Posterior leaflet augmentation improves leaflet tethering in repair of ischemic mitral regurgitation

J. Daniel Robb c,1, Masahito Minakawa c,1, Kevin J. Koomalsingh c, Takashi Shuto c, Arminder S. Jassar a,c, Sarah J. Ratcliffe b, Robert C. Gorman a,c, Joseph H. Gorman III a,c,*

Departments of Surgery, University of Pennsylvania, Philadelphia, PA, USA
b Department of Biostatistics & Epidemiology, University of Pennsylvania, Philadelphia, PA, USA
c Gorman Cardiovascular Research Group, University of Pennsylvania, Philadelphia, PA, USA

Received 17 September 2010; revised 16 February 2011; accepted 21 February 2011; Available online 4 May 2011

Abstract

Objectives: Ischemic mitral regurgitation (IMR) occurs from annular dilatation, leaflet tethering and leaflet flattening. Undersized annuloplasty corrects annular dilatation but worsens leaflet tethering and flattening. This exacerbation of abnormal leaflet geometry may contribute to poor repair results for ischemic mitral regurgitation (IMR). Using a sheep model of IMR, we hypothesized that posterior leaflet augmentation and less-extreme annular undersizing would relieve tethering and increase leaflet curvature. Methods: Eight weeks after postero-lateral infarct, 10 sheep with ≥2+ IMR underwent either a 24-mm planar ring annuloplasty (n = 5) or a 30-mm planar ring annuloplasty with concomitant posterior leaflet augmentation (n = 5). Real-time three-dimensional echocardiography allowed measurement of indices of leaflet curvature and tethering before and after annuloplasty. Results: Comparing pre- and post-repair values in the P1, P2, and P3 leaflet regions, undersized 24-mm ring annuloplasty made no significant difference to mean septal lateral curvature (0.23–0.26, 0.33–0.29, and 0.27–0.37 cm⁻¹, respectively), whereas leaflet augmentation in combination with a 30-mm ring annuloplasty increased septal lateral curvature (P1 0.30–1.02, P2 0.31–1.23, and P3 0.35–0.84 cm⁻¹, p-values < 0.05). The mean tethering angle formed between the annular plane and the posterior leaflet increased in all three posterior regions for the 24-mm ring group (P1 12–23°, P2 26–31°, and P3 16–25°), but decreased in all regions for the group undergoing leaflet augmentation (P1 <5° to –6°, P2 <13° to –13°, P3 <16–15°, all p-values < 0.05). Conclusions: Undersized annuloplasty exacerbates leaflet tethering. Posterior leaflet augmentation with less severe annular reduction increases leaflet curvature and decreases tethering; this technique more completely addresses the pathologic mechanism of IMR and may improve repair durability.

1. Introduction

Ischemic mitral regurgitation (IMR) occurs when a structurally normal mitral valve (MV) is rendered incompetent as a result of left-ventricular (LV) remodeling induced by myocardial infarction (MI) [1]. IMR is present in some degree in over 50% of patients with reduced LV ejection fraction, who undergo coronary artery bypass grafting (CABG) [2,3]. The magnitude of this clinical problem is significant and is expected to grow substantially over the next two decades as the population ages [2]. IMR increases mortality even when mild, with a strongly graded relationship between severity and reduced survival [3,4]. MV repair with undersized ring annuloplasty, typically performed in conjunction with CABG, has become the preferred treatment [5,6]. However, this therapeutic approach is associated with a 30% recurrence rate of significant IMR at 6 months after surgery with longer-term (3–5 years) rates of recurrence approaching 60% [7–12]. For patients with IMR, this lack of durability is likely to contribute to the difficulty in demonstrating a survival advantage of MV repair compared with either medical management, or with revascularization alone [11,13,14].

Post-infarction LV remodeling causes IMR secondary to two distinct anatomical perturbations: leaflet tethering and annular dilatation (see Fig. 1B). While ring annuloplasty is effective in treating annular dilatation, it does not improve...
and indeed may potentiate leaflet tethering (see Fig. 1(C)) [15]. Leaflet tethering decreases leaflet curvature and results in increased leaflet and chordal stress [16]. This exacerbation of abnormal leaflet geometry may contribute to the suboptimal repair results for IMR.

Using an established sheep model of IMR, we tested the hypothesis that posterior leaflet augmentation combined with less extreme annular undersizing would relieve leaflet tethering and increase leaflet curvature as suggested by Fig. 1(D).

2. Materials and methods

2.1. Surgical protocol

The animals used in this study received humane care in compliance with the European Convention on Animal Care, and the study was approved by the institute’s ethics committee, the University of Pennsylvania School of Medicine Institutional Animal Care and Use Committee (IACUC). The 14 adult male sheep were pre-treated with buprenorphine (2 μg kg⁻¹) and then induced with intravenous (IV) sodium thiopental (10—15 mg kg⁻¹), intubated, and anesthetized with isoflurane (1.5—2.0%) and oxygen. All animals received glycopyrrolate (0.02 mg kg⁻¹ IV) and cefazolin (1.0 g IV). The electrocardiogram, arterial blood pressure, and pulmonary artery pressure were monitored throughout the procedure. Under sterile conditions, all animals underwent right thoracotomy to allow ligation of all distal branches of the left circumflex coronary artery between the lateral cardiac vein and the middle cardiac vein [17,18]. Permanent occlusion of these arteries reliably results in a transmural posterobasal myocardial infarction that involves approximately 20% of the LV mass and typically includes the entire posterior papillary muscle [17,18]. Animals received magnesium sulfate (1 g IV), amiodarone (90 mg IV infusion over an hour), and lidocaine (3 mg kg⁻¹ IV bolus, then 2 mg min⁻¹ infusion) before infarction as anti-arrhythmic prophylaxis. After hemodynamic and electrophysiological stabilization, the thoracotomy was closed and the animal permitted to recover.

Eight weeks after infarction, the surviving animals were returned to the operating room. Anesthesia was once more induced, as described above, and all animals had chest-wall echocardiography to assess the degree of IMR. Animals with < 2+ IMR were euthanized and excluded from further analysis. The remaining animals (those therefore with ≥ 2 IMR) were randomized to undergo either surgical placement of an undersized (size 24) mitral annuloplasty ring (Carpentier-Edwards Physio annuloplasty ring, Edwards Life Science, Irvine, CA, USA), or to undergo posterior MV leaflet augmentation using a patch of autologous pericardium with concomitant placement of a less aggressively undersized (size 30) mitral annuloplasty ring (Carpentier-Edwards Physio annuloplasty ring, Edwards Life Science, Irvine, CA, USA), or to undergo posterior MV leaflet augmentation using a patch of autologous pericardium with concomitant placement of a less aggressively undersized (size 30) mitral annuloplasty ring (Carpentier-Edwards Physio annuloplasty ring, Edwards Life Science, Irvine, CA, USA). Following separation from bypass and acquisition of echocardiographic data (see below), animals were euthanized by an overdose of potassium administered into a clamped aortic root. The heart was excised. The right ventricle and atria were removed from the specimen and the LV opened through the interventricular septum. A digital photograph of the opened left ventricle was taken and the infarct location was verified. All photographs were imported into an image analysis program (Image Pro Plus, MediaCybernetics; Silver Spring, MD, USA) and computer-assisted planimetry was performed on the photographic image to quantify the infarct size as a percentage of the LV.

2.2. Annuloplasty and posterior leaflet augmentation technique

Valve repair was performed via a left thoracotomy using cardiopulmonary bypass (CPB) and standard cardic surgical techniques. Once the heart had been dissected free from pericardial adhesions, a piece of pericardium was harvested and maintained in a saline bath at room temperature, until required for those animals undergoing leaflet augmentation. The heart was arrested with antegrade cold crystalloid cardioplegia (Plegisol®, Hospira Inc, Lake Forest, IL, USA) and the MV approached via a left atriotomy. The annulus was measured using standard mitral sizers. Interrupted 2/0 braided sutures were then placed in the annulus. For those animals undergoing leaflet augmentation, an incision was then made in the posterior leaflet 2 mm from and parallel to the annulus and extending from the mid-P1 to mid-P3 regions. A piece of the previously harvested pericardium was cut to 45 mm in length and 10 mm in width and its ends were tapered. Using 6/0 polypropylene, this was sutured into place, first along its annular edge and then along the edge opposed to the cut edge of the main part of the leaflet. The chosen annuloplasty ring was seated and tied into place. The valve was tested in standard fashion and the atriotomy was closed, following which the heart was de-aired and the animal weaned from CPB. Following euthanasia, the ventricle was opened as described above and the repair was inspected (Fig. 2).
2.3. Echocardiographic protocol

All echocardiograms were recorded by a single operator using a Philips iE33 platform with a 2–7 MHz matrix array real-time three-dimensional (3D) ultrasound probe (Philips X7-2, Philips, Bothell, WA, USA).

Epicardial real-time 3D echocardiogram (rt-3DE) was performed prior to instituting CPB and again after valve repair, approximately 1 h after separation from CPB. Both rt-3DE studies were performed at an arterial systolic pressure of 150 mmHg and in each case, electrocardiogram-gated, full-volume data sets of the MV were acquired. During study, the degree of MR was determined quantitatively using two-dimensional (2D) color Doppler flow imaging, by assessing the area of the regurgitant jet as a percentage of left atrial area in the apical four-chamber view. The following grading scale was used: grade 0 = no MR; grade 1 < 20%; grade 2 = 20–40%; grade 3 = 40–60%; and, grade 4 > 60% [19]. Subsequently, each full-volume data set was exported to a dedicated Cardio-View (TomTec Imaging Systems, Munich, Germany) software workstation for image manipulation and analysis.

2.4. Image analysis

Image analysis was performed in Cardio-View, which allows the interactive manipulation—including rotation, translation, surface rendering, and measurement—of fully 3D ultrasound data sets. All analysis was performed under peak loading conditions in mid-systole, which was defined as...
the frame midway between the first frame demonstrating closure of the MV and the first frame demonstrating closure of the aortic valve. In Cardio-View, the plane of the MV orifice was rotated into a short-axis view. The geometric center of the MV was then translated to the intersection of the two corresponding long-axis planes, which then corresponded to the intercommissural and septolateral axes of the MV orifice. To trace the mitral annulus, a rotational template consisting of 18 long-axis cross-sectional planes separated by 10° increments was superimposed on the 3D echocardiogram [20]. The two annular points intersecting each of the 18 long-axis rotational planes were identified by orthogonal visualization of each plane, resulting in a 36-point representation of the mitral annulus (Fig. 3(A) and (B)). To segment the mitral leaflets, measurement planes were then marked at fixed 1-mm intervals along the entire length of the intercommissural axis, from the anterior commissure to the posterior commissure. The anterior mitral leaflet (AML), the posterior mitral leaflet (PML), and the co-apartition point (CP), were then traced in each cross section (Fig. 3(C)), resulting in a 600- to 1200-point data set for each MV, examples of which are presented in Fig. 4(A) and (B).

2.5. Calculation of annular geometry

Geometric modeling and analysis of each data set, consisting of 36 annular points, were performed using a series of Matlab (The Mathworks Inc., Natick, MA, USA) algorithms. The least-squares plane of the 3D data set was then calculated by means of orthogonal distance regression and the annular model rotated such that this MV orifice plane was aligned with the x−y plane. Mitral annular area (MAA), anterior (AAA) and posterior (PAA) annular arcs on the mitral annular circumference were then calculated by projection onto this least-squares plane.

2.6. Calculation of leaflet curvature

Smoothing splines were constructed for each leaflet data set using the Matlab TPAPS function. The smoothing parameter was assigned automatically for each data set by the function. A Delaunay triangulation was used to exclude mesh points that fell outside the borders described by the annular and leaflet data points.

The intercommissural axis of each MV data set was then subdivided into equal thirds, and the PML divided into its three regions P1, P2, and P3. Mean septolateral 2D leaflet curvature (K_SL) was calculated for each region of the PML.

2.7. Calculation of alpha (tethering) angle

Linear regression was used to compute the tangents to the surface of the leaflet spline at each leaflet mesh plane from commissure to commissure for the posterior leaflet. The angles between these tangents and the lines connecting the anterior annulus to the corresponding posterior annulus are designated α, representing the degree of tethering. This is demonstrated in Fig. 5. Regional averages were obtained for each third of the posterior leaflet. According to this definition, the more positive α is, the more the annular portion of the leaflet is directed toward the LV, indicating greater tethering. The more negative α is, the more the annular portion of the leaflet is directed toward the left atrium, indicating less tethering.

2.8. Visualization and statistics

All MV geometric parameters and hemodynamic parameters were compared between groups prior to repair using Mann-Whitney U-tests. Post repair MAA, AAA and PAA were compared between groups using Mann-Whitney U-tests. Post-repair regional changes in leaflet curvature and tethering angle were also compared between groups using these tests. The level of significance selected for all variables was p ≤ 0.05. Numerical results are presented as mean ± standard deviation.

3. Results

3.1. Animal survival and MR

Four animals died prior to the 8-week post-MI randomization time point. All of these animals died either perioperatively or within the first 2 weeks after infarction, the cause being arrhythmia or heart failure. The remaining 10 animals were all found to have ≥2+ IMR at the time of the 8-week post-MI echocardiographic studies and were randomized to the undersized 24-mm group (n = 5, MR = 2.6 ± 0.5) or to the augmentation + 30-mm ring group (n = 5, MR = 2.6 ± 0.9). In the undersized ring group, the degree of MR post annuloplasty was 0.1 ± 0.2 (p < 0.01 vs pre-bypass). In the augmentation group, MR was 0.3 ± 0.4 immediately after annuloplasty placement (p < 0.01 vs pre bypass and p = 0.9 vs the undersized ring group post annuloplasty).

3.2. Hemodynamic data

No significant differences in LV end diastolic pressure, central venous pressure, mean arterial pressure, pulmonary
artery pressures, or cardiac output were observed between groups, either before or after annuloplasty. When the undersized ring group was compared with the group undergoing 30-mm ring annuloplasty + leaflet augmentation, there were significant differences in both CPB time (85 ± 16 vs 149 ± 26 min, respectively, p < 0.01) and aortic cross-clamp time (52 ± 9 min vs 105 ± 22 min, respectively, p < 0.01).

3.3. Annular size

All measures of annular size (MAA, AAA, and PAA) were not significantly different prior to repair. After repair, MAA, AAA, and PAA were all significantly greater in the leaflet augmentation group than in the undersized annuloplasty group (Table 1).

3.4. Leaflet curvature data

There was no significant difference in regional leaflet curvature between groups prior to repair. Septolateral leaflet curvature ($K_{SL}$, cm$^{-1}$) after posterior leaflet augmentation increased significantly in all three regions (P1, P2, the P3) when compared with undersized annuloplasty alone (Table 1 and Fig. 6(A) and (B)).

3.5. Alpha (tethering) angle data

There were no significant differences in tethering angle between groups prior to repair. In regions P1 and P2, the tethering angle decreased significantly in the leaflet augmentation group when compared with undersized annuloplasty (Table 1 and Fig. 6(C) and (D)).

3.6. Pathology

Post-mortem assessment demonstrated that the infarct size as a percentage of the LV was similar in the 24-mm ring annuloplasty group (19.4 ± 3.4%) and in the leaflet augmentation + 30-mm ring annuloplasty group (15.7 ± 4.1%) indicating that the remodeling stimulus was the same in both groups (Table 1).

4. Discussion

IMR carries a poor prognosis. There is little evidence that surgical intervention on the valve significantly improves clinical outcomes. The most widely accepted and applied surgical treatment for IMR is annular reduction with annuloplasty devices, with or without concomitant CABG. Unfortunately, although some investigators have reported good results, particularly with aggressively undersized annuloplasty [21,22], most groups have experienced very high rates of early recurrence of moderate or severe MR after such repairs [7–12].
Animal models and clinical studies have demonstrated the multifaceted pathophysiological origin of IMR. In brief, infarction-induced LV remodeling leads to papillary muscle displacement in relation to the plane of the annulus; this produces tethering of the chordae tendineae and impaired co-aptation of the leaflets during systole. This subvalvular pathology is usually compounded by significant but variable annular dilatation. Reduction annuloplasty treats only this annular dilatation component of the pathological process, and often acts to exacerbate posterior leaflet tethering.

A small but growing body of clinical and animal studies has focused on investigating the use of leaflet augmentation as a means to reduce the high rate of recurrent IMR so often experienced with reduction annuloplasty alone. Kincaid and colleagues were early proponents of leaflet augmentation as an adjunct to annuloplasty for IMR [23]. Unfortunately, these investigators used pericardium to augment the ‘anterior’ leaflet in conjunction with undersized annuloplasty. This approach resulted in the recurrence of moderate to severe MR in 19% of patients within 2 years of surgery. Langer and colleagues from the Stanford University group reported an initial laboratory study using an ovine model of acute IMR in which a pericardial patch was sutured into the middle scallop of the posterior MV leaflet and furled in with a reefing stitch placed in the radial axis [24]. Postero-lateral LV myocardial ischemia was created by using proximal circumflex occlusion to induce acute IMR. Under open-chest conditions, 3D marker coordinates were measured by using biplane video fluoroscopy at baseline and during acute ischemia both before and after release of the reefing stitch (leaflet extension). Posterior MV leaflet extension ameliorated acute IMR, but did not correct the abnormal apically restricted systolic posterior MV leaflet closing motion. The acute nature of the IMR, limited extent of leaflet augmentation, and lack of any annuloplasty made the results of this study difficult to extrapolate to the care of patients; however, the work did stimulate interest in posterior leaflet augmentation for IMR. Most recently, de Varennes and colleagues have reported a clinical study of 44 patients with severe IMR, all of whom underwent posterior leaflet extension with pericardium and undersized annuloplasty [25]. The actuarial freedom from moderate or severe recurrent MR was 90% at 2 years. While these results are encouraging, the study was limited by the lack of a control group, location of leaflet augmentation (isolated to P3 region), and aggressive annular reduction that could have reduced the efficacy of leaflet extension.

In the experiment reported here, we employed a well-established and clinically relevant ovine model of chronic IMR, which results from both progressive annular dilatation and leaflet tethering, to compare aggressive annular downsizing alone, with moderate annular downsizing combined with extensive posterior leaflet augmentation. Our technique for leaflet augmentation was unique in that it involved virtually the entire posterior leaflet, resulting in extension of all three regions of the posterior leaflet. Both techniques resulted in effective relief of MR immediately after surgery. As expected, aggressive undersizing led to increased posterior leaflet tethering. Less aggressive annular reduction combined with posterior leaflet augmentation decreased the tethering angle of the P1 and P2 segments. The extensive nature of the augmentation actually resulted in increased septolateral curvature of the posterior leaflet, which is consistent with billowing of the posterior leaflet into the left atrium. Although not quantitatively assessed in this study, the increased leaflet curvature would likely be associated with reduced leaflet and chordal stress. While the current study did not assess the durability of the repair technique, it is reasonable to speculate that by restoring a more normal leaflet and annular geometry, a leaflet augmentation procedure would promote a more normal valve stress profile, which would have the effect of optimizing or improving repair durability.

Severely undersized ring annuloplasty to repair IMR has also been associated with ring dehiscence as a mode of repair failure. While not measured or assessed in the current study, it is also reasonable to speculate that by requiring less severe annular downsizing, posterior leaflet augmentation procedures would have the effect of reducing strain between the dilated IMR annulus and the annuloplasty ring, and, hence, reduce the incidence of ring dehiscence as a cause of repair failure.

We believe that as result of limited annular downsizing in combination with leaflet augmentation in IMR patients, reduced posterior leaflet tethering, and reduced valvular stress should result in improved long-term function of the MV and also possibly the LV. Despite our optimism regarding the potential efficacy of this technique, it must be kept in mind that the augmentation procedure described would be technically more complex than simple annuloplasty and may carry more operative complication. More extensive animal studies, and, ultimately, controlled clinical trials will be needed to confirm this hypothesis.

While the results reported above are encouraging and thought provoking, more work is necessary to assess the influence of posterior leaflet augmentation on leaflet stress, annuloplasty ring-annular dynamics, and, ultimately, repair durability. Important limitations of the current study include: (1) lack of long-term follow-up and (2) failure to assess the effect of leaflet augmentation combined with aggressive undersized annuloplasty. Both issues are important and are the focus of experiments that are beginning in our laboratory.

References


Appendix A. Conference discussion

Dr R. Dion (Genk, Belgium): The authors have developed a well-recognized chronic heart failure model in the sheep, and in this experiment they use this model after an evolution of eight weeks. In the introduction of the manuscript and of the presentation, the authors state that the six-month recurrence of mitral regurgitation usually amounts to 30% and that it becomes 60% at three to five years. This statement is largely based on the experience of the Cleveland Clinic already published in 2004 in the Journal of Thoracic and Cardiovascular Surgery. If one reads the material and methods paragraph of this manuscript, one has to concede that the grade of undersizing, the devices used, and the surgical strategy were rather inhomogeneous. More recent papers, based on a homogeneous surgical strategy, have demonstrated much lower mitral regurgitation recurrence rates at early and late follow-up. The Leiden group, for instance, have demonstrated a recurrence rate of 13% at four years following a well-conducted restrictive annuloplasty, certainly in patients presenting preoperatively with an end-diastolic diameter of 65 mm or less. The Leiden group were also using the Physio ring with an undersizing by two sizes, precisely two sizes. If the height of the anterior leaflet was measured at 32, a 28 Physio ring was placed. A leaflet coaptation length of 8 mm was requested at the end of the operation.

This leads to my first question about the sizing of your rings. How was the ring size 24 selected? What was the normal dimension of the mitral annulus? If I read in your manuscript that a 32 ring was still undersizing, it would mean that the mitral annulus of these animals amounted to at least 34. In this case, a 24 ring would be far too small and would indeed induce an increase in tethering.

I have a second question. In the patch group, the patch measures 10 mm in width, which means an effective augmentation of not more than 5 mm of the posterior leaflet if you consider the stitches on both sides. I believe that if the authors aim at an increase of the leaflet curvature, they should probably place a much wider patch to guarantee a higher effective augmentation.

Finally, one should remember that the leaflet tissue in ischemic mitral regurgitation is normal and that the augmentation of a thin, friable and transparent posterior leaflet in an old woman is not always going to be very safe in clinical conditions.

Dr Robb: Certainly I agree with you that the leaflet tissue in question is very friable. We chose 10 mm because, really, in these animals it seemed to augment the leaflet by quite some degree, and if we go back to my picture perhaps, in the lower right-hand panel you can see the bowing of the leaflet one had been augmented. Really, this technique produced a posterior leaflet which was augmented by 10 mm. Again, in the lower right-hand panel you can see that the measurement of the patch even after stitching approached 10 mm. So that is with regard to the sizing of the leaflet.

With regard to the sizing of the annular rings, these animals mostly have annular sizes at operation of 30 to 32 mm. So we chose 24 mm as an aggressive undersizing. This represents more than two sizes in term of undersizing. And the 30 mm ring was really chosen as marginal undersizing or perhaps more like true sizing. So the comparison was going to be between aggressively undersized and really a true or a slightly undersized ring.

Dr J. Aranenidi (Bilbao, Spain): These ideas have already been taken into clinical practice. We published our own technique in the Asian Annals in 2002 for ischemic regurgitation with restricted leaflet motion, and it has become our technique of choice in ischemic mitral regurgitation. And so far the results last over time and are reliable, and we haven’t found a friable posterior leaflet that could not be enlarged.

Furthermore, the main concern in congenital mitral regurgitation is also restricted leaflet motion, and most kids are repaired with patch enlargement, even in young babies, and the repair is consistent and lasts over time.