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Do Annuloplasty Rings Designed to Treat Ischemic/Functional Mitral Regurgitation Alter Left-Ventricular Dimensions in the Acutely Ischemic Ovine Heart?

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35 **Glossary of Abbreviations**

36 IMR/FMR = ischemic/functional mitral regurgitation

37 APM/PPM = anterolateral/posteromedial papillary muscle

38 LCx = left circumflex artery

39 PHY/ETL/GEO = Carpentier-Edwards Physio 1/Edwards IMR ETlogix/Edwards GeoForm annuloplasty ring

40 S-L/C-C = septal-lateral /commissure-commissure dimension

41 LV = left ventricle

42 LV1/LV2/LV3 = basal/equatorial/apical level of the left ventricle

43 ED/ES = end-diastole/end-systole

45 LV dimensions with IMR/FMR rings
LV dimensions with IMR/FMR rings

Central Picture

Septal-Lateral

Commissure-Commissure

NO RING vs. RING

* p < .004
Central Message

Despite radical reduction of mitral annular size, disease-specific IMR/FMR annuloplasty rings do not induce relevant changes of left ventricular dimensions in the acutely ischemic ovine heart.
Perspective Statement

The disproportionate septal-lateral downsizing of annuloplasty rings to treat IMR/FMR intends to maximize leaflet coaptation and reshape the dilated, spherical left ventricle. If the findings from this acute ischemic preparation do translate to patients, implantation of an etiology-specific designed ring alone may not be sufficient to restore acutely the ventricle to its normal elliptical shape.
Structured Abstract

Objective: To quantify the effects of annuloplasty rings designed to treat ischemic/functional mitral regurgitation (IMR/FMR) on left ventricular septal-lateral (S-L) and commissure-commissure (C-C) dimensions. Methods: Radiopaque markers were placed as opposing pairs on the S-L and C-C aspects of the mitral annulus and the basal, equatorial and apical level of the left ventricle (LV) in 30 sheep. Ten true-sized Carpentier-Edwards Physio 1 (PHY), Edwards IMR ETlogix (ETL), and GeoForm (GEO) annuloplasty rings were inserted in a releasable fashion. After 90sec of LCx occlusion with the ring implanted (RING), 4-D marker coordinates were obtained using biplane videofluoroscopy. After ring release, another dataset was acquired after another 90sec of LCx occlusion (NO RING). S-L and C-C diameters were computed as the distances between the respective marker pairs at end-diastole. Percent change in diameters was calculated between RING vs. NO RING as 100*(diameter in cm (RING) —diameter in cm (NO RING))/ diameter in cm (NO RING)). Results: Compared to NO RING, all ring types (PHY, ETL and GEO) reduced mitral annular S-L dimensions by -20.7±5.6, -26.8±3.9 and -34.5±3.8%, respectively. GEO reduced the S-L dimensions of the LV at the basal level only by -2.3±2.4%, while all other S-L dimensions of the LV remained unchanged with all three rings implanted. PHY, ETL and GEO reduced mitral annular C-C dimensions by -17.5±4.8%, -19.6±2.5 and -8.3±4.9% respectively, but none of the rings altered the C-C dimensions of the LV. Conclusions: Despite radical reduction of mitral annular size, disease-specific IMR/FMR annuloplasty rings do not induce relevant changes of left-ventricular dimensions in the acutely ischemic ovine heart.
Introduction

During left ventricular remodeling after acute myocardial infarction, the normal elliptical shape of the left ventricle (LV) may become more spherical resulting in papillary muscle displacement, leaflet tethering, malcoaptation, and mitral regurgitation. These changes, if not attenuated or reversed by intervention, are associated with a poor clinical prognosis.

The implantation of an undersized annuloplasty ring represents the contemporary standard surgical approach for treating ischemic/functional mitral regurgitation (IMR/FMR), but this procedure is associated with suboptimal clinical results due to ongoing LV remodeling and recurrent leaflet tethering/malcoaptation. Under the assumption that the spherical geometry of the LV may be altered by a mitral annular intervention, disease specific IMR/FMR annuloplasty rings (Edwards IMR EtiLogix [ETL] and Edwards GeoForm [GEO], Edwards Lifesciences, Irvine, CA) have been introduced in clinical practice. These annuloplasty rings include a disproportionate downsizing of the septal-lateral (S-L) dimension, thereby aiming to improve leaflet coaptation and – potentially - to restore a more elliptical shape of the LV. Furthermore, in the GEO ring, the mid-lateral mitral annular segment (P2, Fig 1a) is elevated by ~5mm to lift up the displaced posteromedial papillary muscle (PPM).

Clinically, implantation of IMR/FMR rings has been associated with reverse LV remodeling, restoration of LV geometry, and reduced leaflet tethering. Such changes have, however, also been reported with conventional rings and it is currently unknown whether these geometrical alterations are i) due to a postoperative myocardial recovery (e.g. caused by better myocardial perfusion after coronary artery bypass surgery) eventually leading to LV reverse remodeling or ii) an immediate, annuloplasty ring-related effect on the geometry of the LV.
We hypothesized that disease-specific IMR/FMR rings reduce left-ventricular S-L, but not C-C dimensions and that the GEO ring lifts up the PPM during acute ovine posterolateral ischemia.

**Methods**

**Surgical preparation**

These data, including the experimental methods, have in part been published previously. In brief, 30 adult male sheep (49±4kg) were premedicated with ketamine (25mg/kg intramuscularly), anesthetized with sodium thiopental (6.8mg/kg intravenously), intubated and mechanically ventilated with inhalational isoflurane (1.0-2.5%). All animals received humane care in compliance with the *Principles of Laboratory Animal Care* formulated by the National Society of Medical Research and the *Guide for Care and Use of Laboratory Animals* prepared by the National Academy of Sciences and published by the National Institute of Health (DHEW NIHG publication 85-23, revised 1985). This study was approved by the Stanford Medical Center Laboratory Research Animal Review committee and conducted according to Stanford University policy.

Through a left thoracotomy, 12 radiopaque markers were implanted to silhouette the LV at the cross-section points of four equally spaced longitudinal and three transverse meridians and one on the LV apex (Figure 1). Using cardiopulmonary bypass and cardioplegic arrest, 8 radiopaque markers were implanted equidistantly along the mitral annulus, with one marker sewn on the anterolateral and one on the posteromedial papillary muscle tip (APM and PPM, respectively). Three different annuloplasty ring types were implanted (one ring per animal), one conventional (Carpentier-Edwards Physio 1 [PHY], Edwards Lifesciences, Irvine, CA) and two etiology specific (Edwards IMR ETlogix [ETL] and Edwards GeoForm [GEO], Edwards Lifesciences, Irvine, CA). In order to allow each animal to serve as its own Control, annuloplasty
LV dimensions with IMR/FMR rings were implanted in a releasable fashion as described previously. In brief, the annuloplasty rings were prepared before the operation in the following manner: the middle parts of 8 double-armed polyester braided sutures were stitched evenly spaced around the ring from the bottom to the top side using a “spring eye” needle. The resulting loops were “locked” with 2 polypropylene sutures. The polyester sutures were stitched equidistantly in a perpendicular direction from the ventricular to the atrial side through the mitral annulus. The annuloplasty devices were secured to the mitral annulus by tying these sutures. The locking sutures (polypropylene) and the drawstrings were exteriorized before the atrium was closed (see Ref.\textsuperscript{11} for details). All operations were performed by two experienced cardiac surgeons (W.B. and J.P.E.K.). All prostheses were “true-sized” by assessing height and entire area of the anterior mitral leaflet, and all received a size 28 mm ring. The left circumflex artery (LCx) was then encircled immediately distal to the first obtuse marginal branch with a vessel loop. The animals, while intubated and anesthetized, were then transferred with the chest open to the experimental catheterization laboratory.

**Data acquisition**

Videofluoroscopic images (60 frames/sec) of all radiopaque markers were acquired using biplane videofluoroscopy (Philips Medical Systems, North America, Pleasanton, CA, USA). Acute left ventricular ischemia was induced by tightening the LCx vessel loop for 90 sec, and a dataset under ischemic conditions with ring was obtained (RING). After hemodynamic values returned to baseline (determined by hemodynamic values return to normal) and myocardial contraction (no regional wall motion abnormalities in the echocardiography) following release of the LCx vessel loop, the ring was released from the mitral annulus by removing the ‘locking sutures’ (see above) and pulling the ring to the roof of the left atrium using the drawstring sutures\textsuperscript{11}. Another data acquisition was performed with the ring released and re-occlusion of the LCx for 90 sec (NO RING).
Marker coordinates from three consecutive sinus rhythm beats from each of the biplane views were then digitized and merged to yield the time-resolved 3-D coordinates of each marker centroid in each frame using semi-automated image processing and digitization software\textsuperscript{16,17}. ECG and analog left ventricular pressures were recorded in real-time on the video images. The degree of mitral regurgitation after each data acquisition run was graded by an independent echocardiographer (D.H.L.) on the basis of color Doppler regurgitant jet extent and width and categorized as none (0), mild (+1), moderate (+2), moderate-to-severe (+3), or severe (+4) and then – according to the American Society of Echocardiography (ASE) guidelines \textsuperscript{18} – sorted into the categories mild, moderate or severe. Quantitative methods such as effective regurgitant orifice area and quantitative Doppler were not possible due to limited image quality.

**Data analysis**

For each beat, end-diastole (ED) was defined as the videofluoroscopic frame containing the peak of the R-wave on the ECG and end-systole (ES) as the frame preceding maximum left ventricular dP/dt.

**Hemodynamics**

Instantaneous left ventricular volume was computed from the epicardial left ventricular markers using a space-filling multiple tetrahedral volume method \textsuperscript{16,17}. Hemodynamic data were calculated from marker derived instantaneous left ventricular volumes and analog left ventricular pressures as published previously\textsuperscript{13}.

**Mitral annular and left ventricular dimensions**

Septal-lateral (S-L) and commissure-commissure (C-C) dimensions were computed as distances between the respective marker pairs on the mitral annular (ANN) as well as basal (LV1), equatorial (LV2) and apical (LV3) levels of the LV (Figure 1A and B). Percent change in
measured parameters between RING vs. NO RING was calculated as $100\% \times \frac{(\text{diameter in cm (RING)} - \text{diameter in cm (NO RING)})}{\text{diameter in cm (NO RING)}}$.

Interpapillary muscle distance

Interpapillary muscle distance was calculated as distance in 3-D space between respective papillary muscle tip markers at ED and at ES.

Distances of APM and PPM to the left ventricular apical plane

In order to assess whether the implanted rings – due to their height profile (e.g. the P2-elevation of the GEO ring) – are able to lift up the papillary muscle tips, the orthogonal distances of APM and PPM markers to a least-squares reference plane were calculated at ED and ES. The mitral annular plane is, however, significantly affected by ring implantation and, thus, does not serve as a stable reference plane. A plane generated from the four ventricular markers on the apical level (LV3) was therefore used under the assumption that the markers with the largest distance to the mitral annulus are least affected by the ring implantation (Figure 1C).

To simplify the understanding of the effects of ring implantation, differences between RING and NO RING were calculated as distance in cm (RING) — distance in cm (NO RING), i.e. positive/negative values reflect an increase/decrease, respectively, induced by ring implantation.

Spline curves displaying changes in transverse and longitudinal dimensions of mitral annulus, LV1, LV2 and LV3

In order to provide a more visual, qualitative description of geometric changes of the LV induced by ring implantation, changes in the transverse and longitudinal dimension of mitral annulus and LV were calculated and displayed on spline curves: To calculate continuous transverse changes along the mitral valve annulus (ANN) and the three left-ventricular transverse meridians (LV1, LV2, LV3) before and after ring implantation, we used a least-squares approach
to position the knot locations in such a fashion that the distance between the fiduciary marker coordinates and the spline were minimized. We chose the number of knots equal to the number of fiduciary markers with equal weights. Next, we computed the distance vectors between all points on the splines and the centers of their respective spline fits (before and after ring implantation), and projected these vectors onto their splines' best-fit plane. Finally, we subtracted those transverse distance values after ring release (NO RING, Fig 1D) from the same values with ring implanted (RING). We computed cubic spline curves during occlusion for RING and NO RING. We did not center the two conditions, but instead compared the distances to the respective centers.

Continuous height profile was defined as the best-fit spline through the fiduciary markers from their best fit plane. To calculate continuous height profile changes, we employed the same spline representations of annulus/transverse meridians and again calculated their best fit planes. Then, we determined the orthogonal distance of all points along the annulus/transverse meridians from the best fit plane and subtracted those values without ring implantation from those with ring implantation (RING — NO RING, Fig 1E). We repeated this procedure for all ring types and their respective controls for both, ED and ES.

Statistical analysis

As mentioned above, the presented data are a secondary analysis from datasets which have in part been published previously. The sample size was initially determined to assess differences in mitral annular and leaflet strains with and without five different annuloplasty ring types using SamplePower (SPSS, Inc, Chicago, IL). Data are reported as mean ±1 SD unless otherwise stated. Hemodynamic data were analyzed using paired t-test except for the grading of mitral regurgitation where the non-parametric Wilcoxon rank sum test was applied. For the statistical analysis of ring effects (RING vs. NO RING) on S-L/C-C diameters and distances (interpapillary muscle distance, distance of APM and PPM to the LV apical plane) we used a mixed effect
model approach to account for inter-related measurements within the sheep. For each of the
measurement conditions (ED and ES) as well as their combination with S-L and C-C for the
diameter data we applied a separate mixed effect model. In each model we included presence of
ring (RING or NO RING), ring type (PHY, ETL, GEO) and location (ANN, LV1, LV2, LV3) for
the diameter (S-L/C-C) and distance data (interpapillary muscle distance, distance of APM and
PPM to the LV apical plane) as fixed factors together with their interactions into the model. To
account for inter-relation and for different variation (which could be seen by an explorative data
analysis) we incorporated a ring type specific random intercept as well as a location-specific (for
the diameter data) and muscle-specific (for the distance data) random effect. The level of
significance was set at 5%. For each statistical analysis we reported the nominal p-values which
were basis for the Bonferroni adjustments: i) For the hemodynamic data we adjusted each
parameter separately with respect to the three ring types (PHY, ETL and GEO), i.e. the
Bonferroni adjusted level of significance was set to 0.05/3. ii) For mitral annular and left
ventricular diameters the adjustment was made separately for each combination of diameters (C-
C, S-L) and measurement conditions (ED, ES) based on 4 location (ANN, LV1, LV2, LV3) and
the 3 ring types, i.e. the Bonferroni adjusted level of significance was set to 0.05/12. iii) For
distances of APM and PPM to the LV apical plane the adjustment was based on the two different
papillary muscles (APM and PPM) and the three ring types, so the Bonferroni adjusted level of
significance was set to 0.05/6. All analyses were performed using SAS 9.4 (SAS Institute Inc.,
Cary, NC, USA).

Results

Hemodynamics

Table 1 summarizes the hemodynamic data. No differences between RING vs. NO RING
with respect to heart rate, left ventricular end-diastolic volume, dP/dt\textsubscript{max} or left-ventricular
pressure (LVP_{max}) were observed. All three rings effectively prevented mitral regurgitation during acute left ventricular ischemia.

**Mitral annular and left ventricular dimensions**

Table 2 displays mitral annular as well as left ventricular S-L and C-C diameters at ED and at ES. Figure 2A illustrates differences in S-L and C-C diameters between NO RING vs. RING state at ED and at ES. At both time-points all ring types (PHY, ETL and GEO) significantly reduced mitral annular S-L dimensions (ED: -20.7±5.6, -26.8±3.9 and -34.5±3.8%, ES: -15.4±4.12, -21.2±4.4 and -30.4±4.4%, respectively) compared to NO RING. GEO reduced the S-L dimension of the left ventricle at the basal level (LV1) by -2.3±2.4% and -1.8±1.9% at ED and ES, respectively, while all other S-L dimensions of the LV were not affected by any of the ring types implanted. PHY, ETL and GEO reduced mitral annular C-C dimensions (ED: -17.5±4.8%, -19.6±2.5 and -8.3±4.9%, ES: -17.3±4.3, -19.0±2.4 and -7.2±6.1%, respectively), while left-ventricular C-C dimensions remained unchanged with any of the implanted ring types.

**Interpapillary muscle distance**

Interpapillary muscle distances were not altered by ring implantation either at ED or at ES for PHY (NO RING vs. RING, ED: 3.19±0.31 vs. 3.21±0.31cm, p=0.584; ES: 2.63±0.39 vs. 2.67±0.39cm, p=0.080), ETL (NO RING vs. RING, ED: 3.59±0.23 vs. 3.61±0.24cm, p=0.424; ES: 3.01±0.22 vs. 3.04±0.24cm, p=0.347) or GEO (NO RING vs. RING, ED: 3.17±0.24 vs. 3.18±0.25cm, p=0.823; ES: 2.72±0.26 vs. 2.75±0.27cm, p=0.183).

**Distances of APM and PPM to the left ventricular apical plane**

Table 3 and Figure 2B demonstrate the distances and mean differences in distances, respectively, of the APM and PPM to the left ventricular apical plane. APM and PPM distances to the left ventricular apical plane were not altered by ring implantation.
LV dimensions with IMR/FMR rings

**Spline curves displaying transverse and longitudinal changes of mitral annulus, LV1, LV2 and LV3**

Figures 3 and 4 show marker-derived spline curves of the mitral valve annulus (ANN) as well as the three transverse meridians (LV1, LV2, LV3) displaying continuous transverse and longitudinal changes, respectively, at end-diastole (ED) and end-systole (ES) for Physio (PHY), IMR ETlogix (ETL) and GeoForm (GEO) ring. While ring-induced alterations in both transverse and longitudinal direction were observed on the annular level (ANN), no significant changes were seen on any of the ventricular levels (LV1, LV2 or LV3).

**Discussion**

As compared to the ischemic heart without ring, the key findings of this *in-vivo* ovine study were that: 1) all annuloplasty ring types (PHY, ETL and GEO) significantly reduced mitral annular S-L and C-C dimensions, but – except from a small reduction with GEO on the basal ventricular level (LV1) in the S-L dimension (-2.3±2.4% and -1.8±1.9% at ED and ES, respectively) - no significant changes of left-ventricular S-L and C-C dimensions were induced; 2) interpapillary muscle distances were not reduced by any ring type (PHY, ETL and GEO) used; and, 3) none of the rings altered the distance of the APM or PPM tip to the left ventricular apical plane during acute posterolateral ischemia.

A reduction of left ventricular diameters after annuloplasty ring implantation in patients with IMR/FMR has been observed for both conventional and disease-specific ring types. It is unclear whether the observed changes are caused by improved myocardial perfusion (after concomitant coronary artery bypass surgery) or immediate, annuloplasty-related effects on the geometry of the LV. While immediate effects of mitral annular downsizing on the curvature of the LV have been observed in the experimental setting, the effects of annuloplasty rings on the
geometry of the ventricle is unclear. This is particularly true for annuloplasty rings specifically designed to address the pathophysiologic alterations of the LV during IMR/FMR. These prostheses (GEO and ETL) incorporate a disproportionate downsizing of the septal-lateral dimension in their design compared to the PHY ring. In our analysis, the GEO ring reduced the S-L diameter by approximately 35% during acute ischemia, yet despite such radical downsizing of the annular S-L dimension, the reduction of the left ventricular S-L dimension was only ~2%. Assuming a 60mm LVEDD in a patient with heart failure, the degree of ventricular S-L reduction that could be expected by implantation of the GEO ring would be 1.2mm. Such magnitude of left-ventricular S-L reduction appears too small to effectively restore a more elliptical LV shape.

Consequently, the observed reduction of left ventricular diameters after annuloplasty ring implantation in patients with IMR/FMR is most probably due to restored valve competence or improved myocardial perfusion and contractility.

We did not observe any ring effects on the position of APM or PPM. This was true for both the distance to the left ventricular apical plane and the inter-papillary muscle distances. It therefore appears reasonable to conclude that disease-specific IMR/FMR rings are not effective in repositioning displaced papillary muscles and thus decreasing tethering forces in patients with IMR/FMR.

In this study we qualitatively analyzed changes in height profiles of the three left ventricular meridians induced by the implantation of IMR/FMR specific annuloplasty rings. Although relevant changes in the mitral annular height profile can be observed, ring implantation did not affect the height profile of the left ventricular meridians (LV1, LV2 or LV3, Fig. 4) These data suggest that the geometry of the LV cannot be altered in the longitudinal direction by interventional changes of the mitral annular height profile.
The surgical repair of IMR/FMR remains challenging. Early clinical data appeared promising in small patient cohorts\textsuperscript{9,20}, but in a recent multi-center randomized study of IMR patients, addressing the mitral annulus alone with a reductive ring annuloplasty was associated with almost 60% recurrent insufficiency rates at a two year follow-up\textsuperscript{4}. It is unclear whether disease-specific IMR/FMR rings have the potential to improve these outcomes, and only sporadic clinical data have been reported\textsuperscript{6,8,21–28}. Timek et al. reported freedom from recurrent mitral regurgitation at 5-years of 86% using the GeoForm annuloplasty ring in 86 patients with 32 patients remaining at risk\textsuperscript{8}. These results are in sharp contrast to the CTSNET trial perhaps driven by differences in inclusion criteria. As compared to the GeoForm study, more patients with severe MR were included in the CTSNET trial. The observed improvement could therefore in part be due to patient selection rather than to an effect of the GeoForm ring\textsuperscript{27}.

In a retrospective study of 156 patients undergoing implantation of an IMR ETLogix ring, preoperative IMR grades were higher (92.3\%>grade 2) than in the GeoForm study. Despite high preoperative IMR grades, Campisi and colleagues reported a freedom from greater than mild regurgitation in 89% of the 156 patients 28 months after surgery\textsuperscript{28}. These results are promising, but must be validated in larger, prospective studies with longer follow-up. Based on our ovine study, we hypothesize that improvements in clinical outcomes are a result of more radical, disproportionate downsizing of the mitral annulus and not subvalvular ring effect on the left ventricle.

**Clinical Inferences**

If the findings of this study translate to IMR/FMR patients, two main inferences may be drawn. First, the left ventricular geometry cannot be effectively altered through a mitral annular intervention using IMR/FMR-specific annuloplasty rings. Consequently, the restoration of a more elliptical left ventricular shape observed weeks/months after annuloplasty in IMR/FMR patients
LV dimensions with IMR/FMR rings is most probably a result of left ventricular reverse remodeling/myocardial recovery resulting from increased myocardial perfusion and/or restored valve competence. Second, since ring-induced alterations of the mitral annular geometry do not influence papillary muscle tip geometry, IMR/FMR annuloplasty rings may not be effective in relieving tethering forces induced by displaced papillary muscles. Consequently, if potential future trials using disease-specific IMR/FMR rings demonstrate a better long-term freedom from recurrent mitral regurgitation compared to conventional, undersized rings, such an improvement in outcomes may be more attributable to the ring-inherent radical, disproportionate S-L mitral annular downsizing rather than to a subvalvular effect of the annuloplasty ring on the left ventricle. If conventional rings are used, additional, subvalvular procedures (such as e.g. papillary muscle relocation or approximation) appear mandatory.
Study Limitations

Clinical extrapolation from this acute, ischemic ovine open-chest model has several limitations. First, compared to our acute ischemic model, left ventricular and mitral annular dilatation as well as the MR grade is significantly greater both, in a chronic animal model or in IMR/FMR patients. It may therefore be feasible that the ring effect on left ventricular geometry in the acute model differs from chronic experimental IMR or from patients with IMR/FMR. We have, however, observed in previous ovine experiments that ventricular changes during acute myocardial ischemia are similar to those observed in the chronic setting. Second, our experimental approach precisely tracks distinct anatomic landmarks in all three dimensions and therefore includes displacements of the respective structures in any direction in 3-D space. Consequently, our results may differ from measurements obtained from clinical imaging techniques where tracking of anatomical structures is significantly more difficult. Third, true-sized PHY rings were used in our study and we cannot infer any information about the effects of downsized PHY rings. Since the GEO and ETL rings disproportionately downsize the mitral annulus in the S-L direction, we assume that the effects of downsized PHY rings are similar to those changes observed with ETL or GEO. Fourth, no statistical comparisons between ring types were performed. However, since none of the ring types had any relevant effects on the LV or the papillary muscle geometry, such a statistical analysis appears unnecessary. Fifth, baseline was determined solely based on assessing hemodynamic values (return to normal) and myocardial contraction (no regional wall motion abnormalities in the echocardiography). Neither blood samples nor myocardial tissue were harvested. Minor ischemic myocardial damage induced by LCx occlusion may therefore be possible, but major damage appears – due to the macroscopically normal cardiac performance and shortness of the ischemia time – unlikely. Sixth, distances from both papillary muscles to a plane generated from four ventricular markers on the apical level
LV dimensions with IMR/FMR rings

(LV3) were calculated. This calculation requires that there is no change of these markers in the longitudinal position. The plane was chosen under the assumption that the markers with the largest distance to the mitral annulus are least affected by the ring implantation, but minor changes cannot be fully excluded. Seventh, our analyses have been performed from datasets which have in part been published previously and the sample size was initially determined to assess differences in mitral annular and leaflet strains with and without five different annuloplasty rings. The possibility of different outcomes with different animal numbers can therefore not be fully excluded. Lastly, our releasable ring implantation technique may have been insufficient in conforming the mitral annulus to the shape of the annuloplasty ring. Past analyses have, however, demonstrated that the annuli conform to the ring shape in terms of both, S-L/C-C dimensions and height profile\textsuperscript{11,15}.

In conclusion, despite radical alterations to mitral annular geometry, disease-specific IMR/FMR annuloplasty rings do not induce relevant changes to the left ventricular S-L and C-C dimensions or the geometry of the papillary muscles in the acutely ischemic ovine heart. If the findings from this acute ischemic preparation do translate to patients with chronic clinical IMR/FMR, implantation of an etiology-specific designed ring alone may not be sufficient to restore acutely the ventricle to its normal elliptical shape or to reduce tethering forces induced by papillary muscle displacement.
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References


Legends to figures

Central Picture: Mean differences in diameters between NO RING vs. RING at end-diastole/-systole (ED/ES).

Figure 1: Septal-lateral (S-L, A) and Commissure-Commissure (C-C, B) diameters were calculated from the respective marker pairs on the mitral annulus (ANN) and the basal (LV1), equatorial (LV2) and apical (LV3) levels of the left ventricle. In order to assess whether the implanted rings lift up the papillary muscle tips, the orthogonal distances of anterolateral and posteromedial papillary muscle (APM and PPM, respectively) markers to a least-squares reference plane were calculated (red arrows, C). Interpapillary muscle distance was calculated as distance in 3-D space between APM and PPM tip (black arrow, C) D) To calculate continuous transverse changes along the mitral valve annulus (ANN) and basal, equatorial and apical transverse left-ventricular meridians (LV1, LV2 or LV3, respectively) before and after ring implantation, we used a least-squares approach to position the knot locations in such a fashion that the distance between the fiduciary marker coordinates and the spline were minimized. We chose the number of knots equal to the number of fiduciary markers with equal weights. Next, we computed the distance vectors between all points on the splines and the centers of their respective spline fits (before and after ring implantation), and projected these vectors onto their splines' best-fit plane. Finally, we subtracted those transverse distance values with ring implanted (RING) from the same values after ring release (NO RING); E) Continuous height profile was defined as the best-fit spline through the fiduciary markers from their best fit plane. To calculate continuous height profile changes, we employed the same spline representations of annulus/transverse meridians and again calculated their best fit planes. Then, we determined the orthogonal distance of all points along the annulus/transverse meridians from the best fit plane and subtracted those values without ring implantation from those with ring implantation (RING — NO RING, Fig 1E).
We repeated this procedure for all ring types and their respective controls for both, ED and ES. The schematics D) and E) display four markers, i.e. representing the calculations for LV1-3. Note that eight markers were used for the calculations (transverse changes and height profile) of the mitral annulus. P2=mid-lateral mitral annular marker.

**Figure 2:** (A) Mean differences (±1SD) in septal-lateral (S-L) and commissure-commissure (C-C) diameters between NO RING vs. RING on the mitral annulus (ANN), basal (LV1), equatorial (LV2) and apical (LV3) levels of the left ventricle for Physio (PHY), IMR ETlogix (ETL) and GeoForm (GEO) rings at end-diastole (ED) and end-systole (ES). (B) Mean differences (±1SD) in distances from the anterior and posterior papillary muscle (APM and PPM, respectively), to the left-ventricular apical plane for PHY, ETL and GEO at ED and ES.

Differences were calculated as RING − NO RING, i.e. positive or negative values reflect an increase or decrease, respectively, induced by ring implantation. Asterisks represent a statistically significant difference between NO RING vs. RING according to Table 2.

**Figure 3:** Marker-derived spline curves displaying continuous transverse changes (i.e. differences in distance vectors between all points on marker-generated cubic spline curves and the centers of their respective spline fits between NO RING vs. RING) of the mitral valve annulus (ANN) as well as basal, equatorial and apical transverse meridians (LV1, LV2 and LV3, respectively) at end-diastole (ED) and end-systole (ES) for Physio (PHY), IMR ETlogix (ETL) and GeoForm (GEO) rings (see Methods and Fig. 1D).

**Figure 4:** Marker-derived spline curves displaying continuous longitudinal changes (i.e. differences in the normal distance of all points along the mitral annulus as well as along basal, equatorial and apical transverse left-ventricular meridian (LV1, LV2 and LV3, respectively) from the best fit plane between NO RING vs. RING at end-diastole (ED) and end-systole (ES) for Physio (PHY), IMR ETlogix (ETL) and GeoForm (GEO) rings (see Methods and Fig 1E).
Video: Presentation illustrating the key findings of this study
### Table 1: Hemodynamic data

<table>
<thead>
<tr>
<th></th>
<th>PHYSIO</th>
<th>ETL</th>
<th>GEO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO RING</td>
<td>RING</td>
<td>p-value</td>
</tr>
<tr>
<td>MR grade</td>
<td>1.0 (1.0 – 2.0)</td>
<td>0.5 (0.0 – 0.5)</td>
<td>&lt;0.004</td>
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<tr>
<td>HR (min⁻¹)</td>
<td>90±11</td>
<td>90±14</td>
<td>0.833</td>
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<tr>
<td>LVEDV (ml)</td>
<td>133±34*</td>
<td>135±36</td>
<td>0.068</td>
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<tr>
<td>dP/dt_max (mmHg/sec)</td>
<td>1005±231*</td>
<td>1077±225</td>
<td>0.130</td>
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<tr>
<td>LVP_max (mmHg)</td>
<td>71±7*</td>
<td>75±9</td>
<td>0.460</td>
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Results for MR grade is represented as median with interquartile range and the remaining hemodynamic data are presented with mean ± 1SD; p-values for MR grade are based on a Wilcoxon rank-sum test and for the remaining hemodynamic data on paired t-test. Bonferroni adjusted level of significance p<.017. MR = mitral regurgitation; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVP = left ventricular pressure; PHY, ETL and GEO=Physio1, IMR ETlogix and GeoForm annuloplasty rings, respectively.
Table 2: Mitral annular and left ventricular diameters

<table>
<thead>
<tr>
<th></th>
<th>S-L</th>
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<th>C-C</th>
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<tr>
<td></td>
<td>ED</td>
<td>ES</td>
<td>ED</td>
<td>ES</td>
</tr>
<tr>
<td></td>
<td>NO RING</td>
<td>RING</td>
<td>NO RING</td>
<td>RING</td>
</tr>
<tr>
<td></td>
<td>% change</td>
<td>p-value</td>
<td>% change</td>
<td>p-value</td>
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</tr>
<tr>
<td>ANN</td>
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<td>3.17±0.37</td>
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<td>-26.8±3.9</td>
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<td>3.10±0.21</td>
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<td>-34.5±3.8</td>
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<td>LV1</td>
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<tr>
<td>PHY</td>
<td>5.81±0.48</td>
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<td>-0.96±1.5</td>
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<td>ETL</td>
<td>6.07±0.42</td>
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<td>GEO</td>
<td>5.93±0.26</td>
<td>5.79±0.22</td>
<td>-2.26±2.4</td>
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<td>LV2</td>
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<td>PHY</td>
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<td>0.09±1.5</td>
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<td>LV3</td>
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<td>3.62±0.48</td>
<td>0.32±0.8</td>
<td>0.733</td>
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All values are in cm, mean ± 1SD, p-values are based on a mixed effect model. Bonferroni adjusted level of significance p<.004, ED=end-diastole, ES=end-systole, SL=Septal-lateral, C=Commissure-Commissure, ANN=mitral annulus, LV1, LV2 and LV3=basal, equatorial and apical level of the left ventricle, respectively, PHY, ETL and GEO=Physio1, IMR ETlogix and GeoForm annuloplasty rings, respectively, a)=NO RING vs. RING
LV dimensions with IMR/FMR rings

### Table 3: Distances of APM and PPM to the LV apical plane at ED and ES

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<th></th>
<th>Distance to LV apical plane</th>
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<td>ES</td>
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</tr>
<tr>
<td></td>
<td>NO RING</td>
<td></td>
<td></td>
<td>RING</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>p-value</td>
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<tr>
<td></td>
<td>APM</td>
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<tr>
<td>PHY</td>
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<td>ETL</td>
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<td>GEO</td>
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<td>0.868</td>
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All values are in cm, mean ±1SD, p-values are based on a mixed effect model. Bonferroni adjusted level of significance p<.008.

APM and PPM= anterolateral and posteromedial papillary muscle, respectively.

ED=end-diastole, ES=end-systole, PHY, ETL and GEO=Physio1, IMR ETlogix and GeoForm annuloplasty rings, respectively.
Do Annuloplasty Rings Designed to Treat IMR/FMR Alter Left-Ventricular Dimensions in the Acutely Ischemic Ovine Heart?

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