Surgical Management of Ischemic Mitral Regurgitation

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Case presentation: A 62-year-old man visited his cardiologist describing a 6-month history of increasing fatigue and shortness of breath on exertion. His medical history included an inferoposterior myocardial infarction (MI) 3 years previously that was treated with drug-eluting stents to his left circumflex and right coronary arteries. The result of physical examination was remarkable for crackles audible throughout the lower half of both lung fields, an elevated jugular venous pulse 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 (LVEF) of 15% to 20%, severe mitral regurgitation (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 he was given general anesthesia, and 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. Inasmuch as the valve leaflets appeared structurally normal, a mitral valve repair procedure using a complete rigid annuloplasty ring was performed. A postoperative echocardiogram revealed trace MR, and the patient experienced no postoperative 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 MR; greater degrees of MR portend an even worse prognosis.1 With almost a fifth of patients who experience an MI followed by the development of 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 circle of IMR and heart failure, patients with IMR undoubtedly seek medical attention and are admitted to the hospital repeatedly for management of their heart failure. The 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 5-year survival of 55%.5 The debate over 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 supporting either intervention.6 However, mitral valve repair has shown the most promise because it can relieve IMR with some evidence of less morbidity and mortality than is associated with mitral valve replacement.2,7–9 To our knowledge, all of the studies to date examining surgery to correct IMR have been retrospective analyses and are limited by inherent selection bias, although a few recent attempts to use multivariable propensity matching have been published.5,10 Furthermore, interpreting the results of mitral valve repair is often difficult.11 Unfortunately, conflicting results favoring replacement over repair and vice versa have been published, and no clear answer has been found to the question of which intervention is better. The early mortality benefit attributed to valvular repair is balanced by a high rate of
Pathophysiology of IMR
The pathophysiology of IMR is complex. 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. Indeed, in as many as 19% of patients who experience an acute MI, IMR then develops. The remodeling of the left ventricle 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 IIb 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 circle of IMR and left ventricular 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. Gillinov et al have demonstrated that papillary muscle rupture portends a superior survival compared with either functional IMR or IMR resulting from papillary muscle infarction. This observation likely reflects preserved left ventricular function and geometry in the setting of papillary muscle rupture, because 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 in patients with MR from other causes. In fact, IMR is a predictor of mortality. The SAVE (Survival and Ventricular Enlargement) trial examined the 5-year results of 727 patients after 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 endpoint of cardiovascular mortality, severe heart failure, or recurrent MI (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 in patients without IMR (62% versus 39%; \( P < 0.001 \)). Moreover, they observed that the risk of mortality 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.

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. Other surgical interventions to address left ventricular dilatation, such as remodeling procedures and passive restraint devices, have been attempted but are not widely used and can be considered experimental at this time. Most patients with IMR that can be revascularized undergo revascularization to correct any reversible ischemia potentially contributing to left ventricular 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 coronary artery bypass grafting (CABG) should have concomitant mitral valve repair. The indication for surgical correction of mild to moderate IMR is unclear; however, some limited data have shown a benefit in these patients who undergo CABG and mitral valve surgery. 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.

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. Alternatively, mitral valve repair in addition to revascularization for IMR has been advocated by several authors; however, no study to date, as far as we know, has clearly demonstrated a survival benefit with this combination of surgical therapy over revascularization alone.

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). Interestingly, the overall 5-year survival in their series was 91 ± 5% (mean ± SD) for the replacement group versus 56 ± 10% for the repair group. The authors dissected the results further by comparing the survival of those with functional IMR versus those with structural IMR and found that those undergoing repair for functional IMR had the worst 5-year survival (43 ± 13%). Thus, they con-
cluded that the underlying pathophysiological 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 2 issues. First, their retrospective analysis was inherently subject to selection bias. Second, on 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 after surgery for IMR.\textsuperscript{39} Thus, although their conclusion regarding the importance of the pathophysiological 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,\textsuperscript{38} Gillinov et al\textsuperscript{5} and Grossi et al\textsuperscript{10} have more recently reported that mitral valve repair in their retrospective analyses is superior to replacement in the majority of their patients with IMR. Gillinov et al\textsuperscript{5} used 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\textsuperscript{10} used multivariable analyses to control for confounding preoperative characteristics. Their analysis of 223 patients revealed that patients undergoing mitral valve 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 because (1) they did not include a control group with patients undergoing revascularization alone, (2) they did not examine the change in left ventricular function postoperatively or the adequacy of repair by serial echocardiography, and (3) neither demonstrated 5-year survival much better than 50%, which is clearly suboptimal.\textsuperscript{40}

Kim et al\textsuperscript{41} reviewed their experience with 355 patients with IMR who underwent revascularization alone (\(n=168\)) or revascularization with mitral valve repair (\(n=187\)). Their combined surgical group had a greater reduction in IMR grade; however, actuarial survival at 5 years showed no significant difference between the 2 surgical strategies (44% for repair plus revascularization versus 52% for revascularization alone; \(P=NS\)). When only patients with 3+ or 4+ IMR were 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% in the combined group versus 4% in the revascularization-alone group. Unfortunately, the preoperative mean LVEF 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 after surgical revascularization. Additionally, given the retrospective nature of this study, the results are again limited by potential selection bias.

Mihaljevic et al\textsuperscript{47} more recently performed a propensity-matched study comparing the outcomes in 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% versus 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 plus mitral valve annuloplasty patients versus 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.\textsuperscript{37} However, it is worth noting that <30% of patients undergoing mitral valve annuloplasty in this study received a downsized rigid complete annuloplasty ring. The use of a rigid or semirigid complete annuloplasty ring is currently considered the gold standard for IMR in many centers because it is thought to prevent and treat the mitral annular dilatation that occurs as the left ventricle dilates. Thus, the study by Mihaljevic et al\textsuperscript{47} may not adequately reflect the potential benefits of using a rigid or semirigid complete annuloplasty ring. In fact, recent advances in annuloplasty ring technology for IMR have generally evolved from the complete annuloplasty ring concept.

Despite several studies suggesting outcomes that are better than those with mitral valve replacement, repair with undersized flexible bands or rings or with symmetrical remodeling rings still leaves 10% to 30% of patients with recurrent or residual IMR.\textsuperscript{5,18,24,42} Recent insight into the pathophysiology of IMR sheds some light on why recurrent or residual IMR occurs. Studies by Kwan et al\textsuperscript{13} using real-time 3-dimensional echocardiography have demonstrated that in IMR there is an asymmetrical deformation of the mitral valve from the posteromedial to the anterolateral 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 43 recently reported their experience with this ring used in mitral repair in 59 patients with ≥2+ IMR and demonstrated 97% of patients to have 0 or 1+ MR postoperatively. This type of tailored repair may provide a more effective 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 2 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 Magne et al 44 characterized mitral valve hemodynamic performance after restrictive mitral valve annuloplasty for IMR. Their results demonstrated higher peak (13±4 versus 4.5±0.6 mm Hg) and mean (6±2 versus 1.5±0.2 mm Hg) transmitial gradients with increased systolic pulmonary artery pressures (42±13 versus 31±11 mm Hg) 13±3 months postoperatively compared with preoperative values in 24 patients undergoing undersized restrictive mitral annuloplasty combined with CABG. Furthermore, 13 of the 24 patients had a postoperative 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 after restrictive mitral annuloplasty for IMR, recent longer-term results reported by Braun et al 45 provide evidence that this strategy benefits patients, in particular those who do not have excessively dilated left ventricles. Their study evaluated 100 consecutive patients with IMR who underwent restrictive mitral annuloplasty and CABG with a mean late follow-up of 46 months. The mean transmitial gradient was 3.9±1.7 mm Hg at this late follow-up, which when compared with the results of Magne et al 44 suggests that there may be some resolution of the functional mitral stenosis observed early postoperatively. The most important finding from this study was that patients with a preoperative left ventricular end-diastolic dimension (LVEDD) of ≤65 mm had a significantly higher 5-year survival rate than did those with a preoperative LVEDD >65 mm (80±5.2% versus 49±11%). This particular finding identifies patients with an LVEDD ≤65 mm as optimal candidates for undersized restrictive annuloplasty, whereas those with a preoperative 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) has been developed to address left ventricular dilatation and has been demonstrated to successfully reduce left ventricular volume, improve 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 multicenter, randomized trial that aims to determine (1) whether CABG surgery provides benefit over optimal medical management in patients with coronary artery disease and heart failure and (2) whether SVR in combination with CABG provides benefit compared with CABG surgery alone. The results of the CABG versus 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% to 18% of patients in each group had moderate or greater (3+/4+) MR preoperatively; accordingly, 17% to 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 who underwent concomitant mitral valve procedures (hazard ratio for events 0.94, 95% confidence interval of 0.65 to 1.36). Further analysis of the results examining the effect of SVR on excessively dilated left ventricles may provide new insight into a subgroup of patients who may benefit from SVR, in particular those with concomitant IMR.

As mentioned previously, leaflet tethering due to the papillary muscle displacement that occurs with left ventricular 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 result 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 effective in animal models by Messas et al\(^49,50\) (Figure 3). 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 left ventricular contractility.\(^49–51\)

Borger et al\(^52\) have recently reported the largest experience with chordal cutting in 43 patients undergoing mitral valve repair, comparing them with 49 patients undergoing conventional mitral valve repair for IMR. Despite an increased prevalence of recent MI, left main disease, diabetes mellitus, and lower LVEF among 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, \(P=0.9\)). The mean preoperative grade of MR was no different between groups; however, the postoperative MR grade was significantly lower in the chordal-cutting group (1.4±1.3 versus 0.9±0.9, \(P=0.4\)). Survival 2 years postoperatively was 82±6% in the control group and 79±9% in the chordal-cutting group (\(P=0.8\)). Recurrence of significant (≥2+) MR within the first 2 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 2-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, these current data suggest that chordal cutting may offer an incremental benefit over undersizing annuloplasty alone.

Given the current 9- to 12-year median survival after heart transplantation,\(^33\) some have suggested that this may be a therapeutic option for a subset of patients with IMR, particularly those with severe left ventricular dysfunction (ejection fraction <0.30).\(^32,41\) However, in addition to advanced age, these patients may have several contraindications to transplantation; moreover, the scarce supply of organs makes this therapeutic option particularly limited.

**Conclusion**

Several retrospective studies have been summarized above and provide
some insight into the benefit (or harm) that surgery to correct IMR may provide. 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 left ventricular function benefit more from repair or replacement—or neither? What is the impact of left ventricular size? Do patients with significant left ventricular dilatation have an unacceptable rate of recurrent MR after repair, and can for-
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