Valvular Heart Disease

Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification

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Background—Surgery for severe mitral regurgitation is indicated if symptoms or left ventricular dilation or dysfunction occur. However, prognosis is already reduced by this stage, and earlier surgery on asymptomatic patients has been advocated if valve repair is likely, but identifying suitable patients for early surgery is difficult. Quantifying the regurgitation may help, but evidence for its link with outcome is limited. Cardiovascular magnetic resonance (CMR) can accurately quantify mitral regurgitation, and we examined whether this was associated with the future need for surgery.

Methods and Results—One hundred nine asymptomatic patients with echocardiographic moderate or severe mitral regurgitation had baseline CMR scans and were followed up for up to 8 years (mean, 2.5±1.9 years). CMR quantification accurately identified patients who progressed to symptoms or other indications for surgery: 91% of subjects with regurgitant volume ≤55 mL survived to 5 years without surgery compared with only 21% with regurgitant volume >55 mL (P<0.0001). A similar separation was observed for regurgitant fraction ≤40% and >40%. CMR-derived end-diastolic volume index showed a weaker association with outcome (proportions surviving without surgery at 5 years, 90% for left ventricular end-diastolic volume index <100 mL/m² versus 48% for ≥100 mL/m²) and added little to the discriminatory power of regurgitant fraction/volume alone.

Conclusions—CMR quantification of mitral regurgitation was associated with the development of symptoms or other indications for surgery and showed better discriminatory ability than the reference-standard CMR-derived ventricular volumes. CMR may be able to identify appropriate patients for early surgery, with the potential to change clinical practice, although the clinical benefits of early surgery require confirmation in a clinical trial. (Circulation. 2016;133:2287-2296. DOI: 10.1161/CIRCULATIONAHA.115.017888.)

Key Words: magnetic resonance imaging • mitral valve • mitral valve insufficiency • outcome assessment (health care) • prognosis

Mitral regurgitation (MR) is usually well tolerated, and even those patients with severe asymptomatic regurgitation can survive many years, although about a third develop indications for surgery by 5 years.1 Mitral valve repair or replacement is indicated once symptoms or adverse cardiac features develop2 (eg, left ventricular [LV] dysfunction/excess dilation) because prognosis is significantly worse without treatment.3–5 However, even with surgery, prognosis may be worse at this stage, and early surgery for severe regurgitation has been advocated.6,7 The latest guidelines now consider this to be reasonable (Class IIa indication) if severe MR is present, the chance of mitral repair is high (>95%), and the surgery is carried out in a center of excellence with a very low mortality or other conditions exist (pulmonary hypertension or new-onset atrial fibrillation).2 This aggressive approach has to be balanced against the favorable natural history of untreated MR without symptoms or other adverse features and the risks of early surgery, particularly in an elderly population in whom the risks of surgery are higher. There is therefore considerable debate between those who advocate a “watchful waiting” strategy1 and those who favor early surgery.8,9 Determining the correct clinical approach is hindered by the lack of any controlled trial of early surgery and the difficulty in identifying which patients should be offered surgery while asymptomatic. Advance identification of those patients likely to progress to symptoms or other indications for surgery in the near future

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could highlight the group most likely to benefit and facilitate early surgery before the prognosis is worsened.

Quantifying the MR in those with significant regurgitation (rather than qualitative grading) might be one method to identify such patients. This can be achieved with echocardiography, although echocardiographic quantification is used primarily to aid grading as mild, moderate, and severe regurgitation rather than identifying patients for surgery. One important study has shown an association of quantitative echocardiographic MR grading with mortality in medically treated patients, but this study did not address the identification of patients for surgery.

Cardiovascular magnetic resonance (CMR) is able to quantify MR with high accuracy and reproducibility using a combination of LV volumetric measurements and aortic flow quantification with phase-contrast velocity mapping. Given that LV volumes and function are also important for MR assessment and that CMR is considered the reference-standard method for measuring them, CMR would appear to be an optimal technique for the assessment of MR. We previously used this technique in patients with aortic regurgitation and demonstrated a strong association of the quantification of regurgitation with outcome. We therefore sought to examine whether a similar approach using CMR quantification of MR and LV indexes might be able to predict which asymptomatic patients with significant (moderate or severe) MR were likely to progress to symptoms or other established indications for surgery. We also aimed to compare the CMR quantification of MR and LV volume/function indexes for their relative predictive ability.

Methods

Subjects and Follow-Up

Patients at least 18 years of age were recruited from 4 high-volume CMR centers in Oxford, Leeds, London (UK) and Auckland (New Zealand). All asymptomatic patients with moderate or severe chronic organic MR on echocardiography were eligible for inclusion and underwent baseline CMR scanning. Exclusion criteria included the presence of functional MR (secondary to annular dilation or LV dysfunction), other significant valve disease, and clinical or angiographic evidence of coronary disease.

Subjects were followed up for up to 8 years. Those who remained asymptomatic and under conservative management were designated the conservative group; those who developed symptoms or other established indications for surgery were designated the crossover group, with the decision for surgery taken as the point of crossover. In Oxford, patients were identified from the clinical CMR databases (having a predesignated CMR scan en route to surgery). All clinical decisions were made by the treating physician. In Oxford, patients participated in a research study, and clinical decisions were made without knowledge of the CMR data. In the other 3 centers, study patients were identified from the clinical CMR databases (having been initially diagnosed with echocardiography), and clinicians had access to the CMR data, although as indicated above, there are no CMR-based criteria for surgery.

A third group was also included to compare CMR parameters with both the conservative and crossover groups. This group included patients who had already developed established indications for surgery and were scheduled for mitral valve repair/replacement (the surgical group). They underwent CMR scans identical to those of the other groups.

The research study was approved by the Oxfordshire Central Research Ethics Committee (project code C02.020) and the Wellington District Health Board Knowledge Center in New Zealand (project No. RM0980711302). All research subjects gave written informed consent.

CMR Scanning

All scans were performed on clinical 1.5-T scanners (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany; or Philips Intera, Philips Healthcare, Best, the Netherlands) and analyzed in each center with dedicated software (Argus, Siemens; CMR42, Circle Cardiovascular Imaging, Calgary, AB, Canada; or CMRtools, Cardiovascular Imaging Solutions, London, UK) for both volumes and flow according to standard acquisition guidelines. All images were ECG gated, and most were obtained during an 8- to 16-second breath-hold to remove cardiac motion resulting from the respiratory cycle. Subjects underwent an LV function study consisting of a stack of contiguous short-axis cine images from base to apex, from which LV end-diastolic volume (LVEDV) and LV end-systolic volume and mass were measured, and LV stroke volume was derived as LVEDV minus LV end-systolic volume. Each value was also indexed to body surface area. Cine image sequences were steady-state free precession (temporal resolution, 35–45 milliseconds; echo time, 1.40–1.54 milliseconds; repetition time, 2.80–3.08 milliseconds; flip angle, 50°–60°).

Aortic forward flow was quantified with through-plane phase-contrast velocity mapping as previously described, with the image plane placed either just above the aortic valve or at the sinotubular junction (Figure 1). If significant turbulence or aliasing was seen in the velocity image, the acquisition was repeated a few millimeters further from the valve or with a higher-velocity window. Free-breathing flow sequences were used in Oxford; breath-hold flow sequences were used in the other 3 centers. Our previous work has shown that the choice of pulse sequence (free breathing versus breath hold) does not significantly affect the quantitative results. In all centers, the potential for background flow offset errors was reduced by ensuring that flow sequences were acquired with the region of interest located at the isocenter of the magnet to minimize any inhomogeneities in the magnetic field. Image parameters were as follows: temporal resolution, 25 to 55 milliseconds; echo time, 2.6 to 3.2 milliseconds; repetition time, 4.3 to 7.8 milliseconds; field of view, 320×320 mm; velocity window, 2.0 to 2.5 m/s; signal averages, 1 for breath-hold sequences and 3 for free-breathing sequences; and typical acquisition times, 12 to 16 seconds for breath-hold sequences and 2 to 3 minutes for free-breathing sequences.

Standard CMR quantification of MR involves the deduction of aortic flow from LV stroke volume (aortic forward flow). In the absence of interventricular shunting, this equates to the volume of MR. This technique is robust in the presence of changing degrees of MR during systole, in addition to eccentric or mobile mitral regurgitant jets. Regurgitant fraction was also determined (regurgitant volume/LV stroke volume×100%).

Echocardiography

Transthoracic echocardiograms were acquired for clinical management a mean of 47.1±71.6 days from the baseline CMR scan, according to standard protocols. The images for the subjects who were prospectively followed up (conservative and crossover groups) were reassessed by the researchers who were blinded to CMR and outcome data, and determination of the grade of MR on echocardiography was made. This determination was based on multiple 2-dimensional imaging parameters, as described in the American Society of Echocardiography guidelines. These were both qualitative and semiquantitative, and quantitative assessments were used whenever...
followed for up to 8 years (mean±SD, 2.5±1.9 years; median, 1.6 years; 25th and 75th percentiles, 0.8 and 3.5 years). Twenty-five patients (23%) underwent mitral valve repair/replacement during the follow-up period (crossover group), having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilatation [end-systolic diameter >4.0 cm], n=4; or pulmonary hypertension [>50 mmHg] with a repairable valve, n=2). The mean time from CMR scan to the decision on surgery in this group was 1.9 years (median, 1.1 years; 25th and 75th percentiles, 0.4 and 3.0 years), with 85% of events occurring within 4 years. Seven patients underwent mitral surgery but did not have conventional indications. They remained in the conservative group but were censored at the time of surgery. The surgery in these 7 subjects was mainly mitral repair for severe MR but without clear indications of adverse prognosis; the mean regurgitant fraction was 36% (range, 26%–56%).

Association With the Need for Surgery

The receiver-operating characteristic analyses identified several baseline CMR parameters that were associated with the development of indications for surgery (Table 1). Quantitative measures of MR (mitral regurgitant volume and fraction) had a high area under the curve with good sensitivity and specificity. CMR LV volumetric indexes also showed good discriminatory ability. LV mass showed some predictive power, but this parameter is closely related to LVEDV, and the similar mass-to-volume ratios in all groups (Table 2) suggest that LVEDV is likely to be the main determinant of LV mass. Cox regression analysis showed independent associations for regurgitant volume (b exponent, 1.03 [95% confidence interval, 1.01–1.05] per 1-mL increase; P=0.01) and for regurgitant fraction (b exponent, 1.05 [95% confidence interval, 1.01–1.09] per 1% increase; P=0.01) if assessed separately from regurgitant volume. Otherwise, this was too closely related. Assessment of the best dichotomous cutoff threshold for discrimination of the need for surgery was performed for regurgitant volume, regurgitant fraction, and LVEDV index (LVEDVi). For regurgitant volume, cutoff levels between 30 and 65 mL were analyzed with Cox proportional hazards, and the highest values of the Harrell C and Somers D statistics were used to separate groups in the survival analyses. CMR measures of regurgitation demonstrated substantial separation of groups over time. Subjects with a regurgitant volume ≤55 mL had a very high chance of remaining free of symptoms or surgery; 95% at the median time (1.6 years) and 91% at 5 years. This contrasted with 54% at 1.6 years and 21% at 5 years for patients with regurgitant volume >55 mL (P<0.0001 by log rank; Figure 2A). Similar differences in survival without surgery were seen for regurgitant fraction >40% and ≤40%. However, inclusion of an additional threshold at a regurgitant fraction of 50% (dividing the cohort into 3 subgroups of ≤40%, 41%–50%, and >50%) revealed a further separation in survival without surgery, and we have illustrated

Results

One hundred nine asymptomatic patients with at least moderate MR on echocardiography were included in the study and
this incremental risk of surgery with increasing regurgitant fraction in Figure 2B. There were no significant differences in survival curves among the participating centers ($P=0.80$ by log-rank test).

LVEDV also showed a reasonable association with outcome over time, although slightly weaker than for measures of regurgitation (proportions surviving without surgery at the median of 1.6 years: 96% for LVEDVi $<100$ mL/m$^2$ versus 71% for $\geq100$ mL/m$^2$; $P=0.0001$; Figure 2C). However, stratiﬁng groups by LVEDV in addition to regurgitant volume in the survival analysis did not provide any further separation of the curves than those for regurgitant volume alone, which was a better predictor (Figure 3A). There were only 2 subjects with high regurgitant volumes ($>55$ mL) but lower LVEDVi ($<100$ mL/m$^2$), suggesting that in almost all cases, once a high volume of MR was present, LVEDV was increased (as might be expected).

Echocardiographic grading of MR performed less well in predicting subjects who progressed to surgery despite the use of quantitative assessment to guide grading when feasible (n=53, 49% of the total). Many of those identiﬁed as having severe MR on echocardiography had MR volumes on CMR $<55$ mL and remained asymptomatic (n=28). There was a much smaller tendency to underestimate the MR with echocardiography (compared with CMR), with only 5 subjects with moderate MR on echocardiography and regurgitant volume $>55$ mL by CMR. Overall, if the CMR threshold of a regurgitant volume $>55$ mL is used to deﬁne severe MR, 33 subjects (30% of the total) were reclassiﬁed by CMR compared with echocardiographic grading. The prediction of events with the use of only quantitative echocardiographic thresholds for severity (effective regurgitant orifice area $>0.40$ and $<0.40$ cm$^2$) showed only modest separation of survival curves (Figure 2D), although numbers in this subgroup were smaller (n=53) and the difference in outcome was not statistically signiﬁcant. Using echocardiography-derived regurgitant volume $>60$ mL (the guideline threshold for severe MR) as the threshold provided very similar results (data not shown). Furthermore, in both the moderate and severe echocardiographic MR subgroups, there was a similar separation of survival curves by CMR quantification (Figure 3B). Sixty-five subjects had follow-up echocardiograms during the study period, which were also analyzed in the same blinded fashion as the initial studies. Nearly all had ﬁndings similar to the ﬁrst scan, with only 1 subject who progressed to surgery showing a change in the grade of MR by echocardiography (from moderate to severe), but this may not be surprising given the tendency for the initial echocardiography to overestimate the severity of MR, highlighted above.

**Comparison With the Surgical Group**

Descriptive data from all groups, including the surgical cohort, are shown in Table 2. Statistical comparisons were not made between groups, however, because the time-dependent (ie, incomplete) nature of the separation into conservative and crossover groups would make this statistically inappropriate. The surgical cohort showed mean MR and LV volumetric indexes similar to those of the crossover group, and both parameters were larger than in the conservative group. There were no signiﬁcant differences in ejection fraction or right ventricular (RV) parameters. Systolic blood pressure was lower in the surgical compared with the conservative group.

**Discussion**

**The Association of MR Quantification With Outcome**

Quantifying MR with CMR showed a strong association with the future need for surgery over the subsequent 5 years, demonstrating the potential value of this approach. Patients already destined for surgery (the surgical group) also had measures of MR that were similar to those of the crossover group, suggesting that a similar threshold of regurgitation had been reached in the surgical group before symptoms occurred. These CMR parameters might thus be useful clinical predictors of the need for surgery. In addition to the potential for high quantitative indexes of regurgitation to identify candidates for early surgery, subjects with lower amounts of MR (regurgitant volume $\leq55$ mL or fraction $\leq40\%$) had a very low chance of requiring surgery over the subsequent few years and could be followed up less frequently, with a favorable impact on healthcare resources. We identiﬁed the best single thresholds to predict

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Threshold</th>
<th>$P$ Value for ROC Curve</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitant volume, mL</td>
<td>0.81</td>
<td>&gt;55</td>
<td>$&lt;0.0001$</td>
<td>72</td>
<td>87</td>
</tr>
<tr>
<td>Regurgitant volume index, mL/m$^2$</td>
<td>0.79</td>
<td>&gt;29</td>
<td>$&lt;0.0001$</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Regurgitant fraction, %</td>
<td>0.79</td>
<td>&gt;40</td>
<td>$&lt;0.0001$</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>LVEDV index, mL/m$^2$</td>
<td>0.75</td>
<td>&gt;95</td>
<td>$&lt;0.0001$</td>
<td>91</td>
<td>56</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>0.77</td>
<td>&gt;171</td>
<td>$&lt;0.0001$</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>LVESV index, mL/m$^2$</td>
<td>0.71</td>
<td>&gt;36</td>
<td>0.0008</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>0.71</td>
<td>&lt;65</td>
<td>0.0006</td>
<td>60</td>
<td>76</td>
</tr>
<tr>
<td>RV ejection fraction, %</td>
<td>0.62</td>
<td>&lt;59</td>
<td>0.08</td>
<td>58</td>
<td>54</td>
</tr>
</tbody>
</table>

Threshold is the value for each parameter that best identiﬁed the crossover group with the Youden index used for optimal sensitivity and speciﬁcity. AUC indicates area under the curve; CMR, cardiovascular magnetic resonance; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; ROC, receiver-operating characteristic; and RV, right ventricular.

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Table 1. Receiver Operating-Characteristic (ROC) Data: Comparison of the Ability of Each CMR Parameter to Identify the Initially Asymptomatic Patients Who Would Develop Indications for Surgery
some important limitations to the study. The cohort was only
illustrates (Figure 2B). The thresholds identified in this study
is an increasing risk with increasing values of the parameters,
the groups with different outcomes, but it is likely that there
an increasing risk with increasing values of the parameters,
as the separation of the 3 groups for mitral regurgitant fraction
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Table 2. Comparison of CMR Parameters Between the 3 Groups of Patients With MR

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Crossover</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in group, n</td>
<td>84</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>Age, y</td>
<td>65.1±14.9</td>
<td>63.8±12.6</td>
<td>66.3±7.5</td>
</tr>
<tr>
<td>Male subjects, %</td>
<td>65</td>
<td>76</td>
<td>60</td>
</tr>
<tr>
<td>In atrial fibrillation, %</td>
<td>19</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.8±10.1</td>
<td>174.2±10.4</td>
<td>171.3±9.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.8±12.0</td>
<td>75.8±10.6</td>
<td>75.2±14.1</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.88±0.18</td>
<td>1.89±0.24</td>
<td>1.91±0.17</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68.5±13.9</td>
<td>67.3±10.3</td>
<td>73.0±13.8</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>143.9±23.1</td>
<td>132.1±20.1</td>
<td>120.9±13.2</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>77.8±10.8</td>
<td>77.4±8.8</td>
<td>73.9±11.3</td>
</tr>
<tr>
<td>Regurgitant volume, mL</td>
<td>39.4±20.0</td>
<td>65.9±23.7</td>
<td>70.1±29.5</td>
</tr>
<tr>
<td>Regurgitant fraction, %</td>
<td>32.1±12.4</td>
<td>45.7±11.7</td>
<td>46.7±14.0</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>182.7±50.3</td>
<td>224.3±47.8</td>
<td>229.1±49.4</td>
</tr>
<tr>
<td>LVEDV index, mL/m²</td>
<td>97.9±25.1</td>
<td>117.5±23.0</td>
<td>121.2±23.8</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>62.1±26.1</td>
<td>81.8±29.0</td>
<td>82.7±36.7</td>
</tr>
<tr>
<td>LVESV index, mL/m²</td>
<td>33.5±13.8</td>
<td>42.5±13.3</td>
<td>44.2±18.3</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>66.9±7.6</td>
<td>63.9±7.4</td>
<td>64.9±9.3</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>144.5±49.9</td>
<td>192.9±61.6</td>
<td>192.9±61.6</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>76.2±24.6</td>
<td>102.7±23.9</td>
<td>103.4±25.6</td>
</tr>
<tr>
<td>LV mass/LVEDV ratio, g/mL</td>
<td>0.83±0.27</td>
<td>0.89±0.17</td>
<td>0.87±0.23</td>
</tr>
<tr>
<td>Echocardiographic LVEDD, cm*</td>
<td>5.4±0.8</td>
<td>6.2±0.5</td>
<td>6.1±0.8</td>
</tr>
<tr>
<td>Echocardiographic LVESD, cm</td>
<td>3.3±0.7</td>
<td>3.6±0.6</td>
<td>3.8±0.9</td>
</tr>
<tr>
<td>Echocardiographic ERO, cm²*</td>
<td>0.58±0.75</td>
<td>0.57±0.28</td>
<td></td>
</tr>
<tr>
<td>Echocardiographic regurgitant volume, mL*</td>
<td>74.3±73.9</td>
<td>89.3±35.8</td>
<td></td>
</tr>
<tr>
<td>RVEDV, mL</td>
<td>149.1±45.1</td>
<td>147.2±36.3</td>
<td>154.8±40.7</td>
</tr>
<tr>
<td>RVESV, mL</td>
<td>66.8±25.7</td>
<td>68.0±26.8</td>
<td>71.4±27.4</td>
</tr>
<tr>
<td>RV ejection fraction</td>
<td>56.0±8.5</td>
<td>54.1±9.9</td>
<td>52.4±11.3</td>
</tr>
</tbody>
</table>

Values are mean±SD. Note that statistical comparisons are not made between groups because the time-dependent nature of the allocation to the conservative and crossover groups would make this inappropriate. BP indicates blood pressure; CMR, cardiovascular magnetic resonance; ERO, effective regurgitant orifice area; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-diastolic volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; and RVESV, right ventricular end-systolic volume.

Comparison With LV and RV Volumetric Indexes

The highly accurate measurements of LVEDV by CMR showed a reasonable association with survival without surgery over time, but regurgitation quantification showed a better separation of survival curves. Furthermore, combining LVEDV and regurgitant volume subgroups did not improve survival curves over regurgitant volume alone, and subjects with low regurgitant volumes (Figure 3A) had similarly low rates of surgery regardless of the LVEDVi. This suggests that LVEDV may partly be a function of the quantity of regurgitation (supported by the strong association of LVEDV with mitral regurgitant volume).20 This would be logical given that regurgitation is the physiological stimulus for LV dilation in this patient group, although this is not conclusively proven with our data, and the fact that several subjects with higher
LVEDVi had low regurgitant volume (Figure 3A) suggests that other factors influence LVEDV. Despite its long-standing use in previous guidelines, LV end-systolic volume did not have a particularly strong association with outcome. However, LV volumes and function are important in overall assessment and readily available from a standard CMR scan. LV mass showed an apparent association with progression to surgery, but this parameter is closely related to LV volume and was not an independent predictor. Other studies have not shown any predictive power of wall thickness, and LV mass-to-volume ratios were similar for all 3 groups in our study, suggesting that there is no excess increase in mass over that required for the chamber volume increase and that the apparent association of LV mass with outcome is likely to be confounded by its close relation to LV volume. The lack of any notable association of RV parameters (including volumes and ejection fraction) with outcome, together with the similar (normal) values in all 3 groups, suggests that RV dilation or dysfunction may be a late and uncommon occurrence and may occur only secondary to LV dysfunction and the resulting pulmonary hypertension.

**Systemic Blood Pressure**

Systemic blood pressure was lower in the crossover and surgical groups, which may reflect the larger mitral regurgitant...
volumes (and reduced aortic forward flow) in these groups. It is possible the lower blood pressure was a confounding factor that might have increased the chance of developing indications for surgery, although no previous study has suggested a causal link between blood pressure and the need for surgery in MR. Furthermore, systolic blood pressure was not a good discriminator on the initial receiver-operating characteristic analysis (area under the curve=0.64).

**Comparison Between Echocardiography and CMR**

In our study, transthoracic echocardiographic grading showed a more modest ability to discriminate between subjects progressing to surgery and those remaining asymptomatic, with significant spread of the echocardiographic grades across the conservative and crossover groups and a tendency for echocardiography to overestimate the degree of regurgitation compared with CMR. However, we were able to apply quantitative echocardiographic grading in only ≈50% of subjects. Had this been possible in all subjects, it may have improved the results for echocardiography. Previous studies also suggest only moderate agreement between CMR and echocardiography and limited reproducibility for quantitative echocardiographic grading. This may be due in part to assumptions in the PISA technique (the commonest echocardiographic quantitative method). The peak PISA measurement assumes a static degree of regurgitation throughout...
systole, and this may not hold true for some subjects, particularly those with mitral prolapse, which could result in overestimation of the degree of regurgitation.\textsuperscript{22} Other aspects may also reduce the accuracy of PISA echocardiographic quantification, including irregular regurgitant jets (eccentrically directed, fan shaped/crescentic, or multiple), nonhemispheric geometry of the PISA shell, and difficulty in identifying the regurgitant orifice.\textsuperscript{26–29} Although it is acknowledged there is no ideal gold standard for comparison, CMR quantification of regurgitation has shown better intraobserver and interobserver variability\textsuperscript{20} and good agreement with in vitro models\textsuperscript{23} and postsurgical LV remodeling.\textsuperscript{24}

### Previous Studies of Outcome in MR

Earlier studies examined outcomes after mitral valve surgery, demonstrating poorer 10-year survival after the development of symptoms\textsuperscript{3} or LV impairment\textsuperscript{4} and poorer postoperative LV function once preoperative end-systolic dimension exceeded 5.0 cm (an indicator of both dilation and reduced function).\textsuperscript{10} These studies informed the current guideline indications for surgery in MR\textsuperscript{2} and, like the present study, highlight the value of identifying patients before symptoms or significant LV dilation/dysfunction. Chronic MR also increases left atrial size and can raise pulmonary pressure, resulting in RV dysfunction. Both increased atrial size\textsuperscript{21,31} and reduced RV or biventricular function\textsuperscript{12} have been shown to predict medium- and long-term survival after mitral surgery. Reduced RV function on exercise has also shown some association with symptoms and outcome.\textsuperscript{32,33} The lack of an association of RV function with future progression to surgery in our study might indicate that this is a late sign in decompensated MR, which is usually absent in an asymptomatic population such as ours (several of the previous studies involved patients with symptoms). We also did not assess RV function during exercise, and it is unclear whether this might explain some of the difference.

Few studies have predicted outcome (mostly progression to surgery) in an initially asymptomatic group of patients. The Mayo Clinic study\textsuperscript{11} showed a significant association of quantitative echocardiographic grading with prognosis (both mortality and cardiac events), although this study did not specifically assess the progression to cardiac surgery, which was not included as a cardiac event. Subjects with moderate MR also had a significant cardiac event rate (40\%, versus 62\% for severe MR), which suggests a weaker ability of quantitative echocardiography to identify patients at risk of events, and highlights the difficulty in separating moderate and severe MR in some patients, the very group examined in our study.

### Clinical Utility

Accurate assessment of the severity of MR and LV volumes/ function is crucial in clinical decision making,\textsuperscript{1} and CMR would already seem well suited for this. The additional ability to predict the onset of symptoms or other indications for surgery just before their occurrence would be clinically important and might identify a suitable cohort for careful surveillance and early surgery. Conversely, patients with less severe MR might be reassured of the good medium-term prognosis and require less frequent follow-up, thereby improving the efficient use of healthcare resources.

Observational studies have shown better outcomes in patients undergoing early surgery for MR,\textsuperscript{6,25} but their limitations are well recognized. A randomized trial comparing early surgery with surgery based on conventional indications is required to demonstrate patient benefit, and our study may provide the basis for such a trial, with quantitative CMR indexes providing the appropriate tool for identifying suitable patients.

### Limitations

The moderate sample size and relatively small number of events limit the strength of our conclusions, although follow-up was for a reasonable period of time (mean, 2.5 years; maximum, 8 years). Although the study suggests that CMR may be used to identify candidates for early mitral surgery, there is no evidence that operating earlier achieves a clinical benefit. This would require a clinical trial, which we strongly encourage. In addition, our thresholds for separating groups were derived from a single cohort without a separate validation cohort to confirm the cut points or the degree of separation. Therefore, it is likely that the degree of separation between subgroups may be lower than in this study or the thresholds for separating groups may vary. A validation cohort is required to confirm these thresholds. In addition, the use of single cut points to separate groups may underestimate the degree to which there is an incremental risk with increasing values of the parameters. Although we identified further separation with multiple thresholds for only mitral regurgitant fraction, larger sample sizes and different cohorts may reveal an incremental risk for other parameters.

The lack of blinding to the CMR data in 3 of the investigating centers may also have biased outcome. However, there are no current CMR criteria/thresholds for recommending surgery, and we attempted to minimize bias when possible and confirmed that there were no significant differences in the association with the progression to surgery between centers. Nevertheless, remaining bias is possible, particularly given the subjective nature of symptom assessment.

The echocardiographic studies were acquired for clinical purposes, and it is possible that they were not as comprehensive as those performed specifically for a research study might be. Every effort was made, however, to ensure the best-quality assessment, including blinded reanalysis by the researchers.

This study relies on events over time, and it is possible that some subjects assigned to the conservative group were censored before they had developed symptoms. However, these subjects would be likely to have higher degrees of MR, which would have likely resulted in a greater separation between groups if more time had occurred rather than a reduction in the discriminatory ability observed in the study.

We did not include data on subjects’ medication, and it is possible that outcome may have been influenced by this. However, no previous studies have shown a significant effect of any drug on outcome in MR.

### Conclusions

Quantification of MR with CMR showed a significant association with the future need for mitral valve surgery and was...
superior to CMR-derived LV volume and echocardiographic grading of regurgitation. These CMR parameters might prove useful for identifying suitable patients for early mitral valve repair/replacement, and a randomized, controlled trial is recommended to confirm these findings and to determine clinical benefit. The same parameters may also be used to identify patients at low risk of future events, potentially facilitating reduced frequency of follow-up and efficient use of healthcare resources.

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Disclosures
None.

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CLINICAL PERSPECTIVE

Early surgery has been advocated for asymptomatic patients with severe mitral regurgitation if valve repair is likely, but identifying suitable patients is difficult because many would remain asymptomatic for years without surgery. A greater ability to identify those who might benefit from early surgery would be highly advantageous, so we assessed the ability of cardiovascular magnetic resonance (CMR) quantification of mitral regurgitation to predict the development of symptoms or other conventional indications for surgery in the near future. One hundred nine asymptomatic patients with echocardiographic moderate or severe mitral regurgitation had baseline CMR scans and were followed up for up to 8 years. CMR quantification showed a strong ability to predict patients who progressed to require surgery: 91% of subjects with regurgitant volume ≤55 mL survived to 5 years without surgery compared with only 21% with regurgitant volume >55 mL (P<0.0001). A similar separation was observed for regurgitant fraction ≤40% and >40%. CMR-derived end-diastolic volumes and function did not add to the discriminatory power of regurgitant fraction/volume alone but are important for overall patient assessment. CMR may thus be able to identify patients likely to develop symptoms or other conventional indications for surgery in the near future, who would be an appropriate target group for early surgery, to avoid the potential reduced prognosis by the time symptoms occur. The clinical benefits of early surgery require confirmation in a clinical trial, however.
Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification
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