Quantification of Left Ventricular Interstitial Fibrosis in Asymptomatic Chronic Primary Degenerative Mitral Regurgitation

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Methods and Results—A cross-sectional study of 35 patients (age 60±14 years) with asymptomatic moderate and severe primary degenerative MR (mean effective regurgitant orifice area, 0.45±0.25 cm²) with no class I indication for surgery were compared with age and sex controls. Subjects were studied with cardiopulmonary exercise testing, echocardiography, and cardiac MRI. Longitudinal and circumferential myocardial deformation was reduced with MR when left ventricular ejection fraction (67%±10%) and N-terminal pro B Natriuretic peptide (126 [76–428] ng/L) were within the normal range. Myocardial extracellular volume was increased (0.32±0.07 versus 0.25±0.02, P<0.01) and was associated with increased left ventricular end-systolic volume index (r=0.62, P<0.01), left atrial volume index (r=0.41, P<0.05) but lower left ventricular ejection fraction (r=−0.60, P<0.01), longitudinal function (mitral annular plane systolic excursion, r=−0.46, P<0.01), and peak VO₂ max (r=−0.51, P<0.05). In a multivariable regression model, left ventricular end-systolic volume index and left atrial volume index were independent predictors of extracellular volume (r²=0.42, P<0.01).

Conclusions—Patients with asymptomatic MR demonstrate a spectrum of myocardial fibrosis associated with reduced myocardial deformation and reduced exercise capacity. Future work is warranted to investigate whether left ventricle fibrosis affects clinical outcomes. (Circ Cardiovasc Imaging. 2014;7:946-953.)

Key Words: magnetic resonance imaging ▪ mitral valve regurgitation ▪ myocardial fibrosis

Mitral regurgitation (MR) is the most common form of valve disease in the developed world, and the prevalence of severe MR is expected to double by 2030, in part because of the growth of the older population. Current guidelines recommend expectant management with careful supervision until class I indications for surgery are met. At present, there are no randomized data to separate the optimal management of patients with asymptomatic severe primary degenerative MR with preserved left ventricular ejection fraction (LVEF) and normal left ventricle (LV) size between a conservative approach with expectant management verses early mitral valve repair, where a delay might be perceived as consigning such patients to surgery.

Editorial see p 860

Clinical Perspective on p 953

Traditionally, the response of the LV to MR has been conceptualized in stages: initially a compensatory response with LV dilatation and eccentric hypertrophy in response to chronic volume overload, a transitional stage when functional recovery is possible with intervention and decompression with progressive and irreversible structural and functional deterioration at which stage surgical outcomes are poor. More recently, it has been suggested that LV dysfunction may be progressive from the earliest stages of MR, with reduction in early myocardial relaxation velocity and global strain. Although interstitial fibrosis is well recognized as a reaction to pressure overload states, an increase in the interstitial space and myocyte hypertrophy has also been confirmed on autopsy in severe primary MR. The ability of cardiac MRI T1 mapping techniques to quantify expansion of the myocardial interstitial space by fibrosis has strong histological correlation in several disease entities, including aortic stenosis, diabetes mellitus, and after cardiac transplantation. In this observational study, we examined whether patients with asymptomatic moderate

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to severe primary degenerative MR would have expansion of the extracellular space, despite normal LV size and ejection fraction and the association with subclinical parameters of LV function and functional exercise capacity.

Methods

Setting and Participants
Between April 2012 and April 2014, 35 consecutive patients with asymptomatic chronic, moderate or severe primary degenerative MR without a class I indication for surgery were prospectively identified from the valve clinic at the Queen Elizabeth Hospital Birmingham, UK. Additional inclusion criteria were LVEF ≥60% calculated using the modified Simpsons rule and linear LV internal dimension in systole ≤40 mm measured from the parasternal long axis view on transthoracic echocardiography (TTE). The pathogenesis, lesion, and severity of MR were defined by echocardiography (see below) as part of routine care. Exclusion criteria included history of previous myocardial infarction or symptomatic coronary disease; history or evidence on echocardiography or at surgery of rheumatic heart disease; history or evidence on echocardiography or at surgery of uncontrolled hypertension (≥160/100 mm Hg); and known contraindication to MRI. Coronary angiography was performed if patients were considered for surgery on the basis of a class IIa indication (atrial fibrillation [AF], pulmonary hypertension, high likelihood of durable repair). Patients were compared with age and sex-matched healthy controls with no history of cardiac disease, identified from convenience sampling, which is a nonprobability method of drawing representative data by selecting people because of the ease of their volunteering, availability, or easy access. The study was approved by the National Research Ethics Service – South Birmingham (12/WM/0250), and all subjects gave informed consent. All subjects underwent the following investigations.

Echocardiography
MR was assessed by means of resting TTE or transoesophageal echocardiography performed by accredited sonographers and physicians according to the British Society of Echocardiography Minimum Datasets for Transthoracic and Transoesophageal Echocardiography (www.bsecho.org). Quantification of MR and classification of mechanism was performed according to the recommendations of the European Association of Echocardiography.13 Severe MR was defined as an effective regurgitant orifice area ≥0.4 cm² using the flow convergence method (proximal isovelocity surface area method). If the effective regurgitant orifice was ≤0.4 cm² or was inaccurate because of angulation of MR, the assessment of the severity of MR was guided by an integrative approach, including width of the vena contracta, density of the continuous-wave Doppler profile of mitral systolic function, transmitral forward early velocity, and pulmonary vein systolic flow pattern.

Cardiac MRI
Left and right ventricular volumes and mass and left atrial volumes were acquired in line with standard cardiovascular MRI (1.5T Avanto; Siemens Healthcare, Erlangen, Germany) protocols.14,15 Mitral valve anatomy was assessed using basal short axis and long axis steady-state free-precession cines of the mitral valve after a standardized approach.14 Mitral regurgitant volume was calculated as the difference of LV stroke volume and the aortic forward stroke volume. The regurgitant fraction was calculated from the ratio of the mitral regurgitant volume divided by the LV stroke volume (regurgitant fraction (%)=[mitral regurgitant volume÷LV stroke volume]×100). Three short-axis tagged images at the LV base (mitral valve), mid (papillary muscle) apex, and horizontal long axis were acquired using prospective electrocardiographic gating. A uniform tag grid was created on the images using spatial modulation of magnetization as previously described.17 A steady-state free precession, single breath hold modified Look-Locker inversion recovery sequence was used for T1 mapping in the LV base and mid-ventricular short axis levels before and between 15 and 20 minutes after contrast administration (11 phases [3, 3, 5 scheme], total breath hold 17 R-R intervals).18 Late enhancement imaging was performed 7 to 10 minutes after 0.15 mmol/kg of gadolinium contrast bolus (Gadovist Buyer Healthcare).

Cardiac MRI Image Analysis
Cardiac MRI image analysis was performed offline using Argus Software (Siemens®) according to the Society for Cardiovascular MR guidelines.19 Tagged images were analyzed with CIMTag2D software (Cardiac Image Modelling, University of Auckland, Auckland, NZ) to calculate global peak systolic strain, peak systolic strain rate (myocardial deformation), and peak early diastolic strain rate (an indicator of diastolic function).20 Quantitative parametric images of myocardial extracellular volume (ECV) were generated with manual contouring to define a region of interest in the left ventricular septum, basal and mid-ventricular level using validated formulæ: ECV=[(AR1 myocardium]/(AR1 blood pool)×(1−Hct)]. Hct refers to the haematocrit recorded on a venous blood sample at the time of scan and AR1=I/T1 postcontrast−I/T1 precontrast.22 ECV within the LV septum at a basal and mid-short axis levels was averaged to yield a global ECV measurement and included areas of diffuse noninfarction pattern late gadolinium enhancement (LGE), but excluded areas of LGE consistent with previously undiagnosed infarction. All T1 data were analyzed by an individual blinded to clinical data (N.C.E.). Intraobserver variability was high: intraclass correlation, 0.96 (95% CI, 0.88–0.98).

Cardiopulmonary Exercise Testing
Patients underwent cardiopulmonary exercise testing on a treadmill using an incremental RAMP protocol based on American Thoracic Society guidelines.21 Subjects wore a tight facemask to permit estimation of peak oxygen consumption (peak VO₂) and anaerobic threshold using a modified V-slope method. Blood pressure, 12-lead ECG, and arterial pulse oximetry readings were continuously recorded throughout. The Borg Scale was used to record patients rating of perceived exertion.22

Biochemistry
Venous blood samples were collected for routine hematology and biochemistry. Serum N-terminal pro B Natriuretic peptide (ng/L) was measured by sandwich immunoassay with magnetic particle separation and chemiluminescent detection on an Elecsys analyzer (Roche Diagnostics, Burgess Hill) with a lower limit of detection of 0.6 pmol/L.

Data Analysis and Statistics
Continuous variables are expressed as means SD if normally distributed or median (25th and 75th percentiles) if non-normally distributed by the Shapiro–Wilks test. Paired group comparisons were performed using paired t test or signed rank test. Pearson correlations between variables were assessed by bivariate analysis. A multivariable regression model was used to assess predictors of ECV using variables associated with myocardial fibrosis. Statistical tests were 2-tailed, and a P<0.05 was considered to indicate statistical significance.

Results
Thirty-five asymptomatic patients with MR were compared with healthy controls. Demographic data are presented in Table 1.

Echocardiography
All patients were studied with TTE. In total, 27/35 (77%) patients also underwent transesophageal echocardiography. In all patients, imaging appearances supported a degenerative pathogenesis with type II Carpenter mechanism. The involvement of the posterior leaflet was the most common finding (n=20), with anterior mitral valve leaflet (n=7) and bileaflet involvement (n=8) the other causes of MR. Median effective regurgitant orifice area was 0.41cm² (0.30–0.52), with 21 patients classified as severe and 14 patients with moderate MR on echocardiography. Complete Doppler profiles allowed estimation of pulmonary systolic artery pressure on echocardiography in 21/36 with estimated peak pulmonary artery systolic pressure of 35±14 mm Hg.
Ventricular Structure and Function on CMR

Data are presented in Table 2. Patients had increased indexed LV end-diastolic, LV end-systolic, and stroke volumes compared with controls. LVEF was lower in patients with MR but within normal range. Four patients subsequently had an LVEF ≤60% on CMR and were referred for surgery. Mean regurgitant volume was 41±17 mL. Using CMR criteria, 8 patients had severe MR (regurgitant fraction ≥42%) based on the difference between LV and aortic stroke volumes. Global longitudinal and circumferential systolic myocardial deformation were reduced in patients with MR compared with healthy controls (Table 2). MR was associated with increased right ventricular end-diastolic and end-systolic volumes and lower right ventricular EF, although there was no difference in right ventricular stroke volume (Table 2).

Mean global ECV was higher in MR than controls, but with wider variation and overlap at the upper end of the normal range (Figure 1). Sixteen patients (46%) had an ECV above the upper limit observed for controls (0.297). There were no differences in age or prevalence of AF, hypertension, or diabetes mellitus in these subjects. Increased ECV above normal limits was associated with higher septal precontrast (native) T1 (1009±58 versus 939±93 ms, P<0.05) but no difference in postcontrast T1 (418±73 versus 467±89 ms, P=0.13). Increased ECV above normal limits was also associated with increased left ventricular end-systolic volume index and LA volume, but relative reductions in LVEF and mitral annular plane systolic excursion (MAPSE; Table 3). ECV remained elevated in MR compared with controls (0.31±0.07 versus 0.25±0.02, P<0.01) even after exclusion of patients with possible confounding comorbidities, including diabetes mellitus, AF, hypertension, and asymptomatic coronary disease on preoperative angiography (see below).

Patients with severe MR (by echo criteria, n=21) had elevated ECV compared with controls (0.32±0.05 versus 0.25±0.02, P<0.01), and all parameters of LV size and function remained significantly different from controls. Patients with moderate MR also had elevated ECV (0.30±0.06 versus 0.25±0.02, P<0.05) compared with controls with elevated left ventricular end-diastolic volume, left ventricular end-systolic volume, and reduced MAPSE. There were no differences in LVEF or LV mass. Severe MR was associated with higher indexed LV end-diastolic volume but no differences in ECV or parameters of LV function compared with moderate MR.

Diffuse LGE distributed in a noncoronary artery pattern (Figure 2) was present in 11/35 (31%) patients with MR. These patients had a significantly increased ECV (0.35±0.02 versus 0.27±0.03, P<0.01), increased native T1 times (1021±48 versus 910±122 ms, P<0.05), and increased indexed left atrial volumes (65±14 versus 54±12 mL/m², P<0.05) than MR patients with no LGE. There were no differences in postcontrast T1 (424±66 versus 458±88 ms, P=0.33). The presence or absence of LGE was not associated with differences in LV volumes, ejection fraction, or myocardial deformation (Table 2). In contrast, an ECV above normal limits with or without LGE was associated with lower EF and MAPSE and increased left ventricular end-systolic volume index and LA volume. (Table 3). Two patients had LGE in a subendocardial distribution; one of these patients had no CV risk factors and had a normal coronary angiogram. A biopsy at the time of surgery confirmed severe fibrous endocardial thickening with hypertrophy, chronic inflammation, mild myocardial fibrosis but not typical of infarction. The second patient had a normal TTE, but on CMR had LGE with associated thinning and regional wall motion abnormality consistent with infarction. Both patients were excluded from all subsequent statistical analyses.

Cardiopulmonary Exercise Testing

In total, 19 patients underwent cardiopulmonary exercise testing as part of routine clinical surveillance. Mean exercise workload was 9.4±3 metabolic equivalents. Mean BORG score (perceived level of exercise) was 16 (hard), with a minimum of 13 (somewhat hard) and maximum of 19 (very hard). Mean peak VO₂max was 25 mL/kg/min (9) with a mean respiratory exchange ratio of 1.2 (0.1). The mean percentage predicted VO₂max for age and sex was 90±16%. Only 6 patients had a VO₂ below 90% predicted for age and sex. The minute ventilation and carbon dioxide production slope was abnormal (>35) in 4 patients. Global ECV was correlated with total exercise time (r=−0.54, P<0.05), metabolic equivalent (r=−0.54, P<0.05), peak VO₂ (r=−0.51, P<0.05), and BORG scale (r=0.68, P<0.01).

Myocardial Fibrosis

Global ECV correlated with age (r=0.31, P<0.05), left ventricular end-systolic volume index (r=0.62, P<0.01), LVEF (r=0.60, P<0.01), MAPSE (r=−0.46, P<0.01) and left atrial volume (r=0.41, P<0.05; Figure 3). There was no correlation with N-terminal pro B Natriuretic peptide or myocardial deformation. Factors shown to correlate with ECV were entered into a multivariable linear regression model. Variables with collinearity (Variance Inflation Factor>2); end-systolic volume and LVEF;
metabolic equivalent and VO₂ max were entered into separate models; ESVi (unstandardized β coefficient 0.04, P <0.01) and left atrial volume index (unstandardized β coefficient 0.02, P <0.05) were both independently associated with ECV (r²=0.42, P <0.01).

**Referral for Surgery**

Twelve patients with severe MR underwent surgery over the study period; 4 patients had an LVEF <60% on CMR (normal on TTE). Class IIa indications were onset of AF (n=3), resting systolic pulmonary artery pressure >50 mm Hg (n=1), and quoted risk of success durable repair >90% with low surgical risk (n=4). Preoperative coronary angiography was performed in 10/12 patients, with 1/12 patient aged 33 years undergoing computed tomography coronary angiography and 1/12 referred without coronary imaging in view of young age and absence of cardiovascular risk factors. Two patients had asymptomatic coronary artery disease requiring single vessel coronary artery bypass grafting at the time of mitral valve surgery, one of whom had diffuse LGE on CMR. There were no deaths or major morbidity. Average length of stay was 8±2 days. Mitral repair was successfully performed in all 12 subjects. Excision of respective prolapsing scallops, chordal transfer, and insertion of an appropriately sized annuloplasty ring was the primary surgical technique. Left ventricular biopsies taken at the time of mitral valve repair in 2 patients confirmed evidence of diffuse interstitial fibrosis in a noncoronary distribution (Figure 4).

**Discussion**

In patients with asymptomatic chronic moderate or severe degenerative MR with type II mechanism, diffuse interstitial fibrosis as measured by elevated global ECV, was a common finding and occurred before any conventional class I

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**Table 2. Functional and Morphological Data on Cardiac MRI for Patient and Controls**

<table>
<thead>
<tr>
<th></th>
<th>Controls, n=35</th>
<th>MR, n=35</th>
<th>MR + diffuse LGE, n=11</th>
<th>MR + no LGE, n=21</th>
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<tbody>
<tr>
<td>LV ejection fraction, %</td>
<td>74±6</td>
<td>67±10**</td>
<td>67±7</td>
<td>71±6</td>
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<tr>
<td>LV end-diastolic volume index, mL/m²</td>
<td>62±11</td>
<td>88±21**</td>
<td>91±23</td>
<td>86±21</td>
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<td>LV end-systolic volume index, mL/m²</td>
<td>17±7</td>
<td>30±13**</td>
<td>30±10</td>
<td>26±10</td>
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<tr>
<td>LV stroke volume, mL</td>
<td>86±16</td>
<td>113±35**</td>
<td>120±35</td>
<td>117±36</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>59±13</td>
<td>69±13**</td>
<td>73±14</td>
<td>71±123</td>
</tr>
<tr>
<td>Presence of noninfarct pattern of LGE, n</td>
<td>0</td>
<td>11**</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Presence of infarct pattern of LGE, n</td>
<td>0</td>
<td>2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>68±9</td>
<td>56±7**</td>
<td>56±6</td>
<td>55±6</td>
</tr>
<tr>
<td>RV end-diastolic volume index, mL/m²</td>
<td>67±13</td>
<td>78±18**</td>
<td>87±21</td>
<td>76±13</td>
</tr>
<tr>
<td>RV end-systolic volume index, mL/m²</td>
<td>22±10</td>
<td>35±11**</td>
<td>38±11</td>
<td>34±9</td>
</tr>
<tr>
<td>RV stroke volume, mL</td>
<td>83±15</td>
<td>81±22</td>
<td>92±18</td>
<td>81±23</td>
</tr>
<tr>
<td>Mean global ECV</td>
<td>0.25±0.02</td>
<td>0.32±0.07**</td>
<td>0.35±0.05</td>
<td>0.27±0.03‡‡</td>
</tr>
<tr>
<td>LA volume index, mL/m²</td>
<td>34±7</td>
<td>57±13**</td>
<td>65±14</td>
<td>54±12‡</td>
</tr>
<tr>
<td>MAPSE, mm</td>
<td>16±3</td>
<td>14±3*</td>
<td>13±1</td>
<td>15±2</td>
</tr>
<tr>
<td>Regurgitant volume, mL</td>
<td>1±7</td>
<td>41±17**</td>
<td>45±15</td>
<td>40±19</td>
</tr>
<tr>
<td>Regurgitant fraction, %</td>
<td>1±8</td>
<td>34±9**</td>
<td>35±5</td>
<td>34±10</td>
</tr>
<tr>
<td>Global longitudinal strain, %</td>
<td>16.3±2.4</td>
<td>11.3±3.3**</td>
<td>9.8±4.3</td>
<td>11.7±2.9</td>
</tr>
<tr>
<td>Global longitudinal strain rate, s⁻¹</td>
<td>0.85±0.2</td>
<td>0.64±0.2*</td>
<td>0.54±0.17</td>
<td>0.56±0.33</td>
</tr>
<tr>
<td>Global circumferential strain, %</td>
<td>18.2±2.2</td>
<td>15.4±4.0**</td>
<td>15.4±5.0</td>
<td>15.5±4.0</td>
</tr>
<tr>
<td>Global circumferential strain rate, s⁻¹</td>
<td>1.0±0.2</td>
<td>0.77±0.3**</td>
<td>0.71±0.28</td>
<td>0.84±16.0</td>
</tr>
</tbody>
</table>

Mean±SD. MR volume calculated by difference between LV and aortic stroke volumes.
ECV indicates global septal extracellular volume; LA, left atrium; LGE; late gadolinium enhancement; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; MR, mitral regurgitation; and RV, right ventricle.
Controls vs MR, *P<0.05, **P<0.01.
MR+LGE vs MR+no LGE, ‡P<0.05, ‡‡P<0.01.

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**Figure 1. Box scatter plot of global extracellular volume in patients with mitral regurgitation (MR) and controls. Error bars are standard error of the mean×2. Extracellular volume (ECV) was assessed in the left ventricle from the basal and mid-ventricular levels and averaged to yield a global ECV measurement, including areas of diffuse but noninfarction pattern late gadolinium enhancement. *P<0.01.**
indications for surgery were reached on echocardiography. Expansion of ECV was independently associated with LV end-systolic and atrial volumes, long-axis function, and exercise capacity. These findings provide evidence in support of the hypothesis that there is no physiological compensatory phase in MR and that high volume loads may induce pathological changes in left ventricular structure and function at an earlier stage than considered to date. This is a small study and requires confirmation in further research with well-defined populations that excludes potential confounders, including AF. If these studies confirm expansion of the ECV, CMR assessment of ECV has the potential to become an imaging biomarker useful in MR that is independent of loading conditions.

Although endomyocardial biopsy was not widely performed in this study, there is indirect evidence from other studies that the presence of LGE and expansion of the ECV are a result of coarse and diffuse interstitial fibrosis, respectively. The histological basis for LGE as a noninvasive method of imaging coarse fibrosis is well established in a range of disease states. While endomyocardial biopsy was not widely performed in this study, there is indirect evidence from other studies that the presence of LGE and expansion of the ECV are a result of coarse and diffuse interstitial fibrosis, respectively. The histological basis for LGE as a noninvasive method of imaging coarse fibrosis is well established in a range of disease states. In this study, LGE was also unexpectedly prevalent in mid-wall diffuse patterns, not consistent with a coronary artery territory. There were, however, no differences in parameters of LV size or function depending on the presence or absence of LGE. In contrast, an ECV above the upper limit for normal controls was associated with lower MAPSE and relative reduction in LV ejection fraction within normal range. Using T1 mapping techniques, a strong graded association has been demonstrated between ECV and histological collagen volume fraction measured in the explanted hearts of patients undergoing heart transplantation. Both the expansion of the ECV and presence of LGE are consistent with data from autopsy studies that diffuse interstitial fibrosis is present in volume loading with MR. Indeed, the severity of interstitial fibrosis has been shown to be greater in the autopsied hearts of patients with MR than in those of patients with AS. The independent association of ECV with reduced parameters of LV function in our patients with MR provides supportive evidence of the functional consequences.

Table 3. Functional and Morphological Data on Cardiac MRI According to Extracellular Myocardial Volume in Patients With Mitral Regurgitation

<table>
<thead>
<tr>
<th></th>
<th>MR ECV ≥0.297</th>
<th>MR ECV ≤0.297</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>67±7</td>
<td>71±5*</td>
</tr>
<tr>
<td>LV end-diastolic volume index, mL/m²</td>
<td>84±19</td>
<td>77±20</td>
</tr>
<tr>
<td>LV end-systolic volume index, mL/m²</td>
<td>28±11</td>
<td>23±7*</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>72±14</td>
<td>64±14</td>
</tr>
<tr>
<td>Presence of noninfect pattern of LGE, n</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Mean global ECV</td>
<td>0.35±0.06</td>
<td>0.26±0.03**</td>
</tr>
<tr>
<td>LA volume index, mL/m²</td>
<td>64±16</td>
<td>54±8*</td>
</tr>
<tr>
<td>MAPSE, mm</td>
<td>13±2</td>
<td>16±4*</td>
</tr>
<tr>
<td>CMR Regurgitant volume, mL</td>
<td>44±13</td>
<td>41±22</td>
</tr>
<tr>
<td>CMR Regurgitant fraction, %</td>
<td>39±9</td>
<td>32±8</td>
</tr>
<tr>
<td>Global longitudinal strain, %</td>
<td>13±2</td>
<td>16±4</td>
</tr>
<tr>
<td>Global longitudinal strain rate, s⁻¹</td>
<td>0.65±0.18</td>
<td>0.72±0.17</td>
</tr>
<tr>
<td>Global circumferential strain, %</td>
<td>17.3±4.1</td>
<td>16.8±3.6</td>
</tr>
<tr>
<td>Global circumferential strain rate, s⁻¹</td>
<td>0.81±0.27</td>
<td>0.89±0.17</td>
</tr>
</tbody>
</table>

Mean±SD. CMR indicates cardiac MRI; ECV, global extracellular volume; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; and MR, mitral regurgitation.

*P<0.05.
**P<0.01.

Figure 2. Examples of diffuse late gadolinium enhancement and corresponding precontrast T1 maps in patients with mitral regurgitation. Upper, late gadolinium enhancement images with diffuse mid-wall enhancement in the left ventricular basal inferolateral segment (arrows). Lower, corresponding precontrast T1 maps with increased native T1 (*1045 ms; *1102 ms).
of fibrotic change, specifically LA dilatation, loss of contractile reserve, and abnormal myocardial stiffness. Reduc-

tion in longitudinal function (measured by MAPSE) is an indicator of subclinical heart disease in many conditions associated with fibrosis and, in our study, was highly correlated with ECV. This association is the same as that found in patients with aortic stenosis, in whom reduction in MAPSE was found to be a sensitive marker not only of histological severity of fibrosis but also of postoperative outcome. Likewise, in MR, longitudinal and circumferential strain were reduced, which may also be a reflection of increased wall stress and sustained afterload in these cases. Reduction in longitudinal strain is considered the functional consequence of preferential fibrosis within the sub-endocardial fibres, similar to that seen in Fabry disease, and is a marker of postoperative outcome after mitral valve surgery.

The demonstration of reductions in exercise time and peak VO₂ max with increasing ECV is an important finding. Onset of symptoms is considered the culmination of the pathophysiology of MR but is a negative prognostic event because, once these have occurred, operative mortality is higher and postoperative survival is lower even when there has been no change in chamber size or function. Subjects with higher ECV also had larger end-systolic volumes and lower ejection fraction, albeit within the normal range. Thus, diffuse fibrosis might be a key intermediary phenotype indicative of an adverse outcome without (and perhaps with) surgery. Further research is required to determine whether the presence of increased ECV or LGE might provide a method of identifying patients who would benefit from early intervention rather than waiting until symptoms or a threshold of chamber size or ejection fraction.

Conversely, patients with lower values of ECV or LGE might be more appropriately managed by watchful waiting. If so, this has the potential to be a useful method by which to track patients because it is readily quantifiable, is independent of filling, and may not be susceptible to the recognized variability of echocardiographic measures, such as effective regurgitant orifice area and vena contracta.

**Limitations**

Subjects did not routinely undergo testing for ischemia or have angiography to exclude coronary artery disease unless referred for surgery. However, all were recruited without a history of chest pain and with no known cardiovascular disease. Of the patients who completed cardiopulmonary exercise testing testing, none had exertional chest pain during stress and none developed ECG changes during stress. Except in 2...
cases (excluded in analysis), the LGE documented in our cases was nonischemic in pattern, and no patient had regional wall motion abnormalities at rest. Of the 12 patients who proceeded to surgery and had preoperative angiography, 2 (1 with diffuse LGE on CMR) were found to have single vessel coronary disease and went on to have by-pass grafting. The rate of occult, significant (>50%) stenosis is consistent with that found in large scale angiographic and computed tomography studies of asymptomatic adults with no history of cardiovascular disease.30 Analysis excluding the 2 patients with subendocardial LGE, single vessel CABG, diabetes mellitus, and hypertension consistently demonstrated higher ECV than controls.

One other potential confounder relating to expansion of the ECV relates to the presence of AF and relationship with pulmonary artery pressure, both of which may be associated with ventricular fibrosis but with numbers too small to be analyzed usefully. Future study should concentrate on the role of these factors.

There was a difference in the numbers graded with severe MR using echocardiography and CMR.13 Although CMR is accepted as the gold standard for volumetric measurement, the primary method for assessing severity in this study was echocardiography using quantitative methods, which has prognostic validation.31 The cut-off for severe MR used in this study for CMR was a regurgitant fraction above 42%, but there are no accepted or established criteria for such a grading. In the article by Chan used to identify this cut-off, reference values are selected based on limited data from 3 small studies that used qualitative grading on TTE and recruited almost no patients with severe MR.32 Indeed, no differences in LV size, function, or exercise capacity were found in our study between patients with asymptomatic severe or moderate MR assessed by CMR. In contrast, patients with severe MR on echo did have higher LV end-diastolic, end-systolic volumes, and LV mass. There were no differences in ECV, MAPSE, or LVEF compared with patients with moderate MR.

Not all subjects were referred for cardiopulmonary exercise testing in our cohort. We acknowledge that 11/15 patients with elevated ECV expansion above the normal cut-off had associated diffuse mid-wall LGE. These patients, however, had elevated precontrast T1 values above patients with normal ECV, which could potentially negate the need for contrast. In a cross-sectional study of this nature, we are unable to imply causality that expanded ECV is a precursor to the development of coarse fibrosis (demonstrated by LGE). This requires longitudinal follow-up data from patients with less advanced mitral valve disease.

Conclusions
This study has demonstrated that patients with asymptomatic moderate to severe MR demonstrate a spectrum of myocardial fibrosis associated with reduced myocardial deformation and reduced exercise capacity. Further studies in larger populations may be warranted to further define the role of ECV measurement in degenerative MR and whether it affects clinical outcomes.

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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

Chronic volume overload is a stimulus for adverse adaptive left ventricular (LV) remodeling. Subclinical reduction in LV systolic deformation and impaired diastolic relaxation before mitral valve repair predict a worse outcome following surgery, and these changes have been ascribed to diffuse interstitial fibrosis within the myocardium. Although interstitial fibrosis is often considered a reaction to pressure overload, afterload measured by wall stress is increased in chronic mitral regurgitation, and an increase in the interstitial space and myocyte hypertrophy have been confirmed on autopsy in severe primary mitral regurgitation, although data are limited to small studies. In patients with asymptomatic chronic moderate or severe degenerative mitral regurgitation with type II mechanism, a spectrum of myocardial fibrosis is observed with associated reductions in myocardial deformation and reduced exercise capacity before any conventional class 1 indications for surgery are reached. Elevated global extracellular volume is associated with increased LV end-systolic volume, increased left atrial volumes, reduced LV ejection fraction and long axis function within the normal range. The timing of mitral valve repair in asymptomatic severe mitral regurgitation remains controversial. If extracellular volume is increased because of interstitial fibrosis from wall stress, future studies should be performed to identify whether this impacts on LV recovery following surgery and whether extracellular volume has the potential to be an imaging biomarker that could improve the safety of watchful waiting in patients who do not want to undergo repair unless absolutely necessary.
Quantification of Left Ventricular Interstitial Fibrosis in Asymptomatic Chronic Primary Degenerative Mitral Regurgitation
Nicola C. Edwards, William E. Moody, Mengshi Yuan, Peter Weale, Desley Neal, Jonathan N. Townend and Richard P. Steeds

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