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Isolated Effect of Geometry on Mitral Valve Function for In-Silico Model Development

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Abstract

Computational models for the heart's mitral valve (MV) exhibit several uncertainties which may be reduced by further developing these models using ground-truth data sets. The present study generated a ground-truth data set by quantifying the effects of isolated mitral annular flattening, symmetric annular dilatation, symmetric papillary muscle displacement, and asymmetric papillary muscle displacement on leaflet coaptation, mitral regurgitation (MR), and anterior leaflet strain. MVs were mounted in an *in vitro* left heart simulator and tested under pulsatile hemodynamics. Mitral leaflet coaptation length, coaptation depth, tenting area, MR volume, MR jet direction, and anterior leaflet strain in the radial and circumferential directions were successfully quantified for increasing levels of geometric distortion. From these data, increasing levels of isolated papillary muscle displacement resulted in the greatest mean change in coaptation depth (70% increase), tenting area (150% increase), and radial leaflet strain (37% increase) while annular dilatation resulted in the largest mean change in coaptation length (50% decrease) and regurgitation volume (134% increase). Regurgitant jets were centrally located for symmetric annular dilatation and symmetric papillary muscle displacement. Asymmetric papillary muscle displacement resulted in asymmetrically directed jets. Peak changes in anterior leaflet strain in the circumferential direction were smaller and exhibited non-significant differences across the tested conditions. When used together, this ground-truth data may be used to parametrically evaluate and develop modeling assumptions for both the MV leaflets and subvalvular apparatus. This novel data may improve MV computational models and provide a platform for the development of future surgical planning tools.

Keywords

Mitral Valve; Computational Modeling; In-Vitro Simulation; Functional Mitral Regurgitation; Surgical Planning; Heart Valve Disease

1. Introduction

The heart's mitral valve (MV) is a complex structure whose competence relies on the precise interaction of the mitral annulus, leaflets, chordae tendineae, and papillary muscles (Bolling et al. 2012). In the setting of left ventricular dysfunction, the geometric relationship between these structures can be grossly altered, leading to incomplete leaflet closure and functional mitral regurgitation (FMR) (Borger et al. 2006). Today, FMR is a significant clinical burden with suboptimal long-term survival (Borger et al. 2006; Trichon et al. 2003). While a number of surgical procedures exist for restoring mitral competence, heated debate remains for which procedure may be best for the widely varying MV geometries within the FMR population (Braun et al. 2012).

Matching the best FMR surgical procedure to a given patient MV geometry may soon be possible with *in-silico* MV models. These models hold significant potential for preoperative surgical planning, assessing repair complexity, and accelerating training for surgical techniques. These models began as idealized mitral leaflets and have grown to incorporate *in vivo* tissue architecture, anisotropic nonlinear material properties, structural representation of the subvalvular apparatus, and the left ventricle (Burlina et al. 2013; Ionasec et al. 2010; Lau et al. 2010; Mansi et al. 2011; Pouch et al. 2012; Rim et al. 2013; Stevanella et al. 2011; Votta et al. 2009; Wenk et al. 2010; Wang et al. 2013). While significant technological advances have been made, many challenges remain for these virtual MV models.

A significant challenge for MV models is recreating the complex architecture of the chordae tendineae. Current standard-of-care echocardiography is unable to spatially resolve the detailed chordal architecture (Wang et al. 2013). As a consequence; computational models have relied on anatomical studies to guide the modeling of idealized chordal distributions. The resulting modeled chordae can vary greatly from native valves and significantly impacts subsequent simulations of FMR or repair (Mansi et al. 2011; Wang et al. 2013). These uncertainties are compounded by the choice of tissue mechanical properties whose values can differ both within and between experimental investigations (Rabbah et al. 2013). These challenges have resulted in a wide-range of finite element modeling results and have limited confidence for routine use of *in silico* models in clinical practice.

One step towards addressing these challenges is the use of *in vitro* ground-truth data sets to further develop and evaluate computational MV models. While numerous *in vivo* and *in vitro* studies that describe valvular geometry in FMR exist (Vergnat et al. 2011; Lee et al. 2009; Tibayan et al. 2003; He et al. 2003; Nielsen et al. 1999), no studies comprehensively evaluate the isolated effects of MV geometry on leaflet coaptation, mitral regurgitation, and tissue mechanics. Quantitatively comparing between ground-truth data and computational MV models can provide the ability to optimize chordal architecture, material properties, and mechanical measures across a range of conditions and MV geometries. This may not only improve modeling accuracy but will additionally increase confidence for preoperative clinical decision making. To this end, the aim of this study was to generate an *in vitro* ground-truth data set to quantify the isolated effects of mitral annular flattening, symmetric annular dilatation, symmetric papillary muscle displacement, and asymmetric papillary muscle displacement on leaflet coaptation, anterior leaflet strain, and mitral regurgitation.

2. Material and Methods

2.1. In Vitro Mitral Valve Simulator

In vitro simulation of mitral valve function was conducted in the extensively studied Georgia Tech Left Heart Simulator (He et al. 2005; He et al. 2003; Jimenez et al. 2007; Jimenez et al. 2003; Nielsen et al. 1999). This closed-loop simulator allows for precise control of annular and subvalvular MV geometry at physiological left heart hemodynamic conditions (Figure 1). Excised ovine MVs were sutured to an adjustable annulus, designed to allow dilatation, and to create an annular saddle shape. The annulus could symmetrically dilate from a 6.5 cm² D-shaped orifice to 13 cm² and flatten from an annular-height-to-commissural-width ratio of 20%. PM positions were controlled by two mechanically adjustable positioning rods capable of adjustment to varying positions in the apical, lateral, and posterior directions at a resolution of ± 0.25 mm. Transmitral flow was measured using an electromagnetic probe (calibrated accuracy 5 mL/min) (Carolina Medical Electronics, FM501D, East Bend, NC) mounted upstream of the atrium. Transmitral pressure was monitored with transducers (calibrated accuracy ± 1 mmHg) mounted in the atrium and ventricle (Validyne DC-40, Northridge, CA).

2.2. Dual Camera Stereo-Photogrammetry

Dual camera stereo-photogrammetry has been successfully used in previous studies to measure *in vitro* MV leaflet strains (He et al. 2005; Jimenez et al. 2007). In this method, tissue dye (Thermo Scientific, Waltham, MA) was used to mark the A2 cusp with a 3 $\times$ 3 rectangular dot array (Figure 2). Each leaflet marker was separated by approximately 1.5 mm and was 0.5 mm in diameter. These fiduciary markers were tracked throughout the cardiac cycle to calculate the strain of the central portion of the anterior mitral leaflet at peak systolic leaflet closure.

During experimentation, two synchronized high-speed cameras (Basler 510K; Basler Corp, Exton, PA) with Nikon macro lenses (105mm, f2.8; Nikon, Melville, NY) were used to image the rectangular marker array throughout the cardiac cycle at 250 Hz. For image calibration, a 10 mm steel cube was positioned within the volume occupied by the MV leaflets such that each high-speed camera could image 7 of the cube's corners. These calibration images were digitized within a custom MATLAB program (Mathworks, Natick, MA).

Using the cube calibration images and those recorded during each experiment, direct linear transformation was used to calculate the 4D coordinates of each leaflet marker (Marzan et al. 1975). These coordinates were exported into a custom MATLAB program utilizing biquintic finite element interpolation to fit a surface to the recorded marker coordinates. Generated surfaces were used to determine the peak radial and circumferential strains of the anterior leaflet at peak systolic closure. Based on the magnification of the high-speed cameras, pixel size, and calibration cube, the 3D leaflet marker coordinates was determined to an accuracy of 68 μ m. This accuracy is in good agreement with previous investigations (He et al. 2005; Jimenez et al. 2007).

3. Experimental

Fresh ovine hearts were obtained and MVs were excised (N=9) preserving their annular and subvalvular anatomy. MVs with an anterior leaflet height of 18–19 mm, type I or II PMs, and with all leaflet chordae inserting directly into each PM were selected for experimentation (Carpentier et al. 2010). Selected MVs were sutured to the simulator's annulus using a Ford interlocking stitch. For control conditions, the annulus was set to an area of 6.5 cm² and annular-height-to-commissural-width-ratio of 20%. This configuration resulted in a saddle height of approximately 8 mm. During valve suturing, care was taken to place each suture just above the valve's natural hinge and not through the leaflet tissue. Additionally, normal annular-leaflet geometric relationships were respected, with the anterior leaflet occupying 1/3 of the annular circumference and commissures aligned in the 2 and 10 o'clock positions.

After annular suturing, each PM was attached to the PM control rods. Each PM was carefully positioned and fine-tuned to establish the control MV geometry as previously described.¹³ Transmitral pulsatile conditions were simulated (5.0 L/min cardiac output, 70 beats/min, 120 mmHg systolic transmitral pressure). Mitral coaptation was then inspected via echocardiography such that the anterior leaflet spanned approximately 2/3rds of the A2-P2 diameter and the mitral valves characteristic "smiley face" could be viewed. If the control valve geometry conditions were successfully achieved, transmitral hemodynamics, 3D echocardiography (Philips iE-33 xMatrix Echocardiography System, Phillips, Andover, MA), and dual camera high-speed images of the valve were acquired (Figure 1(b)).

Annular flattening and dilatation are valvular lesions that contribute to valvular incompetence in FMR. These geometric MV distortions that are associated with FMR were then tested for their independent contributions to leaflet malcoaptation, regurgitation, and anterior leaflet strain. Isolated annular flattening was simulated by flattening the annulus from a 20% to 0% annular-height-to-commissural-width-ratio (8 mm to 0 mm annular saddle height). For isolated symmetric annular dilatation, the valve annulus was held in its flattened configuration and symmetrically dilated to 200% (13 cm²) of the control annular area in 20% (1.3 cm²) intervals. To simulate isolated symmetric PM displacement, the annulus was returned to its control configuration and 20% AHCWR. Each PM was simultaneously displaced 2 mm, then 4 mm, and then 6 mm in the apical, anterior-posterior, and lateral directions. Asymmetric PM displacement was additionally simulated by holding one PM in the control position and displacing the opposite PM 2 mm, 4 mm, and 6 mm in the apical, anterior-posterior, and lateral directions. At each experimental condition, A2-P2 leaflet coaptation length, coaptation depth, tenting area, MR volume, MR jet direction, and anterior leaflet strain were quantified (Figure 2).

4. Data and Statistical Analyses

Anterior leaflet strain was analyzed using previously described methods (He et al. 2005; Jimenez et al. 2007). Similar to previous studies, the referential leaflet strain configuration corresponded with the minimum LV pressure. All *in vitro* hemodynamic data was processed offline within a custom MATLAB program and averaged over 10 consecutive cardiac

cycles. Mitral regurgitation was calculated as the total retrograde volume. Echocardiography data were analyzed using Phillips QLab (v.7.0; Philips Healthcare; Andover, MA).

Measured endpoints were checked for normality using the Anderson-Darling test. A general linear model using each valve as a random factor was used to investigate the effect of the valve and geometric MV distortion on each of the measured endpoints. A Dunnett's post hoc test was used to determine if significant differences in each metric existed between the baseline condition and elevated levels of geometric distortion. A paired-samples t-test was additionally used to determine if a significant difference existed between a flat and saddled annulus for each of the measured end points. All statistical analyses were completed using Minitab 16 (Minitab Inc, State College, PA). All end points are expressed as a mean and 95% confidence interval.

5. Results

5.1. Isolated Mitral Annular Flattening and Symmetric Annular Dilatation

Isolated annular flattening was successfully simulated. Reducing the mitral annulus from a 20% to a 0% AHCWR (flat configuration) resulted in a significant decrease in coaptation depth ($p<0.01$) and radial leaflet strain ($p<0.05$) (Table 1 and 2). Conversely, no significant differences were observed in coaptation length, tenting area, MR volume, and circumferential anterior leaflet strain. From the flat annular configuration, isolated symmetric annular dilatation was successfully simulated (Table 1). For increasing levels of dilatation, tenting area significantly increased ($p<0.001$) while coaptation depth significantly decreased ($p<0.001$). These changes were accompanied by significant decreases in coaptation length ($p<0.001$) and increases in MR volume ($p<0.001$). The majority of Doppler observed regurgitation jets were centrally located (7 of the 9 MVs) (Figure 3(a)) with the remaining jets observed closer to either commissure (2 of the 9 MVs). Beyond changes in leaflet geometry and regurgitation, leaflet strain in the radial direction was observed to significantly increase with increasing levels of dilatation ($p<0.001$). Conversely, no significant differences in circumferential leaflet strain were observed across increasing levels of dilatation.

5.2. Isolated Symmetric Papillary Muscle Displacement

Among all of the tested MV geometric distortions, symmetric PM displacement resulted in the greatest change in A2-P2 leaflet coaptation (Table 2). The downward and outward displacement of the PMs displaced the coaptation zone apically resulting in significant decreases in coaptation length ($p<0.001$), significant increases in coaptation depth ($p<0.001$), and significant increases in tenting area ($p<0.001$). The resulting MR volumes were observed to significantly increase with PM displacement but were lower in comparison to those observed with isolated annular dilatation. Radial anterior leaflet strain was found to increase with PM distortion ($p<0.005$) with each step in displacement creating greater strain. Similar to isolated annular dilatation, no significant differences were observed for circumferential leaflet strain between increasing levels of PM displacement.

5.3. Isolated Asymmetric Anterolateral and Posteromedial Papillary Muscle Displacement

Asymmetric papillary muscle displacement was observed to result in directional tethering of the leaflets towards the displaced papillary muscle. At the septal-lateral annular diameter; echocardiography revealed significant decreases in coaptation length and significant increases in coaptation depth and tenting area for isolated posteromedial and isolated anterolateral PM displacement (Table 3 and 4). MR volumes were observed to increase with PM displacement and reached mean values that were similar in magnitude to those which were achieved with symmetric PM displacement. MR jets observed with Doppler echocardiography were asymmetric and consistently originated from the tethered leaflet region (Figure 3(b)). The observed MR volumes were similar to those achieved with symmetric PM displacement (Table 2). Asymmetric PM displacement resulted in significant increases in radial leaflet strain; however, no significant differences were found for circumferential strain in either of the isolated PM displacements.

5.4. Correlation of Valvular Distortions with Measured Endpoints

To assess the relative effect of each isolated valvular distortion on the measured endpoints, a least-squares equation was generated for the mean values of each endpoint that significantly differed across the tested conditions (Table 5). These equations provide a means to evaluate the relative effect of each geometric distortion on the measured endpoints. Moreover, this eases the comparison of the observed trends with the results and trends of future computational MV simulations.

6. Discussion

Significant advances in computational MV models have been demonstrated in the past decade. These accomplishments have been enhanced by clinical imaging modalities, from which the gross MV geometry and dynamics can be extracted. At present, several challenges have led to modeling uncertainties which may be improved by further developing these models with ground-truth data sets. The continuous improvement of these models is essential for reaching the ultimate goal of patient-specific surgical/interventional planning for patients suffering from FMR.

While numerous *in vitro* studies have described FMR MV geometry and function, several challenges exist with using prior data to develop *in-silico* MV models. The first challenge is that no prior studies provide simultaneous measures of MV geometry, leaflet coaptation, MR, and leaflet strain (Vergnat et al. 2011; Lee et al. 2009; Tibayan et al. 2003; He et al. 2003; Nielsen et al. 1999). Our presentation of these data in combination reduces the modeling uncertainty that can be attributed to implementing intra-study differences in MV size, species, methods of measurement, and transvalvular hemodynamics (Rabbah et al. 2013). A second challenge with developing MV models is the lack of available data that isolates the effect of a given geometric distortion on valvular function (He et al. 2003; Nielsen et al. 1999). While FMR patients present with combined annular and subvalvular distortions, assessing the effects of isolated, step-wise geometric valve distortions provides an ability to parametrically evaluate MV models and fine-tune model assumptions.

The isolated, step-wise geometric distortions presented herein can be used to improve in-silico modeling of the chordae tendineae. Computational models can assume a given chordal geometry and test the effect of isolated geometric distortions under similar transmitral hemodynamics. The computationally observed values or trends (Table 1–5) for leaflet closure can be compared to the results herein to parametrically evaluate how the chosen chordal geometry influences coaptation. Based on these differences, the assumed chordal geometry can be iteratively adjusted to more accurately achieve the expected coaptation over a wide range of geometric distortions. With a more finely tuned chordal architecture, higher confidence will exist for subsequent simulations of progressive disease or surgical repairs.

Another route by which the present study can aid computational models is to provide greater insight for how altered valvular geometry translates abnormal loading of the leaflet tissue. The results presented herein provide simultaneous measures of leaflet coaptation and anterior leaflet strain at varying valvular geometries. Computational models therefore can use these data to optimize the combinations of material models, healthy valve mechanical properties, and MV modeling to improve the accuracy of the models and confidence in the simulated mechanical findings. Such evaluations can contribute to the computational design and testing of MV repairs that avoid excessive loading of the leaflet tissue, mitral annulus, and surgical sutures (Gillinov et al. 2001; Jimenez et al. 2007; Rausch et al. 2012; Votta et al. 2009; Wenk et al. 2010).

The choice and use of material and mechanical properties for in-silico MV models remains dependent on values derived from freshly excised tissues and inverse finite element modeling within large-animal models (Rabbah et al. 2013). While the majority of *in vitro* studies have been completed with porcine tissue, the present study utilized ovine mitral valves. Sheep MVs exhibit similar annular areas and leaflet lengths who's tethering with left ventricular ischemia produces well-defined models of human MV incompetence (Carpentier et al. 2010; Dixon et al. 2009; Llaneras et al. 1994; Rausch et al. 2011). Ovine mitral leaflets are however thinner than those found in humans, which may contribute with active leaflet contraction, to the larger in-vivo elastic modulus of ovine mitral leaflets (Krishnamurthy et al. 2009; Grande-Allen et al. 2005). Until methods are developed to safely determine the material and mechanical properties of patient-specific MVs, the use of ovine or porcine data to supplement computational models of human MV function must be carefully weighed for their application and effect in computationally simulations.

For this study, values and trends in coaptation are in good agreement with prior *in vitro* studies. While different sized MVs and geometric distortions were previously evaluated, the present study's data compares well with reported ranges in coaptation length (1.0–7.5 mm vs. 0–16 mm), coaptation depth (1.6–6.1 mm vs. 5.6–15.9 mm), and tenting area (0.05–0.50 cm² vs. 0–1.6 cm²) (He et al. 1997; Nielsen et al. 1999; He et al. 2003). Regurgitation was additionally similar to previous *in vitro* studies (12–55 mL/beat vs. 0–53 mL/beat) (He et al. 1997; He et al. 2003; Croft et al. 2007). In comparison to large-animal models, similar agreement is observed in coaptation and regurgitation in both ovine and porcine studies (Siefert et al. 2013; Nielsen et al. 2005). When comparing these data to FMR patient cohorts, approximate ranges in patient coaptation length (0.3–10 mm), coaptation depth (3–

14 mm), and tenting area (0.2–4.2 cm²) are additionally similar to those observed within this study (Braun et al. 2008; Lee et al. 2009).

While anterior leaflet strain in the circumferential direction is in good agreement with previous studies, strains in the radial direction were elevated in comparison to previous healthy MV conditions within *in vitro* and large animal models (Rabbah et al. 2013). In this study we utilized ovine valves with anterior leaflet heights that were smaller than previously utilized porcine MVs (He et al. 2003, Sacks et al. 2002). Due to the smaller size of the ovine anterior leaflets, the tissue dye grid occupied a larger portion of the anterior leaflet whose upper row of markers were in close proximity to the annular hinge. As a result, we believe additional strain from the leaflet annular-suture line was introduced and ultimately increased the peak radial strain magnitude. This study's radial strains are additionally larger than those measured in large-animal models. In addition to the aforementioned reasons, these discrepancies are attributed to our chosen reference configuration (Rausch et al. 2011) and absence of active leaflet contraction as observed in-vivo (Amini et al. 2012). While radial strains were elevated, the observed trends are analogous to those observed in previous studies of FMR.

Despite the advantages of the present study, there are limitations associated with both the described apparatus and the methods. The described MV simulator can recreate the systolic geometric configuration of the mitral valve, but at present does not incorporate the intricate mechanics associated with valvular-ventricular interactions. Their inclusion would likely increase the accuracy of mimicking dynamic *in vivo* valve function whose effects should be isolated in future studies. The measurement of leaflet strain was limited to the central anterior leaflet and could be improved by simultaneous measures of the entire anterior and posterior leaflet surfaces. The evaluation of leaflet coaptation was limited to the A2-P2 annular plane.

7. Conclusions

The present study provides for the first time a novel comprehensive data set for the development of computational mitral valve models. It is the first study to parametrically evaluate the effect of isolated geometric MV distortions on MV coaptation, MR, and leaflet mechanics. These data may be used for MV models and optimizing assumptions for the subvalvular apparatus. The anterior leaflet strain measurements provide additional data to evaluate the assumptions of material properties and mechanical response of the complex mitral leaflet tissue. Combined, these results provide a ground-truth data set for the future development of MV computational models and a platform for the development of future surgical planning tools.

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Figure 1.

A. Schematic representation of the left-heart simulator with components and flow direction identified; B. 2D slices of a 3D echocardiography image of a mitral valve mounted within the simulator during systolic closure and diastolic opening.

Figure 2.

A. Schematic representation of the surgeon's view of the mitral valve with the A2-P2 echocardiography measurements of leaflet coaptation identified; B. Direct linear transformation is used to calculate the radial and circumferential anterior leaflet strain using two high-speed cameras tracking nine fiduciary leaflet markers.

Figure 3.

Representative central and skewed mitral regurgitation jets occurring from A. Symmetric annular dilatation at 160% of the control annular area and B. Asymmetric posteromedial papillary muscle displacement of 6 mm.

Table 1

	Symmetric Annular Dilatation					
	100%	120%	140%	160%	180%	200%
A2-P2 CL [mm]	3.7(3.0–3.9)	3.1(2.6–3.6) ‡	2.6(2.2–3.1) ‡	2.3(1.7–2.9) ‡	2.1(1.5–2.8) ‡	1.8(1.4–2.4) ‡
A2-P2 CD [mm]	3.0(2.6–3.5)	2.7(2.2–3.1)	2.6(2.2–3.0) *	2.5(2.0–2.9) †	2.4(1.8–3.1) **	2.1(1.5–2.7) ‡
A2-P2 TA [cm ²]	0.19(0.13–0.25)	0.22(0.15–0.28)	0.25(0.20–0.31) †	0.28(0.23–0.33) ‡	0.30(0.23–0.38) ‡	0.32(0.25–0.40) ‡
MRV [mL]	15.7(13.7–17.7)	17.3(14.3–20.2)	19.3(16.1–22.5)	23.4(19.3–27.5) †	28.4(34.1–22.7) ‡	36.7(28.0–45.4) ‡
A2 RLS [mm mm]	0.46(0.33–0.61)	0.54(0.42–0.65)	0.58(0.45–0.70) †	0.59(0.47–0.71) ‡	0.61(0.48–0.74) ‡	0.62(0.50–0.74) ‡
A2 CLS [mm mm]	0.13(0.07–0.18)	0.14(0.09–0.19)	0.13(0.07–0.19)	0.14(0.09–0.20)	0.14(0.07–0.20)	0.14(0.07–0.22)

Effect of symmetric annular dilatation on A2-P2 coaptation length (CL), coaptation depth (CD), tenting area (TA), mitral regurgitation volume (MRV), A2 radial leaflet strain (RLS), and A2 circumferential leaflet strain (CLS) expressed as a mean and 95% confidence interval in parentheses with significance reported to the 100% dilatation condition within each metric denoted as

* p<0.05,

† p<0.01,

** p<0.005, and

‡ p<0.001.

Table 2

	Symmetric Papillary Muscle Displacement			
	0 mm	2mm	4 mm	6 mm
A2-P2 CL [mm]	3.6 (3.3–4.0)	2.9 (2.4–3.3) [‡]	2.5 (2.1–2.9) [‡]	2.3 (2.0–2.6) [‡]
A2-P2 CD [mm]	2.5(1.9–3.0)	3.2 (2.7–3.8) [‡]	3.8 (3.5–4.2) [‡]	4.3 (4.0–4.6) [‡]
A2-P2 TA [cm ²]	0.15(0.11–0.20)	0.24(0.19–0.29) **	0.32 (0.28–0.37) [‡]	0.38 (0.32–0.43) [‡]
MRV[mL]	15.4(13.5–17.2)	16.3 (14.0–18.6)	17.4 (14.5–20.3)	20.6(15.8–25.4) [‡]
A2RLS [mm/mm]	0.41 (0.32–0.49)	0.49 (0.36–0.63) *	0.51 (0.39–0.63) [‡]	0.53 (0.41–0.64) **
A2 CLS [mm/mm]	0.12(0.05–0.20)	0.12(0.05–0.20)	0.14(0.06–0.22)	0.15(0.07–0.23)

Effect of symmetric papillary muscle displacement on A2-P2 coaptation length (CL), coaptation depth (CD), tenting area (TA), mitral regurgitation volume (MRV), A2 radial leaflet strain (RLS), and A2 circumferential leaflet strain (CLS) expressed as a mean and 95% confidence interval in parentheses with significance reported to the 100% dilatation condition within each metric denoted as

*
p<0.05,

[‡]
p<0.01,

**
p<0.005, and

[‡]
p<0.001.

Table 3

	Asynlmetric Anterolateral Papillary Muscle Displacement			
	0 mm	2 mm	4 mm	6 mm
A2-P2 CL [mm]	3.6(3.3–4.0)	3.0(2.5–3.5) **	2.4 (2.1–2.8) ‡	1.9(1.7–2.2) ‡
A2-P2 CD [mm]	2.5(1.9–3.0)	2.7 (2.2–3.2)	3.1(2.7–3.6) **	3.5(3.1–3.8) ‡
A2-P2 TA [cm ²]	0.15(0.11–0.20)	0.20(0.15–0.26) *	0.22 (0.17–0.27) †	0.27 (0.23–0.31) ‡
MRV[mL]	15.4(13.5–17.2)	15.5(12.8–18.2)	17.9(15.8–19.9) *	19.6(18.3–21.00) ‡
A2 RLS [mm/mm]	0.41 (0.32–0.49)	0.52 (0.39–0.66) **	0.54 (0.40–0.68) **	0.55 (0.41–0.68) ‡
A2 CLS [mm/mm]	0.12(0.05–0.20)	0.11(0.04–0.18)	0.10(0.04–0.16)	0.10(0.04–0.16)

Effect of asymmetric anterolateral papillary muscle displacement on A2-P2 coaptation length (CL), coaptation depth (CD), tenting area (TA), mitral regurgitation volume (MRV), A2 radial leaflet strain (RLS), and A2 circumferential leaflet strain (CLS) expressed as a mean and 95% confidence interval in parentheses with significance reported to the 0 mm condition within each metric denoted as

*
p<0.05,

†
p<0.01,

**
p<0.005, and

‡
p<0.001.

Table 4

	Asymmetric Posteromedial Papillary Muscle Displacement			
	0 mm	2 mm	4 mm	6 mm
A2-P2 CL [mm]	3.6 (3.3–4.0)	3.1 (2.5–3.7) **	2.4(1.8–3.0) ‡	2.3 (1.7–2.9) ‡
A2-P2 CD [mm]	2.5 (1.9–3.0)	2.6 (2.0–3.2)	3.0 (2.4–3.7) *	3.4 (2.8–3.9) ‡
A2-P2 TA [cm ²]	0.15(0.11–0.20)	0.20(0.14–0.27) *	0.25 (0.18–0.32) ‡	0.28 (0.21–0.35) ‡
MRV [mL]	15.4(13.5–17.2)	17.2(13.9–20.1)	19.7(15.4–24.1) *	23.3 (16.7–29.8) ‡
A2 RLS [mm/mm]	0.41 (0.32–0.49)	0.48 (0.39–0.57) ‡	0.51(0.43–0.60) ‡	0.56 (0.44–0.67) ‡
A2 CLS [mm/mm]	0.12(0.05–0.20)	0.14(0.03–0.25)	0.14(0.03–0.26)	0.13(0.03–0.24)

Effect of asymmetric posteromedial papillary muscle displacement on A2-P2 coaptation length (CL), coaptation depth (CD), tenting area (TA), mitral regurgitation volume (MRV), A2 radial leaflet strain (RLS), and A2 circumferential leaflet strain (CLS) expressed as a mean and 95% confidence interval in parentheses with significance reported to the 0 mm condition within each metric denoted as

*
p<0.05,

‡
p<0.01,

**
p<0.005, and

‡
p<0.001.

Table 5

Line-of-best-fit for the mean values of A2-P2 coaptation length (CL), coaptation depth (CD), tenting area (TA), mitral regurgitation volume (MR), and anterior leaflet radial leaflet strain (RS) for the tested mitral valvular geometric perturbations.

	Line of Best Fit for Mean Values	R ² Coefficient
Symmetric Annular Dilatation (SD)	CL [mm] = $1E-4 (SD [\%])^2 - 0.054 (SD [\%]) + 7.9$	0.995
	CD [mm] = $-8E-3 (SD [\%]) + 3.7$	0.949
	TA [cm ²] = $1.3E-3 (SD [\%]) + 0.063$	0.991
	MR [mL] = $2E-3 (SD [\%])^2 - 0.406(SD [\%]) + 36.3$	0.997
	RS [mm mm] = $-2E-5 (SD [\%])^2 + 0.007(SD [\%]) + 0.06$	0.973
Symmetric Papillary Muscle Displacement (SPM)	CL [mm] = $3.1E-2 (SPM [mm])^2 - 0.40 (SPM [mm]) + 3.59$	0.999
	CD [mm] = $0.30 (SPM [mm]) + 2.55$	0.995
	TA [cm ²] = $0.39 (SPM [mm]) + 0.16$	0.992
	MR [mL] = $0.14 (SPM [mm])^2 - 0.03 (SPM [mm]) + 15.49$	0.988
	RS [mm mm] = $-3.7E-3 (SPM [mm])^2 - 0.04 (SPM [mm]) + 0.41$	0.978
Asymmetric Anterolateral Papillary Muscle Displacement (ALPM)	CL [mm] = $6.2E-2 (ALPM [mm])^2 - 0.32 (ALPM [mm]) + 3.61$	0.999
	CD [mm] = $0.17 (ALPM [mm]) + 2.44$	0.979
	TA [cm ²] = $1.9E-2 (ALPM [mm]) + 0.15$	0.975
	MR [mL] = $0.1 (ALPM [mm])^2 + 0.15 (ALPM [mm]) + 15.25$	0.963
	RS [mm mm] = $-6.2E-3 (ALPM [mm])^2 + 0.06 (ALPM [mm]) + 0.41$	0.974
Asymmetric Posteromedial Papillary Muscle Displacement (PMPM)	CL [mm] = $2.5E-2 (PMPM [mm])^2 - 0.38 (PMPM [mm]) + 3.64$	0.972
	CD [mm] = $0.15 (PMPM [mm]) + 2.41$	0.947
	TA [cm ²] = $2.2E-2 (PMPM [mm]) + 0.15$	0.988
	MR [mL] = $0.1 (PMPM [mm])^2 + 0.63 (PMPM [mm]) + 15.42$	0.999
	RS [mm mm] = $-1.2E-3 (PMPM [mm])^2 + 0.03 (PMPM [mm]) + 0.41$	0.985