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Vigorous exercise in patients with hypertrophic cardiomyopathy☆,☆☆,★

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ABSTRACT

Background: We aimed to investigate if history of vigorous exercise was associated with changes in left ventricular morphology, left ventricular function and ventricular arrhythmias (VAs) in hypertrophic cardiomyopathy genotype positive, phenotype negative (Genotype + LVH −) and in phenotype positive (HCM LVH +).

Methods: In this cross sectional study we included 187 subjects (age 49 ± 16 years, 89(48%) female, 121(65%) HCM LVH + and 66 (35%) Genotype + LVH-) who answered a questionnaire on physical activity history. Exercise ≥6 metabolic equivalents was defined as vigorous. Subjects with a history of vigorous exercise ≥4 h/week during ≥6 years were defined as athletes. All underwent echocardiography and Holter monitoring. VAs were defined as aborted cardiac arrest, sustained or non-sustained ventricular tachycardia.

Results: In both Genotype + LVH − and HCM LVH +, lifetime vigorous exercise correlated with larger left ventricular end-diastolic volume (rho 0.44 and 0.38 respectively, both $p < 0.001$). Lifetime vigorous exercise correlated with increased left ventricular mass in Genotype + LVH − (rho 0.28, $p = 0.03$), but not in HCM LVH + ($p = 0.53$).

Left ventricular systolic function was similar between athletes and non-athletes in Genotype + LVH − and HCM LVH +. HCM LVH + athletes had lower E/e' ($p = 0.03$) and higher e' ($p = 0.02$) compared to non-athletes, while this difference was not observed in Genotype + LVH −. Lifetime vigorous exercise was similar among HCM LVH + with and without VAs ($p = 0.89$).

Conclusions: Increased lifetime vigorous exercise was associated with larger left ventricular volumes in hypertrophic cardiomyopathy, but correlated to left ventricular mass only in Genotype + LVH −. Vigorous exercise was associated with favorable diastolic function in HCM LVH +, and was not associated with VAs.

1. Introduction

Regular physical activity is the cornerstone of a healthy lifestyle, and is inversely related to cardiovascular disease, obesity and multiple lifestyle diseases [1]. Cardiac adaptations to regular vigorous exercise include increased left ventricular mass and volume [2], as a physiological response to altered left ventricular loading conditions and are together with resting bradycardia referred to as "athlete's heart" [3,4]. Hypertrophic cardiomyopathy (HCM) have genetic etiology in 60–70% of cases and is also characterized by increased left ventricular mass, but usually displays a normal or small left ventricular cavity [5]. HCM at early stages can be difficult to distinguish from physiologic left ventricular hypertrophy [6,7].

Patients with HCM are discouraged from participating in competitive sports [5], as the risk of ventricular arrhythmias (VAs) and sudden cardiac death may increase during exercise [8]. Current American and European guidelines restrict competitive sports in patients with phenotypic HCM (HCM LVH +), but diverge in the recommendations on exercise in HCM genotype positive, phenotype negative (Genotype + LVH −), reflecting the need for more knowledge on this topic. American guidelines do not advocate exercise restriction in Genotype + LVH − [9,10], while European guidelines recommend a slightly more cautious, individualized approach [5]. Furthermore, it remains unclear how exercise influences cardiac structure, disease penetrance and outcome in HCM LVH + and in Genotype + LVH −.

Considering the benefit from regular exercise and the importance of avoiding adverse effects of a sedentary lifestyle, exercise restriction

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should be given cautiously and based on solid knowledge. We aimed to explore the relationship between lifetime vigorous exercise and cardiac morphology and function in Genotype + LVH − and in HCM LVH +. Secondly we aimed to investigate the relation between vigorous exercise and occurrence of VAs in HCM patients.

2. Methods

2.1. Study participants

We consecutively recruited 144 unrelated HCM index patients, between 2001 and 2015 from the Unit for Genetic Cardiac Diseases, Department of Cardiology, Oslo University Hospital, Rikshospitalet, Norway. Patients with previous myectomy or alcohol septal ablation were excluded. We identified 130 genotype positive family members by cascade genetic screening and examined them at our center. Subjects fulfilling HCM diagnostic criteria were defined as HCM LVH + [5], while genotype positive family members with no significant left ventricular hypertrophy were defined as Genotype + LVH −. All 274 Genotype + LVH − and HCM LVH + were included in our prospective registry database. The study complied with the Declaration of Helsinki and the research protocol was approved by the Regional Committee for Medical Research Ethics. All study participants gave written informed consent.

2.2. Physical activity questionnaire

In May 2015, all registry participants were crosschecked with the Norwegian death registry and cause of death was collected from the registry or from medical records when available. All live registry participants were approached by letter and asked to complete a physical activity questionnaire. Non-responders were contacted by phone and offered to complete the physical activity questionnaire via a structured interview. The physical activity questionnaire included a detailed history of exercise from school age (6–7 years old) to present time, or to age 60 years. Exercise was reported as type of activity/sport, each graded at intensity level 1–3 (light, moderate, vigorous) and duration as hours per week, months per year and years.

Two investigators (L.A.D., M.R.) assessed the physical activity questionnaires. The intensity of the reported activities was quantified in metabolic equivalents (METs) [11], and rated according to Compendium of Physical Activities with corresponding updated online tools [12]. Exercise intensity ≥6 METs, the equivalent of jogging, was defined as vigorous. We summarized yearly vigorous exercise from age 7 years until study echocardiogram/inclusion in each participant and calculated lifetime vigorous exercise. To correct for possible lifestyle changes related to HCM disease, we also summarized vigorous exercise between age 7 and 20, since symptomatic HCM disease is rare before age 20.

Subjects with a history of vigorous exercise for ≥4 h/week (averaging yearly), during ≥6 years were defined as athletes [13]. Furthermore, we defined subjects who were currently participating in organized sports or competitions at study inclusion as competitive athletes, and performed separate subgroup analyses in this smaller population.

2.3. Echocardiography

Echocardiograms were obtained 3.4 ± 2.9 years prior to physical activity survey. Transthoracic echocardiography was performed using Vivid 7 or Vivid E9 (GE Healthcare, Horten, Norway) and data were analyzed off-line (EchoPac® version 112 GE Healthcare), by two independent observers blinded to all clinical information.

Maximal wall thickness was measured from all left ventricular segments from the base to the apex of the left ventricle in parasternal short-axis view [5]. Left ventricular end-diastolic diameter and left ventricular end-systolic diameter were measured by M-mode or two-dimensional imaging. Left ventricular end-diastolic volume, end-systolic volume, stroke volume and ejection fraction (EF) were calculated by modified Simpson's biplane method [14]. Diastolic left ventricular function was evaluated by transmitral pulsed wave Doppler and average e' tissue Doppler samplings [15]. Left ventricular mass was calculated using Cube formula and was indexed to body surface area [14]. Left atrial diameter was determined from parasternal long axis view [5] and left atrial area was planimetered from apical four-chamber view and indexed to body surface area [14]. Left ventricular outflow tract gradients were assessed at rest and with Valsalva maneuver in the supine position, and a pressure gradient of ≥50 mm Hg was defined as clinically significant obstruction. If the patient had symptoms and resting or provoked left ventricular outflow tract gradient was <50 mm Hg, we performed supine bicycle stress-echocardiography [5].

Mitral regurgitation was graded according to guidelines [5]. Left ventricular strain analyses were performed by 2D speckle tracking, traced from the three apical views at a frame rate of >50 frames/s. Peak negative longitudinal strain was assessed in 16 left ventricle segments and averaged to left ventricular global longitudinal strain [16].

2.4. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) was performed in a subset of patients on clinical indication within 1 year of the echocardiographic recording, using 1.5 T clinical scanner (Magnetom Sonata or Magnetom Avanto Siemens, Erlangen, Germany) as previously described [17,18].

2.5. Ventricular arrhythmias

Data on VAs were collected up to time of inclusion/echocardiogram from patients' medical records, including outpatient Holter registrations performed at least yearly or when indicated by clinical symptoms, telemetry observations during in-hospital stays and interrogations of implantable cardiac defibrillators. VAs were defined as previous aborted cardiac arrest or documented sustained or non-sustained ventricular tachycardia. Non-sustained ventricular tachycardia was defined as ≥3 consecutive ventricular beats <30 s with heart rate >100 beats per minute [19].

2.6. Genetic analyses

Genetic analyses were performed as part of the clinical evaluation as previously described [17]. (Table B.3 in [20]) Genetic screening was performed in family members of HCM LVH + patients with pathogenic mutations. Family members of patients with variants of uncertain significance were not included.

2.7. Statistics

Parametric data were presented as mean ± standard deviation and comparisons were performed using unpaired Student's *t*-test or by χ^2 or Fischer's exact test as appropriate. Exercise data were not normally distributed and were presented as median (range) and compared by Mann-Whitney U test. We used Spearman's bivariate correlation to explore the relation between exercise and cardiac parameters. Univariate logistic regression was used to identify markers of VAs and HCM phenotype and multivariate analyses included significant ($p < 0.05$) variables from the univariate analyses except when collinearity was observed (SPSS version 21.0, SPSS Inc., Chicago, IL, USA). Kaplan-Meier curves were created to analyze arrhythmia-free survival in HCM LVH + non-athletes and athletes. Two-sided *P*-values <0.05 were considered significant.

3. Results

3.1. Study participants

Of 274 Genotype + LVH − and HCM LVH + included in the registry, 260 were alive at study start May 2015 and eligible for study participation. Of the 14 deceased, 6 died of probable HCM related causes, however, none died during exercise (Fig. A in [20]). Of the 260 live individuals, 187 (72%) completed the physical activity questionnaire and were included in the study. Mean age was 49 ± 16 years, 121 (65%) were HCM LVH + and 89 (48%) were female. Median lifetime vigorous exercise was 1690 h (0–35,776 h) and 46 participants (25%) had no history of vigorous exercise. Seventy (37%) of the participants were actively engaging in vigorous exercise at study inclusion.

The Genotype + LVH − ($n = 66$) were younger than HCM LVH + ($n = 121$) ($p < 0.001$), had lower BMI ($p < 0.001$) and were more frequently female ($p = 0.001$) (Table 1). By definition, HCM LVH + patients had increased Maximal wall thickness. The HCM LVH + had enlarged left atrium and smaller indexed left ventricular volumes compared to Genotype + LVH − (all $p < 0.001$).

3.2. Physical exercise and echocardiographic results

Lifetime vigorous exercise was similar in Genotype + LVH − and HCM LVH + ($p = 0.65$). There was a tendency towards more vigorous exercise at young age in the Genotype + LVH − compared to the HCM LVH + ($p = 0.06$) (Table 1). In both Genotype + LVH − and in HCM LVH +, lifetime vigorous exercise correlated moderately with left ventricular end-diastolic volume (both $p < 0.001$) (Fig. 1). Lifetime vigorous exercise correlated with left ventricular mass in Genotype + LVH − ($p = 0.03$), but not in HCM LVH + ($p = 0.53$) (Fig. 1). Separate analyses of vigorous exercise age 7–20 years correlated with left ventricular end-diastolic volume in both Genotype + LVH − (rho 0.43, $p < 0.001$) and in HCM LVH + (rho 0.31, $p = 0.001$), but not with left ventricular mass (Genotype + LVH −: rho 0.22, $p = 0.09$, HCM LVH +: rho 0.005, $p = 0.96$).

Table 1
Clinical and echocardiographic characteristics of 187 study participants, grouped according to HCM phenotype.

	Genotype + LVH − (n = 66)	HCM LVH + (n = 121)	P
Age, years	38 ± 15	55 ± 14	<0.001
Athletes, n (%)	28 (42)	44 (36)	0.44
Atrial fibrillation, n (%)	0	19 (16)	<0.001
Body mass index, kg/m^2	24.0 ± 4.1	26.4 ± 4.1	<0.001
Family history of sudden cardiac death, n (%)	8 (12)	17 (14)	0.82
Female, n (%)	42 (64)	47 (39)	0.001
Hypertension, n (%)	3 (4.5)	12 (9.9)	0.27
Implantable cardiac defibrillator at study start, n (%)	0	16 (13)	0.002
Primary prevention, n (%)		13 (11)	
Secondary prevention, n (%)		3 (2)	
Lifetime vigorous exercise, h	1508 (0–10,384)	2002 (0–35,776)	0.65
Sarcomere protein mutation, n (%)	66 (100)	61 (50%)	<0.001
Unexplained syncope, n (%)	2 (3)	16 (13)	0.04
Ventricular arrhythmias, n (%)	0	28 (23)	<0.001
Cardiac arrest, n (%)		3 (11)	
Non-sustained ventricular tachycardia, n (%)		25 (89)	
Vigorous exercise age 7–20 years, h	1396 (0–8752)	728 (0–10,067)	0.06
Vigorous exercise at inclusion, n (%)	36 (55)	34 (28)	<0.001
Competitive athletes at inclusion, n (%)[#]	16 (24)	11 (9)	0.005
Echocardiography			
E/A ratio	1.6 ± 0.6	1.3 ± 0.6	0.003
Ejection fraction, %	60 ± 5.5	62 ± 6.9	0.17
Global longitudinal strain, %	−21.4 ± 2.2	−16.6 ± 3.5	<0.001
Interventricular septal diameter, mm	8.5 ± 1.6	16.6 ± 4.3	<0.001
Left atrium diameter, mm	34 ± 6	43 ± 8	<0.001
Left atrium area index, cm^2/m^2	8.8 ± 2.5	12.5 ± 3.3	<0.001
LV end-diastolic diameter, mm	49 ± 4	47 ± 6	0.04
LV end-diastolic diameter index, mm/m^2	27 ± 3	24 ± 4	<0.001
LV end-diastolic volume, cm^3	93 ± 30	83 ± 31	0.03
LV end-diastolic volume index, cm^3/m^2	50 ± 14	42 ± 13	<0.001
LV end-systolic diameter, mm	31 ± 4	29 ± 6	0.001
LV end-systolic diameter index, mm/m^2	17 ± 2	15 ± 3	<0.001
LV end-systolic volume, cm^3	37 ± 14	32 ± 14	0.01
LV end-systolic volume index, cm^3/m^2	20 ± 6	16 ± 7	<0.001
LV mass, g	134 ± 33	256 ± 92	<0.001
LV mass index, g/m^2	72 ± 15	132 ± 46	<0.001
LV posterior wall diameter	7.7 ± 1.3	10.2 ± 2.2	<0.001
Maximal wall thickness, mm	8.6 ± 1.2	18.8 ± 4.1	<0.001
Maximal wall thickness ≥30 mm, n (%)	0	3 (3)	<0.001
Mitral regurgitation, n (%)	15 (23)	79 (65)	<0.001
Mild regurgitation, n (%)	15 (100)	49 (62)	0.01
Moderate regurgitation, n (%)	0	26 (33)	<0.001
Severe regurgitation, n (%)	0	4 (5)	0.30
Stroke volume, cm^3	56 ± 18	51 ± 19	0.10
Stroke volume index, cm^3/m^2	30 ± 9	26 ± 9	0.003

Values are mean ± SD or n (%) or median (range). *P*-values are calculated by unpaired student *t*-test, χ^2 or Mann-Whitney *U* test when appropriate.
Genotype + LVH − = hypertrophic cardiomyopathy genotype positive, phenotype negative; HCM LVH + = phenotype positive hypertrophic cardiomyopathy patient; LV = left ventricle.
[#] Competitive athletes are a subset of individuals vigorously exercising at study inclusion. Competitive athletes are engaged in competitions or organized sports.

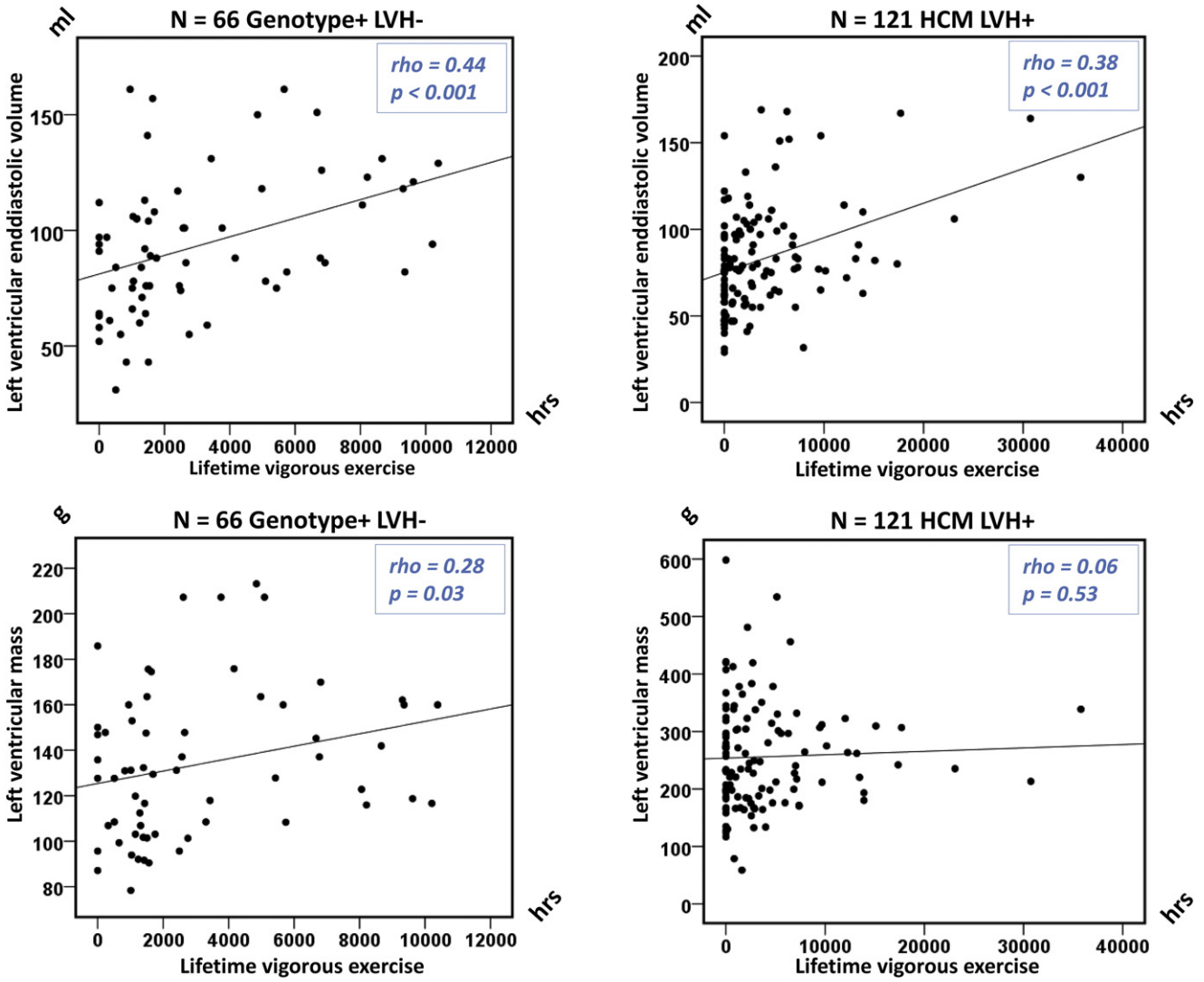

Fig. 1. Correlation plots of lifetime vigorous exercise and echocardiographic parameters in 121 hypertrophic cardiomyopathy phenotype positive (HCM LVH+) and 66 hypertrophic cardiomyopathy genotype positive, phenotype negative (Genotype+ LVH−). There was a moderate, significant positive correlation between left ventricular volume and lifetime vigorous exercise in both HCM LVH+ and Genotype+ LVH−. In Genotype+ LVH− there was a correlation between left ventricular mass and lifetime vigorous exercise, while no correlation was found in HCM LVH+.

Seventy-two (39%) fulfilled our athlete definition with a similar proportion of athletes among Genotype+ LVH− and HCM LVH+ (28/66 (42%), vs. 44/121 (36%) $p = 0.44$) (Table 1). Cycling and running were the most common types of sports conducted (Table B.5 in [20]).

Among HCM LVH+, athletes had better NYHA functional class ($p = 0.03$) and were more frequently male compared to HCM LVH+ non-athletes ($p < 0.001$). Medication, comorbidities and left ventricular outflow tract obstruction did not differ between HCM LVH+ athletes and non-athletes (Table 2).

Both Genotype+ LVH− and HCM LVH+ athletes had larger left ventricular end-diastolic volume and left ventricular end-systolic volume compared to non-athletes (all $p < 0.01$). Genotype+ LVH− athletes had increased left ventricular mass ($p = 0.003$) compared to non-athletes. In contrast, HCM LVH+ athletes had similar left ventricular mass compared to HCM LVH+ non-athletes ($p = 0.38$) (Table 2). Maximal wall thickness and left atrial area index did not differ between athletes and non-athletes in Genotype+ LVH− or in HCM LVH+. Status as an athlete was not a marker of HCM LVH+ in univariate analysis or when adjusted for age, body mass index and gender in multivariate logistic regression (Table B.1 in [20]).

Left ventricular systolic function determined by EF and global longitudinal strain did not differ between athletes and non-athletes in neither Genotype+ LVH− nor in HCM LVH+ (Table 2). HCM LVH+ athletes had lower E/e' ratio ($p = 0.03$) and higher e' ($p = 0.02$) compared to non-athletes, while this difference was not observed in Genotype+ LVH−.

Parameters of left ventricular hypertrophy and function did not differ between tertiles of exercise in HCM LVH+. Comparisons between the sedate and the most active tertile showed similar maximal wall thickness (19.3 ± 4.2 mm vs. 18.6 ± 3.6 mm, $p = 0.47$), left ventricular mass (259 ± 100 g vs. 257 ± 66 g, $p = 0.92$), global longitudinal strain (−16.3 ± 3.9% vs. −17.0 ± 2.9%, $p = 0.43$), age (57 ± 14 years vs. 52 ± 12 years, $p = 0.14$) and body mass index (27.1 ± 4.5 kg/m^2 vs. 26.2 ± 3.9 kg/m^2, $p = 0.42$).

Subjects with ongoing competitive level exercise at inclusion, defined as competitive athletes ($n = 25$), were more frequently Genotype+ LVH− than HCM LVH+ (Table 1). Subgroup analyses of competitive athletes demonstrated mainly similar results as the primary athlete analyses, with the exception that HCM LVH+ competitive athletes had thinner MWT compared to HCM LVH+ not meeting competitive athlete criteria (Table B.4 in [20]).

Table 2
Clinical and cardiac imaging characteristics of 187 study participants, grouped according to phenotype and exercise status.

	Genotype + LVH − ($n = 66$)			HCM LVH + ($n = 121$)		
	Non-athlete ($n = 38$)	Athlete ($n = 28$)	P	Non-athlete ($n = 77$)	Athlete ($n = 44$)	P
Age, years	39 ± 16	36 ± 15	0.42	57 ± 13	51 ± 14	0.01
Atrial fibrillation, n (%)	0	0		11 (14)	8 (18)	0.57
Betablocker therapy, n (%)	6 (16)	2 (7)	0.45	64 (83)	32 (73)	0.24
Body mass index, kg/m^2	24.7 ± 4.7	23.1 ± 3.1	0.12	26.2 ± 4.3	26.6 ± 3.9	0.62
Female, n (%)	28 (74)	14 (50)	0.13	41 (53)	6 (14)	<0.001
Heart rate, bpm	69 ± 13	67 ± 13	0.65	63 ± 12	63 ± 12	0.96
Hypertension, n (%)	2 (5)	1 (4)	0.99	10 (13)	2 (5)	0.21
Implantable cardiac defibrillator, n (%)	0	0		8 (10)	8 (18)	0.27
Primary prevention, n (%)				6 (8)	7 (16)	0.17
Secondary prevention, n (%)				2 (3)	1 (2)	0.99
Lifetime vigorous exercise, h	888 (0–3307)	5083 (1399–10,384)	<0.001	156 (0–9464)	6672 (1456–35,776)	<0.001
New York Heart Association class				2.0 ± 0.9	1.6 ± 1.0	0.03
Sarcomere protein mutation, n (%)	38 (100)	28 (100)		35 (46)	26 (59)	0.15
Ventricular arrhythmias, n (%)	0	0		17 (22)	11 (25)	0.82
Cardiac arrest, n (%)				2 (12)	1 (9)	0.99
NSVT, n (%)				15 (88)	10 (91)	0.82
Vigorous exercise age 7–20 years, h	492 (0–2501)	2686 (1399–8752)	<0.001	0 (0–2366)	2902 (0–10,067)	<0.001
Vigorous exercise at inclusion, n (%)	16 (42)	20 (56)	0.02	13 (17)	21 (48)	<0.001
Echocardiography						
E/A	1.5 ± 0.6	1.7 ± 0.6	0.28	1.3 ± 0.7	1.3 ± 0.7	0.9
e', cm/s	11 ± 3	12 ± 3	0.38	5.7 ± 2.6	7.1 ± 2.7	0.02
E/e'	7.1 ± 2.2	6.6 ± 1.9	0.36	16.0 ± 9.3	12.1 ± 5.9	0.03
Ejection fraction, %	61 ± 6	59 ± 4	0.14	62 ± 7	61 ± 6	0.40
Global longitudinal strain, %	−21.6 ± 2.4	−21.1 ± 2.0	0.37	−16.4 ± 3.7	−16.9 ± 3.3	0.46
Interventricular septal diameter, mm	8.1 ± 0.1	9.0 ± 0.2	0.03	17.0 ± 0.4	16.0 ± 0.4	0.18
Left atrium diameter, mm	34 ± 7	34 ± 4	0.71	43 ± 8	42 ± 9	0.36
Left atrium area index, cm^2/m^2	8.3 ± 2.9	9.5 ± 2.0	0.09	12.9 ± 3.5	11.8 ± 2.9	0.09
LV end-diastolic diameter, mm	48 ± 4	50 ± 4	0.09	47 ± 6	48 ± 6	0.34
LV end-diastolic diameter index, mm/m^2	26 ± 3	27 ± 2	0.23	25 ± 4	24 ± 3	0.32
LV end-diastolic volume, cm^3	84 ± 29	106 ± 26	0.002	76 ± 27	96 ± 33	<0.001
LV end-diastolic volume index, cm^3/m^2	50 ± 13	57 ± 12	<0.001	39 ± 12	47 ± 14	0.001
LV end-systolic diameter, mm	30 ± 5	33 ± 4	0.05	28 ± 6	29 ± 5	0.56
LV end-systolic diameter index, mm/m^2	17 ± 3	18 ± 2	0.13	15 ± 4	14 ± 2	0.39
LV end-systolic volume, cm^3	33 ± 12	44 ± 14	0.001	29 ± 13	37 ± 15	0.001
LV end-systolic volume index, cm^3/m^2	18 ± 5	23 ± 7	<0.001	15 ± 6	19 ± 7	0.001
LV mass, g	123 ± 28	147 ± 34	0.003	262 ± 99	246 ± 77	0.38
LV mass index, g/m^2	67 ± 12	79 ± 16	0.001	138 ± 49	122 ± 37	0.07
LV posterior wall diameter, mm	7.4 ± 0.1	8.0 ± 0.1	0.08	10.3 ± 0.3	10.1 ± 0.2	0.70
LVOT max gradient, rest/Valsalva, mm Hg				16 (2−130)	8 (2−110)	0.07
LVOT max gradient, stress-echo, mmHg[§]				51 (4–170)	65 (13–115)	0.88
LVOT max gradient ≥50 mm Hg, n (%)				30 (39)	15 (34)	0.59
Maximal wall thickness, mm	8.5 ± 1.3	8.6 ± 1.2	0.65	19 ± 4	19 ± 4	0.81
Mitral regurgitation, n (%)	11 (29)	4 (14)	0.16	50 (65)	29 (66)	0.91
Mild regurgitation, n (%)	11 (100)	4 (100)	0.16	30 (60)	19 (66)	0.65
Moderate regurgitation, n (%)	0	0		17 (34)	9 (31)	0.83
Severe regurgitation, n (%)	0	0		3 (6)	1 (3)	0.99
Stroke volume, cm^3	51 ± 19	62 ± 15	0.01	47 ± 17	58 ± 21	0.001
Stroke volume index, cm^3/m^2	27 ± 9	33 ± 7	0.007	24 ± 8	29 ± 9	0.009
Cardiac magnetic resonance, n (%)	0	0		$n = 50$ (65)	$n = 26$ (59)	0.49
Ejection fraction, %				70 ± 9	68 ± 9	0.39
LGE, n (%)[#]				26 (53)	19 (73)	0.09
LGE, % of LV mass[#]				0 (0−23)	0 (0–17)	0.64
LV mass, g				221 ± 92	233 ± 90	0.66
LV mass index, g/m^2				115 ± 46	117 ± 44	0.91
Maximal wall thickness, mm				22 ± 5	23 ± 8	0.35

Values are mean ± SD or n (%) or median (range). *P*-values are calculated by unpaired student *t*-test, χ^2 or Mann-Whitney U test when appropriate. Genotype + LVH − = hypertrophic cardiomyopathy genotype positive, phenotype negative; HCM LVH + = hypertrophic cardiomyopathy phenotype positive; LGE = late gadolinium enhancement; LV = left ventricle; LVOT = left ventricular outlet tract; NSVT = non-sustained ventricular tachycardia.

[§] $n = 36$.

[#] $n = 74$.

3.3. Ventricular arrhythmias in HCM LVH + patients and relation to lifetime exercise

VAs occurred in 28 (23%) of the 121 HCM LVH + patients (Table 1). Patients with VAs had greater maximal wall thickness (21 ± 4 mm vs. 18 ± 4 mm, $p < 0.01$), worse global longitudinal strain (−14.9 ± 3.1% vs. −17.1 ± 3.5%, $p < 0.01$) and slightly lower EF (59 ± 6% vs. 63 ± 7%, $p = 0.03$) compared to patients without VAs. There were no differences in lifetime vigorous exercise between subjects with and without VAs (2088 (0–17,701) h vs. 1820 (0–35,776) h, $p = 0.89$) and proportion of athletes was similar ($p = 0.82$)(Table 2). Kaplan Meier analysis showed no difference in age at first arrhythmic event between HCM LVH + athletes and non-athletes (log rank $p = 0.36$) (Fig. 2). Being an athlete was not a marker of VAs in HCM LVH + patients in univariate analysis, or when adjusted for global longitudinal strain and maximal wall thickness in multivariate analysis (Table B.2 in [20]).

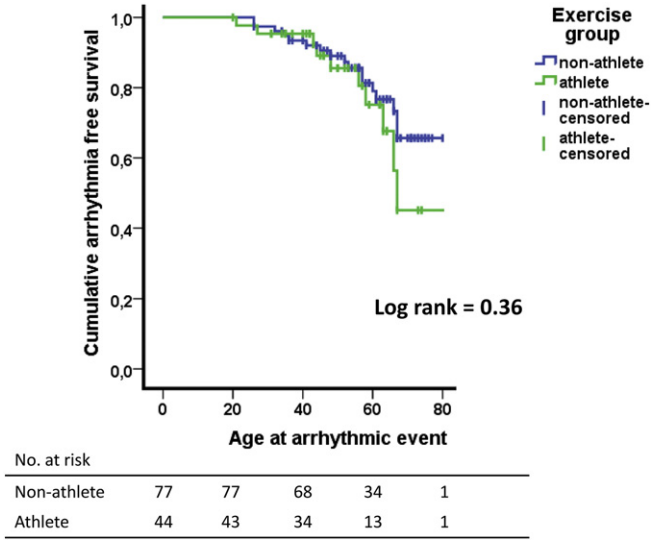

Fig. 2. Kaplan Meier analyses of age at arrhythmic event in 121 patients with phenotype positive hypertrophic cardiomyopathy (HCM LVH+). Event rate and age at arrhythmic event were similar in non-athletes and athletes.

3.4. Cardiac magnetic resonance and relation to exercise in HCM LVH +

We performed CMR in 76 (63%) HCM LVH + patients. Seventy-four patients received gadolinium contrast agents and 2 completed CMR without LGE due to renal failure. HCM LVH + athletes and non-athletes had similar, mass, maximal wall thickness, EF and prevalence and extent of LGE (Table 2). LGE did not correlate to lifetime vigorous exercise (rho −0.06, $p = 0.65$).

4. Discussion

Our study demonstrated that lifetime vigorous exercise correlated to increased left ventricular mass within physiologic levels, but was not associated with pathologic left ventricular hypertrophy in HCM subjects. Furthermore, lifetime vigorous exercise was related to larger cardiac volumes in HCM, a disease normally characterized by small cavity sizes. Lifetime vigorous exercise did not seem to relate to VAs or with age at first arrhythmic event.

4.1. Effect of vigorous exercise on myocardial structure and function

Vigorous exercise can induce cardiac remodeling in the healthy heart, including increased cardiac mass and dilatation of cardiac chambers. The magnitude of exercise induced changes will depend on exercise duration, intensity and type of activity. Cardiac hypertrophy among HCM mutation carriers is highly variable [21], and the effects of exercise on left ventricular hypertrophy or disease penetrance in HCM subjects is not known. Our study showed no difference in lifetime vigorous exercise between Genotype + LVH − and HCM LVH +, possibly indicating that exercise was not a determinant of pathological left ventricular hypertrophy.

Vigorous exercise was associated with increased left ventricular mass, although still within normal range and only in Genotype + LVH −, demonstrating expected physiologic exercise induced changes in line with what we expect from healthy athletes [22]. In contrast, athletic level exercise was not associated with left ventricular hypertrophy in HCM LVH +, indicating that active HCM disease overshadows the influence of exercise on left ventricular hypertrophy.

We defined athlete as ≥6 METs for more than 4 h a week for minimum 6 years. Exercise at this level does not necessarily induce "athlete's heart". However, this cut off is far higher than minimum recommended physical activity for healthy individuals.

Left ventricular systolic function determined by global longitudinal strain or EF was similar in athletes and non-athletes in both Genotype + LVH − and HCM LVH +, while left ventricular diastolic function was better in HCM LVH + athletes compared to non-athletes. More lifetime vigorous exercise was associated with greater left ventricular and stroke volumes in all participants. It is possible that exercise might counteract left ventricular remodeling and the typical feature of smaller cardiac volumes in HCM patients.

A subset of HCM LVH + patients underwent CMR with LGE, in which we found no correlation between myocardial fibrosis and lifetime vigorous exercise. However only a subset of patients completed CMR, and the results may have been influenced by selection bias.

4.2. Impact of vigorous exercise on arrhythmic events

Previous studies have debated whether or not competitive exercise increases risk of VAs in HCM [23–26]. The effect of accumulated vigorous exercise on VAs has not been investigated previously. In our study, HCM LVH + with VAs had nearly identical history of exercise as the arrhythmia free patients. Age at first VAs was not influenced by athlete status. While we did not explore the effect of acute exercise, our results indicated no adverse effect of lifetime exercise on prevalence or timing of VAs.

Our results were in line with a recent prospective study which found no defibrillator shocks, sustained VAs or sudden cardiac deaths in an exercise intervention group of HCM LVH + patients [27]. However, the recent study and our negative results regarding VAs must be interpreted with caution due to low frequency of arrhythmic events. Future larger studies should further investigate this relationship.

4.3. Clinical implications

HCM LVH + patients are recommended to avoid competitive sports due to the increased risk of ventricular arrhythmias [5,9]. Guidelines are, however, ambiguous regarding Genotype + LVH − family members. Our study indicated no harmful long-term effects of vigorous exercise on left ventricular structure or function, neither in HCM LVH + nor in Genotype + LVH −. We therefore question the assertion that vigorous exercise in patients with HCM is necessarily harmful and believe that current recommendations on physical activity may be too restrictive.

Previous reports have indicated adverse clinical outcome and left ventricular remodeling in overweight HCM patients [28]. Our study underlines the importance of motivating a healthy and active life style in HCM to prevent weight gain and adverse left ventricular remodeling.

4.4. Limitations

Our study was cross sectional and arrhythmic events were collected retrospectively with the inherent limitations of this design. Our study could not evaluate if patients were influenced by their HCM disease in exercise level. Patients who did not engage in vigorous physical activity may have had more initial symptoms or were considered to have more serious HCM than the athletic HCM patients, or they may have been influenced by other factors influencing physical activity.

Although exercise questionnaire response rate was high (72%), there is a potential for sampling bias and recall bias. The number of patients with VAs was limited and sample size not adequate for drawing conclusions on this endpoint. Results on VAs are hypothesis generating and should be confirmed in larger studies. We do not know the exercise history in the 6 patients that died from HCM related disease in our cohort during 2001–2015 and who were not included in the study, though none of these deaths occurred during exercise.

Fifty-seven (45%) out of 127 genotype positive participants were heterozygous for the three most frequent mutations in Norway, which could reduce the generalizability of our results. (Table B.3 in [20]).

5. Conclusions

Lifetime vigorous exercise was related to increased left ventricular volumes, but was not related to left ventricular hypertrophy above physiologic values in HCM. Vigorous exercise was associated with favorable diastolic function in HCM LVH+. Lifetime exercise was not associated with occurrence of VAs or with age at first VAs, but further studies are needed to confirm these findings.

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Conflicts of interest

None declared.

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