Ecocardiographic Evaluation of Mitral Insufficiency in Patients with Hypertrophic Cardiomyopathy

Avaliação Ecocardiografica da Insuficiência Mitral em Pacientes com Cardiomiopatia Hipertrófica

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Abstract

Background: Hypertrophic Cardiomyopathy (HCM) is a genetic disease that affects thousands of people around the world.

Objectives: The present study aims to evaluate the presence of mitral regurgitation in patients with HCM, as well as its relationship with left ventricular Doppler echocardiographic variables. The mitral valve failure found in these patients is an extremely important finding, since it is able to predict the survival and mortality rate of the patients affected by HCM.

Materials and Methods: All echocardiograms performed from 2006 to 2016 in the echocardiographic service of Hospital de Base de São José do Rio Preto were evaluated. A total of 112,930 tests were gathered, of which those with HCM diagnosis or wall thickness >15 mm were selected and 132 patients were included in the analysis.

Results: Moderate and major mitral valve regurgitation is present in 25% and 5.3% of the patients, respectively, and MRI is independently correlated with the obstructive form of HCM.

Conclusion: Mitral regurgitation is a frequent finding in patients with CMP, however, significant MI is extremely uncommon and is correlated with the obstructive form of the disease.

Keywords: Cardiomyopathy, Hypertrophic; Mitral Valve Insufficiency; Echocardiography.

Resumo

Fundamentos: *A cardiomiopatia hipertrófica é uma doença de origem genética, que afeta milhares de pessoas em todo o mundo.*

Objetivos: *Avaliar a presença de regurgitação mitral em pacientes com cardiomiopatia hipertrófica, bem como sua relação com variáveis ecodopplercardiográficas do ventrículo esquerdo. A disfunção de valva mitral encontradas nesses pacientes mostra-se um dado de extrema relevância, visto que é capaz de predizer a sobrevida e a taxa de mortalidade dos enfermos acometidos pela cardiomiopatia hipertrófica.*

Métodos: *Foram avaliados todos os ecocardiogramas realizados no período de 2006 a 2016 no serviço de ecocardiografia do Hospital de Base de São José do Rio Preto, sendo o total de 112.930 exames. Foram selecionados aqueles com diagnóstico de cardiomiopatia hipertrófica ou espessura parietal > 15 mm, e incluídos na análise 132 pacientes.*

Resultados: *Regurgitação valvar mitral de grau moderado e importante esteve presente em 25% e 5,3% dos pacientes, respectivamente, sendo que a regurgitação mitral esteve independentemente correlacionada com a forma obstrutiva de cardiomiopatia hipertrófica.*

Conclusão: *A regurgitação mitral é achado frequente em pacientes com CMP, no entanto, a insuficiência mitral importante é extremamente incomum e está correlacionada com a forma obstrutiva da doença.*

Palavras-chave: *Cardiomiopatia Hipertrófica; Insuficiência da Valva Mitral; Ecocardiografia.*

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Introduction

Hypertrophic cardiomyopathy (HCM) was described in 1958 by pathologist Donald Teare from the analysis of eight cases of sudden death, representing a pattern of asymmetric ventricular hypertrophy.[1] It is an autosomal-dominant disease caused by 50 mutations isolated in genes involved in the coding of proteins present in the cardiac sarcomere.[2] More than seven genes may be involved in the etiology of the disease and are responsible for the coding of cardiac troponin T, tropomyosin, myosin binding C protein, essential myosin light chains and regulatory myosin, cardiac troponin I and cardiac actin.[3]

This disease is considered relatively common in the population, with prevalence of 1:500, affecting both men and women, equally.[4]

HCM usually has a benign and asymptomatic course.[5] Some patients may develop secondary complications and evolve to sudden death. It is reported in the statistics as the leading cause of death among young people and athletes under 35.[6] Symptoms prevail between the second and fourth decade of life and are more severe when older patients are affected.[7]

Notably, HCM was defined in the echocardiographic study by the presence of maximum left ventricular wall thickness ≥15 mm in any left ventricular segment. However, analyzing the different types of HCM, there was a predominance of the septal form (88% to 90%); the mid-ventricular and lateral (11.3%) forms were the least found.[8] The range of disorders contributes to left ventricular diastolic function damage. Such changes lead to increased left ventricular end-diastolic pressure and symptoms of heart failure associated with reduced exercise tolerance.

The first test recommended for patients with suspected HCM is the 12-lead electrocardiogram. Conditions like T-wave abnormality, ST-segment, left ventricular overload criteria, as well as pathological T-waves[9] are observed in 94% of suspected patients.

Transthoracic echocardiography is of significant importance in the diagnosis and follow-up of HCM, as it is capable of identifying the presence of structural and functional disorders. The main parameters analyzed include: cavity dimensions; hypertrophy site; evaluation of intraventricular gradient, mitral systolic anterior motion, mitral regurgitation; and diastolic function. Also, Doppler echocardiography is capable of differentiating nonobstructive and obstructive forms of the disease.[2]

HCM also affects other cardiac structures, such as the entire mitral valve apparatus. It is possible to identify, in 45% of obstructive cases, that the anterior leaflet of the mitral valve is elongated or anomalously inserted directly into the papillary musculature.[10] As a result, an abnormality is seen in the left ventricular outflow tract and a pressure gradient develops.[11-15] As a consequence, there are several abnormalities of the mitral valve cusps. There is an abnormal systolic anterior motion (SAM) of the anterior cusp. The SAM can be classified as mild (approximation between the cusp and the septum but no contact), moderate (presence of slight contact between the cusp and the septum) or severe (contact greater than 30% of echocardiographic systole).[16]

Major mitral regurgitation (MR) may be present in up to 10–20% of the cases, probably due to anterior systolic movement (ASM) of the anterior cusp with coaptation failure.

In this context, evaluating the presence of major MR implies worse prognosis because it correlates with greater ventricular and valvular abnormality. This study aims to assess the presence of MR in a sample of HCM patients and to correlate this condition with the degree of valve involvement.

Methods

Retrospective study conducted by reviewing an online database of 112,930 echocardiographic scans performed from 2006 to 2016 at the echocardiography service of a tertiary hospital specializing in the treatment of cardiomyopathies, the echocardiography service of which was a reference in the state of São Paulo, with a flow greater than 10,000 tests per year, with a registry base of more than 180,000 tests on file (Figure 1).

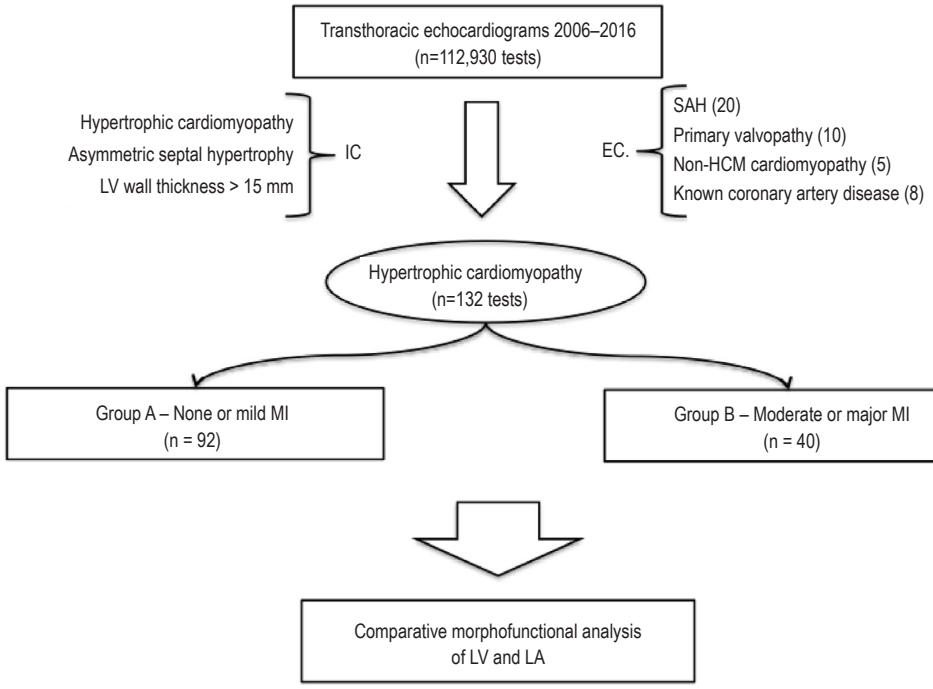
Inclusion criteria were diagnosis of HCM with wall thickness greater than 15 mm in the absence of other causes of ventricular hypertrophy, such as hypertension, valvular or primary myocardial cardiomyopathy, and significant coronary disease. The 132 patients who met the criteria were divided into two groups: Group A (n=92) with none or mild mitral regurgitation (grade zero and 1) and Group B (n=40), with moderate or severe mitral regurgitation (grades 2 and 3). Left ventricular and left atrial demographic and morphofunctional variables, pulmonary artery systolic pressure (PSAP), obstructive form of HCM, LVOT gradient and greater wall thickness were evaluated (Table 1).

All patients underwent transthoracic echocardiography to assess the degree and extent of hypertrophy and the severity of mitral regurgitation. LVOT gradient was determined by acquiring LVOT velocity using the Bernoulli equation (peak gradient=$4v^2$). The severity of mitral regurgitation was estimated according to the current guidelines, based on the MR jet area, vena contracta, regurgitant orifice area and pulmonary venous flow reversal. All cases were evaluated by more than one echocardiographer.

Statistical analysis

The statistical analysis was performed with the Statistical Package for Social Science (SPSS) software, version 23. Categorical variables were expressed as number and percentages and continuous variables as median and interquartile range or mean and confidence interval according to their distribution. The groups were evaluated separately, determining which variable was significantly different. Then, linear regression analysis was performed involving the different variables and the degrees of MR. Comparative analysis between groups was performed using Fischer's exact test for categorical variables and Mann-Whitney's and Kruskal Wallis' nonparametric test for numerical variables.

The relationship between the significantly different variable (obstructive form) and the degree of MR was tested by linear and multiple regression.



LV: left ventricle; IC: Inclusion criteria; EC: Exclusion Criteria; SAH: systemic arterial hypertension; HCM: hypertrophic cardiomyopathy; MR: mitral regurgitation; LA: left atrium.

Figure 1 – *Methodology adopted for this study.*

Results

Analyzing a population sample of 132 patients diagnosed with hypertrophic cardiomyopathy, it was found that mitral regurgitation of any severity degree was present in 84.3% (n=112) of HCM patients, with 54.5% of mild degree (n=72), 25% of moderate degree (n=33) and 5.3% (n=7) of major degree (Figure 2).

According to the degree of mitral valve involvement, patients were categorized into the following groups: Group A — Mitral regurgitation grade 0 and 1, and Group B — Mitral regurgitation grade 2 and 3. Group B and A differed significantly only as to the obstructive form (22.5% vs. 2.2%, $p<0.001$) and moderate or major left atrial enlargement (57.1% vs. 26.1%, $p<0.001$) (Table 2).

No significant statistical association with the other data analyzed was observed in this population sample ($p>0,05$). These include age, association with the male sex, Left atrium diameter (LAD), Left ventricular diastolic dysfunction (LVDD), Left Ventricular Systolic Debt (LVSD), Interventricular septum (IVS), left ventricular posterior wall (LVPW), S/P ratio, fractional shortening (fenc), LVEF, grade 2 or 3 diastolic dysfunction, LVOT, right ventricular hypertrophy) (RVH) or Right Ventricular Systolic Pressure (RVSP) gradient.

Discussion

Diagnosis of HCM, defined as the presence of increased LV wall thickness not associated with abnormal loading conditions, is based on the detection of ≥15 mm thickness in one or more LV segments by any imaging test, such as echocardiography, cardiac magnetic resonance imaging or computed tomography. However, due to the diverse etiology of the disease, laboratory tests and genetic analysis can be performed.

Echocardiography is considered an indispensable method to distinguish between the obstructive and non-obstructive forms of HCM, as well as to evaluate the mechanisms that cause obstruction. Consequently, M-mode echocardiography revealed that flow restriction does not result from muscle constriction,[18] but is determined by the close interaction between the interventricular septum, mitral valve and flow vectors originating in the ventricular cavity.[19] HCM can be considered obstructive in the presence of a systolic gradient greater than 30 mmHg at rest; values greater than 50 mmHg turn out to be hemodynamically important.

Contact between the anterior valve leaflet and the septum is related to the anterior displacement of the papillary muscles and the valve apparatus, favoring a reduction of the LVOT area.[20]

Table 1 - Echocardiographic variables analyzed.

Left atrium	LA anterior-posterior diameter
	Presence and degree of LA enlargement
	Left atrial volume (Simpson)
	LA volume index
Left ventricle	LV end-diastolic diameter
	LV end-systolic diameter
	LV interventricular septum thickness
	LV posterior wall thickness
	LV shortening fraction
	LV ejection fraction
	Presence of LV diastolic dysfunction
	Degree of LV diastolic dysfunction
	Greater LV wall thickness
	LV hypertrophy standard
	Presence of LV gradient – LVOT at rest
	Presence of LV mid-ventricular gradient
	Minimum LVOT gradient
	Presence and degree of mitral regurgitation
Right ventricle	Presence of RV hypertrophy
	RV systolic pressure

LA: left atrium; LV: left ventricle; LVOT: left ventricular outflow tract.

The presence of LVOT obstruction and mitral regurgitation occur simultaneously due to the mitral valve ASM, which begins in the rapid left ventricular ejection phase. Therefore, in most patients with obstructive HCM, the degree of mitral regurgitation is dependent on ASM.[20-24]

Previous studies have reported a direct relationship between the presence of LVOT obstruction and the degree of mitral regurgitation. Previous disagreements related to the severity of mitral regurgitation and left ventricular pressure gradient are due to the absence of diseases associated with the leaflets, annulus and papillary muscles of the mitral valve apparatus. In the treatment of patients with obstructive HCM and mitral regurgitation resulting from ASM, myectomy promotes reduced severity of mitral regurgitation.[25]

The finding of mitral regurgitation resulting from valve failure was frequent in patients with obstructive HCM and is directly associated with ASM. However, severe MR is an uncommon finding in HCM, as it is more common in cases of mild/moderate MR. Thus, data obtained in the study were consistent with literature references.

Therefore, transthoracic echocardiography has proven decisive in the diagnosis, follow-up and in the perioperative management of patients with mitral regurgitation associated with HCM.

Conclusion

Major mitral regurgitation is uncommon in patients with hypertrophic cardiomyopathy, where mild and moderate forms prevail. Besides, the obstructive form of the disease correlated significantly with the finding of mitral regurgitation.

Authors' contributions

Research creation and design: Oliveira MB, Noriega AF, Miranda JR, Ricci GA, Ribeiro MBM, Oliveira MB, Murad Jr AJ. Data acquisition: Oliveira MB, Miranda JR, Ricci GA,

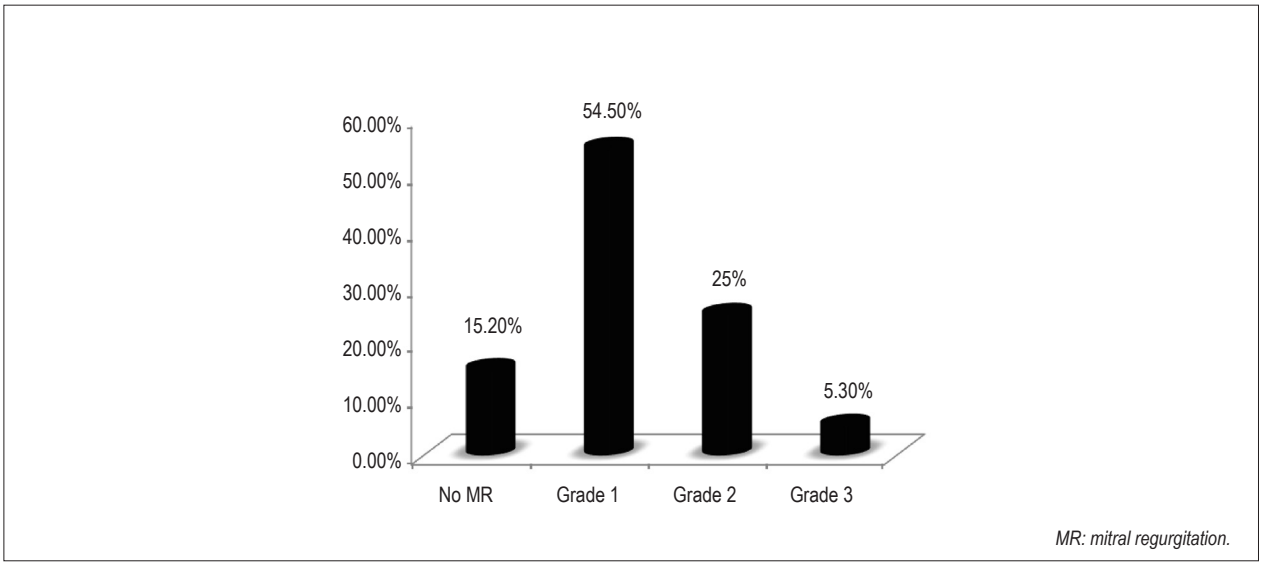


Figure 2 – *Presence and degree of mitral regurgitation in HCM patients.*

Table 2 - Baseline characteristics in the total group (n=132) and comparison between group A (n=92) and group B (n=40).

Variables	Total (n = 132)	MR grade 0 or 1	MR grade 2 or 3	P value
Age	53 (41-56)	50 (37-64.75)	55.5 (48.5-68)	0.092
Male	76 (57.6)	58 (63)	18 (45)	0.059
LAD	42.5 (38-48)	42 (38-46.75)	44.5 (36.5-49)	0.317
Moderate/major LA enlargement	**47 (35.1)**	**24 (26.1)**	**23 (57.5)**	**0.001**
LVDD	46 (41-50)	46 (42-50)	44 (37.25-50.75)	0.38
LVSD	26 (23-30)	27 (24-30)	25 (17.25-21.75)	0.264
IVS	18.75 (17-21)	18 (16.25-20)	20 (17.2-21.7)	0.058
LVPW	11 (9.25-12)	11 (9-12)	11 (10-14)	0.119
S/P ratio	1.68 (1.46-2)	1.7 (1.46-2)	1.64 (1.36-2)	0.559
Fenc	41 (36-46)	40 (35-46)	42.5 (36.2-48)	0.168
LVEF	71.5 (65-78)	71 (65-77)	74 (65.2-79)	0.167
Diastolic dysfunction grade 2 or 3	16 (11.9)	9 (9.8)	7 (17.5)	0.706
Obstructive form	**11 (8.2)**	**2 (2.2)**	**9 (22.5)**	**<0.001**
LVSD gradient	73 (44-103.75)	44 (41-60)	92 (62.5-111)	0.078
LVH	5 (3.8)	3 (3.3)	2 (5)	0.639
RVSP	42 (29-50.5)	38 (27.7-43.7)	46 (31-51)	0.184

MR: mitral regurgitation; LA: left atrium; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract.

Basaglia B, Oliveira MB, Murad Jr AJ. Data analysis and interpretation: Oliveira MB, Noriega AF, Ricci GA, Basaglia B, Ribeiro MBM, Oliveira MB, Murad Jr AJ. Statistical analysis: Noriega AF, Miranda JR, Ricci GA, Oliveira MB, Murad Jr AJ. Manuscript writing: Oliveira MB, Noriega AF, Miranda JR, Ricci GA, Basaglia B, Ribeiro MBM. Critical revision of the manuscript for important intellectual content: Oliveira MB, Noriega AF, Miranda JR, Ricci GA, Basaglia B, Ribeiro MBM, Oliveira MB, Murad Jr AJ.

Conflict of interest

The authors declare that there is no conflict of interest regarding this manuscript.

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