Aortic Regurgitation Quantification Using Cardiovascular Magnetic Resonance Association With Clinical Outcome

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Background—Current indications for surgery in patients with significant aortic regurgitation (AR) focus on symptoms and left ventricular dilation/dysfunction. However, prognosis is already reduced by this stage, and earlier identification of patients for surgery could be beneficial. Quantifying the regurgitation may help, but there are limited data on its link with outcome. Cardiovascular magnetic resonance (CMR) can accurately quantify AR, and we examined whether this was associated with the future need for surgery.

Methods and Results—One hundred thirteen patients with echocardiographic moderate or severe AR were monitored for up to 9 years (mean 2.6±2.1 years) following a CMR scan, and the progression to symptoms or other indications for surgery was monitored. AR quantification identified outcome with high accuracy: 85% of the 39 subjects with regurgitant fraction >33% progressed to surgery (mostly within 3 years) in comparison with 8% of 74 subjects with regurgitant fraction ≤33% (P<0.0001); the area under the curve on receiver operating characteristic analysis was 0.93 (P<0.0001). This ability remained strong on time-dependent Kaplan–Meier survival curves. CMR-derived left ventricular end-diastolic volume >246 mL had good, although lower, discriminatory ability (area under the curve 0.88), but the combination of this measure with regurgitant fraction provided the best discriminatory power.

Conclusions—High degrees of CMR-quantified AR were associated with the development of symptoms or other indications for surgery. Quantifying AR showed slightly better discriminatory ability than “gold standard” CMR ventricular volume assessment. This could provide a new paradigm for the timing of surgical intervention but requires confirmation in a clinical trial. (Circulation. 2012;126:1452-1460.)

Key Words: aortic regurgitation ■ aortic valve replacement ■ cardiovascular magnetic resonance ■ outcome ■ prognosis

Aortic regurgitation (AR) remains an important cardiac condition,1,2 although substantial chronic regurgitation can be tolerated for many years, with patients remaining asymptomatic. Aortic valve replacement is usually reserved for when symptoms or significant left ventricular (LV) dilation or dysfunction occur,3,4 but prognosis is already reduced by this stage.5–7 Earlier surgery has been advocated,3,8 but it is also important to avoid the increased risks associated with premature surgery. Optimizing the timing of surgery in these patients can therefore be difficult. Quantifying the AR could be valuable for guiding management, especially in asymptomatic patients with significant regurgitation, and might be used for the early identification of patients requiring aortic valve surgery.

Clinical Perspective on p 1460

Cardiovascular magnetic resonance (CMR) is able to directly quantify AR with high accuracy and reproducibility by using the technique of phase-contrast velocity mapping.9–11 Because CMR also provides highly accurate measurements of LV mass, volumes, and function12–15 (and is considered the

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“gold standard” for measuring these), it would appear to be an ideal technique for the assessment of aortic regurgitation, but the utility of CMR to guide clinical management has not been evaluated. We sought to examine whether CMR quantitation of AR and LV indices could identify which asymptomatic patients with significant AR were likely to progress to symptoms or other established indications for surgery in the near future. We also aimed to compare the CMR quantitation of AR and LV volume/function indices 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, London, Leeds (United Kingdom), and Auckland (New Zealand). All asymptomatic patients with moderate or severe chronic AR on echocardiography by standard (semiquantitative) assessment were eligible for inclusion and had a baseline CMR scan. Exclusion criteria included the presence of other significant valve disease or clinical or angiographic evidence for coronary disease.

Patients had a baseline CMR scan and were followed for up to 9 years. Those who remained asymptomatic and under conservative management were designated the conservative group, whereas those that developed symptoms or other established indications for surgery were designated the crossover group, with the decision for surgery taken as the point of censoring. All clinical decisions were taken by the treating physician. In Oxford, patients participated in a research study, with annual CMR scans, 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 (although they were initially diagnosed with echocardiography) and clinicians had access to the CMR data. Events were only counted, however, if the reason for aortic valve surgery was for established indications (primarily symptoms, excess LV dilation, or LV dysfunction). Patients undergoing aortic valve replacement for indications outside the established criteria (which do not include CMR assessment), or when surgery was primarily for other surgery (e.g., aortic root replacement) were considered to be in the conservative group, but censored at the time of surgery. In addition, a minimum period of 2 months was required between the CMR scan and the decision for surgery to avoid the potential bias of patients having a CMR scan en route to surgery that had already been planned.

A third group was also included to compare CMR parameters with both the conservative and crossover groups. This group included patients already due for aortic valve replacement (the surgical group), having developed established indications for surgery.3

The research study was approved by the Oxfordshire Central Research Ethics Committee (project code C02.020) and the Waitemata District Health Board “Knowledge Centre” in New Zealand (project number RM0980711302); all research subjects gave written informed consent.

CMR Scanning

All scans were performed on 1.5 T scanners (either Siemens Avanto [Siemens Medical Solutions, Erlangen, Germany] or Philips Achieva scanners [Philips Healthcare, Best, The Netherlands]) and analyzed in each center by using the manufacturer’s software (Siemens Argus and Philips ViewForum, respectively) for both volumes and flow. All images were ECG-gated, and most were obtained during an 8- to 16-second breath hold to remove cardiac motion due to the respiratory cycle. Subjects underwent a LV function study as previously described, 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. Each value was also indexed to body surface area. Cine image sequences were steady-state free precession (Siemens TrueFISP or Philips balanced fast field echo): temporal resolution 45 ms; echo time 1.40 to 1.54 ms; repetition time 2.80 to 3.08 ms; field of view 380×380 mm; flip angle 50 to 60°.

Forward and regurgitant aortic flow were quantified by using through-plane phase-contrast velocity mapping. This involves placing an image slice perpendicular to the direction of flow in the aortic root and measuring the velocity of flow through the image plane within each voxel. From the resulting images, a region of interest identifying the aortic root is defined, and flow is integrated for the whole cardiac cycle to provide forward and regurgitant flow through the aortic valve per cardiac cycle. The image plane was placed ~0.5 cm above the aortic valve at end-diastole, but a position in the aortic root was maintained throughout the cardiac cycle (Figure 1). Imaging closer to the valve reduces the underestimation of regurgitation that can occur, and, although increased turbulent flow can occur close to the valve, we have not found this to be a problem in practice. If significant turbulence or aliasing was seen in the velocity image, the acquisition was repeated a few millimeters further from the valve, and/or with a higher-velocity window. The original flow sequences acquire data over many cardiac cycles, taking ~2 minutes with patients breathing freely, whereas newer magnetic...

![Figure 1. CMR flow measurement in aortic regurgitation. Top, Still frame from steady-state free precession cine showing left ventricular outflow tract view in diastole with the aortic regurgitation jet (arrowed) and the slice location for through-plane flow measurement (parallel lines). Middle, Example through-plane flow images; Left, (magnitude) image in systole; Center, flow (phase) image in systole showing forward flow in white; Right, flow (phase) image in diastole showing regurgitant flow in black. Bottom, Resulting flow-time curve showing volume of regurgitation. LV indicates left ventricle; LA, left atrium; Ao, aorta; CMR, cardiovascular magnetic resonance.](http://circehjournals.org/)

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resonance sequences can acquire flow data within a single breath hold (12–16 heart beats). Others have suggested that the older free-breathing techniques may be more accurate for flow quantification, because the newer sequences may be more prone to background flow offset errors from the faster switching of magnetic field gradients (which can potentially cause significant errors in flow quantification), but this has not been systematically examined. Free-breathing flow sequences were used in Oxford and Leeds, whereas breath-hold flow sequences were used in the other 2 centers. In all centers, the potential for background flow offset errors was reduced by (1) ensuring that all flow sequences were acquired with the region of interest in the image slice located at the isocenter of the magnet to minimize any inhomogeneities in the magnetic field, and (2) by using retrospective ECG gating for all flow sequences, which also helps to ensure coverage of the entire cardiac cycle. Image parameters were the following: temporal resolution 25 to 55 ms; echo time 2.6 to 3.2 ms; repetition time 4.3 to 7.8 ms; field of view 320×320 mm; velocity window 2.5 to 4.0 m/s; signal averages: 1 for breath-hold sequences, 3 for free-breathing sequences; typical acquisition time 12 to 16 seconds for breath-hold sequences, 2 to 3 minutes for free-breathing sequences. From these images, forward and regurgitant aortic flow were measured by integrating the flow in each frame over 1 cardiac cycle as previously described. Regurgitant fraction (regurgitant volume/forward volume×100%) was also calculated.

Echocardiography
Clinical echocardiograms were acquired a mean of 22.9±8.15 days from the baseline CMR scan according to standard protocols. Assessment of the grade of AR on echocardiography was based on multiple semiquantitative and qualitative 2-dimensional imaging parameters, as suggested in the American Society of Echocardiography guidelines, with senior advice sought in difficult cases. The echocardiograms were not performed specifically for the research study, however, and did not include the quantification of LV volumes or AR as current guidelines recommend. Because of this limitation, LV end-diastolic and end-systolic diameters and the semiquantitative echocardiographic grading were not included in the predictive analysis for comparison with CMR parameters.

Data Assessment and Statistical Analysis
Receiver operating characteristic curve (ROC) analysis was used to determine the ability of the various parameters to discriminate patients who would develop symptoms or other indications for surgery during follow-up, from those that remained asymptomatic. Differences in ROC area were compared by using the method of DeLong et al. Cox proportional hazards and multiple logistic regression analyses were applied to any parameters with reasonable discriminatory ability (area under the curve [AUC] on ROC analysis >0.70) to determine whether any of these were independent predictors. Cox proportional hazard analysis was performed in a binary fashion, comparing groups above and below the optimal threshold identified on ROC analysis. Multiple logistic regression analysis was performed with the use of continuous variables, with subsequent binary analysis for independent variables, again based on the thresholds identified from ROC analysis. Kaplan–Meier survival curves are better for time-dependent events, and these were generated for any independent parameters to illustrate their association with the progression to symptoms/surgery. For group comparisons of CMR parameters, including the surgical group, 1-way analysis of variance was used, with Bonferroni post hoc analysis, after confirming normal distributions of the variables with the use of the Kolmogorov-Smirnov test. All analyses were performed with SPSS version 17.0 (SPSS Inc, IL) with the exception of the ROC and Cox regression analyses that were performed with MedCalc version 9.3.1 (MedCalc Software, Mariakerke, Belgium). Values shown are means ± standard deviation, and a probability value of <0.05 was considered the threshold for statistical significance.

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, Using Receiver Operating Characteristic (ROC) Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Threshold</th>
<th>p</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitant fraction (%)</td>
<td>0.93 (0.87 to 0.97)</td>
<td>&gt;33</td>
<td>&lt;0.0001</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>0.96 (0.90 to 0.99)</td>
<td>&gt;42</td>
<td>&lt;0.0001</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>Regurgitant volume index (m/l/m²)</td>
<td>0.95 (0.89 to 0.98)</td>
<td>&gt;23</td>
<td>&lt;0.0001</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>0.88 (0.80 to 0.93)</td>
<td>&gt;246</td>
<td>&lt;0.0001</td>
<td>87</td>
<td>77</td>
</tr>
<tr>
<td>LVEDV index (m²/m²)</td>
<td>0.86 (0.79 to 0.92)</td>
<td>&gt;129</td>
<td>&lt;0.0001</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>LVESE (ml)</td>
<td>0.78 (0.70 to 0.86)</td>
<td>&gt;88</td>
<td>&lt;0.0001</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>LVESE index (m²/m²)</td>
<td>0.77 (0.68 to 0.84)</td>
<td>&gt;45</td>
<td>&lt;0.0001</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.55 (0.45 to 0.65)</td>
<td>&lt;59</td>
<td>0.43</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>0.74 (0.64 to 0.81)</td>
<td>&gt;187</td>
<td>&lt;0.0001</td>
<td>72</td>
<td>68</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>0.73 (0.63 to 0.81)</td>
<td>&gt;90</td>
<td>&lt;0.0001</td>
<td>74</td>
<td>64</td>
</tr>
</tbody>
</table>

AUC, area under the curve; LVEDV, left ventricular end-diastolic volume; LVESE, left ventricular end-systolic volume; p, value for ROC curve; Sens, sensitivity; Spec, specificity; threshold, value for each parameter which best identified the ‘crossover’ group.

Results
One hundred eighteen asymptomatic patients, who had at least moderate AR on echocardiography, were considered for inclusion in the study. Five were excluded because aortic valve surgery occurred within 2 months of the CMR scan, leaving 113 patients, who were followed for up to 9 years (mean 2.6±2.1 years). Thirty-nine patients (35%) underwent aortic valve replacement during the follow-up period, having developed symptoms (n=19) or other established echocardiographic indications for surgery (excessive LV dilation [end-diastolic diameter >7.5 cm or end-systolic diameter >5.5 cm], n=17; or reduced LV function [echocardiographic ejection fraction <50%], n=3). These were designated the crossover group. The mean time from CMR scan to the decision on surgery in this group was 21 months (median 11 months), with 90% of events occurring within 3 years. Eight patients underwent surgery primarily for aortic dilation and remained in the conservative group but were censored at the time of surgery; mean regurgitant fraction in this group was 19% (range 5%–30%). One patient underwent aortic valve replacement surgery without the conventional established indications and was also retained in the conservative group. This patient was asymptomatic and had surgery for LV dilation, but the echocardiographic end-diastolic diameter was 6.5 cm; his regurgitant fraction on CMR was 19%, and end-diastolic volume was 222 mL.

Association With Events
The ability of CMR parameters to identify patients at baseline who would develop indications for surgery is shown by ROC
analyses (Table 1). Quantitative measures of AR showed excellent discriminatory power, with the aortic regurgitant volume having an AUC of 0.96 (P < 0.0001), and the regurgitant fraction having an AUC of 0.93 (P < 0.0001), with no statistical difference between the two parameters. CMR LV volumetric indices also showed good discriminatory ability, although slightly lower than regurgitation quantification, with an AUC of 0.88 for LVEDV and AUC 0.78 for LV end-systolic volume (both P < 0.01 versus regurgitant volume). On multivariate analyses (Table 2), only regurgitant fraction, regurgitant volume, and LVEDV remained as independent predictors. Binary analyses (comparing groups above/below the threshold identified from ROC analysis) showed higher hazard ratios for regurgitant volume and fraction than LVEDV. The differences in AUC and hazard ratios were small, however, with some overlap of the confidence limits, the latter likely because of the binary nature of the analyses and moderate sample size. In general, regurgitant volume and fraction showed very similar discriminatory power; regurgitant fraction has the modest advantage of being a body size–independent variable.

Regurgitant fraction >33% had high sensitivity (85%) and specificity (92%) for identifying patients who progressed to symptoms and surgery (Figure 2). A single threshold value may not provide all information, however, and the data showed further useful thresholds: all patients with a regurgitant fraction >51% (n = 8) progressed to surgery (100% positive predictive value), whereas all but 2 patients with a regurgitant fraction >43% (n = 20) progressed to surgery (90% positive predictive value). At the other end of the scale, no patients with a regurgitant fraction <26% (n = 45) progressed to surgery (100% negative predictive value). Survival curves are better, however, for assessing the effect of time on events (to account for the fact that some events require adequate follow-up to occur). There was significant separation of the groups over time, with survival without surgery at the median time point (2.0 years) of 95% for patients with regurgitant fraction ≤33% in comparison with 33% for patients with regurgitant fraction >33% (P < 0.0001 by log-rank test). The data were also analyzed by the use of the highest regurgitant fraction during follow-up (20 patients had serial CMR scans). This may allow for increasing values over time and may also be closer to clinical practice (waiting until a threshold is reached). The use of the highest regurgitant fraction showed similar discriminatory power on ROC analysis (AUC 0.93), and similar separation of survival curves at

Table 2. Cox Proportional Hazard Regression and Multiple Logistic Regression Analyses for the Variables With Significant Discriminatory Ability on ROC Analysis (AUC > 0.70)

<table>
<thead>
<tr>
<th>Continuous Variables Odds Ratio per Unit Increase</th>
<th>Binary Analysis Odds Ratio</th>
<th>Hazard Ratio (B-Exponent)</th>
<th>P-Value</th>
<th>Hazard Ratio (B-Exponent)</th>
<th>P-Value</th>
<th>Hazard Ratio (B-Exponent)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitant fraction (%)</td>
<td></td>
<td>16.0 (6.7 to 38.3)</td>
<td>&lt;0.0001</td>
<td>7.4 (3.0 to 18.6)</td>
<td>&lt;0.0001</td>
<td>1.23 (1.11 to 1.35)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td></td>
<td>13.2 (3.8 to 45.8)</td>
<td>&lt;0.0001</td>
<td>13.2 (3.8 to 45.8)</td>
<td>0.0001</td>
<td>1.14 (1.08 to 1.20)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td></td>
<td>16.3 (5.8 to 45.9)</td>
<td>&lt;0.0001</td>
<td>6.1 (2.0 to 19.1)</td>
<td>0.002</td>
<td>1.02 (1.00 to 1.03)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td></td>
<td>7.0 (3.2 to 15.3)</td>
<td>&lt;0.0001</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td></td>
<td>3.2 (1.6 to 6.5)</td>
<td>0.0007</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Analysis was binary for the Cox regression (comparing groups above/below the optimal threshold identified from ROC analysis); and continuous for multiple logistic regression (per unit increase), with subsequent binary analysis. Only absolute rather than indexed values were used, as these showed marginally better discriminatory power on ROC analysis and including both would result in significant confounding of the closely related variables. On multivariate analysis, values are shown for the variables with significant independent predictive value. 95% confidence limits are shown in brackets for all results.

Figure 2. Discriminatory ability of aortic regurgitant fraction. Top, Receiver operating characteristic (ROC) curve for the ability of aortic regurgitant fraction to identify asymptomatic patients who would develop symptoms or other indications for surgery. Bottom, Dot plot showing regurgitant fraction in the conservative and crossover groups, with the optimal threshold of 33% shown. Reg_Frac indicates regurgitant fraction; Sens, sensitivity; Spec, specificity.
the median time point of 1.9 years; surgery-free survival was 93% and 34% for regurgitant fractions ≤33% and >33%, respectively (Figure 3). In patients with highest regurgitant fraction >33%, longer-term surgery-free survival at 8 years showed a slight increase in comparison with analysis with the use of the first recorded regurgitant fraction (91% and 83%, respectively), indicating the few patients that developed higher degrees of regurgitation over time and were moved to the crossover group. All patients with a regurgitant fraction >33% eventually had surgery over 8 to 9 years of follow-up, but subject numbers were small in the later years. The average time to surgery when using the highest regurgitant fraction was slightly reduced, as would be expected (mean 2.4 years, median 1.9 years).

The association of aortic regurgitant fraction with outcome remained robust in subgroup analyses. There was no significant difference between Oxford and the other participating centers; Table 3, \( P=0.59 \) by log-rank test on Kaplan–Meier survival analysis (Figure 3C). Comparison of the centers using free-breathing CMR flow sequences (Oxford and Leeds) with the other 2 centers using breath-hold sequences also showed no difference in the association of regurgitant fraction with outcome \( (P=0.84 \) by log-rank test on Kaplan–Meier survival analysis). Restricting the analyses to only those patients that developed LV dilation or dysfunction as an indication for surgery (excluding patients for whom symptoms developed) again showed a similar association with outcome to the whole group. The AUC on ROC analysis was

### Table 3. Proportion of Asymptomatic Patients Developing Indications for Surgery Over Time, According to CMR Regurgitant Fraction, and Stratified by CMR Centre

<table>
<thead>
<tr>
<th>CMR Centre</th>
<th>n</th>
<th>Highest CMR Regurgitant Fraction ≤33%</th>
<th>Kaplan–Meier P-Value for Difference by Logrank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxford</td>
<td>39</td>
<td>0.04 (n=24)</td>
<td>0.59</td>
</tr>
<tr>
<td>Other centers</td>
<td>74</td>
<td>0.08 (n=48)</td>
<td>0.81 (n=26)</td>
</tr>
</tbody>
</table>
that LVEDV is likely to be a significant confounding factor. Similar mass-to-volume ratios in all groups (Table 4) suggests but this parameter is closely related to LVEDV, and the mass showed some predictive power (AUC 0.74; not able to predict events (AUC 0.55; <0.0001 vs the conservative group; §P=0.05 surgical vs crossover groups).

Table 4. Comparison of CMR Parameters Between the Three Groups of Patients With Aortic Regurgitation

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Crossover</th>
<th>Surgical</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. in group</td>
<td>74</td>
<td>39</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.8±16.8</td>
<td>45.7±18.7</td>
<td>55.6±16.5§</td>
<td>0.04</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.4±10.0</td>
<td>176.6±9.0</td>
<td>173.8±8.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Proportion of male subjects</td>
<td>0.69</td>
<td>0.92*</td>
<td>0.91*</td>
<td>0.002</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.1±16.4</td>
<td>83.0±13.0</td>
<td>83.2±18.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.94±0.22</td>
<td>2.00±0.18</td>
<td>1.98±0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>Bicuspid valve frequency</td>
<td>0.29</td>
<td>0.55*</td>
<td>0.24</td>
<td>0.006</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>132.9±19.3</td>
<td>134.2±16.0</td>
<td>135.1±21.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>68.8±15.0</td>
<td>59.4±13.5</td>
<td>63.5±16.3</td>
<td>0.17</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>27.5±15.5</td>
<td>74.7±28.5‡</td>
<td>80.5±38.7‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant volume index (ml/m²)</td>
<td>14.1±7.6</td>
<td>37.4±14.5‡</td>
<td>41.4±21.0‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>21.8±9.8</td>
<td>42.0±9.5‡</td>
<td>45.6±11.0‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>209.5±54.7</td>
<td>301.1±61.6§</td>
<td>315.8±91.1§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV index (ml/m²)</td>
<td>108.0±25.3</td>
<td>151.6±31.6‡</td>
<td>160.6±48.6‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>78.7±35.5</td>
<td>113.0±33.0†</td>
<td>138.4±59.4‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV index (ml/m²)</td>
<td>40.5±17.8</td>
<td>57.1±17.3*</td>
<td>70.3±31.8‡§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV Ejection fraction (%)</td>
<td>63.6±8.7</td>
<td>62.9±6.4</td>
<td>57.1±10.9§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echo LVEDD (cm)</td>
<td>5.9±0.6</td>
<td>6.6±0.7†</td>
<td>6.6±0.8‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echo LVESD (cm)</td>
<td>3.7±0.6</td>
<td>4.1±0.6*</td>
<td>4.4±0.8§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>173.2±73.1</td>
<td>232.2±80.1†</td>
<td>277.4±77.8‡§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>88.5±34.8</td>
<td>117.1±40.0‡</td>
<td>143.7±41.1‡§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass/LVEDV ratio (g/ml)</td>
<td>0.83±0.26</td>
<td>0.78±0.25</td>
<td>0.91±0.24</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Abbreviations same as for table 1. Values are means±standard deviation; *P-values shown for one-way ANOVA with the exception of bicuspid valve frequency and proportion of male subjects which were by chi-squared analysis.

0.91, and survival without surgery to 2.0 years (the median time point) was 97% for those with regurgitant fractions ≤33%, and 39% for those with regurgitant fraction >33% (P=0.0001 by log-rank test).

The association of LVEDV with outcome appeared slightly lower than regurgitation quantification (Figure 3B), although the differences were slight and confidence limits overlap. Combining LVEDV with regurgitant fraction provided further improvement on either parameter alone, however (Figure 3D). The combination may thus provide the most robust discrimination, especially given that both parameters are measured in one CMR examination. LV ejection fraction was not able to predict events (AUC 0.55; P=0.43). CMR LV mass showed some predictive power (AUC 0.74; P<0.0001), but this parameter is closely related to LVEDV, and the similar mass-to-volume ratios in all groups (Table 4) suggests that LVEDV is likely to be a significant confounding factor.

Comparison With the Surgical Group
Data from the surgical group are shown in Table 4. This showed mean AR and LV volumetric indices similar to the crossover group, and both were significantly larger than in the conservative group. Ejection fraction was lower in the surgical group (mean 57.1% versus 62.9% and 63.6% for the crossover and conservative groups, respectively; P<0.01 for both comparisons), perhaps reflecting a more advanced stage of the disease. The higher proportion of bicuspid valves in the crossover group (0.55 compared with 0.29 in the conservative group, P=0.003 by χ² analysis), might be explained by the slightly higher mean regurgitant fraction (mean 33.4% versus 25.8% for trileaflet valves; P=0.004).

Discussion

Association of AR Quantitation With Outcome
Our data demonstrate the potential value of quantifying AR with CMR, which showed a significant association with the future need for surgery, including patients who developed asymptomatic LV dilation or dysfunction. Patients already destined for surgery (the surgical group) also had measures of AR that were not significantly different from 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 predictors of future events, but this requires testing in a future prospective study.

Comparison With LV Volumetric Indices
Quantifying the regurgitation showed a slightly better association with events than CMR-derived LV indices, despite highly accurate measurements of LV volumes and function by CMR. LVEDV still had good discriminatory power,
however, and was an independent predictor on multivariate analyses. The combination of LVEDV with regurgitant fraction provided a slight enhancement over AR alone, and LV volumes and function are important in the overall assessment of the patient. Given these factors, and that both are readily available from a standard CMR scan, the combination of CMR quantification of AR and LV volumes could be a valuable component of the workup in patients with AR. The slightly stronger association of outcome with AR indices in comparison with LV volumes, and the ability of regurgitant fraction to identify patients who would develop excess LV dilation or dysfunction as indications for surgery, suggests that increases in regurgitation may occur before LV dilation. 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.

LV mass showed reasonable discriminatory ability in identifying patients likely to progress to surgery (AUC 0.74). It is, however, closely related to LV volume and was not an independent predictor on multivariate analysis. Other studies have not shown any predictive power of wall thickness, although the LV mass-to-volume ratios were similar for all 3 subject 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 link to LV volume.

**Comparison With Previous Studies of Outcome**

Bonow et al’s 1991 study had similar methodology to our own, in a similarly sized group of patients, and examined the prediction of clinical events in initially asymptomatic patients who underwent echocardiography. Both this and the 1995 Tornos study showed a predictive ability for end-diastolic diameter (≥7.0 cm) and end-systolic diameter (≥4.0 cm, but especially ≥5.0 cm). These findings are in keeping with our data that showed an association with outcome for end-diastolic and end-systolic volumes, although the addition of CMR measurements of LV volume and quantification of AR adds to these existing studies with more modern imaging techniques. Other studies have examined the prediction of outcome post-surgery in patients with AR, and confirmed that symptoms, reduced ejection fraction, and excess LV dilation are associated with worse long-term outcome. These studies helped inform the current guidelines for surgery in AR, but also highlight the value in identifying patients before symptoms or significant LV dilation or dysfunction, as this study aims to do.

**Clinical Utility**

The ability to identify patients before symptoms or excess LV dilation/dysfunction would be clinically important. These patients might be considered for early surgery, and at the very least could be followed more closely. Our sample size was modest, however, and to support a change in clinical practice, particularly where cardiac surgery is concerned, requires better demonstration of patient benefit in a randomized trial comparing early surgery with surgery based on conventional indications. Quantitative CMR indices may provide the appropriate tool for identifying suitable patients for such a trial. Conversely, patients with lower quantities of AR and LVEDV might be reassured of the good medium-term prognosis and may require less frequent follow-up, aiding the efficient use of healthcare resources.

**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 2.6 years, and up to 9 years).

The lack of blinding to the CMR data in 3 of the centers may have biased results. There are no current CMR criteria/thresholds for recommending surgery, however, and we attempted to minimize any bias where possible and confirmed that there were no significant differences in the association with the progression to surgery between centers. It is possible that some bias remains, particularly given the subjective nature of symptom assessment.

The CMR sequence for flow measurement also differed between centers, as did the analysis software, but the associations with outcome were no different between these subgroups, which suggests the results may be generalizable for both types of sequence and different vendor software. There remain a limited number of contraindications to MRI, including most pacemakers and other implanted metallic devices, and a few patients are unsuitable for CMR. Prosthetic heart valves are not a contraindication, however.

**Conclusions**

Quantification of AR with CMR showed significant associations with outcome, particularly when combined with CMR-
derived LV volume. The study was of moderate size, however, and not all clinicians were blinded to the CMR results. These CMR parameters might prove useful for identifying suitable patients for early aortic valve replacement, but a clinical trial is recommended to confirm this and determine clinical benefit.

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Disclosures
None.

References
17. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Steward WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463.
Timing surgery in patients with significant aortic regurgitation (AR) can be difficult. Currently, surgery is advised for severe regurgitation once symptoms, excess left ventricular (LV) dilation or dysfunction, occur. However, prognosis is already reduced by this stage, and earlier identification of patients suitable for surgery might be beneficial. Accurate quantification of the regurgitation may help, but is difficult with echocardiography. Cardiovascular magnetic resonance can accurately quantify AR and also provides highly accurate measurements of LV volume, but the clinical utility of this has not been established. Our study examined whether quantification of AR and LV volumes with cardiovascular magnetic resonance was associated with the future development of symptoms or other indications for surgery in an initially asymptomatic group with moderate to severe AR. We showed that both severity of AR and LV volumes had significant associations with outcome over the subsequent few years. AR quantification showed a stronger association than LV end-diastolic volume, but the combination of these 2 parameters was better still. Cardiovascular magnetic resonance measurements of AR and LV volumes might enable the identification of potential candidates for early surgery, and this should be tested in a large-scale clinical trial.
Aortic Regurgitation Quantification Using Cardiovascular Magnetic Resonance: Association With Clinical Outcome

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