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Evaluation and implications of mitral regurgitation using cMRI in patients with hypertrophic cardiomyopathy

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Abstract. – OBJECTIVE: Mitral regurgitation (MR) represents an important feature in patients with hypertrophic cardiomyopathy (HCM) due to left ventricular outflow tract (LVOT) obstruction and mitral valve systolic anterior motion (SAM). Mitral valve anatomical variants associated with HCM also contribute to the severity of MR. The aim of this study is to evaluate MR severity and its correlation with different parameters in patients with HCM using cardiac magnetic resonance imaging (cMRI).

PATIENTS AND METHODS: 130 patients with HCM underwent cMRI. Parameters assessed for the quantification of MR severity were mitral regurgitation volume (MRV) and mitral regurgitation fraction (MRF). cMRI was also used to characterize LV function, left atrium volume (LAV) index, filling pressures and structural abnormalities associated with HCM, all in correlation to MR.

RESULTS: Patients with HCM had mild (26.9%), moderate (52.3%) or severe (20.7%) MR. Most relevant parameters related to MR severity were MRV and MRF; other parameters with strong correlation with MR were LAV index and E/E' ratio, both increasing with its severity. Patients with LVOT obstruction had more severe MR (70.3%), 79% of them due to SAM. LV ejection fraction (LVEF) increased proportionally with the severity of MR, while LV strain (LAS) was inversely correlated with it. Independent predictors for quantifying the severity of MR, after the adjustment for covariates, were MRV, MRF, SAM, LAV index and E/E'.

CONCLUSIONS: cMRI can accurately assess MR in patients with HCM, especially by using novel indicators, MRV and MRF respectively, along with LAV index and E/E' ratio. Severe MR, due to SAM, is more frequent in the obstructive form of HCM (HOCM). Also, the severity of MR is significantly associated with significantly associated with MRV, MRF, LAV index and E/E' ratio.

Key Words:
Hypertrophic cardiomyopathy, Cardiac magnetic resonance imaging, Mitral regurgitation, Left atrium volume.

Abbreviations
CT: Computed Tomography; CBCT: Cone Beam Computed Tomography; ANOVA: Analysis of Variance; IAN: Inferior Alveolar Nerve; USA: United States of America; IBM SPPS: International Business Machines

Introduction

The complexity of hypertrophic cardiomyopathy (HCM) derives from its distinctive pathophysiology, primary involving the left ventricular (LV) hypertrophy, with important consequences on adjacent structures, including the mitral valve apparatus. Mitral regurgitation (MR) has confounding mechanisms in patients with HCM. Besides LV outflow tract (LVOT) obstruction and the systolic anterior motion (SAM) of the mitral valve, the physiology of MR in HCM implies also primary structural abnormalities of the mitral apparatus, as part of the phenotypic variability of HCM[1,2]. Thus, mitral valve pathology in patients with HCM is compound of primary and secondary MR mechanisms, having major implications in the prognostic and treatment strategies[3,4]. Characterization of the mitral valve and quantification of MR remains in the spotlight of imaging techniques in patients with HCM.

Although echocardiography is the initial imaging method used for the assessment of MR, cardiac

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magnetic resonance imaging (cMRI) offers a more reliable and accurate evaluation of the mitral valve pathology[5,6]. The contribution of cMRI in patients with HCM is of highly importance both for MR evaluation and for tissue characterization of the myocardium[7].

The importance of conventional cMRI in the evaluation of MR for patients with HCM consists in deciding the optimal surgical strategy (by removing the LVOT obstruction *via* myomectomy, one can lower the severity of MR and even eliminate the necessity of concomitant mitral valve surgery), as well as in improving the clinical status of the patients (heart failure symptoms, onset of atrial fibrillation (AF)][8,9].

Cine-cMRI can accurately describe the valve morphology: anterior and posterior leaflets, the mitral annulus, the chordae, papillary muscles, and any structural abnormalities associated with HCM[10]. There are multiple cMRI methods for the quantification of MR, independent of the characteristics of the jet. The mitral regurgitation jet can be visualized by 2D cine imaging but is not a reliable method for evaluating MR severity. The recommended cMRI tool for quantitative assessment of MR severity is an indirect method, which combines 2D cine imaging and phase-contrast velocity mapping to quantify the mitral regurgitant volume (MRV) and fraction (MRF)[11].

However, considering the complexity of HCM, imaging methods, specifically cMRI, should integrate the mitral valve pathology among the others intrinsic consequences of the disease. It is well known that the left atrium (LA) and filling pressure are modified in HCM[9] and also in MR, independent of HCM. An overview of the correlation between LA, LV function, filling pressures and MR in patients diagnosed with HCM can provide valuable information for both a more accurate diagnosis and therapeutic conduit.

The aim of this study was to evaluate MR severity in patients with HCM by cMRI, along with different parameters that can optimize the diagnosis of MR.

Patients and Methods

Study Population

This is a prospective study conducted on 130 consecutive patients with a diagnosis of HCM who underwent a cMRI for HCM assessment between March 2019 and January 2022. The inclusion criteria[12] comprised: LV hypertrophy ≥15 mm in one or more LV myocardial segments in adults or ≥13 mm in adults with relatives with HCM, in the absence of other diseases that could cause LV hypertrophy, by echocardiography or cMRI. The exclusion criteria were represented by: history of coronary artery disease, other cardiomyopathies, significant valvular heart disease and congenital heart disease; history of septal myectomy or alcoholic septal ablation; AF permanent or at the time of cMRI; contraindications to cMRI (incompatible metallic devices, chronic renal disease with estimated glomerular filtration rate <30 mL/min/1.73 m^2 or claustrophobia); refusal to participate in the study (Figure 1).

We recorded demographic data including age, gender, height, weight, medical history, cardiovascular symptoms (dyspnoea, syncope, palpitations) and current medication. We performed a 12-lead ECG, 24-hour Holter monitoring, transthoracic echocardiography and cMRI; N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) was also determined.

All patients were informed about the investigation protocol and a written informed consent was obtained from all study participants. The current research has been approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca - decision number 75/11.03.2019. The study was conducted in accordance with the principles of the Declaration of Helsinki.

cMRI Imaging Protocol

All cMRI images were ECG-gated and were acquired during apnoea with a 1.5 T Open Bore system MR scanner (Magnetom Altea, Siemens Medical Solutions, Erlangen, Germany). A standard scanning protocol, in accordance with current international guidelines, was used[13]. The acquisition of fast imaging, employing steady-state free precession (SSFP) sequences, was performed to detect ventricular function and mass in the conventional cardiac short-axis and long-axis planes. This included two-chamber, three-chamber, and four-chamber view, to enclose both ventricles from base to apex. Sequence parameters SSFP were as follows: repetition time (TR) 3.6 ms; echo time (TE) 1.8 ms; flip angle 60°; slice thickness 6 mm; field of view (FOV) 35×35 cm; image matrix of 192×192 pixels; voxel size 1.9×1.9×6 mm; 25-40 ms temporal resolution reconstructed to 25 cardiac phases. Late gadolinium enhancement (LGE) imaging was performed to detect focal myocardial fibrosis, acquired 10 minutes after intravenous administration of 0.2 mmol/kg ga-

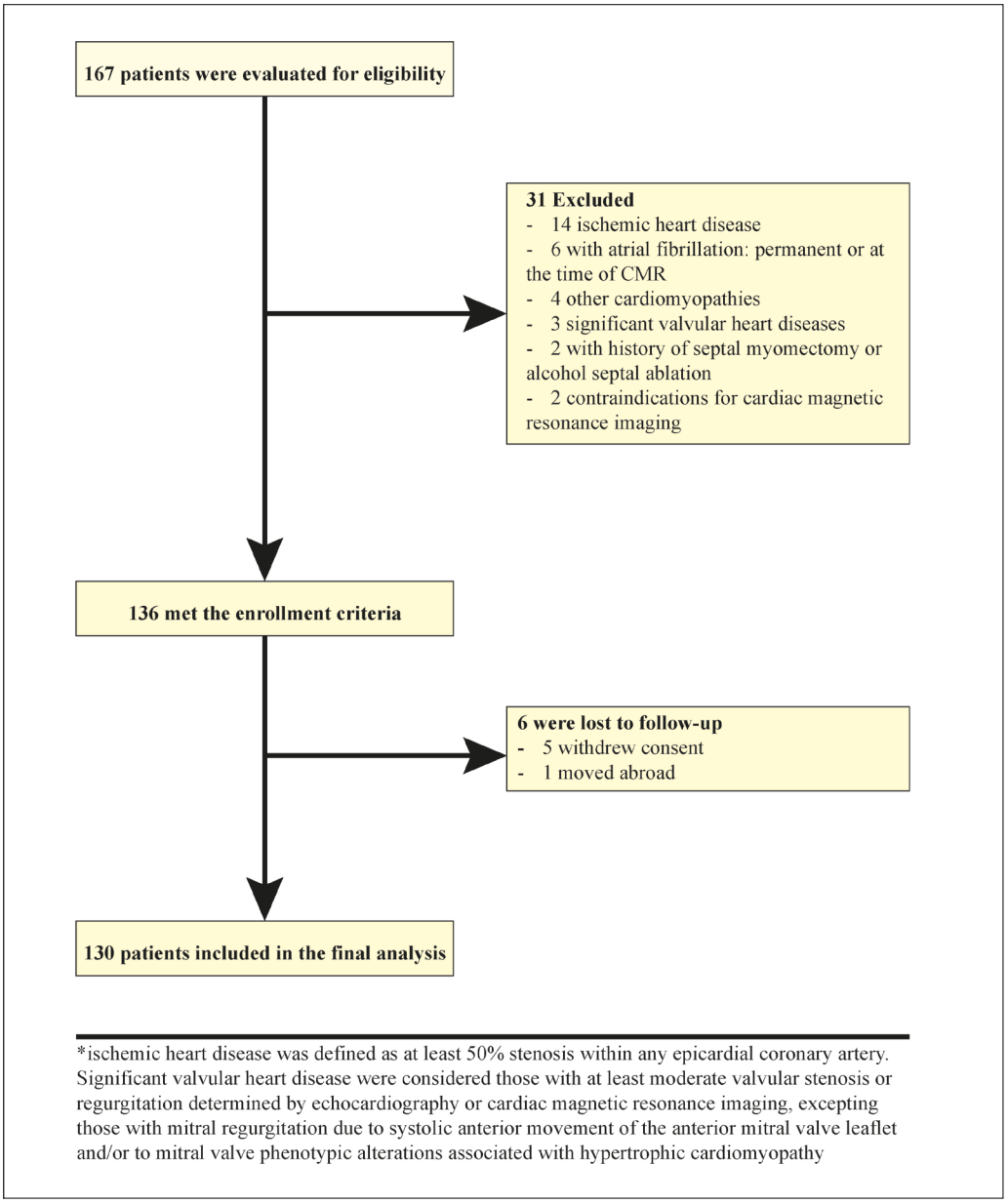

Figure 1. Flow chart detailing the identification of the study cohort.

doxetic acid (Clariscan, GH Healthcare AS, Oslo, Norway), in long- and short axis-views, using a segmented inversion-recovery gradient-echo sequence. LV-LGE sequence parameters were presented as: TR 4.8 ms; TE 1.3 ms; slice thickness 8 mm; spacing 10 mm; image matrix of 224×160 and inversion time 200 to 300 ms. Inversion time was adjusted to optimize nulling of apparently normal myocardium. Brachial blood pressure was monitored during cMRI-SSFP acquisitions.

The method used for quantifying MR severity was the indirect method, based on cine-SSFP imaging and 2D PC- cMRI velocity mapping. PC images were acquired perpendicular to the proximal pulmonary artery and/or aorta, quantifying flow using nominal parameters: TR 7.5 ms; TE 2.9 ms; 6 views per segment; velocity encoding 250 cm/s; FOV 35×35 cm; image matrix of 256×128; slice thickness 4 mm; temporal resolution 25-45 ms and flip angle of 20°. This method generated an enlarged image that showed

the anatomy of the aortic valve and the phase map that encodes the velocities in each voxel. Transmitral flows were measured from a single retrospectively ECG-gated two-dimensional through-plane velocity-encoded PC-cMRI dataset acquired under the breath-hold duration of 22-30 seconds. The transmitral acquisition plane was positioned at the tips of the mitral valve leaflets and orthogonal to the diastolic filling flow direction for the two ventricles. The scan parameters for transvalvular PC-cMRI were TR 3.7 ms; TE 1.5 ms, acquisition matrix 260×192; flip angle of 50°; FOV of 32×42 cm; slice thickness 8 mm; 2 views per segment; velocity encoding 150 cm/s, and effective temporal resolution 15 ms. PC myocardial tissue longitudinal velocity imaging was performed using the same acquisition parameters but with a lower encoding velocity of 20 cm/s, in a short-axis view parallel to both the mitral valve annulus and the tricuspid valve annulus.

cMRI Imaging Analysis

LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction and end-diastolic LV mass (LVM) were measured on short-axis cine-SSFP images. Epicardial and endocardial borders were traced semi-automatically at end-diastole and end-systole using a specialized software (Syngo Virtual Cockpit, Erlangen, Germany). All volumes were indexed to body surface area (BSA). Furthermore, to accurately characterize LV's function, LV longitudinal-axis strain (LAS) was assessed[13]. LV-LGE was assessed using short-axis images, with a 17-segments model, as suggested by the American Heart Association[14] and quantified using a signal intensity threshold of >5 standard deviation (SD) above a remote reference for normal myocardium. We used a threshold of 5 SD above the signal intensity of normal myocardium for LGE quantification because this threshold demonstrated the best agreement with visual assessment and best reproducibility among different technique thresholds[15].

Blood flow and myocardial velocity PC-cMRI data were analyzed by two operators, with 10 years of experience in the field of cardiovascular imaging (LAC and CC) blind to clinical data using the semi-automatically Syngo Flow software (Syngo Flow Quantification, Siemens Healthineers, Erlangen, Germany). Correction for baseline flow offsets was performed as previously described. Flow measurements from 2 or 3 acquisitions were averaged. Post-processing analysis of blood flow through the aortic plane generated a flow curve, which allowed the calculation of aortic forward flow (AFF). MRV was defined as the difference between LV stroke volume (LVSV) and the AFF, and MRF as MRV divided by the LVSV, expressed as a percentage. LVSV was obtained on short axis cine SSFP images. AFF was calculated from phase-contrast velocity flow at the level of the aortic valve. For each patient, two flow acquisitions were made, and the flow values were averaged[11]. According to current American[5] and European recommendations[16], MR severity was classified using MRV as follows: mild (10-30 mL), moderate (30-50 mL) and severe (>50 mL); in addition, severe MR was considered if MRF exceeded 50%.

Further, as additional parameters, we evaluated the left atrium (LA) and LV filling pressures. LA volume (LAV) was measured using the biplane area length method[17], on 2- and 4-chamber cine images, at different moments during the cardiac cycle. LA linear dimension was the long-axis length of LA from each chamber. LAV was calculated using LAV = (0.848×area-4ch×area2-ch)/[(length-4ch+length-2ch)/2][18].

LV diastolic function and filling pressures were evaluated using three basic waveforms which were obtained with PC-cMRI: transmitral early (E, in cm/s) and late (A, in cm/s) peak velocities; early (EQ, in mL/s) and late (AQ, in mL/s) peak flow-rates. The trans-mitral filling volume (FV) was estimated as the area under the transmitral curve and the flow-rate curve, which were automatically detected; myocardial longitudinal early (E', in cm/s) and late (A', in cm/s) peak velocity on LV lateral wall were also determined using the same technique.

The semi-automated delineation of transmitral flow, from PC transvalvular velocity images during the cardiac cycle, provided time-resolved mean velocity and flow rate curves. Another semi-automated delineation of the myocardium on PC tissue images provided LV myocardial longitudinal maximal velocity curves. Automated detection of peak velocities and flow rates through both diastole and systole was performed, together with semi-automated linear fitting of down-slopes and up-slopes on flow-rate curves.

Statistical Analysis and Inter-Observer Reproductibility

Statistical analysis was achieved using MedCalc Software 19.2 (Mariakerke, Belgium). Data normality was tested using the Kolmogorov-Smirnov test. Given the relatively limited sample si-

ze, continuous values were reported as median [interquartile range (IQR)], and IQR is reported as [25%, 75%]. Categorical data was reported as percentage. Comparisons between groups were performed using the two-tailed *t*-test or Wilcoxon test for continuous variables as appropriate and the Fisher's exact test for categorical variables.

We performed a receiver operating characteristic curve analysis using MRF, MRV and mitral ratio E/E' to evaluate the area under the curve for predicting severe *vs.* non-severe MR.

Multivariate analysis was performed by constructing a multiple logistic regression model, including the OR (95% CI) calculation, in order to assess independent associations between severe MR and confounding factors[19]. All tests were two tailed, a *p*-value<.05 was considered significantly statistical.

Results

Study Cohort

The final study cohort consisted of 130 patients with HCM divided in three subgroups, according to the severity of MR: 35 patients with mild MR (26.9%), 68 with moderate MR (52.3%) and 27 with severe MR (20.7%). Clinical and cMRI parameters are summarized in Table I.

Among the clinical characteristics, we noticed a difference between the groups for the NT-proBNP level, which was increasing as MR was more severe. There was no significant difference between the subjects of the three groups regarding hypertension, AF, gender, age or heart failure symptoms.

On cMRI evaluation we could noticed that MRV and MRF were significantly correlated to the severity of MR (*p*-value<.001), which increased as the severity of MR evolved. Furthermore, there were many parameters that could be related to the severity of MR as follows: LVEDV index, LV ejection fraction, E/E' ratio were increasing proportional to the severity of MR. Contrariwise, LAS decreased as MR was more severe. LAV index showed a marked rise according to the grade of MR, with statistical significance (*p*-value<.001): 65.9 mL/m^2 in mild MR, 86.2 mL/m^2 in moderate MR and 147.9 mL/m^2 in severe MR.

Factors Associated with MR Severity

There was a significant correlation between LAV and the severity of MR (Figure 2A-B). LAV was considerably higher as MR was more severe. Figure 2A shows a positive correlation between LAV index and MRV, while Figure 2B illustrates also that LAV index increases as MRF is greater.

In addition, we pointed out the increase in MRV and MRF when considering the categories of mild, moderate and severe MR quantified by cMRI (Figure 3A-B).

Thereafter, the ability of MRV, MRF, mitral ratio E/E' in predicting severe *vs.* non-severe MR was evaluated using ROC curve analyses (Figure 4). For MRV, ROC curve analysis showed an area under the ROC curve (AUC) of 0.837 (95% CI: 0.762 to 0.896, *p*-value<.0001). The cut-off value for 47 ml was established at 36%, yielding 97.1% sensitivity, 91.4% specificity, for identifying severe or non-severe MR in HCM patients. For MRF, ROC curve analysis showed an area under the ROC curve (AUC) of 0.825 (95% CI: 0.748 to 0.886, *p*-value<.0001). The cut-off value for 48.2% was established at 33%, yielding 97.9% sensitivity, 94.8% specificity, for identifying severe or non-severe MR in HCM patients.

For E/E' ratio, ROC curve analysis showed an area under the ROC curve (AUC) of 0.763 (95% CI: 0.703 to 0.823, *p*-value<.0001). The cut-off value for 9.4 was established at 26%, yielding 77.2% sensitivity, 75.8% specificity, for identifying severe or non-severe MR in HCM patients.

MR in Patients with HOCM vs. HNOCM

We analyzed clinical and cMRI parameters in HCM patients regarding LVOT obstruction. In our study there were 62 patients with LVOT obstruction and 68 with non-obstructive hypertrophic cardiomyopathy (HNOCM). As we can notice in Table II, there are many differences between the two groups. First of all, we observed that severe MR was encountered in 70% of the patients with HOCM, compared to 29% in the HNOCM group. Thus, patients with HOCM had more severe MR as compared to the HNOCM ones: MRV (39.7 ml *vs.* 33.5 ml) and MRF (40.1% *vs.* 34.9%). In HOCM group, both LAV index and E/E' ratio had greater values as in the compared group. Regarding the LV function, we noticed that LVEF was greater in patients with LVOT obstruction (66.9% *vs.* 62.7%) and LAS was significantly decreased in the same group (-10.2% *vs.* -14.7%), in comparison with patients with HNOCM.

In the HOCM group we observed that SAM-dependent MR was more frequent (79%) than intrinsic, SAM-independent MR (21%).

As for clinical characteristics, symptoms of heart failure were more severe in the HOCM and also

Table I. Baseline characteristics of patients in study.

	HCM All patients n=130	HCM Mild MR n=35 (26.9%)	HCM Moderate MR n=68	HCM Severe MR n=27	*p*-value
Clinical characteristics					
- Age, mean (SD), years	53 (13.3)	52 (15.1)	52 (13.2)	55 (10.4)	NS
- Male gender, n (%)	94 (72.3)	25 (71.4)	53 (77.9)	16 (59.2)	NS
- Body-mass index, kg/m^2	29.2 (4.7)	28.8 (4.9)	29.1 (4.9)	30.3 (4.2)	NS
- Hypertension, n (%)	40 (30.7)	11 (31.4)	22 (32.3)	7 (25.9)	NS
- Diabetes mellitus, n (%)	22 (16.9)	4 (11.4)	16 (23.5)	6 (22.2)	NS
- Smoking, n (%)	38 (29.2)	7 (20)	21 (30.8)	10 (37.0)	<.001
- Atrial fibrillation paroxysmal, n (%)	14 (10.7)	4 (11.4)	8 (11.7)	2 (7.4)	NS
- Left bundle branch block, n (%)	14 (10.7)	2 (5.7)	9 (13.2)	3 (11.1)	<.001
- Right bundle branch block, n (%)	10 (7.7)	1 (2.8)	7 (10.3)	2 (7.4)	NS
- NYHA II-IV, n (%)	37/74/19	8/24/3	19/39/7	7/11/9	NS
- NT-proBNP, pg/mL	676 (176-2,227)	374 (216-956)	540 (176-1,420)	734 (254-2,227)	.043
CMR systolic and diastolic parameters					
- LVEDV index, mL/m^2	74.2 (18.4)	66.1 (17.9)	75.1 (15.8)	82.9 (20.9)	.001
- LVESV index, mL/m^2	26.7 (12.1)	26.3 (12.2)	26.2 (11.5)	28.4 (13.9)	NS
- LVM index, g/m^2	103.5 (30.7)	100.3 (26.1)	99.1 (26.7)	119.2 (40.2)	.011
- LVEF, %	64.7 (9.6)	61.2 (10.2)	65.8 (8.6)	66.6 (10.3)	.036
- LAS, %	-13.1 (3.1)	-14.5 (2.8)	-12.9 (3.1)	-10.1 (3.7)	.049
- LV-LGE mass, g	33.1 (14.5)	35.0 (17.5)	31.4 (24.7)	34.9 (25.6)	NS
- LAV index	93.5 (34.5)	65.9 (18.4)	86.2 (22.7)	147.9 (58.5)	<.001
- RVEDV index, mL/m^2	43.1 (16.7)	41.2 (16.3)	41.6 (14.7)	49.5 (20.5)	NS
- RVESV index, mL/m^2	17.1 (7.9)	16.8 (8.1)	15.8 (6.4)	20.8 (9.8)	.019
- RVEF, %	60.7 (6.1)	59.9 (6.1)	62.1 (6.2)	58.2 (5.3)	.014
- TAPSE, mm	19.0 (5.4)	18.1 (4.3)	15.8 (6.4)	20.8 (9.8)	NS
- E/A ratio	1.31 (0.43)	1.21 (0.45)	1.33 (0.39)	1.30 (0.52)	NS
- E/E' ratio	9.57 (2.7)	8.02 (2.7)	8.82 (2.6)	9.92 (2.7)	.035
- MRV, mL	38.5 (10.9)	15.1 (2.3)	35.2 (4.2)	51.5 (5.2)	<.001
- MRF, %	37.4 (10.6)	17.3 (4.3)	35.8 (3.8)	50.4 (6.9)	<.001

n, number of patients; SD, standard deviation; IQR, interquartile range; LAS, left ventricular longitudinal-axis strain; LV-LGE, left ventricular late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAV, left atrial volume; LA-LGE, left atrial late gadolinium enhancement; A, late peak mitral flow velocity; A', myocardial longitudinal late diastolic peak myocardial velocity; E, early peak mitral flow velocity; E', myocardial longitudinal early diastolic peak myocardial velocity; TAPSE, tricuspid annular plane systolic excursion; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; MRV, mitral regurgitant volume; MRF, mitral regurgitation fraction; MR, mitral regurgitation. Data are reported as mean (standard deviation) or median (IQR) or n (%).

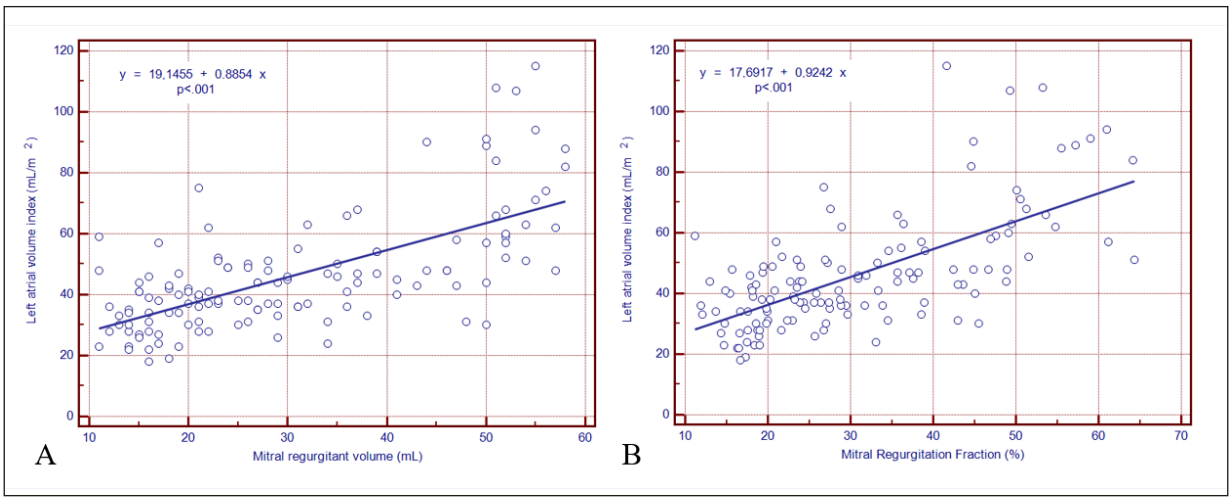

Figure 2. Pearson's correlation of LAV index with MRV (**A**) and MRF (**B**) evaluated by cMRI in HCM patients.

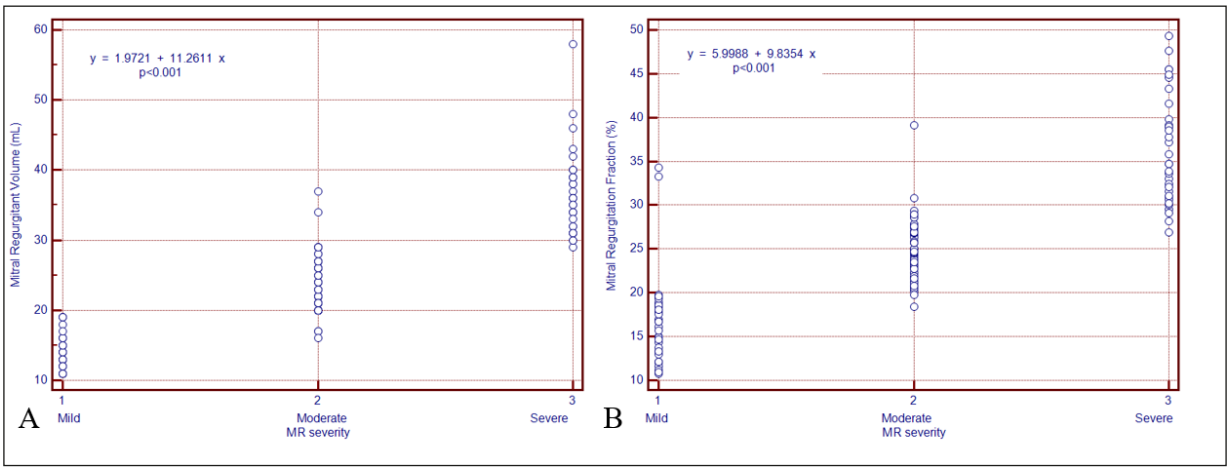

Figure 3. Comparison of categories of MR severity by cMRI with MRV (**A**) and MRF (**B**) in patients with HCM.

the NT-proBNP level was had a higher increase in these patients.

Muscle and Leaflet Abnormalities Associated with HCM

We evaluated the primary structural abnormalities of the mitral apparatus in the patients studied. Most anomalies were found within the papillary muscles (58 patients, 44%): anomalous insertion of one or both heads of the anterolateral papillary muscle (28 patients, 21%), hypertrophy of the muscles (29%), antero-apical displacement (31 patients, 23%) and bifid papillary muscles (16 patients, 12%). Regarding the mitral valve, 56 patients had MV prolapse with thickening of the leaflets, and 49 had SAM. There was no significant correlation between the structural abnormalities and MR or LVOT obstruction.

Table II. Baseline characteristics of patients with HOCM and HNOCM.

	HOCM n=62	HNOCM n=68	*p*-value
- Age, mean (SD), years	53 (13.4)	52 (13.2)	NS
- Male gender, n (%)	44 (70.9)	51 (75.0)	NS
- Body-mass index, kg/m^2	29.5 (4.1)	71.7 (18.5)	NS
- NYHA II-IV, n (%)	27/25/10	20/18/13	.001
- NT-proBNP, pg/mL	892 (240-2,227)	489 (176-1,320)	.019
- LVEDV index, mL/m^2	77.1 (17.9)	66.1 (17.9)	NS
- LVESV index, mL/m^2	25.8 (10.9)	27.5 (13.1)	NS
- LVM index, g/m^2	111.4 (35.7)	96.3 (23.2)	.005
- LVEF, %	66.9 (8.8)	62.7 (9.9)	.014
- LAS, %	-10.2 (3.6)	-14.7 (2.9)	.011
- LV-LGE mass, g	35.1 (16.3)	31.2 (18.9)	NS
- LAV index	51.8 (26.1)	41.9 (14.7)	.008
- E/A ratio	1.32 (0.41)	1.28 (0.46)	NS
- E/E' ratio	9.88 (2.5)	8.79 (2.7)	.021
- MRV, mL	39.7 (11.8)	33.5 (9.2)	.001
- MRF, %	40.1 (11.7)	34.9 (9.1)	.005
- Severe MR, n (%)	19/27 (70.3)	8/27 (29.7)	.001

n, number of patients; SD, standard deviation; IQR, interquartile range; HOCM, hypertrophic obstructive cardiomyopathy; HNOCM, hypertrophic non-obstructive cardiomyopathy; LAS, left ventricular longitudinal-axis strain; LV-LGE, left ventricular late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAV, left atrial volume; LA-LGE, left atrial late gadolinium enhancement; A, late peak mitral flow velocity; E, early peak mitral flow velocity; E', myocardial longitudinal early diastolic peak myocardial velocity; TAPSE, tricuspid annular plane systolic excursion; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; MRV, mitral regurgitant volume; MRF, mitral regurgitation fraction. Data are reported as mean (standard deviation) or median (IQR) or n (%).

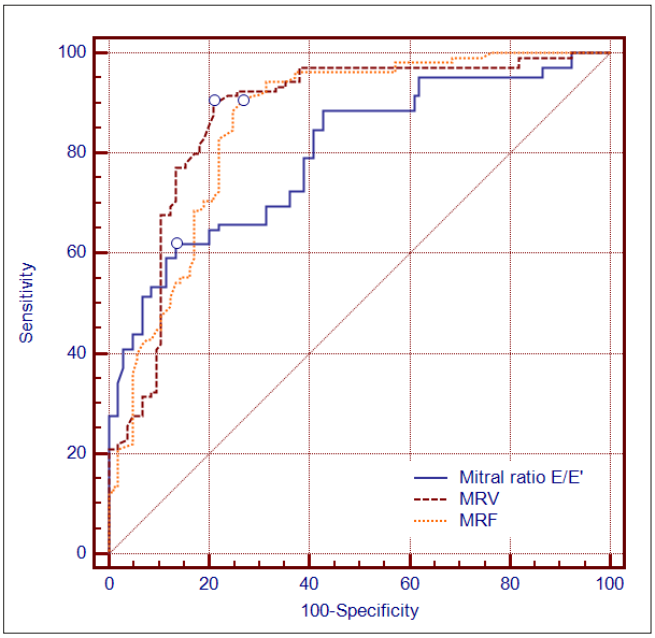

Figure 4. Receiver operating characteristic curve for MRV, MRF, mitral ratio E/E' predicting severe *vs.* nonsevere MR.

Univariate and Multivariate Analysis

In univariate analysis, besides age and gender, multiple cMRI parameters showed significant correlations with the severity of MR in HCM patients. However, after the adjustment for confounders, only MRV, SAM, LAV index and E/E' ratio remained independent predictors for the quantification of MR (Table III).

Discussion

The present study is the first to demonstrate relevant correlations between the severity of MR and several parameters, such as MRV, MRF, LAV index, E/E' ratio and SAM, determined by cMRI, in patients with HCM. The main findings in our study are: (I) MRV and MRF are the main parameters in determining the grade of MR; (II) LAV index and filling pressure, expressed by E/E' ratio, are correlated to both MRV and MRF, implied with the severity of MR; (III) severe MR is associated with an increased LAV index and E/E' ratio, as well with the presence of SAM; (III) severe MR is more frequent in patients with HOCM, strongly related to SAM; (IV) the severity of MR influences LV function.

For patients with HCM, cMRI represents a valuable technique for the evaluation of MR, being able to measure both the severity of MR and the hemodynamic consequences of the volume overload[20]. Taking in consideration the variability of the MR mechanism in these patients, including the eccentricity of the MR jet, echocardiography can lead to an incorrect estimation of MR severity[21,22]. In addition, cMRI can provide characterization of adjacent structures and a detailed assessment of the mitral apparatus[23].

Evaluation of MRV and MRF, in order to quantify the severity of MR by cMRI, is considered an accurate noninvasive imaging method[24,25]. The concerns regarding this method are raised in the lack of large trials to validate this technique as "gold standard". According to current guidelines[5,6], the same echocardiographic cut-off (MRV>60 ml, MRF>50%) should be used for the diagnosis of severe MR by cMRI. In a study, Myerson et al[26] demonstrated that MRV and MRF, evaluated through cMRI, were the most discriminatory parameters in establishing the surgery conduit, using a threshold of 55 ml for MRV and 40% for MRF. To establish the reliability of cMRI in the quantification of MR, some authors[27,28] demonstrated a relevant correlation between MRV and the decrease in LV volume after surgical mitral valve correction.

The mechanisms involving LA volume variation are heterogeneous, depending on both HCM and MR. It is well known[29] that LA function is altered, while LAV is increased in patients with HCM, mostly related to AF[30,31]. At the same time,

Table III. Factors associated with the severe mitral regurgitation by cMRI. Univariable and Multivariable Logistic Regressions Analyses in patients with HCM.

	Univariable Analysis		Multivariable Analysis	
	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	1.01 (0.97-1.03)	.045		
Gender	0.97 (0.90-1.37)	.049		
Body mass index	0.92 (0.84-1.01)	NS		
LVEDV index, mL/m^2	0.96 (0.94-0.99)	.003		
LVESV index, mL/m^2	0.98 (0.95-1.01)	NS		
LVEF, %	0.97 (0.93-1.02)	NS		
LVM index, g/m^2	1.12 (1.03-1.28)	<.001		
LAS, %	1.88 (1.52-2.44)	<.001		
LAV index, mL/m^2	1.93 (1.76-2.61)	<.0001	1.62 (1.37-2.02)	.001
E/E' ratio	1.10 (1.03-1.32)	<.001	1.04 (1.02-1.66)	.05
MRV, mL	1.89 (1.85-2.09)	<.0001	1.64 (1.55-1.78)	<.001
MRF, %	1.90 (1.87-1.98)	<.0001		
Systolic anterior motion	1.11 (0.98-1.34)	.001	1.18 (1.01-1.47)	.05
Increased number of papillary muscles	0.83 (0.58-1.17)	NS		
Anterior and apically displaced papillary muscle	1.01 (0.98-2.30)	NS		
Aberrant chordals	1.48 (0.79-2.77)	NS		
MV prolapse and thickening	0.41 (0.28-0.93)	.032		

cMRI, Cardiac Magnetic Resonance Imaging; LV, left ventricle; LVEDV; left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAV, left atrial volume; LAV, left atrial volume; E, early peak mitral flow velocity; E', myocardial longitudinal early diastolic peak myocardial velocity; MRV, mitral regurgitant volume; MRF, mitral regurgitation fraction. Adjustment models: age, gender with the addition of significant parameters of univariable analysis.

LAV can be modified due to MR or MR can result secondary to LA dilation[32,33].

The importance of LAV assessment by cMRI in HCM patients derives from the possibility to use it as a marker of severity for MR. As we demonstrated in this study for the first time to the best of our knowledge, LAV is strongly correlated to MRV and MRF.

Another parameter associated with severe MR was E/E' ratio, indicating that increased filling pressure could be a marker for MR severity. Although diastolic dysfunction represents a feature of HCM, together with increased filling pressure[34], the overlap of MR can exacerbate the hemodynamics of the process.

Thus, in HCM patients, in the absence of more than moderate MR, both LAV and E/E' ratio represent indices of LA pressure. If severe MR is present, other markers should be evaluated to characterize the filling pressures of LA[35,36], emphasizing what our study demonstrated, namely that increased LAV index and E/E' ratio are factors associated with severe MR.

The contribution of mitral valve, through SAM, to LVOT obstruction in HCM is well known in literature[37,38]. All factors implied in LVOT obstruction can influence the severity of MR, therefore cMRI provides nowadays a better understanding of the mitral valve apparatus[38,39]. Maron et al[3] evaluated mitral valve leaflets in HCM patients by cMRI and demonstrated no significant relationship between the length of the leaflet and LV maximal wall thickness or LV mass. Also, the leaflet size was not correlated to resting LVOT obstruction, compared to patients without resting obstruction. This perspective only consolidates that LVOT gradient has a high variability in individual patients[40,41].

In our research, we were able to confirm that severe MR, quantified by MRV and MRF, is more frequent in patients with LVOT obstruction. As a mention, symptoms of heart failure were dependent on LVOT obstruction and not by the degree of MR. Using cMRI alternatively to echocardiography to evaluate MR in the presence of LVOT obstruction offers a precise quantification and demarcation between the two; by echocardiography, errors can be present due to the close anatomic proximity of the LVOT flow and MR jet[42].

Regarding the correlation between MR severity and LV function in HCM patients, we noticed in our studied cohort that LVEF increases proportional, while LAS is decreasing, in accordance with the severity of MR. A characteristic of HCM is a normal to hyperdynamic LVEF; yet, even in these

patients, systolic strain demonstrates that regional and global abnormalities are present, located especially in the hypertrophied segments[43]. On this basis, we confirmed that MR, through volume overload, has an impact on LV function in patients who already have an apparently normal LV function.

Study Limitation

Firstly, there is a lack of a true reference standard for MR quantification by cMRI. This method is considered accurate based on the physiological response of the LV and clinical outcomes[10]. Although many studies[22,44] demonstrated only modest agreement between echocardiography and cMRI regarding MR quantification, we used the same values for MRV and MRF to evaluate the severity of valve pathology. There is evidence that MR is likely to be severe if MRF is over 40%, evaluated by cMRI, but larger trials are needed to set the proper cMRI cut-offs[45,46].

Further, the indirect volumetric cMRI method that we used for MR quantification has its own limitation. AFF is calculated from different sequences which have physiologic variability due to heart rate fluctuation between acquisitions. In addition, errors can arise from subtracting LV volumes and AFF from each other, which are challenging measurements in patients with LVOT obstruction[8,47].

According to current guidelines[7], echocardiography should be the method of choice for the evaluation of MR in HCM patients. In our cohort we used only cMRI for the assessment of MR severity. Further studies should focus on comparing cMRI parameters with 3-dimensional echocardiography for these specific patients, in order to establish the best method for the evaluation of the mitral apparatus.

Also, we excluded from the study patients with AF, a frequent arrhythmia in patients with HCM and MR; it is well-known[9] that the lack of atrial contraction influences LAV and the filling pressures.

Although we evaluated by cMRI the structural abnormalities that are frequent associated with HCM, we did not focus on the relationship and consequences they could have to MR.

Conclusions

In patients with HCM, cMRI has demonstrated to be a valuable imaging technique, both for an assessment of MR severity and for an characterization of specific features associated with the underlying disease, HCM.

In the assessment of MR severity, we confirmed that MRV, MRF and LVOT obstruction remain the most important parameters in cMRI. This study is the first of its kind to show the correlation between severe MR and other parameters such as LAV index, E/E' ratio and SAM in HCM patients, suggesting that new markers of MR severity should be integrated into the complexity of HCM. Therefore, our study brings new insights for patients diagnosed with HCM and MR, implying that an accurate assessment of the mitral valve may have major benefits in the prognosis and treatment of these patients.

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Conflicts of Interest

The authors declare no conflict of interest.

Availability of Data and Material

Not applicable.

Informed Consent

All patients were informed about the investigation protocol and a written informed consent was obtained from all study participants.

Ethics Approval

The current research has been approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca - decision number 75/11.03.2019.

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Authors' Contributions

I.D.M. and L.A.C. - conception and design of the study; L.A.C. - acquisition, analysis and interpretation of data; statistical methods and interpretation of results; project administration. R.A., A.S., S.C.D.M., S.C., A.Z., B.O.C.M., R.I.O., C.C. and D.H. - acquisition, analysis and interpretation of data; critical revision of the manuscript for intellectual content. I.D.M. and L.A.C. - drafting of the manuscript. All authors granted final approval of the manuscript submitted.

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