Late Enhancement and Myocardial Perfusion in Hypertrophic Cardiomyopathy (Comparison between Groups)

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Summary

Background: The magnetic resonance imaging (MRI) is an effective method to study hypertrophic cardiomyopathy (HCM).

Objective: To evaluate, using MRI, the parameters of systolic function, perfusion and myocardial viability in patients with HCM, comparing the groups with and without obstruction of the left ventricular outflow tract.

Methods: Twenty-one patients with a diagnosis of HCM underwent the assessment of myocardial function, viability and perfusion under stress and at rest through MRI.

Results: The ventricular segments most severely impaired by hypertrophy were those of the septal region. The obstructive group presented segmental myocardial thickening distribution similar to the non-obstructive group, but with higher means than the first group. The mean ejection fraction of the patients in the obstructive group was higher than in the non-obstructive group, whereas the means of the end systolic and diastolic volumes were lower in the obstructive group. There was a positive correlation between the ventricular segmental thickening and the late enhancement segmental mass. The stress induction resulted in an increase in the number of segments with perfusion alterations and this alteration was more evident in the obstructive group.

Conclusion: The thickest ventricular segments are the septal ones. The hypertrophic regions are associated to a greater extension of late enhancement. There was a positive correlation between the areas of ventricular hypertrophy and altered myocardial perfusion and these findings were more evident in the obstructive group. (Arq Bras Cardiol 2009; 93(3) : 396-402)

Key Words: Myocardial perfusion; hypertrophic cardiomyopathy; comparative study; resonance imaging.

Introduction

The cardiomyopathies are diseases of unknown cause, characterized by the primary involvement of the ventricular myocardium, and, therefore, are not secondary to the pre-existing diseases of the heart or the circulation[1].

The hypertrophic cardiomyopathy (HCM) is characterized by the hypertrophy of the myocardium, without an apparent cause[2]. The disease results from genetic abnormalities established in approximately 63% of the patients[3,4]. The main genes related to the disease are located in chromosome 14 – the locus responsible for the heavy chain of cardiac β-myosin; in chromosome 1 – o locus responsible for troponin T; and in chromosome 11, responsible for the binding of myosin to C-protein[5].

Usually, the disease clinically manifests in adolescence, with progressive myocardial hypertrophy during the growth spurt, but occasionally it can present in childhood or even before birth[6].

Patients with HCM can be classified as obstructive or non-obstructive, regarding the obstruction of the left ventricular outflow tract (LVOT). The obstruction has an important role in the prognosis and clinical evolution[7], consequently being an important independent factor for the development of severe symptoms of heart failure and death[2]. The Doppler-echocardiographic assessment characterizes as significant the type of obstructive HCM with intraventricular gradients > 30 mmHg[8].

Epidemiological analyses have demonstrated an estimated prevalence of the phenotypic expression of HCM in the general adult population of approximately 0.2% (1:500). It is estimated that there are 320,000 individuals with HCM in our country[9]. The study was carried out in a reference center in our country, which demonstrated a higher incidence of HCM in young adults, with a slight predominance of the female gender. The obstructive forms were observed in 53% of the patients[9].

The left ventricle (LV) hypertrophy is characteristically asymmetric, and the anterior septal wall is characteristically the one most often involved; but occasionally, the concentric form of the LV can be observed, which equally involves the septum and the free LV wall[2].

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Manuscript received October 02, 2007; revised manuscript received February 13, 2008; accepted March 04, 2008.

During a long time, the two-dimensional echocardiogram was considered the gold-standard method to evaluate the HCM[10].

Comparative studies between the echocardiogram and the cardiac magnetic resonance imaging (MRI) showed a higher capacity of the latter diagnostic method to study all LV segments, mainly in cases in which the disease affects other heart segments rather than the interventricular septum, as it occurs in the apical forms of hypertrophy[2].

The MRI allows the assessment, similarly to the echocardiogram, of the parameters of contractile ventricular function; however, it presents a higher accuracy in the calculation of volumes, mass and ejection fraction (EF), as it uses geometric models that combine the LV morphology with mathematical figures.

Therefore, the MRI has become the reference technique in cases where the exact calculation of the EF is necessary[10]. It also allows the assessment of myocardial viability parameters and perfusion alterations[11].

This study aimed at evaluating the myocardial perfusion and viability in patients with HCM through the MRI technique.

Methods

A total of 21 patients were studied prospectively, from December 2002 to August 2005, from the Myocardiopathy Clinic Unit of Instituto do Coracão (The Heart Institute – InCor) of the School of Medicine of the University of Sao Paulo (HCFMUSP), who had a confirmed diagnosis of HCM. The diagnosis of HCM was based on the echocardiographic demonstration of LV asymmetric hypertrophy, in the absence of any heart or systemic disease that could cause it. The criterion for the diagnosis of hypertrophy was LV septal telediastolic thickness ≥ 15 mm[12].

The study protocol was initiated after its approval by the Ethics Committee of Hospital das Clinicas and InCor. All patients received oral and written explanations on the study proposals and objectives and all of them signed the Free and Informed Consent Form.

Patients aged 18 to 60 years, with a previous diagnosis of asymmetric HCM and normal LV function, confirmed by echocardiogram, were enrolled in the study. The exclusion criteria included patients with contraindication to undergo MRI – those with hypertensive cardiomyopathy, non-sinusal rhythm, previous heart transplant, confirmed aortic stenosis, congenital heart defects, previous myocardial infarction and complex arrhythmias.

The patients were divided in two groups: obstructive and non-obstructive hypertrophic cardiomyopathy. The criterion used to consider the obstruction as significant was the presence of intraventricular gradients > 30 mmHg[8].

A venous access was obtained (Gelco 18) and connected to the pump used to administer the contrast into the antecubital vein, model Spectris MR Injector – Medrad, Pittsburgh, PA, USA. The chest was routinely prepared for the monitoring with four electrodes (Hewlett Packard MR, Massachusetts, USA) in the precordial region. The contrast used was gadopentetate dimeglumine, associated to Diethylene Triamine Penta Acetic Acid (Gd-DTPA) (Magnevist® – Schering AG, Berlin, Germany). The dose used in this protocol was 0.1 mMol/kg at each phase of perfusion (stress and rest), a dose considered to be safe for patients in good clinical condition.

Single Shot EPI with prospective ECG coupling was used with a repetition time of 9 ms (RT=9 ms), echo time of 4 ms (ET=4 ms), Flip angle (FA) = 40º, cut thickness of 10 mm, number of excitations (NEX) of 2 to 4, field of vision (FOV) of 380 to 420 mm, and matrix of 128 x 128, interpolated to 256 lines.

From the sagittal locator, the long LV axis was obtained using the echo-gradient sequence (Single Shot EPI), with prospective ECG coupling, repetition time of 9 ms (RT = 9 ms), echo time of 4 ms (ET=4 ms), Flip angle (FA) = 40º, cut thickness of 10 mm, number of excitations (NEX) of 2 to 4, field of vision (FOV) of 380 to 420 mm, and matrix of 128 x 128, interpolated to 256 lines (4-chamber view) to obtain the cine MRI.

From the 4-chamber view, the LV short axis planning was obtained to analyze the myocardial perfusion. The perfusion pulse sequence used was the Enhanced Fast Gradient Echo Train (EFGRET).

After the acquisition of LV short axis (6 to 8 slices), the pharmacological stimulation for hyperemia was performed with dipyridamole, at a dose of 0.54 mg/kg of body weight, infused in 4 minutes. During the peak action of dipyridamole (approximately on the second minute after the end of the infusion), gadolinium was administered (Magnevist – Schering) in *bolus* at a dose de 0.1 mmol/kg of weight peso (0.2 ml/kg of weight).

At the end of the perfusion image acquisition, aminophylin was administered at a dose of 3 mg/kg of body weight (maximum of 5 mg/kg) to antagonize the vasodilation effects of dipyridamole.

The patients were considered as having returned to the initial test conditions when the heart rate (HR) returned to the levels observed at the start of the study. When the HR returned to normal, we started the acquisition at rest. In the perfusion studies during the first passage, the acquisition of the stress sequence before the rest must be carried out due to the necessity of obtaining a first passage of contrast in a muscle without contrast. We repeated the perfusion sequence with a new injection of gadolinium at a dose of 0.1 mmol/kg, (0.2 ml/kg of weight) to obtain the basal pattern of perfusion at rest.

Images of the LV short axis and long axis were acquired using the sequence of Fast Card VT, coupled to ECG, FOV: 32-36, matrix: 256 x 192, thickness: 8,0 mm, Flip angle: 20, Prep Pulse (TI): variable, with a mean of 150 ms, NEX: 2, for the identification of late enhancement (LE).

The images obtained were submitted to post-processing with the software Report Card 3.0, by General Electric Medical System (Milwaukee, WI, USA) to evaluate the LV segmental thickness at the short axis of the 17 segments, according to the parameters defined by the American Heart Association in 2002 (Figure 1).

To evaluate the LV mass, the epicardial and endocardial borders were traced manually, excluding the papillary muscles and trabeculations in the images of the end-diastolic phase. The LV final volume was calculated by the Simpson's method, multiplying each planimetered myocardial area by the cut

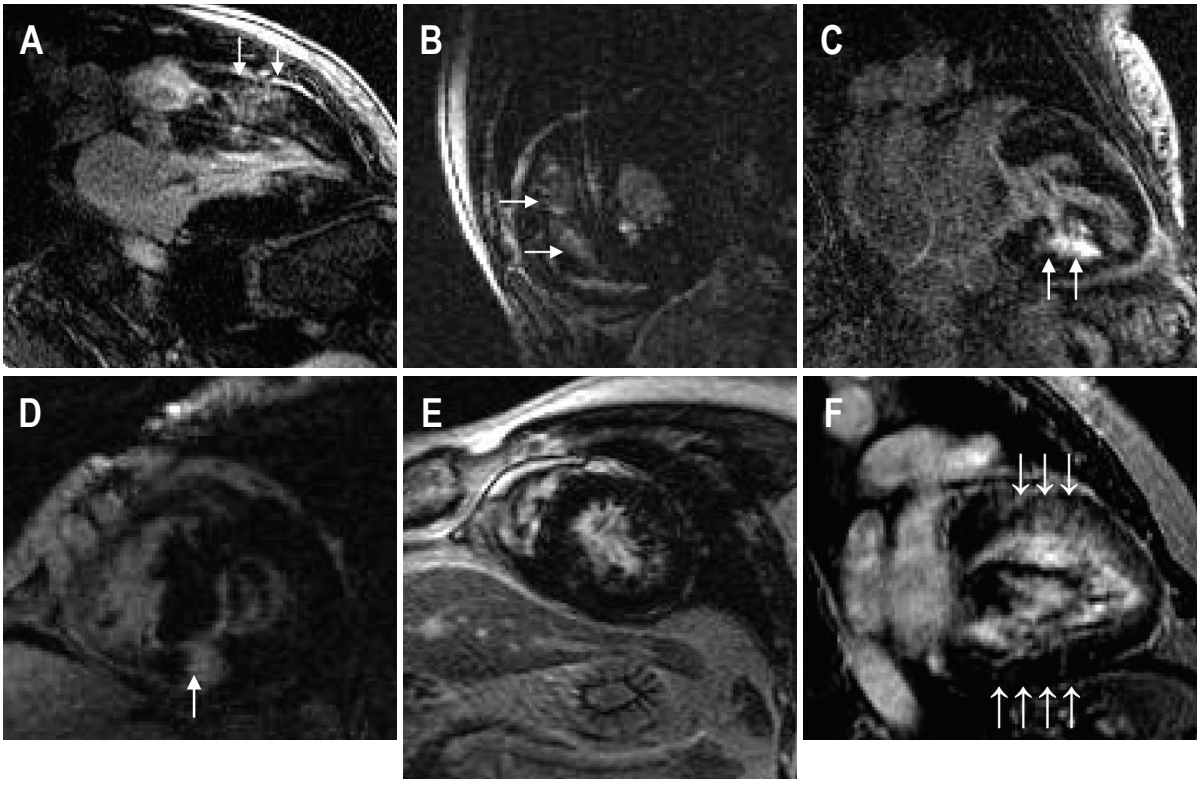

Fig. 1 – Transseptal-type diffuse late enhancement (A); confluent at the ventricular junction (B); multifocal (C); sub-endocardial (D). Arrows indicate areas of late enhancement.

thickness (10.0 mm) and adding the volumes of the sections obtained separately. The myocardial mass was calculated by multiplying the volume by the density of the myocardium (1.05 g/ml). The calculations of ESV and EDV were carried out in a similar way, using the areas of the end-diastolic short axis and end-systolic short axis, respectively. The ejection volume was calculated by subtracting the ESV from the EDV. The global EF was calculated by dividing the contraction volume by the EDV.

The myocardial images with late enhancement (LE) (white myocardium) were planimetered on the short axis after their visual identification, and the signal intensity difference > 2 SD above the remaining myocardium was considered significant. These areas were measured in each one of the 17 segments, according to the segmentation used by the American Heart Association and classified regarding the distribution as diffuse or confluent.

The perfusion data were analyzed through the visual identification method, associated to the signal intensity difference between the areas of normal myocardium and those with altered perfusion during the phases of stress and rest, by two experienced observers in each one of the 17 segments. The perfusion deficit areas appear black, whereas the remaining myocardium appears white with the contrast uptake. After the assessment of each observer, the data were correlated. The areas that presented LE were not considered as areas with perfusion deficit.

The divergent results between the two observers were unified through a consensus.

Statistical Analysis

Means, standard deviations (SD), medians and minimum and maximum values were used to compare the variables and for the analysis of the continuous variables. For the categorical variables, absolute and relative frequencies were used. The pattern of LV segmental thickness was analyzed by ANOVA (analysis of variance) and by multiple comparisons using Tukey's test. The comparisons of EF, EDV and ESV were obtained through *t* test for independent samples. The degree of correlation between the LV thickness and LE mass was obtained by Pearson's method for each one of the segments. The perfusion assessment data at rest and at stress were presented descriptively. The level of statistical significance was set at $p < 0.05$. The analyses were carried out using the statistical software Minitab, version 14.0.

Results

Of the 21 patients with HCM, 10 belonged to the non-obstructive group and 11 to the obstructive group, considering a pressure gradient at the outflow tract of 30 mmHg for the o obstructive group at the echocardiographic study. The proportion of male patients was higher in the non-obstructive

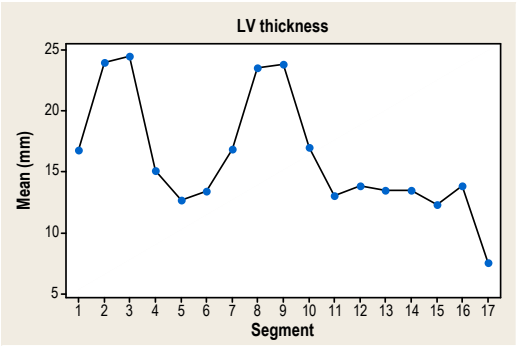

Chart 1 – Pattern of LV segmental thickness.

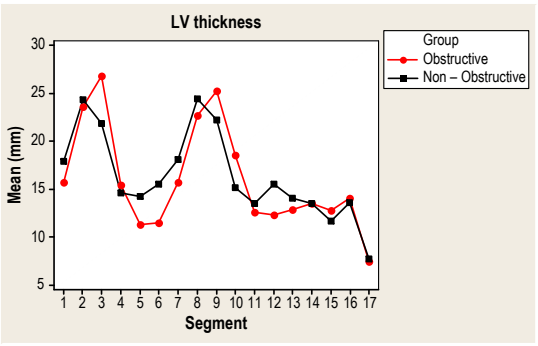

Chart 2 – LV segmental thickness per group.

group; however, it was not significant, according to Fisher's exact test (p = 0.659). There was no statistical difference regarding the mean age of the patients between the groups, according to the *t* test for independent samples, being 32.2 years in the non-obstructive group and 36.5 years in the obstructive group (Chart 1 and 2).

The LE distribution was classified as diffuse or confluent. The diffuse type was subdivided as transseptal and right ventricular septal and the confluent type, as multifocal, subendocardial and of ventricular junction[12]. In the present study, the transseptal diffuse distribution form predominated (n = 10), followed by the confluent multifocal form (n = 6).

The greatest LV thickness means were those of the basal anteroseptal, basal inferoseptal, mid-anteroseptal and mid-inferoseptal segments (2, 3, 8 and 9), and the lowest mean was the one found in the apical segment. The ANOVA test showed that there is actually a statistically significant difference among these means (p < 0.001). The multiple comparisons carried out by Tukey's test confirmed the findings (Figure 2).

The mean EF in the group of patients with obstructive HCM was higher than that observed in the non-obstructive group (mean ±SD = 77.6±7.8% in the obstructive group and 71.0±12.2% in the non-obstructive group); however, there was no statistically significant difference, according to the result of the *t* test for independent samples (p = 0.156) (Chart 3 and 4).

The ESV as well as the EDV mean was lower in the obstructive group when compared to the non-obstructive group; however, there was no statistically significant difference, according to the result of the *t* test for independent samples (ESV p = 0.495 and EDV p = 0.643).

The correlation between the LV segmental thickness and the LE segmental mass was statistically significant in most of the assessments, that is, in the basal-anterior, anteroseptal, inferoseptal, basal-inferior, mid-anterior, mid-anteroseptal, mid-inferolateral, apical-anterior, apical-septal and apical-lateral segments (1, 2, 3, 4, 7, 8, 11, 13, 14 and 16). The correlation was positive in all these segments, that is, the greater the segmental thickness, the greater the segmental mass of the LE.

The LV total mass was similar in the obstructive and non-obstructive groups, with no statistically significant difference between them (p = 0.901). The LE total mass did not present a statistically significant difference between the groups (p = 0.194), but the mean was lower in the obstructive group (19.7 g) than in the non-obstructive group (48.8 g). The linear correlation between these two parameters – LV mass and LE mass – was positive and significant, r = 0.613 (p = 0.003). Analyzing the groups separately, there was also a positive and significant correlation, with r = 0.725 (p = 0.012) for the obstructive group and r = 0.756 (p = 0.011) for the non-obstructive group.

The number of segments with altered perfusion was greater in the obstructive group (63.9%) when compared to the patients in the non-obstructive group (30%). The most severely affected segments in the non-obstructive group were 3 and 4 (basal-inferoseptal and basal-inferior segments), whereas in the obstructive group, they were 2, 3 and 8 (basal anteroseptal, basal inferoseptal and mid – anteroseptal segments).

Most of the patients from the assessed group did not present perfusion deficit at the rest phase, except for 1 patient from the obstructive group and 1 from the non-obstructive group. After the stress induction, 7 more patients (5 from the obstructive group and 2 from the non-obstructive group) started to present perfusion alterations in some segment. The statistical comparison by the Chi-square test showed that, during the stress perfusion, more segments were affected (p < 0.001), when compared to the rest phase.

There was a positive correlation between the greatest LV thickness with focal areas of perfusion deficit, being in the non-obstructive group in segments 1 (basal-anterior), 2 (basal-anteroseptal), 3 (basal inferoseptal), 7 (mid-anterior) and 8 (mid-anteroseptal); whereas in the obstructive group this correlation showed to be evident only in segments 2 (basal anteroseptal), 3 (basal inferoseptal), 14 (apical-septal) and 15 (apical-inferior). Considering the two groups together, the correlation was more evident in segments 1 (basal-anterior), 3 (basal inferoseptal), 7 (mid-anterior) and 14 (apical-septal).

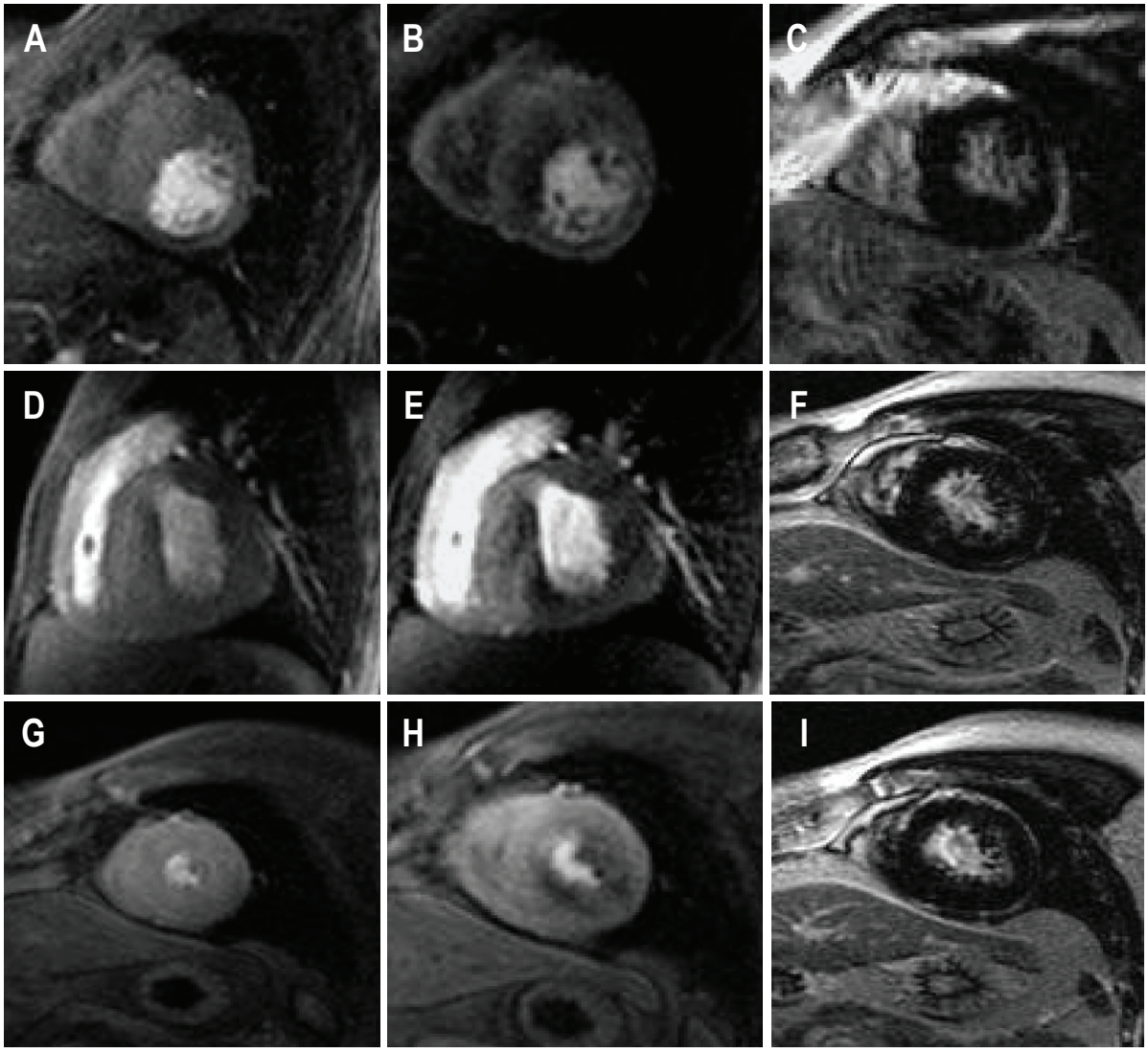

Fig. 2 – Short-axis images of the LV during the phases of perfusion at rest (A), undergoing stress (B) and of late enhancement (C). The arrows indicate areas of perfusion déficit.

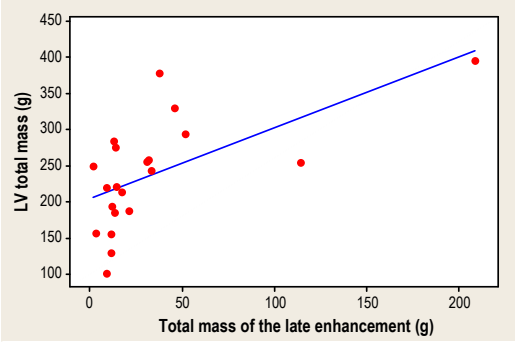

Chart 3 – Correlation between the LV total mass and total mass of the late enhancement.

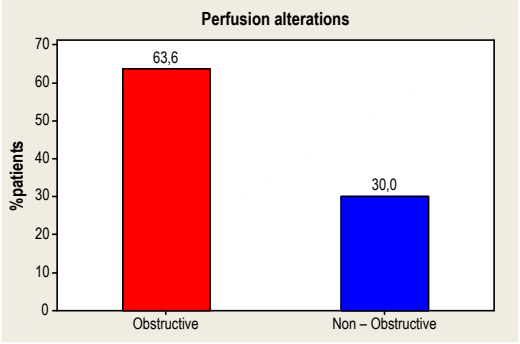

Chart 4 – Distribution of the percentage of patients with perfusion alterations in some segment (per group).

Discussion

The option to study the morphological and physiological aspects of the two groups of patients with HCM (obstructive and non-obstructive) by MRI was based on the premise that the differences between the interventricular gradients and between the ventricular segment thicknesses affected by hypertrophy could reveal important imaging findings, useful for the diagnostic, therapeutic and prognostic management of these patients.

As expected, considering the previous selection in the present study of patients with asymmetric septal hypertrophy by the echocardiogram, the evaluation of the segmental thickness in the obstructive and non-obstructive groups showed a predominance of a greater LV thickness in segments 2 (basal-anteroseptal), 3 (basal-inferoseptal), 8 (mid-anteroseptal) and 9 (mid-inferoseptal) – ($p < 0.001$) –, and a smaller thickness in segment 17 (apical) in the two groups. A previous study carried out an assessment of the role of MRI in determining the magnitude of LV hypertrophy in patients with HCM, comparing the MRI findings with echocardiographic data and verified that, similarly to our study, the hypertrophy predominated in the region of anterior ventricular septum in both the echocardiogram and the MRI[13]. Although the anterior portion of the ventricular septum is the area most commonly affected in the process of hypertrophy, the focal parietal thickening can compromise other myocardial areas, such as the posterior septum, apex, anterolateral wall, or even the posterior free wall[2,14,15]. Regarding the obstructive and non-obstructive groups, the overlap of the curves of the segmental ventricular thickness means showed a linear distribution that presented a similar aspect in the two groups, with slightly higher means being obtained in the obstructive group only in some segments, although without statistical significance. This information suggests that the obstruction is not a determinant factor for the increase in the myocardial thickness.

There was no statistically significant difference between the EF means in the obstructive and non-obstructive groups. These data show that the obstruction at the LV outflow tract did not directly interfere with the EF, at least in our study group. It is noteworthy that, in the present study, the parameters of systolic function were evaluated at the rest phase. This is important, considering that some patients have labile obstruction, that is, absent at rest, but triggered by alterations in the pre-load, post-load and contractility.

A study carried out in patients with HCM caused by the substitution of aspartic acid by asparagine (mutation Asp 175Asn) in the gene, to investigate the association between the myocardium contractile deficit and the LV hypertrophy by MRI demonstrated, similarly to the present study, that there is no difference in the EF measurement of hypertrophic patients (58%) when compared to the control group (61%); however, the authors observed that the fractional shortening values were lower in hypertrophic patients than in the controls (62%)[11].

In the present study, the ESV and EDV values were lower in the obstructive group when compared to the non-obstructive group, although the data were not statistically significant (ESV – $p = 0.495$ and EDV – $p = 0.643$). Literature data showed that the obstructive HCM is associated to the LV hyperdynamic contractile performance, presenting an EF level slightly above normal range, with compliance and diastolic dysfunction below the normal range, which is probably due to the several degrees of compensatory hypertrophy associated to variable phenotypic expression[15].

The present study showed a positive correlation between the increased ventricular segmental thickness and the presence of segmental perfusion alterations only in some segments. It is worth mentioning that it was difficult to obtain data with statistical significance, considering that the number of patients with affected segments was small in both groups.

When evaluating the first-passage perfusion during the rest and stress phases in 17 patients, Sipola et al[16] demonstrated that the degree of perfusion deficit in patients with HCM was associated with the intensity of ventricular hypertrophy, which suggests that these defects were possibly related to these patients' phenotype. Additionally, the authors observed a negative correlation between the maximum ventricular thickness and the global and segmental reserve index of the first passage of the contrast (signal intensity *vs*. time curve)[16]. These findings suggest that the ischemia occurs more often in the hypertrophic sites and that it is a potential risk of sudden death in patients with HCM, especially the young ones. Therefore, the extension of the hypertrophy seems to be related to the increased risk of sudden death.

In the present study, most patients did not present a perfusion deficit at the rest phase; however, at the stress perfusion, more segments are affected, mainly in the obstructive group.

These findings have an important clinical implication, suggesting that the ischemia is a risk factor in the pathogenesis of sudden death among patients with HCM, especially the young ones. These data can also have a prognostic value, as they demonstrate that, beyond the margins of the late enhancement areas (myocardium substituted by fibrosis/collagen), there are foci of perfusion alterations (ischemic), mainly during stress.

The positive correlation between the regions with greater LV segmental thickness and the LE segmental mass was verified in most of the segments evaluated in the present study. Similarly, a positive and significant correlation, $r = 0.613$ ($p = 0.003$),was demonstrated between the LV total mass and the LE total mass, also between the groups, with $r = 0.725$ ($p = 0.012$) for the obstructive group and $r = 0.756$ ($p = 0.011$) for the non-obstructive group. These findings can be related to the presence of the myocardial fascicular disarray associated to numerous tissue "grooves" and destruction of the normal circular architecture in the middle muscular layer of the hypertrophied myocardial regions[17], allowing the increased deposition of contrast, associated to its slower depuration, as mentioned before. At the sites that present fibrosis and increased extracellular space, there is an increased accumulation of gadolinium-DTPA and the kinetics of its distribution is slower than in the normal myocardium. These two effects result in a delayed and persistent gadolinium concentration in areas of the heart in which the extracellular space is abnormal[18,19].

Moon et al[20] carried out a histopathological study in the heart of a 28-year-old patient with HCM that was submitted to a heart transplant and obtained images of the hypertrophic tissue through MRI. The authors found an excess of collagen interlaced with

the myocardial cells that comprised up to 20% of the analyzed material. They also affirmed that there was a preferential distribution for the mesocardium, more than the endocardium or the epicardium. Also, according to this report, there was a similar distribution of the myocardial fibers that showed disarray, but this finding was independent from the presence or not of the collagen. The most relevant aspect, however, was that the areas with higher presence of LE corresponded to those in which there was a higher presence of collagen, reinforcing the hypothesis that the higher contrast intensity at the late phase, after the injection of the paramagnetic contrast medium, corresponds to the regions in which there is a higher presence of collagen[20].

In agreement to the present study, several authors confirmed the presence of LE in patients with HCM, demonstrating the positive correlation between the increased ventricular wall thickness and LE extension[21,22].

Conclusion

This study demonstrated that the LE was capable of effectively evaluating the global parameters of systolic function, myocardial perfusion and viability in HCM. It was demonstrated that the ventricular segments most severely affected by hypertrophy are the septal ones and that this distribution is similar in the obstructive and non-obstructive groups, although the first group presented greater mean thickness.

The regions with greater LV segmental thickness also presented greater LE segmental mass.

Although there was no statistical significance, there were more segments with perfusion alterations in the group with obstructive HCM, mainly after the stress induction.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Clarissa Almeida Sarmento, from Instituto do Coração (INCOR) da Universidade de São Paulo (USP).

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