

MYOCARDIAL HYPERTROPHY

Differentiation of athlete's heart from pathological forms of cardiac hypertrophy by means of geometric indices derived from cardiovascular magnetic resonance

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Purpose. Determination of the underlying etiology of left ventricular hypertrophy (LVH) is a common, challenging, and critical clinical problem. The authors aimed to test whether pathological LVH, such as occurs in hypertrophic cardiomyopathy (HCM), hypertensive heart disease, or aortic stenosis, and physiological LVH in athletes, can be distinguished by means of left ventricular volume and geometric indices, derived from cardiovascular magnetic resonance imaging. **Methods.** A total of 120 subjects were studied on a 1.5 Tesla MR (Sonata, Siemens Medical Solutions, Erlangen, Germany) scanner, comprising healthy volunteers (18), competitive athletes (25), patients with HCM (35), aortic stenosis (24), and hypertensive heart disease (18). Left ventricular mass index, ejection fraction, end-diastolic, end-systolic and stroke volume index, diastolic wall thickness, wall thickness ratio and diastolic and systolic wall-to-volume ratios were determined. **Results.** Left ventricular (LV) mass indices were similar for all forms of LVH ($p > 0.05$), which were at least 35% higher than those obtained in healthy volunteers ($p < 0.05$). Multiple logistic regression showed that the percentage of correctly predicted diagnoses was 100% for athlete's heart, 80% for hypertrophic cardiomyopathy, 54% for aortic stenosis, and 22% for hypertensive heart disease. Using a receiver operating curve-determined cut-off value for diastolic wall-to-volume ratio of less than $0.15 \text{ mm} \times \text{m}^2 \times \text{ml}^{-1}$, athletes' hearts could be differentiated from all forms of pathological cardiac hypertrophy with 99% specificity. **Conclusions.** Athlete's heart can be reliably distinguished from all forms of pathological cardiac hypertrophy using CMR-derived LV volume and geometric indices, but pathological forms of LVH present with overlapping cardiac hypertrophy phenotypes. This capability of CMR should be of high clinical value.

Key Words: Magnetic resonance imaging; Hypertrophy; Cardiomyopathy; Hypertension; Valves; Athletes

1. Introduction

Determining the underlying etiology of left ventricular (LV) hypertrophy in patients is often a challenging clinical problem. Various pathological forms of LV hypertrophy, such as hypertrophic cardiomyopathy (HCM), hypertensive heart disease or aortic stenosis, and physiological forms of LV hypertrophy, such as in athlete's hearts, can present with overlapping cardiac hypertrophy phenotypes as determined by 2D-echocardiography or ECG. However, in clinical practice, the distinction between physiological hypertrophy occurring in athletes and pathological hypertrophy is critical because

HCM accounts for about one-third of exercise-related sudden deaths in young competitive athletes (1–4). Furthermore, in athletes with hypertension, the relative contributions of increased blood pressure and physical training to the degree of LV hypertrophy detected need to be clarified, and this has implications as to the recommendation of treatment with antihypertensive agents in this situation.

Various pathophysiological mechanisms are responsible for the development of LV hypertrophy. In aortic stenosis and hypertensive heart disease, the resulting chronic LV pressure overload leads to compensatory concentric hypertrophy. An athlete's heart is thought to represent a physiological adaptation either to pressure overload (strength-trained athletes) or volume overload (endurance-trained athletes), leading to concentric or eccentric LV hypertrophy, respectively. Most sport disciplines yield a combination of both mechanisms (5–11). The precise pathophysiological mechanisms underlying LV hypertrophy in patients with HCM remain controversial (12); however, in contrast to pressure or volume overload LV hypertrophy, the hypertrophic stimulus in HCM is intrinsic to the myocardium.

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We therefore, hypothesized that these differences in pathophysiology lead to subtle differences in the cardiac hypertrophy phenotype, which can be detected by a highly sensitive imaging technique (13). Cardiac magnetic resonance (CMR) provides a high image quality and is intrinsically three-dimensional, not relying on geometric assumptions, and is, thus, the currently accepted gold standard method for the measurement of cardiac volumes and mass (14).

Therefore, we employed CMR imaging to test whether CMR-derived LV volume parameters and geometric indices accurately predict the underlying etiology of LV hypertrophy. This hypothesis was tested in groups of patients with HCM, hypertension, and aortic stenosis, and in athletes.

2. Methods

2.1. Ethics

The study was carried out according to the principles of the Declaration of Helsinki and was approved by our institutional

ethics committee. Informed written consent was obtained from each patient.

2.2. Study participants

A total of 120 subjects were studied. Patients with LV hypertrophy and a preserved LV ejection fraction (greater than 50%) were enrolled (n = 102). Each participant with LV hypertrophy fell into one of the following groups: competitive athletes (n = 25; 25 ± 4 years), hypertrophic cardiomyopathy (n = 35; 43 ± 17 years), hypertensive heart disease (n = 18; 52 ± 12 years), and aortic stenosis (n = 24; 67 ± 15 years). Eighteen healthy volunteers served as a reference group (41 ± 13 years).

Athletes were recruited solely on the basis of participation in high-level competitive sports, which were principally rowing, swimming, running, and cycling for at least the previous 18 months with an average of 19.2 ± 6.8 hours training per week for the last 8.5 ± 4.9 years. None of the athletes were hypertensive or had any cardiovascular disease or risk factors. HCM

Table 1. Baseline characteristics and left ventricular volume results

Diagnosis (∑ n = 120)	Healthy volunteers (n = 18)	Groups with LVH				p-Value
		AH (n = 25)	HCM (n = 35)	HHD (n = 18)	AS (n = 24)	
Age [years]	41 ± 13 (26–68)	25 ± 4* (20–35)	43 ± 17 (15–78)	52 ± 12 (20–71)	67 ± 15* (33–89)	P < 0.01
Gender	6m/12f	12m/13f	26m/9f	15m/3f	15m/9f	n.s. [§]
BSA [m ²]	1.75 ± 0.19 (1.28–2.07)	1.87 ± 0.15 (1.61–2.28)	1.98 ± 0.29 (1.14–2.48)	2.07 ± 0.25 (1.69–2.47)	1.94 ± 0.23 (1.51–2.40)	n.s.
Body weight [kg]	66 ± 12 (38–88)	70 ± 10 [†] (55–94)	82 ± 18 (36–119)	88 ± 19 [†] (60–120)	80 ± 15 (55–117)	P < 0.01
Heart rate [bpm]	67 ± 16 (50–112)	61 ± 9 (46–78)	58 ± 11 (44–91)	65 ± 12 (49–100)	64 ± 9 (49–80)	n.s.
Mean BP [mmHg]	98 ± 7 (92–116)	82 ± 8 [‡] (67–106)	92 ± 10 [‡] (65–113)	112 ± 20* (90–170)	88 ± 14 (73–118)	P < 0.01
LV mass index [g/m ²]	55.6 ± 9.9 (40.3–78.9)	75.8 ± 15.5 (55.0–125.7)	85.0 ± 27.3 (48.1–161.3)	75.6 ± 10.1 (51.4–93.6)	93.7 ± 40.1 (46.9–218.2)	n.s.
LVEF [%]	72 ± 6 (60–80)	68 ± 6* (58–88)	76 ± 6 (61–86)	76 ± 6 (67–86)	76 ± 10 (54–90)	P < 0.01
LVEDVI [ml/m ²]	79 ± 12 (63–101)	99 ± 11* (80–115)	77 ± 14 (47–111)	76 ± 12 (58–94)	76 ± 25 (44–134)	P < 0.01
LVESVI [ml/m ²]	23 ± 6 (14–34)	31 ± 7* (13–45)	19 ± 7 (9–41)	19 ± 6 (11–29)	20 ± 13 (6–56)	P < 0.01
LVSVI [ml/m ²]	56 ± 9 (42–72)	68 ± 10* (51–96)	58 ± 10 (33–76)	58 ± 9 (44–73)	57 ± 16 (34–98)	P < 0.01

HCM = hypertrophic cardiomyopathy; HHD = hypertensive heart disease; AS = aortic stenosis; AH = athlete's heart; BSA = body surface area; bpm = beats per minute; LV = left ventricular; LVEF = LV ejection fraction; LVEDVI = LV end-diastolic volume index; LVESVI = LV end-systolic volume index; LVSVI = LV stroke volume index. One-way ANOVA with Bonferroni post-hoc corrections was applied for the four groups of left ventricular hypertrophy unless stated otherwise. Results of healthy volunteers' are presented for reference purposes. As the aim of this study was the identification of differences in various forms of LV hypertrophy, only these groups were used for statistical analysis.

*p < 0.01 versus all other cardiac hypertrophy groups.

[§]The Kruskal-Wallis-test for qualitative parameters was applied.

[†]p < 0.01 between the groups with this symbol.

[‡]p < 0.05 between the groups with this symbol.

n.s. = not significant (p > 0.05).

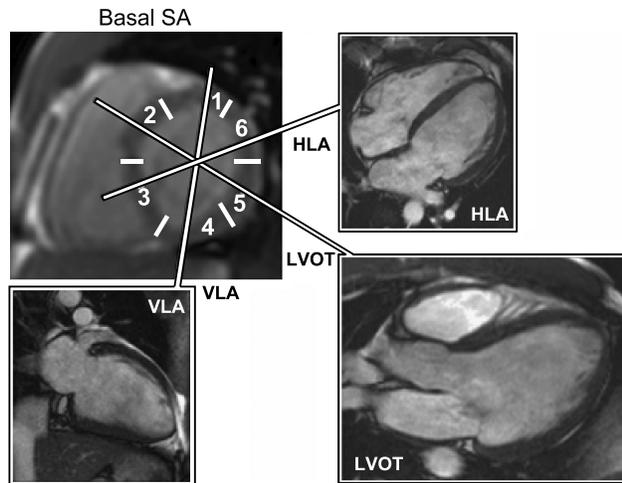


Figure 1. Planning image positions to allow three-dimension analysis of wall thickness distribution. By rotating imaging planes by 60° around an imaginary axis at the centre of the left ventricular cavity in pilot short axis views (SA), the left ventricular outflow tract (LVOT) can be imaged, and horizontal (HLA) and vertical long axis (VLA) views can be generated. The basal short axis slice shows 6 segments according to the AHA convention.

patients were recruited from the University of Oxford Cardiomyopathy and Heart Failure Clinic at the John Radcliffe Hospital, and the clinical diagnosis of HCM was based on family history, standard electrocardiographic, and echocardiographic criteria (end-diastolic wall thickness of greater 13 mm) in the absence of secondary causes for left ventricular hypertrophy. None of the HCM patients had hypertension. Hypertensive patients were enrolled if they showed an end-diastolic wall thickness of greater 13 mm on echocardiography. Additionally, a history of longstanding hypertension, documentation of hypertension on 24 hour ambulatory blood pressure readings

(> 140/90 mmHg) and at least one antihypertensive medication were required. The average number of antihypertensive drugs was 3.3 ± 1.5 . In patients with aortic stenosis, the peak instantaneous aortic valve gradient was 71 ± 27 mmHg. In addition, all aortic stenosis patients showed echocardiographic evidence of LV hypertrophy (end-diastolic wall thickness of greater 13 mm). Although aortic stenosis is clinically easily diagnosed by examination and echocardiography, this group was included in our study to compare the LV morphologic phenotype arising from this form of pressure overload with the phenotypes caused by other forms of pathological and physiological LV hypertrophy. All groups other than athletes did not perform physical training at a level or duration that would be expected to cause LV hypertrophy. Baseline characteristics of subjects are also given in Table 1.

2.3. MR imaging

All CMR exams were performed on a 1.5 Tesla MR scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). After piloting, steady-state free precession cine images (TE/TR 1.5/3.0ms, flip angle 60°) were acquired in long-axis views, i.e. horizontal and vertical long axis and LV outflow tract. Additionally, a complete short axis stack covering the entire left ventricle was obtained.

2.4. Data analysis

Cine images were analysed with the Argus and Syngo 2002B Software package (Siemens Medical Solutions, Erlangen, Germany) with an experienced analyser (SEP) blinded to the diagnosis. For each set of Cine studies, standard LV volume parameters were generated: LV ejection fraction (LVEF), LV mass index, LV end-diastolic (LVEDVI), end-systolic (LVESVI) and stroke volume index (LVSVI). Geometric

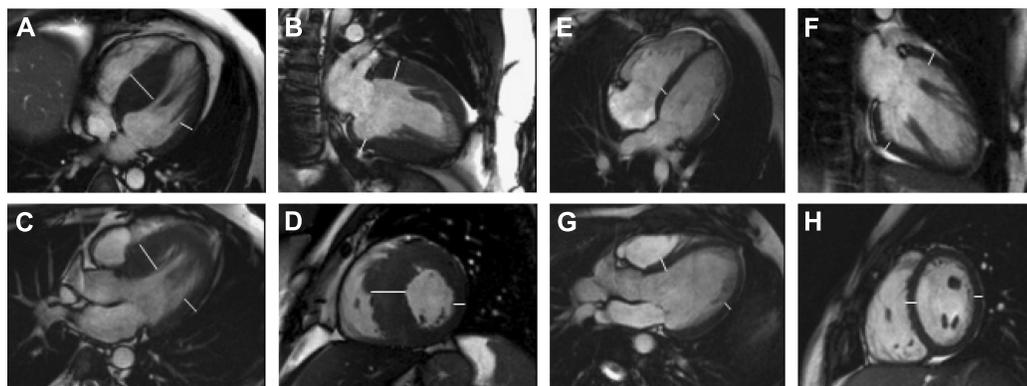


Figure 2. End-diastolic TrueFISP Cine images in a patient with hypertrophic cardiomyopathy (A–D) and in a competitive athlete with athlete's heart (E–H). A/E: horizontal long axis, B/F: vertical long axis, C/G: left ventricular outflow tract and D/H: basal short axis view. In each of the three diastolic long axis views and in a basal short axis slice at a level between the LV outflow tract and the papillary muscles (Fig. 1), the segment with the thickest and the thinnest myocardial diameter was chosen for measurement (white lines). Only the maximal (i.e. thickest) and the minimal (i.e. thinnest) end-diastolic wall thickness were then used for analysis. These values were then used to calculate maximal end-diastolic wall thickness (diastolic wall thickness) and end-diastolic maximal-to-minimal wall thickness ratios (wall thickness ratio).

Table 2. Geometric indices

Diagnosis (\sum n = 120)	Healthy volunteers (n = 18)	Groups with LVH				p-Value
		AH (n = 25)	HCM (n = 35)	HHD (n = 18)	AS (n = 24)	
Diastolic wall thickness [mm]	11.1 ± 1.1 (9.3–12.6)	12.8 ± 1.8* (9.7–16.6)	21.5 ± 5.9 [†] (14.3–36.5)	17.0 ± 2.6 [†] (13.2–22.4)	19.4 ± 3.8 (13.1–26.6)	P < 0.01
Wall thickness ratio [a.u.]	1.43 ± 0.22 (1.11–2.03)	1.42 ± 0.17 [†] (1.09–1.87)	2.25 ± 1.07 ^{†,‡} (1.01–7.45)	1.77 ± 0.41 (1.27–2.77)	1.76 ± 0.35 [‡] (1.28–2.70)	P < 0.01
Diastolic wall-to-volume ratio [mm × m ² × ml]	0.14 ± 0.03 (0.1–0.2)	0.13 ± 0.02* (0.1–0.2)	0.29 ± 0.10 (0.2–0.5)	0.23 ± 0.07 (0.2–0.4)	0.28 ± 0.10 (0.1–0.6)	P < 0.01
Systolic wall-to-volume ratio [mm × m ² × ml]	0.56 ± 0.23 (0.3–1.0)	0.42 ± 0.15* (0.2–1.0)	0.86 ± 0.32 [‡] (0.4–1.9)	0.92 ± 0.36 (0.4–1.7)	1.22 ± 0.82 [‡] (0.3–3.3)	P < 0.01

HCM = hypertrophic cardiomyopathy; HHD = hypertensive heart disease; AS = aortic stenosis; AH = athlete's heart; a.u. = arbitrary units; Diastolic wall thickness = maximal end-diastolic wall thickness; wall thickness ratio = ratio of maximal-to-minimal wall thickness; diastolic wall-to-volume ratio = maximal end-diastolic wall thickness-to-left ventricular end-diastolic volume index; systolic wall-to-volume ratio = minimal end-systolic wall thickness-to-left ventricular end-systolic volume index. The data are presented as mean ± standard deviation (range). One-way ANOVA with Bonferroni post-hoc corrections was applied for the four groups of left ventricular hypertrophy. Results of healthy volunteers' are presented for reference purposes. As the aim of this study was the identification of differences in various forms of LV hypertrophy, only these groups were used for statistical analysis.

*p < 0.01 versus all other cardiac hypertrophy groups.

[†]p < 0.01 between the groups with this symbol.

[‡]p < 0.05 between the groups with this symbol.

indices were computed to analyse the three-dimensional distribution of cardiac hypertrophy assessing all myocardial segments (15). In each of the three diastolic long axis views and in a basal short axis slice at a level between the LV outflow tract and the papillary muscles (Fig. 1), the segment with the thickest and the thinnest myocardial diameter was chosen for measurement. Only the maximal (i.e. thickest) and the minimal (i.e. thinnest) end-diastolic wall thickness were then used for analysis. These values were then used to calculate maximal end-diastolic wall thickness (diastolic wall thickness) and end-diastolic maximal-to-minimal wall thickness ratios (wall thickness ratio). End-diastolic maximal wall thickness-to-LVEDVI (diastolic wall-to-volume ratio: a measure of wall thickness in relation to heart size) and end-systolic minimal wall thickness-to-LVESVI (systolic wall-to-volume ratio: a measure of contractility in the least hypertrophied region of the heart) were also calculated.

2.5. Statistical analysis

Results of healthy volunteers are presented for reference purposes. As the aim of this study was the identification of differences amongst various forms of LV hypertrophy, only

these groups were used for statistical analysis. All data are presented as mean ± SD (range) unless stated otherwise. Nominal data were tested for differences between multiple groups using the Kruskal-Wallis test. Continuous data were analysed using ANOVA with post-hoc Bonferroni analysis to establish differences between the individual groups. A p-value of < 0.05 was considered statistically significant. Multiple logistic regression analysis was performed to identify the values of LV volume and geometric indices to allow correct diagnosis of LV hypertrophy. Receiver operating characteristics were used to generate cut-off values for optimised sensitivity and specificity to distinguish athlete's heart from pathological cardiac hypertrophy. All computations were done with SPSS 11.0 (SPSS Inc., Chicago, IL, US).

3. Results

3.1. Characteristics of subject and patient groups

All groups with LV hypertrophy had similar LV mass indices (p > 0.05 for all four LV hypertrophy groups), which were, on average, at least 35% higher than those obtained in

Table 3. Diagnostic accuracy for differentiation of physiological from pathological LV hypertrophy

	Sens	Spec	pos pred	neg pred	AUC
Diastolic wall thickness <13 mm	40%	100%	100%	84%	0.955
Wall thickness ratio <1.3	28%	95%	64%	95%	0.862
Diastolic wall-to-volume ratio <0.15 mm × m ² × ml	80%	99%	95%	94%	0.993
Systolic wall-to-volume ratio <0.26 mm × m ² × ml	4%	100%	100%	76%	0.926

Sens = sensitivity; spec = specificity; pos pred = positive predictive value; neg pred = negative predictive value; AUC = area under the curve for analysis based on receiver operating curves.

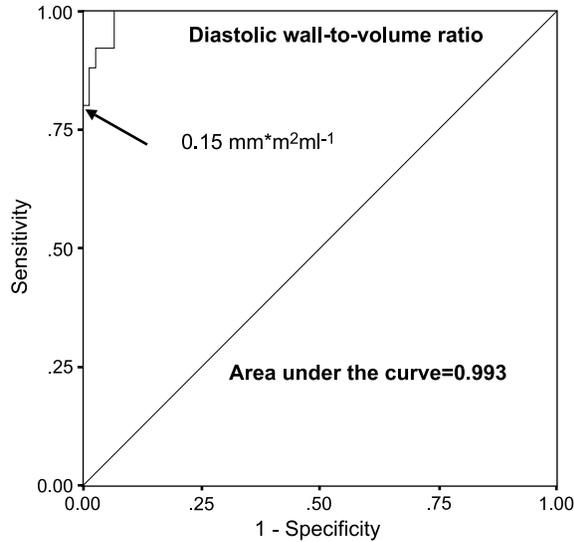


Figure 3. Receiver operating characteristics of the diastolic wall-to-volume ratio to distinguish athlete's heart from pathological left ventricular hypertrophy. The area under the curve is 0.993 and, for a cut-off value of 0.15 mm×m²×ml, this parameter provides a sensitivity and specificity of 80% and 99%, respectively. The positive and negative predictive values were 95% and 94%, respectively.

healthy volunteers ($p < 0.05$ for combined LV hypertrophy groups versus healthy volunteers; t -test for unpaired variables, Table 1). The four LV hypertrophy groups were also similar with regard to gender, heart rate, and body surface area ($p > 0.05$ for all, Table 1). As expected, mean blood pressure was higher in hypertensive patients ($p < 0.01$ vs. all groups). Hypertensive patients had a higher body weight compared to athletes ($p < 0.01$). As is typical for athlete's heart, LV end-diastolic, end-systolic, and stroke volume indices were all higher in the athletes group ($p < 0.01$ for all three parameters versus all groups). All ECG findings were normal in athletes.

3.2. Geometric indices

Diastolic wall thickness was significantly lower in athletes (Fig. 2; Table 2) as compared to the other three groups with pathological cardiac hypertrophy ($p < 0.01$). Ten of 25 (40%)

athletes showed a diastolic wall thickness greater than 13 mm, and 1 of 25 showed (4%) a wall thickness of greater than 16 mm. HCM patients showed the largest diastolic wall thickness, which was also significantly higher than wall thickness in hypertensive heart disease ($p < 0.01$, Table 2). However, only 7 of 35 (20%) HCM patients presented with a wall thickness above the highest values of the other LV hypertrophy groups. Wall thickness ratio was highest for HCM ($p < 0.01$ vs. AH, $p < 0.05$ vs. AS), lowest for athletes, and intermediate for hypertensive patients (n.s. versus all other groups) and aortic stenosis. Two of the 35 patients (6%) with HCM showed symmetric LV hypertrophy with a wall thickness ratio of less than 1.3. Diastolic wall-to-volume ratio was lowest in athletes ($p < 0.01$ compared to all other groups) and was highest in HCM patients (Table 2). Athletes also had the lowest systolic wall-to-volume ratio ($p < 0.01$ compared to all other groups), while aortic stenosis patients showed the highest ratio ($p < 0.05$ compared to HCM, $p < 0.01$ compared to athletes).

3.3. Diagnostic accuracy of geometric indices to differentiate the underlying etiology of cardiac hypertrophy

Receiver operating characteristics identified the diastolic wall-to-volume ratio as the best parameter (i.e. the highest area under the curve of 0.993) to differentiate athlete's heart from all other pathological hypertrophy forms. A cut-off value for diastolic wall-to-volume ratio of less than 0.15 mm×m²×ml discriminated between physiological and pathological LV hypertrophy with a sensitivity of 80%, a specificity of 99%, a positive predictive value of 95%, and a negative predictive value of 94% (Table 3, Fig. 3).

To analyze the diagnostic accuracy of CMR in differentiating between all four forms of cardiac hypertrophy studied, MR parameters derived from LV volume studies (LV mass index, LVEF, LVEDVI, LVESVI, LVSVI) and geometric indices (diastolic wall thickness, wall thickness ratio, diastolic wall-to-volume ratio and systolic wall-to-volume ratio) were subjected to multiple logistic regression analysis. The number and percentage of patients correctly classified with these parameters were computed (Table 4). Athlete's hearts were correctly classified in 100% of cases, HCM in 80%, aortic stenosis patients in 54%, and hypertensive heart disease in

Table 4. Classification table showing the prediction of diagnosis based on a multiple logistic regression analysis including left ventricular volume parameters (LVEF, LVEDVI, LVESVI, LVSVI, LV Mass index) and geometric indices (diastolic wall thickness, wall thickness ratio, diastolic wall-to-volume ratio, systolic wall-to-volume ratio)

Real diagnosis	Predicted diagnosis				Percent correct
	HCM	HHD	AS	AH	
HCM (n = 35)	28 (80%)	3 (9%)	4 (11%)	0 (0%)	80%
HHD (n = 18)	10 (56%)	4 (22%)	4 (22%)	0 (0%)	22%
AS (n = 24)	8 (33%)	3 (13%)	13 (54%)	0 (0%)	54%
AH (n = 25)	0 (0%)	0 (0%)	0 (0%)	25 (100%)	100%

22%. Importantly, no athlete was misclassified as having HCM in spite of a maximal wall thickness of 16 mm and no patient with HCM as athlete's heart. Hypertensive heart disease was the most commonly misclassified condition and could be mistaken for any form of pathological cardiac hypertrophy but, importantly, not for an athlete's heart. Aortic stenosis was sometimes misclassified as hypertensive heart disease or HCM but, again, never as an athlete's heart. Thus, no single LV geometric index could identify athletes with 100% diagnostic accuracy, but multiple logistic regression analysis, taking into account all measured parameters, was 100% correct in distinguishing athlete's heart from all other forms of LV hypertrophy.

4. Discussion

Our principal finding is that physiological LV hypertrophy can reliably be distinguished from pathological LV hypertrophy, such as in HCM, hypertensive heart disease and aortic stenosis, based on CMR-derived LV geometric indices. In contrast, these forms of pathological LV hypertrophy present with an overlapping cardiac hypertrophy phenotype.

4.1. Identification of athlete's hearts by CMR indices

Distinction of pathological and physiological LV hypertrophy remains a frequent clinical dilemma. In current clinical practice, one strategy of distinguishing an athlete's heart from pathological LV hypertrophy is to document the deconditioning effect after training cessation for several months (16–18). However, this is often not acceptable to athletes. Metabolic exercise testing has been shown to facilitate the differentiation between athlete's hearts and HCM (19). Our study suggests a novel approach to distinguish an athlete's heart from various forms of pathological LV hypertrophy by means of three-dimensional CMR-derived LV volume and geometric indices, obviating the need for 'de-training' to make this distinction.

Importantly, in our study, no athlete was misdiagnosed as having HCM in spite of a wall thickness of greater 16 mm, and no patient with HCM was diagnosed as having physiological LV hypertrophy. This is of clinical importance, as labelling athletes with a diagnosis of HCM would disqualify them from competitive exercise in addition to the psychological and socioeconomic impact of this diagnosis. On the other hand, missing HCM in athletes would expose them to a high risk of sudden cardiac death, as HCM is the most common cause of sudden death in the population under 35 years of age (2–4).

Our findings also confirm that cardiac morphologic changes in athletes are different from those induced by pressure overload LV hypertrophy. Athlete's hearts are characterised by larger LV volumes, smaller ejection fractions, and less pronounced wall thickness, despite a similar LV mass index. The differentiation of athlete's heart from hypertensive

heart disease is clinically relevant, and athletes with additional LV hypertrophy secondary to hypertension should be treated vigorously with antihypertensive medication. This is supported by a recent meta-analysis (20) showing that regression of LV hypertrophy by antihypertensive treatment is associated with a marked reduction in risk for subsequent cardiovascular disease.

Our findings are in keeping with one previous study using echocardiography, which suggested that geometric indices are useful in distinguishing athlete's heart from hypertrophic cardiomyopathy (21). However, this study did not include other forms of pathological LV hypertrophy. In principle, CMR can detect changes of LV parameters with a much smaller sample size than echocardiography (for equivalent statistical power) due to the high inter-study reproducibility and the observer-independence of the method. As in our study, the measurements by Grothues and colleagues were based on manual detection of endo- and epicardial contours with coefficients of variability for inter-study reproducibility of 3.6% for CMR and 13.5% for echocardiography in LV hypertrophy patients (13). Thus, to detect a 10 g difference in LV mass index, CMR allows a reduction of the sample size by 90%.

4.2. Pathological forms of LV hypertrophy

The differential diagnosis of patients with pathological cardiac hypertrophy remains difficult, even with a high-resolution, three-dimensional technique, such as CMR. The finding of similar patterns of cardiac hypertrophy amongst different pathological hypertrophy etiologies is of clinical relevance. The American College of Cardiology/European Society of Cardiology (ACC/ESC) Clinical Expert consensus document (22) states that in HCM, LV wall thickening is found in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident. However, coexistence of pathologies, for example of hypertension and HCM, is not unusual. In addition, genotype-phenotype correlations have shown that virtually any LV wall thickness is compatible with HCM (23). In our cohort, only 20% of HCM patients presented with a wall thickness above the maximal values seen in hypertension and aortic stenosis. Consequently, in the presence of coexisting pathologies that cause LV hypertrophy, a majority of the HCM patients in our study could not have been classified as affected by the ACC/ESC criteria. Genetic analysis to identify HCM mutations may be particularly valuable in patients with multiple potential causes of LV hypertrophy, such as in HCM family members with hypertension.

One possible explanation for the similarity of the cardiac muscle phenotypes in pathological hypertrophy may be a common intracellular signalling pathway mediating myocardial growth. A rise in intracellular calcium elicited by mechanical stretch (in aortic stenosis and hypertension) or altered bioenergetics (in HCM) (12, 24–26) has been identified as the

key step leading to the activation of calcium-sensitive signalling pathways (including calcineurin-NFAT) and myocardial growth. Conversely, recent findings have indicated that physiological hypertrophy may result from the activation of Akt through a phosphoinositide 3-kinase (PI3K) pathway (27).

4.3. Hypertrophy and cardiac asymmetry

Asymmetric LV hypertrophy is considered the hallmark of HCM, and, traditionally, the wall thickness ratio has been widely used for the diagnosis of this disease. However, the results of this study indicate that this parameter provides the least diagnostic accuracy for the differentiation of LV hypertrophy compared to the other geometric indices used. Cardiac muscle asymmetry, thus, is not solely associated with HCM. Furthermore, symmetric forms of HCM appear to be more common than may be appreciated; six percent of patients with HCM in our cohort showed symmetrical LV hypertrophy. For the distinction of physiological LV hypertrophy from HCM, this is particularly problematic as symmetrical HCM appears to be more common in the athletic HCM sub-population. Maron and colleagues found that up to 43% of athletes who suffered sudden death due to HCM had normal septum to LV wall ratios in the heart arrested in systole at autopsy (3).

Cardiac muscle asymmetry also shows a wide and overlapping spectrum in both athletes and in pathological cardiac hypertrophy. Furthermore, even in the absence of LV hypertrophy, our findings in healthy volunteers show a degree of asymmetry in line with previous reports (28, 29). Consequently, asymmetry as determined by high-resolution, three-dimensional CMR cannot reliably differentiate HCM from pressure overload LV hypertrophy. The pathoanatomical substrate underlying the phenomenon of asymmetric hypertrophy, as seen across the spectrum of groups studied, maybe denser sympathetic innervation of the interventricular septum compared to the lateral wall (30).

4.4. Limitations

Our study populations were, inevitably, dissimilar with regards to age (athletes were younger, aortic stenosis patients were older) and weight (despite a similar body surface area, the hypertensive patients were more obese). However, echocardiographically determined geometric indices have been shown to be independent of sex and body size (31). Additionally, we normalized all volume parameters to body surface area. Furthermore, our results were unchanged when we normalized LV parameters to body height instead of surface area.

Athletes were ascertained if they participated in high-level physical training and athletic competition so as to be representative of the type of patient in whom the differential diagnosis of cardiac hypertrophy presents a problem. This selection resulted in similar elevation of mean LV mass index as was seen in the pathological hypertrophy groups, but not

all athletes had a diastolic wall thickness of greater than 13 mm. Thus the distribution of geometric measurements will be somewhat different in the athletes as wall thickness of greater than 13 mm was an inclusion criterion for HCM, hypertensive heart disease, and aortic stenosis. Probably as a result of the very stringent selection, many of the elite athletes (40%) had a wall thickness of greater than 13 mm. CMR may tend to yield higher numbers for diastolic wall thickness than echocardiography. The inclusion of athletes with both increased and normal wall thickness but all with increased LV mass indices appears important as HCM patients may be phenotype negative gene carriers.

While we cannot rule out HCM with absolute certainty in athletes with increased wall thickness, none of these athletes had an abnormal ECG, a positive family history, or cardiovascular symptoms; therefore, a diagnosis of HCM is statistically highly unlikely.

5. Conclusions

We propose the use of CMR-derived LV volume and geometric indices for clinical practice to distinguish athlete's hearts from pathological forms LV hypertrophy. These indices, however, cannot differentiate HCM and LV hypertrophy secondary to systemic hypertension or aortic stenosis.

6. Abbreviations

CMR	cardiovascular magnetic resonance
ECG	electrocardiogram
HCM	hypertrophic cardiomyopathy
LVH	left ventricular hypertrophy
LVEDVI	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
LVESVI	left ventricular end-systolic volume index
LVSVI	left ventricular stroke volume index
SD	standard deviation

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