Ischemic Mitral Regurgitation: Recent Advances

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Opinion statement

This article reviews recent developments in the pathophysiology and management of ischemic mitral regurgitation. Recent imaging studies using three-dimensional echocardiography have added clarity to the mechanism responsible for this condition. This article also discusses recent studies on outcomes of surgical repair, including current results and potential risks of restrictive annuloplasty. Because of the limitations imposed by restrictive annuloplasty, adjunctive surgical methods focusing on the left ventricle or papillary muscles are being investigated to address this disease. In the interim, a downsized complete rigid or semirigid annuloplasty repair appears to offer good midterm outcomes.

Introduction

Recently, we reviewed the pathophysiologic concepts governing the current management of severe mitral valve regurgitation of ischemic etiology [1]. Surgery remains the mainstay of therapy for this condition as attempts at medical and percutaneous interventional treatment have thus far been unsuccessful. Ischemic mitral regurgitation continues to portend a poor prognosis, hence the need for continued investigation into pathophysiologic concepts, diagnostic modalities, and novel therapeutic approaches. This article reviews the progress in this field over the past 2 years, mainly as it relates to surgical therapy.

UNDERSTANDING ISCHEMIC MITRAL REGURGITATION

Carpentier's pathophysiologic triad [2] remains the cornerstone for defining ischemic mitral regurgitation. Crucial to describing and understanding therapies for ischemic mitral regurgitation is an understanding of the etiology, lesions (pathologic changes in the valve that result in valve dysfunction), and dysfunction (abnormalities of leaflet motion) that may contribute to valve incompetence [3•]. To introduce consistency in the approach to diagnosis and therapy, a uniform definition of ischemic mitral regurgitation is required; otherwise, varying outcomes may reflect varying opinions as to what constitutes ischemic mitral regurgitation, rather than differences in applied therapy [3•]. To define *chronic* ischemic mitral regurgitation, there should first be clear documentation of an ischemic *etiology* in the form of coronary artery disease and prior myocardial infarction with resultant global or regional alteration of left ventricular geometry or function. Echocardiography should demonstrate that the *dysfunction* causing regurgitation is restriction of leaflet motion occurring in systole (Carpentier type IIIb). If the dysfunction is leaflet prolapse (Carpentier type II) or the leaflet motion is normal (Carpentier type I dysfunction), alternative etiologies should be excluded. Chronic mitral valve prolapse secondary to ischemic heart disease is possible but rare; a diagnosis of degenerative mitral valve disease with coexisting coronary artery disease is more likely if a combination of valve prolapse and coronary artery disease is seen. Simple annular dilatation without leaflet restriction is not typical in ischemic mitral regurgitation, although it may occur in the setting of isolated basilar myocardial infarction. Acute ischemic mitral regurgitation, such as that which occurs following ischemic papillary muscle rupture, is not considered in this review.

The key events in the pathogenesis of ischemic mitral regurgitation are postinfarction wall motion abnormalities and subsequent left ventricular remodeling, which result in displacement of papillary muscles toward the ventricular apex. This papillary muscle displacement causes tethering of the valve leaflets, which is typically predominant in the region of the posterior-medial scallop of the posterior leaflet (P-3). This tethering of the posterior leaflet is the principal *lesion* of ischemic mitral regurgitation and results in restriction of leaflet motion, which is the principal *dysfunction*. Absence of obvious posterior leaflet tethering and restriction should lead the echocardiographer or surgeon to consider alternative diagnoses, particularly if there has not been anterior infarction (which may result in more diffuse tethering of both leaflets). Mitral annular dilatation often accompanies leaflet tethering but is a secondary, rather than primary, *lesion*. Therefore, a strict definition of ischemic mitral regurgitation by Carpentier's triad requires the following: 1) the patient has coronary artery disease with a global or regional wall motion abnormality, 2) echocardiography shows restricted leaflet motion in systole and/or annular dilatation, and 3) the valve leaflets are tethered but otherwise look macroscopically normal.

CONCEPTS IN THE PATHOPHYSIOLOGY OF ISCHEMIC MITRAL REGURGITATION

Experimental and clinical imaging studies in the 1990s demonstrated that the primary mechanism for ischemic mitral regurgitation is not papillary muscle dysfunction, as was previously thought, but lateral and apical displacement of the papillary muscles with resultant leaflet tethering. Recent imaging studies, particularly three-dimensional (3D) echocardiography, have improved the clarity of our understanding of this disease's pathophysiology.

Limitations of two-dimensional echocardiography

Until recently, most of our understanding and the clinical management of ischemic mitral regurgitation was based on two-dimensional (2D) echocardiography. Several methods of measuring the degree and location of leaflet tethering have been defined. However, variability in measurement planes and mitral annular shape made these measurements generally inconsistent and unreliable. The application of 3D echocardiography has improved our ability to localize and quantify tethering and allows us to assess volumes and areas rather than single measures of distance, as in 2D echocardiography. In assessing the degree of leaflet tethering, 3D echocardiography has an advantage in that it considers the entire valve and is independent of the plane of selection, asymmetry of tenting, and annular dilatation [4•]. Using 3D echocardiography in an ovine model, Ryan et al. [5], for example, described methods that allow comprehensive analysis of tethering of the entire valve; using this technique, they produced data suggesting that tenting and valve remodeling may be more widespread than is appreciated on 2D echocardiography and may not be as limited to the posterior annulus as generally assumed.

Geometric differences between anterior and inferior infarction

Using 3D echocardiography, several investigators have demonstrated differences in the mechanism of regurgitation according to area of infarction. Watanabe et al. [6•], for example, found a more localized tethering involving the posterior leaflet in patients with inferior infarction, compared with widespread tethering of both anterior and posterior leaflets in anterior infarction; this observation highlights the critical role of regional (rather than global) ventricular geometry and function in the pathophysiology of ischemic myocardial regurgitation. Song et al. [7] found that an inferoposterior infarction coexisting with an anterior wall infarct leads to a more severe regurgitation with an effect independent of ventricular volume, suggesting that the geometry of the valve apparatus is a more important determinant of regurgitation than left ventricular volume or ejection fraction. It is possible, therefore, to have severe ischemic mitral regurgitation in the setting of relatively preserved ventricular function. Patients in whom inferoposterior infarction coexists with anterior infarction do not have the classic, severe asymmetry in tethering seen in isolated inferoposterior infarction [7]. The differences in geometry observed between anterior and inferior infarctions have led some to question whether therapy should differ depending on location of infarction and whether a lack of emphasis of the annuloplasty on areas of greatest tethering could explain some recurrences after surgical repair. For example, the Carpentier-McCarthy-Adams ETlogix ring (Edwards Lifesciences, Irvine, CA) is specifically designed to address asymmetric tethering of inferior infarction [8] so may not be as applicable to the more widespread tethering of anterior infarction.

NATURAL HISTORY OF ISCHEMIC MITRAL REGURGITATION

Recent data continue to highlight ischemic mitral regurgitation after myocardial infarction as a major risk factor for death and cardiac events. Aronson et al. [9••] prospectively studied 1190 patients who had sustained acute myocardial infarction between 2001 and 2005 stratified according to degree of mitral regurgitation. Within 3 years, 30% of those with moderate or severe regurgitation had been hospitalized for heart failure, compared with 5% of those with no regurgitation. The mortality rates were also substantially higher in those with moderate or severe regurgitation (35% at 3 years; hazard ratio [HR], 5.5; 95% CI, 2.3–9.1) compared with those with no regurgitation (8% at 3 years). Of note was that even mild regurgitation was a risk factor for midterm mortality

(HR, 2.0; 95% CI, 1.4–3.0). These observations suggest that little has changed from earlier epidemiologic studies [10] and that ischemic mitral regurgitation remains associated with a substantial increase in mortality and morbidity. Of particular note, Aronson et al. [9••] observed this effect to be independent of left ventricular function.

Ineffectiveness of percutaneous coronary intervention in the setting of ischemic mitral regurgitation

Although it remains controversial whether surgery can alter ischemic mitral regurgitation's natural history, it seems certain that current nonsurgical therapies do not reduce the risk associated with this condition. One recent study supports this claim. Investigators examined long-term outcomes in 711 patients who had undergone percutaneous coronary intervention (PCI) and found that moderate to severe mitral regurgitation at time of PCI was associated with a 5-year survival of 57%, compared with 97% for those with no regurgitation [11•]. Again it was observed that even mild regurgitation was a risk factor for midterm mortality (5-year survival, 83%). These data mirror the historical series from Ellis et al. [12] and show that there has been no improvement in outcomes with percutaneous therapy for ischemic mitral regurgitation in the past 10 years, thus raising questions regarding the continued use of PCI as primary therapy for coronary stenoses in patients who have associated ischemic mitral regurgitation. In contradistinction, a recently published surgical series found a 75% 5-year survival rate for patients with ischemic mitral regurgitation treated with bypass surgery alone between 1991 and 2003. The better survival with bypass surgery as compared with PCI may reflect a more complete and definitive revascularization in these patients, who by definition have some degree of ischemic cardiomyopathy. Because of the more definitive revascularization and the potential for surgical intervention on the mitral valve, the coexistence of ischemic mitral regurgitation in patients with severe coronary disease needing revascularization should generally be an indication for surgical rather than percutaneous revascularization, although individual circumstances may dictate otherwise.

Surgery for ischemic mitral regurgitation

Questionable efficacy of mitral valve annuloplasty for ischemic mitral regurgitation

- Several papers published in the early half of this decade suggest that mitral valve annuloplasty is ineffective, as many patients developed recurrent regurgitation early after surgery. In previous work, we discussed flaws in most of these studies [3•] that make it impossible to draw reliable conclusions from the literature regarding the efficacy of this procedure. The vast majority of studies are of limited applicability to current practice because the surgical techniques were inconsistent, inadequate, or dated; the follow-up was incomplete; the cohorts were poorly defined or heterogeneous; or the methodologic and statistical approaches were flawed.
- Recent papers continue to add to the controversy as to whether mitral valve annuloplasty alters the natural history of ischemic mitral regurgitation. Although additional series have been reported showing disappointing outcomes with annuloplasty, there is a commonality across all these series in that they still suffer from some of the critical flaws in study design or surgical methods observed in earlier studies [3•]. For example, three recent papers questioning the efficacy of ischemic mitral valve repair [13,14,15•] are summarized in Table 1. A common theme in all these papers is that a substantial number of patients did not receive the current standard operation for ischemic mitral regurgitation—a restrictive annuloplasty using a complete rigid or semirigid ring—with a varying proportion of patients receiving incomplete annuloplasty with flexible rings or pericardium. Most authorities today would not recommend flexible incomplete rings for ischemic mitral regurgitation, as the anterior portion of the mitral annulus between the commissures has the propensity to dilate in the setting of progressive ventricular remodeling (Fig. 1). Table 1 lists the other limitations of these recent studies questioning the efficacy of annuloplasty.
- It can be demonstrated logically that a substantial component of the published data suggesting ineffectiveness of annuloplasty for ischemic mitral regurgitation can be explained by limitations in the data, study

Table 1. Principal outcomes, conclusions, and limitations of recent studies suggesting limited efficacy of restrictive annuloplasty in ischemic mitral regurgitation

Study	Main result	Conclusion	Limitations and flaws
Crabtree et al., 2008 [13]	52% survival at 5 y; 28% of patients with moderate or severe MR at latest echo	Questions the benefit of adding annuloplasty to CABG	Use of inadequate technique: 44% of patients received an incomplete (posterior) annuloplasty with a flexible band. Such bands have limited efficacy as they do not address tethering and dilatation of the anterior annulus. Echo follow-up available in only 57% of patients
Gelsomino et al., 2008 [14]	Reverse remodeling seen in only 41% of patients	Annuloplasty + CABG is ineffective in a large percentage of patients	Suboptimal early results: 7% repair failure or residual MR rate Limited revascularization approach: average of 2 bypasses per patient suggests incomplete revascularization
Mihaljevic et al., 2007 [15•]	CABG + annuloplasty did not improve long-term functional status or survival compared with CABG alone	Annuloplasty is insufficient to improve long-term clinical outcomes	Historical cohort: patient inclusion began in 1991 so does not fully reflect recent advances in surgery; eg, downsized annuloplasty, the current therapy for ischemic regurgitation, became routine only in the late 1990s Unusually high survival rate in CABG-only group: 5-y survival of 75% not typical in most surgical series Ineffective technique: 15% of propensity-matched patients had annuloplasty with pericardium strips, a technique shown to be ineffective, with unacceptably high recurrent MR rate [29] Inadequate technique: 59% of patients received flexible posterior bands, which do not address anterior tethering and dilatation

CABG—coronary artery bypass surgery; echo—echocardiogram; MR—mitral regurgitation.

methodology, or surgical technique [3•]. Of note, there are no methodologically robust studies in the surgical literature that demonstrate a lack of effectiveness of annuloplasty in ischemic mitral regurgitation.

Excellent midterm outcomes with consistent rigid or semirigid downsized annuloplasty

- In cases in which downsized complete rings have been applied systematically, the results of annuloplasty appear to be comparatively excellent. A notable series is the one from Braun et al. [16••], who recently reported on midterm outcomes of 100 patients who systematically underwent restrictive annuloplasty for ischemic regurgitation. Echocardiography at an average follow-up of 4.3 years showed that 85% of the patients had no or mild regurgitation, and the 5-year survival rate was 71%, substantially better than reported in other surgical series. Also observed was a relationship between the preoperative left ventricular end-diastolic diameter (LVEDD) and outcome: patients with an LVEDD ≤ 65 mm had better 5-year survival (80%) and developed sustained left ventricular reverse remodeling compared with patients with an LVEDD greater than 65 mm (5-year survival, 49%; no ventricular reverse remodeling). Although this study shows promising outcomes for patients with ischemic regurgitation and an LVEDD less than 65 mm, it also highlights the need for supplemental or alternative approaches in patients with very dilated ventricles (LVEDD > 65 mm).
- The study by Braun et al. [16••] has several notable factors that differentiate it from the many negative reports on the efficacy of annuloplasty

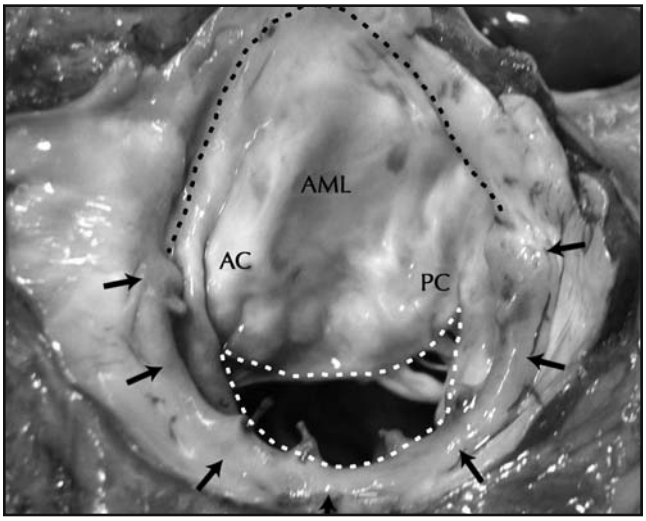

Figure 1. Failure of a flexible posterior annuloplasty band for the repair of ischemic mitral regurgitation. A previously implanted posterior annuloplasty band (*arrows*) extends from the anterior commissure (AC) to the posterior commissure (PC). Although this band successfully prevented dilatation of the posterior annulus, the anterior mitral annulus (*dotted black line*) continued to dilate such that it now constitutes more than half of the annular circumference rather than the usual third. Dilatation of the anterior annulus has led to retraction of the anterior mitral leaflet (AML), leading to failure of leaflet coaptation (*dotted white line*) and severe recurrent mitral regurgitation. This image was taken from a heart explanted at transplantation.

for ischemic regurgitation. Their early results suggest that the surgical technique was effectively and optimally applied, because no patients had residual regurgitation on leaving the operating room, all patients underwent surgery in a recent era (2000–2004), all patients received the same annuloplasty—a semirigid complete ring downsized two sizes, and echocardiographic follow-up was complete and systematic. Another recent series also shows encouraging results of restrictive annuloplasty. Gazoni et al. [17] examined a series of 105 ischemic repairs, 93% of which included a downsized rigid or semirigid annuloplasty, and observed an 84% 5-year survival rate and a low incidence (6.3%) of recurrent regurgitation on midterm (> 12 months) echocardiography.

- Further reports should confirm whether these results can be replicated by other studies in which surgeons systematically apply a rigid (or semirigid) downsized annuloplasty. Two randomized trials of surgical versus nonsurgical therapy for ischemic mitral regurgitation are under way, and their results should be reported in a few years.

Alternative surgical therapies for ischemic mitral regurgitation

- Several groups are investigating adjuncts to annuloplasty that may enable more sustained elimination of mitral regurgitation. All are still in an exploratory phase, and none is in widespread application.

Chordal cutting

- Levine and Schwammenthal [18] previously demonstrated in a series of experiments in sheep that division of secondary mitral valve chordae results in reduced tethering in ischemic mitral regurgitation. Borger et al. [19] reported recently on a series of 43 patients in whom in addition to standard

restrictive annuloplasty, surgeons divided secondary chordae to the anterior leaflet, posterior leaflet, and commissures that arose from the papillary muscle(s) affected by the myocardial infarction. These patients were compared with 49 historical and concurrent controls who underwent annuloplasty only. Analysis showed that the chordal cutting group had less tenting of the valve leaflets and reduced frequency of early recurrence of regurgitation. Although these data suggest a possible clinical benefit with chordal cutting, there is a possibility of bias because the technique was adopted only by some surgeons; therefore, surgical skill may partly confound the findings, as the annuloplasty-only group had a higher than expected incidence of early recurrent regurgitation (37% vs 15% in the chordal cutting group). Chordal cutting via aortotomy (opening of the aorta and identification and division of chordae to the anterior leaflet of the mitral valve) also has been proposed and may offer more complete relief of anterior leaflet tenting [20]. Further study is required to determine whether chordal cutting will confer benefit on survival or quality of life.

Papillary muscle relocation techniques

- A key element in the pathophysiology of ischemic mitral regurgitation is displacement of the papillary muscles. Attempts to restore a normal anatomic relationship of the papillary muscles may therefore result in less tethering of the leaflets and a potential for more durable elimination of ischemic regurgitation. Recently, such potential was re-demonstrated experimentally in a sheep model by Hung et al. [21]. Using a patch balloon device sewn epicardially at the region of induced infarction, they were able to incrementally reduce the degree of papillary muscle displacement, thereby eliminating tethering, with a reduction in regurgitation that persisted up to 8 weeks after the procedure [21]. This epicardial approach has yet to be applied in humans. Prior clinical approaches to reverse papillary muscle displacement have relied on intracardiac surgical techniques. For example, the papillary muscle relocation procedure described by Kron et al. [22] and various modifications have been applied by several groups. Recent data from Kron's group, however, did not show any difference in long-term outcomes from combining papillary relocation with annuloplasty when compared with annuloplasty alone [17]. Midterm data are awaited on other subvalvular surgical approaches designed to reduce papillary muscle displacement.

Mitral valve replacement

- Some surgeons advocate that mitral valve replacement with chordal preservation may yield better outcomes compared with annuloplasty for ischemic mitral regurgitation. This approach would certainly yield more durable elimination of regurgitation, but it is not clear whether this would offset the incremental risk due to higher surgical mortality, morbidity, and late mortality from valve-related complications. Also, there possibly is a lesser degree of reverse remodeling with mitral valve replacement compared with repair. Historical data showed poor outcomes for mitral valve replacement in the setting of advanced cardiomyopathy and led most surgeons to abandon valve replacement in this setting in the 1980s to the degree that advanced left ventricular dysfunction and primary cardiomyopathy were regarded as contraindications to mitral valve replacement. However, the arguments may be different in the subgroup of patients who are prone to experiencing early recurrence of regurgitation after annuloplasty, as a competent prosthetic valve, even with its attendant problems, may be preferable to an

incompetent repaired valve. Although this thinking may sound logical, it is not clear that replacement will necessarily yield a benefit in this subgroup, as patients known to be at high risk of recurrence of symptoms or death after annuloplasty often have advanced ventricular dysfunction or marked distortion of ventricular geometry such that the ventricle, rather than the absence of regurgitation, may be the major determinant of outcome, thus limiting the effectiveness of any valve operation. Some groups recommend the use of bioprosthetic replacement, rather than repair, in cases in which the patient has more advanced disease or comorbidity, but there is no evidence that patients do better with this strategy [23]. Further studies are needed to define the outcomes of contemporary mitral valve replacement in ischemic cardiomyopathy. A randomized trial of mitral valve repair versus replacement in a high-risk subset of patients with ischemic mitral regurgitation would help clarify the role of mitral valve replacement. However, contemporary nonrandomized data do not support widespread application of valve replacement for ischemic mitral regurgitation and suggest that for most patients, the preferred approach is mitral valve repair.

Predictors of surgical failure

- Some recent studies have identified factors that predict failure of surgical repair. Aside from factors related to surgical technique (eg, use of flexible bands or lack of downsizing), the strongest predictor appears to be left ventricular volume or dimension [16••,24]. Data suggest that surgical repair is of limited benefit in advanced or prolonged ischemic cardiomyopathy with severe regurgitation and marked ventricular dilatation. The benefit of surgical repair in the early, as opposed to late, phase of ischemic mitral regurgitation is supported by experimental sheep models from Levine's group showing that early elimination of regurgitation after myocardial infarction results in sustained reverse remodeling on both a cellular and a functional level [25]. As mentioned previously, an LVEDD cutoff of 65 mm has been identified, beyond which reverse remodeling is unlikely and midterm survival is substantially worse [16••]. Other identified risk factors for failure of surgical repair include a large left atrium [16••], previous anterior infarction [16••], and a mitral annular diameter greater than 3.7 cm [26].

Is restrictive annuloplasty harmful?

- The mainstay of current therapy for ischemic mitral regurgitation is the restrictive annuloplasty, whereby the surgeon places a ring that is two sizes smaller than the measured size of the patient's valve (specifically sized with commercially available sizers that measure the surface area of the anterior leaflet). This invariably results in a valve orifice that is smaller than would be expected for that particular valve. With this technique appropriately applied, most patients receive ring sizes on the order of 24 to 28 mm, which could be considered small for other pathologies. Some experts question whether such a reduction in valve orifice could be harmful. Magne et al. [27••] performed dobutamine stress echocardiography to evaluate hemodynamic performance and functional capacity in 24 patients who had undergone successful repair with restrictive annuloplasty. Compared with controls (20 patients with ischemic heart disease but no regurgitation), patients who had restrictive annuloplasty were found to have higher gradients at rest (13 mm Hg vs 4 mm Hg) and peak stress (19 mm Hg vs 6 mm Hg). The indexed orifice valve area at peak stress was 1.0 cm^2/m^2 for patients who had restrictive annuloplasty (compared with 2.4 cm^2/m^2 in controls), with systolic pulmonary artery pressures rising to 58 mm Hg at stress (compared

with 38 mm Hg in controls) [27••]. The authors concluded that restrictive annuloplasty probably induces some degree of functional mitral stenosis, although it is not clear whether this has implications for clinical outcomes (the authors did not correlate their findings with symptoms). Although an accompanying editorial [28] highlights several limitations that affect the robustness and generalizability of this study [27••], the data are a reminder that restrictive annuloplasty is not a perfect therapy and therefore highlight the need to continue investigating alternative and adjunctive approaches.

Disclosures

Dr. Adams is an inventor of mitral annuloplasty rings and receives royalties from Edwards Lifesciences, LLC. No other potential conflicts of interest relevant to this article were reported.

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