

Wall Thickness and Patterns of Fibrosis in Hypertrophic Cardiomyopathy Assessed by Cardiac Magnetic Resonance Imaging

Espesores parietales y patrones de fibrosis en miocardiopatía hipertrófica evaluados con resonancia magnética

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ABSTRACT

Background: Hypertrophic cardiomyopathy is the most common genetic cardiac disease and the main cause of sudden death in the young. Cardiac magnetic resonance imaging can characterize the different forms of hypertrophic cardiomyopathy and detect myocardial fibrosis by late gadolinium enhancement.

Objectives: The aim of this study was to characterize the regional distribution of left ventricular wall thickness and its relation with myocardial fibrosis, and also quantify the percentage and determine the different patterns of left gadolinium enhancement in patients with hypertrophic cardiomyopathy evaluated with cardiac magnetic resonance imaging.

Methods: This observational study evaluated patients with hypertrophic cardiomyopathy undergoing contrast-enhanced cardiac magnetic resonance imaging. The results were compared with a group of control patients. Hypertrophic cardiomyopathy morphology was evaluated and the percentage of late gadolinium enhancement was determined.

Results: Maximum wall thickness was observed in the mid inferoseptal (16.8 ± 5.3 mm), basal anteroseptal (16.5 ± 6.2 mm), and mid anteroseptal segments (15.4 ± 6.2 mm). Thirty patients (71%) with hypertrophic cardiomyopathy presented late gadolinium enhancement in 141/672 (21%) of the segments evaluated. Late gadolinium enhancement was predominantly intramyocardial ($n = 103$, 73%). A significant association was found between the percentage of late gadolinium enhancement in the left ventricle and maximum myocardial wall thickness.

Conclusions: Maximum wall thickness was more frequently observed in the basal and mid septal segments. Two-thirds of these patients presented late gadolinium enhancement which was associated with maximum wall thickness.

Key words: Cardiomyopathy, Hypertrophic - Magnetic Resonance - Heart

RESUMEN

Introducción: La miocardiopatía hipertrófica es la enfermedad cardiovascular hereditaria más frecuente y la principal causa de muerte súbita en los individuos jóvenes. La resonancia magnética cardíaca permite caracterizar las distintas formas de miocardiopatía hipertrófica y detectar fibrosis miocárdica a través del realce tardío.

Objetivos: Caracterizar la distribución regional de los espesores miocárdicos y su relación con la fibrosis miocárdica, así como cuantificar el porcentaje y determinar los diferentes patrones de realce tardío en pacientes con miocardiopatía hipertrófica evaluados con resonancia magnética cardíaca.

Material y métodos: El presente es un estudio observacional en el que se evaluaron pacientes con diagnóstico de miocardiopatía hipertrófica a través de la resonancia magnética cardíaca con contraste endovenoso. Los resultados se compararon con un grupo de pacientes control. Se efectuó la evaluación morfológica y se determinó el porcentaje total de realce tardío.

Resultados: El espesor máximo de los pacientes con miocardiopatía hipertrófica se evidenció en el segmento inferoseptal medio ($16,8 \pm 5,3$ mm), seguido por los segmentos anteroseptal basal ($16,5 \pm 6,2$ mm) y anteroseptal medial ($15,4 \pm 6,2$ mm). Presentaron realce tardío 30 (71%) pacientes con miocardiopatía hipertrófica y 141/672 (21%) de los segmentos evaluados. La distribución del realce tardío fue predominantemente intramiocárdica ($n = 103$, 73%). Se encontró una relación significativa entre el porcentaje total de realce tardío del ventrículo izquierdo y el espesor miocárdico máximo.

Conclusiones: La localización más frecuente del espesor parietal máximo se encontró a nivel septal basal y medial. En dos tercios de estos pacientes se detectó realce tardío, el cual se asoció con el espesor miocárdico máximo.

Palabras clave: Cardiomiopatía hipertrófica - Resonancia magnética - Corazón

REV ARGENT CARDIOL 2016;84:202-208. <http://dx.doi.org/10.7775/rac.v84.i3.7168>

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Received: 09/19/2015 – Accepted: 01/27/2016

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Abbreviations

CMRI	Cardiac magnetic resonance imaging	LV	Left ventricle
DLVOTO	Dynamic left ventricular outflow tract obstruction	RV	Right ventricle
HCM	Hypertrophic cardiomyopathy	ET	Echo time
LGE	Late gadolinium enhancement	TR	Repetition time
LVEF	Left ventricular ejection fraction		

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disorder, with a prevalence of 1:500 in the general population, and the most common cause of sudden death in the young. (1-3) The natural history of HCM is benign in most patients, with an incidence of sudden death reaching 6% in tertiary care centers and <1% in unselected populations. (4)

In recent years, cardiac magnetic resonance imaging (CMRI) has become a useful tool to characterize the different forms of HCM due to its ability to measure wall thickness in all the cardiac segments and to detect the presence of myocardial fibrosis using late gadolinium enhancement (LGE) sequences. (5-7)

One of the distinctive features of the natural history of HCM is the risk of sudden death, mainly associated with ventricular arrhythmias originating in areas of structurally abnormal myocardium with myofibril disarray, which commonly include fibrotic regions. (8-12) The extent of LGE estimated by CMRI, expressed as a percentage of myocardial fibrosis, has been associated with the risk of sudden death and with the development of systolic dysfunction and heart failure, particularly in patients who would have otherwise been considered at low risk. (13)

Hypertrophic cardiomyopathy needs to be evaluated in different populations due to its great genotypic diversity and the different phenotypic expressions. In our setting, the number of reports is scarce; therefore, the aim of this study was to characterize the regional distribution of myocardial wall thickness and its relation with the presence of myocardial fibrosis, determine the different patterns of LGE and quantify the percentage of myocardial fibrosis in patients with HCM evaluated with CMRI.

METHODS

We conducted an observational study of consecutive patients with documented or suspected HCM referred for contrast-enhanced CMRI to evaluate left ventricular morphology and function. The cohort consisted of patients >18 years retrospectively selected from our database between September 2013 and September 2014. Patients with moderate to severe heart valve disease or cardiomyopathies associated with hypertrophy were excluded from the study. Patients with wall thickness ≥ 15 mm with a diagnosis of HCM based on clinical, electrocardiographic and echocardiographic findings, and those with suspected HCM confirmed by CMRI findings, were retrospectively included. The results were compared with age- and gender-matched controls. The control group comprised subjects without diabetes or uncontrolled

hypertension, with normal CMRI who had been referred to undergo this study to rule out cardiomyopathy due to ventricular arrhythmia, syncope or non-conclusive echocardiograms. A normal CMRI was defined as the presence of cardiac chambers with normal dimensions and normal wall thickness, normal global and regional systolic function, absence of abnormal increase in T1- and T2-weighted sequences, pericardium with normal thickness and signal, great vessels with normal dimensions, absence of heart valve disease, congenital heart disease and/or cardiac masses, and absence of myocardial LGE.

Cardiac magnetic resonance imaging acquisition

Images were acquired using a 1.5-Tesla Achieva system (Philips Medical Systems, Best, The Netherlands). A vector-ECG-triggered scanner with a 5-element phased array cardiac coil was used for signal collection. The anatomic and functional test was done with balanced cine MRI images in stationary conditions, parallel image acceleration acquired during breath-hold using a repetition time (TR) of 3.5 ms, an echo time (ET) of 1.8 ms and an angle of 60° in the 2-chamber, 4-chamber, and short-axis views covering all the extension of the left ventricle (LV) and the outflow tract. Turbo spin-echo images and proton density images were also used with the black blood technique with TR of 1,935 ms and ET of 40 ms. Late gadolinium enhancement images were acquired using T1-weighted gradient-echo sequences after 10 minutes of intravenous gadolinium administration at a dose of 0.2 mmol/kg.

Cardiac magnetic resonance image analysis

The analysis was done on a workstation (ViewForum; Philips Medical Systems) using specific software. End-diastolic volume, end-systolic volume, end-diastolic diameter, end-systolic diameter, left ventricular ejection fraction (LVEF) and myocardial mass were determined. The end-systolic atrial area was estimated after delimitation of the borders, excluding the vein ostia and the left atrial appendage in the 2-chamber and 4-chamber views. The length of the anterior mitral leaflet was measured in the 3-chamber plane at end-systole. Left ventricular outflow tract obstruction was considered as the presence of systolic flow void at the outflow tract level.

Ventricular end-diastolic and end-systolic volumes were determined in the short axis cine sequences involving the entire ventricle. Endocardial and epicardial borders were contoured in a semi-automatic fashion excluding the papillary muscles. Maximum wall thickness was measured in 16 of 17 myocardial segments of the American Heart Association (AHA) classification, excluding the apex (AHA 17-segment model). (14) Myocardial mass was determined at end-diastole. Right ventricular hypertrophy was defined as right ventricular free wall thickness >5 mm. (15, 16)

Late gadolinium enhancement was visually defined as significant increase in signal intensity compared with remote

myocardium in the T1-weighted gradient-echo post-contrast images. This analysis has a high correlation with the one obtained using a threshold of 6 standard deviations above the mean signal intensity for the normal myocardium. (17-20) All the areas of LGE measured by semiautomated planimetry in relation with the area of normal myocardium were added and the total percentage of LGE in all the short axes was determined (Figure 1). The LGE patterns were divided in subendocardial, mid-wall, epicardial and transmural.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables with parametric and non parametric distribution were presented as mean±standard deviation or median with their corresponding 25-75% interquartile range, respectively. Student's t test or the Mann-Whitney U test was used to compare two groups with normal or non-normal distribution, respectively. Categorical variables were compared using Fisher's exact test. The association between continuous variables was analyzed by linear regression analysis, calculating Spearman's correlation coefficient. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 22.0 statistical package (Chicago, Illinois, USA).

Ethical considerations

All procedures were conducted according to the ethical standards of the institutional Research Committee and the recommendations of the 1964 Declaration of Helsinki and subsequent amendments. All the patients signed an informed consent form before participating in the study.

RESULTS

The cohort consisted of 42 patients with HCM and 31 controls. Mean age was 51.2±17.2 years and 46.6±15.9 years, respectively (p=0.25) and 67% (n=28) in the HCM group and 45% (n=149) in the control group (p=0.25) were men.

Morphological and functional evaluation

Statistically significant differences were observed in ejection fraction, end-systolic diameter, left atrial area and in the presence of mitral regurgitation between

patients with HCM and controls (Table 1).

Mean maximum wall thickness in HCM was 20.7±4.2 mm. In patients with HCM, the highest values of mean wall thickness were observed in the mid inferoseptal (16.8±5.3 mm), basal anteroseptal (16.5±6.2 mm), and mid anteroseptal segments (15.4±6.2 mm). Wall thickness >15 mm was more frequently observed in the basal anteroseptal (n=26, 69%), mid inferoseptal (n=24, 57%), mid anteroseptal (n=21, 50%) and basal anterior (n=15, 36%) segments. A median of 2.0 (1.75-4.0) segments had wall thickness >15 mm, whereas no segments ≥15 mm were identified in the control group. The prevalence of segments with wall thickness <4 mm was significantly lower in patients with HCM [HCM 0.0 (0.0; 2.0) segments versus control 3.0 (1.0; 4.0) segments, p<0.0001].

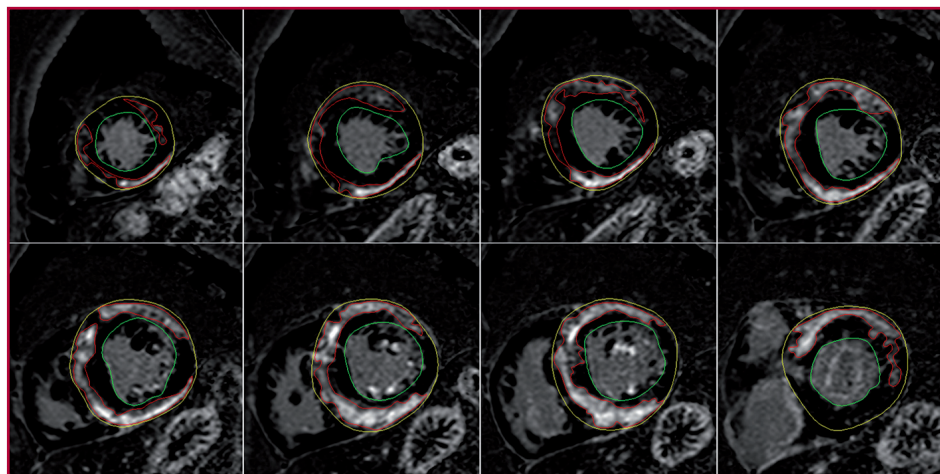
Dynamic left ventricular outflow tract obstruction (DLVOTO) was observed in 15 patients with HCM (36%) while 2 HCM patients (5%) had mid-ventricular obstruction. The anterior mitral leaflet length was significantly higher in patients with HCM compared with the control group (22.2±5.2 mm vs. 18.4±2.3 mm, respectively; p <0.001). Right ventricular hypertrophy was identified in 5 (12%) patients with HCM and in none of the patients in the control group.

Late gadolinium enhancement

Thirty patients (71%) with HCM had evidence of LGE in 141/672 (21%) of the segments evaluated. Late gadolinium enhancement was predominant in the mid-wall (n=103, 73%) and less frequent at the subendocardial (n=24, 17%), epicardial (n=10, 7%) and transmural (n=4, 3%) level (Figure 2). Late gadolinium enhancement was identified in 58/116 (50%) segments with wall thickness ≥15 mm and in 83/556 (15%) segments with wall thickness <15 mm (p<0.001) (Figure 3). The median number of segments with LGE per patient was 4.0 (0.0; 5.0).

After differentiating the HCM group according to the median extent of LGE, maximum wall thickness was significantly higher in the subgroup of pa-

Fig. 1. Calculation of total percentage of late gadolinium enhancement using manual planimetry. The outline between the internal and external lines (see color image in the web: red line) delimits the areas of late gadolinium enhancement at the level of the left ventricular myocardium. The internal and external lines (see color image in the web: green and yellow lines) encircle the endocardium excluding the papillary muscles and the epicardium, respectively.



tients with a larger extent of LGE (23.0 ± 4.0 mm vs. 18.2 ± 2.9 mm, $p < 0.0001$). Five (12%) patients were identified with LGE comprising 10% to 20% of myocardial mass and 2 (5%) patients with LGE% encompassing ≥ 20 % of myocardial mass. A significant association was found between total percentage

of LV LGE and maximum myocardial wall thickness ($r=0.43$, $p=0.0004$) and between total percentage of LV LGE and mean myocardial wall thickness ($r=0.38$, $p < 0.01$). However, the correlation between total percentage of LGE and myocardial mass indexed by body surface area was not significant ($r=0.17$, $p=0.29$).

	HCM (n=42)	Control (n=31)	p
Maximum wall thickness, mm±SD	20.7±4.2	8.9±1.8	<0.0001
LVEDD, mm±SD	48.8±5.1	50.3±5.8	0.26
LVESD, mm±SD	30.5±5.9	36.4±6.2	<0.0001
Myocardial mass, g±SD	158.1±52.2	83.1±27.2	<0.0001
LVEF, %±SD)	64.5±9.1	55.0±6.9	<0.0001
Cardiac index, L/min/m ² ±SD)	2.7±0.6	2.5±0.6	0.046
Left atrial area, cm ² ±SD	26.4±7.9	20.4±4.8	<0.0001
Right atrial area, cm ² ±SD	21.4±6.6	19.2±3.5	0.10
Mitral regurgitation, n (%)	12 (39%)	3 (10%)	0.02
Anterior mitral leaflet length, mm±SD	22.2±5.2	18.4±2.3	<0.0001
LVOT obstruction, n (%)	15 (36 %)	0	<0.0001

Table 1. Morphologic characteristics of patients with hypertrophic cardiomyopathy (HCM) and of subjects without evidence of structural heart disease

HCM: Hypertrophic cardiomyopathy. SD: Standard deviation. LVEDD: Left ventricular end-diastolic diameter. LVESD: Left ventricular end-systolic diameter. LVEF: Left ventricular ejection fraction. LVOT: Left ventricular outflow tract.

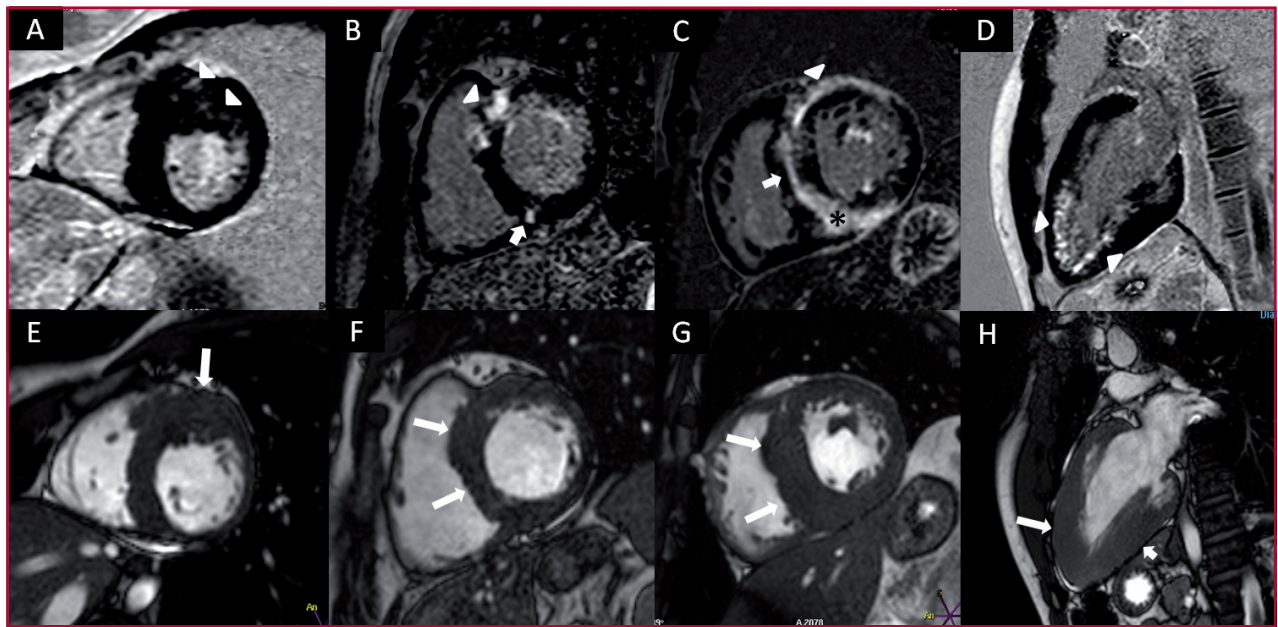


Fig. 2. Different patterns of late gadolinium enhancement in hypertrophic cardiomyopathy. The upper row shows images of late gadolinium enhancement and the lower row the cine-sequences at end diastole. **A** and **E**: Predominantly basal anterior segment hypertrophy (arrow) with mild mid-wall enhancement (arrowheads) and late gadolinium enhancement encompassing 7% of the left ventricular mass. **B** and **F**: Predominantly septal hypertrophy with areas of late gadolinium enhancement at the level of right ventricular insertion: anteroseptal (arrowhead) and inferoseptal (short arrow), with late gadolinium enhancement encompassing 8% of left ventricular mass. **C** and **G**: Predominantly septal hypertrophy (long arrows) with different patterns of late gadolinium enhancement: epicardial (arrowhead), mid-wall (short arrow) and transmural (asterisk), with late gadolinium enhancement encompassing 35% of the left ventricular mass. **D** and **H**: Apical hypertrophy (long arrow) and mid-ventricular hypertrophy (short arrow) with subendocardial enhancement typical of apical hypertrophic cardiomyopathy (arrowhead), with late gadolinium enhancement encompassing 12% of the left ventricular mass.

DISCUSSION

Although echocardiography is the initial tool for the diagnosis of HCM, the incorporation of CMRI to the diagnostic algorithm provides better morphologic characterization of the disease and can identify the presence of LGE as expression of fibrosis, with independent prognostic value. (5-7, 13)

In our population, mean maximum wall thickness was similar to the one reported in the literature. (5, 13) The study showed maximum wall thickness at basal and mid septal level.

The presence of segments with wall thickness <4 mm in the control group could be associated with the fact that there were more women in this group. Probably, the presence of thinner myocardial areas reported in HCM could be associated with the relative difference between hypertrophic and non-hypertrophic segments rather than with abnormal thinning. It is important to notice that we evaluated all the myocardial segments and not only the basal and mid segments usually measured by echocardiography.

About two thirds of patients with HCM present an asymmetric pattern with sigmoid septal contour and dynamic obstruction. (21-23) Two types of obstruction are identified: subaortic, which is the most common, and mid-ventricular. The former is mainly due to systolic anterior movement of the anterior mitral leaflet or to chordal movement towards the septum due to Venturi effect.

Patients with significant DLVOTO (>30 mm Hg) and mild symptoms are more likely to present progression to severe symptoms, heart failure and death. (24) Elongation of mitral valve leaflets, confirmed in our population, has been postulated as a morphological abnormality responsible for DLVOTO in combination

with a reduction in LV outflow tract diameter. (25)

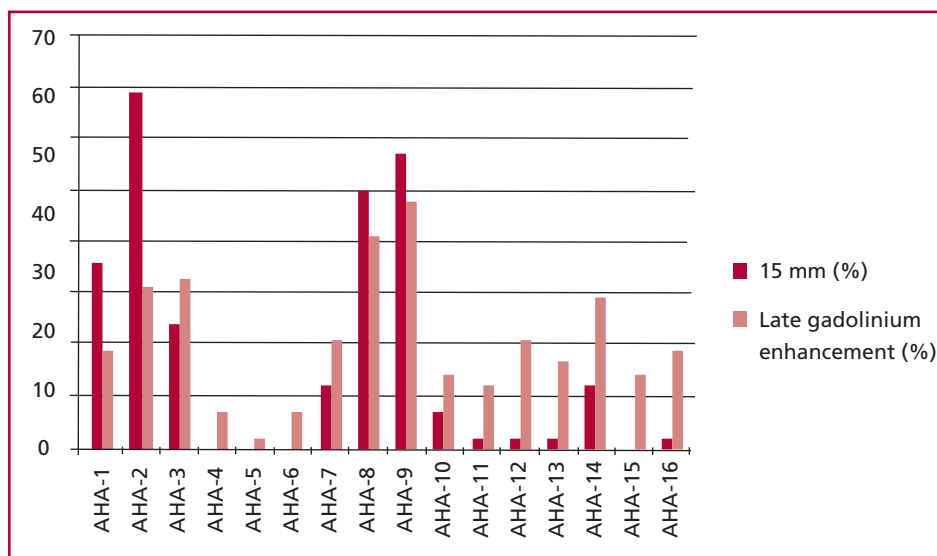
Considering the heterogeneity in the phenotypic expression of patients with HCM and the presence of LGE in a significant number of apical segments with wall thickness <15 mm, CMRI could provide a better and integral approximation of myocardial involvement.

Even though the exact pathophysiological mechanism of LGE in HCM is not clear, the most accepted theory is that gadolinium would accumulate in areas of fibrotic replacement secondary to ischemia, with subsequent myocardial necrosis resulting from structural involvement of intramural arteries, increased end-diastolic pressure and increased metabolic demand of the hypertrophied myocardium. (26)

In our population, 70% of the patients presented LGE, similar to the range between 40% and 80% reported in the literature. (27) In these patients, LGE was predominantly in the mid-wall, consistent with the report by Teraoka et al. who found gadolinium enhancement with a patchy distribution in 89% of patients with HCM. (28) The subendocardial pattern was less common and associated with apical HCM. (29) Notably, a significant percentage of apical segments presented LGE despite having wall thickness <15 mm.

Similar to previous publications reporting a significant though modest correlation between hypertrophy and LGE, we observed a significant (though weak) correlation between maximum myocardial wall thickness and the percentage of LGE, but no correlation between LGE and myocardial mass. (30, 31) Another interesting point was that 50% of the segments with ventricular wall thickness ≥ 15 mm presented LGE compared with only 15% of the segments with lower wall thickness.

Fig. 3. Bar chart showing the prevalence and spatial distribution of segments with wall thickness ≥ 15 mm and late gadolinium enhancement according to the classification of the American Heart Association (AHA1 basal anterior; AHA2 basal anteroseptal, AHA3 basal inferoseptal; AHA4 basal inferior; AHA5 basal inferolateral; AHA6 basal anterolateral; AHA7, mid anterior; AHA8 mid anteroseptal, AHA9 mid inferoseptal; AHA10 mid inferior; AHA11 mid inferolateral; AHA12 mid anterolateral; AHA13 apical anterior; AHA14 apical septal; AHA15 apical inferior; AHA16 apical lateral).



Late gadolinium enhancement was determined using the visual gray-scale method recommended in clinical practice. (13) Previous studies had reported a LGE pattern of intermediate signal intensity (“border zone”) which was associated with the reentrant mechanism and nonsustained ventricular tachycardia on ambulatory Holter monitoring. (32) The same group reported in a larger population that visual quantification of total LGE was a better predictor of sudden death than automated quantification of intermediate LGE intensity. Late gadolinium enhancement has been proposed as a potential arbiter to resolve implantable cardioverter defibrillator decision for sudden death primary prevention in patients with HCM and ambiguous risk stratification based on conventional risk factors. (13, 27) The mere presence of LGE would not be associated with an adverse outcome. The presence of greater extent of fibrosis is associated with higher risk of sudden death and with the development of systolic dysfunction and “end-stage” heart failure. (13) Our findings emphasize the importance of quantifying the percentage of myocardial mass with LGE in clinical practice as it is an easy technique that provides prognostic information when performed by expert hands.

Study limitations

As the study was performed at a single center, the number of patients included was relatively low; thus, a multicenter study including a larger sample would be necessary. The selection of patients with wall thickness >15 mm could have excluded patients with apical HCM. Therefore, these results should be considered for patients with HCM predominantly in basal and mid segments. However, this cut-off point is used in all the studies of patients with HCM. (13) The results comparing patients with HCM with a control group should be considered in the context that the study was not designed to compare both groups.

CONCLUSIONS

In patients with HCM evaluated with CMRI, maximum wall thickness was predominantly observed at basal and mid septal level. Two-thirds of these patients presented mainly an intramyocardial LGE pattern, with a significant association with maximum wall thickness but not with myocardial mass.

Conflicts of interest

None declared. (See authors’ conflicts of interest forms in the website/Supplementary material).

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