Preoperative left atrial volume index is associated with postoperative outcomes in mitral valve repair for chronic mitral regurgitation

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ABSTRACT

Objective: To assess determinants of left atrial reverse remodeling after mitral valve repair and to evaluate the impact of preoperative left atrial volume on postoperative outcomes.

Methods: We reviewed the records of 720 patients who underwent mitral valve repair from September 2008 to July 2015 and had preoperative measurement of left atrial volume index. We analyzed the association of preoperative left atrial volume index on early and late outcomes, and determined which baseline characteristics are associated with left atrial reverse remodeling, as measured by changes in left atrial volume index in 512 patients who had at least 1 postoperative measurement.

Results: The median (interquartile range) preoperative left atrial volume index was 54.0 (44.0-66.0) mL/m2. Preoperative left atrial volume index, age, body mass index, and atrial fibrillation were independently associated with the degree of left atrial reverse remodeling over the follow-up period. Reverse remodeling was greatest in patients with higher baseline left atrial volume index (P < .001), but less reverse remodeling was observed in patients with advanced age (P < .001), preoperative atrial fibrillation (P < .001), and extreme values of body mass index (P = .004), although these effects were moderately attenuated when limiting the analysis to 6-month follow-up. Secondary analysis demonstrated marginally significant effects of preoperative left atrial volume index on risks of early postoperative atrial fibrillation (P = .030) and late mortality (P = .077) after adjusting for age and sex.

Conclusions: In patients with degenerative mitral valve regurgitation who had mitral valve repair, preoperative left atrial volume index was associated with extent of left atrial reverse remodeling, risk of early postoperative atrial fibrillation, and late mortality. The majority of reverse remodeling occurs within the first month after operation and is greatest in younger patients. (J Thorac Cardiovasc Surg 2020;160:661-72)

Central Message
Preoperative LAVI is an important predictor of postoperative outcomes in patients undergoing MV repair for chronic MR.

Perspective
In patients with degenerative MV regurgitation who undergo MV repair, higher preoperative LAVI was associated with higher postoperative LAVI and with marginally increased risks of early postoperative AF and late mortality. These results suggest that LAVI should be considered in decision-making regarding timing of MV repair.

See Commentary on page 673.

Chronic mitral regurgitation (MR) leads to a prolonged state of volume overload of the left atrium (LA) leading to its enlargement. LA enlargement is associated with

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This work was supported by the Paul and Ruby Tsai Family.

Read at the 98th Annual Meeting of The American Association for Thoracic Surgery, San Diego, California, April 28-May 1, 2018.

Received for publication April 30, 2018; revisions received July 28, 2019; accepted for publication Aug 1, 2019.

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0022-5223/$36.00 Copyright © 2019 Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

https://doi.org/10.1016/j.jtcvs.2019.08.040

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many risk factors for mortality in the general population. In chronic MR, LA size is proportionate to the regurgitant volume, which is a marker of the burden of MR. Thus, LA size is a quantifiable measurement of the severity and chronicity of the valve disease and, in turn, influences outcomes after mitral valve (MV) repair (Video 1). Echocardiography is the most common method used to assess LA size, but reliable measurement of LA size can be problematic. The available LA measurements are area, volume, and anteroposterior diameter. It is crucial to standardize methods for quantification of LA size and correlate reference ranges to severity of MR. The knowledge gaps in standardized LA size measurements are also reflected in clinical assessment of LA size reduction, known as “LA reverse remodeling,” which occurs after surgical repair of MV.

The American Society for Echocardiography and American College of Cardiology recommend LA volume measurements to assess LA size and remodeling. The age and gender-based difference in LA size is adjusted by correcting LA volume for body surface area (meters squared), which is generalizable to all patients irrespective of their age or gender. The recommended upper normal limit for 2-dimensional echocardiographic LAVI is 34 mL/m². There are few data on the association of extent of LA enlargement as measured by LAVI and outcomes after MV surgery.

According to the current American Heart Association/American College of Cardiology (AHA/ACC) guidelines, recommendations for surgical intervention in chronic MR are based on left ventricular (LV) function determined by ejection fraction and end-systolic dimension and grade of MR determined by effective regurgitant orifice, regurgitant volume, and regurgitant fraction. Because of uncertainty in measurement, LA size is not considered in the decision-making of surgical management of chronic MR in the AHA/ACC guidelines, but the 2017 European Society of Cardiology and European Association for Cardiothoracic Surgery guidelines list LA enlargement (LAVI > 60 mL/m²) as a class IIa indication for intervention in asymptomatic patients with preserved ejection fraction and low surgical risk.

The main focus of this study is to explore LAVI as a standardized measurement of LA size and to establish the significance of preoperative LAVI as a predictive factor of postoperative outcomes, thus potentially aiding in surgical decision-making.

PATIENTS AND METHODS
Study Population

The study was approved by the Mayo Clinic Institutional Review Board for research participation of patients. From September 2008 to July 2015, 2303 adult patients underwent MV repair at the Mayo Clinic, Rochester, Minnesota. We excluded patients (Figure 1) who had a prior cardiac surgery (n = 478) or index surgery with concomitant valve, aorta, atrial fibrillation (AF)-related, or other select cardiac procedures (n = 567). In addition, we excluded patients whose MV regurgitation was not of a degenerative etiology (n = 340), as well as those who did not consent to the use of their records for research (n = 46). Of the remaining 872 patients, 720 had a LAVI measured preoperatively and were included in the study. Of these, 512 patients had at least 1 LAVI measurement postoperatively and were included for longitudinal analyses.

Relevant history and preoperative and postoperative study variables were obtained from clinical records. LAVI (mL/m²) was obtained from echocardiograms to ascertain LA remodeling in patients with MV regurgitation due to degenerative disease and reverse remodeling after MV repair. LAVI was calculated from LA volume (milliliters) measured from standard apical 4-chamber views at end systole just before MV opening and corrected for body surface area (meters squared).

We collected baseline demographic and clinical characteristics to determine the baseline effects of these variables on postoperative outcomes. The baseline variables collected were age at the time of surgery, sex, body mass index (BMI, kg/m²), body surface area (m²), and modeling.
hypertension, recent AF or atrial flutter, concomitant mitral stenosis, and pulmonary artery systolic pressure. We collected baseline measurements of left ventricular ejection fraction (LVEF), left ventricular end-systolic dimension (LVESD), and left ventricular end-diastolic dimension (LVEDD), tricuspid valve (TV) regurgitant systolic peak velocity (TVmax), and LA VI from preoperative echocardiograms. We also collected these measurements from postoperative echocardiograms whenever available. We assessed postoperative outcomes for LA reverse remodeling (based on all serial LA VI measurements), occurrence of AF within 30 days of surgery, and survival over long-term follow-up. Vital status was ascertained for the majority of these patients using LexisNexis Accurint (New York City, NY) via linkage with the Social Security Death Master File, state death records, and other sources, which was most recently searched in February 2018. For the minority of patients who could not be linked, vital status was determined by reviewing electronic medical records and censoring at the last follow-up visit.

**Surgical Technique**

Indications for operation and techniques of MV repair in the study population have been described.\(^{10-12}\) MV repair most commonly involved simple posterior leaflet repair by triangular resection or plication or anterior leaflet repair using chordal replacement with polytetrafluoroethylene sutures or edge-to-edge suture.\(^{13}\) All leaflet repairs were reinforced with annuloplasty, usually a standard posterior band.\(^{14}\)

**Statistical Analysis**

Descriptive statistics are presented as quartiles (median with interquartile range [IQR]) for continuous variables and as frequencies and percentages for categoric variables. To assess whether MR repair had an immediate effect on LAVI and other echocardiographic variables, preoperative and postoperative (in-hospital) measurements were compared by the Wilcoxon signed-rank test among patients with paired data. Longitudinal analysis based on generalized least squares (GLS) was used to model the entire time course of LAVI using all available repeated
assessments from a subset of patients measured at least once postoperatively. GLS modeling allows each patient to have a different number of measurements and different measurement times, with analysis of data using the actual time of echocardiogram. To take into account the correlations between outcome measurements on the same patient, the model included a first-order autoregressive correlation structure that assumes exponential decline over longer time spans. The time variable was modeled flexibly using a restricted cubic spline function with 5 knots so as not to assume linearity in the time-response profile. Longitudinal LAVI responses were transformed to natural logarithmic scale to satisfy multivariate normality and constant variance assumptions of the GLS model. Predicted mean responses for log LAVI were then transformed back to the original scale by using the anti-log function to estimate geometric mean LAVI responses.

We used exploratory statistical and graphical methods to examine the sensitivity of our analysis to missing LAVI patterns within discretized follow-up intervals (Figure E1), for example, using binary logistic regression to predict LAVI missingness from baseline variables. Separate GLS models were fitted to describe the longitudinal trends in LVEF, TV max, LVESD, and LVEDD outcomes.

GLS models were further used to relate the postoperative LAVI responses to the following baseline variables: log-transformed preoperative LAVI, age, sex, BMI, recent AF, hypertension, LVESD, and pulmonary artery pressure. An interaction between preoperative LAVI and time since surgery was also included in the model to test for a differential influence of the baseline LAVI over follow-up. By default, the continuous predictors were entered as 3-knot restricted cubic spline functions to allow for nonlinear relationships; the spline for the time variable was also assigned 3 knots to avoid an overly complex test for interaction. Missing baseline data were handled by multiple imputation using the aregImpute function in the R Hmisc package. This procedure used additive semiparametric models and predictive mean matching to generate 30 imputation datasets, from which separate fits of the GLS model were averaged and corrected for uncertainty by means of the bootstrap method. The fitted model was depicted by plotting geometric mean predicted values when varying each predictor and holding the other factors to constants (median values for continuous predictors and modes for categoric predictors) and by reporting fold changes (ratio of geometric means) with 95% confidence intervals (CIs). For continuous predictors, fold changes are computed as the geometric mean predicted LAVI when the predictor is set to its 75th percentile divided by the geometric mean predicted LAVI when the predictor equals its 25th percentile. In a sensitivity analysis, we repeated the GLS analysis, truncating follow-up to LAVI measured within 6 months to limit the influence of late assessments when data become increasingly sparse and susceptible to selection bias.

For secondary analyses, the association of preoperative LAVI with early postoperative AF and with long-term mortality was analyzed in logistic and Cox regression models, respectively, adjusting for age and sex. Given the fairly high number of AF events, 2-way interactions among the 3 predictors were also included in the logistic model to facilitate graphical inspections of risk over the range of baseline LAVI by levels of age and sex. In both models, LAVI values were analyzed on log scale and modeled with restricted cubic splines, thus allowing flexibility for nonlinear relationships with the outcome. We report the median follow-up for the longitudinal analysis based on the last available LAVI assessment, and median follow-up for mortality was computed with Kaplan–Meier quantile estimates when analyzing time until censor (and censoring on the original event of death). All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.4.2 (R Programming; https://www.r-project.org/).

RESULTS

Patient Characteristics

The study population consisted of 720 patients who met the inclusion criteria (Figure 1). Baseline demographic and clinical characteristics are listed in Table 1. The median (IQR) age was 61.1 (52.7–69.1) years, and 72% were male. Three percent of the study population had preoperative AF or flutter and did not undergo surgical ablation at the time of MV repair. Thus, any postoperative rhythm changes observed were independent of targeted interventions.

Preoperative echocardiographic measurements of the patients are shown in Table 1. The median (IQR) LAVI was 54 (44–66) mL/m² with only 4% of patients below the clinical threshold of 34 mL/m², indicating that LA remodeling occurred because of chronic pressure and volume overload associated with MV regurgitation. The median levels of preoperative measurements of LVESD and LV ejection fraction were within normal limits; LVEDD was larger than normal.

Patterns of Left Atrial Volume Changes

Of the 720 patients included in the study, we identified 512 (71%) who had at least 1 postoperative LAVI measured during a median follow-up of 4.5 (0.1–21.8) months. Those with follow-up data were younger, had less hypertension, had slightly better echocardiographic indices, and had lower incidence of early postoperative AF compared with patients excluded from these analyses (Table E1). For a subset of 349 patients measured before and after (in-hospital) MR repair, the median LAVI decreased from 55 to 42 mL/m² (P < .001 by Wilcoxon signed-rank test), indicating beneficial LA reverse remodeling (Table 2 and Figure 2, A). Longitudinal analysis used to model the trend across the entire time course on all 512 patients demonstrated a significant, nonlinear decrease in LAVI over time (P < .001, 4 degrees of freedom). After the
sharp decrease at hospital discharge, model-predicted LAVI decreased further after 6 months (geometric mean = 31.5 mL/m², 95% CI, 29.9-33.2) and leveled off or gradually increased thereafter (Figure 2, B). Additional longitudinal analyses showed significant time-dependent decreases in LVEF, TVmax, LVEDD, and LVESD (all \( P < .001 \)) similar to that of LAVI, except improvement in LVEF did not progress after hospital discharge, whereas improvement in LVESD did not become evident until outpatient follow-up (Figure E2).

Impact of Preoperative Left Atrial End-Systolic 2-Dimensional Volume Index on Left Atrial Reverse Remodeling

Multivariable repeated-measures analysis was performed to model the postoperative course of LAVI as a function of measurement times and preoperative LAVI, adjusting for the effects of other baseline factors. Results of the primary analysis using all available follow-up (981 repeat measurements from 512 patients; Figure 3, A) and from the secondary analysis with data limited to 6 months of follow-up (544 measurements from 445 patients) showed highly significant effects of time and preoperative LAVI overall (both \( P < .001 \)) but no evidence of an interaction (\( P = .144 \)). The latter result is depicted graphically with the predicted responses plotted (on the y-axis) against time (x-axis) for 3 different values of baseline LAVI (Figure 4, A) and plotted against baseline LAVI (x-axis) at 3 follow-up times (Figure 4, B), each while holding the values of the other model covariates to constants listed at the bottom. These results indicated that higher preoperative LAVI was predictive of higher postoperative LAVI, and that

### TABLE 2. Changes in echocardiographic measures at in-hospital postoperative assessment for subgroups with paired data

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Preoperative, median (IQR)</th>
<th>Postoperative, median (IQR)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAVI, mL/m²</td>
<td>349</td>
<td>55 (45-66)</td>
<td>42 (36-50)</td>
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</tr>
<tr>
<td>LVEF, %</td>
<td>620</td>
<td>62 (58-65)</td>
<td>53 (47-58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TV regurgitant systolic peak velocity, m/s</td>
<td>594</td>
<td>2.5 (2.3-2.9)</td>
<td>2.5 (2.3-2.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>689</td>
<td>58 (55-62)</td>
<td>52 (48-56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>620</td>
<td>36 (33-39)</td>
<td>36 (32-40)</td>
<td>.574</td>
</tr>
</tbody>
</table>

IQR, Interquartile range; LAVI, left atrial end-systolic 2-dimensional volume index; LVEF, left ventricular ejection fraction; TV, tricuspid valve; LV, left ventricle.

FIGURE 2. Longitudinal changes in LAVI (A) immediately after surgery in 349 patients and (B) over the entire follow-up period using all available measurements made in 512 patients. Spaghetti plots are used to show the raw data, with faint lines depicting the observed LAVI trajectories for each patient. Trend lines derived by quartile values (left) or by GLS modeling (right) are superimposed on the figure to summarize the trend over time. LAVI improved in the period immediately after surgery (\( P < .001 \) by Wilcoxon rank-sum test) and further improved during subsequent months of follow-up before leveling off and gradually worsening (\( P < .001 \) for test of nonlinear time effect from GLS model). LAVI, Left atrial end-systolic 2-dimensional volume index.
this prognostic importance is mostly preserved across follow-up. For example, when baseline LAVI increases from its lower to upper quartile, the model predicts a 1.19-fold higher postoperative LAVI at an early follow-up of 0.1 months, compared with later effects of 1.16- and 1.15-fold higher LAVI at 4.5 and 39.2 months, respectively (Table E2). When relating this effect instead to the postoperative change in LAVI, the same IQR increase in baseline LAVI (as predicted for the median follow-up time of 4.5 months) translates into a 1.28-fold (1.25-1.32) greater improvement. Thus, the magnitude of beneficial LA reverse remodeling is greatest in patients with the highest baseline LAVI, despite their LAVI levels remaining the highest (worst) postoperatively.

**Other Determinants of Left Atrial Reverse Remodeling**

Partial effects of the other predictor variables included in the longitudinal model are shown in Figure 4. Significant baseline predictors of increased postoperative LAVI included older age ($P < .001$), extremes of BMI ($P = .004$), and recent AF ($P < .001$). The relative effects

FIGURE 3. Estimated effects of other variables on postoperative LA VI in the model. Curves (or dots) show the predicted values of the geometric mean LA VI when varying the predictors, as shown in the panels moving one variable at a time. Shaded bands (or error bars) represent pointwise 95% CIs for the estimates of these geometric mean effects. Each predictor being plotted is adjusted for all the other variables by holding them to their median (or mode), thus reflecting predicted values at 4.5 months of follow-up for a patient whose baseline LAVI is 54 mL/m². The chi-square statistic and $P$ value inside each panel are for the partial test of association for that predictor, as derived by Wald tests from the GLS model. LVESD, Left ventricular end-systolic dimension; AF, atrial fibrillation.
of each factor included in the model are summarized in Table E2, which are presented as fold changes (the ratio of geometric mean predicted LAVI values, after adjusting for the other covariates). As an example, when age increases from 51.8 to 68.6 years, the model predicted an increase in postoperative LAVI by a factor of 1.13 (95% CI, 1.10-1.15), holding all other predictors constant. Additionally, those patients with baseline AF had a 1.17-fold (1.07-1.29) higher postoperative LAVI than those who were in sinus rhythm (corresponding to predicted LA VI values of 41.1 and 35.0 mL/m², respectively, when adjusting other variables to their median or mode).

In a sensitivity analysis, the repeated-measures model was refit using only LAVI data measured in the first 6 months after surgery (544 measurements from 445 patients). By restricting the analysis to 6-month follow-up, the importance of BMI was diminished ($P = .138$) and the effects of age (fold-change, 1.10; 95% CI, 1.06-1.13; $P < .001$) and AF (fold-change, 1.15; 95% CI, 1.01-1.32; $P = .040$) were slightly attenuated, although results were otherwise similar (Table E2 shows a summary of partial effects from both models). Furthermore, the 2 models showed consistency in ranking the importance of the risk factors, with preoperative LAVI, time since surgery,
and patient age as the dominant predictors of reverse remodeling (Figure E3).

Impact of Preoperative Left Atrial End-Systolic 2-Dimensional Volume Index on Postoperative Outcomes

We assessed the association between preoperative LAVI and the risk of early postoperative AF and long-term mortality (Table E3). Of the 720 patients analyzed, 200 (28%) developed early postoperative AF. In a flexibly fitted logistic regression model allowing for interactions with age and sex, the overall effect of preoperative LAVI on risk of developing AF was statistically significant ($P = .030$) (Figure 5, A).

Additionally, we analyzed the association between preoperative LAVI and long-term survival after surgery. A total of 31 patients died over a median follow-up time of 4.6 (3.3-5.9) years, corresponding to 3- and 5-year survival estimates of 98% and 96%. Age- and sex-adjusted Cox regression analysis revealed a potential relationship between preoperative LAVI and increased mortality, although this result was not statistically significant (IQR hazard ratio, 2.35; 95% CI, 0.88-6.27; $P = .077$). The risk relationship illustrated in Figure 5, B was nonlinear.
over the range of LAVI, and for both values lower than 40 mL/m² and greater than 50 mL/m², there appeared to be an incrementally higher risk of mortality.

DISCUSSION

LA enlargement is an indicator of poor prognosis in various cardiovascular diseases including but not limited to MV regurgitation, dilated cardiomyopathy, and AF. In chronic MV regurgitation, the excess volume of blood ejected into a relatively low pressure LA leads to LA enlargement, a process known as “remodeling.” LA remodeling occurs at structural, functional, and electrical levels and has been attributed to various pathophysiologic mechanisms. Metabolic derangements, reduced cellular energy production, neurohormonal disequilibrium, and systemic inflammation have been described in the initiation and progression of LA remodeling and fibrosis. The rate and extent of LA remodeling depend on specific stressors associated with the underlying disease condition. Further studies on maladaptive changes of the LA have shown that reversal of 1 or more of these stressors leads to functional and structural reverse remodeling of the LA in a systematic temporal fashion. However, structural and functional parameters for definitive measurements of LA remodeling and reverse remodeling are poorly defined in the clinical setting.

There is a general relationship between the extent of LA enlargement and the severity of MV regurgitation. An important objective of surgical repair in chronic MR is LA reverse remodeling. LA size after MV surgery correlates with patient survival and risk of AF, but there is little information on the effect of extent of reverse remodeling on outcomes. Furthermore, there has been debate on an easily quantifiable, standardized echocardiographic measurement of LA size. After careful consideration and literature review, we elected to use LAVI for our analyses, and the results demonstrate that LAVI is a useful standardized indicator for quantifying LA remodeling and reverse remodeling. Among patients undergoing MV repair in our study, median preoperative LA size as measured by LAVI was 54 mL/m², which is higher than the established normal upper limit of 34 mL/m², which suggests that LA remodeling occurred in these patients due to chronic pressure and volume overload associated with MV regurgitation. We have shown that higher preoperative LAVI is predictive of postoperative LAVI and is potentially predictive of early postoperative development of AF and late mortality.

Volumetric LA enlargement due to increased blood volume occurs first in the natural evolution of structural, functional, and electrical changes in LA remodeling; enlargement may occur as early as the first week of volume overload. In the chronic setting, functional strain ensues, and atrial fibrosis and electrical remodeling follow thereafter depending on the underlying disease condition. Consequently, during LA reverse remodeling, acute reduction in LA size occurs as the result of elimination of volume overload. This was apparent in our study in which much of the LA size reduction was seen in the immediate postoperative period. Complete or partial reversal of functional strain and fibrosis contributed to further reverse remodeling, but this occurs at a slower pace over early follow-up, during which time the median LAVI was 34 mL/m². Our study documents that in the majority of patients with chronic MR undergoing MV repair, the LA is capable of reverse remodeling and attains near normal size within the first few months after surgery.

As discussed previously, functional strain, fibrosis, and neurohormonal changes contribute to LA electrical remodeling, mostly manifested as AF. The risk to develop AF in chronic MR is as high as 8% to 18% at 5 years and 27% to 47% at 10 years on conservative management. The 2014 AHA/ACC guidelines advocate a concomitant maze procedure at the time of MV repair in patients with chronic MR and persistent AF; however, the clinical and functional benefits have been difficult to prove. The present study excluded patients undergoing concomitant surgical ablation of AF, and this accounts for the relatively small number of patients from our study, 3% overall, who had preoperative AF or flutter. Nevertheless, the presence of preoperative AF was an independent risk factor that negatively affected LA reverse remodeling.

AF occurs early after isolated MV repair in approximately 20% to 30% of patients. We observed early postoperative AF in 28% of our study cohort in whom the risk tended to increase with higher preoperative LAVI. The chance of developing early postoperative AF appeared to increase in patients with preoperative LAVI greater than 50 mL/m², incrementally starting at preoperative LAVI values well below the currently used threshold of 60 mL/m². For example, in patients who developed early postoperative AF, 63% had preoperative LAVI greater than 50 mL/m². This sensitivity for a hypothetical threshold set at 50 mL/m² compares favorably to a threshold of 60 mL/m² (45%) but had worse specificity (42% vs 66%). Despite a greater degree of reverse remodeling in patients with higher preoperative LAVI, the relatively higher postoperative LAVI increases the risk to develop postoperative AF.

There is wide variability (27%-97%) in survival reported in the natural evolution of chronic MR. In patients with chronic MR managed conservatively, 5-year mortality risk increases 3-fold with an LA diameter greater than 55 mm. After elective surgical repair of chronic MR, the 5-year mortality rate is reduced, as low as 1%/year in some series. The present study suggests a potential association between preoperative LAVI and long-term
mortality after isolated MV repair. This increased risk of mortality, although not statistically significant and not limited to higher levels, was more than 2-fold higher when increasing preoperative LAVI from its lower to upper quartile (from 44 to 66 mL/m²; hazard ratio, 2.35). In a graphical exploration of this relationship, risk of 5-year mortality is incrementally higher for increasing LAVI values greater than 50 mL/m² and for decreasing values lower than approximately 40 mL/m².

**Study Strengths and Limitations**

The major strengths of this study are the relatively large sample size, follow-up data that capitalized on repeat measurements, and standardized indications and techniques for surgery in the study population. This enabled a detailed examination of the time trends and the baseline risk factors of postoperative LAVI via multivariable regression analyses. The main limitation is sample attrition over the follow-up period. Patients did not have echocardiograms taken on a uniform time schedule, resulting in imbalances in follow-up data. We relied on a method of longitudinal analysis that could handle such imbalances and make optimal use of incomplete records. We also conducted sensitivity analyses to investigate the robustness and generalizability of our results. There were some baseline differences for the subgroup used in longitudinal analyses, which might reflect that those with echocardiographic follow-up represent a younger, healthier set of patients. Given that younger age is strongly associated with greater LA reverse remodeling, the over-representation of younger patients in our longitudinal analysis likely resulted in a larger estimate of reverse remodeling than would be expected for the total study population; thus, some of our findings may not be generalizable to other settings. Furthermore, these analyses did not account for the type of MV repair and thus are susceptible to uncontrolled confounding.

**CONCLUSIONS**

In the AHA/ACC guidelines, LA size is not considered as an important factor in the clinical decision-making. In contrast, the European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines list LA enlargement (LAVI >60 mL/m²) as a class IIa indication for intervention in asymptomatic patients with preserved ejection fraction and low surgical risk. Overall, our study findings tend to support the European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines because preoperative LAVI was marginally associated with increased risk of postoperative AF and late death, independent of age and sex. Moreover, our data suggest that the LA size threshold for consideration as a risk factor may be less than the 60 mL/m² threshold advocated by the European Society of Cardiology/European Association for Cardiothoracic Surgery.

**Conflict of Interest Statement**

Dr Daly discloses potential royalties per institutional policy for Neochord, Inc, as well as a licensed patent (transapical, off-pump placement of artificial chordae tendineae). All other authors have nothing to disclose with regard to commercial support.

The authors thank Dr Monali Mohan for assistance with data collection.

**References**


Key Words: mitral valve regurgitation, mitral valve repair, left atrial volume index

Discussion

Dr Tomasz A. Timek (Grand Rapids, Mich). These are important and timely data, as we have already discussed today. I have 3 questions for you. You have shown that the rate of perioperative AF is related to atrial size preoperatively. Now, this is perioperative. Did you look at 1-month and 1-year rates of AF? Is there any continued morbidity from AF related to size?

Dr Parvathi Balachandran (Rochester, Minn). In this study we examined only early postoperative AF. Dr Timek. In terms of imaging, cardiac magnetic resonance imaging is now widely available almost in every hospital. The advantage of cardiac magnetic resonance imaging is that we can simultaneously and reliably look at LA size, function, and fibrosis and therefore potentially look at structural, functional, and maybe even electrical remodeling. Should we be doing magnetic resonance imaging on all these patients? Have you done this on any of these patients at Mayo?

Dr Balachandran. In clinical practice, we do not follow patients with MR with cardiac magnetic resonance imaging. Dr Timek. In terms of imaging, cardiac magnetic resonance imaging is now widely available almost in every hospital. The advantage of cardiac magnetic resonance imaging is that we can simultaneously and reliably look at LA size, function, and fibrosis and therefore potentially look at structural, functional, and maybe even electrical remodeling. Should we be doing magnetic resonance imaging on all these patients? Have you done this on any of these patients at Mayo?
Dr David H. Adams (New York, NY). This is a really important topic. Now, the first thing I want to ask you about is LAVI versus LA dimension. I know that Maurice has published before and taught us to pay attention to LA dimension over 55 as a real marker for mortality in terms of patients. Since then, we have paid a lot of attention to the number 5 in terms of dimension. So tell me a bit about LAVI versus LA dimension. Which one should we be hanging our head on now?

Dr Balachandran. The reason why we decided to go with LAVI is because it was generalizable for age and gender. We looked into LA size, diameter, and other dimensions, but LAVI is the most generalizable and reliable.

Dr Adams. My next question is about high LAVI. Going forward now, what would we take home to take better care of patients? For instance, if they have a high LAVI, should we be thinking about prophylaxis for AF? Are there other things that we might want to consider in that population postoperatively?

Dr Balachandran. This is one takeaway from the study. The finding of increased risk of AF in patients with increased LAVI should trigger concern for AF.

Dr Adams. Because tying the presentations together, one thing I am taking home from this session is if you have a high LAVI and a higher risk of AF, this may certainly be one group of patients you want to anticoagulate, because their risk of AF and other complications may be higher.

Dr Steven F. Bolling (Ann Arbor, Mich). I have a question along the theme that David had. These patients with high LAVI or LA size probably have a higher fibrotic index, and the question was brought up about magnetic resonance imaging. In the postoperative period, do you consider using some type of antifibrotic agent such as low-dose spironolactone or eplerenone in this group of patients? Do you think that’s indicated in them?

Dr Balachandran. The reverse remodeling that’s occurring at a structural level can be attributed to both physical and physiologic effects. The physical effect is volume reduction, whereas the physiologic effect relates to tissue characteristics such as fibrosis and scarring. Your suggestion regarding antifibrotic therapy is a good one and something that might be studied prospectively.

Dr Bolling. I agree. Much of the reverse remodeling you saw is probably just mathematical because the LA is actually physically holding less volume. In your time course, much of the volume dropped within the first week or so. Of course that is not an antifibrotic or even change in the atrial myocytes, but over time you got lesser volume. Did you put those patients on any antifibrotic agents such as spironolactone or eplerenone? We do in our practice for larger LAs, but we really don’t know if it works or not.

Dr Balachandran. Again, your suggestion regarding antifibrotic therapy is a good one and something that might be studied prospectively.

Dr Hartzell V. Schaff (Rochester, Minn). The short answer, Steve, is no, we haven’t. I just wanted to add, though, a point to David’s question, and that has to do with how does this impact surgical practice. We believe the most important point has less to do with how you treat the patient after the operation and much to do with decision-making in patients with MR. The European guidelines include LA size as a potential trigger for operation. Their LA size threshold, as I understand it, is 60. Is that right, Parvathi?

Dr Balachandran. Yes, it is 60 in asymptomatic patients with preserved ejection fraction.

Dr Schaff. In our study we could start seeing a difference in late mortality with a LAVI of 50. So it might be that the guideline cut point needs to be modified, and for sure, LAVI should be considered in the US guidelines.
FIGURE E1. Patterns of missing LAVI data across follow-up within the 512-patient subset followed longitudinally for LAVI, we assessed missing data patterns at discretized time intervals (immediate follow-up [before hospital discharge], early follow-up [outpatient follow-up <6 months], and late follow-up (>6 months]) by plotting the proportion of missing LAVI values stratified by the levels of the baseline variables. This provides a general impression of which types of patients tended to lack a LAVI measurement over time. As shown, the tendency for LAVI to be missing at immediate follow-up was more apparent with lower baseline levels of LAVI and pulmonary arterial systolic pressure, and possibly in the presence of AF or the absence of hypertension. We then analyzed the effects of these variables simultaneously at each time interval with multivariable logistic regression. Pulmonary arterial systolic pressure, LVESD, and AF were important predictors of LAVI missingness at discharge, but patterns were less clear for later time intervals (only increasing age showing marginally higher rate of missing data at early follow-up). No baseline variables were capable of predicting missing LAVI at late follow-up. Overall, these results suggest some systematic tendencies of missingness, but this is mostly limited to whether the in-hospital assessment was obtained. LAVI, Left atrial end-systolic 2-dimensional volume index; BMI, body mass index; AF, atrial fibrillation; Htn, hypertension; PASP, pulmonary artery systolic pressure; LVESD, left ventricular end-systolic dimension.
FIGURE E2. Longitudinal trends of additional echocardiographic response variables. A GLS model was fitted for each echocardiographic parameter, with preoperative value of the outcome variable included as the first longitudinal response and the time of measurement modeled continuously with a restricted cubic spline function (5 knots). In response to MR repair, all 4 measures demonstrated significant improvements with nonlinear decreases over time (each $P < .001$). Most or all of the therapeutic effect for LVEF and LVEDD occurred by the time of discharge, whereas improvements in TRmax and LVESD were more gradual. LVEF, Left ventricular ejection fraction; TR, tricuspid regurgitation; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension.
FIGURE E3. Relative importance of all variables in the 2 models predicting changes in LAVI using all available follow-up and when restricting follow-up measurements to within 6 months of surgery. PA, pulmonary artery; LVESD, left ventricular end-systolic dimension; LAVI, left atrial end-systolic 2-dimensional volume index; AF, atrial fibrillation.
## TABLE E1. Demographic and clinical characteristics for patients with and without left atrial end-systolic 2-dimensional volume index follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>No LAVI follow-up n = 208</th>
<th>LAVI follow-up n = 512</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, y</td>
<td>64.6 (55.1-70.8)</td>
<td>60.0 (51.8-68.6)</td>
<td>.003*</td>
</tr>
<tr>
<td>Male sex</td>
<td>146 (70.2%)</td>
<td>375 (73.2%)</td>
<td>.407†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4 (23.5-29.6)</td>
<td>25.8 (23.3-28.6)</td>
<td>.121*</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.0 (1.8-2.1)</td>
<td>2.0 (1.8-2.1)</td>
<td>.614*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>110 (52.9%)</td>
<td>229 (44.7%)</td>
<td>.047†</td>
</tr>
<tr>
<td>Recent AF or atrial flutter</td>
<td>10 (4.9%)</td>
<td>14 (2.8%)</td>
<td>.159</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>55.5 (45.0-70.0)</td>
<td>54.0 (43.5-65.0)</td>
<td>.067*</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure, mm Hg</td>
<td>32.0 (28.0-41.0)</td>
<td>30.0 (26.0-39.0)</td>
<td>.156*</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61.0 (57.0-65.0)</td>
<td>62.0 (58.0-66.0)</td>
<td>.038*</td>
</tr>
<tr>
<td>TV regurgitant systolic peak velocity, m/s</td>
<td>2.6 (2.4-2.9)</td>
<td>2.5 (2.3-2.8)</td>
<td>.049*</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>36.0 (33.0-39.0)</td>
<td>36.0 (33.0-39.0)</td>
<td>.060*</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>59.0 (55.0-62.0)</td>
<td>58.0 (55.0-62.0)</td>
<td>.452*</td>
</tr>
<tr>
<td>Postoperative AF</td>
<td>75 (36.1%)</td>
<td>125 (24.4%)</td>
<td>.002</td>
</tr>
</tbody>
</table>

LAVI, Left atrial end-systolic 2-dimensional volume index; BMI, body mass index; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; TV, tricuspid valve; LV, left ventricle. *Wilcoxon rank-sum test. †Chi-square test.

## TABLE E2. Fold-changes for individual predictors of left atrial end-systolic 2-dimensional volume index response in models using all available follow-up measurements or 6-month truncated follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model of all available follow-up</th>
<th>Model of 6-mo truncated follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative LAVI, mL/m²</td>
<td>65:43.8</td>
<td>71:47.5</td>
</tr>
<tr>
<td>0.10 mo</td>
<td>1.19 (1.16-1.23)</td>
<td>1.12 (1.09-1.14)</td>
</tr>
<tr>
<td>4.5 mo</td>
<td>1.16 (1.13-1.19)</td>
<td>1.04 (0.99-1.09)</td>
</tr>
<tr>
<td>39.2 mo</td>
<td>1.15 (1.10-1.21)</td>
<td>-</td>
</tr>
<tr>
<td>Time since surgery, mo</td>
<td>21.8:0.13</td>
<td>0.82 (0.78-0.86)</td>
</tr>
<tr>
<td>Age, y</td>
<td>68.6:51.8</td>
<td>1.13 (1.10-1.15)</td>
</tr>
<tr>
<td>Sex-female:male</td>
<td>0.97:1.05</td>
<td>1.01 (0.98-1.02)</td>
</tr>
<tr>
<td>28.6:23.3</td>
<td>1.00 (0.98-1.01)</td>
<td>1.00 (0.97-1.02)</td>
</tr>
<tr>
<td>AF/flutter yes: no</td>
<td>1.07:1.05</td>
<td>1.17 (1.01-1.29)</td>
</tr>
<tr>
<td>Hypertension yes: no</td>
<td>0.98:1.05</td>
<td>1.01 (0.98-1.05)</td>
</tr>
<tr>
<td>PA systolic pressure 39:26</td>
<td>0.95:1.01</td>
<td>0.98 (0.95-1.01)</td>
</tr>
<tr>
<td>LVESED 39:33</td>
<td>1.00:1.04</td>
<td>1.02 (1.00-1.04)</td>
</tr>
</tbody>
</table>

For continuous predictors, fold-changes are computed as the geometric mean predicted LAVI when the predictor is set to its 75th percentile divided by the geometric mean predicted LAVI when the predictor is set to its 25th percentile (actual values corresponding to these percentiles are shown to the right of the predictor label). Significant effects are bolded for emphasis. CI, Confidence interval; LAVI, left atrial end-systolic 2-dimensional volume index; df, degrees of freedom; BMI, body mass index; AF, atrial fibrillation; PA, pulmonary artery; LVESED, left ventricular end-systolic dimension. *The overall effect of the predictor was based on a composite test of its main effect and interaction terms. †The interaction effect of the predictor was evaluated by testing the interaction terms for significance, and described by fold-changes estimated for levels of the interacting factors.
TABLE E3. Relative effects of baseline left atrial end-systolic 2-dimensional volume index, age, and sex on risk of postoperative atrial fibrillation/flutter and long-term mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Outcome: AF complication OR (95% CI)</th>
<th>Test statistics</th>
<th>Outcome: Time to death Hazard ratio (95% CI)</th>
<th>Test statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative LAVI, mL/m² (66:44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age = 50 y, Sex = M</td>
<td>2.19 (1.19-4.04)</td>
<td>$P_{\text{overall}} = .030$, $P_{\text{interaction}} = .094$</td>
<td>2.35 (0.88-6.27)</td>
<td>$P_{\text{overall}} = .077$</td>
</tr>
<tr>
<td>Age = 50 y, Sex = F</td>
<td>2.47 (1.18-5.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age = 70 y, Sex = M</td>
<td>0.94 (0.69-1.27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age = 70 y, Sex = F</td>
<td>1.06 (0.60-1.87)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (69.1:52.7)</td>
<td><strong>2.34 (1.49-3.69)</strong></td>
<td>$P_{\text{overall}} &lt; .001$, $P_{\text{interaction}} = .163$</td>
<td><strong>3.94 (2.16-7.19)</strong></td>
<td>$P_{\text{overall}} &lt; .001$</td>
</tr>
<tr>
<td>Sex (female:male)</td>
<td>1.57 (0.75-3.31)</td>
<td>$P_{\text{overall}} = .448$, $P_{\text{interaction}} = .323$</td>
<td>0.64 (0.27-1.53)</td>
<td>$P_{\text{overall}} = .314$</td>
</tr>
</tbody>
</table>

Given the relatively high prevalence of postoperative AF complication, a logistic regression model was flexibly fitted to allow the splined effect of baseline LAVI to interact with age and sex, thereby allowing the shape of the LAVI effect to differ by these interacting factors. In contrast, because of constraints imposed by the limited number of deaths, the age and sex-adjusted effect of baseline LAVI on time to death was modeled in Cox regression without interactions and assuming a linear functional form of age. Results are shown as odds or hazard ratios, with 95% CIs, varying predictors over IQRs or data values. Significant effects are bolded for emphasis. AF, Atrial fibrillation; OR, odds ratio; CI, confidence interval; LAVI, left atrial end-systolic 2-dimensional volume index. *The overall effect of the predictor was based on a composite test of its main effect and interaction terms. †The interaction effect was evaluated by testing all interaction terms involving that predictor for significance; because the odds ratios in the table depend on the setting of the interacting factors, separate estimates for baseline LAVI are shown for some combinations of age and sex.