

Article

Magnetic Resonance for Differential Diagnosis of Left Ventricular Hypertrophy: diagnostic and prognostic implications

Giovanni Donato Aquaro, ^{1,*}, Elisabetta Corsi ², Giancarlo Todiere ¹, Crysanthos Grigoratos ¹, Andrea Barison ¹, Valerio Barra ¹, Gianluca Di Bella ³, Michele Emdin ^{1,4}, Fabrizio Ricci, Alessandro Pingitore ⁵.

¹ Fondazione Toscana G. Monasterio, Pisa, Italy

² Università degli studi di Pisa, Pisa, Italy

³ Università di Messina, Messina, Italy

⁴ Scuola Superiore Sant'Anna, Pisa, Italy

⁵ University of Chieti, Chieti, Italy

⁶ Istituto di Fisiologia Clinica, CNR, Pisa, Italy

* Correspondence: Email: aquaro@ftgm.it; Phone: +39 - 050315 2818; Fax +39 - 050 315 2166

ABSTRACT: Background: Left ventricular hypertrophy (LVH) may be due to different causes, ranging from benign secondary forms to severe cardiomyopathies. Transthoracic Echocardiography (TTE) and ECG are the first level examination for LVH diagnosis. Cardiac magnetic resonance (CMR) defines accurately LVH type, extent and severity. **Objectives:** to evaluate the diagnostic and prognostic role of CMR in patients with TTE and/or ECG evidence of LVH. **Methods:** We performed CMR in 300 consecutive patients with echocardiographic and/or ECG signs of LVH. **Results:** Overall, 275 patients had TTE evidence of LVH with initial suspicion of hypertrophic cardiomyopathy (HCM) in 132 (44%), cardiac amyloidosis in 41 (14%), hypertensive LVH in 48 (16%), aortic stenosis in 4 (1%), undetermined LVH in 50 (16%). The initial echocardiographic diagnostic suspicion of LVH was confirmed in 172 patients (57.3%) and changed in 128 patients (42.7%, $p < 0.0001$): the diagnosis of HCM increased from 44% to 71% of patients; hypertensive and undetermined LVH decreased significantly (respectively to 4% and 5%). CMR allowed a diagnosis in 41 out of 50 (82%) with undetermined LVH at TTE. CMR also identified HCM in 17 out of 25 patients with apparently normal echo but with ECG criteria for LVH. Finally, the reclassification of the diagnosis by CMR was associated with a change of survival risk of patients: after CMR reclassification no events occurred in patients with undetermined or hypertensive LVH. **Conclusions:** CMR changed echocardiographic suspicion in almost half of patients with LVH. In the subgroup of patient with abnormal ECG, CMR identified LVH (particularly HCM) in 80% of patients. This study highlights the indication of CMR to better characterize the type, extent and severity of LVH detected at echocardiography and suspected with ECG.

Keywords: Left ventricular hypertrophy; Echocardiography; Magnetic Resonance; Prognosis

1. INTRODUCTION

The presence of left ventricular hypertrophy (LVH) is a recognized independent risk factor for cardiac-related morbidity and mortality (1). However, LVH does not represent a unique disease entity but rather the phenotypic expression of a large spectrum of diseases, such as hypertrophic cardiomyopathy or amyloidosis, as well as a physiologic adaptation, as in the case of athlete's heart. Thus, the clinical and prognostic weight depends on the type of the disease causing LVH and also the extent and the severity of myocardial damage (2). This highlights the need to characterize as best as possible LVH in terms of diagnosis and severity. Currently, transthoracic echocardiography (TTE) represents the diagnostic entrance door of LVH, providing with high accuracy to measure LV wall thickness and to stratify patients for the risk of sudden death on the basis of the entity of wall

thickness (3). In addition, also LV outflow tract obstruction (LVOT) and left atrial enlargement are included in the risk score assessment of sudden death (4). Cardiac magnetic resonance (CMR) has higher potential to define wall thickness and the extent of LVH in comparison to TTE due to higher spatial resolution and multiplanar approach that makes it a three dimensional imaging technique. This is in particular evident in the apical region that is barely valuable with TTE (5,6). In addition, CMR provides information regarding myocardial tissue characterization with the identification of fibrosis and edema (7-9), that have potential relevance in the risk stratification of patients with LVH (10). In particular, late gadolinium enhancement (LGE) provides the opportunity to define accurately the diagnostic nature of LVH according to the intramyocardial distribution and the wash out curve of the gadolinium (11). The majority of the studies comparing CMR and TTE for the LVH diagnosis is mainly focused on HCM (12-15). Actually, there are no studies showing the additive value of CMR over TTE in the definition of LVH of different nature. Therefore, the aim of the present study was to assess the diagnostic impact of CMR in comparison to TTE for the detection of LVH and the diagnostic definition on the nature of LVH. Moreover, we also assessed the prognostic impact of CMR in patients with LVH diagnosis as defined with this technique.

2. METHODS

We performed CMR in 300 consecutive patients with the suspicion of LVH, defined as the presence of at least one of the following criteria: 1) LVH detected by echocardiography; 2) ECG criteria for LVH (ECG voltage criteria for LVH, 16). The following inclusion criteria were further used: 12-leads resting ECG and TTE; age > 18 years; absence of contraindication for CMR; known history of cardiac disease and/or systemic disease potentially involving heart; LV ejection fraction >45%.

2.1. LVH at echocardiography

Standard echocardiographic examinations of any patients was performed following the current ESC guidelines (17). LV hypertrophy during TTE was defined as maximal diastolic wall thickness ≥ 11 mm with a two dimensional (2D) echocardiography-guided M-mode approach in the parasternal long axis. (14) The initial echocardiographic diagnostic suspicion was performed as follows. Briefly, HCM was suspected in presence of asymmetric LVH with maximal end diastolic wall thickness ≥ 15 mm with or without LVOT obstruction (defined as an instantaneous peak Doppler LV outflow tract pressure gradient ≥ 30 mmHg at rest or during physiological provocation such as Valsalva manoeuvre, standing and exercise). In patients with concentric hypertrophy (maximal end diastolic wall thickness ≥ 15 mm), the presence of LVOT functional obstruction was used as suspected HCM (3).

Cardiac amyloidosis was suspected in presence of concentric hypertrophy, ground glass appearance of ventricular myocardium on 2D echocardiography, diastolic dysfunction, thickening of interatrial septum, global LV hypokinesia with or without apical sparing (3).

Hypertensive LVH was defined for patients with systemic arterial hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg during office measurements), LVH with maximal end diastolic wall thickness ≤ 14 mm, in absence of any other secondary cause of LVH.(18).

In patients with LVH, the presence of moderate-severe aortic stenosis was considered as the main cause of hypertrophy in absence of any other causes. Patients were assigned to aortic stenosis group in the presence of moderate ($V_{max} \leq 4$ m/s, $\Delta P_{m} \leq 40$ mmHg, $AVA > 1$ cm 2) or severe ($V_{max} \geq 4$ m/s, $\Delta P_{m} \geq 40$ mmHg).(19)

Athlete's heart was defined in patients practicing intense sport training ≥ 2 hours per day for at least 5 days per week in the last 12 months having eccentric hypertrophy, LV dilation, preserved systolic and diastolic function with normal regional wall motion.(20).

Finally, undetermined LVH was defined in case of absence of any of the above mentioned criteria.

2.2. Cardiac Magnetic Resonance evaluation

The examination was performed using 1.5 Tesla scanner (Signa Hdx, General Electric Healthcare, Milwaukee, Wisconsin) with dedicated cardiac phased array coil. Study protocol included functional evaluation with short axis cine images, acquired from the mitral plane valve to the left ventricular (LV) apex, and these images were acquired using a steady-state free precession pulse sequence with the following parameters: 30 phases, slice thickness 8 mm, no gap, views per segment 8, FOV 35-40 cm, phase FOV 1, matrix 224×224, reconstruction matrix 256×256, 45° flip angle, and a TR/TE near to 2. Cine images with the same parameters were acquired also in 2-, 3- and 4 chamber views.

According to the protocols recommended by the Society for Cardiovascular Magnetic Resonance, we acquired T1 mapping sequence using a Modified Look-Locker Inversion Recovery (MOLLI) method with 3(3)3(3)5 protocol. A 3(3)3(3)5 scheme indicates that there are a total of 3 inversions; 3 images are acquired after the first inversion, this is followed by a waiting period of 3 RR intervals, then 3 images are acquired followed by another 3 RR waiting period, finally a third inversion after which 5 images are acquired, for a total of 11 images over 17 heartbeats.

We obtained three parallel short-axis slices, including the base, mid-cavity, and apex of the left ventricle, at the same cardiac phase (end diastole).

LGE images were acquired 10 minutes after the administration of Gd-DTPA with a dosage of 0.2 mmol/kg in short-axis views. An inversion recovery T1-weighted gradient-echo (GRE) sequence was used with the following parameters: field of view 35-40 mm, slice thickness 8 mm, no gap between each slice, repetition time 3-5 msec, echo time 1-3, a flip angle of 25°, matrix 224×224, reconstruction matrix 256×256. The appropriate inversion time was set to null for normal myocardium using a TI-scout.

All CMR studies were analysed offline in the core laboratory of Pisa by three experienced observers with III level EACVI accreditation for CMR investigators who were blinded to the clinical data. A commercially available research software package (Mass Analysis, Leyden, The Netherlands) was used to quantify the functional parameters using conventional method. Left ventricular mass was measured by the analysis of the cine short-axis images. The endocardial and epicardial contours of LV myocardium were manually traced in the end-diastolic and the end-systolic phases. End-diastolic volume index, end-systolic volume index, mass, and mass index were measured as previously described (21,22). Maximal LV end diastolic wall thickness was measured as previously described. The pattern of LVH was defined as asymmetric (septal, septo-apical, apical, inferolateral), concentric and eccentric. The maximal end diastolic wall thickness was measured. The pattern of LGE was measured and classified as follows: ischemic pattern (subendocardial/transmural, located in coronary artery territory), non-ischemic (midwall or subepicardial, non-respecting coronary artery territory) (11). The presence of the specific pattern of cardiac amyloidosis was also detected (diffuse subendocardial enhancement, early darkening of the cavity, nulling defect of myocardium) (23).

Native myocardial T1 was evaluated by the generation of T1 maps and the measurement of myocardial T1 performed for each myocardial segments.

Combining morphological, functional and tissue findings, the differential diagnosis of LVH was performed as follows. Briefly, HCM was diagnosed in patients with asymmetrical LVH with maximal diastolic wall thickness ≥ 15 mm (or an apex/base wall thickness ratio >1 for apical pattern), with or without LGE. In patients with concentric LVH, the presence of LVOT functional obstruction was considered as a proof of HCM. Cardiac amyloidosis was identified in patients with concentric LVH with the specific pattern of LGE. Hypertensive LVH was defined for patients with LVH with maximal end diastolic wall thickness ≤ 14 mm, negative LGE and with the exclusion of any other secondary cause of LVH. In patients with LVH, the presence of moderate/severe aortic stenosis was

considered as the main cause of hypertrophy in absence of LGE and any other causes. Athlete's heart was defined in patients practicing intense sport training ≥ 2 hours per day for at least 5 days per week in the last 12 months having eccentric hypertrophy, balanced biventricular dilation (RV EDV/LV EDV in the range 0.85-1.15), preserved systolic function with normal regional wall motion and absence of LGE. Finally, undetermined LVH was defined in case of absence of any of the above mentioned criteria and absence of LGE.

2.3. Additional evaluation

In order to confirm the diagnosis after the echocardiographic and CMR suspicion, patients underwent to further evaluations based on clinical indication. For instance, in the suspicion of cardiomyopathy, genetic evaluation was performed for the identification of specific pathogen mutations, and in the suspect of cardiac amyloidosis, diphosphonate scintigraphy and umbilical fat biopsy was performed.

2.4. Clinical follow-up

After the CMR examination, a follow-up was performed. A clinical questionnaire was compiled by a clinical physician during periodic ambulatory visitations in each hospital, by contacting their relatives by telephone, or by a general practitioner. The clinical questionnaire included the definition of the following cardiac events: cardiac death, resuscitated cardiac arrest and appropriate implantable cardioverter defibrillator (ICD) shock, anti-tachycardia pacing, sustained ventricular tachycardia on Holter electrocardiogram monitoring, heart failure hospitalization. A complete analysis of the ICD was performed by the referring cardiologist in order to confirm the appropriateness of the shock. A panel of expert investigators adjudicated the occurrence of cardiac events.

2.5. Statistical analysis

Values are presented as the mean \pm standard deviations (SD) or as the median (interquartile range IQR) for variables with normal and non-normal distributions, respectively. Values with non-normal distribution according to Kolmogorov-Smirnov test were logarithmically transformed for parametric analysis. Qualitative data are expressed as percentages. Categorical variables were compared by the chi-square test or the Fisher exact test when appropriate. Continuous variables were compared by the ANOVA t test and analysis of variance or by the Wilcoxon nonparametric test when appropriate. Bonferroni correction was used when needed. The Kaplan-Meier time-to-event method was used to calculate and compare longitudinal curves among groups. A p value lower than 0.05 was considered statistically significant.

3. RESULTS

Among the 300 enrolled patients: 275 (92%) had LVH at echocardiography; 151(50%) had ECG abnormalities (ECG criteria of LVH in 76, 25%); 25 had ECG signs of LVH with negative TTE (8%).

The characteristics of the population are summarized in Table 1. Table 2 shows TTE diagnostic suspicions, CMR diagnosis of LVH and the diagnostic discrepancies between the two techniques. In particular, after CMR, the initial TTE diagnostic suspicion of LVH was confirmed in 173 patients (57.7%) and changed in 127 patients (42.3%, $p < 0.0001$) (Figure 1)

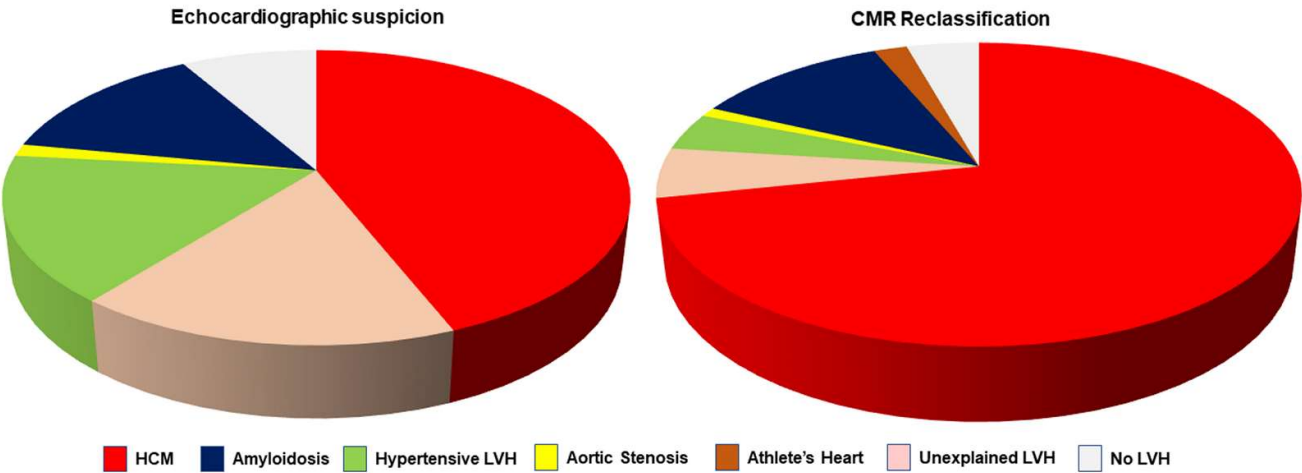


Figure 1. The left graph shows the distribution of initial diagnostic suspicion by transthoracic echocardiography (TTE). The right graph shows the reclassification of diagnosis by cardiac magnetic resonance (CMR). As evident by the comparison of the two graphs, CMR allowed a significant decrease of cases with undetermined left ventricular hypertrophy (LVH), as well a decrease of the percentage of hypertensive LVH. HCM, hypertrophic cardiomyopathy.

Table 1. Characteristics of the whole population (n= 300 patients).

Age(year)	56 ± 18
Males, n(%)	220 (73%)
Height (cm)	171 ± 9
Weight (Kg)	76 ± 14
Hypertension, n (%)	119 (40%)
Dyslipidaemia, n (%)	64 (21%)
Diabetes, n (%)	29 (10%)
Familial history of CAD, n (%)	24 (8%)
Familial history of cardiomyopathy, n (%)	17 (6%)
Familial history of SCD, n (%)	23 (8%)
Atrial fibrillation, n (%)	26 (9%)
ECG abnormalities:	151(50%)
Sokolow LVH criteria, n (%)	76 (25%)
T negative, n (%)	89 (20%)
Left bundle branch block, n(%)	9 (3%)
Low voltages on peripheral leads, n(%)	4 (1%)
Short PR interval, n (%)	2 (1%)
Echographic criteria of LVH, n (%)	275 (92%)
LVH patterns at echo:	
Septal, n (%)	131 (44%)
Concentric, n (%)	127 (42%)
Septo-apical, n (%)	2 (0.7%)
Apical, n (%)	7 (2%)
Infero-lateral, n (%)	1 (0.3%)
Maximal end-diastolic wall thickness at echo (mm)	15 (13-18)
Diastolic dysfunction, n (%)	193 (64%)
Grade 1, n (%)	127 (42%)
Grade 2, n (%)	37 (12%)
Grade 3, n (%)	29 (10%)
LVOT obstruction, n (%)	31 (10%)
Systolic dysfunction, n (%)	35 (12%)
Aortic valvular stenosis, n (%)	4 (1%)

CAD: coronary artery disease; SCD: sudden cardiac death; LVH: left ventricular hypertrophy; LVOT: left ventricular outflow tract.

Table 2. Comparison between echocardiographic suspicion and CMR final diagnosis in the different groups; in the grey boxes, the matches for each group, n (%). LVH: left ventricular hypertrophy.

TTE suspicion:	CMR Reclassification:							Sum
	HCM	CA	Hypertensive LVH	Aortic stenosis	Undetermined LVH	Athlete's heart	No LVH	
HCM	124 (94%)	2	2	0	1	0	3	132 (44.0%)
CA	9	23 (56%)	2	0	5	0	2	41 (13.7%)
Hypertensive LVH	36	3	8 (17%)	0	0	0	1	48 (16.0%)
Aortic stenosis	1	0	0	3 (75%)	0	0	0	4 (1.4%)
Undetermined LVH	28	7	0	0	9 (18%)	4	2	50 (16.7%)
No LVH	17	0	0	0	1	2	5 (20%)	25 (8.3%)
	215 (71.7%)	35 (11.7%)	12 (4.0%)	3 (1.0%)	16 (5.0%)	6 (2%)	13 (4.3%)	300

*Others diagnosis were made by CMR in 3 patients (1%): 1 ischemic heart disease, 2 with no LVH but non ischemic LGE.

Among the 48 patients with TTE suspicion of hypertensive LVH, CMR excluded any other different diagnosis in 8 cases (17%), whereas a CMR suggested a different diagnosis in 40: HCM in 36 cases (75%); patients typical LGE features of cardiac amyloidosis in 3(6%); non-ischemic LGE without hypertrophy in 1 (example in figure 2).

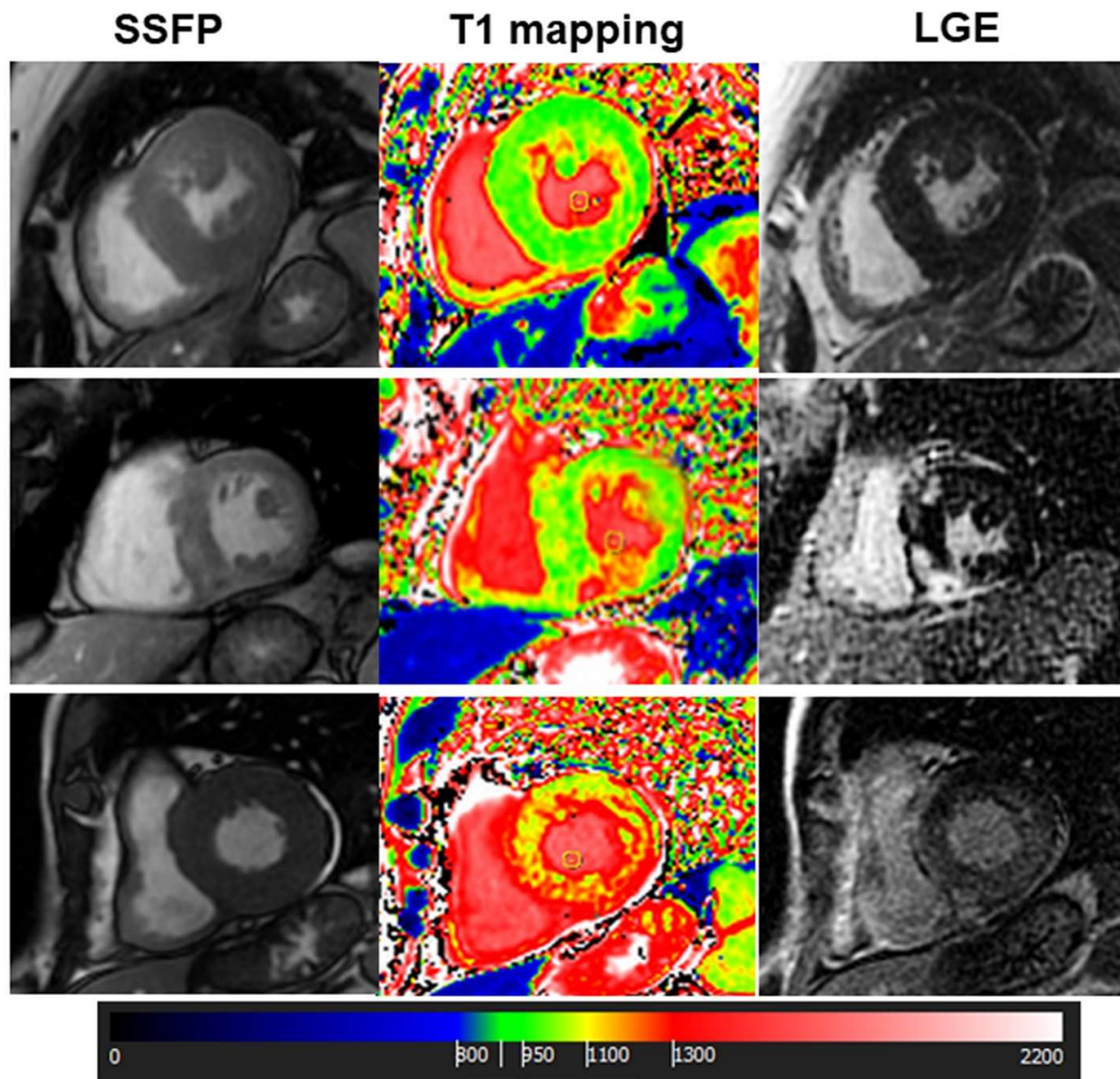


Figure 2. Cardiac Magnetic Resonance of 3 different cases of left ventricular hypertrophy: The upper panels show a case of hypertensive left ventricular hypertrophy (LVH) with concentric hypertrophy, normal native T1 values and negative late gadolinium enhancement (LGE). The middle panels show a case of Hypertrophic cardiomyopathy (HCM) with asymmetrical LVH, focal areas of myocardial fibrosis at LGE and focal increase of native T1 corresponding to the fibrotic areas. Finally, a case of cardiac amyloidosis is reported in the lower panels. In this case LVH is concentric, native T1 is diffusely increased and a diffuse subendocardial enhancement was found at LGE.

Among 132 patients with TTE suspicion of HCM, CMR confirmed this diagnosis in 124 out of 132 patients (94%), while the remaining 8 patients were reclassified as follows: 2 patients with cardiac amyloidosis (1.5%); 2 with hypertensive LVH (1.5%), 1 case with concentric hypertrophy without LGE (0.8%) having a short native myocardial T1 (with subsequent genetic diagnosis of Fabry disease, figure 3); in the last 3 cases hypertrophy was excluded and LGE was negative (2.2%).

Grade 2, n (%)	108(50%) ^{2,4}	5 (14%) ^{1,3}	8 (67%) ^{2,4}	0 ^{1,3}	2 (67%)	2 (14%)	
Grade 3, n (%)	17 (8%) ²	16 (46%) ^{1,4}	2 (17%)	0 ²	0	0 ²	
	15 (7%) ²	14 (40%) ^{1,3,6}	0 ²	0	0		
CMR parameters							
Max telediastolic wall thickness (mm)	19 ± 4	19 ± 4	14 ± 2	13 ± 2	18 ± 2	15 ± 3	0.001
LVEF (%)	69 ± 11 ²	54 ± 4 ^{1,3,4,6}	66 ± 14 ²	70 ± 8 ²	53 ± 12	68 ± 9 ²	<0.001
LVEDVi (ml/mq)	73 ± 19	76 ± 27	77 ± 23	97 ± 21	87 ± 27	77 ± 18	0.14
Mass (g/mq)	95 ± 26	115 ± 36	87 ± 26	104 ± 18	130 ± 37	96 ± 28	<0.001
RVEF (%)	69 ± 9 ²	53 ± 14 ¹	67 ± 13	66 ± 7	62 ± 9	65 ± 11	<0.001
RVEDVi (ml/mq)	67 ± 17 ⁴	66 ± 17 ⁴	71 ± 17	105 ± 23 ^{1,2}	62 ± 10	80 ± 23	<0.001
Septal LVH, n (%)	155 (72%) ^{2,4,6}	8 (23%) ¹	6 (50%)	1 (14%) ¹	1 (33%)	4 (27%) ¹	<0.0001
Septal apical LVH, n (%)	12 (6%)	0	0	0	0	0	0.83
Apical LVH, n (%)	18 (8%)	0	0	0	0	0	0.58
Concentric LVH, n (%)	28 (13%) ^{2,3,4,6}	26 (74%) ¹	6 (50%) ¹	5 (72%) ¹	2 (67%)	10 (67%) ¹	0.88
Inferior and inferolateral LVH, n (%)	2 (1%)	0	0	0	0	0	0.98
Presence of LGE, n (%)	163 (76%) ^{2,3,4,6}	34 (97%) [*]	0 ^{1,2}	0 ^{1,2}	1 (33%) ²	0 ^{1,2}	<0.001
Abnormal native T1	104(48%)	35(100%)	0	0	1(33%)	0	<0.001

A p value <0.05 was considered significant. ¹ vs HCM; ² vs amyloidosis; ³ vs hypertensive LVH; ⁴ vs athlete's heart; ⁵ vs aortic stenosis; ⁶ vs undetermined LVH; *vs all other groups. CAD: coronary artery disease; LVH: left ventricular hypertrophy; LVEF: left ventricle ejection fraction; LVEDVi: left ventricle end diastolic volume indexed; RVEF: right ventricle ejection fraction; RVEDVi: right ventricle end diastolic volume indexed

3.1. Factors determining CMR vs TTE changes in LVH diagnosis

Maximal wall thickness (MWT), LVH site, LGE pattern and native T1 mapping were considered as key element to change CMR diagnosis of LVH in respect to TTE. In general, the calculation of MWT between the 2 techniques significantly correlated ($r = 0.80$, $p < 0.001$). However, average maximal thickness was higher in CMR (17, 15-21) vs echo (16, 14-19 mm; median difference 1 mm, range 1-3 mm, $p < 0.0001$). The higher difference was in the HCM group (median 2 mm, range 1-4 mm, $p < 0.001$) and in the amyloidosis group (median 2 mm, range 1-3 mm). In 65 patients, CMR detected a MWT higher than 15 mm whereas at TTE MWT was lower.

TTE identified 98 out of 155 (63%) with septal hypertrophy at CMR, 15 out 30 (50%) with apical hypertrophy, 11 of the 28 (39%) with concentric hypertrophy and none of the 2 with inferior/inferolateral hypertrophy. TTE was more able to detect septal HCM than other patterns ($p = 0.008$). LGE pattern was also useful for the final diagnosis. The typical LGE pattern of amyloidosis allowed to identify 34 patients (97%), while in 1 patient a diffuse and severe increase of native T1, summed to concentric hypertrophy allowed the diagnosis. In HCM, LGE was found in the mid-wall layer of hypertrophic segments in 163 patients (76%). LGE with ischemic pattern was found in 1 patient with LVH due to aortic stenosis. Finally, as mentioned above, in 1 patient with concentric hypertrophy and negative LGE, the finding of decrease native myocardial T1 suggested the diagnosis of Fabry disease that was confirmed through the genetic evaluation.

3.2. Clinical follow-up

Clinical follow-up was performed in 272 patients for a median of 2440 (937-3421) days, 45 major cardiac events occurred (20 cardiac deaths, 3 appropriate ICD intervention and 22 hospitalization for heart failure). The Kaplan Meier curves of figure 3, show the survival-free from events of patients with one of the major 4 diagnoses: HCM, cardiac amyloidosis, hypertensive LVH and undetermined LVH. As shown in the figure, the reclassification of diagnosis made by CMR was also associated with a change in the risk of events among the groups. Indeed, after the CMR reclassification 23 out of 45 events occurred in patients with cardiac amyloidosis and 22 in those with HCM, whereas no events occurred in hypertensive or undetermined LVH.

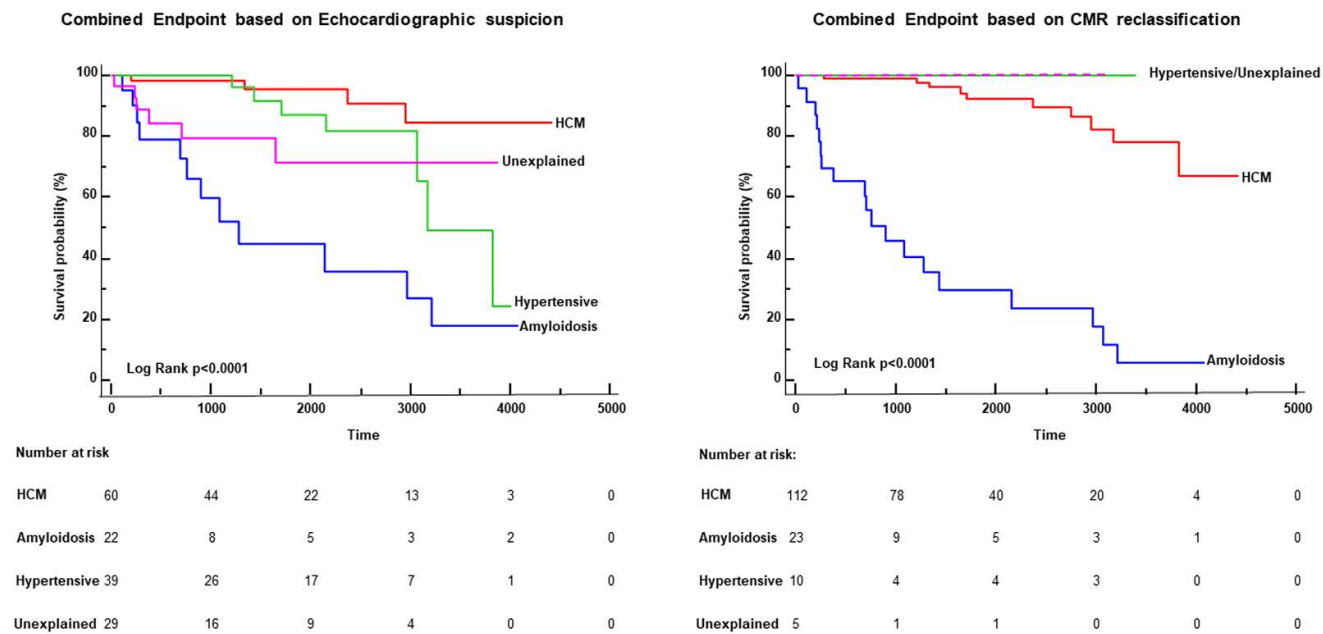


Figure 4. Kaplan-Meier curves: The graphs represent the survival-free from events curve of the patients with the 4 major diagnosis in this population: hypertrophic cardiomyopathy (HCM), cardiac amyloidosis, hypertensive left ventricular hypertrophy (LVH) and undetermined LVH. The left graph shows the curves based on the initial echocardiographic suspicion, the right graph was the result of the reclassification made by cardiac magnetic resonance (CMR). As evident, the reclassification allowed a prognostic change in survival curves: no events occurred in patients with hypertensive LVH and those with undetermined LVH based on CMR diagnosis. .

4. DISCUSSION

The main results of this study can be summarized in the following points:

1. In patients with LVH at echo or with ECG signs of hypertrophic phenotype, CMR changed the initial echocardiographic suspicion in 42.3% cases, in particular changing the diagnosis of hypertensive LVH in 43% cases
2. The factors changing diagnosis were MWT measurement, the pattern of LVH, with average MWT higher in CMR vs echo. Tissue characterization, with LGE and T1 mapping, was also effective to identify HCM and cardiac amyloidosis.
3. The final diagnosis by CMR was prognostically relevant providing an accurate patient risk stratification, in line with the type of diagnosis.

In general, this study showed that CMR allows a more accurate differentiation among the phenotypes of hypertrophy than echocardiography. This was due mainly to higher precision in the measurement of MWT, the identification of hypertrophic segments that are unlikely visualized with echocardiography, and tissue characterization by the assessment of the presence and the pattern of myocardial fibrosis or amyloid material, defined according to LGE technique and by the T1 mapping technique. Previous studies showed that TTE can both underestimate or overestimate LV wall thickness, the first one due to poor acoustic window or focal hypertrophy, the second one due to LV trabeculation, right ventricular myocardium, papillary muscle, imaging plane obliquity apical septal bundle (13-15). However, in the study of Bois JB et al, CMR identified higher number of patients with massive LV hypertrophy than TTE, confirming a discrepancy between these 2 techniques (13). Interestingly, a recent study showed that the prevalence of unexplained LV hypertrophy in a population based cohort was 1.4% with CMR (24) Whether these discrepancies were mainly documented in the setting of patients with HCM, in this study, we documented that the discrepancies involve also other types of LVH. Indeed,

CMR changed diagnosis of the type of LVH in 42% of patients. In particular, this occurred in the group of TTE-diagnosed hypertensive LVH, in which CMR confirmed diagnosis only in 17% of patients, and changed diagnosis mainly in the type of HCM. The identification of asymmetrical LVH with MWT >15 mm (underestimated or undetected by TTE), summed, in many cases, by the detection of mid-wall LGE in hypertrophied segments, were the major reasons for the change of diagnosis from hypertensive LVH to HCM.

Also, CMR changed TTE-diagnosis of amyloidosis in a large number of patients, that is 56% of them. Among these, 22% of patients had CMR-diagnosis of HCM, and the others had variegated type of LVH. In this setting of patients, changes in diagnosis was due to the assessment of LGE pattern, that provides accurate information on the presence of amyloid material, in which the most common pattern is a diffuse or sub-endocardial distribution of LGE with a non-coronary artery distribution, early darkening of the blood pool, and defect of myocardial nulling (25). T1 mapping played also an important role in the evaluation of cardiac amyloidosis, showing a diffuse and severe increase of myocardial native T1 (whereas T1 increased patchy in HCM, decreased in Fabry disease and was normal in hypertensive LVH). T1 mapping was also crucial for the diagnosis of the patient with Fabry disease: the finding of a decreased myocardial T1, summed to the inferolateral midwall LGE, allowed to suspect this diagnosis (figure 4)

Also, CMR provided certain diagnosis in patients with undetermined diagnosis at TTE; in this group the main CMR diagnosis was HCM, with an average difference between MWT at CMR and at TTE of 3.8 ± 2 mm.

Differently, CMR confirmed TTE-diagnosis of HCM in 94% of patients. Among these, 40 had LVOT obstruction. It is noteworthy that 76% of these patients had intramyocardial LGE. Several studies have already shown that the presence and the extent of LGE is associated to wall thickness, and is an independent predictor of severe ventricular arrhythmias and sudden death (10,26). Further, fibrosis is a progressive phenomenon over the years and its increment is associated to a worse clinical status, highlighting the need of a CMR longitudinal follow up (27).

The effectiveness of CMR in the diagnosis of the different types of LVH is expressed in terms of prognosis. Indeed, event did not occur in patients with a final CMR diagnosis of hypertensive LVH and in those who remained with undetermined LVH diagnosis. This reclassification of the risk of cardiac events made by CMR is consistent with the available data about the risk of cardiac events in cardiomyopathy as amyloidosis and HCM compared to hypertensive LVH (28,29). An important point is that prognostic risk stratification profile due to CMR diagnostic changes in LVH patterns, suggests that TTE risk stratification profile worsened, in particular in TTE groups of hypertensive LVH due to the erroneous presence of other more prognostically severe LVH forms. Accordingly, in this study, we showed that in the TTE group of LVH hypertension, patients with HCM or amyloidosis were also included. Therefore, it is reasonable to consider again the prognostic weight of TTE LVH in hypertensive patients. Thus, the clinical impact of these data is that CMR may be useful to define the prognostic risk of LVH.

Limitations of the study

This is a real life study and it was performed without the use of more advanced echocardiographic techniques as speckle tracking, 3D-echo. These more complex echocardiographic techniques could have probably improved the accuracy of the echocardiographic diagnosis, mainly in the cases of uncertain diagnosis.

5. CONCLUSIONS

In this study, we showed that CMR and TTE have discrepancies in the diagnostic definition of the type of LVH, depending by several factors that include the identification of LVH of myocardial segments poorly visualized by TTE, the maximal wall thickness, the availability of a more accurate analysis of myocardial tissue characterization with

LGE. Thus, this study asks the question whether CMR may be more frequently used in patients with TTE evidence of LVH with the goal of a more accurate diagnostic and prognostic definition. Further studies are needed to answer this query.

Clinical perspective

Clinical competency in medical knowledge: Cardiac magnetic resonance enhance (CMR) our ability to identify the causes of left ventricular hypertrophy compared to transthoracic echocardiography. After CMR the initial diagnostic suspicion changes in >40% of cases and this is associated with a substantial variation of the risk of cardiac events of the patients. This study highlights that CMR should be performed in every patients with echocardiographic evidence of left ventricular hypertrophy.

Translational outlook: The reclassification of the risk of cardiac events of patients with left ventricular hypertrophy consequent to CMR diagnosis, suggests the need to re-evaluate the data of the prognostic risk associated with some cardiac conditions, obtained in pre-CMR era.

REFERENCES

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561–1566
2. Devereux RB, Roman MJ. Left ventricular hypertrophy in hypertension: stimuli, patterns, and consequences. *Hypertens Res* 1999;22:1–9
3. Authors/Task Force members, Elliott PM, Anastakis A, Borger MA et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;35:2733–2779
4. O'Mahony C. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;35:2010–2020
5. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart*. 2004;90:645–649
6. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. *Am J Hypert* 1995;8:221–228
7. Aquaro GD, Positano V, Pingitore A et al. Quantitative analysis of late gadolinium enhancement in hypertrophic cardiomyopathy. *J Cardiovasc Magn Reson* 2010; 7:12–21
8. Burrage MK, Ferreira VM. Cardiovascular magnetic resonance for the differentiation of left ventricular hypertrophy. *Current Heart Failure Reports* 2020;17:192–204
9. Karamitsos TD, Arvanitaki A, Karvounis H, Neubaer S, Ferreira VM. Myocardial tissue characterization and fibrosis by imaging. *JACC Cardiovascular Imaging*. 2020;13:1221–1234
10. Chan RH, Maron BJ, Olivetto I et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130:484–495
11. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J* 2005;26:1461–1474
12. Rickers C, Wilke NM et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. *Circulation* 2005;112:855–861
13. Bois JP, Geske JB, Foley TA, Ommen SR, Pellikka PA. Comparison of maximal wall thickness in hypertrophic cardiomyopathy differs between magnetic resonance imaging and transthoracic echocardiography. *Am J Cardiol* 2017; 119:643–650
14. Devlin AM, Moore NR, Ostman-Smith I. A comparison of MRI and echocardiography in hypertrophic cardiomyopathy. *Br J Radiol* 1999;72:258–264
15. Hindieh W, Weissler-Snir A, Hammer H, Adler A, Rakowski H, Chan RH. Discrepant measurements of maximal left ventricular wall thickness between cardiac magnetic resonance imaging and echocardiography in patients with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging* 2017;10:e006309
16. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar and limb leads. *Am Heart J* 1949;37:161–86
17. Lang, Badano LP, Mor-Avi V et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
18. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–3104
19. Baumgartner H, Falk V, Bax JJ et al. ESC Scientific Document Group, 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791

-
20. Pelliccia A, Maron MS, Maron BJ, Assessment of Left Ventricular Hypertrophy in a Trained Athlete: Differential Diagnosis of Physiologic Athlete's Heart From Pathologic Hypertrophy. *Prog Cardiovasc Dis* 2012;54:387-96
 21. Aquaro GD, Camastra G, Monti L et al. Working group "Applicazioni della Risonanza Magnetica" of the Italian Society of Cardiology. Reference values of cardiac volumes, dimensions, and new functional parameters by MR: A multicenter, multivendor study. *J Magn Reson Imaging*. 2017;45:1055-1067.
 22. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson*. 2020;22:17
 23. Fontana, M., Chung, R., Hawkins, P.N. et al. Cardiovascular magnetic resonance for amyloidosis. *Heart Fail Rev* 2015;20: 133
 24. Massera D, McClelland RL, Ambale-Venkatesh B et al. Prevalence of unexplained left ventricular hypertrophy by cardiac magnetic resonance imaging in MESA. *J Am Heart Assoc* 2019;8:e012250
 25. Syed IS, Glockner JF, Feng DL et al. Role of Cardiac Magnetic Resonance Imaging in the Detection of Cardiac Amyloidosis. *JACC: Cardiovascular Imaging* 2010;3:155-164
 26. Weng Z, Yao J, Chan RH, He J, Yang X, Zhou Y, He Y, Prognosis value of LGE-CMR in HCM: a meta-analysis. *JACC Cardiovasc Imaging* 2016;9:1392-1402
 27. Todiere G, Aquaro GD, Piaggi P et al. Progression of myocardial fibrosis assessed with cardiac magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2012;10:922-929
 28. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. *Am Heart J* 2001;141:334-341
 29. Levy D, Garrison RJ, Savage DD et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham heart study. *NEJM* 1990;322:1561-1566