Title
Three-Dimensional Strain Reveals Regional Myocardial Dysfunction After Mitral Annuloplasty

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Author
McCabe, Melissa Dawn

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Three-Dimensional Strain Reveals Regional Myocardial Dysfunction
After Mitral Annuloplasty

A dissertation submitted in partial satisfaction of the
Requirements for the degree of Master of Science
in Clinical Research

by

Melissa Dawn McCabe

2016
ABSTRACT OF THE THESIS

Three-Dimensional Strain Reveals Regional Myocardial Dysfunction
After Mitral Annuloplasty

by

Melissa Dawn McCabe
Master of Science in Clinical Research
University of California, Los Angeles, 2016
Professor Elliot Landaw, Chair

Background: Mitral valve (MV) repair reduces morbidity and mortality in patients with severe mitral regurgitation (MR). Though postoperative left ventricular (LV) dysfunction has been recognized, regional changes in myocardial function accompanying MV repair have not been well described. Regional myocardial deformation can be quantified by myocardial strain analysis. We hypothesize that altered annular mechanics after MV repair will be associated with discrete changes in regional myocardial function as measured by three-dimensional (3D) myocardial strain.

Methods: A 3D transthoracic echocardiogram was performed preoperatively and 48-72 hours postoperatively in adult cardiac surgery patients (MV repair, n=48 and CABG, n=50). Global 3D area (GAS$_{3D}$), circumferential (GCS$_{3D}$), and longitudinal (GLS$_{3D}$) strain were measured simultaneously from a full volume dataset. Segmental 3D area (AS), circumferential (CS), and longitudinal (LS) strain were also measured.
**Results:** After MV repair, global myocardial strain was significantly reduced (GAS\textsubscript{3D}: -35\%, GCS\textsubscript{3D}: -38\%, GLS\textsubscript{3D}: -35\%, p<0.0001). However, the largest relative reductions in strain were seen regionally in the LV anterior (AS: -41\%, CS: -43\%, LS: -40\%, p<0.05), inferior (AS: -34\%, CS: -45\%, p<0.05), and apical (AS: -38\%, CS: -37\%, LS: -40\%, p<0.01) regions. MV repair was also associated with persistently greater reductions in LV anterior (AS: -41\% vs. -36\%, p=0.035) and inferior (-34\% vs. -18\%, p=0.005) regional strain as compared to CABG.

**Conclusions:** MV repair is associated with global and regional myocardial dysfunction. Annuloplasty alters mitral annular mechanics and is associated with reduced myocardial strain within the LV anterior and inferior regions, these regional changes contribute to postoperative LV dysfunction.
The dissertation of Melissa Dawn McCabe is approved.

Kimberly Howard-Quijano

Aman Mahajan

David Elashoff

Elliot Landaw, Committee Chair

University of California, Los Angeles

2016
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Acknowledgments

Thank you Dr. Aman Mahajan and the Department of Anesthesiology and Perioperative Medicine for supporting me in my pursuit of a Master of Science in Clinical Research. A special thanks to my committee members for their guidance and input.

With sincere gratitude, I would like to acknowledge Dr. Kimberly Howard-Quijano for her mentorship, Jennifer Scovotti for her diligent database management, and Einat Mazor for performing all echocardiograms.
Mitral regurgitation is the most prevalent valvular disease in the United States; when regurgitation is severe it is associated with heart failure, arrhythmia, and a 6% annual risk of mortality [1, 2]. Even though, incipient left ventricular dysfunction is prevalent amongst patients with severe mitral regurgitation, left ventricular (LV) ejection fraction may appear to be preserved as regurgitation increases preload and decreases afterload [3-6]. Mitral valve repair reduces morbidity and mortality, because decreased regurgitant flow promotes systemic cardiac output and improves heart failure symptoms [7]. Despite the benefits of surgical intervention, mitral valve repair has been shown to cause LV dysfunction by increasing afterload and altering the configuration of the mitral apparatus [8-10]. Although repair preserves function better than replacement, the ejection fraction (EF) may be reduced significantly after repair, even when the preoperative EF is normal [8, 11]. Persistent LV dysfunction after mitral valve repair has been observed in up to two-thirds of patients on long-term follow-up [12].

Myocardial strain is a sensitive, quantitative measure of myocardial deformation. Speckle-tracking echocardiography analyzes the natural acoustic markers (“speckles”) present in an echocardiographic image to measure myocardial strain, a quantification of the relative change in myofibril length throughout the cardiac cycle. These measures have been validated with sonomicrometry and magnetic resonance imaging and have been shown to accurately measure global and regional myocardial function [13-17]. Three-dimensional myocardial strain is a robust measure of complex myocardial deformation. Two-dimensional (2D) myocardial strain only tracks speckles moving within the imaging plane, while three-dimensional (3D) myocardial strain has the advantage of tracking speckles as they translocate through the imaging plane. Since myofibrils are discretely oriented throughout the left ventricular myocardium [18, 19], myocardial strain measures global and segmental myocardial deformation in the circumferential and longitudinal
directions, capturing deformation related to LV twist and apical to basal shortening. Area strain simultaneously assesses circumferential and longitudinal myocardial deformation (Figure 1).

Although global LV dysfunction is well recognized after mitral valve repair, changes in regional myocardial function associated with mitral annuloplasty have not been well described. Normally, the mitral apparatus is a dynamic structure, coordinating LV contraction and twist mechanics [20]. During systole, the saddle-shape of the mitral annulus is accentuated by folding along the intercommissural diameter (Figure 2), but mitral annuloplasty likely alters annular mechanics and restricts annular folding [9, 21, 22]. Identifying changes in regional myocardial deformation associated with altered annular mechanics provides insight to the mechanisms contributing to LV dysfunction after mitral valve (MV) repair. Therefore, the aim of this study was to examine changes in myocardial deformation associated with mitral valve repair using 3D speckle-tracking strain. We hypothesize that alteration of annular mechanics after mitral valve repair will be associated with discrete changes in regional myocardial deformation when measured by 3D speckle-tracking strain.

**METHODS**

After institutional review board approval and written informed consent, this prospective study included 98 adult cardiac surgery patients scheduled for elective mitral valve repair and annuloplasty (MVR, n=48) or coronary artery bypass grafting (CABG, n=50) with cardiopulmonary bypass between October 2011 and November 2015 at the Ronald Reagan UCLA Medical Center. Patients with cardiac arrhythmias (such as atrial fibrillation), history of congenital heart disease, inadequate imaging windows for transthoracic echocardiography, and patients scheduled for combined surgical interventions (such as aortic valve replacement and coronary bypass artery grafting) or emergent surgery were excluded.
Clinical Data Collection

Age, gender, body mass index, and NYHA class data were collected preoperatively. History of hypertension, hyperlipidemia, cerebrovascular accident, diabetes mellitus, and renal insufficiency was obtained from retrospective chart review. Cardiac catheterization reports were reviewed to evaluate for the presence of coronary artery disease; disease severity was based on angiographic assessment of the degree of stenosis. Aortic cross clamp times were obtained from intraoperative documentation and recorded in minutes.

Echocardiography

A 3D transthoracic echocardiogram was obtained preoperatively and 48-72 hours after surgical intervention, when patients were extubated and chest tubes were removed. All exams were acquired by the same experienced echocardiographer using GE Vivid E9 Dimension ultrasound system equipped with a four-dimensional, 1.7-3.3 MHz phased-array transducer (GE Vingmed, Horton, Norway). Three-dimensional images were obtained from the apical four chamber view in awake, spontaneously breathing patients during a four beat breath hold and acquired at a frame rate of 25-55 frames/sec. Images were optimized for speckle-tracking analysis by manually adjusting sector widths to optimize speckle quality; all images were stored for offline analysis. Left ventricular ejection fraction was measured from 3D volumetric analysis: end-diastolic and end-systolic frames were identified and endocardial contours were defined by semi-automated LV border tracking software and ejection fraction (EF_{3D}) was calculated from end-diastolic and end-systolic volumes.

3D Speckle-Tracking Myocardial Strain

Strain analysis was completed offline by one of three experienced, blinded echocardiographers using speckle-tracking software (EchoPac PC Clinical Workstation v.113, GE Vingmed Ultrasound, Horton, Norway). After identification of mitral annular and apical points in
end-diastolic and end-systolic frames, the software’s semi-automated border tracking algorithm automatically defined the myocardial contour and calculated myocardial strain. The integrity of automated tracking was confirmed manually; the region of interest was manually adjusted in 10% of images to optimize speckle-tracking. Global peak systolic 3D area (GAS$_{3D}$), circumferential (GCS$_{3D}$), and longitudinal (GLS$_{3D}$) strain were measured simultaneously from a full volume dataset. Segmental peak systolic 3D area (AS), circumferential (CS), and longitudinal (LS) strain were also measured from the same full volume dataset. A representative 3D LV area strain diagram is shown in Figure 3. Peak systolic area, circumferential, and longitudinal strain measures have negative values as they measure LV systolic shortening.

Statistical Analysis

Myocardial segments were divided into apical, anterior, anteroseptal, septal, inferior, posterior, and lateral regions by averaging the corresponding segments. Global and regional myocardial strain were reported as mean with standard deviation or mean change expressed as a percentage. Three-dimensional LV ejection fraction was reported as mean with standard deviation or mean change expressed as a percentage. Baseline 3D global and regional myocardial strain measures were compared between MV repair and CABG groups using an unpaired student’s t-test with a Benjamini-Hochberg corrected p-value (FDR 5%) to control for multiple comparisons [23, 24].

Changes in global and regional myocardial strain after MV repair and cardiopulmonary bypass were assessed after controlling for aortic cross clamp time. A mixed effects model was constructed for each global and regional measure and stratified by strain type (area, circumferential, and longitudinal). A corresponding model was also constructed for EF$_{3D}$. Fixed effects included perioperative time (preoperative vs. postoperative) and aortic cross clamp time (duration in minutes) with a subject random effect. The absolute magnitude of change was compared between regions using a mixed effects model. Fixed effects included myocardial region
and aortic cross clamp time (duration in minutes) with a random subject effect. All regional pairwise comparisons were assessed with a Benjamini-Hochberg corrected p-value (FDR 5%) to control for multiple comparisons.

Changes in global and regional myocardial strain after surgical intervention and cardiopulmonary bypass were compared between MV Repair and CABG groups after controlling for aortic cross clamp time. A final mixed effects model was constructed for each myocardial region and stratified by strain type (area, circumferential, and longitudinal). Fixed effects included procedure (MV repair vs. CABG), perioperative time (preoperative vs. postoperative), aortic cross clamp time (duration in minutes), and a procedure by perioperative time interaction term with a subject random effect. Since the analysis accounted for multiple comparisons, p-values <0.05 were considered statistically significant. All statistical analysis was completed using JMP Pro v12.0 (SAS, Cary, North Carolina).

Reproducibility Analysis

The intraobserver and interobserver reproducibility of 3D myocardial strain measures was evaluated in 20% of patients. Patients were selected at random. Intraobserver reproducibility was assessed by blinding the same echocardiographer to the previous results and repeating the analysis of each study more than two weeks from the date of original analysis. Interobserver reproducibility was evaluated by one of the three expert echocardiographers, who had not previously analyzed the studies. Each echocardiographer was blinded to the previous results and analysis was repeated for each study. Intraobserver and interobserver agreement was measured using intraclass correlation coefficients (ICC) with 95% confidence intervals (CI).
RESULTS

Demographics

Age at enrollment was 61 ± 12 (mean ± SD) years in the MV repair group and 64 ± 11 years in the CABG group with a predominately male population (MV repair: 63% vs. CABG: 84%). Past medical history was notable for hypertension (MV repair: 38% vs. CABG: 70%), hyperlipidemia (32% vs. 70%), and diabetes mellitus (2% vs. 43%) as shown in Table 1. Every CABG patient had high-grade coronary artery stenosis, 98% had stenosis in the left anterior descending artery.

Baseline 3D Global and Regional Myocardial Function

Baseline global strain was significantly higher in the MV repair group as compared to the CABG group (GAS$_{3D}$: -30.2 ± 7.3 vs. -24.0 ± 6.2, GCS$_{3D}$: 19.3 ± 4.1 vs. -15.7 ± 3.9, GLS$_{3D}$: -15.5 ± 5.4 vs. -11.8 ± 4.1, p<0.002). However, MR was associated with regional heterogeneity, with significantly higher preoperative myocardial strain in the LV anterior (AS: -31.1 ± 13.9 vs. -24.0 ± 6.2, CS: -21.5 ± 8.1 vs. -17.2 ± 7.5, LS: -15.1 ± 5.4 vs -11.8 ± 4.1, p<0.05) and inferior (AS: -28.9 ± 12.0 vs. -22.5 ± 9.7, CS: -19.1 ± 7.4 vs. -13.9 ± 6.5, p<0.001) regions as compared to CABG. As expected, EF$_{3D}$ was also significantly greater in the MV repair group at baseline (55 ± 8 vs. 46 ± 9, p<0.001).

Changes in 3D Global and Regional 3D Myocardial Function After MV Repair

After controlling for aortic cross clamp time, a significant reduction in global strain was observed following MV repair (GAS$_{3D}$: -30.2 ± 7.3 vs. -19.6 ± 7.5, GCS$_{3D}$: -19.3 ± 4.1 vs. -12.0 ± 5.3, GLS$_{3D}$: -15.5 ± 5.4 vs. -10.1 ± 4.3, p<0.001). However, these changes were not distributed equally across the LV myocardium. Instead, a discrete pattern involving the anterior, inferior, and apical regions was observed. The greatest relative reductions in both area and circumferential
strain were seen in the LV anterior, inferior, and apical regions (Figure 4A and 4B). Longitudinal strain followed a similar pattern, with the largest relative reductions observed in the LV anterior and apical regions (Figure 4C). EF\textsubscript{3D} was also significantly reduced, as anticipated after MV repair (55 ± 8 vs. 42 ± 12, p<0.001).

*Comparison of Changes in 3D Global and Regional Myocardial Function Between MV Repair and CABG*

To differentiate changes in myocardial function associated with MV repair from myocardial dysfunction after cardiopulmonary bypass, we compared postoperative changes in global and regional myocardial function between MV repair and CABG while controlling for aortic cross clamp time. Even though global myocardial strain was decreased after CABG, the reduction was significantly greater after MV repair than CABG (Table 2). Myocardial strain was not reduced homogenously throughout the LV myocardium following MV repair; when compared to CABG, a discrete pattern was observed with larger reductions in the LV anterior and inferior myocardium. Greater decreases in area strain were observed in the anterior (-41% vs. -36%, p<0.05) and inferior (-34% vs. -19% p<0.005) regions following MV repair as compared to CABG. Likewise, similarly significant decreases in circumferential strain were seen in the anterior and inferior regions, while there were no regional differences in longitudinal strain measures (Table 2). In accordance with greater decreases in myocardial strain, MV repair was associated with a significantly larger reduction in postoperative EF\textsubscript{3D} (-24% vs -6%, p<0.001).

*Reproducibility Analysis*

Intraobserver reproducibility was strong for preoperative 3D myocardial strain [ICC (95% CI), AS: 0.92 (0.85 - 0.96), CS 0.88 (0.77 – 0.94), and LS: 0.94 (0.89 – 0.97)]. Interobserver reproducibility was also strong [AS: 0.92 (0.83-0.96), CS: 0.84 (0.69 – 0.92), and LS 0.90 (0.81 – 0.95)]. No difference was observed between preoperative and postoperative ICC.
DISCUSSION

The results of this study show that mitral valve repair is associated with an acute reduction in regional myocardial function. While global myocardial strain was found to be reduced after MV repair, the greatest relative reductions were seen in the LV anterior, inferior, and apical regions. Furthermore, comparison of postoperative changes between MV repair and CABG, demonstrated significantly larger decreases in LV anterior and inferior regional myocardial strain following MV repair. Although, apical function has been shown to decline after cardiac surgery and cardiopulmonary bypass, we have demonstrated a new association between changes in LV anterior and inferior myocardial function and mitral valve repair. These regional changes in myocardial function likely reflect increased annular rigidity and altered annular mechanics after mitral annuloplasty.

In this study, patients with mitral regurgitation were observed to have a normal preoperative EF$_{3D}$, but decreased GLS$_{3D}$. As mitral regurgitation produces a high preload, low afterload state EF may be normal even when incipient dysfunction is present [3-6]. Conversely, GAS$_{3D}$ and GCS$_{3D}$ were consistent with reference ranges for healthy controls [25]. With chronic MR, long-axis dysfunction has been shown to precede onset of short-axis dysfunction [26], consistent with our observation of reduced preoperative longitudinal strain, but normal circumferential strain. Preoperative 2D global longitudinal strain has also been shown to predict postoperative myocardial dysfunction, morbidity, and mortality; baseline measures <19% predict long-term postoperative LV dysfunction [27-29].

Regionally, MR was associated with increased preoperative myocardial strain in the LV anterior and inferior regions. Perhaps a reflection of the distorted annular anatomy and mechanics associated with chronic MR [30]. The saddle-shaped mitral annulus is composed of a fibrous ring; the fibrous structure is most substantial at the aortomitral continuity where the annulus arises from continuations of the right and left trigones. Otherwise, the fibrous structure of the annulus is relatively intangible, with the LV myocardium composing the remainder of the mitral annulus [31].
As the fibrous structure is sparse, the mitral annulus is exceptionally flexible. The trough of the mitral saddle lies along the intercommissural diameter that connects the anterolateral and posteromedial commissures. In systole, folding along the intercommissural diameter accentuates the saddle-shape of the mitral annulus resulting in an increase in annular height and a decrease in the anteroposterior diameter of the mitral valve (Figure 2) [32]. The anterior and inferior regions of the myocardium coincide with the intercommissural hinge (Figure 5), the observed differences in preoperative regional strain may be related to distorted annular mechanics in the setting of chronic mitral regurgitation [33].

After MV repair, global myocardial strain was reduced significantly, however, regional changes were not distributed uniformly throughout the LV myocardium. Rather distinct regional differences emerged; the greatest reductions in postoperative myocardial strain were observed within the LV anterior, inferior, and apical regions following MV repair. To account for myocardial dysfunction associated with cardiopulmonary bypass, changes in regional myocardial function were compared between MV repair and CABG groups while controlling for aortic cross clamp time. Left ventricular anterior and inferior regional area and circumferential strain were found to be reduced significantly more following MV repair than CABG. While apical depression has been previously demonstrated following cardiac surgery and cardiopulmonary bypass [34], decreased myocardial strain within the LV anterior and inferior regions is likely a distinct effect of mitral annuloplasty.

Chronic mitral regurgitation is associated with impaired long-axis function, whereas mitral annuloplasty predominately affects short-axis function as evidenced by decreased GCS$_{3D}$ and discrete reductions in regional circumferential strain. Annuloplasty compounds annular dysfunction, as annuloplasty does not restore normal annular mechanics and may exacerbate annular flattening [10, 35]. Although rigid annuloplasty devices partially restore annular shape and flexible devices better preserve annular mechanics, flexibility has not been shown to impact overall survival, MR recurrence, or reoperation rates [9, 21, 22]. This may be a reflection of
insufficient flexibility within the physiologic force range of the mitral apparatus. Overall, annuloplasty devices have not been shown to have a favorable effect on annular anatomy and annular mechanics [10]. As the mitral apparatus coordinates global and regional myocardial function, restriction of annular mechanics produces global myocardial dysfunction and discrete changes in regional myocardial function.

**Limitations**

This study investigated regional changes in myocardial function following MV repair with annuloplasty in patients with isolated degenerative mitral regurgitation, as such, these conclusions may not apply to functional mitral regurgitation. Selection of an appropriate control group was imperative, as it was important to distinguish changes in myocardial function associated with mitral valve annuloplasty as opposed to cardiac surgery and cardiopulmonary bypass. Cardiac surgery patients scheduled for isolated CABG or aortic valve replacement (AVR) were carefully evaluated as potential control groups, as both utilize cardiopulmonary bypass and cardioplegia without cardiotomy. CABG is advantageous because myocardial and valvular structure are not modified; whereas, AVR may affect the mitral annulus. The aortic and mitral valves share fibrous structure at the aortomitral continuity and introduction a rigid prosthetic valve may have untoward effects on mitral annular mechanics. Therefore, CABG patients were selected as a control group for this study. However, this may be a limitation as CABG patients were predisposed to global and regional myocardial dysfunction.

**CONCLUSION**

This study demonstrates that global and regional myocardial strain were significantly decreased after mitral valve repair. Regionally, the greatest relative reductions were seen in the LV anterior and inferior. The observed relationship between LV anterior and inferior myocardial dysfunction and mitral valve repair implies that these changes are related to altered mitral annular
mechanics after annuloplasty. These findings not only demonstrate the impact of regional myocardial dysfunction on global ventricular function, but they also have implications for annuloplasty design. As the dynamic mitral apparatus coordinates LV twist as well as global and regional myocardial deformation [8, 20, 36], annuloplasty design should aim to optimize annular mechanics. Our findings suggest that enhancing annuloplasty flexibility at the intercommissural hinge to the physiologic force range would improve mitral annular mechanics, regional myocardial deformation, and possibly global and regional LV function after MV repair.
Figures and Tables

**Figure 1. Three-Dimensional Myocardial Strain.** Peak systolic strain can be measured in the longitudinal and circumferential directions, while area strain assesses both circumferential and longitudinal changes simultaneously.

**Figure 2. Mitral Annular Mechanics.** During systole the saddle-shape of the mitral annulus is accentuated by folding along the intercommissural (IC) hinge with a resultant increase in annular height and a decrease in the anteroposterior (AP) diameter. The entire plane of the annulus is also translated towards the left ventricular apex.
Figure 3. Area Strain Diagram. Representative three-dimensional peak systolic area strain A. preoperative and B. postoperative following mitral valve repair. The white line represents left ventricular global area strain and each yellow line represents the area strain curve of an individual myocardial segment.
<table>
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<th>Demographics</th>
<th>MV Repair (n=48)</th>
<th>CABG (n=50)</th>
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<tr>
<td>Age (Years)</td>
<td>61 ± 12</td>
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<tr>
<td>Men</td>
<td>30 (62.5%)</td>
<td>41 (82%)</td>
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<td>BMI (kg/m²)</td>
<td>24 ± 4</td>
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<td>Renal Disease</td>
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<td>10 (20%)</td>
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Table 1. Patient demographics. Cardiac surgery patients with severe mitral regurgitation had fewer comorbidities than cardiac surgery patients without mitral regurgitation undergoing CABG. Among the 48 patients with mitral regurgitation, three patients (6%) were not evaluated for coronary artery disease. Continuous variables expressed as mean ± standard deviation.
Figure 4. Reduction in Regional Strain Following Mitral Valve Repair. Global and regional strain was reduced after mitral valve repair. A. area, B. circumferential, and C. longitudinal Strain. Strain measures are displayed as mean change expressed as a percentage, bolded values = AS p<0.001, CS p<0.005, LS p<0.05. Regionally, a greater magnitude of reduction was observed in the LV anterior, inferior, and apical regions (shaded, p<0.05). The central region is the LV apex. Shaded region is significantly different than *all unshaded regions, †all unshaded regions except the anteroseptal region, ‡posterior and lateral regions, §anteroseptal, septal, inferior, and posterior regions.
Comparison of Global and Regional Myocardial Strain Changes Between MVR and CABG

<table>
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Table 2. Comparison of Regional Myocardial Strain Changes Between Mitral Valve (MV) Repair and Coronary Artery Bypass Grafting (CABG). Global myocardial strain was reduced significantly more after MV repair as compared to CABG. Regionally, area and circumferential strain were reduced significantly more in the LV anterior and inferior regions following MV repair.

Figure 5. Relationship Between Segmental Anatomy and Mitral Annuloplasty Band Placement. The left ventricular anterior and inferior segments are positioned along the intercommissural (IC) hinge where folding occurs during systole.
CHAPTER 2: STATISTICAL APPENDIX

The mitral valve (MV) repair group had a unique barrier to enrollment. Mitral regurgitation (MR) is associated with an increased incidence of atrial arrhythmia; arrhythmias such as atrial fibrillation precludes myocardial strain analysis by speckle-tracking echocardiography. The speckle-tracking software assesses peak systolic strain by synchronizing measurements with the electrocardiogram, the accuracy of synchronization depends on the regularity of the R-R interval. Atrial fibrillation produces a variable R-R interval and myocardial strain measures cannot be reliably synchronized with the electrocardiogram. As such, this excluded a considerable proportion of the patients with mitral regurgitation presenting for mitral valve surgery.

However, the main challenge of this study was selection of a control group, as controls must be selected from the cardiac surgery population. Preferable controls include elective cardiac surgical procedures requiring cardiopulmonary bypass, cardioplegia, and cardiotomy only for bypass cannulation. The best control group would be patients scheduled for elective aortic surgery, however, few patients have isolated aortic surgery, and a sizable control group was not available. Coronary artery bypass grafting (CABG) and aortic valve replacement (AVR) also require cardiopulmonary bypass with limited cardiotomy, but each group introduces new covariates.

The aortic valve shares its fibrous structure with the mitral valve; AVR alters this aortomitral continuity and may have untoward effects on mitral annular mechanics. Severe aortic stenosis, the most common indication for AVR, can be associated with incipient myocardial dysfunction. Accordingly, measures of global myocardial strain may be depressed with chronic aortic stenosis. Incipient myocardial dysfunction is also prevalent with severe mitral regurgitation, but the influence of AVR on the aortomitral continuity may obscure the effect of mitral annuloplasty on annular mechanics. In contrast, CABG does not modify myocardial or valvular structure. Although, coronary artery disease does impact global and regional myocardial function. Cardioplegia is delivered via the coronary vasculature, and coronary stenosis may also impair
delivery of cardioplegia during cardiopulmonary bypass rendering the myocardium more susceptible to injury during aortic cross clamping. Despite these limitations, CABG patients were selected as the control group.

The primary outcomes in this study were changes in global and regional myocardial strain and volumetric ejection fraction after MV repair. A histogram of the absolute difference between preoperative and postoperative measures was plotted for volumetric ejection fraction and for each strain type and region. Representative plots are shown in Appendix Figure 1. A normally distributed continuous fit line was constructed for each histogram plot and the goodness of fit was estimated with the Shapiro-Wilk W test. All measures were normally distributed and analysis was completed with parametric statistics.

Global and regional myocardial strain were reported as means with standard deviation or mean change and expressed as a percentage. As area, circumferential, and longitudinal strain measure systolic shortening, these myocardial strain measures have a negative value. Although the statistical analysis was completed using the raw myocardial strain measures, mean changes were reported as percentages in accordance with reporting conventions in the myocardial strain literature. For example, if preoperative myocardial strain was -35 and postoperative myocardial strain was -17, the reduction in myocardial strain would be calculated as (preoperative strain – postoperative strain)/preoperative strain * 100 = [-17 - (-35)]/(-35) * 100 and reported as -50%.

An exploratory analysis was performed to assess global and segmental changes for each type of myocardial strain using a CABG control group. Since the primary outcomes were continuous and normally distributed, within group change in myocardial strain (preoperative vs. postoperative) were evaluated with paired t-tests. Global and segmental myocardial strain were significantly reduced after MV repair and CABG. These changes were compared between MV repair and CABG groups using a mixed effects model. A mixed effects model was selected to accommodate correlated measures while accounting for subject heterogeneity. The primary aim of this study was to distinguish the effect of MV repair on global and regional myocardial function.
Therefore, it was important to control for subject heterogeneity as well as the effects of cardiac pulmonary bypass. The two most important clinical factors influencing the effects of cardiac pulmonary bypass on the myocardium are cardioplegia and the duration of aortic cross clamping. The impact of the type of annuloplasty device was also considered. After a base model was constructed, cardioplegia and annuloplasty model terms were evaluated using a manual forward stepwise approach. Aortic cross clamp time was not evaluated in the exploratory analysis, however, it was included in the manuscript models as the duration of myocardial ischemia has paramount clinical importance.

A base mixed effects model was constructed for each global and segmental myocardial strain measure and stratified by strain type. Fixed effects included procedure (MV repair vs. CABG), perioperative time (preoperative vs. postoperative), and a procedure by time interaction term with a subject random effect. The procedure by time interaction term was used to determine if there were global or segmental differences in myocardial strain between the MV repair and CABG groups, global and segmental myocardial strain were reduced significantly more after MV repair as compared to CABG.

Next, the influence of cardioplegia on postoperative myocardial strain was assessed. Every cardioplegia solution contains potassium chloride to arrest the heart, but each solution has adjuvants with unique contributions to myocardial protection. These adjuvants include buffers to regulate pH, free radical scavengers or calcium chelators to limit reperfusion injury, and antiarrhythmics. To evaluate the influence of cardioplegia type on myocardial strain, a cardioplegia term was added to the model. Fixed effects included procedure, perioperative time, cardioplegia type (THAM vs. BiCarb vs. DelNido), and a perioperative time by procedure interaction term with a random subject effect. Adding cardioplegia type to the model, did not significantly influence the perioperative time by procedure interaction term, as cardioplegia type did not have a meaningful effect on the primary end point it was not included in the final model.
The effect of annuloplasty band type was also evaluated. Each annuloplasty device differs in shape and flexibility (Appendix Table 1), to evaluate the influence of different annuloplasty devices on myocardial strain, an annuloplasty term was added to the mixed effects model. Fixed effects included procedure (MVR vs. CABG), perioperative time (preoperative vs. postoperative), annuloplasty device (Appendix Table 1), a procedure by time interaction, an annuloplasty device by time interaction. The type of annuloplasty device did not have a significant effect on global myocardial strain and the effect on segmental myocardial strain was at the threshold of false discovery. Consequently, annuloplasty band type was not included in the final model. This is consistent with mitral annuloplasty literature; irrespective of individual device characteristics, mitral annuloplasty devices do not have a favorable effect on mitral annular anatomy or mitral annular mechanics.

In this exploratory analysis, we found that MV repair and annuloplasty significantly decreased myocardial strain in most myocardial segments. To determine which segments were most affected by annuloplasty, the magnitude of change was compared between myocardial segments within the MV group. Since three-dimensional strain analysis divides the myocardium into seventeen segments, there are seventeen segmental measurements for each strain type. To compare the relative magnitude of change between myocardial segments, 136 pairwise comparisons would be required per procedure for each type of strain. After correction for multiple hypothesis testing, meaningful results might be obscured. To alleviate the burden of multiple hypothesis testing, the segmental analysis approach was converted to a regional analysis. Myocardial segments were divided into apical, anterior, anteroseptal, septal, inferior, posterior, and lateral regions by averaging the corresponding segments.

Accordingly, the final exploratory analysis included two models to evaluate within and between group changes in myocardial strain. A mixed effects model was constructed to evaluate changes in myocardial strain within each group. The model was stratified by myocardial strain type and fixed effects included myocardial region, perioperative time (preoperative vs.
postoperative), and a myocardial region by time interaction term with a subject random effect. For myocardial regions with a significant myocardial region by time interaction, all pairwise comparisons were analyzed to determine which regions had the largest magnitude change.

To compare changes in myocardial strain after MV repair to changes after CABG, a second mixed effects model was constructed for each myocardial region and strain type. Fixed effects included procedure (MVR vs. CABG), perioperative time (preoperative vs. postoperative), and a procedure by time interaction term with a subject random effect. To determine which myocardial regions MV repair affected differently than CABG, all pairwise comparisons were assessed for myocardial regions with a significant procedure by time interaction term.

The exploratory analysis demonstrated that global and regional myocardial strain measures were decreased for all strain types after MV repair and CABG. After MV repair, the greatest relative reduction in myocardial strain was seen in the anterior, inferior, and apical segments. Whereas after CABG, the greatest relative reduction in myocardial strain was seen in the anterior, anteroseptal, and apical regions (Appendix Figures 2-4) consistent with the predominance of high-grade stenosis within the left anterior descending artery. Global myocardial strain was decreased significantly more after MV repair as compared to CABG for all strain types. Regionally, the anterior and inferior regions were reduced significantly more after MV repair as compared to CABG (Appendix Table 2).

The analysis used in the manuscript controlled for aortic cross clamp time. As discussed previously, aortic cross clamp time is one of the most important clinical factors determining the effects of cardiopulmonary bypass. When the aorta is clamped the myocardium is ischemic, although cardioplegia provides myocardial protection during this time, the myocardium remains susceptible to injury. However, the aortic cross clamp time was not significant in any of the models, nonetheless it was included in the final analysis given the clinical importance of myocardial ischemia during cardiopulmonary bypass.

The analysis used in the manuscript also addressed multiple hypothesis testing. A total of
8 pairwise comparisons were used to assess differences in preoperative global and regional myocardial strain between the MV repair and CABG groups. However, 21 pairwise comparisons were needed to evaluate the magnitude of change between myocardial segments following MV repair. Given the number of comparisons required in the analysis, controlling for the familywise error rate with a Bonferroni correction or Tukey's HSD is overly conservative. Instead, multiple hypothesis testing was accounted for by controlling for the false discovery rate. The Benjamini-Hochberg procedure for adjusted p-values was selected as it is less restrictive than the familywise error corrections. The false discovery rate was set at 5% to maintain a reasonably conservative type I error rate.

The results of the final manuscript and exploratory analyses were similar. Global and segmental myocardial strain were found to be significantly reduced following MV repair. Regionally, the greatest relative reduction was observed in the LV anterior, inferior, and apical regions following MV repair. A representative example of the results of the mixed effects model evaluating myocardial strain after MV repair is shown in Appendix Figure 5. When compared to CABG, myocardial strain within the LV anterior and inferior regions was also found to be reduced significantly more following MV repair than CABG. While apical dysfunction has been shown to occur after cardiac surgery and cardiopulmonary, the changes in the anterior and inferior regions are characteristic of mitral valve repair and annuloplasty.

In a post hoc analysis the correlation between myocardial strain and EF$_{3D}$ was examined. Myocardial strain has previously been shown to correlate with ejection fraction. We evaluated the correlation between the absolute magnitude of change in EF$_{3D}$ and global myocardial strain (GAS$_{3D}$, GCS$_{3D}$, and GLS$_{3D}$) using Pearson correlation coefficients. The correlation between EF$_{3D}$ and the myocardial regions with the greatest absolute magnitude of change after MV repair were also evaluated. Changes in global myocardial strain (GAS$_{3D}$, GCS$_{3D}$, and GLS$_{3D}$) correlated with changes in EF$_{3D}$. LV apical AS, CS, and LS changes also correlated with changes in EF$_{3D}$. However, changes in AS and CS, but not LS, within the LV anterior and inferior regions correlated
with changes in $\text{EF}_\text{3D}$ (Appendix Table 3), suggesting that mitral annuloplasty has a greater impact on short-axis myocardial function. These correlations were not included in the final analysis because myocardial strain is a superior measure of myocardial deformation and it has independent predictive value for postoperative left ventricular function, morbidity, and mortality following cardiac surgery.
Histogram Plots of Absolute Myocardial Strain and EF₃D Differences

A. 3D Global Circumferential Strain

B. 3D Area Strain: Anterior Region

C. EF₃D

**Figure 1.** Representative normal quantile plots for the absolute difference in myocardial strain and EF₃D. All measures followed a normal distribution. A. Global 3D Circumferential Strain: W=0.96, p=0.1. B. 3D Area Strain: Anterior Region: W=0.99, p=0.8. C. EF₃D: W=0.96, p=0.1.
Annuloplasty Device Characteristics

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<th>Anterior Flexibility</th>
<th>Posterior Flexibility</th>
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*Table 1. Annuloplasty devices vary in shape and flexibility.*

**Figure 2A. Area Strain After MVR.** Area strain was significantly decreased globally (-35%, \(p<0.0001\)) and regionally \((p<0.01)\). The magnitude of reduction was significantly greater in the shaded regions as compared to the non-shaded regions \((p<0.05)\).

Values are percent reductions. Bolded regions were significantly reduced after MVR.

*Inferior region not significantly different from anteroseptal region.

**Figure 2B. Area Strain After CABG.** Area strain was significantly reduced globally (-28%, \(p<0.0001\)) and in the the anterior, anteroseptal, inferior, and apical regions \((p<0.01)\). The magnitude of reduction was significantly greater in the shaded regions as compared to the non-shaded regions \((p<0.05)\).

Bolded regions were significantly reduced after CABG.

*Anteroseptal region not significantly different than inferior region.
Figure 3A. Circumferential Strain After MVR. Global circumferential strain was significantly decreased (−38%, \( p<0.0001 \)). Regionally, only the posterior region was not significantly reduced (\( p<0.05 \)). The magnitude of change was significantly greater in the shaded regions as compared to the lateral, posterior, and septal regions (\( p<0.05 \)). \(^{\text{a}}\)Apical region was not significantly different than the septal region.

Figure 3B. Circumferential Strain After CABG. Global circumferential strain was significantly decreased (−30%, \( p<0.0001 \)). Regionally, only the septal and posterior segments were not significantly reduced (\( p<0.05 \)). The magnitude of change was significantly greater in the shaded regions as compared to the lateral and posterior regions.

Figure 4A. Longitudinal Strain After MVR. Longitudinal strain was significantly decreased globally (−35%, \( p<0.0001 \)) and the anterior, inferior, posterior, lateral, and apical regions were also significantly reduced (\( p<0.05 \)). The magnitude of change was significantly greater in the shaded regions as compared to the non-shaded regions (\( p<0.05 \)).

Figure 4B. Longitudinal Strain After CABG. Longitudinal strain was significantly reduced globally (−27%, \( p<0.0001 \)), only the anterior and apical regions were significantly reduced (\( p<0.05 \)). The largest magnitude reduction was observed in the apex (\( p<0.001 \)).
Comparison of Global and Regional Myocardial Strain Changes Between MVR and CABG

<table>
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<td>CABG</td>
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Table 2. Comparison of Global and Regional Myocardial Strain Changes Between MVR and CABG. Values are percent reduction. Global strain decreased more after MVR than after CABG for all strain types. The anterior and inferior regions were reduced more by MVR than CABG for area, circumferential and radial strain. *p<0.05, **p<0.001

Figure 5. Evaluation of Myocardial Strain After Mitral Valve Repair. Model results are shown for area strain in the LV anterior region. After controlling for aortic cross clamp time, area strain was significantly reduced in the LV anterior region following MV repair. Time 2= perioperative time (preoperative vs. postoperative).
<table>
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<td>0.50**</td>
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Table 3. Pearson’s correlation between changes in myocardial strain and EF<sub>3D</sub>. Changes in EF<sub>3D</sub> are correlated with changes in GAS<sub>3D</sub>, GCS<sub>3D</sub>, and GLS<sub>3D</sub>. Changes in apical AS, CS, and LS were also correlated with changes in EF<sub>3D</sub>. Only changes in AS and CS within the anterior and inferior regions were correlated with changes in EF<sub>3D</sub>. *p<0.05, **p<0.001
REFERENCES


