Mitral valve annular downsizing forces: Implications for annuloplasty device development

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Objective: Mitral valve repair with annulus downsizing is a popular surgical procedure for functional mitral regurgitation. We investigated the effects of externally applied downsizing on the observed in-plane forces and valvular dimensions.

Methods: Five animals were included in an acute porcine study. Three traction sutures were anchored at the right fibrous trigone (T) and suspended across the annulus for externalization at the P1, P2, and P3 annular segments. The annulus was downsized with the sutures in controlled increments while measuring the tension force in the sutures. Downsizing percentages ranged from a 2% to 32% reduction of the T-P distances. Sonomicrometry was used to measure the resulting valvular dimensions.

Results: No difference in force was found between the P1, P2, and P3 segments across all levels of downsizing. The peak forces at 32% downsizing were 1.2 ± 0.9 N, 1.5 ± 1.0 N, and 0.8 ± 0.2 N for the T-P1, T-P2, and T-P3 segments, respectively. The maximum total suture forces in the mitral plane during downsizing increased from 0.12 ± 0.03 N to 3.5 ± 1.3 N ($P < .005$). Sonomicrometry showed a decrease in the systolic thickening of the posterior myocardial wall at the annular level with annular downsizing (0%-32%) from 5 ± 3 mm to 1 ± 1 mm ($P < .05$).

Conclusions: Segmental mitral valve annulus downsizing increased in-plane traction suture forces and has a significant influence on the in-plane biomechanics. These results have implications for device design in terms of mechanical strength requirements and can be used to supplement boundary conditions for computational left heart models. (J Thorac Cardiovasc Surg 2014;148:83-9)

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Downsizing the mitral valve (MV) annulus with annuloplasty is a popular surgical procedure to increase leaflet coaptation and restore valvular competency, especially in functional mitral regurgitation. A wide selection of devices exists in many different sizes, shapes, and with varying flexibility properties. The optimal device often is debated because some argue that one annuloplasty ring works for all and others advocate the use of dedicated etiology-specific devices or rings.[1,2] New innovative devices exist that use external approaches to reshape the MV annulus. These include percutaneous transvenous mitral annuloplasty, percutaneous septal-lateral diameter shortening, and ventricular approaches using external restraint devices.[2-5]

Detailed 3-dimensional dynamic morphology of the MV with and without annuloplasty is well documented.[6-11] However, the observed largest deformation in the MV apparatus does not necessarily match the location of the largest forces,[12] which is an important concept because images can be deceiving. Hence, components defining a framework for the free body diagram of the MV apparatus to map the complete force balance of the valve has been reported with in vitro and in vivo measurements of the annular in-plane forces,[13-16] annular out-of-plane forces,[12] chordal forces,[17] and papillary muscle forces.[18,19]

To fully understand the impact of a repair technique using an annuloplasty device to downsize the MV annulus, it is important to investigate the force in the device as the downsizing progresses. This information is relevant also to understand how downsizing affects the rest of the MV apparatus.[20] The hypothesis for this study was that annuloplasty devices used for downsizing the MV annulus experience a force load that is dependent on dynamic annular motion, myocardial contractility, and the amount of downsizing applied. We aimed to investigate this by using externally

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Abbreviations and Acronyms
LV = left ventricular
MV = mitral valve

manipulated traction sutures that measure the effects of continuous downsizing on valve dimensions and observed suture forces. This information has implications on device design in terms of mechanical strength requirements as well as mathematic modeling and simulations of the MV.

MATERIALS AND METHODS

Surgical Protocol

Five mixed Yorkshire and Danish Landrace pigs with a mean body weight of 80 kg were used in an acute experimental set-up. All animals were bred under standard laboratory conditions and the experiment complied with the guidelines from the Danish Inspectorate of Animal Experimentation, which also approved the current study. Animals were sedated with an intramuscular injection of midazolam (0.5 mg/kg) before transport. Upon arrival to the laboratory, the animals received 30 mg intravenous etomidate and then were intubated and coupled to a ventilator. Continuous analgesia was maintained during the experiment with intravenous fentanyl (10 mg/kg/h) and propofol (4 mg/kg/h). Muscle relaxation was obtained by infusion of 12 mg/h rocuronium. The pigs were euthanized with an injection of 50 mL 20% pentobarbital directly into the left ventricle at the end of each experiment. Details of the animal model have been described previously.[17]

Transducer Implantation and Exteriorization

After establishment of cardiopulmonary bypass and cardiac arrest, the MV was exposed through a left atriotomy and a small incision was made in the apex of the heart for sonomicrometry crystal localization. Three polytetrafluoroethylene (Gore-Tex 2-0 traction sutures; W. L. Gore & Associates, Inc, Flagstaff, Ariz) were anchored at the right trigone (T) and suspended across the MV annulus and exteriorized through the posterior annulus at the 3 lateral scallops: the P1 scallop, the center of the posterior annulus (P2 scallop), and the P3 scallop. The right (posterior) trigone was chosen because of the high concentration of fibrous tissue suitable for anchoring as well as exteriorization direction of the sutures through the posterior annulus, allowing the sutures to exit the heart on the anterior side. The epicardial points at which the suture was exteriorized from the posterior annulus segments were chosen because of their easily identifiable and evenly distributed locations. Miniature strain gauge–based force transducers[21] were attached to each suture and suspended at a central location in the annulus (Figure 1).

The transducers were calibrated before and after experiments to ensure measurement accuracy. The mean value of the 2 calibration constants was used. The difference between the calibration constants before and after experiments was consistently less than 10%, equaling a maximum error from calibration within the range of forces observed in this study of ±0.2 N. Use of the average minimized the risk of difference in calibration, translating into significant differences in measured values. Based on previous experience from measurements in the MV apparatus, the transducers were calibrated in a force range of 0 to 5 N in steps of 1 N.[18,19,21,22] This type of transducer has been used successfully in previous in vivo studies, showing high accuracy, resolution, and frequency response for intracardiac measurements.[17,21]

The externalized end of each suture was stabilized with a rubber pad and fed through a flexible channel of spherical pearls (Figure 1). This enabled the downsizing length to be manipulated along the direction of each suture during measurements by using a customized caliper device.[22] At each level of annular downsizing, the force in individual sutures could be measured.

To assess the cyclic 3-dimensional geometry of the mitral annulus, 7 sonomicrometry crystals were placed in the annulus and 1 crystal was placed in the apex as illustrated in Figure 1 (Sonometrics Corporation, London, Ontario, Canada).[12] The crystals placed around the annulus were used to verify the actual downsizing measured as the decrease in the trans-annular T-P distance. This was compared with the reduction of total length of the suture extending from the right trigone, across the annulus, and through the ventricular wall (Figure 1). The apex crystal was placed to define a reference direction in case 3-dimensional analysis was necessary. Before closure of the cardiac cavities, pressure catheters were placed in the left ventricle and left atrium to monitor left ventricular and left atrial pressure, respectively.

Downsizing and Force Measurements

Signals from the strain gauges were monitored continuously during the experiments. Baseline was defined as the point at which the sutures were no longer slack and was determined by tightening the sutures until a clear, periodic force signal variation was observed.[22] Subsequently, the sutures were tightened incrementally on a beating heart, with an interval of 2 mm at a time. All sutures were tightened at the same interval before the distance and force measurements were recorded.

Sonomicrometry was used to quantify myocardial thickness at each level of T-P downsizing. Because the suture length was kept constant during each measurement, systolic thickening of the myocardial wall was measured as the difference between the maximum and minimum distance between the T and P1, P2, and P3 crystals.

Data Acquisition

A data recording was made simultaneously from strain gauges, pressure catheters, and sonomicrometry crystals for each interval of suture tightening. Strain gauge bridge completion, supply current, and data acquisition was performed with dedicated hardware (compact DAQ model 9172 and NI-9237; National Instruments, Austin, Tex). Left ventricular and left atrial pressures were acquired with Mikro-Tip pressure catheters (SPC-350MR; Millar Instruments, Inc, Houston, Tex) and digitalized by a dedicated hardware module (compact DAQ model 9215; National Instruments). Strain and pressure data were recorded with custom-built virtual instrumentation software, using graphic programming (LabVIEW version 8.2; National Instruments). Sonomicrometry data were recorded on a system consisting of an external ultrasound transceiver and a dedicated PC with a digital circuit board installed (Sonometrics Corporation).

Data Analysis

Midsystole and mid-diastole were defined as center points between maximum rate of increase and decrease of left ventricular (LV) pressure (dP/dt). An ensemble average of 10 heart cycles was used to find the maximum and minimum values of the absolute force for each measurement. The total force from the trigone to the P1, P2, and P3 segments (T-P1, T-P2, and T-P3) was found by adding the forces from the individual segments. Cyclic traction forces were found as the variation within each heart cycle and were calculated as the difference between the absolute maximum and the absolute minimum force.

Sonomicrometry distance measurements of the trans-annular diameters were used to determine the effect of the external tightening on the annulus diameter and compression of the myocardial tissue.

Force magnitudes were reported as a function of annulus downsizing percentage relative to the baseline trans-annular diameter for each subject. This percentage was calculated by using a conversion function correlating the suture tightening and sonomicrometry data (see the Results section for more detail).

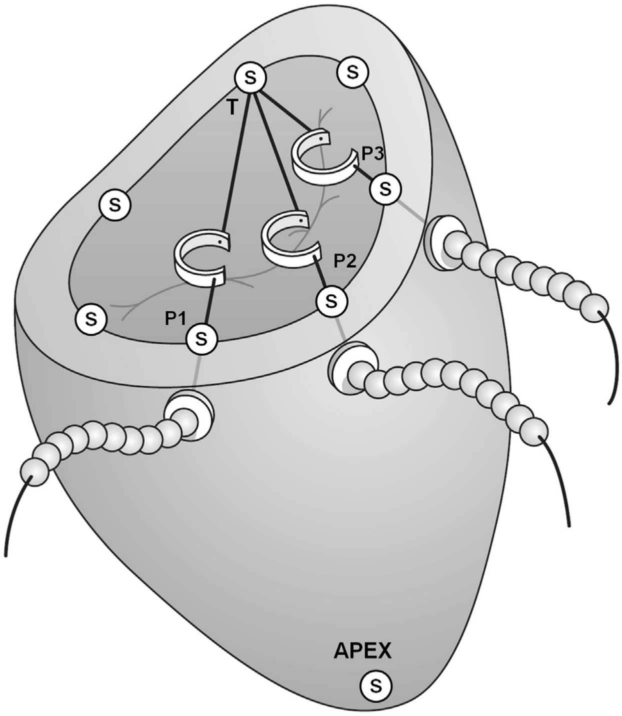

FIGURE 1. Experimental set-up. Miniature force transducers were suspended across the MV annulus on traction sutures. The externalized end of each suture was stabilized at the epicardium with a rubber pad and fed through a flexible channel of spherical pearls. The sutures are anchored at the right trigone (*T*) and externalized at the posterior annulus at the 3 scallops: P1, P2, and P3. Seven sonomicrometry crystals (*S*) were implanted at the annulus and 1 at the apex (*S*) of the left ventricle. The annular crystals were positioned as follows (clockwise direction): right trigone; posterior commissure; center of P3, P2, and P1 posterior annular segments, respectively; anterior commissure; and left trigone.

Statistical Analysis

All data are reported as mean ± 1 standard deviation. Statistical analysis was performed using the statistical calculation software (IBM SPSS Statistics for Windows Version 19, IBM Corp, Armonk, NY). A least-squares model was used to generate the line of best fit for the annular downsizing suture tightening distance versus the actual measured percentage of downsizing with sonomicrometry. The Wilcoxon matched pairs signed-rank nonparametric test was used to test if differences existed in left ventricular pressure before and after annular downsizing as well as to test if myocardial thickening existed with increasing annular downsizing. A P value of less than .05 was considered statistically significant.

Evaluating the effect of downsizing on observed traction forces was performed using the Friedman test with the Wilcoxon-signed rank test between each level of downsizing. To evaluate whether traction forces differed between directions, the Kruskal-Wallis test was used. If significance was found, the Mann-Whitney U test was used to determine between which directions differences existed. In addition, bivariate analysis was used to determine the correlation between cyclic force magnitudes and T-P downsizing in the T-P1, T-P2, and T-P3 directions.

Downsizing Analysis

To determine the relationship between tightening of the annular sutures to the degree of T-P1, T-P2, and T-P3 downsizing, the maximum annular distances measured by sonomicrometry were correlated to suture tightening lengths. The resulting linear equations of best-fit and coefficients of determination were as follows: (1) downsizing (T-P1) (%) = 1.8 * distance tightened + 0.5 (mm), $R^2 = 0.77$, $P < .0005$; (2) downsizing (T-P2) (%) = 2.3 * distance tightened + 0.2 (mm), $R^2 = 0.50$, $P < .0005$; and (3) downsizing (T-P3) (%) = 1.5 * distance tightened + 1.0 (mm), $R^2 = 0.94$, $P < .0005$.

Based on these linear best-fit equations, each of the 3 T-P diameters decreased by approximately 2% for each millimeter of external suture tightening. All use of T-P downsizing refers to the percentage of downsizing, calculated using this relationship.

RESULTS

The average cross-clamp time was 71 ± 11 minutes and the average pump time was 146 ± 17 minutes. The peak LV pressure was 95 ± 25 mm Hg at baseline and 89 ± 20 mm Hg at maximum reduction of T-P diameter ($P > .5$).

Traction suture forces were measured successfully throughout the cardiac cycle. Representative curves illustrating the observed dependency of traction suture force on annular downsizing are shown in Figure 2. Forces were observed to increase from ventricular diastole and peak between isovolumic contraction and midsystole. Figure 3 shows the force magnitudes as a function of T-P downsizing percentage for the individual annular segments. Bivariate analysis showed strong positive correlations between the T-P downsizing percentage and cyclic traction suture forces in the T-P1 ($r^2 = 0.786$, $P < .0005$), T-P2 ($r^2 = 0.735$, $P < .0005$), and T-P3 ($r^2 = 0.891$, $P < .0005$) directions. With increasing annular downsizing, the minimum (diastolic) and maximum (systolic) forces increased (Figure 3), but maintained a similar dynamic variation throughout the cardiac cycle.

Cyclic traction suture forces were observed to increase with increasing levels of downsizing in the T-P1 ($P < .01$), T-P2 ($P < .001$), and T-P3 ($P < .001$) directions. No statistically significant difference in the maximum and cyclic forces was found between the P1, P2, and P3 segments across all levels of downsizing ($P > .10$). The peak forces at 32% downsizing were 1.2 ± 0.9 N, 1.5 ± 1.0 N, and 0.8 ± 0.2 N for the T-P1, T-P2, and T-P3 segments, respectively. The cyclic forces at 32% downsizing were 0.9 ± 0.7 N, 1.1 ± 0.8 N, and 0.5 ± 0.1 N for the T-P1, T-P2, and T-P3 segments, respectively. For this interval, the total combined maximum force (P1 + P2 + P3) from the trigone to the P1, P2, and P3 annulus segments increased from 0.12 ± 0.03 N to 3.5 ± 1.3 N ($P < .005$), and the total combined cyclic force increased from 0.23 ± 0.07 N to 2.5 ± 1.0 N ($P < .01$).

No statistically significant difference was found in myocardial thickening between the 3 posterior segments. Figure 4 shows the average changes in myocardial thickening as the downsizing progressed. On average, systolic thickening of the myocardial wall decreased with annular downsizing from 5 ± 3 mm at 0% downsizing to 1 ± 1 mm at 32% downsizing ($P < .05$).

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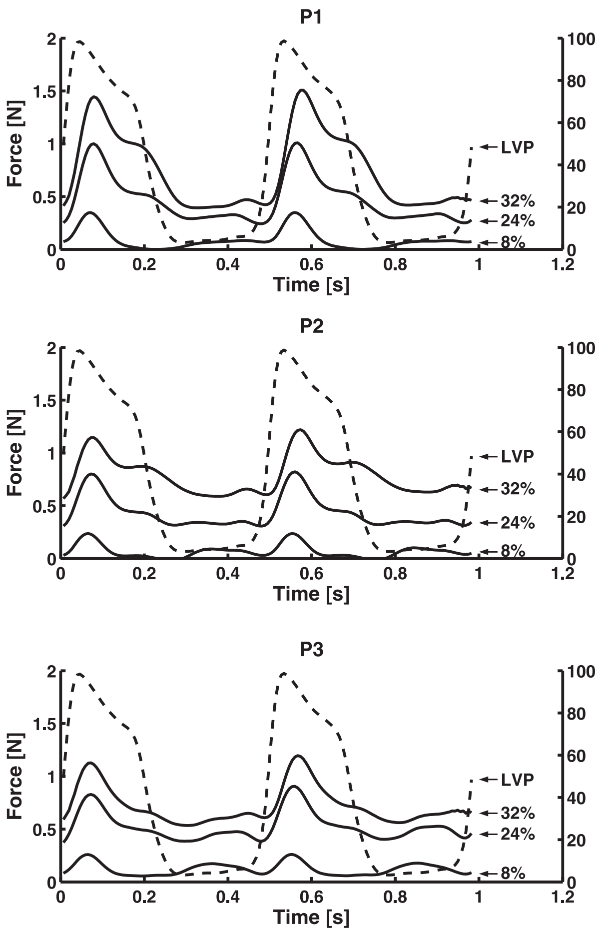

FIGURE 2. Representative traction suture force curves throughout the cardiac cycle. *Broken line*, left ventricular pressure (*LVP*). *Solid lines*, force curves at downsizing percentages of 32%, 24%, and 8%, corresponding to approximately 16 mm, 12 mm, and 4 mm external suture tightening, respectively.

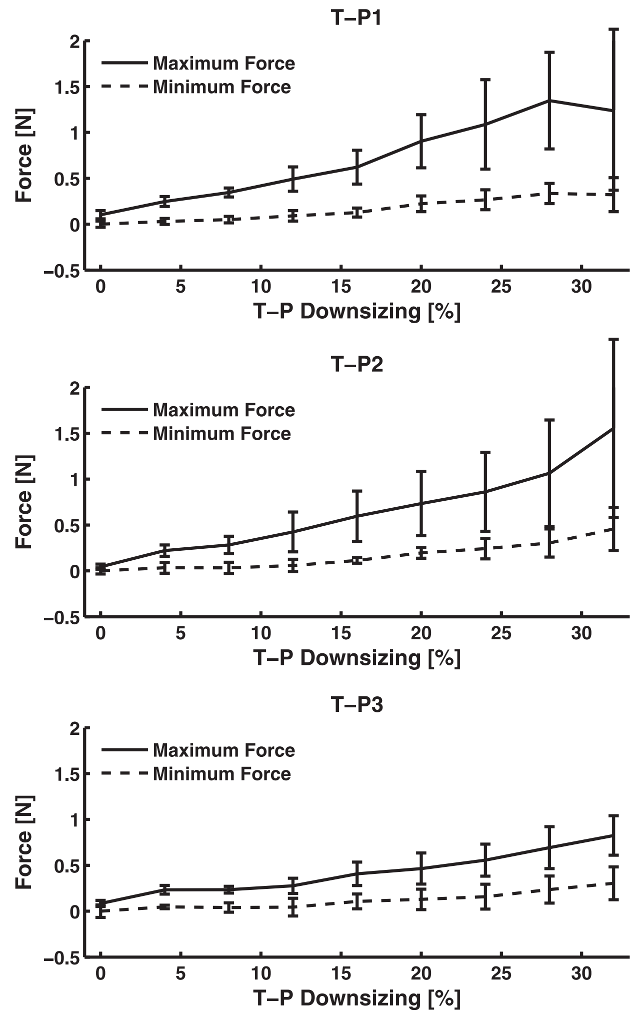

FIGURE 3. Absolute maximum and minimum force magnitudes as a function of incremental annular downsizing (%, mean ± one standard deviation). The values are average measurements of the downsizing and force measurements between the right trigone (T) and the posterior annulus segments (P1, P2, and P3).

DISCUSSION

Downsizing of the mitral annulus with annuloplasty has been proven safe and effective to treat functional MV disease.[23] However, there has been concern that excessive annular deformational forces resulting from a significant mismatch between true mitral annulus size and the annuloplasty device may lead to dehiscence, repair failure, or adversely affect valvular biomechanical forces. Isolated external reductions of the septal-lateral diameter of up to 30% have been shown previously to create a force of 147 g (1.44 N) in the downsizing device.[3] This result is highly comparable with the forces measured in the current study.

Past research in annular force measurements has used novel transducers with fixed dimensions that inherently influence the measured system. The in-plane components of MV annulus forces was first identified by Hasenkam et al,[13] who reported the force on a mechanical valve prosthesis to be between 6 and 8 N. Similar results were obtained by observing the deformations of a valvular stent implanted in the mitral position and simulating this while identifying the corresponding forces with finite element analysis.[16] More recently, a study by Siefert et al[14,15] identified the in-plane force development in relation to the left ventricular pressure in a novel designed device. Thus far, these measurements have been performed while the transducer and valve were set to a fixed (or semirigid) annular dimension.

In this study it was shown that forces in traction suture associated with annular downsizing increase with increasing suture tightening. Segmental downsizing and valvular/ventricular restraint systems such as the now discontinued Coapsys and iCoapsys devices (developed by Myocor Inc, Maple Grove, Minn, rights owned by Edwards Lifesciences, Irvine, Calif) and the PS3 annuloplasty device (developed by Ample Medical Inc, Foster City,

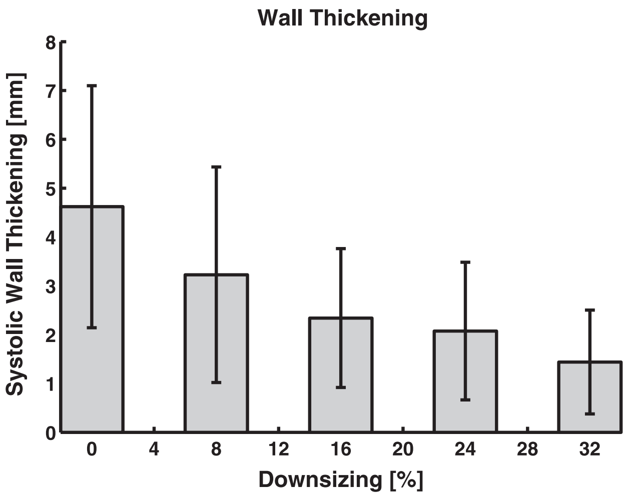

FIGURE 4. Myocardial wall thickening as a function of annulus downsizing (mean ± 1 standard deviation). Because no statistically significant difference was found between the posterior segments (P1, P2, and P3), the data were pooled. All comparisons between groups were statistically significant ($P < .05$), except between 16% and 24% downsizing.

Calif),[2,4] with similar placing of support pads and sutures, may benefit from realizing that the suture force varies significantly throughout the cardiac cycle and peaks during systole, which also has been suggested in a finite element model of the Coapsys device.[24] Comparisons with previous in-plane force measurements in the mitral annulus should be performed carefully. Traditional annuloplasty devices are sized for the desired systolic configuration, and fundamentally are mechanically different from the traction suture devices. In addition, it is important to recognize the difference between measuring the compression in a fixed, stiff device that was designed to fit the annulus in the normally sized diastolic configuration[25] and the tension in downsizing sutures as used in this study. However, the action/reaction principle may be used to compare the two because the muscle working to put tension in the suture devices is the same muscle activity that compresses the stiff annuloplasty device. In addition, these results also may support the recommendation of using pledgeted annular sutures (especially on the posterior annulus), which should be considered in downsized mitral annuloplasty. The specific information that may be important is the fact that no significant difference was observed between the posterior segments and the right trigone suspension, and probably even more important is the actual strength requirements for the development of percutaneous beating heart techniques. An estimate of the total septal-lateral maximum force obtained by adding the numeric force values from Figure 3 at the upper downsizing percentages (T-P1 + T-P2 + T-P3) is approximately 3.5 N. This result is similar to the septal-lateral force that was obtained in a previous ovine model with a stiff, flat, normal, diastolic-sized annuloplasty device.[15]

Interventions of the annular dynamics were performed in healthy porcine hearts with no ischemic or valvular pathology. Hence, extrapolating the data into a clinically relevant conclusion may be compromised. However, one needs to take the type of pathology into consideration because the annular dynamics may be significantly different in degenerative MV disease compared with cardiomyopathic dilatation. To understand the effects of disease, this study aimed to understand the magnitude of these forces in a healthy model. Future studies will be required to evaluate how these forces change with downsizing of a dilated pathologic annulus.

The downsizing sutures attached externally were shortened incrementally with an interval of approximately 2 mm between each measurement, which resulted in a reduction of the maximum (diastolic) T-P diameter by 4% between each measurement. This maximum diameter of the annulus is reached toward the end of diastole at the time point in which the myocardium of the LV base is expanded and relaxed. Counterintuitively, however, the maximum force is not observed in the traction sutures at this time. The maximum force as tension in the sutures is observed consistently during systole after peak left ventricular pressure. The explanation for this has been shown and documented previously. In diastole, the ventricular muscle is relaxed, and the highest suture tension is experienced when the ventricular myocardium is activated at the highest early systolic left ventricular volume, during or immediately after isovolumic contraction. The myocardium thickens and generates an outward-directed force at any structure attached to the MV apparatus, whether it is a traction suture suspended across the annulus or hoisting the papillary muscle from the trigone.[22] In addition, timing of annular size versus atrial/ventricular systole has been debated,[26] and the maximum forces in downsizing sutures with external length fixation may rather be influenced by the mechanics of LV myocardial thickening than by annulus dimensions per se. These observations also are linked to the principles of Frank-Starling's law. This concept is important especially when developing devices for external manipulation of annulus downsizing, but also may be useful in the design of annuloplasty rings. Normal and oversized interventions of the mitral annulus previously has shown radially compressive forces at systole,[13,15] which as described earlier is a simple function of action and reaction. Future experiments with these fixed devices in a downsized configuration could be important to compare the current results of forces pointing radially outward in early systole during isovolumic contraction. It may be hypothesized that the direction and size of forces on annuloplasty interventional devices strongly depend on the shape and size of these devices, which needs to be

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considered during the design and for which purpose the device will be designed to fulfill.

The decrease in maximum T-P diameter between each measurement is relatively constant, limited by the nonflexible suture length. The absolute forces increase with increased downsizing, as the annulus is tightened further away from its original configuration. Figure 3 suggests that the rate at which the peak force increases with downsizing is larger than the rate at which the minimum force increases with downsizing, which is consistent with a statistically significant correlation between downsizing magnitude and cyclic force changes ($P < .05$). The dynamics of a downsized annulus was investigated previously in an ovine model, in which it was found that annular contraction was not affected by downsizing with sutures.[27] Externally applied suture downsizing is not rigid at the annular site, which results in an observed cyclic variation in downsizing dimensions measured with sonomicrometry. Although the maximum distance from the trigone to the external myocardial wall is fixed, these phenomena are explained by the fact that the myocardial tissue is thinner and more compliant in the relaxed diastolic state, and hence the effect of downsizing is more pronounced on the systolic peak force, where the myocardium, as described earlier, thickens and stiffens.

On the contrary, the progressive decrease in systolic wall thickening as the annulus is downsized may indicate that ventricular contractility is impaired. The mechanism of this observation may be explained by a previous study showing that ring annuloplasty restricts mitral annular dynamics.[28] Restricting the myocardium may have an unfavorable effect by reducing the ability to contract, thus decreasing systolic wall thickening. Furthermore, isometric myocardial forces are dictated by a length-tension relationship. If the preload of myocardial fibers moves beyond the optimal force-generating plateau, the force the myofibrils can generate decreases, rendering the ability of the affected myocardium unable to contract efficiently. This observation of thickness decrease also may be an effect of the downsizing method used in the study because the external pads (Figure 1) are pushing the posterior myocardium anteriorly. In the case of ring annuloplasty, myocardium thickness is not limited in the posterior direction.

The results from this experiment confirm the concept that images can be deceiving. It is essential to understand that annuloplasty devices act as constricting bodies within a dynamic annulus, and the creation of compressive and tensile strain within this body is governed by both direct forces as well as secondary forces acting in other locations, creating momentum at the point at which the body is suspended. Hence, the largest deformation in the annulus before device implantation does not necessarily result in the largest force in that same location of the annuloplasty device. For the annuloplasty rings, these traction forces across the annulus may reflect the deformation forces acting on semirigid or partial rigid devices that are not stabilized in the entire circumference of the ring, for example, the Medtronic semi-rigid CG Future Annuloplasty Ring and Band Systems (Medtronic Inc, Minneapolis, Minn) and the Edwards Lifesciences Cosgrove-Edwards Annuloplasty System. This means that actual force measurements are essential to understand the true biomechanical load on devices and procedures in heart valve surgery.

In summary, it has been shown that downsizing of various degrees has had a significant impact on implanted devices in the mitral annulus and results in a significant change in valvular biomechanics and force dynamics. This has implications for determining the biomechanical properties such as stiffness, flexibility, as well as mechanical strength of new remodeling annuloplasty device designs and surgical procedures for optimized endurance as well as predicting the structural integrity of the sutures used to attach any devices in the MV annulus.[29] Future work involves providing a map for mathematical modeling and simulations of the MV annulus using these dynamic force measurements.

Limitations

The present set-up measures only one component of the complex valvular force balance during annular downsizing, and the direct implications on the possibility for subvalvular tethering and its influence on repair effectiveness needs to be investigated.

It was assumed that the results of this study would be similar if the anchoring of the sutures had originated from the left trigone. Naturally, the assumption of anatomic and physiological symmetry can be disputed as another pitfall of the concept that images can be deceiving. Hence, a counterbalance control of sutures anchored at the left trigone to each of the posterior segments must be part of a future study protocol that uses the same measurement techniques. This protocol could include ischemic dilatation, and the force magnitudes might not be similar when anchoring from the 2 trigones because the ventricle tends to dilate in an asymmetric fashion.

Minimization of the drift in the strain gauge signal has been described previously.[21] This error cannot be eliminated completely. This may explain the small amount of negative force measurements at 0% downsizing, resulting in the standard deviation error bars in Figure 3 at 0% downsizing reaching just below the 0 N line.

In this acute study, as the sutures were tightened, the decreased forward flow annular area eventually must cause a decrease in LV filling, and the midsystolic and peak LV pressure decreased as expected, although this pressure decrease was not statistically significant. This may have the opposite effect on the force generation in the traction sutures suspended across the MV annulus, and hence a negative feedback loop may be created. Another possible secondary effect of excessive downsizing is the risk of aortic valve regurgitation. Although optimally performed mitral annuloplasty results in an anterior displacement of the posterior annulus, it is possible that the anterior annulus is disturbed. Monitoring this development needs to be part of future investigations.

The time course and magnitude of forces measured in the MV annulus is to a large extent dependent on the type of device applied. Comparable acute studies in literature from our own and other groups have shown uncertainty in the reported magnitude of cyclic and absolute in-plane mitral annular forces.[13,15,16] Matching the physiological annulus dimensions precisely with a force transducer is problematic because any small variation in septal-lateral diameters at different time points of the cardiac cycle between test subjects can cause a significant difference in measured forces, as illustrated in Figure 3. This is also relevant in the current study. Naturally, as the annulus is downsized by simultaneous suture tightening, neighboring sutures will have an influence on the force balance of each other. The need for more experiments that cover the force development as sutures are tightened individually is certainly an important next step of this research strategy, which also will be of significant interest to any future development of single suture annuloplasty septal-lateral downsizing devices.

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