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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.