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FULL RESEARCH PAPER
Exercise training

Distinguishing left ventricular hypertrophy from hypertrophic cardiomyopathy in adolescents: a longitudinal observation study

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Aims

Echocardiographic characteristics to distinguish physiological left ventricular (LV) hypertrophy from pathology are warranted in early adolescent athletes. This study aimed to explore the phenotype, progression, and potential grey zone of LV hypertrophy during adolescence in athletes and hypertrophic cardiomyopathy (HCM) genotype–positive patients.

Methods and results

In this longitudinal observation study, we compared seventy-six 12-year-old athletes with 55 age-matched and sex-matched HCM genotype–positive patients. Echocardiographic parameters were evaluated by using paediatric reference values (*Z*-scores). Hypertrophic cardiomyopathy genotype–positive patients were included if they had no or mild LV hypertrophy [maximum wall thickness <13 mm, *Z*-score <6 for interventricular septum diameter (ZIVSd), or posterior wall thickness]. We collected clinical data, including data on cardiac events. The mean follow-up-time was 3.2 ± 0.8 years. At baseline, LV hypertrophy was found in 28% of athletes and 21% of HCM genotype–positive patients ($P = 0.42$). Septum thickness values were similar (ZIVSd 1.4 ± 0.9 vs. 1.0 ± 1.3, $P = 0.08$) and increased only in HCM genotype–positive patients {ZIVSd progression rate −0.17 [standard error (SE) 0.05], $P = 0.002$ vs. 0.30 [SE 0.10], $P = 0.001$}. Left ventricular volume Z-scores (ZLVEDV) were greater in athletes [ZLVEDV 1.0 ± 0.6 vs. −0.1 ± 0.8, $P < 0.001$; ZLVEDV progression rate −0.05 (SE 0.04), $P = 0.21$ vs. −0.06 (SE 0.04), $P = 0.12$]. Cardiac arrest occurred in two HCM genotype–positive patients (ages 13 and 14), with ZIVSd 8.2–11.5.

Conclusion

Left ventricular hypertrophy was found in a similar proportion in early adolescence but progressed only in HCM genotype–positive patients. A potential grey zone of LV hypertrophy ranged from a septum thickness Z-score of 2.0 to 3.3. Left ventricular volumes remained larger in athletes. Evaluating the progression of wall thickness and volume may help clinicians distinguish physiological LV hypertrophy from early HCM.

Lay summary

It is important to distinguish exercise-induced cardiac left ventricular (LV) hypertrophy from hypertrophic cardiomyopathy (HCM), because athletes with HCM may have an increased risk of sudden cardiac death. Limited data are available on this distinction in adolescent athletes. Therefore, we performed a longitudinal observation study comparing the development of LV hypertrophy during adolescence in athletes and HCM genotype–positive patients.

- In early adolescence, LV hypertrophy was found in a similar proportion of athletes and HCM genotype–positive patients, with a potential grey zone ranging from a septum thickness *Z*-score of 2.0 to 3.3. After 3 years of follow-up, LV hypertrophy had progressed only in HCM genotype–positive patients, while athletes had larger LV volumes throughout the study period.
- Evaluation of LV volume and septum thickness progression may assist clinicians in distinguishing exercise-induced LV hypertrophy from early HCM disease in adolescents.

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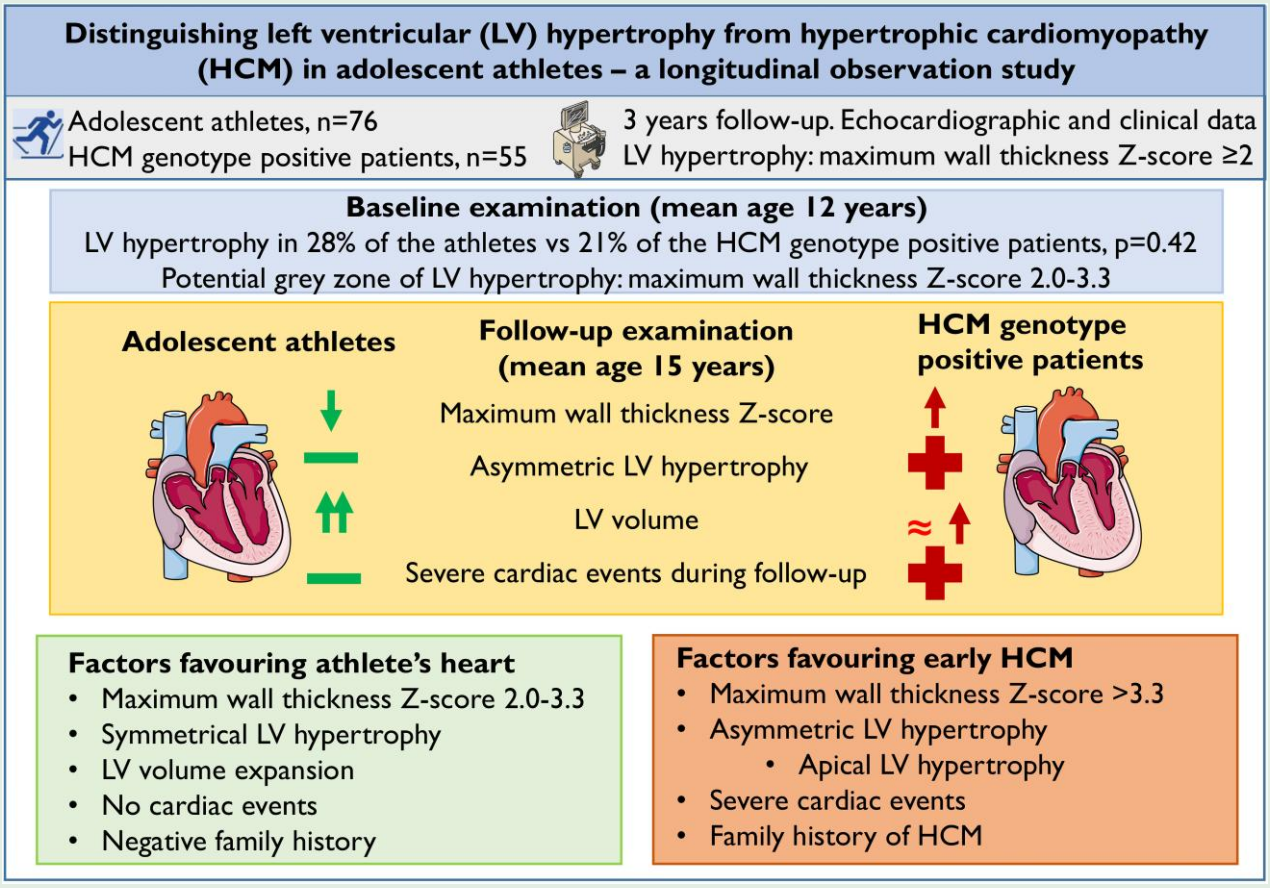
Graphical Abstract



Keywords Athlete • Exercise • Adolescent • Left ventricular hypertrophy • Cardiac remodelling • Hypertrophic cardiomyopathy • Echocardiography

Introduction

Distinguishing physiological left ventricular (LV) hypertrophy from hypertrophic cardiomyopathy (HCM) can be challenging in adolescent athletes. Previous studies, including reports from our group, describe physiological LV remodelling in early adolescent athletes.[1–4] Some of them have a wall thickness above paediatric reference values.[2,4–6] Guidelines feature typical characteristics to distinguish physiological LV hypertrophy from HCM in adult athletes, but these are not validated for adolescent athletes.[7–10]

Accurate identification of HCM in athletes has significant clinical implications. Hypertrophic cardiomyopathy is a leading cause of sudden cardiac death (SCD) in adolescent athletes and can represent the basis for disqualification from competitive or professional sports.[7,8,11] Children and adolescents with HCM have an increased risk for ventricular arrhythmias, heart failure, and SCD, but the clinical course is heterogeneous and unpredictable.[12–14]

Recent American guidelines recommend family screening for HCM at the time when HCM is diagnosed in another family member, while current European guidelines suggest screening from age 10.[15,16] However, European guidelines advocate that screening at a younger age should be considered in families with early-onset disease or if a child is engaged in a particularly demanding physical activity.[7] However, differentiating between physiological and pathological LV hypertrophy is challenging. There is an ongoing discussion regarding the current paediatric maximum wall thickness (MWT) threshold, which is low compared with the threshold in adults.[15,17] This may lead to overdiagnosis in adolescents. Distinguishing physiological LV hypertrophy from HCM is important for diagnosis, risk prediction, exercise recommendations, and evaluation of treatment indications.

In this study, we aimed to compare the phenotype and progression of LV hypertrophy in athletes during adolescence with that in HCM genotype–positive patients, including the incidence of cardiac events. We further aimed to explore a potential grey zone of LV hypertrophy and describe the echocardiographic features that may help distinguish physiological LV hypertrophy from HCM in adolescents.

Methods

We performed a longitudinal observation study comparing early adolescent athletes with age-matched and sex-matched HCM genotype–positive patients. Clinical and echocardiographic data were collected at baseline and after a minimum of 2 years of follow-up. Electrocardiographic (ECG) data were collected in HCM genotype–positive patients. In order to distinguish the progression of physiological LV hypertrophy from HCM, HCM genotype–positive patients were included only if they had no or mild LV hypertrophy at baseline. We defined this as an MWT *Z*-score <6 and absolute MWT <13 mm, in accordance with current guidelines.[15]

The study evaluated the following three outcomes:

(1) Presence and progression of LV hypertrophy, defined as an MWT *Z*-score ≥2.
(2) Grey zone of LV hypertrophy, defined as an MWT *Z*-score 2–6.
(3) Severe cardiac events, defined as severe ventricular arrhythmias, cardiac syncope, cardiac death, or heart transplantation. Severe ventricular arrhythmias were defined as aborted cardiac arrest, sustained ventricular tachycardia, or ventricular fibrillation, documented on 12-lead ECG, Holter, or terminated by appropriate implantable cardioverter defibrillation therapy.

Written informed consent was provided by the legal guardian of the study participants or by the study participant if their age was >16 years. The study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics (ref. 2011/659 S-08702d, 2014/462).

Adolescent athletes

We included healthy adolescent athletes from a previous longitudinal cohort study.[3] They were recruited from regional cross-country skiing clubs in 2013 and defined as athletes due to their participation in regular, organized training and competitions.[8] The athletes were evaluated with echocardiography at baseline, age 12, and after 3 years of follow-up, at age 15. Information on physical activity and participation in organized training (hours/week) and data on prior illness and family history of cardiac disease were gathered by using questionnaires and interviews. In 12-year-old athletes, endurance and non-endurance exercise was grouped as one unit due to the playful nature of their exercise regime. A detailed description of the study cohort has been reported previously.[18] The athletes underwent a final examination at age 18, which was excluded from the present study due to limited normative data for this age group in paediatric reference databases.[6,19]

Hypertrophic cardiomyopathy genotype–positive patients

We evaluated study eligibility in HCM genotype–positive patients, both probands and relatives referred for family screening, followed up at our national referral centre (Oslo University Hospital, Rikshospitalet) between March 2008 and August 2022. We included patients with baseline echocardiography performed at age 10–15 years, with an MWT <13 mm and *Z*-score <6. Clinical data were collected until the last examination before age 18. Subsequent follow-ups of echocardiographic examinations were included if they were performed at a minimum of 2 years after baseline, before 18 years of age. Patients were excluded if image quality was insufficient for the evaluation of LV wall thickness or if cardiac evaluation resulted in other diagnoses, e.g. dilated cardiomyopathy. Examinations performed in relation to an arrhythmic event were analysed in order to describe the phenotype at the time of the event but were not included in the statistical analysis.

Genetic analysis in hypertrophic cardiomyopathy genotype–positive patients

During the period between 2008 and 2018, we used Sanger-based panels. From 2018, we used larger next-generation sequencing–based gene panels for genetic testing.[20] All identified variants were manually curated according to the American College of Medical Genetics 2015 guidelines.[21] Only variants classified as pathogenic/likely pathogenic were included.

Echocardiography

All participants underwent an echocardiographic examination at the time of inclusion (Vivid 7, E9 or E95, GE Vingmed, Horten, Norway). Images were obtained from parasternal long-axis, short-axis, apical four-chamber, three-chamber, two-chamber, and subcostal views in accordance with recommendations from the European Association of Cardiovascular Imaging.[22] Left ventricular ejection fraction was calculated by the biplane Simpson's method. Relative wall thickness (RWT) was defined as (2 × posterior wall thickness)/[LV internal diameter at end-diastole (LVIDd)]. We used paediatric reference values to calculate *Z*-scores in accordance with recommendations.[4,6] The *Z*-score reported the number of standard deviations (SDs) a measurement is above or below the population mean for a given body surface area (BSA). The *Z*-score was considered normal between −2 and 2. We calculated *Z*-scores for interventricular septum diameter (IVSd), LV posterior wall thickness (LVPWd), LVIDd, LV end-diastolic volume, and left atrial diameter. Left ventricular hypertrophy was defined as an MWT (highest value of IVSd or LVPWd) *Z*-score ≥2.[15] Wall thickness distribution (at mitral, mid-LV, and apical levels) and symmetry were evaluated in accordance with ESC guidelines, where asymmetric interventricular hypertrophy was defined as a septal to posterior wall thickness ≥1.5.[7] A.W.B. analysed all examinations performed in the athletes. M.I.F. analysed all examinations conducted in the HCM genotype–positive patients. A.W.B. and M.I.F. were blinded for clinical outcomes at the time of echocardiographic analysis. Intra-observer and inter-observer analyses have been published in a previous study.[2]

Electrocardiography

Resting ECG data were collected at baseline, at follow-up, and, if relevant, at the last examination before an arrhythmic event, in HCM genotype–positive patients. We evaluated ECG parameters by age-specific normal values.[23] The following were noted: signs of left ventricular hypertrophy (LVH) as defined by Sokolow–Lyon criteria (SV1 or SV2 + RV5 or RV6 ≥ 35 mm), pathological T-wave inversions (TWIs; >1 mm beyond V1 in patients ≥14 years or beyond V3 in patients <14 years), giant negative T waves (≥10 mm), giant positive T waves (≥10 mm), ST depression (≥2 mm), ST-elevation (≥2 mm in V1–V3 and ≥ 1 mm in other leads), depolarization abnormalities (epsilon waves), and left or right bundle branch block.[24]

Statistical analysis

Statistical analyses were performed using STATA SE 15.1 (StataCorp LLC, College Station, TX, USA). Values were presented as mean with SD or standard error (SE), or frequencies with percentages as appropriate.

Between-group differences at baseline were assessed by using Student's *t*-test. Progression analyses for repeated echocardiographic measurements were performed by using a linear mixed model analysis with random slope and random individual intercept.

Results

Baseline characteristics

Seventy-six athletes (37% female) were included, with baseline echocardiography performed at age 12 (*Table 1*). They had been engaged in organized sports for 5.4 ± 1.2 years at inclusion. The athletes reported a mean of 7.0 ± 2.3 weekly hours of organized exercise at age 12. Athletes had a lower BSA at baseline examination.

Of 120 patients evaluated, 55 (44% female) HCM genotype–positive patients fulfilled the inclusion criteria. All 55 were relatives referred for family screening. No probands fulfilled the inclusion criteria. Thirty-four of fifty-five (62%) patients had a variant in the *myosin-binding protein C* (*MYBPC3*) gene, 17 (31%) in the *myosin heavy chain* (*MYH7*) gene, and 4 (7%) in the *fast skeletal muscle troponin-T3* (*TNNT3*) gene.

At baseline, LV hypertrophy (MWT *Z*-score ≥2) was observed in a similar proportion of athletes and HCM genotype–positive patients (28 vs. 21%, $P = 0.42$), most frequently located in the interventricular septum (*Figure 1*). There was no difference in septum thickness values at baseline (*Table 1*). Athletes had larger LVPWd (*Z*-score) and LV volumes. Relative wall thickness values were similar (*Table 1*). Asymmetric LV hypertrophy was found in two HCM genotype–positive patients at baseline. The maximum wall thickness was 10–11 mm, septally and/or apically located (corresponding to an *Z*-score of 2.8–3.7). Left ventricular systolic and diastolic functions were normal in both athletes and HCM genotype–positive patients (*Table 1*).

Electrocardiographic data were available for 47/55 HCM genotype–positive patients. Baseline ECG was normal in 28/43 (65%) HCM genotype-positive and phenotype-negative patients. Positive Sokolow–

Table 1 Baseline clinical and echocardiographic data in 76 athletes compared with 55 hypertrophic cardiomyopathy genotype–positive patients

	Athletes, *N* = 76	HCM, *N* = 55	*P*-value
Baseline characteristics			
Female, *n* (%)	28 (37%)	25 (46%)	0.33
Age, years	12.1 ± 0.2	12.4 ± 1.3	0.08
Height, cm	152 ± 7	158 ± 10	**<0.001**
Weight, kg	40.7 ± 5.6	48.7 ± 12.2	**<0.001**
BSA, m^2	1.32 ± 0.12	1.48 ± 0.21	**<0.001**
LV hypertrophy, baseline	21 (28%)	12 (21%)	0.42
Follow-up data	47 (62%)	31 (56%)	0.69
Follow-up time	3.1 ± 0.2	3.2 ± 1.2	0.70
Echocardiography, absolute measures			
IVSd, mm	7.8 ± 0.9	7.8 ± 1.5	0.96
LVIDd, mm	41.2 ± 3.2	42.6 ± 4.5	**0.04**
LVPWd, mm	7.2 ± 0.9	7.1 ± 1.3	0.57
Wall thickness ratio (IVSd/LVPWd)	1.1 ± 0.1	1.1 ± 0.2	0.33
RWT	0.35 ± 0.05	0.34 ± 0.07	0.13
LV EDV, mL	105 ± 14	101 ± 27	0.27
LV ESV, mL	44 ± 7	43 ± 14	0.48
LV mass, g	91 ± 16	97 ± 32	0.14
LA volume, mL	36.1 ± 8.2	31.9 ± 12.4	**0.02**
LA diameter, mm	2.8 ± 0.3	2.9 ± 0.4	0.60
Z-scores			
IVSd	1.4 ± 0.9	1.0 ± 1.3	0.08
LVIDd	−0.6 ± 0.9	−0.9 ± 0.9	0.09
LVPWd	0.8 ± 0.8	0.4 ± 1.2	**0.02**
LV EDV	1.0 ± 0.6	−0.1 ± 0.8	**<0.001**
LV mass	1.3 ± 1.3	0.8 ± 1.7	0.054
LA diameter	0.4 ± 0.7	0.1 ± 1.0	0.05
Systolic and diastolic function			
LV EF	58 ± 3	58 ± 6	0.78
E	0.96 ± 0.12 (*N* = 75)	0.89 ± 0.19 (*N* = 46)	**0.02**
A	0.47 ± 0.11	0.43 ± 0.12	0.13
E/A	2.14 ± 0.45	2.15 ± 0.48	0.91
DCT	123 ± 24	167 ± 34	**<0.001**
e′ septal	0.12 ± 0.02 (*N* = 74)	0.16 ± 0.03 (*N* = 9)	**<0.001**
e′ lateral	0.17 ± 0.03 (*N* = 74)	0.18 ± 0.04 (*N* = 8)	0.37
E/e′	7.0 ± 1.2	5.5 ± 0.6 (*N* = 7)	**0.001**

Values are mean ± SD. *P*-values are calculated by using Student's *t*-test. Significant *P*-values (<0.05) are highlighted in bold.
BSA, body surface area; LV, left ventricle; IVSd, interventricular septum diameter; LVIDd, left ventricular internal diameter at end-diastole; LVPWd, left ventricular posterior wall thickness; RWT, relative wall thickness; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrium; EF, ejection fraction; DCT, deceleration time.

Lyon criteria were the only pathological finding, detected in 9/43 (21%) patients. The ECGs were not stored for later interpretation in six patients, but were described as normal by paediatric cardiologists in the hospital journal.

At baseline, ECG was pathological in 8/12 (66%) HCM genotype–positive patients with grey zone LVH (phenotype positive). The most common finding was positive Sokolow–Lyon criteria, reported in 4/12 (33%) patients. In these four patients, one of the following findings were reported, respectively: pathological TWI in both limb and precordial leads, giant positive T-waves, left bundle branch block or pre-exitation, and Wolf–Parkinson–White syndrome. Baseline ECG was normal in 2/12 (17%) HCM genotype–positive patients with grey zone LVH. Electrocardiographic data were excluded due to misplaced electrodes in one patient and were not stored for later interpretation in the other patient. For the latter patient, ECG were described as normal by paediatric cardiologists in the hospital journal.

Follow-up data

Forty-seven athletes (29% female) subsequently underwent an echocardiography at age 15 and were included in the progression analysis. The mean follow-up time between echocardiographies was 3 years by study protocol (*Table 1*). Follow-up echocardiographic data were available in 31/55 HCM genotype–positive patients (50% female).

A progression of septum thickness was seen only in HCM genotype–positive patients, while most athletes normalized their elevated septum

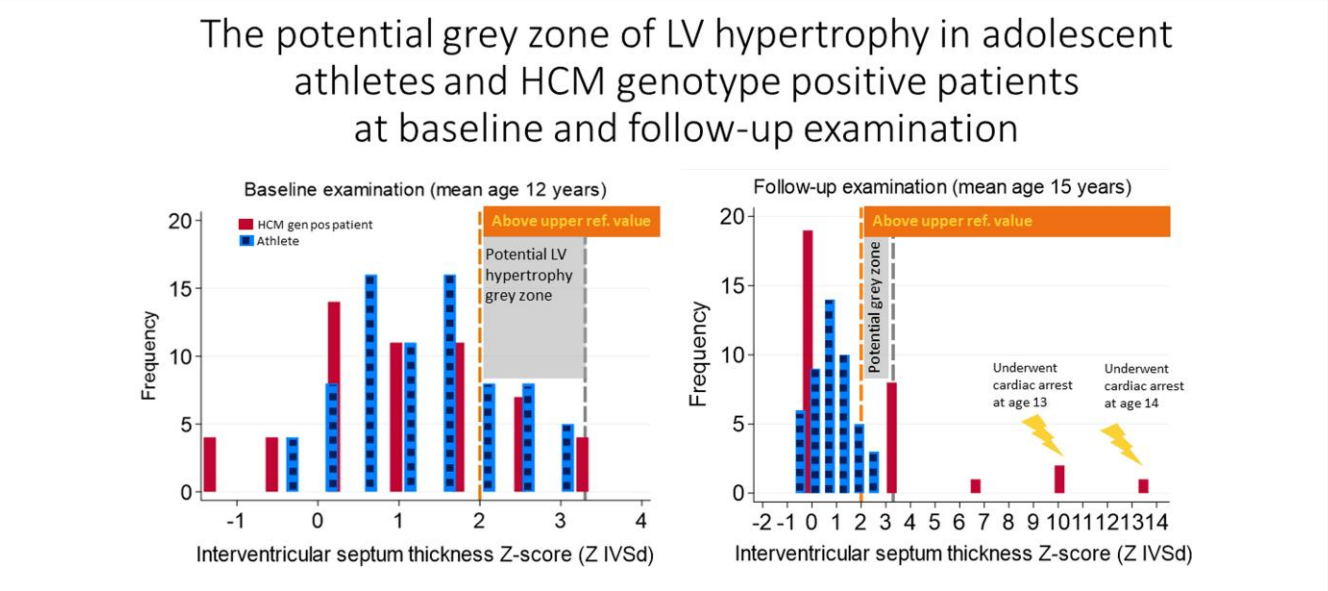


Figure 1 The potential grey zone of left ventricular hypertrophy. Distribution of an interventricular septum thickness *Z*-score in adolescent athletes (dotted, blue bar) and hypertrophic cardiomyopathy genotype–positive patients (solid, red bar) at baseline (left panel) and at follow-up examination (right panel). The orange line demarks the upper reference value at an *Z*-score of 2.0, and the grey line demarks the potential highest *Z*-score observed in an athlete. The potential grey zone of left ventricular hypertrophy (marked in grey) ranged from a septum thickness *Z*-score of 2.0 to 3.3. During the follow-up examination, only hypertrophic cardiomyopathy genotype–positive patients had a septum thickness *Z*-score above the potential grey zone, while most athletes had normalized their septum thickness *Z*-score. IVSd, interventricular septum diameter.

thickness (*Z*-score) with increasing body size (*Figure 2*). A septum thickness *Z*-score of 2.0–3.3 represented a potential grey zone of overlap between the athletes and the HCM genotype–positive patients (*Figure 1*). The athletes had a larger progression rate of volumes in absolute values (mL) from baseline to follow-up (*Figure 3*).

At follow-up, three HCM genotype–positive patients had asymmetric LV hypertrophy. The maximum wall thickness was septal and/or apical, ranging from 16 to 26 mm (corresponding to a *Z*-score of 8.5–15.2). Two of these three experienced cardiac arrest during follow-up. No athlete presented asymmetric LV hypertrophy or a progression of MWT above 10 mm (corresponding to an MWT *Z*-score of 3.3).

Relative wall thickness declined in the athletes, while it remained unchanged in the HCM genotype–positive patients [RWT progression rate −0.01 (SE 0.00), $P < 0.001$ vs. 0.00 (SE 0.00), $P = 0.13$, P for interaction <0.001]. This was related to a greater increase in LVIDd in the athletes [LVIDd (mm) progression rate 2.6 (SE 0.2), $P < 0.001$ vs. 0.8 (SE 0.2), $P < 0.001$, P for interaction <0.001].

Follow-up ECG analyses of the HCM genotype-positive and phenotype-negative patients showed persisting positive Sokolow–Lyon criteria in four of nine patients (44%). One of these had developed an echocardiographic phenotype during follow-up. Four other patients had developed positive Sokolow–Lyon criteria during follow-up, with the development of an echocardiographic phenotype in two of these.

One of the HCM genotype–positive patients with grey zone LVH and positive Sokolow–Lyon criteria suffered cardiac arrest during follow-up and developed TWI after the arrest. The patient with TWI at baseline suffered cardiac arrest during follow-up and had persisting TWI at follow-up ECG.

Clinical events

Cardiac arrest occurred in two (4%) of the HCM genotype–positive patients during follow-up. Both had a known HCM diagnosis at baseline. The maximum wall thickness (IVSd) *Z*-score progressed rapidly from 3.3–3.6 at baseline to 8.2–11.5 at the time of the event, with an increasingly asymmetric distribution. Implantable cardioverter defibrillation was implanted in both.

One patient experienced syncope at an MWT *Z*-score of 1.9. The syncope was preceded by palpitations and not related to exertion. The patient had a malignant family history of premature cardiac death. The syncope was interpreted as a potential malignant arrhythmia/suspected cardiac syncope, and treatment with a beta-blocker was initiated. Later, the patient had several episodes with palpitations during exertion, followed by near syncope.

There were no deaths or heart transplantations during follow-up. The total event rate was 5%. There were no events among the athletes during follow-up. One athlete underwent ablation for Wolff–Parkinson–White syndrome after age 15.

Discussion

This study was the first to describe the differences in the phenotype and progression of LV hypertrophy in early adolescent athletes compared with that in HCM genotype–positive patients. Mild LV hypertrophy was observed in nearly one-fourth of both athletes and HCM genotype–positive patients at age 12, indicating a grey zone between physiological and pathological hypertrophy in this age group. As many as 5% of HCM genotype–positive patients experienced severe cardiac events during follow-up, reflecting the need for correct identification of pathological hypertrophy.

Phenotype and progression of left ventricular hypertrophy

Important differences in phenotype and progression were observed. Athletes displayed mild and symmetrical LV hypertrophy, with larger

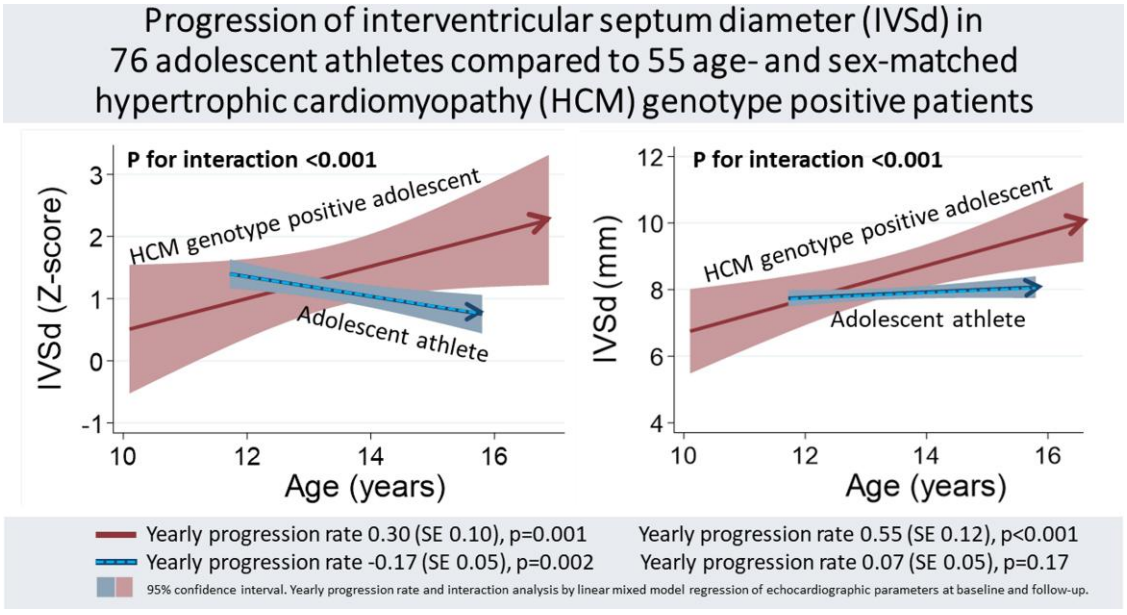


Figure 2 Progression of an interventricular septum diameter. Progression of septum thickness in adolescent athletes (dashed, blue line) compared with age-matched and sex-matched hypertrophic cardiomyopathy genotype–positive patients (solid, red line) during a mean follow-up time of 3.2 ± 0.8 years. The left panel shows the IVSd *Z*-score, and the right panel shows the interventricular septum diameter in millimetres. Septum thickness progressed only in hypertrophic cardiomyopathy genotype–positive patients, while the septum thickness *Z*-score decreased in athletes. IVSd, interventricular septum diameter; SE, standard error.

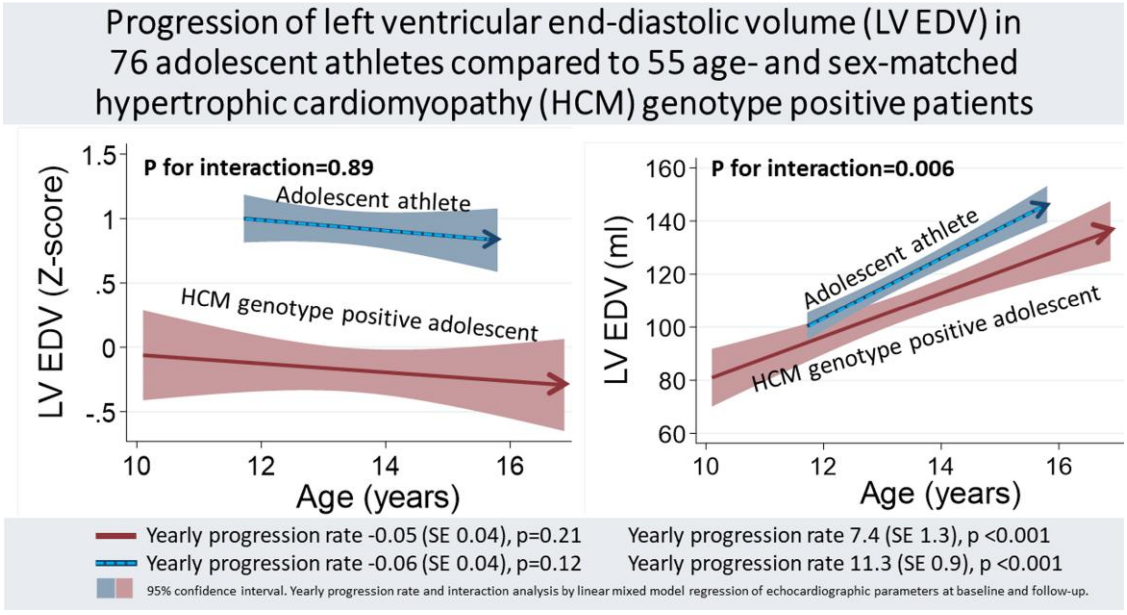


Figure 3 Progression of left ventricular end-diastolic volume. Progression of left ventricular end-diastolic volume in adolescent athletes (dashed, blue line) compared with age-matched and sex-matched hypertrophic cardiomyopathy genotype–positive patients (solid, red line) during a mean follow-up time of 3.2 ± 0.8 years. The left panel shows the left ventricular end-diastolic volume *Z*-score, and the right panel shows left ventricular end-diastolic volume in millilitres. Athletes had larger left ventricular end-diastolic volumes throughout the study period and greater progression in left ventricular end-diastolic volumes in millilitres. LV EDV, left ventricular end-diastolic volume; SE, standard error.

LV volumes and superior volume progression during follow-up compared with HCM genotype–positive patients. Septum thickness progressed only in HCM genotype–positive patients, while most athletes normalized their elevated septum thickness *Z*-scores with increasing body size. Therefore, the echocardiographic features distinguishing the two entities were more evident at age 15.

The overlapping features of LV hypertrophy at baseline may reflect the concentric pattern of remodelling previously described in the athletes at age 12.[3] When compared with age-matched, untrained controls, the athletes had greater septum and posterior wall thickness. The findings were in line with two large review studies comparing adolescent athletes with non-athletes.[1,4] At age 15, the remodelling pattern had changed to balanced or eccentric, with a relatively great increase in ventricular volume and dimension than wall thickness. Relative wall thickness decreased in the athletes, while it remained unchanged in the HCM genotype–positive patients, underscoring the different remodelling patterns. This implied that the phenotype in mid-adolescent athletes started resembling cardiac remodelling in adult athletes, however in a 'down-sized' version. In contrast, the mid-adolescent HCM genotype–positive patients who had increasing septum thickness presented a more typical HCM phenotype.[7] Of note, the two patients with cardiac arrest had shown rapidly progressing, and increasingly asymmetric, LV hypertrophy during follow-up.

Grey zone of left ventricular hypertrophy

Recent guidelines and a review paper debated on the possibility of the present threshold for HCM diagnosis (an MWT *Z*-score ≥2 in an HCM genotype–positive patient and MWT *Z*-score ≥2.5 in an HCM genotype–negative patient) being too low.[15,17] Our findings support this notion, and we suggest a potential grey zone of LV hypertrophy ranging from an MWT *Z*-score of 2.0 to 3.3. Importantly, the majority of the athletes normalized their MWT *Z*-score as their body size increased, in contrast to the HCM genotype–positive patients with progressing disease. The anatomical differences, with larger volumes and symmetrical wall thickness in athletes, resembled findings in previous studies comparing grey zone LV hypertrophy in adult athletes with HCM patients.[7,9] However, the absolute values for volumes and wall thickness were lower in our study, reflecting the participants' younger age and maturation stage. Median and MWT values in our athletes were in line with those of comprehensive review studies on athletes of the same age.[1,4] This highlights the importance of using paediatric reference values when evaluating growing adolescents.

Cardiac events

In our study, the 5% event rate and MWT *Z*-score in patients at the time of cardiac arrest were in line with those of previous findings.[13,14] However, we also observed syncope at lower MWT among the HCM genotype–positive patients. Importantly, one of the HCM patients with cardiac arrest had apical hypertrophy. Apical hypertrophy was not observed in any of the athletes, and it may be an important marker of pathological hypertrophy.

A large study on paediatric HCM patients described 95.6% freedom from SCD within 5 years at an MWT *Z*-score of below 10.[25] This underscored the importance of evaluating additional risk factors in adolescents with mild LV hypertrophy.[11] All our HCM genotype–positive patients had a family history of HCM, as implicated by recruitment from family screening. As mild LV hypertrophy may be an early sign of disease development, a close surveillance of progression, symptoms, and signs of arrhythmias is necessary. This may be particularly relevant in puberty, with rapid changes in body composition and hormonal influences.[17] Isolated signs of LVH at ECG appeared to have low sensitivity and specificity for predicting events, which is in line with a recent, large study on paediatric HCM patients.[24] The observation of the authors of this study might support TWI as a risk marker, although the limited number of events restricted generalization.

Clinical implications

Based on our observations, exercise-induced LV hypertrophy seems less likely if the MWT *Z*-score is above 3.3 or above 10 mm in an early adolescent. In cases where the MWT *Z*-score is between 2.0 and 3.3, repeated examinations may reveal further progression or regression. Increased wall thickness without concomitant ventricular dilatation may point towards pathological remodelling, as it may increase the *Z*-score despite a growing body size. Asymmetric hypertrophy was not observed in our adolescent athletes. Observations of asymmetric hypertrophy may indicate non-exercise–induced LV hypertrophy. Unexplained syncope should always be considered a red flag and investigated further. Furthermore, our findings support the possibility that systolic and diastolic function may be normal in adolescents with mild LV hypertrophy.

Limitations

This was a single-centre study with inherent limitations. Our hospital is the national referral centre for paediatric cardiology. This may lead to higher event rates in patients referred to us. The exclusion of genotype–negative patients referred for the evaluation of HCM reduces generalizability in this population. Norwegian law strictly regulates the genetic testing of asymptomatic paediatric individuals, including healthy athletes. This also applies to clinical studies and in particular healthy athletes without cardiac symptoms or a family history of HCM. Genetic testing requires a clear indication, high pre-test probability, symptoms, and/or family history of cardiac disease.

Cardiologists have interpreted cardiac remodelling in athletes as adaptive exercise–induced changes, with an absence of symptoms or family history of HCM. Hence, in this study, pre-test probability was low, and genetic testing was not recommended.[26] However the results should not be generalized to HCM genotype–positive athletes.

Electrocardiography was not performed in the athletes, and this is a limitation of the study. Therefore, our study does not allow a comparison of ECG findings in athletes and HCM genotype–positive patients. Future studies should compare ECG in adolescent athletes and HCM genotype–positive patients.

Data on exercise hours were collected from the athletes only by way of self-reports and conducting interviews with them, and therefore, data collection may be subject to reporting bias. Exercise data were not collected from the HCM genotype–positive patients. Patients were informed about symptoms necessitating medical attention and discontinuation of physical activity. The attrition rate may introduce selection bias. To evaluate progression and to account for missing data points, a linear mixed model regression analysis with random slope and intercept was performed.

Several studies have reported normal values for wall thickness in different adult athletic populations. Our study was the first to investigate this longitudinally by using *Z*-scores in an adolescent population. While our contribution to the field lies in the results that may indicate a potential grey zone of LV hypertrophy, the reported limitations restrict the establishment of a definitive *Z*-score cut-off. When interpreting *Z*-scores, is it important to be aware that the calculation of *Z*-scores is challenged by different normative data.[17,27] The same echocardiographic value may yield different *Z*-scores in one individual, depending on which calculator is used. We used the Paediatric Heart Network *Z*-scores, in order to compare our findings with large clinical studies and recent guidelines.[15,28] We also reported absolute values.

Conclusions

This is the first longitudinal study comparing LV remodelling in early adolescent athletes with age-matched and sex-matched HCM

genotype–positive patients. We found an overlapping proportion with LV hypertrophy at baseline, with significant differences in phenotype and progression. The athletes displayed mild and symmetric LV hypertrophy, with larger LV volumes. Septum thickness progressed only in HCM genotype–positive patients, while most athletes normalized their septum thickness with increasing body size. While no athlete experienced adverse cardiac events, severe cardiac events occurred in three of the HCM genotype–positive patients. Our findings tentatively suggest the possibility of a grey zone of LV hypertrophy ranging from an MWT *Z*-score of 2.0 to 3.3. Repeated examinations could provide additional insights for distinguishing physiological LV hypertrophy from early HCM. The progressively greater LV volumes in athletes, in contrast to progressing septum thickness in HCM genotype–positive adolescents, may aid in clinical evaluations of exercise-induced vs. pathological LV hypertrophy.

Author contributions

M.I.F., M.K.S., T.E., J.H., S.I.S., and K.H.H. contributed to the conception and design of the work, analysis, and interpretation of the data. T.E., M.I.F., M.K.S., A.F., S.I.S., H.W.L., J.H., and A.W.B. contributed to the acquisition of data. M.I.F. drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of the work.

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Data availability

This article conforms to the ICMJE Recommendations. The approval of the Regional Committee for Medical Research Ethics limits data sharing. The data underlying this article cannot be shared publicly due to the privacy of the individuals that participated in the study. The poster they are referring to here published as an abstract: https://doi.org/10.1093/ehjci/jead119.186.

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