



Heart Failure Symposium

Surgical Management of Ischemic Mitral Regurgitation



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Abstract

Ischemic mitral regurgitation is a growing problem within our aging population. It portends a poor prognosis and presents a therapeutic dilemma. The pathophysiology of ischemic mitral regurgitation primarily involves ventricular remodeling as opposed to structural issues with the mitral valve itself. An understanding of the pathophysiology of ischemic mitral regurgitation has resulted in a refinement of surgical techniques and the design of specific annuloplasty rings for use in repairs. Data regarding long-term outcomes following valve repair versus replacement in these patients is conflicting and underscores the need for continued investigation to address this therapeutic dilemma.

Case Presentation

A 62-year-old man presented to his cardiologist complaining of a 6 month history of increasing fatigue and shortness of breath on exertion. His past medical history included an inferoposterior myocardial infarction 3 years prior that was treated with a drug-eluting stents to his left circumflex and right coronary arteries. Physical examination was remarkable for crackles audible throughout the lower half of both lung fields, an elevated JVP to the angle of the jaw and a grade 3/6 holosystolic murmur loudest at the apex with radiation to the left axilla. An echocardiogram revealed a left ventricular ejection fraction of 15-20%, severe MR, and a left ventricular end systolic dimension of 70 mm. The patient underwent a repeat cardiac angiogram that revealed patent stents in the circumflex and right coronary arteries and no other significant stenoses.

The decision was made to surgically correct the patient's MR with a mitral valve operation. He was brought to the operating room where under general anesthesia a transesophageal echocardiogram was performed. Examination of the mitral valve revealed poor leaflet coaptation with a degree of leaflet tethering that resulted in severe MR. Since the valve leaflets appeared structurally normal, a mitral valve repair procedure using a complete rigid annuloplasty ring was performed. A post-operative echocardiogram revealed trace MR and the patient suffered no post operative complications

Discussion

This patient is a typical example of a growing problem in our aging population, namely ischemic mitral regurgitation (IMR). IMR clearly has a negative impact on survival in patients with coronary artery disease, even in patients with mild to moderate mitral regurgitation (MR); greater degrees of MR portend an even worse prognosis [1].

With almost a fifth of patients who suffer a myocardial infarction (MI) developing IMR [2,3] and over 7.2 million Americans living with a history of MI [4], the burden of illness from this disease and cost to the healthcare system is enormous.

Because of the vicious cycle of IMR and heart failure, patients with IMR undoubtedly seek medical attention and are admitted to hospital repeatedly for management of their heart failure. Management of IMR itself remains a clinical dilemma.

Medical management is suboptimal and mitral valve surgery to correct IMR, though better than uncorrected IMR, also yields less than optimal results with an overall 55% five-year survival [5].

The debate of whether to repair or replace the mitral valve in addition to revascularization in the setting of IMR has continued to date, with a lack of conclusive evidence upporting either intervention [6]. However, mitral valve repair has shown the most promise as it can relieve IMR with some evidence of less morbidity and mortality than is associated with mitral valve replacement [7,8,9]. All of the studies to date examining surgery to correct IMR have been retrospective analyses and are limited by inherent selection bias, though a few recent attempts to utilize multivariable propensity matching have been published [10]. Furthermore, interpreting the results of mitral valve repair is often difficult [11].

Unfortunately, conflicting results favouring replacement over repair and vice versa have been published and no clear answer has been found to the question of which is intervention is better. The early mortality benefit attributed to valvular repair is balanced by a high rate of recurrent mitral insufficiency (up to 40% at 2 years).

Pathophysiology of IMR-

The pathophysiology of ischemic mitral regurgitation is complex [12]. Coronary artery disease results in myocardial ischemia and culminates in an infarction. These acute and chronic insults set the stage for maladaptive left ventricular remodeling (with apical and posterior displacement of the papillary muscles) which in turn, leads to altered left ventricular function and underlies the pathophysiology of IMR [13,14,15,16,17,18]. Indeed, up to 19% of patients who suffer an acute myocardial

infarction go on to develop ischemic mitral regurgitation. The remodeling of the LV further results in subvalvular apparatus dysfunction with leaflet tethering caused by papillary muscle displacement and also results in loss of mitral annular contraction with annular dilatation. As leaflet tethering occurs, the leaflets fail to coapt during systole and on echocardiographic examination are usually found to have restricted motion resulting in Carpentier type IIIb mitral regurgitation. As mitral annular dilatation secondary to left ventricular enlargement occurs, the leaflets also fail to coapt centrally, resulting in Carpentier type I mitral regurgitation. These changes ultimately lead to what is known as "functional" mitral regurgitation. Mitral regurgitation, in turn, leads to left ventricular volume overload and exacerbates maladaptive left ventricular dilatation, completing the vicious cycle of IMR and LV remodeling.

The majority of patients with IMR have functional MR with structurally normal mitral leaflets and subvalvular apparatus.

The remaining patients with IMR have "structural" MR with either papillary muscle rupture or papillary muscle infarction with an intact papillary muscle, each requiring differing surgical repair techniques [19,20]. Gillinov et al. have demonstrated that papillary muscle rupture portends a superior survival compared with either functional IMR or IMR resulting from PM infarction. This observation likely reflects preserved left ventricular function and geometry in the setting of papillary muscle rupture, as this clinical scenario tends to present acutely with acute heart failure demanding prompt surgical correction.

Prognosis of IMR

With the exception of IMR secondary to papillary muscle rupture, the survival of patients with IMR is significantly worse than MR from most other causes.[21]. Ischemic mitral regurgitation is in fact a predictor of mortality. The SAVE (Survival and Ventricular Enlargement) trial examined the 5-year results of 727 patients post-MI and identified patients with IMR. Patients with MR were more likely to experience cardiovascular mortality (29% versus 12%; $P<0.001$), severe heart failure (24% versus 16%; $P=0.0153$), and the combined end point of cardiovascular mortality, severe heart failure, or recurrent myocardial infarction (47% versus 29%; $P<0.001$) More recently, Grigioni et al. examined 303 patients with a recent history of MI and identified patients with IMR by echocardiographic findings. Their results indicate that the 5-year mortality of patients with IMR was significantly higher than those without IMR (62% versus 39%; $P<0.001$). Moreover, they observed that mortality risk was directly related to the degree of IMR. Others have also concluded that without correction, IMR results in reduced long-term survival even after revascularization [22].

Surgical Intervention for IMR

Surgical management of IMR has primarily consisted of revascularization with or without the addition of mitral valve repair with a variety of techniques including suture, band or ring annuloplasty, or mitral valve replacement [23]. Other surgical interventions to address left ventricular dilatation, such as remodeling procedures and passive restraint devices have been attempted but are not widely utilized and can be considered experimental at this time. Most patients with IMR that can be revascularized are revascularized to correct any reversible ischemia potentially contributing to LV dysfunction underlying the IMR.

Given the poor long-term prognosis of uncorrected IMR, some authors have suggested that patients with even mild to moderate IMR undergoing CABG should have concomitant mitral valve repair [24,25]. The indication for surgical correction of mild to moderate IMR is unclear [26], however, there is some limited data revealing benefit in these patients undergoing CABG and mitral valve surgery [27,28,29,30]. Even after mitral valve surgery to correct IMR, the prognosis currently remains poor with a median survival of approximately 6 years. It is also important to consider that the addition of mitral valve surgery to revascularization adds to the operative risk of revascularization alone [31,32,33].

The morbidity and mortality associated with combined mitral valve replacement and revascularization are high and long-term survival after this combination is quite poor. Because of this high morbidity and mortality some authors have suggested revascularization alone for treatment of IMR [34, 35]. Alternatively, mitral valve repair in addition to revascularization for IMR has been advocated by a number of authors [36]. however, no study to date has clearly demonstrated a survival benefit with this combination of surgical therapy over revascularization alone [37]

Cohn et al. stirred the debate about mitral valve repair versus replacement when they published their retrospective analysis of 150 patients with IMR undergoing mitral valve repair ($n=94$) or replacement ($n=56$) [38]. Interestingly, the overall 5-year survival in their series was $91\% \pm 5\%$ for the replacement group versus $56\% \pm 10\%$ for the repair group. The authors dissected the results further by comparing the survival of those with functional IMR versus structural IMR and found that those undergoing repair for functional IMR had the worst 5-year survival ($43\% \pm 13\%$). Thus, they concluded that the underlying pathophysiologic mechanism resulting in IMR was more important to survival than the surgical technique used (repair versus replacement). It is important to note that their results are limited by two issues.

Their retrospective analysis is inherently subject to selection bias. Secondly, upon closer examination of their data it is apparent that most patients with functional IMR underwent repair whereas most patients with structural IMR underwent replacement. Functional IMR with either annular dilatation or restrictive leaflet motion is likely a surrogate of a more chronic process with a greater accumulated insult to left ventricular structure and function. Left ventricular dysfunction has been shown to be the most significant contributor to poor late survival following surgery for IMR [39] Thus, although their conclusion regarding the importance of the pathophysiologic mechanism underlying the IMR is supported by their data, their survival outcomes (repair versus replacement) are difficult to compare.

In contrast to the study by Cohn et al., Gillinov et al. and Grossi et al. have more recently reported that mitral valve repair in their retrospective analyses is superior to replacement in the majority of their patients with IMR.[40]. Gillinov et al. utilized multivariable propensity matching to control for the inherent selection bias of retrospective studies. Their analysis of 482 patients indicates an overall 5-year survival of 36% versus 58% ($P=0.08$) after valve replacement versus valve repair for IMR. In their analysis they conclude that approximately 70% of patients were predicted to benefit from mitral valve repair, and that repair was durable with freedom from repair at 5-years being 91%. Grossi et al. utilized multivariable analyses to control for confounding preoperative characteristics. Their analysis of 223 patients revealed that patients undergoing mitral replacement were sicker with higher New York Heart Association (NYHA) functional class scores and that this likely explained why patients undergoing mitral repair had lower short-term complication and death rates. Unfortunately both studies are limited by the fact that: 1) they did not include a control group with patients undergoing revascularization alone, 2) they did not examine the change in LV function post-operatively or the adequacy of repair by serial echocardiography and 3) neither demonstrated 5 year-survival much better than 50% which is clearly suboptimal.

Kim et al. reviewed their experience with 355 patients with IMR who underwent revascularization alone (n=168) or revascularization with mitral valve repair (n=187) [41]. Their combined surgical group had a greater reduction in IMR grade, however, actuarial survival at 5 years showed no significant difference between the two surgical strategies (44% for repair+revascularization versus 52% for revascularization alone; p=NS). When patients were 3+ or 4+ IMR were only considered, actuarial survival at 5 years again showed no significant difference (44% versus 41%; p=NS). Of note, operative mortality, though not statistically significant, was 11% within the combined group versus 4% within the revascularization alone group. Unfortunately, the preoperative mean left ventricular ejection fraction was lower in the combined group than in the revascularization alone group (p<0.001) and this makes comparisons of outcomes between the groups difficult because preoperative LVEF is a well known predictor of outcomes following surgical revascularization.

Additionally, given the retrospective nature of this study, the results are again limited by potential selection bias.

Mihaljevic et al. more recently performed a propensity-matched study comparing the outcomes of patients with 3+/4+ IMR undergoing CABG with (n=290) or without (n=100) mitral valve annuloplasty. Their experience revealed that although the addition of mitral valve annuloplasty reduced the incidence of 3+/4+ postoperative MR (48% vs. 12% at 1 year, p<0.0001), there was no significant difference in 1-, 5- and 10-year survival between these groups (p=0.6).

Furthermore, at 5 years, the proportion of patients in NYHA functional class III/IV was no different between groups (23% of CABG+MV annuloplasty patient vs. 25% of CABG alone patients, p=0.3). The authors conclude that mitral valve annuloplasty in patients with IMR undergoing CABG is insufficient to improve long-term clinical outcomes. However, it is worth noting that less than 30% of patients undergoing mitral valve annuloplasty in this study received a downsized rigid complete annuloplasty ring. The use of a rigid or semi-rigid complete annuloplasty ring is currently considered the gold standard for IMR in many centers as it is thought to prevent and treat mitral annular dilatation that occurs as the left ventricle dilates. Thus, the study by Mihaljevic et al. may not adequately reflect the potential benefits of using a rigid or semi-rigid complete annuloplasty ring. In fact, recent advances in annuloplasty ring technology for IMR have generally evolved from the complete annuloplasty ring concept.

Despite a number of studies suggesting outcomes better than mitral valve replacement, repair with undersized flexible bands or rings or with symmetric remodeling rings still leaves 10% to 30% of patients with recurrent or residual IMR [44]. Recent insight into the pathophysiology of IMR sheds some light on why recurrent or residual IMR occurs. Studies by Kwan et al. utilizing real-time 3-dimensional echocardiography have demonstrated that in IMR there is an asymmetrical deformation of the mitral valve from the postero-medial to the antero-lateral commissura and that tethering at the medial aspect of the valve distinguishes IMR from MR secondary to dilated cardiomyopathy. To address these nuances of IMR, a new remodeling annuloplasty ring (the Carpentier-McCarthy-Adams IMR ETlogix) was developed to maximize leaflet coaptation in Carpentier type IIIb IMR. Daimon et al. have recently reported their experience with this ring utilized in the mitral repair of 59 patients with $\geq 2+$ IMR, and have demonstrated 97% of patients to have 0 or 1+ MR post-operatively [43]. This type of tailored repair may provide a more efficacious and durable solution to IMR, but further study is clearly required to assess long-term function and survival.

The strategy of performing an undersized restrictive mitral annuloplasty by implanting a ring two sizes smaller than the measured intertrigonal length has become a central component to addressing the mitral annular dilatation that occurs in IMR. A concern with this strategy is the possibility of creating functional mitral stenosis as a result of aggressive undersizing. A recent study by Mange et al. characterized mitral valve hemodynamic performance following restrictive mitral valve annuloplasty for IMR[44]. Their results demonstrated higher peak (13 ± 4 vs. 4.5 ± 0.6 mmHg) and mean (6 ± 2 vs. 1.5 ± 0.2 mmHg) transmitral gradients with increased systolic pulmonary artery pressures (42 ± 13 vs. 31 ± 11 mmHg) 13 ± 3 months post-operatively compared to pre-operative values in 24 patients undergoing undersized restrictive mitral annuloplasty combined with CABG. Furthermore, 13 of the 24 patients had a post-operative mitral valve effective orifice area ≤ 1.5 cm². These results, although limited by small sample size, suggest that a significant proportion of patients undergoing undersized restrictive mitral annuloplasty for IMR are left with at least moderate mitral stenosis. However, the long term consequence of this residual mitral stenosis is unclear and will require further evaluation.

Despite the potential adverse effects of functional mitral stenosis following restrictive mitral annuloplasty for IMR, recent longer term results reported by Braun et al. provide evidence that this strategy benefits patients and in particular, those who do not have excessively dilated left ventricles[45]. Their study evaluated 100 consecutive patients with IMR who underwent restrictive mitral annuloplasty and CABG with a mean late follow-up of 46 months. Mean transmitral gradient was 3.9 ± 1.7 mmHg at this late follow-up, which when compared to the results of Magne et al. suggests that there may be some resolution of the functional mitral stenosis observed early post-operatively. The most important finding from this study was that patients with a pre-operative left ventricular end-diastolic dimension (LVEDD) of ≤ 65 mm had a significantly higher 5-year survival rate compared to those with a pre-operative LVEDD > 65 mm ($80 \pm 5.2\%$ vs. $49 \pm 11\%$). This particular finding identifies patients with an LVEDD ≤ 65 mm as optimal candidates for undersized restrictive annuloplasty, whereas those with a pre-operative LVEDD > 65 mm will likely require an additional ventricular procedure to address their excessively dilated left ventricles to improve their long-term outcomes.

Surgical ventricular reconstruction (SVR) is a procedure that has been developed to address left ventricular dilatation and has been demonstrated to successfully reduce left ventricular volume, improved ejection fraction and improve left ventricular function in patients with ischemic heart failure[46],[47]. The Surgical Treatment for Ischemic Heart Failure (STICH) trial is a multi-center, randomized trial that aims to determine whether CABG surgery provides benefit over optimal medical management in patients with coronary artery disease and heart failure, and secondly whether SVR in combination with CABG provides benefit compared to CABG surgery alone. The results of the CABG vs. CABG + SVR arm of the study have been recently reported.[48] In this arm of the study, 1000 patients were randomized to either CABG with optimal medical management or CABG+SVR with optimal medical management. The primary outcome of this study was death from any cause or hospitalization for cardiac causes. Overall, the trial failed to demonstrate any benefit of adding a SVR procedure with regard to this primary outcome at a median 4 year follow-up (59% in the CABG arm and 58% in the CABG+SVR arm achieved the primary outcome). With regard to concomitant mitral regurgitation, 17-18% of patients in each group had moderate or greater (3+/4+) MR preoperatively, and accordingly 17-19% of patients in each group had a concomitant mitral valve procedure performed at the time of operation (89% in the CABG alone group and 98% in the CABG+SVR group had a mitral valve repair). Subgroup analysis did not demonstrate any benefit in primary outcome with the addition of SVR to CABG in patients with moderate or severe (3+/4+) MR preoperatively, presumably those that

underwent concomitant mitral valve procedures (hazard ratio for events 0.94, 95% confidence interval of 0.65-1.36). Further analysis of the results examining of the effect of SVR on excessively dilated left ventricles may provide new insight into a subgroup of patients that may benefit from SVR, and in particular those with concomitant IMR.

As mentioned previously, leaflet tethering due to papillary muscle displacement that occurs with LV remodeling prevents leaflet coaptation during systole. It is the second order chordae tendineae that attach the belly of the MV leaflets to the papillary muscle (Figure 1) that significantly contribute to this type of tethering and results in a "seagull sign" on echocardiography (Figure 2). This insight into the pathophysiology of IMR has prompted a novel "chordal-cutting" procedure initially demonstrated to be efficacious in animal models by Messas, Levine and colleagues (Figure 3) [49,50]. In both acute and chronic models of IMR secondary to inferobasal infarcts in sheep, these investigators demonstrated that by cutting the central secondary (basal) chordae MR could be reduced to baseline with improved leaflet coaptation and no evidence of further decreased global or segmental LV contractility [51].

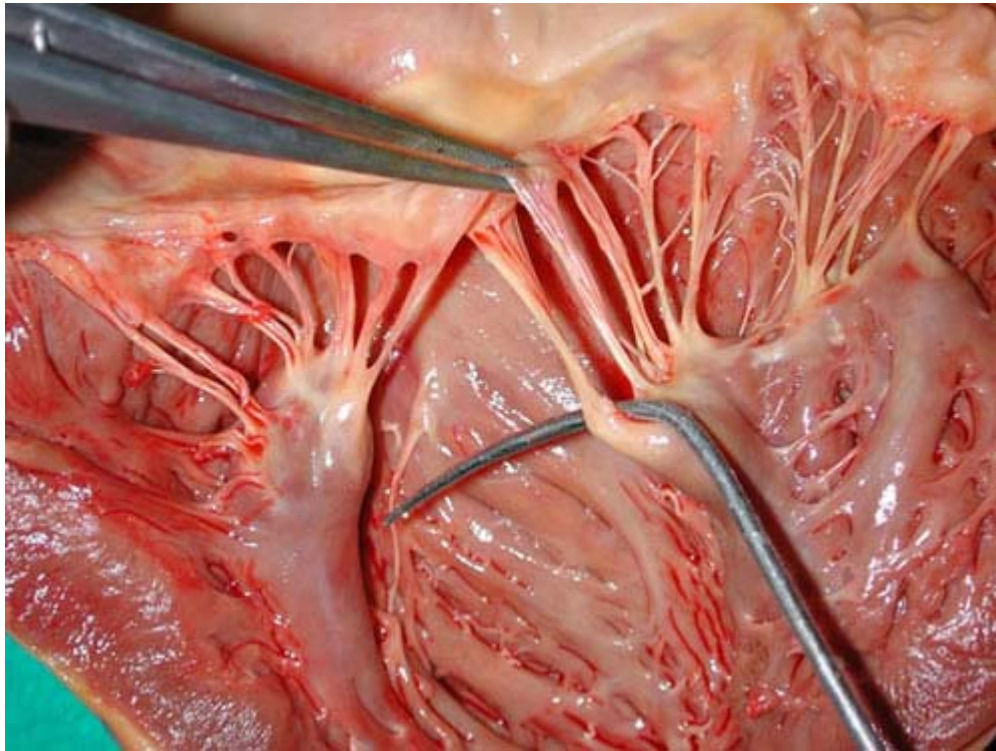


Figure 1. Anterior mitral valve leaflet secondary (strut) chordae tendineae. Photograph of a mitral valve demonstrating the location of the secondary (strut) chordae tendineae. The forceps are holding a primary chordae attached to the edge of the anterior mitral valve leaflet. The hook is demonstrating a secondary chordae attached to the belly of the anterior mitral valve leaflet.

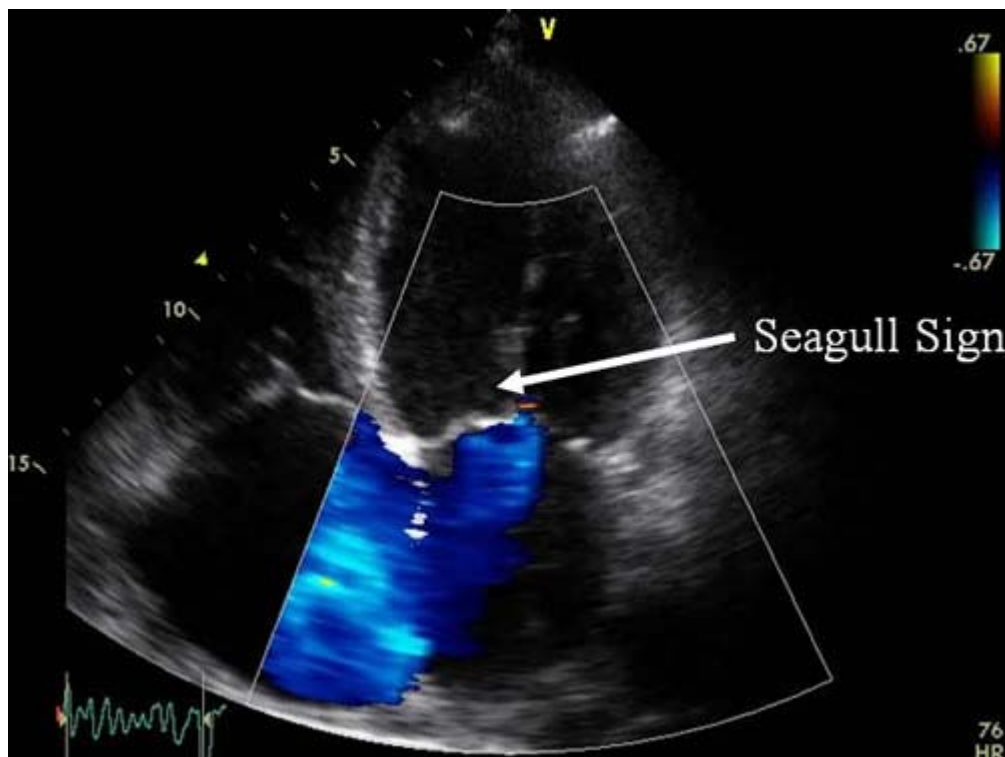


Figure 2. "Seagull sign" on transthoracic echocardiography of moderate-severe IMR. A transthoracic echocardiographic image demonstrating the "seagull sign" present in moderate-severe IMR. The shape of the anterior mitral valve leaflet is distorted by tethering of secondary strut chordae tendineae. This tethering impairs leaflet coaptation resulting in MR.

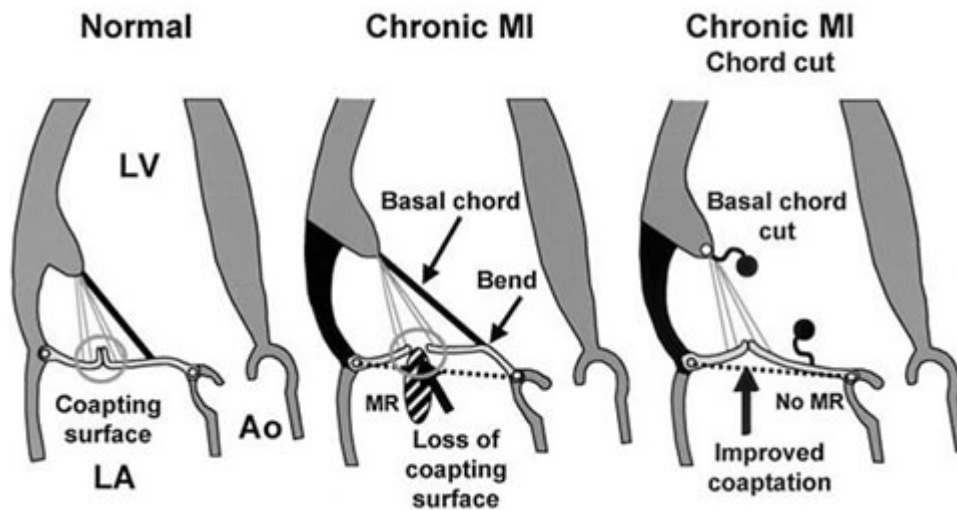


Figure 3. Chordal-cutting procedure to relieve leaflet tethering in IMR. Left, normal coaptation of the mitral valve leaflets. Center, an inferior infarction distorts the base of the anterior leaflet, which is tethered by secondary strut chordae that reduces the coapting surface and causes MR. Right, secondary chordal cutting eliminates this bend, improves coaptation, and reduces MR. (From Messas E, et al. Efficacy of chordal cutting to relieve chronic persistent ischemic mitral regurgitation. Modified from *Circulation* 2003;108 Suppl 1:II111-115).

Borger et al. have recently reported the largest experience with chordal-cutting in 43 patients undergoing mitral valve repair, comparing them to 49 patients undergoing conventional mitral valve repair for IMR.[52] Despite an increased prevalence of recent MI, left main disease, diabetes and peripheral vascular disease, as well as lower left ventricular ejection fraction amongst those in the chordal-cutting group, in-hospital mortality was no different between groups (10% in the conventional repair group and 9% in the chordal-cutting group, $p=0.9$). Mean preoperative grade of MR was no different between groups, however, postoperative MR grade was significantly lower in the chordal-cutting group (1.4 ± 1.3 vs 0.9 ± 0.9 , $p=0.4$). Survival two years postoperatively was $82\% \pm 6\%$ in the control group and $79\% \pm 9\%$ in the chordal-cutting group ($p=0.8$). Recurrence of significant (2+ or greater) MR within the first two postoperative years was 37% in the conventional repair group and 15% in the chordal-cutting group ($p=0.03$). Importantly, the relative change in LVEF

over the two year follow-up period of this study was no different between groups ($p=0.9$). Although the longer-term outcomes with regard to recurrent MR and change in LVEF remain to be seen, this current data suggests that chordal cutting may offer an incremental benefit over undersizing annuloplasty alone.

Given the current 9 to 12 year median survival following heart transplantation,[53] some have suggested that this may be a therapeutic option for a subset patients with IMR, particularly those with severe left ventricular dysfunction (ejection fraction <0.30). However, in addition to advanced age, there are a number of contraindications to transplantation that may exist in these patients; moreover, the scarce supply of organs makes this therapeutic option particularly limited.

Conclusion

A number of retrospective studies have been summarized above and provide some insight into benefit (or harm) surgery to correct IMR may provide patients. Given the tremendous burden of illness that IMR poses, and the dismal long-term survival demonstrated to date with the interventions currently available, determining the optimal management of IMR is critical. We need to determine which intervention, either MV repair or MV replacement, treats IMR best. Do patients with particularly poor LV function benefit more from repair or replacement or neither? What is the impact of LV size? Do patients with significant LV dilatation have an unacceptable rate of recurrent MR following repair and can formal replacement be performed with acceptable risk? Answers to these questions will provide clinicians with better treatment strategies and more importantly, patients with improved quality of life and survival.

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