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Original article

CMR predictors of secondary moderate to severe mitral regurgitation and its additive prognostic role in previous myocardial infarction

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ABSTRACT

Background: We aimed to determine predictors and the additive prognostic role of moderate to severe (MS) ischemic mitral regurgitation (MR) in myocardial infarction (MI).
Methods: Four hundred twenty-two patients with previous MI underwent cardiac magnetic resonance (CMR) imaging for the assessment of left ventricular (LV) ejection fraction (EF), end-diastolic (EDV) and end-systolic volume (ESV), sphericity index, wall motion score index (WMSI), and late gadolinium enhancement (LGE). Echocardiography was performed to assess MR.
Results: Thirty-eight had from moderate to severe MR (MS-MR group) and 384 did not (No MS-MR group). The S-MR group had higher LV volumes, sphericity index, WMSI, and LGE extent, and lower LVEF. At univariate logistic regression analysis, dilated volumes, SI >0.43, dyskinesia of inferolateral wall, papillary muscle (PM)-LGE, and LGE extent >16% were associated with MS-MR. At multivariate analysis, only SI (OR=5.7) and PM-LGE (OR=3) were independently associated with MS-MR. Considering only patients without LV dilatation, only dyskinesia in the inferolateral wall was a predictor of MS-MR (OR 34.8). Thirty cardiac events (cardiac death, appropriate implantable cardioverter-defibrillator firing, and resuscitated cardiac arrest) occurred during a median follow-up of 1,276 days. After adjusting the prognostic variables at univariate analysis by age (>65 years) and selecting those that were significant (EDV > 95 ml/m^2, ESV >53 ml/m^2, EF <30%, WMSI >1.65, LGE >12%, S-MR), only WMSI >1.65 and MS-MR remained an independent predictor of cardiac events.
Conclusions: Increased WMSI and PM-LGE in the overall population and inferolateral dyskinesia in patients without ESV dilatation are predictors of MS-MR; MS-MR and elevated WMSI have independent negative prognostic value.

Introduction

Chronic ischemic mitral regurgitation (MR) is associated with increased mortality independent of patient characteristics or degree of left ventricular (LV) dysfunction [1-3].

From a pathophysiological point of view, the basic mechanism of ischemic MR is commonly attributed to leaflet tethering that occurs when mitral annulus dilatation reduces valvular action and an imbalance develops between the closing and tethering forces acting on the mitral valve [1,4]. Therefore, many tissue abnormalities and functional abnormalities involving myocardial components (papillary muscles and adjacent LV wall) of the mitral apparatus are involved in the genesis of ischemic MR [1,5,6]. This is in line with evidence that a higher incidence and greater severity of MR are found in patients with inferior or inferolateral my-

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ocardial necrosis than in those with anterior myocardial infarction (MI), suggesting that local remodeling and mechanical alterations of the LV base play a relevant role as determinants of ischemic MR [1,7,8]. Additionally, end-systolic volume (ESV) has been shown to be a predictor of worse outcome, and it has recently emerged as a tool for predicting progression of MR [9]. Currently, echocardiography permits accurate evaluation of valvular and subvalvular abnormalities and severity of MR; nevertheless, the pathogenesis of ischemic MR remains incompletely understood [6,7,10-12].

Cardiac magnetic resonance (CMR) imaging permits accurate quantification of LV volumes and global and regional function, demonstrating a prognostic role in patients with previous MI. It also allows identification of the extent of an infarct and its localization on both the LV and papillary muscles [13-18].

The aims of this study were 1) to identify the predictors of moderate to severe (MS)-MR by applying a multiparametric CMR imaging approach—including functional, structural, and morphological LV parameters—in the overall population and in a subgroup without LV dilatation and 2) to assess whether S-MR, when added to CMR imaging predictors of worse prognosis, stratifies the risk of patients with previous MI.

Methods

Patients

From July 2001 to June 2011 we studied 514 consecutive patients with clinical evidence of previous (>90 days) MI and a clinical indication (quantification of LV function and dimensions; identification of LV thrombi, extent of scar tissue, and myocardial viability) for CMR imaging. Previous MI was documented by clinical record, Q-waves, and angiographic evidence of coronary stenosis (luminal diameter reduced ≥50% in the left main stem and >70% stenosis in a major coronary vessel). We excluded patients with the following conditions: 1) unstable angina or recent evidence of myocardial ischemia (n=39); 2) prosthetic annuloplasty and/or prosthetic heart valve and/or more-than-moderate aortic valve diseases (n=16); 3) hypertrophic cardiomyopathy (n=10); 4) history of malignancy and/or prior chemotherapy treatment (n=13); 5) patients with low-quality or incomplete CMR scan (n=14). We also excluded patients with CMR imaging contraindications [implantable cardioverter-defibrillator (ICD) and/or pacemaker implantation and glomerular filtration rate <30 ml/min]. Therefore, a total of 422 patients (336 during hospitalization and 88 as outpatients) were included. Within 4 days, each patient underwent color Doppler echocardiography and CMR imaging. Clinical variables were collected before the CMR scan. The institutional internal review board approved the study; the investigation complies with the principles outlined in the Declaration of Helsinki. All patients gave informed consent before being enrolled in the study.

CMR data acquisition

CMR was performed using a 1.5 T whole-body scanner (GE Medical Systems, Milwaukee, WI, USA). An 8-channel cardiac phased-array receiver surface coil was used. A breath-hold steady-state free-precession sequence was used to evaluate segmental and global LV function with the following parameters: a minimum of 30 cine frames, slice thickness 8 mm, no gap, eight views per segment, NEX 1, field of view 40 cm, phase field of view 1, matrix 224 × 224, reconstruction matrix 256 × 256, flip angle 458, TR/TE 3.5/1.5, and bandwidth 125 KHz. Late gadolinium enhancement (LGE) images were obtained 8-10 minutes after injection of gadolinium-based contrast medium [either Omniscan (GE Healthcare, Amersham, UK) or Magnevist (Schering, Berlin, Germany) at a concentration of 0.1-0.2 mmol/kg] using fast gradient inversion recovery sequences with the following parameters: repetition time 4.2 ms, echo time minimum, flip angle 208, matrix 224 × 224, number of excitations 1.00, field of view 36 mm, slice thickness 8 mm, no inter-slice gap. The inversion time was optimized to null signal from the normal myocardium. Cine and LGE images were acquired, at a minimum, in 1 vertical and 1 horizontal long-axis view and a set of contiguous LV short-axis views.

CMR data analysis

All CMR studies were analyzed offline using a workstation with dedicated cardiac software with consensus among 3 experienced observers who were blinded to the clinical and echocardiographic data.

To determine LV and right ventricular (RV) function, endocardial borders were manually drawn on all LV short-axis cine sequences by means of previously validated software (Mass, Medis, Leiden, The Netherlands). LV mass, LV long axis, LV and RV ESV, LV and RV end-diastolic volumes (EDV), and LV and RV stroke volume (SV), normalized for body surface area, were then calculated and the delta SV (LVSV – RVSV) and RVSV, LV ejection fraction (LVEF), ratio mass/EDV, and sphericity index were derived [16].

A 17-segment model was used to describe LV segmental wall motion (WM) (1 normal, 2 hypokinetic, 3 akinetic, 4 dyskinetic), and a WM score index (WMSI) then was derived. The boundaries of contrast-enhanced areas in each image were automatically traced [using a signal intensity cut-off of >5 standard deviations (SD) over the average of normal remote myocardium] and manually corrected as appropriate [14,15]. The extent of transmural LGE was measured in each segment and expressed as a percentage of the total thickness of the wall segment (subendocardial LGE <50% and transmural LGE >50% of the segment wall thickness). The reproducibility of this method has been previously described [18].

Papillary anterolateral and posterolateral muscle infarction was deemed present if any papillary hyperenhancement was evident on LGE CMR short-axis images in accordance with established criteria (example in Fig. 1).

Mitral geometric variables were measured in 4-chamber orientation during ventricular end-systole. Interpapillary muscle distance was measured in the short-axis view at end-systole. Tenting area encompassed the area enclosed between the annulus and the mitral valve leaflets [19].

To detect the contribution of the inferior/inferolateral (basal and mid segments) walls to the severity of ischemic MR, the following parameters were obtained: WM inferolateral and inferior basal-mid segments score (WM sum of each segment divided by the 4 segments); presence of akinesia or dyskinesia in at least 1 segment of either the inferior or inferolateral wall; presence and transmurality (LGE >50%) of LGE in the inferior or inferolateral wall (in any segment of the inferolateral or inferior wall, respectively); coexistence of akinesia and LGE in the inferior or inferolateral wall if at least 1 segment of the defined wall showed both akinesia and LGE; coexistence of dyskinesia and LGE in the inferior or inferolateral wall if at least 1 segment of the defined wall showed both dyskinesia and LGE.

Echocardiography

A Vivid 7 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a cardiac M4S transducer was used to perform standard 2D transthoracic echocardiography. Echocardiographic images were blinded in respect to CMR results. A prespecified registry protocol applied by our sonographers included an integrative method using color-flow imaging, vena contracta, and effective regurgitant orifice area (EROA). The quantification of EROA was performed in case of at least mild mitral regurgitation.

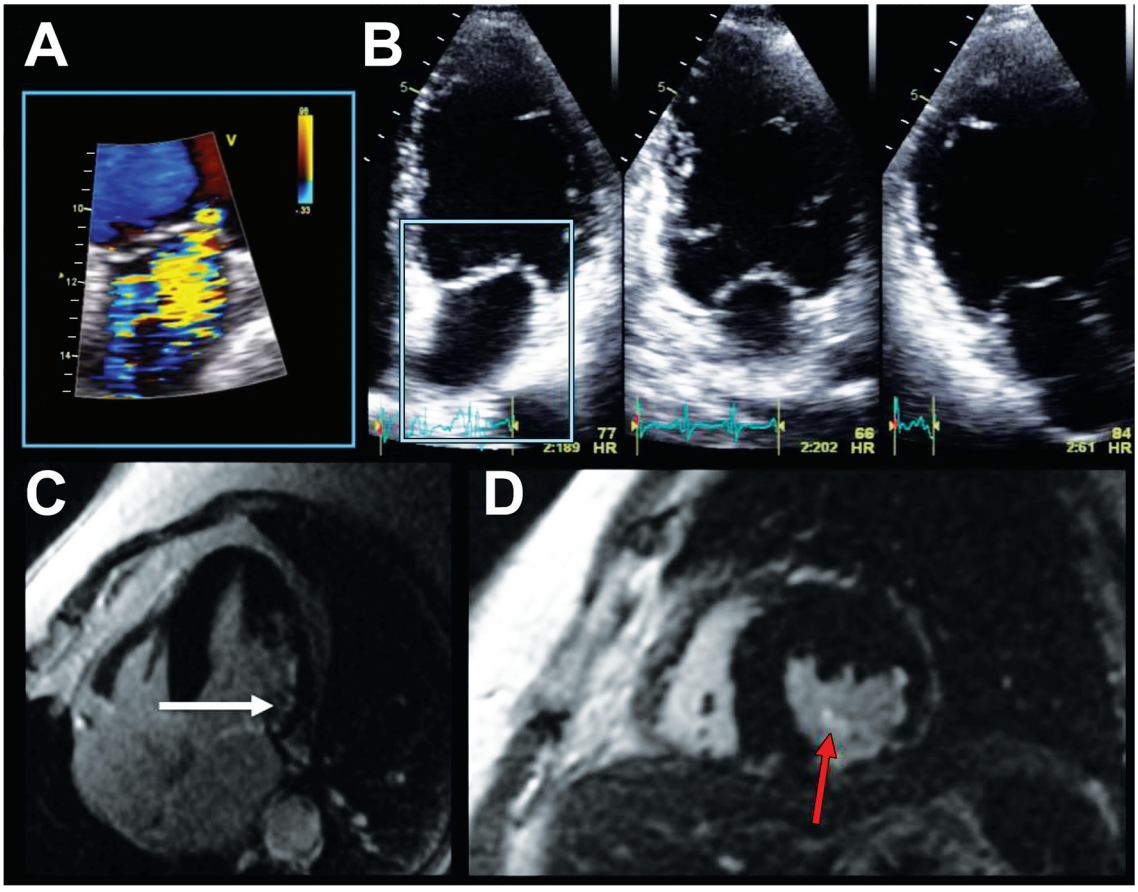

Fig. 1. Moderate/severe mitral regurgitation by effective regurgitant orifice area (30 mm) is found in a patient with inferolateral myocardial infarction without left ventricular dilatation (A, B). Cardiac magnetic resonance images show (C) subendocardial late gadolinium enhancement (white arrow) in the inferior and inferolateral walls and (D) late gadolinium enhancement of inferomedial papillary muscle (red arrow).

According to the American Society of Echocardiography guideline, moderate to severe significant ischemic MR was defined as $\geq$0.2 cm^2 EROA [9,19,20].

The patients were clustered into an MS-MR group and a No MS-MR group.

Follow-up

Follow-up was collected using a questionnaire administered by the clinical physician during periodic ambulatory work-up at our institution (321 patients, 76%) or by telephone call (101 patients, 24%). During follow-up, those patients who underwent ICD implantation after CMR examination also were considered. The cardiac events considered were cardiac death and appropriate ICD shock. The cause of death was documented from medical records or death certificates.

The definition of cardiac death required the documentation of life-threatening arrhythmia or cardiac arrest, or death attributable to congestive heart failure or MI in the absence of any other precipitating factor. In the case of out-of-hospital death not followed by an autopsy, a sudden, unexpected death was considered cardiac death. A complete interrogation of the ICD was performed by the referring physician to confirm the appropriateness of the shock. Follow-up ranged from 3 months to 8 years (median 5.2 years).

Statistical analysis

Continuous variables were expressed as mean±SD or median (25th; 75th percentiles) as appropriate. Categorical variables were expressed as numbers and percentages. Comparisons between continuous variables were performed by Student's independent samples t test or Wilcoxon test, as appropriate. Comparisons between categorical variables were performed by Chi-square test or by Fisher's exact test if an expected cell count was <5. The correlation between continuous variables was tested with Pearson's correlation coefficient. To determine the best value predictors of MS-MR, continuous variables were dichotomized according to receiver operating characteristic (ROC) curve analysis and Youden test. Binary logistic regression was used to determine variables associated with MS-MR. Variables found to be significant at univariate analysis were then included in a multivariate model.

Being interrelated, the Akaike information criterion was used to select the best-fitting model among LVEDV, LVESV, and LVEF. Z-test corrected by Bonferroni post-hoc analysis was used to detect differences in the prevalence of MS-MR between groups with a different number of predictors (0, 1, or 2 predictors). To evaluate variables associated with cardiac events, a univariate Cox regression analysis was performed. Continuous variables were included in the model as dichotomous variables clustered by median value.

WMSI, extent of LGE, LV mass, LV mass/EDV, and LVEDV were dichotomized according to respective median values. Variables found to predict events at univariate analysis were adjusted by age in a post-hoc analysis.

In multivariate stepwise analysis, all significant dichotomous variables at univariate analysis were included as potential predictors. Because LVEDV, LVESV, LVEF, LV mass, and mass/EDV interrelated, five different multivariable models including a single parameter each were computed separately.

Table 1
Clinical characteristics and cardiac magnetic resonance variables in the entire study population and in subgroups with and without severe MR.

	Entire population (n=422)	Non-moderate/severe MR group (n=384)	Moderate/severe MR group (n=38)	*p*-value
Age (years)	65±13	64±13	68±9	0.54
Female (%)	12.7	11.9	9.5	1
Family history of CAD (%)	32.4	37.2	31.6	0.5
Hypertension (%)	54.6	54.3	67.7	0.1
Diabetes (%)	17.9	19.5	31.6	0.08
Hypercholesterolemia (%)	60.5	58.1	71.9	0.1
Smoker (%)	57.2	58.6	53.3	0.6
Anterior MI (%)	50.5	51.1	70.1	0.1
Lateral MI (%)	28.7	30.1	29.4	0.9
Inferior MI (%)	45.5	44.1	23.5	0.1
No. of stenosed vessels	2±1	2±1	2±1	0.14
Prior PCI (%)	68.5	69	75	0.8
Prior CABG (%)	30.3	26.4	64.3	0.005
Beta-blocker (%)	82.8	82.4	100	0.1
Diuretics (%)	49	44.7	100	0.002
ACE-I/ARB (%)	83.2	84	93.3	0.5
Cardiac events (%)	30 (7.1 %)	23 (5.9)	7 (18.4)	<0.01
All mortality (%)	37 (8.9.%)	29 (7.6)	8 (21)	<0.01
Median time to cardiac events (years)	3.6 (1.4-5)	3.7 (1.5-5.4)	3.6 (1-4.5)	0.3
Median follow-up time (days - IQR)	3.5 (1.6-5.3)	3.5 (1-5.4)	2.2 (1-4.5)	0.06
Left atrial volume (ml/m^2)	40±13.3	35.9±12.3	49.1±18.3	<0.0001
E/E'	14.1±9	13.6±9	18.5±7.6	0.001
CMR data				
LV EDV (ml/m^2)	108.73±41.68	105.22±38.90	144.19±51.82	<0.001
LV ESV (ml/m^2)	67.76±42.47	63.93±39.59	106.45±51.03	<0.001
Delta (LV-RV) stroke volume	4±15	3.4±15	8.5±14.9	0.04
Sphericity index	0.46±0.2	0.43±0.1	0.62±0.3	0.04
LVEF (%)	42.24±16.56	43.53±16.44	29.25±11.88	<0.001
WMSI	1.73±0.48	1.69±0.47	2.19±0.36	<0.001
Dilated LV	157 (37.2%)	131 (34.1%)	26 (68.4%)	<0.001
Papillary displacement	18.7±6.3	183±6	22.8±7.7	0.002
Tenting area (cm^2)	2.7±0.9	2.6±0.9	3.3±1.4	0.002
Tenting heat	11±5.5	11.1±5.6	10.8±3.8	0.130
LGE extent (% of mass)	13.3±9	13.6±9	16.8±8	0.035
Segments with LGE (no.)	6±4	6±4	8±4	0.010
LGE transmural extent 1-50% (number of segments)	3±3	3±3	3±3	0.9
LGE transmural extent 51-100% (number of segments)	3±3	3±3	5±3	0.005
Posteromedial papillary LGE	(20%)	(18.6%)	(35%)	0.02
Anterolateral papillary LGE	(9%)	(8.3%)	(13.9%)	0.4
LGE in papillary muscle	98/395 (24.8%)	81/359 (22.6%)	17/36 (47%)	0.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; RV, right ventricular; WMSI, wall motion score index.

Kaplan-Meier curve analysis and Mantel-Cox log-rank test were used to compare the survival of patients with and without MS-MR and adjusted for WMSI ≥1.65. All tests were performed as two-sided. The significance level was set at 0.05.

Results

The majority of patients (324, 77%) in our study had no MR or mild MR. Of the remaining 98 patients (23%), an EROA value ≤0.2 was observed in 60 (14%, EROA=0.18±0.023 cm^2) and only 38/422 patients (9%, 0.30±0.046 cm^2) with an EROA ≥0.2 cm^2 were categorized as MS-MR group.

A CMR scan was performed after a median time of 7.7 months after MI (interquartile range 3.2–84.1 months). The baseline characteristics and CMR data are shown in Table 1.

No difference in localization of MI was found between groups. Higher prevalences of coronary artery bypass graft and diuretic use were found in the MS-MR group. The number of cardiac events was significantly higher in the MS-MR group.

CMR imaging

As shown in Table 1, the MS-MR group had higher LV volumes, delta SV, sphericity index, and WMSI, and lower LVEF. Papillary displacement and tenting area were higher in the MS-MR group. The amount of scarring was greater in the MS-MR group. In particular, the extent of LGE was greater in the MS-MR group. Similarly, the number of segments with LGE was greater in the MS-MR group, as was the number of segments with transmural LGE. Also, scar involvement (LGE) of the papillary muscles, particularly when located in the posteromedial papillary muscle, was more prevalent in the MS-MR group. All patients with LGE of the papillary muscles had LGE located in the inferior and/or inferolateral and/or anterolateral walls.

LV regional function and scar tissue in inferior and inferolateral walls

The MS-MR group had a higher regional dysfunction in the inferolateral and inferior walls (1.80±0.59 vs 1.57±0.61, p=0.02), with a higher prevalence of dyskinesia in the inferolateral wall (10.8 vs 2.1, p=0.01). The presence of LGE and transmurality >50% of LGE in the inferior and inferolateral walls did not differ between groups and neither did the coexistence of akinesia or dyskinesia with LGE in the inferior and inferolateral walls (Table 2).

Table 2
Wall motion abnormalities and scar tissue in inferior and inferolateral walls.

	Entire population (n=422)	Non-moderate/severe MR group (n=384)	Moderate/severe MR group (n=38)	*p*-value
Inferolateral and inferior wall motion score	1.59±0.61	1.57±0.61	1.80±0.59	0.02
Akinesia in inferolateral wall (%)	111 (26.3%)	99 (25.8%)	12 (31.6%)	0.4
Akinesia in inferior wall (%)	108 (25.6%)	94 (24.5)	14 (36.8%)	0.1
Dyskinesia in inferolateral wall (%)	3.4	2.1	10.8	0.01
Dyskinesia in inferior wall (%)	7 (1.7%)	7 (1.8%)	0 (0%)	0.5
LGE in inferolateral wall	38.6	39.6	42.1	0.8
LGE in inferior wall	200 (47.4%)	180 (46.9%)	20 (52.6%)	0.5
Inferior-lateral transmural LGE	19.1	18.5	26.3	0.2
Inferior transmural LGE	93 (22%)	84 (21.9%)	9 (23.7)	0.8
Coexistence of akinesia and LGE in inferolateral segment	85 (20.1%)	79 (20.6%)	6 (15.8%)	0.5
Coexistence of akinesia and LGE in inferior segment	76 (18%)	69 (18%)	7 (18.4%)	0.9
Coexistence of dyskinesia and LGE in inferolateral segment	9 (2.1%)	7 (1.8%)	2 (5.3%)	0.2
Coexistence of dyskinesia and LGE in inferior segment	6 (1.4%)	6 (1.6%)	0 (0%)	0.6

LGE, late gadolinium enhancement; MR, mitral regurgitation.

Table 3
Predictors of moderate/severe mitral regurgitation: Univariate logistic regression.

Variable	AIC	Odds ratio	95% confidence interval	*p*-value
LVEDVi	234	1.02	1.01-1.03	<0.001
LVESVi	230	1.02	1.01-1.03	<0.001
LVEF	232	0.94	0.91-0.96	<0.001
No. of stenosed vessels		1.883	1.121-3.161	0.02
CABG		4.780	2.090-10.9	<0.001
WMSI >1.94 (ROC)		11.05	4.4-27.3	<0.001
Dilated ESV (cut-off 62 ml/m^2)		7	3-16.3	<0.001
Dyskinesia in inferolateral wall (%)		5.7	1.6-19.8	0.007
LGE in anterolateral papillary muscle		1.8	0.6-4.9	0.3
LGE in posteromedial papillary muscle		2.4	1.1-4.9	0.02
LGE in papillary muscle		3.2	1.3-7.9	0.01
Global LGE extent >16%		2.2	1.1-4.4	0.02
LGE transmural extent (no. of segments)		1.1	1-1.3	0.007
Coexistence of dyskinesia and LGE in inferolateral wall		2.9	0.6-14.9	0.2
Akinesia in inferior wall (%)		1.8	0.9-3.6	0.1
Akinesia in inferolateral wall (%)		1.3	0.6-2.7	0.4
LGE in inferior wall		1.2	0.6-2.4	0.5
LGE in inferolateral wall		1.1	0.6-2.2	0.8
Dyskinesia in inferior wall (%)		0	0	1
Sphericity index >0.4		6.2	1.4-28.6	0.02

AIC, Akaike information criterion; CABG, coronary artery bypass grafting; ESV, end-systolic volume; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume indexed; LVESVi, left ventricular end-systolic volume indexed; ROC, receiver operating characteristic; WMSI, wall motion score index.

Predictors of moderate and severe MR

Among many clinical variables (age, sex, family history of coronary artery disease, hypertension, diabetes, hypercholesterolemia, smoking habits, diuretics, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and prior percutaneous coronary intervention), only prior coronary artery bypass graft (OR=5; 95% CI=1.6-15.8; p=0.006) and N° of stenotic vessels (OR=1.9; 95% CI=1.1-3.2; p=0.014) were clinical independent predictors of MS-MR.

At univariate analysis, dilated LVEDV and LVESV, LVEF, sphericity index >0.43, WMSI (both global and in the inferior and inferolateral walls), dyskinesia in the inferolateral wall, extent of LGE (both global and transmural extent), and LGE in the papillary muscle were associated with MS-MR (Table 3).

LVEDV, LVESV, and LVEF were interrelated.

Among volumes, Akaike information criterion revealed that the parameter with the best-fitting model was LVESV (Table 3).

A multivariate stepwise analysis was performed to identify CMR variables independently associated with MS-MR. We included the first 4 variables presenting the highest odds ratio at univariate analysis (dilated LVESV indexed, sphericity index, dyskinesia in inferolateral wall, and LGE in papillary muscles). Sphericity index (OR=5.7; 95% CI=1.2-26.8; p=0.02) and LGE in papillary muscle (OR=3; 95% CI=1-9; p=0.048) were the variables independently associated with MS-MR.

Patients presenting with both risk factors had a higher prevalence of MS-MR than those with zero or one risk factor (p<0.05); no significant difference was found between patients with zero or one risk factor. The risk of MS-MR was 3.8-fold greater per each increase in risk factors (95% CI 1.65–8.78; p=0.002).

Considering only the 211 patients having LVESV value less than the median value, MS-MR was found in 7 (3.3%) subjects; in this subset of patients, only dyskinesia in the inferolateral wall was a predictor of MS-MR at univariate analysis [OR 34.8 (CI 1.9-640.1), p=0.017].

Variables associated with cardiac events

During follow-up (median, 1,276 days), 30 (7.1%) major cardiac events occurred in the entire population. There were 25 cardiac-related deaths and 5 appropriate ICD shocks. An ICD was implanted in 44 patients.

The variables associated with cardiac events at univariate Cox regression analysis are shown in Table 4. Aiming to demonstrate the independent role of the predictors, we performed a post-hoc analysis (5 models in Table 4) by adjusting the significant variables at univariate analysis by age >65 years (median value). MS-

Table 4
Hazard ratios for major cardiac events (cardiac death and appropriate implantable cardioverter defibrillator shocks) in univariate analysis and multivariate analysis adjustment by age >65 years.

	Univariate analysis	Multivariate analysis adjustment by age >65 years				
		Model 1	Model 2	Model 3	Model 4	Model 5
Age >65 years	3.6*** (1.6-7.9)					
EDVi >95 ml/m^2 (median)	2.7* (1.1-6.7)	1.18 (0.391-3.546)				
ESVi >53 ml/m^2 (median)	4.5** (1.6-12.9)		2.616 (0.5-13.7)			
LVEF <30% (cut-off for severe)	2.5** (1.2-5.2)			1.281 (0.57-2.87)		
LV mass index >78 gr/m^2	2.8* (1-5.2)				1.126 (0.68-4.6)	
LV mass/ LVEDV >0.77	0.3** (0.1-0.7)					0.531 (0.33-1.29)
WMSI >1.65 (median)	6.7*** (2.3-19.4)	5.197* (1.313-20.6)	3.717* (0.9-14.6)	5.140* (1.4-18.8)	5.46** (1.52-19.6)	4.587* 1.3-16.5
LGE >12% (median)	1.6** (1.2-2.1)	1.717 (0.666-4.4)	1.608 (0.63-4.1)	1.697 (0.65-4.4)	1.760 (0.68-4.6)	1.802 0.7-4.6
Moderate/severe mitral regurgitation	5*** (2.1-11.8)	2.759* (1.047-7.2)	2.614* (1-6.8)	2.872* (1.1-7.8)	2.850* (1.1-7.4)	2.873* (0.2-1.3)
No. segments with transmural scar >3 (median)	2.1 (1-4.4)					

* $p<0.05$
** $p<0.01$
*** $p<0.001$
EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; WMSI, wall motion score index.

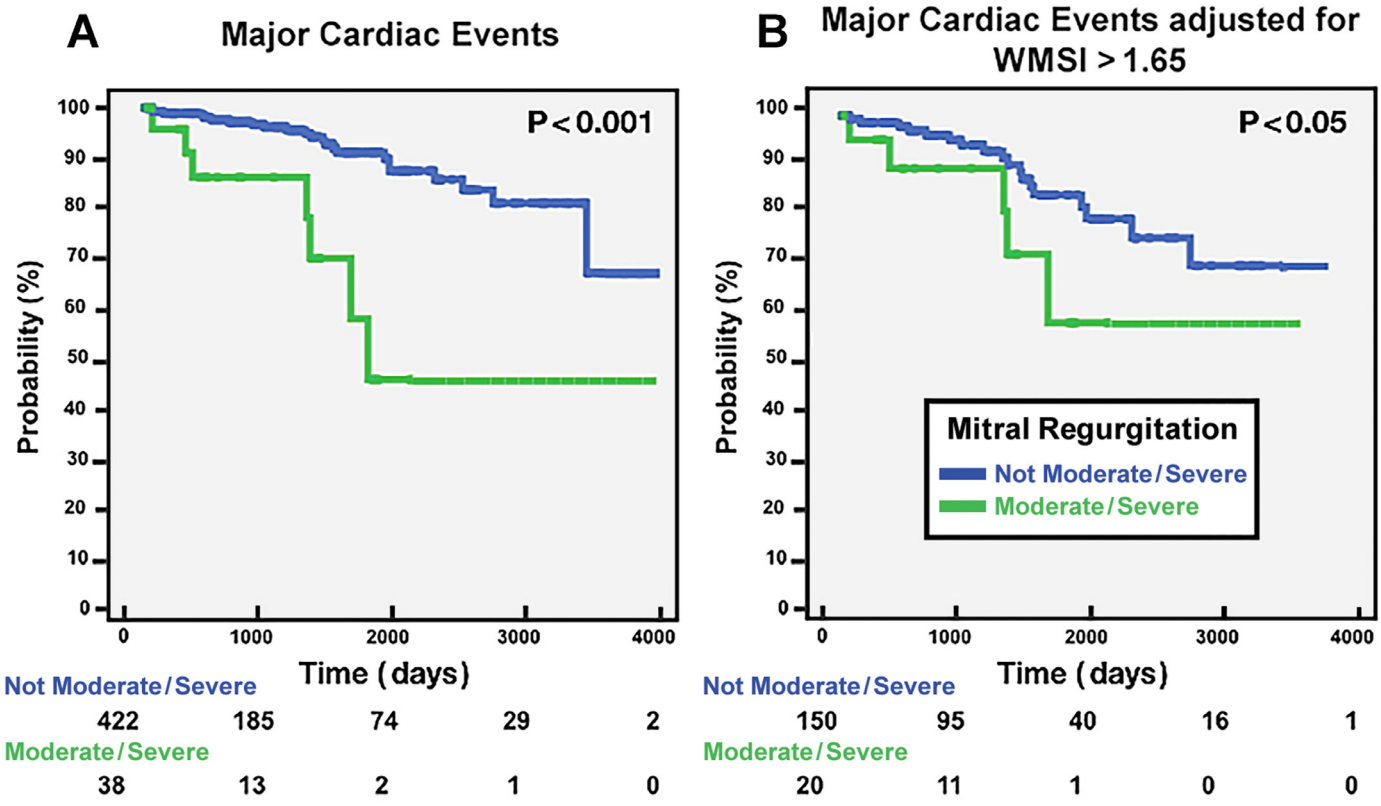

Fig. 2. Survival in moderate/severe mitral regurgitation. Kaplan-Meier survival curves in (A) severe mitral regurgitation alone and (B) adjusted for wall motion score index (WMSI) >1.65.

MR and WMSI >1.65 remained the independent predictors of cardiac events in each of the multivariate models. Survival analysis confirmed that patients with MS-MR had a worse prognosis (log-rank test: $p<0.001$). The survival of patients with MS-MR showed a worse outcome after adjustment for WMSI ≥1.65 (log-rank test: $p<0.05$) (Fig. 2).

Discussion

The main results of this study are: 1) the combination of sphericity index and LGE in papillary muscle (particularly posteromedial papillary muscle) was the variable independently associated with MS-MR in our patient population with previous MI; 2) inferolateral dyskinesia was associated with MS-MR in patients without ESV dilatation; and 3) MS-MR assessed in the chronic phase of MI—in addition to tissue extent, LV cavity dilatation, and regional WM abnormalities—was associated with cardiac events during follow-up.

Post-ischemic LV remodeling is a slow and continuous process that leads to LV enlargement, wall thickness thinning, an increase in wall stress, and progressive impairment of LV function. The consequent change and distortion in LV shape, which becomes spherical instead of elliptical, can play a pathophysiological mechanistic role in the development of ischemic MR, with alterations in mi-

tral valve dynamics linked to papillary muscle dysfunction, mitral annulus dilatation, and incomplete leaflet coaptation [13,20].

In addition to global remodeling (sphericity index), local remodeling (dyskinesia of the inferolateral wall) produces an imbalance between the closing and tethering forces acting on the mitral valve. In the context of the population without LV dilatation, the weight of local remodeling (dyskinesia of the inferolateral wall) is the main determinant of MS-MR.

Myocardial global scar tissue and its transmural extent have a strong relationship with MR but are not independently associated with MS-MR in the absence of papillary muscle involvement. Furthermore, the presence of scar tissue located in the inferior or inferolateral wall shows no relationship with MS-MR in the absence of dyskinesia. In patients with previous MI but without abnormal ESV, the fact that regional dyskinesia of the inferolateral wall was an independent predictor of severe MR highlights the mechanistic role of regional LV remodeling. Dyskinesia can alter mitral geometry and function because of its systolic paradoxical WM away from the LV center during systole [21].

Accordingly, Kalra *et al*. proposed a new mechanism of ischemic MR based on the fact that the loss of wall thickening in the myocardial middle segments of the inferolateral and inferior walls reduces the interpapillary muscle distance shortening that tethers mitral leaflet edges and thus impairs their systolic closure independently of LV dilatation [22].

In line with these data, experimental models of lateral infarction have shown that dyssynergy of the posterolateral wall is the key element in inducing MR and that injury of the papillary muscle alone is not sufficient to cause MR [23]. Similarly, Mittal *et al*., studying a canine model of MS-MR, showed that involvement of papillary muscle infarction only did not produce MS-MR, whereas regional areas of dyskinesia of the LV free wall produced MR in association with papillary muscle dysfunction [24].

In clinical studies in which MR was independently associated with the presence of lateral infarction, infarct size, tethering height, and reduction of interpapillary muscle shortening, WMSI was significantly higher in patients with MS-MR than in those without MS-MR [19]. However, the authors calculated global WM score, whereas we assessed regional WM of the four segments most frequently involved in the pathophysiological mechanisms of ischemic MR, that is, the basal and middle segments of the inferior wall and inferolateral wall.

Lamas *et al*. showed that MR patients had greater ESV and EDV and more spherical ventricles than patients without MR. Furthermore, the shape change from diastole to systole, which normally results in a more ellipsoidal systolic ventricular shape, was reduced in patients with MR [25].

Clinical implications: the prognostic weight of severe ischemic MR

The severity of MR was associated with increased overall and cardiac death in the acute and chronic phases after MI, independent of degree of ventricular dysfunction [2,3]. Furthermore, MR progression was an independent predictor of overall death and heart transplantation even after controlling for the severity of ischemic MR at first evaluation [12]. In addition, the severity of MR was associated with RV dysfunction in patients with previous MI, which itself is associated with increased mortality [26]. In particular, Kwon *et al*. showed that ischemic MR is independently associated with adverse LV remodeling and infarct size in patients with severely depressed EF (<30%) [9]. However, different from Kwon's study, our data were obtained in a population of post-infarction patients with mild and moderate LV dysfunction (EF 42.2±16.6) and showed that MS-MR also predicted cardiac death when adjusted with a strong LV multiparametric score (obtained with EDV index, WMSI, and extent of scar tissue). In this study, we showed that MS-MR provides further prognostic stratification in addition to the morpho-functional cardiac score, including indices of LV remodeling, regional function, and infarct size. This score already has been applied in a previous study, in which we proved the efficacy of this score to prognostically stratify patients with previous MI [26,27]. With regard to MR, the intermingled approach we proposed in this study, including MR severity in addition to morpho-functional cardiac parameters, is justified by the complexity and the multifactorial mechanisms of ischemic MR that have to be considered in order to afford accurate prognostic risk stratification.

Limitations of the study

This was a retrospective, nonrandomized, double-center study that included a selected population of patients with MI having a clinical indication for CMR. Although the population is relatively large in comparison with previous studies enrolling the same patient category, our study suffered from a low number of events at follow-up, consequently limiting the statistical power and reliability of the results. However, our study had the advantage of including only hard adverse cardiac events (cardiac death and appropriate ICD shock). Another limitation is the absence of quantification of systolic RV pressure and/or B-type natriuretic peptide and mitral regurgitant volume (difference between LV stroke volume by cine CMR and forward aortic flow by flow quantification) using CMR imaging. Additionally, we have no data about mitral valve intervention (surgical repair, replacement, or MitraClip) during follow-up.

On the other hand, we have designed our study to investigate CMR predictors.

Conclusion

This study highlights that MS-MR in patients with previous MI is strictly linked to both regional and global LV remodeling processes, which can be considered the primum movens of ischemic MR in which dysfunction of the mitral valve apparatus—including the valve leaflets, annulus, and papillary muscles—is accomplice. Our data suggest that in the context of prognostic risk stratification of patients with previous MI, ischemic MR assessment could be an independent variable to include in a multiparametric assessment including the other morpho-functional cardiac indices. Further studies including many consecutive patients and not only those having indication to CMR examination are needed to confirm our results.

Conflicts of Interest

None.

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None.

Disclosures

The authors declare that there is no conflict of interest.

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