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ORIGINAL ARTICLE

Late gadolinium enhancement CMR in primary mitral regurgitation

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ABSTRACT

Aims The appropriate timing for surgery in severe asymptomatic primary mitral regurgitation (MR) remains controversial. It has been shown that late gadolinium enhancement on cardiovascular magnetic resonance (LGE CMR), which may identify myocardial fibrosis, is associated with a worse outcome in various cardiomyopathies. We sought to investigate the prevalence and significance of delayed enhancement in primary MR.

Methods We prospectively included 41 patients with at least moderate primary MR and without overt signs of left ventricular (LV) dysfunction. Patients with evidence of coronary artery disease, arrhythmias or significant concomitant valvular disease were excluded. All patients were scheduled for transthoracic echocardiography and LGE CMR.

Results A total of 39 patients had interpretable LGE CMR images. Among them, 12 (31%) had late contrast uptake of the LV wall. LGE CMR showed an infarct pattern in three patients, a pattern of mid-wall fibrosis in seven patients and two patients had a combined pattern. Patients with delayed enhancement on CMR had significant higher LV diameters (LV end-systolic diameter 39 ± 4 vs. 34 ± 5 mm, $P = 0{\cdot}002$; LV end-diastolic diameter 57 ± 5 vs. 50 ± 5 mm, $P = 0{\cdot}001$). There was a trend towards a higher indexed left atrial volume (55 ± 21 vs. 44 ± 13 mL/m², $P = 0{\cdot}06$). By contrast, there was no significant association between myocardial contrast uptake and age, LV ejection fraction and MR severity.

Conclusion Left ventricular remodelling seems to be associated with the presence of delayed enhancement on CMR in primary MR. Further data are needed to determine whether LGE CMR can predict a less favourable outcome or could improve risk stratification in asymptomatic primary MR.

Keywords Cardiac magnetic resonance, echocardiography, fibrosis, mitral regurgitation, valve.

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Introduction

Mitral regurgitation (MR) is the second most prevalent valve disease in Europe after aortic stenosis and its origin is predominantly degenerative [1]. The appropriate timing for surgical intervention in severe asymptomatic primary MR with preserved left ventricular (LV) function remains controversial [2]. The recently updated 2012 ESC/EACTS guidelines recommend surgery in patients with severe primary MR and symptoms, or in asymptomatic patients with LV ejection fraction (LVEF) ≤ 60% and/or LV dilatation (end-systolic diameter ≥ 45 mm) (class I), new onset atrial fibrillation or pulmonary hypertension (PHT) [3] (class IIa). In recent years, several large studies have endeavoured to provide evidence for a more favourable clinical course when patients are submitted to surgery before the development of LV dysfunction or PHT [4–7]. Numerous studies have identified certain risk factors which yield a poor outcome such as left atrial enlargement [8,9], decreased exercise capacity [10], impaired global longitudinal strain [11], exercise PHT [12], and elevated both resting [13,14] and exercise B-type natriuretic peptide (BNP) [15]. These parameters could identify a group of patients who may benefit from early referral for surgery.

Cardiovascular magnetic resonance with late enhancement contrast imaging using gadolinium (LGE CMR) represents a noninvasive method to assess myocardial fibrosis. It has been shown that the presence of delayed enhancement on CMR is associated with a less favourable outcome in numerous

valvular and nonvalvular cardiomyopathies [16–18]. In primary MR, however, the prevalence and significance of delayed enhancement has been poorly studied. In 2008, Han *et al.* [19] described for the first time *in vivo* the presence of focal myocardial fibrosis in the papillary muscles of 10 out of 16 patients (63%) with mitral valve prolapse and various degree of MR (i.e. including mild MR) using 3D high-resolution LGE CMR. To the best of our knowledge, no other study has examined the presence and extent of LGE in primary MR as assessed by CMR.

We sought to investigate the presence and significance of LGE and to identify its determinants in moderate to severe primary MR without overt LV dysfunction.

Methods

Study population

We prospectively included 41 patients in two Belgian centres (CHU Sart Tilman Liège and University of Antwerp Hospital) with at least moderate primary MR (defined as an effective regurgitant orifice [ERO] $\geq$ 20 mm² and/or a regurgitant volume [RVol] $\geq$ 30 mL) and without overt signs of LV dysfunction or dilatation (LVEF $\geq$ 60% and LV end-systolic diameter $\leq$ 45 mm) after informed consent. Practically, all patients were asymptomatic or had only mild symptoms (NYHA $\leq$ 2). In 2 of the 3 patients with NYHA class 3, dyspnoea was not MR-related (chronic obstructive pulmonary disease). Patients with a history of coronary artery disease, persistent arrhythmias or other significant concomitant valvular heart disease (> mild mitral/aortic stenosis or regurgitation) were excluded. Moreover, we did not enrol patients in whom CMR with contrast imaging was contra-indicated (CMR-incompatible devices or severe renal failure). Significant coronary artery disease was excluded in all patients by coronary angiography and/or exercise echocardiography. The ethical committee of the two centres approved the study protocol. Reporting of the study conforms to STROBE statement [20].

Transthoracic echocardiography

We performed a comprehensive transthoracic echocardiography in all patients using Vivid 7 or Vivid 9 cardiovascular ultrasound system (GE Healthcare, Little Chalfont, UK). All data obtained by echocardiography were analysed off-line with an EchoPAC workstation (GE Vingmed Ultrasound AS, Horten, Norway). End-systolic and end-diastolic LV diameters were measured with M-mode in the parasternal long-axis view according to current recommendations [21] and were indexed for the body surface area (BSA). The LVEF was quantified by the modified Simpson's method in the apical four- and two-chamber view. The left atrial volume was obtained by the area-length method in the four- and two-chamber view and was indexed for BSA. The severity of MR was assessed as recommended [22]. The ERO and RVol were quantified using the proximal isovelocity surface area method. Moderate primary MR was defined as an ERO between 20 mm² and 40 mm³ and/or a RVol between 30 and 60 mL while an ERO $\geq$ 40 mm² and/or a RVol $\geq$ 60 mL defined severe MR. Mitral E- and A-wave velocities were measured with pulsed wave Doppler at the tips of the mitral leaflets in the apical four-chamber view. The e'-wave velocity was obtained by tissue Doppler imaging in the septal position of the mitral annulus. The transtricuspid pressure gradient was measured by continuous wave Doppler of the regurgitant tricuspid jet in the parasternal short-axis view or the apical four-chamber view.

Cardiovascular magnetic resonance

CMR imaging was performed using a 1·5-T scanner (Symphony TIM, Siemens, Erlangen, Germany). Breath-hold ECG-gated steady-state free precession sequences in standard long-axis and multiple parallel short-axis slices were used for the measurement of end-systolic and end-diastolic LV dimensions and volumes. The acquisition parameters were: repetition time = 35 msec, echo time = 1·1 msec, flip angle = 80°, 25 phases, slice thickness = 6 mm, slice gap = 1·2 mm, acquisition matrix = 192 × 192, and field of view = 272 × 380 mm.

Ten minutes after injection of 0·1 mmol/kg of gadolinium contrast agent (Gadovist, Bayer-Schering, Erlangen, Germany), breath-hold ECG-gated 2D and 3D LGE CMR images were acquired in the same axis and slice thickness used in the cine imaging. Inversion times were adjusted to null the signal from the normal myocardium (varying from 200 to 250 msec). The LGE imaging parameters were as follows: repetition time = 3·2 msec, echo time = 1·65 msec, flip angle = 10°, acquisition matrix = 256 × 128 and field of view = 312 × 400 mm. Myocardial fibrosis was suspected in case of late contrast uptake in the LV wall with a clearly higher signal intensity than apparently normal myocardium. The presence and pattern of LGE on CMR was assessed by agreement of two independent observers (PJB and LD) who were blinded to the clinical data. Areas of LGE were identified by the 'full width half maximum' technique (six standard deviations) with calculation of LGE extent (expressed as percentage of total LV mass) using QMASS 7.2 analytical software package (Medis, Leiden, the Netherlands).

Brain natriuretic peptide

Venous blood samples for baseline BNP measurement were drawn before echocardiography, after 20 min of supine rest. Chilled ethylenediaminetetraacetic acid tubes were centrifuged immediately at 2667 *g* (4 °C) for 15 min. Separated plasma samples were processed by immunofluorescence assay (Biosite, Beckman Coulter, San Diego, California). The inter- and

intra-assay variations were 5% and 4%, respectively. The assay detection limit was 1 pg/mL.

Statistic analysis

All statistical analyses were performed with SPSS version 20 (IBM Statistics). Results are expressed as mean ± SD or percentage unless otherwise specified. Patients were studied in two groups according to the presence of late contrast uptake on CMR. Differences between groups were analyzed for statistical significance with the Student's *t*-test, the Mann–Whitney *U* test, the Chi-square test, or the Fisher's exact test as appropriate. Spearman's rank correlation analysis was used to evaluate the relationship between LGE extent and echocardiographic and CMR data. Values of $P < 0{\cdot}05$ were considered significant.

Results

Demographic and clinical data of the study population are summarized in Table 1. Among the 41 patients scheduled for CMR, two patients had no interpretable LGE CMR images due to low quality images. Among the remaining 39 patients, 12 (31%) had late contrast uptake of the LV wall, which may indicate the presence of myocardial fibrosis. In three patients, LGE CMR showed an infarct-like pattern (2 of these patients had coronary angiography which showed normal coronary arteries, the third patient had a negative exercise echocardiography), while there was a pattern of mid-wall fibrosis in seven patients and an association of both an infarct pattern and mid-wall fibrosis in two patients (see Fig. 1). There were no

Table 1 Demographic and clinical data in patients with (LGE +) and without delayed enhancement (LGE −) on cardiovascular magnetic resonance

	Whole cohort *n* = 41	**LGE + (*n* = 12, 31%)**	**LGE − (*n* = 27, 69%)**	***P***
Demographic data				
Age (years)	58 ± 13	54 ± 14	60 ± 13	0·2
Gender (M/F)	32/9	11/1	20/7	0·4
BMI (kg/m²)	24·7 ± 3·3	24·4 ± 3·2	24·5 ± 3·4	0·9
Clinical data (%)				
Arterial hypertension	21 (53)	6 (50)	14 (52)	1
Hypercholesterolemia	14 (34)	2 (17)	12 (44)	0·15
Diabetes	2 (5)	0 (0)	2 (7)	NA
Smoking	10 (24)	4 (33)	6 (22)	0·7
Medication				
Beta-blockers	12 (29)	2 (17)	9 (33)	0·4
Ace-inhibitors/ARBs	17 (41)	4 (33)	11 (41)	0·7
Diuretics	7 (17)	2 (17)	5 (19)	1
History of atrial fibrillation	7 (17)	1 (8)	5 (19)	0·6
History of acute heart failure	1 (2)	1 (8)	0 (0)	NA
PAPs > 50 mmHg at rest	1 (2)	0 (0)	1 (4)	NA
NYHA				
Class I	10 (24)	4 (33)	5 (19)	0·6
Class II	28 (68)	7 (58)	20 (74)	
Class III	3 (7)	1 (8)	2 (7)	
Class IV	0 (0)	0 (0)	0 (0)	
BNP (pg/mL)	53 ± 62	47 ± 51	58 ± 68	0·6

BMI, body mass index; ARBs, angiotensin II receptor blockers; PAPs, systolic pulmonary arterial pressure; BNP, B-type natriuretic peptide; NA, not applicable.

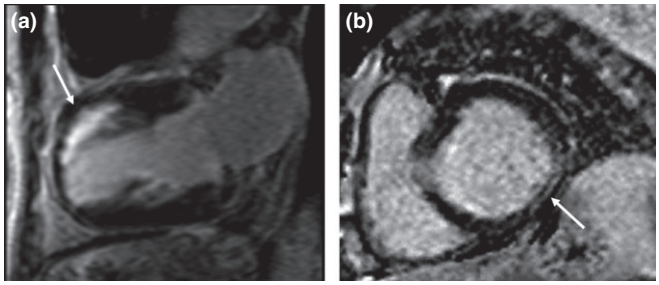

Figure 1 Arrows point at zones of late gadolinium enhancement on CMR, possibly indicating the presence of fibrosis. (a) Infarct-like pattern in a 71-year old male with moderate-to-severe MR due to prolapse of P2. This patient had normal coronary arteries on coronary angiography. (b) Pattern of mid-wall fibrosis in a 41-year old male with severe MR due to bivalvular prolapse.

significant differences between patients with and without delayed enhancement of the myocardium regarding demographic or clinical data (see Table 1). Of note, in our study, the only patient with clear MR-related symptoms had no late contrast uptake on LGE CMR.

The echocardiographic and CMR data are summarized in Table 2. Segmental myocardial thickening was normal in all patients. Patients with delayed enhancement on CMR had significant higher LV end-systolic and end-diastolic diameters as measured by transthoracic echocardiography: 39 ± 4 vs. 34 ± 5 mm (P = 0·002) and 57 ± 5 vs. 50 ± 5 mm (P = 0·001) respectively. These associations were even more significant when LV end-systolic and end-diastolic dimensions were indexed for BSA: 20·6 ± 1·8 vs. 17·7 ± 2·6 mm/m² (P = 0·001) and 29·9 ± 2·4 vs. 26·3 ± 2·8 mm/m² (P < 0·001), respectively. Likewise, these patients had higher LV end-systolic and LV end-diastolic diameters as measured by CMR. Of note, measurement of linear LV dimensions by both imaging modalities were very similar (LV end-systolic dimension: 36 ± 5 mm by transthoracic echocardiography vs. 36 ± 5 mm by CMR, P = 0·9; average bias −0·1 mm, 95% confidence interval −5·7 to +5·5 mm; LV end-diastolic dimension: 53 ± 6 mm by transthoracic echocardiography vs. 54 ± 7 mm by CMR, P = 0·8; average bias −0·8 mm, 95% confidence interval −8·3 to +6·7 mm). Left ventricular end-systolic and end-diastolic volumes as measured by CMR were higher in patients with late contrast uptake, although there was no significant association.

Furthermore, in patients with late gadolinium uptake on CMR, there was also a trend towards a higher indexed left atrial volume: 55 ± 21 vs. 44 ± 13 mL/m² (P = 0·06). By contrast, we did not find a significant correlation between delayed enhancement on CMR and age (54 ± 14 vs. 60 ± 13 years, P = 0·2), BNP level (47 ± 51 vs. 58 ± 68 pg/mL, P = 0·6), LVEF (68 ± 5 vs. 68 ± 5 %, P = 0·9) and MR severity (ERO: 52 ± 22 vs. 39 ± 22 mm², P = 0·1).

After exclusion of the patients with an infarct-like pattern, the LV end-systolic and end-diastolic dimensions remained significantly higher in patients with a pattern of mid-wall fibrosis (39 ± 4 vs. 34 ± 5 mm, P = 0·01 and 58 ± 5 vs. 50 ± 5 mm, P = 0·001, respectively).

In patients with delayed enhancement, mean LGE% of LV mass was 2·15 ± 1·96 (range 0·45 to 7·50). LGE% of LV mass was moderately correlated with indexed LV end-systolic diameter (Spearman's rho = 0·52, P = 0·001) and indexed LV end-diastolic diameter (Spearman's rho = 0·35, P = 0·028). In contrast, measurements of LGE extent were not significantly correlated with LV volumes or LVEF as measured by CMR.

Discussion

The main finding of the present study is that even in the absence of overt LV dysfunction, patients with moderate to severe primary MR may have delayed enhancement on CMR, which may identify the presence of fibrosis. Furthermore, progressive LV dilatation is associated with late contrast uptake on CMR. Interestingly, a substantial part of patients (close to 30%) have developed these signs of myocardial damage well before the LV end-systolic diameter had reached the cut-off value of 45 mm as defined by the recently updated ESC guidelines [3]. A large multicenter observational study by Tribouilloy *et al.* [5] found a worse outcome of patients with severe MR due to flail leaflets with a LV end-systolic diameter ≥ 40 mm, even after mitral valve surgery. However, approximately 2 thirds of patients with LV end-systolic diameter > 40 mm were symptomatic and thus already had class I indication for surgery, regardless of LV dilatation. Based on this study, the current ESC guidelines now recommend referral for surgery in patients with severe MR due to flail leaflets and a LV end-systolic diameter of ≥ 40 mm as a Class IIa indication. In the present study, the degree and extent of contrast uptake on LGE CMR was similar in patients with and without a flail mitral valve.

In a recent CMR study, Schiros and colleagues [23] showed, in a series of patients with degenerative MR, that the end-systolic diameter as measured in the parasternal long-axis at the mitral valve leaflet tips may underestimate the LV volume due to spherical mid to apical remodeling. However, in the present study, linear dimensions were more closely correlated with late contrast uptake of the myocardium than LV volumes. In their study, patients with a LV end-systolic diameter of ≥ 37 mm had more LV dysfunction after mitral valve repair. These findings are in line with our data showing that 53% of patients with a LV end-systolic diameter ≥ 37 mm had delayed enhancement on CMR vs. 9% in patients with smaller LV dimensions.

Table 2 Comparison between patients with (LGE +) and without delayed enhancement (LGE −) on cardiovascular magnetic resonance

	Whole cohort ***n*** **= 41**	**LGE + (*n* = 12, 31%)**	**LGE − (*n* = 27, 69%)**	***P***
Mitral valve analysis (%)				
Mitral valve prolapse	37 (90)	11 (92)	24 (89)	1
Rheumatic MR	3 (7)	1 (8)	2 (7)	1
Other aetiology MR (toxic)	1 (2)	0 (0)	1 (4)	NA
Flail leaflet / no flail leaflet	11/30	5/7	7/20	0·5
Severity of MR				
ERO (mm^2)	42 ± 23	52 ± 22	39 ± 22	0·1
RVol (mL)	64 ± 37	72 ± 30	62 ± 40	0·4
Grade MR (%)				
Moderate MR	21 (51)	4 (33)	15 (56)	0·3
Severe MR	20 (49)	8 (67)	12 (44)	
Echocardiographic measurements				
LVEF (%)	67 ± 5	68 ± 5	68 ± 5	0·9
LV ESD (mm)	35 ± 5	39 ± 4	34 ± 5	0·002
Indexed LV ESD (mm/m^2)	18·5 ± 2·7	20·6 ± 1·8	17·7 ± 2·6	0·001
LV EDD (mm)	53 ± 6	57 ± 5	50 ± 5	0·001
Indexed LV EDD (mm/m^2)	27·2 ± 3·3	29·9 ± 2·4	26·3 ± 2·8	< 0·001
E/e′	12 ± 5	13 ± 4	12 ± 5	0·5
Indexed LA volume (mL/m^2)	47 ± 16	55 ± 21	44 ± 13	0·06
Transtricuspid gradient (mmHg)	27 ± 10	28 ± 7	27 ± 11	0·8
CMR measurements				
LVEF (%)	60 ± 8	60 ± 6	62 ± 8	0·5
LV ESD (mm)	36 ± 5	39 ± 4	34 ± 5	0·003
Indexed LV ESD (mm/m^2)	18·8 ± 2·8	20·7 ± 2·6	17·8 ± 2·7	0·002
LV EDD (mm)	54 ± 7	58 ± 7	52 ± 7	0·03
Indexed LV EDD (mm/m^2)	27·8 ± 4·2	30·5 ± 3·2	26·8 ± 4·1	0·01
LV ESV (mL)	63 ± 28	72 ± 35	59 ± 24	0·2
Indexed LV ESV (mL/m^2)	32 ± 13	36 ± 15	30 ± 12	0·2
LV EDV (ml)	160 ± 65	185 ± 102	150 ± 41	0·3
Indexed LV EDV (mL/m^2)	81 ± 28	93 ± 41	77 ± 20	0·3

MR, mitral regurgitation; ERO, effective regurgitant orifice; RVol, regurgitant volume; LVEF, left ventricular ejection fraction; LV ESD, left ventricular end-systolic diameter; LV EDD, left ventricular end-diastolic diameter; LA, left atrial; CMR, cardiovascular magnetic resonance; LV ESV, left ventricular end-systolic volume; LV EDV, left ventricular end-diastolic volume; NA, not applicable.

The precise pathophysiological mechanisms of myocardial fibrosis in volume overload conditions as aortic and mitral regurgitation are not entirely understood and hardly studied in human subjects. Data from animal studies [24,25] showed that experimentally induced MR causes an increase in LV mast cell density, chymase activity and angiotensin II levels with a

significant decrease of interstitial myocardial collagen content leading to LV dilatation followed by modulation of cardiac fibroblasts resulting in induction of fibrosis by synthesis of collagen and matrix metalloproteinase. This underlying mechanism might explain the relationship between LV volume overload, LV enlargement and signs of myocardial fibrosis in primary MR as observed in our study. A recently published study by Wang *et al.* [26] in a volume overload rat model showed upregulation of pro-fibrotic factors as MicroRNA-208a and endoglin. In their study, inhibition of endoglin expression by treatment with atorvastatin attenuated myocardial fibrosis, which points at the vital role of this factor in the fibrotic process.

In this respect, our study might provide further evidence regarding the poor outcome of patients with progressive LV remodelling and may support a cut-off of ≥ 40 mm for LV dilatation in severe primary MR as advocated by current ACC/AHA guidelines [27].

Furthermore, we found a trend towards an association between late contrast uptake on LGE CMR and left atrial enlargement, which is identified as a marker of chronicity of MR and a potent predictor of outcome in several recent studies [8,9,14]. The dual correlation of late contrast uptake with atrial and ventricular dilatation might be explained by data in animal studies which show that left atrial remodelling precedes and exceeds LV remodelling[28]. Other indicators of diastolic function as E/e′ and the transtricuspid gradient were also higher in the patients with delayed enhancement, although this association was not significant in this rather small cohort. Of note, the updated ESC guidelines have adopted a left atrial volume of ≥ 60 mL/m² as a class IIb indication for mitral valve surgery in case of high likelihood of repairability [3].

The study of Han *et al.* [19] described contrast uptake on LGE CMR at the papillary muscles in patients with mitral valve prolapse. We found a similar phenomenon in several patients with mitral valve prolapse. However, this was not the objective of our study and the difference with stasis of contrast along the papillary muscle (as often seen against the inner contour of the ventricles) might be difficult to make. Han *et al*. did not report additional signs of myocardial fibrosis in their relatively small sample size study of 16 patients, including patients with mild MR. Our study cohort consisted of patients with moderate to severe MR (ERO 42 ± 23 mm²) which might explain the high prevalence of late contrast uptake in the myocardial wall.

The limited number of patients included in the present study did not allow analysis between different forms of late gadolinium uptake. We observed a pattern of mid-wall fibrosis in nine patients and an infarct-like pattern in three patients with strong evidence of absent coronary artery disease. However, subendocardial infarction may be caused by embolization from minimally stenotic but unstable plaques and recanalization might occur after an occlusive coronary event [29] so underlying coronary artery disease remains a possibility. A recent study showed that some patients with regurgitant valvular heart disease present myocardial perfusion abnormalities in the absence of angiographic critical coronary stenosis [30]. Reduced coronary flow reserve might be one of the underlying mechanisms as in hypertensive cardiomyopathy or aortic stenosis. In a recent LGE CMR study in patients with moderate and severe aortic stenosis, both infarct patterns and midwall fibrosis were described, respectively, with a 6-fold and 8-fold increase in all-cause mortality compared to patients without signs of fibrosis on CMR, despite similar severity of aortic stenosis and coronary artery disease [16]. However, these findings cannot be extrapolated to our study data. Further studies are needed to confirm whether delayed enhancement on CMR is associated with a worse outcome and whether it might be a novel parameter for risk stratification in primary MR. Moreover a larger cohort is needed with separate analysis for different patterns of delayed enhancement to elucidate whether higher amounts of LGE are correlated with progressive LV dilatation and worse prognosis.

Limitations

There are several study limitations. First, the lack of association between delayed enhancement on CMR and clinical data, echocardiographic parameters or BNP level may be related to the limited number of patients, resulting in a type II error. However, even with a small sample size, our results showed a direct association between increased LV end-systolic dimension and late contrast uptake on LGE CMR, suggesting a strong relationship between these two parameters.

Second, the majority of patients had mitral valve prolapse. Hence, these results may not be automatically extrapolated to other aetiologies of MR.

Third, there is not yet a consensus about the most appropriate non-invasive method to assess cardiac fibrosis in cardiomyopathies [31–33]. T1 mapping seems superior to classic acquisition with LGE CMR [34], but this technique is not yet widely available. Furthermore, we did not perform myocardial biopsies to validate LGE CMR in primary MR.

Conclusion

Delayed enhancement on CMR could be present in up to 30% of patients with moderate to severe primary MR, even in the absence of significant LV dysfunction or dilatation. Nevertheless, the presence of late contrast uptake on LGE CMR seems essentially predicted by LV end-systolic dimension, suggesting that even early LV dilatation could involve myocardial damage. Further data, in a larger cohort of patients, are needed to determine whether the presence of delayed enhancement on CMR is associated with a less favourable prognosis and could

improve risk stratification and define the optimal timing for surgery in patients with asymptomatic primary MR.

Conflict of interest

None declared.

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