Reverse Myocardial Remodelling Following Valve Repair in Patients with Chronic Severe Primary Degenerative Mitral Regurgitation

Brief Title: Myocardial Fibrosis and Surgery in Primary MR

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Abstract

Background: Myocardial fibrosis complicates chronic severe primary mitral regurgitation (MR) and is associated with left ventricular dilatation and dysfunction. It is not known if this non-ischemic fibrosis is reversible following surgery or if it impacts on ventricular remodelling and patient outcomes.
Objectives: To quantify preoperative myocardial fibrosis using late gadolinium enhancement (LGE), extracellular volume fraction (ECV%) and indexed extracellular volume (iECV) on cardiac magnetic resonance (CMR), determine whether this varies following surgery, and examine impact on postoperative outcomes.
Methods: A multi-centre prospective study of 104 subjects with primary MR undergoing MV repair. CMR and cardiopulmonary exercise stress were performed preoperatively and ≥6 months after surgery. Symptoms were assessed using the Minnesota Living with Heart Failure questionnaire.
Results: MV repair was performed on a Class IIa indication in 65 and Class I indication in 39 patients. 93 patients were followed up at 8.8 [7.4-10.6] months. Following surgery, there were significant reductions in both ECV% (27.4% to 26.6%, P=0.027) and iECV (17.9ml/m^2 to 15.4ml/m^2, P<0.001), but incidence of LGE was unchanged. Neither preoperative ECV% nor LGE affected postoperative function, but iECV predicted LVESVi (β=1.04 [0.49-1.58], P<0.001) and LVEF (β=-0.61 [-1.05 to -0.18], P=0.006). Patients with above-median iECV of ≥17.6ml/m2 possessed significantly larger postoperative LVESVi (30.5±12.7 vs 23.9±8.0ml/m^2, P=0.003), an association that remained significant in sub-cohort analyses of NYHA Class I patients.
Conclusions: Mitral valve surgery results in reduction of ECV% and iECV, which are surrogates of diffuse myocardial fibrosis, and preoperative iECV predicts the degree of postoperative remodelling irrespective of symptoms.

Clinical Trial: clinicaltrials.gov NCT02355418
https://clinicaltrials.gov/ct2/show/NCT02355418

Keywords: Primary mitral regurgitation**,** Myocardial remodelling**,** Myocardial fibrosis**,** Cardiovascular magnetic resonance imaging, Cardiopulmonary exercise testing

Abbreviations:

CMR	Cardiovascular magnetic resonance
DIF	Diffuse interstitial fibrosis
ECV	Extracellular volume
ICV	Intracellular volume
LGE	Late gadolinium enhancement
LV	Left ventricular
LVESVi	Left ventricular end systolic volume index
MLHFQ	Minnesota living with heart failure questionnaire
MR	Mitral regurgitation
NYHA	New York Heart Association
%PredVO_2peak	Percentage predicted of maximum VO_2
CPET	Cardiopulmonary exercise testing

Introduction

Chronic volume overload is a stimulus for adverse adaptive left ventricular (LV) remodelling. The traditional concept in chronic primary mitral regurgitation (MR) has been of progressive enlargement of the LV, a process that ultimately fails, leading to LV dysfunction, and transition to a decompensated phase. Decompensation is associated with progressive and irreversible structural and functional changes in the LV, with evidence of myocardial fibrosis on autopsy studies that were performed predominantly in patients with heart failure (1). Subsequently, observational cardiac magnetic resonance (CMR) studies have demonstrated that myocardial fibrosis develops earlier in response to volume overload (2,3). This fibrosis included both coarse replacement fibrosis identified by late gadolinium enhancement imaging and diffuse interstitial fibrosis (DIF) detected using T1 mapping techniques (2,4). Furthermore, previous imaging studies linked the presence of DIF to LV dilatation and reduced ejection fraction, raising the possibility that this could be a risk factor to improve decision-making in timing interventions in primary MR (2). Although the occurrence of DIF has since been confirmed on histology in patients with asymptomatic severe MR, it is not known whether this fibrosis changes following surgical correction of MR (5). Moreover, it is not known whether the presence of DIF on CMR predicts post-repair myocardial function or patient response. The aims of this study were to assess whether CMR markers of myocardial fibrosis, as represented by absolute (iECV) and fractional extracellular volume (ECV%), are altered by surgery for primary MR; and whether preoperative CMR markers of fibrosis affected response to repair based on ventricular remodelling and patient outcomes.

Methods

Study Population

Patients with chronic severe primary MR were enrolled in the prospective multicentre Mitral FINDER study between August 2015 and March 2018 (clinicaltrials.gov NCT02355418) (6). Rationale and methods for the study have previously been published (6). In brief, consecutive adult patients aged over 18 years were recruited with severe primary degenerative MR quantified on echocardiography according to standard guidelines (7). Patients were excluded if they had primary MR not due to degenerative disease, secondary MR, congenital heart disease, inherited or acquired cardiomyopathy, non-incidental or symptomatic concomitant coronary artery disease, moderate or severe aortic valve disease, pregnancy or could not undergo CMR. The study received favourable ethical review from the UK National Research Ethics Service (15/EM/0243) and conformed to the Helsinki Declaration. Subjects gave written consent to participate. The trial was fully funded by the British Heart Foundation (PG/14/74/31056).

Study Protocol and End Points

All patients underwent assessment before surgery and between 6-9 months following mitral valve repair (6). The primary end point was postoperative LV end-systolic volume index (LVESVi) on CMR, comparing those with extracellular volume fraction (ECV%) above and below the median on preoperative assessment. Secondary endpoints included:

1) exercise capacity (%PredVO_2peak on cardiopulmonary exercise testing (CPET)).
2) cardiac-specific symptoms measured with Minnesota Living with Heart Failure Questionnaire (MLHFQ).
3) ventricular systolic dysfunction measured by postoperative LVEF.

Cardiovascular Magnetic Resonance

CMR was performed using a 1.5T (Avanto; Siemens Healthcare, Erlangen, Germany) scanner. Left and right ventricular volumes and mass, and left atrial volumes were acquired in line with standard CMR protocols (8,9). A single breath hold modified Look-Locker inversion recovery sequence (MOLLI) was used for T1 mapping in the base and mid-ventricular short axis levels before and between 15 and 20 minutes after contrast administration (3, 3, 5 scheme), according to previously published parameters (2). Stability of T1 measurement over time was confirmed by weekly analysis of a phantom within the magnet (10). LGE imaging was performed 7 to 10 minutes after 0.15 mmol/kg of gadolinium based-contrast agent (Gadovist Bayer Healthcare).

CMR studies were anonymised by A.P., with subsequent analyses performed offline using Cvi42® (version 5.3.6, Circle Cardiovascular Imaging, Canada) by B.L. who was blinded to all demographic and descriptive data, and without information regarding clinical parameters. MRI studies were analysed in a random order without knowledge of pre- and postoperative study pairings. DIF as measured by native T1 and ECV, was quantified from two short axis T1 maps (base and mid ventricle) which were manually contoured for endo- and epicardial borders; this included non-infarction LGE and excluded infarction LGE (11). Partial voluming of blood was minimised by using a 20% offset from the endo- and epicardial border (2). Indexed extracellular matrix volume (iECV) was calculated as ECV% x LV end-diastolic myocardial volume normalized to the body surface area (12), with the remaining myocardial volume defined as indexed intracellular volume (iICV). LGE mass was quantified by a 3-SD threshold above reference mean (13).

Exercise Capacity

Exercise capacity was measured using treadmill CPET using incremental ramp protocols as per American Thoracic Society guidelines (14). Gas measurements were made on the commercially available CASE exercise testing system (GE Healthcare, Chicago, USA) fitted with PowerCube-ergo (SCHILLER, UK).

Symptom Quantification

MLHFQ is a patient-reported outcome measure (PROM) validated for cardiac outcomes (15), and was completed by patients in a quiet environment.

Statistical Analysis

Data are expressed as mean ± SD or median [interquartile range] for continuous variables and as counts or percentages for categorical variables. Comparisons of continuous variables between groups were performed using independent samples t-tests for normally distributed variables, or Mann-Whitney U tests otherwise. Paired samples data were assessed with the paired sample t-test for normally distributed variables, or Wilcoxon signed ranks test otherwise. The goodness of fit of regression models was assessed graphically. Multivariable analyses were performed with backward stepwise linear regression modelling. Strong correlative relationships with high collinearity were present between pairs of independent variables including MR volume and MR fraction, LVEF and LVESVi, as well as iICV and LVMi. To avoid high collinearity within models, variables within each pair were used in separate multivariable regression models, with the model possessing the highest R^2 value reported. All statistical analyses were performed using SPSS version 24 (Armonk, NY: IBM Corp), and $P<0.05$ was deemed to be statistically significant. Analyses followed the principles of intention to treat.

Power calculation

Based on pilot data and previously published reports (2,16) the standard deviation of LVESVi in MR patients is 12ml. A survival advantage has previously been shown with a 7ml postoperative difference in LVESVi (16). A volume difference of this magnitude was therefore chosen as a clinically significant difference when comparing patients with above- and below-median ECV%. An independent T-test with 48 patients per group (96 total), and a within group standard deviation of 12ml yields a minimal detectable difference of 7ml at 80% power, with alpha=0.05.

Results

Baseline Characteristics

105 patients underwent baseline assessment: 1 was excluded from analyses due to previous percutaneous coronary intervention for myocardial infarction. 65 proceeded to MV surgery on a Class IIa indication (asymptomatic, LVEF >60%, LVESD <40mm, >95% chance successful and durable repair, mortality <1%) whilst 39 proceeded on a Class I indication due to the presence of overt symptoms (n=31 NYHA Class II, n=8 NYHA Class III classified by the clinician responsible for the patients' care). ECV quantification was available in 101 patients, as 3 were unable to tolerate the full CMR protocol due to claustrophobia. Median time from study enrolment to surgery was 3.4 [1.3-6.0] months. 93 patients attended follow-up investigations at 8.8 [7.4-10.6] months postoperative (**Figure 1**).

The median ECV% pre-surgery was 26.8% (IQR 25.0–29.2%); mean ECV% 27.4±3.3%; and mean iECV was 18.0±3.9ml/m^2. Characteristics of patients according to above and below median ECV% are given in Table 1. There was a positive correlation between MR severity

and iECV (MR volume R=0.47, P<0.001; MR fraction R=0.36, P<0.001), and iICV (MR volume R=0.54, P<0.001; MR fraction R=0.35, P<0.001), but not ECV% (MR volume R=-0.06, P=0.557; MR fraction R=0.040, P=0.688).

Coarse replacement fibrosis as detected by LGE within the left ventricular mid-myocardium was present in 34 (33%) of patients with a median mass of 1.0g [interquartile range (IQR) 0.3-2.5g]; 8 of whom possessed papillary muscle enhancement. LGE status was unrelated to ECV% and symptom status including MLHFQ. Patients with LGE had higher iECV (19.1±3.5ml/m^2 vs 17.4±3.9ml/m^2, P=0.037) and more severe MR (MR volume 74.6±32.2ml vs 57.5±27.8ml, P=0.006) compared to those without LGE.

The mean histological collagen volume fraction (CVF_{mean}) of this patient cohort, quantified via invasive myocardial biopsy at the time of surgery, has previously been reported (5). A statistically significant correlation was present between CVF_{mean} and ECV% (n=56, rho=0.33, P=0.015) when limiting analyses to biopsy samples containing only myocardium (without endocardial contamination). Additionally, iICV significantly correlated with histologically determined cardiomyocyte hypertrophy (n=83, rho=0.28, P=0.010), but CVF_{mean} and iECV did not significantly correlate (n=56, rho=0.00, P=1.000).

Surgical Outcomes

Successful MV repair was achieved in all but one patient who received mechanical valve replacement (**Online table 1**). 15 patients received concomitant coronary artery bypass graft (CABG) for coronary disease incidentally discovered at the time of preoperative coronary angiography. These cases were included within the main analyses because the patients were

asymptomatic without prior history of coronary disease, had no evidence of ischemia on maximal CPET and none had evidence of prior infarction on LGE during CMR.

Eight patients (n=6 NYHA class I, n=1 NYHA class II, n=1 NYHA class III) declined study follow-up. There was a trend for patients declining follow-up to be younger (55±18 vs 63±13 years, P=0.076) with no other between-group differences. Three NYHA Class I patients died during the follow-up period due to non-cardiovascular events. Compared to those who returned for follow-up, patients who died were older (77±3 vs 63±13years, P<0.001) with borderline lower LVEF (59.3±11.5 vs 68.9±8.1%, P=0.049) but with no other differences, including ECV%, iECV or extent of LGE.

Impact of MV Surgery on Fibrosis and Left Ventricular Remodelling

92 out of 93 surgical patients who attended follow-up visits underwent postoperative CMR; one was excluded following implantation of a non-CMR conditional pacemaker. MV repair was followed by reverse remodelling in LVESVi (32.3ml/m^2 to 26.9ml/m^2, P<0.001), and LVEF (69.0% to 63.3%, P<0.001) (**Table 2, Figure 2**), with the magnitude of change in postoperative LVEF being inversely related to preoperative LVEF (**Figure 3A**). Overall postoperative systolic function was good across the cohort with a mean postoperative LVEF of 63.3±8.3; only 6 (6%) patients had LVEF <50%.

Surgery was accompanied by a postoperative reduction in indexed left ventricular mass (LVMi; 68.7g/m^2 to 60.1g/m^2, P<0.001) and ECV% (27.4% to 26.6%, P=0.027), which equated to reductions in iECV (17.9ml/m^2 to 15.4ml/m^2, P<0.001, 14.4% relative reduction) and iICV (47.7±9.9 to 42.0±7.8, P<0.001, 12.0% relative reduction; **Figure 4**). The impact of mitral annular ring implantation during MV repair was assessed using phantom samples; the

presence of an annular ring resulted in minimal changes to phantom T1 values (**Online table 2**).

There was no difference in the change in measures of fibrosis between asymptomatic vs symptomatic patients (ECV% -0.5±2.7% vs -1.4±4.0%, P=0.209; iECV -2.7±3.1ml/m^2 vs -2.5±4.1ml/m^2, P=0.800), nor by LGE burden (**Table 3**). There were only 8 patients with LGE in the papillary muscles, and analyses limited to changes in pre- and post-operative ECV%, iECV or LVEF in this small group were not significant. The magnitude of both ECV% and iECV reduction correlated closely with their preoperative expansion (ECV% R=-0.64, P<0.001, **Figure 3B**; iECV R=-0.55, P<0.001, **Figure 3C**). On multivariable regression analyses, preoperative ECV%, LVMi, LVEF and MR volume remained independent predictors of iECV regression (**Table 3**).

No statistically significant difference in measures of postoperative systolic function was found between patients with above- and below-median preoperative ECV% of 26.8% (LVESVi 26.1±9.7 vs 28.0±12.2ml/m^2, P=0.416; LVEF 62.8±8.3 vs 63.9±8.5%, P=0.530). There was a significant difference in postoperative systolic function between patients with above- and below-median preoperative iECV of 17.6 (LVESVi 30.5±12.7 vs 23.9±8.0ml/m^2, P=0.003; LVEF 61.1±8.7 vs 65.1±7.7% P=0.023), with higher preoperative iECV correlated to worse postoperative LV systolic function (**Table 3**). A comparison of patient subgroups with the highest (>20.0ml/m^2) and lowest (<15.0ml/m^2) quartile of preoperative iECV further magnified these differences in postoperative LV remodelling (LVESVi 34.0±12.9 vs 23.5±9.0ml/m^2, P=0.003; LVEF 59.5±6.7 vs 65.4±8.5%, P=0.016). Statistical significance was neither affected by excluding patients who required CABG for incidental coronary disease (**Online table 3**), nor by limiting analyses to NYHA Class I patients (n=55, iECV

correlation with LVEF R=-0.32, P=0.018; LVESVi R=0.48, P<0.001). On multivariable linear regression modelling, preoperative iECV and LVEF remained independent predictors of postoperative LVEF. Meanwhile, preoperative LVESVi and MR fraction were independent predictors of postoperative LVESVi (**Table 3**). The presence of LGE did not influence postoperative LVESVi or LVEF (**Table 3**).

Symptom Burden and Exercise Capacity

Pre-operatively, iICV, MR volume, NTproBNP and age were independent predictors of MLHFQ, whilst iICV and MR fraction remained significant independent predictors of %PredVO_2peak (**Online table 4A**).

As might be expected, successful MV surgery only improved symptom scores (MLHFQ Physical domain) in symptomatic patients. Likewise, statistically significant improvements in peak exercise capacity were observed only in symptomatic patients, although both subgroups experienced an improvement in O_2 pulse and VE/VCO_2, suggesting that asymptomatic patients benefit from improvements in cardiac efficiency (**Table 4)**.

Postoperatively, iICV remained a significant predictor of MLHFQ, whilst MR fraction predicted postoperative exercise capacity on CPET. However, none of these effects were independent of pre-operative MLHFQ and %PredVO_2peak respectively (**Online table 4B**).

Despite the postoperative improvements in symptom burden and exercise capacity in symptomatic individuals, this sub-group of patients did not achieve the same level of exercise capacity or symptom score as asymptomatic patients (%PredO_2peak 92.2±18.8% vs 102.9±21.1%, P=0.017, MLHFQ 10 [5-22] vs 3 [0-10], P<0.001). Preoperative symptom

status was not associated with statistically significant changes on postoperative reverse remodelling measured on CMR (**Online table 5**).

Impact of MR subtype

Classification into fibroelastic deficiency (FED) versus Barlow's disease (BD) was based on independent review of echocardiographic and CMR imaging by two experienced imaging cardiologists (RPS, NCE) according to pre-specified criteria (**Online table 6**) in conjunction with surgical findings (17). Preoperative CMR parameters were similar between patients with fibroelastic deficiency (FED, n=59) and those with Barlow's disease (BD, n=35) (5). Similarly, there were no differences in LGE, ECV% or iECV status between the two subtypes (**Online table 7**). Postoperatively, FED patients on average had higher LVEF than patients with BD (64.9±8.2% vs 60.6±7.8%, P=0.020) with a trend towards lower LVESVi (24.8±9.7ml/m2 vs 29.3±10.7ml/m2, P=0.052) but this change did not vary according to LGE, ECV% or iECV. No postoperative differences in symptom burden (MLHFQ score) or exercise capacity (%PredVO_2peak) were present (all P values >0.30).

Discussion

In this prospective multicenter observational study of 104 patients, we demonstrate for the first time that surgical repair of chronic primary MR is associated with postoperative reductions in both ECV% and iECV. The extent of regression was proportionate to the degree of preoperative expansion, suggesting that patients with more extensive fibrosis before surgery undergoes larger reductions on follow-up (**Central Illustration**). Although neither preoperative ECV% nor extent of LGE predicted LV remodelling following repair, higher iECV was associated with worse postoperative LV systolic function (higher LVESVi and lower LVEF). These changes were found in a predominantly asymptomatic population with

normal preoperative LV size and ejection fraction and were not associated with change in exercise capacity or symptom scores. Our data suggest that whilst patients with more preoperative fibrosis measured on LGE, ECV% and iECV continue to benefit from surgery, a deleterious effect on LV function remains. Future study assessing the long-term impact of ECV%, iECV and LGE on outcome following surgery is needed.

Reverse myocardial remodelling

We observed an association between preoperative iECV and postoperative LV function. It has been widely proposed that the accumulation of myocardial fibrosis is associated with subclinical LV systolic and diastolic dysfunction (18,19). This relationship is supported by animal models of volume overload induced myocardial fibrosis (20-22), and has been specifically documented in primary MR (5). Furthermore, ECV% offers incremental prognostic value compared to traditional parameters of ventricular structure and function in mutliple cardiovascular diseases (23). Extrapolating these findings, a postoperative 'normalization' of myocardial collagen networks may also lead to improvements in LV function, and offer a biological basis for our findings. However, the exact mechanism behind collagen accumulation and LV function requires further study, and may be related more to the extent of collagen cross-linking rather than total collagen quantity (19). Our study has demonstrated a fall in ECV% and iECV in response to MV repair without a change in LGE (**Figure 5**). This is consistent with the concept of two different patterns of fibrosis in valvular heart disease: reactive DIF which follows volume-loading myocardial shear-stress induced myofibroblast activity and collagen deposition in early disease that is potentially reversible, and later replacement fibrosis that is irreversible (24). This mixed pattern of both replacement and diffuse fibrosis has been found in both primary MR (2) and aortic stenosis (25). Remodelling of the interstitial space is considered an adaptive response to molecular injury

that can become maladaptive, hence the relationship between increasing ECV% and worse outcome in aortic stenosis (26). While there are no other postoperative data on reversal of fibrosis in MR, plasticity of DIF has been shown in multiple animal models, for example in myocardial responses to angiotensin converting enzyme inhibitors (27). Indeed, this potential for degradation of myocardial fibrosis and reversal of cross-linking remains the subject of intense research activity (28).

A recent reverse remodelling study in aortic stenosis reported a postoperative increase in ECV% (29). However, with a significant decrease in overall LV mass, this implied that the intracellular compartment had regressed proportionately more than the extracellular matrix. The changes following repair in primary MR included not only a fall in LV mass but also a small reduction in ECV%, suggesting a proportionately larger reduction in the extracellular matrix than the intracellular compartment. This is plausible given the timeframe to repeat CMR of 6-9 months following surgery, considering the estimated 5% daily turnover of the extracellular matrix. It is unlikely the changes in ECV% and iECV are due to fall in myocardial oedema or fat, although T2 imaging was not performed in our protocol. Although intramyocardial fat was found on histology in our primary MR patients, the amount was small and was found in a minority of patients (5). In summary, the fall in ECV% and iECV following MV repair without change in LGE may suggest a reduction in DIF, without change in coarse replacement fibrosis, a finding consistent with data from other studies of myocardial response to therapy.

Reverse remodelling and symptom burden

Assessment of ECV% in asymptomatic MR has been proposed as a potential imaging biomarker of patient outcome due to its association with preoperative symptom development.

In a prospective registry study of 144 patients with moderate-severe primary MR (regurgitant fraction >30%), patients who decompensated within three-years follow-up had higher median ECV% (28.1% vs 27.1%, P<0.001) (3). The relationship between preoperative imaging biomarkers and postoperative outcomes, however, has not been previously studied. Despite our cohort possessing a lower median ECV of 26.8% (suggesting a less advanced stage of myocardial remodelling), we observed that iICV and MR fraction predicted postoperative symptoms and exercise capacity respectively. However, this relationship was not independent of preoperative MLHFQ and %PredVO_2peak.

It is conceivable that further studies limiting recruitment of patients with lower iICV, higher ECV% and higher iECV might find an association with adverse remodelling and higher rates of impaired LVEF, but recruitment might prove difficult given the preference for early repair in asymptomatic patients at low risk.

The association between iICV and symptom status, as well as higher postoperative MLHFQ scoring, is hypothesis-generating but may be limited in clinical impact by the overlap of ECV% values and standard deviations between groups. ECV% has been recently reported as the most powerful independent prognostic biomarker, outperforming conventional surgical indications, in a large international prospective observational study of patients with severe aortic stenosis (26). It remains to be demonstrated whether the same will apply for the volume overloaded state of MR (5). Pertinently, even within a cohort of patients with normal LV size and function, postoperative exercise fitness and symptom status in our symptomatic cohort failed to improve back to a level that was comparative with the preoperatively asymptomatic cohort. These findings support the benefits of early surgery before Class I indications are met.

Limitations

Firstly, this was a study of predominantly asymptomatic, low risk and relatively fit patients given their symptom scores, body mass index and exercise capacity on formal testing. As a result, our cohort of patients had a comparatively low burden of fibrosis as quantified by ECV%, which may have weakened our ability to detect correlations. Secondly, the study was underpowered as per the original power calculation with 92 out of the required 96 patients undergoing postoperative CMR. However, our prior hypothesis was that patients with above-median ECV% would possess LVESVi 7ml/m^2 higher than those with below-median ECV. Instead, the direction of our data was reversed with higher ECV patients possessing a trend for lower postoperative LVESVi, suggesting that a larger patient cohort would not have made a difference to our study outcomes. Thirdly, we are not able to determine the exact timing of onset of MR in our population, although all patients were referred for surgery as routine, with no acute, urgent or emergency indications for rapid deterioration in clinical state. Finally, we did not exclude patients who had incidental coronary disease requiring CABG. However, these patients did not have angina symptoms on CPET, nor infarct pattern LGE on CMR, and their inclusion likely increases the ability of this study cohort to reflect that of the general MR population (predominantly male, over the age of 60 years).

We also accept there may be multiple factors, including local factors altering wall stress, ventricular-vascular and venous coupling, vortical flow, referral practice, and surgical approach that could affect myocardial response to repair that could not be explored due to sample size in this study.

Summary

MV repair for predominantly asymptomatic severe primary MR with good systolic function leads to a fall in myocardial mass with reduction in both ECV% and iECV, which are surrogate markers of diffuse interstitial fibrosis, although there was no change in focal replacement fibrosis. Regression of DIF biomarkers was greatest in those with the highest imaging burden of myocardial fibrosis before surgery, confirming plasticity in volume overload. Similarly, symptomatic improvement was greatest in those with the highest starting symptom burden; albeit a significant symptom burden did remain despite surgery in those with overt symptoms. Although there was no association between preoperative ECV% and postoperative systolic function, there was a relationship between iECV and LV structure and function after surgery, irrespective of preoperative symptom status. These data highlight the potential prognostic value of fibrosis imaging in MR and are supportive of early surgery in asymptomatic patients with chronic severe primary MR.

Clinical Perspectives

Competency in Medical Knowledge: Determining the ideal time for intervention in patients with chronic severe mitral regurgitation remains an important challenge, since patients have worse outcomes if surgery is delayed until symptoms, LV dilatation or dysfunction are present. Many older patients can delay surgery however without adverse outcome. Myocardial fibrosis is detectable in patients with severe MR and may be an imaging biomarker helpful in timing surgery.

Translational Outlook 1: Following mitral valve repair, coarse replacement fibrosis does not resolve but CMR based quantification of myocardial mass, cellular hypertrophy, and diffuse interstitial fibrosis all regress.

Translational Outlook 2: Although regression is accompanied by structural and functional improvements in the LV, in this cohort with few symptoms, good exercise capacity and normal preoperative ventricular function. Further research is needed to identify whether imaging biomarkers measuring late gadolinium enhancement and extracellular volume predict longer-term prognosis in mitral regurgitation.

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Figure legends

Figure 1. Flow diagram summarising patient recruitment and follow-up.
A total of 105 patients undergoing mitral valve surgery were recruited for the study. Exclusions and follow-up status are displayed.

Figure 2. Line graph illustrating individual trajectories of (A) LVEF, (B) ECV and (C) iECV) following mitral valve surgery.
Changes following mitral valve surgery are displayed on an individual patient basis.

Figure 3. Scatter plot demonstrating the negative correlation between preoperative and magnitude of change in postoperative CMR parameters for A) LVEF, B) ECV and C) iECV.
Linear regression line of best fit with corresponding R^2.

Figure 4. Cellular and extracellular remodelling 9 months after mitral valve repair.
At 9 months post mitral valve repair, there were significant reductions in (A) indexed left ventricular mass (68.7±13.5 to 60.1±11.4g/m2, P<0.001) (B) extracellular volume fraction (27.4±3.3 to 26.6±2.8, P=0.027) (C) derived indexed cellular volume (indexed left ventricular myocardial volume x [1 – ECV%]; 47.7±9.9 to 42.0±7.8, P<0.001) and (D) derived indexed extracellular volume (indexed left ventricular myocardial volume x ECV%; 17.9±4.0 to 15.4±3.6, P<0.001).

Figure 5. Reverse myocardial remodelling following mitral valve repair in a 67-year-old man with severe mitral regurgitation due to P1 prolapse. Cardiac magnetic resonance shows postoperative reduction in left ventricular mass, volumes and ejection fraction to reflect the removal of the hyperdynamic state. Focal fibrosis (late gadolinium enhancement) remained unchanged, meanwhile extracellular volume fraction (ECV%), indexed extracellular volume (iECV) and indexed intracellular volume (iICV) regresses.

Central illustration. Preoperative and postoperative myocardial remodelling in mitral regurgitation. (A) The in vivo myocardium consists of cardiomyocytes and the surrounding extracellular matrix. Mitral regurgitation triggers cardiomyocyte hypertrophy and reactive fibrosis with extracellular matrix expansion. Mitral valve repair is associated with regression of left ventricular mass, volumes, and removal of the hyperdynamic circulatory state. **(B)** On cardiovascular magnetic resonance, with left ventricular mass regression, coarse replacement fibrosis remains unchanged. **(C)** Conversely, patients with higher degrees of preoperative extracellular matrix expansion will tend to undergo larger magnitudes of indexed extracellular volume (iECV) and extracellular volume fraction (ECV%) postoperative regression.