)	Non-athletes ($n = 34$)	Athletes ($n = 20$)	*P*-value
LVEDVI (mL)	74 ± 18	74 ± 19	74 ± 16	0.97
Index		84 ± 14	75 ± 18	0.12
Non-index		62 ± 18	73 ± 11	0.19
LVESVI (mL)	37 ± 12	35 ± 12	40 ± 12	0.15
Index		39 ± 12	40 ± 14	0.74
Non-index		31 ± 11	40 ± 5	0.08
LVEF (%)	50 ± 8	53 ± 8	46 ± 6	<0.01
Index		54 ± 10	46 ± 7	0.02
Non-index		52 ± 6	47 ± 3	<0.05
RVEDVI (mL)	89 ± 36	82 ± 34	99 ± 38	0.09
Index		99 ± 35	111 ± 39	0.36
Non-index		63 ± 19	73 ± 18	0.28
RVESVI (mL)	56 ± 32	47 ± 28	70 ± 34	0.01
Index		57 ± 34	81 ± 36	0.06
Non-index		36 ± 11	46 ± 12	0.10
RVEF (%)	39 ± 11	43 ± 10	32 ± 8	<0.001
Index		45 ± 13	30 ± 9	<0.001
Non-index		41 ± 7	37 ± 5	0.17

LVEDVI, left ventricular end-diastolic volume indexed; LVESVI, left ventricular end-systolic volume indexed; LVEF, left ventricular ejection fraction; RVEDVI, right ventricular end-diastolic volume indexed; RVESVI, right ventricular end-systolic volume indexed; RVEF, right ventricular ejection fraction.

Athletes were younger at time of ICD implantation ($P < 0.01$; *Table 1*). The age of onset of training correlated to the age at ICD implantation ($R = 0.48$, $P = 0.02$).

Exercise-induced VA occurred in 41 (37%) subjects and occurred more frequently in athletes ($P < 0.001$). Amount of METs × min/week was higher in those with exercise induced arrhythmias compared with those without (2373 ± 1369 METs × min/week vs. 929 ± 864 METs × min/week, $P < 0.001$). An amount of 900 METs × min/week (≥2.5 h vigorous exercise/week) during a minimum of 6 years showed a C-statistics of 0.80 (95% CI 0.71–0.90) to discriminate subjects with exercise-induced VA [sensitivity 76% (95% CI 0.60–0.88), specificity 79% (95% CI 0.67–0.88)].

Five patients, all athletes, underwent cardiac transplantation, while no non-athletes were transplanted (log rank $P < 0.001$; *Figure 3*). Of the five transplanted, all had biventricular end-stage heart failure and four had additional repetitive untreatable VA.

Genetic findings

Genetic testing for ARVC-related mutations was performed in 100 of the study subjects. In these, 76 ARVC-related mutations/variants were identified in 75 (75%) subjects (one patient had two mutations). We observed eight different pathogenic mutations in *PKP2* ($n = 68$) and in *DSP* ($n = 2$). Variants of uncertain significance were

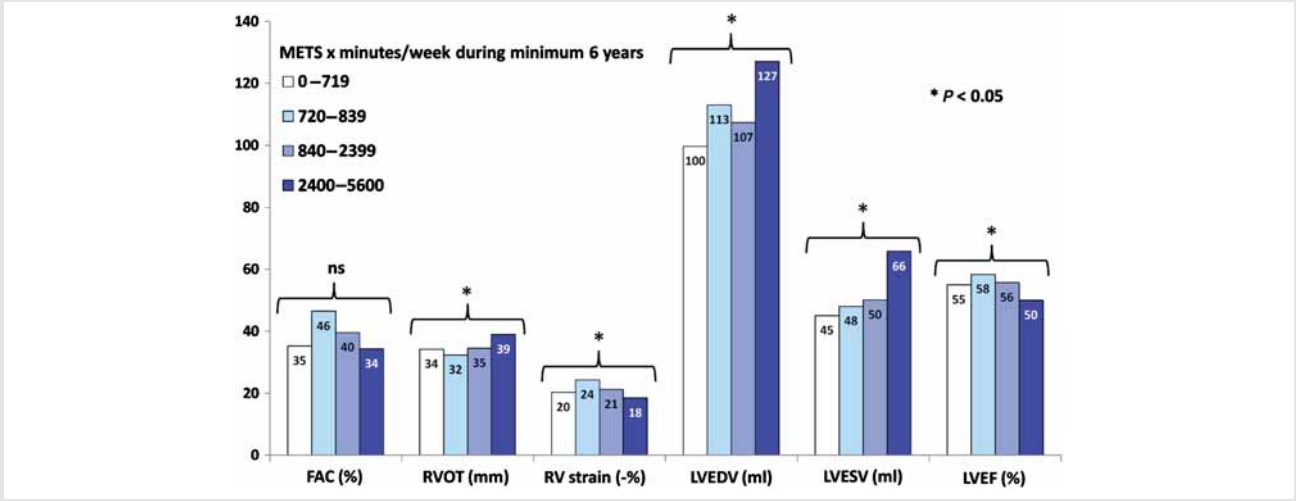

Figure 1 Bar charts displaying relationship between the amount of physical activity expressed as quartiles of metabolic equivalents (METs) × minutes/week during a minimum of 6 years and echocardiographic findings in the right ventricle and left ventricle in 110 arrhythmogenic right ventricular cardiomyopathy (ARVC) subjects. There was a significant correlation between increasing activity in quartiles and increased right ventricular outflow tract (RVOT) diameter, increased left ventricular (LV) volumes and reduced function by right ventricular (RV) strain and left ventricular ejection fraction (LVEF) (all $P < 0.05$). The *P*-values are from Pearson's bivariate correlation. FAC, fractional area change; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

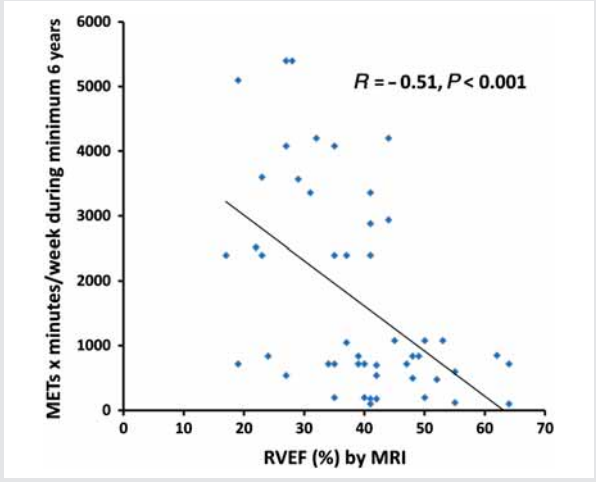

Figure 2 Scatter plot and regression line of 54 arrhythmogenic right ventricular cardiomyopathy (ARVC) subjects examined with cardiac magnetic resonance imaging (MRI). The amount of physical activity in metabolic equivalents (METs) × min/week during a minimum of 6 years correlated with reduced right ventricular ejection fraction (RVEF) by MRI.

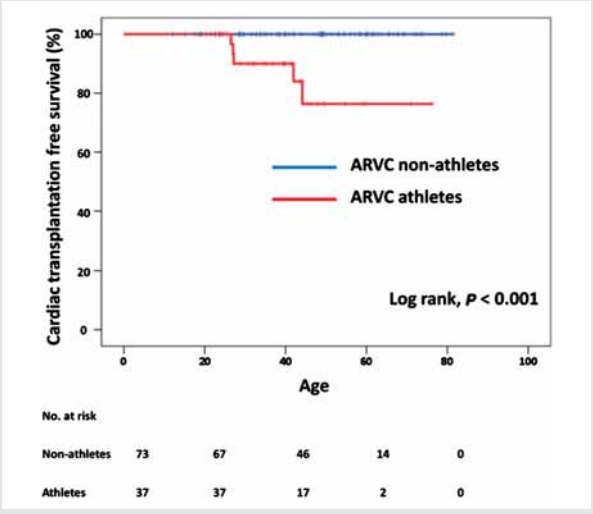

Figure 3 Kaplan Meier analysis of 110 arrhythmogenic right ventricular cardiomyopathy (ARVC) patients and their mutation-positive family members. Athletes had significantly worse outcome regarding cardiac transplantation ($n = 5$) compared with non-athletes (Log rank, $P < 0.001$).

found in three index patients (*PKP2*, $n = 1$; *DSC2*, $n = 1$; *DSP*, $n = 1$) fulfilling definite ARVC diagnosis. In 25 index patients, no pathogenic mutation was found and no genetic testing was performed in 10 index patients. All these 35 fulfilled 2010 TFC for definite ARVC diagnosis. Family members of mutation negative or not-tested index patients were not included. Two family members of the index patients with a VUS in DSP were included because of familial co-segregation of the ARVC phenotype and their ARVC symptoms.

Discussion

This study showed that ARVC patients with a history of athletic activity had reduced RV and LV function compared with ARVC

non-athletes. Athletes among the asymptomatic mutation-positive family members had lower LV function and more RV abnormalities compared with non-athletic family members. The results were consistent by several echocardiographic and MRI parameters. Athletic activity was related to worse outcome, with a higher frequency and earlier onset of VA and only athletes needed cardiac transplantation. These findings suggest that athletic activity accelerates and aggravates ARVC progression and outcome.

Impact of athletic activity on myocardial function in ARVC

Experimental studies have indicated physical activity in ARVC mice to be associated with worse outcome.[9] Case reports and a recent study have shown that athletic activity was associated with worse arrhythmic outcome in ARVC patients.[4,18] Our study adds to the current knowledge showing a relationship between amount and intensity of athletic activity and reduced biventricular function by echocardiography and MRI in a comprehensive study of ARVC patients and in mutation positive-family members. As expected, RV function was reduced in ARVC patients.[13] Importantly, ARVC athletes had a consistently reduced RV function by several parameters, and a more dilated RV compared with ARVC non-athletes; this was also found in separate analyses of index patients only. The LV function was more reduced in ARVC athletes compared with non-athletes, as shown by echocardiographic and MRI studies. Interestingly, LV function was also slightly but significantly reduced in family members with a history of athletic activity compared with non-athlete family members.

Physiological cardiac changes caused by athletic activity include hypertrophy and dilatation of the LV, leading to larger LV volumes, larger stroke volume, and lower resting heart rate. Healthy athletes may therefore have LVEF in the lower normal range[19] and our results could hypothetically be a result of physiological athletic changes. Indeed, cardiac volumes were increased in athletes compared with non-athletes. However, heart rate, cardiac output and BMI were not different. Furthermore, LVEF in ARVC index patients was reduced below values that could be considered as physiological in athletes. Reduced LV function in athletes below physiological values was further underscored by the finding of reduced LV global strain. LVGLS is not expected to be lower in athletes,[19–21] and even better LVGLS has been reported in healthy athletes compared with healthy non-athletes.[22]

A slightly reduced RV function and increased RV diameters have been reported in healthy athletes.[23–27] while others have reported normal RV function.[19,28] In the present study, ARVC athletes had clearly dilated RV dimensions and severely reduced RV function.[19,29] Combined, our findings showed reduced LV and RV function in ARVC athletes compared with ARVC non-athletes.

It has been previously proposed that extreme exercise can promote an ARVC phenotype in genotype negative individuals.[25–27] Our ARVC mutation-positive subjects seemed to have more severe myocardial damage, despite lower levels of exercise compared with the mutation-negative athletes from the previous studies. These findings support the theory that higher levels of physical activity are necessary to impair myocardial function in athletes with normal or non-severely altered desmosomes. We speculate that while there may be a threshold value for exercise in desmosomally healthy individuals, causing the 'acquired ARVC', no threshold value may exist in desmosomal mutation carriers. We demonstrated a linear relationship between amount of physical activity and reduced RV and LV function in our study, indicating that myocardial damage relates to a continuum of physical activity. Therefore, there may be no threshold value for recommendations of physical activity in ARVC mutation-positive subjects to prevent negative effects on myocardial function.

Clinical implications

Athletes had reduced RV and LV function and only athletes had heart transplantation, indicating that athletic activity aggravates biventricular myocardial dysfunction. Furthermore, athletes were younger at the time of ARVC diagnosis and ICD implantation indicating that athletic activity accelerated the onset of life-threatening symptoms in ARVC. The present study underlines current guidelines that recommend patients with definite ARVC to refrain from competitive sports. However, current guidelines do not sufficiently address mutation-positive family members and sparse evidence has been available to justify restrictions in physical activity in these subjects. The benefit of physical activity on individual health is indisputable and unnecessary restrictions must be avoided. This study was not designed to fully answer whether ARVC mutation positive family members should be restricted in physical activity. Prospective follow-up studies are needed to further advise the family members.

Limitations

This study had a cross-sectional design; however, data on athletic activity was collected retrospectively. Future studies should follow ARVC patients with athletic activity prospectively over an appropriate period of time.

Athletes were more frequently male and more frequently index patients than non-athletes. We expected index patients to have more severe disease and therefore, every result was analysed separately in index patients only. Furthermore, all results were adjusted for gender in addition to age. The majority of RV and LV parameters remained decreased in index athletes only and results could therefore not be attributed to the higher proportion of index patients in athletes. Adjustment for gender and age did not change our results. Only a subset of subjects ($n = 54$) had an appropriate MRI study that may have influenced our results.

Conclusions

The ARVC subjects with a history of athletic activity showed reduced RV and LV function compared with non-athletes by echocardiography and by MRI. The LVEF was reduced in athletes, both in index patients and in asymptomatic mutation-positive family members. Higher levels of physical activity correlated with reduced LV and RV function, and only athletes had cardiac transplantation. Diagnosis of ARVC and onset of VA occurred at younger age in

athletes compared with non-athletes. These findings indicate that athletic activity aggravates LV and RV myocardial dysfunction in ARVC patients and in mutation-positive family members and accelerate the onset of life-threatening symptoms.

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Conflict of interest: A.G.H. is currently an employee at Novo Nordisk, Denmark. The other authors have no conflicts of interest to report.

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