Review

Meta-analysis of short-term and long-term survival following repair versus replacement for ischemic mitral regurgitation

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Summary

The optimal surgical strategy for the management of ischemic mitral regurgitation (IMR) is still debated. The purpose of this study was to perform a meta-analysis summarizing the evidence favoring one technique over another (repair vs replacement). A search of the English literature in PubMed was performed using 'ischemic mitral regurgitation' and 'repair or replacement or annuloplasty' in the title/abstract field. Articles were excluded if they lacked a direct comparison of repair versus replacement, or used Teflon/pericardial strip or suture annuloplasty in >10% of the repairs. Nine articles were selected for the final analysis. All studies except one were relatively recent (2004—2009). The patient characteristics between treatment groups were similar across studies. All studies excluded patients with degenerative etiology and used a rigorous definition of IMR. Most patients had concomitant coronary artery bypass graft. In the patients with mitral valve replacement, at least the posterior and, in many cases, the entire subvalvular apparatus were preserved. Mean ejection fraction and proportion of patients with severe ventricular dysfunction were similar between the repair and replacement groups. The odds ratios for the studies, comparing replacement to repair, ranged from 0.884 to 17.241 for short-term mortality and the hazard ratios ranged from 0.677 to 3.205 for long-term mortality. There was a significantly increased likelihood of both short-term mortality (summary odds ratio 2.667 (95% confidence interval (CI) 1.859—3.817)) and long-term mortality (summary hazard ratio 1.352 (95% CI 1.131—1.618)) for the replacement group compared to the repair group. Based on the meta-analysis of the current relevant literature, mitral valve repair for IMR is associated with better short-term and long-term survival compared to mitral valve replacement. Our conclusion should be interpreted in the context of the inherent limitations of a meta-analysis of retrospective studies including heterogeneity of patient characteristics, which may have influenced the physician’s decision to perform mitral valve repair or replacement. In the absence of any published randomized studies, mitral procedure selection should be individualized.

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1. Introduction

Mitral regurgitation (MR) complicates 13—50% of the cases of acute myocardial infarction (MI) [1,2]. The exact frequency with which it is detected largely depends on the modality used to look for its presence and the timing with respect to the acute MI [3,4]. In earlier published studies in the literature, using angiography to document MR, it was reported in 13—19% of patients with acute MI [1,5—7]. Subsequent studies using mainly color Doppler echocardiography report MR with higher frequency between 35% and 74% [2,4,8—13].

MR after MI is classified as acute or chronic ischemic MR (IMR) based on the pathophysiologic mechanism responsible for the regurgitation. Acute IMR is secondary to papillary muscle rupture with resultant volume overload, leading to hemodynamic instability, often progressing to cardiogenic shock. The definition of acute IMR is included for completeness and, in the remainder of the article, MR refers to chronic IMR, which is functional in nature. The incomplete mitral leaflet coaptation in this case is a consequence of the two main factors, which may coexist: (1) annular dilatation secondary to left ventricular (LV) enlargement, and (2) local LV remodeling with papillary muscle displacement, leading to restricted leaflet motion with apical tethering and tenting of the mitral leaflets.

The optimal surgical strategy for the management of IMR is still debated. The advocates of mitral valve repair note its salutary effects with respect to survival, preservation of ventricular function, and avoidance of long-term anticoagulation therapy. The proponents of mitral valve replacement point out that the poor long-term survival of patients with IMR warrants consideration for bioprosthetic valve, avoiding the anticoagulation-related complications of mechanical prosthesis. In addition, current replacement...
techniques include preservation of the subvalvular apparatus, which may largely explain the survival benefit of repair over replacement. Moreover, the risk of residual MR and concerns of mitral valve repair durability in this population of patients, who often have severely dilated left ventricles, are avoided by prompt replacement of the mitral valve.

There are no published prospective randomized trials comparing repair with replacement in patients with chronic IMR. Comparison between published retrospective series has been limited not only by the lack of uniform definition of chronic IMR but also by the heterogeneity of the patient groups across studies in terms of ventricular function and proportion of patients with acute IMR and/or cardiogenic shock. The purpose of this study was to perform a meta-analysis of relevant articles to summarize the evidence favoring one technique over another (repair vs replacement) in patients with chronic IMR.

2. Materials and methods

A literature search was performed using PubMed using the following search terms in the title/abstract field: 'ischemic mitral regurgitation' and 'repair or replacement or annuloplasty or reconstruction'. Non-English articles were excluded. The abstracts of the identified articles were reviewed and publications that did not include a direct comparison of repair versus replacement were excluded as well. Articles on repair versus replacement in nonischemic dilated cardiomyopathy were eliminated. The remaining articles were reviewed in full text because the abstract did not provide sufficient information to make a decision. In addition, the full text and references of all review articles were examined in detail to further identify other relevant publications. The following exclusion criteria were used to select the final articles for the meta-analysis: (1) no direct comparison of repair versus replacement, (2) nonischemic dilated cardiomyopathy, (3) ischemic etiology of the MR only in a subset of the patients and repair versus replacement outcomes not specifically provided for the ischemic subset, (4) lack of annuloplasty or suture/Teflon strip/pericardial strip annuloplasty in >10% of the patients in the repair group, (5) preoperative hemodynamic instability, (6) no survival curves or hazard ratios, (7) beating heart procedures, and (8) concomitant surgical ventricular restoration.

2.1. Statistical methods

For each individual study, hazard ratios reflecting long-term survival and odds ratios for short-term survival, along with their corresponding variances, were calculated. The survival curves comparing repair and replacement from each study were inspected and the survival rates were estimated using 6-month intervals. These estimates were initially abstracted by one of the authors and then independently verified by another author. In instances of disagreement, the authors reached consensus as to the appropriate survival estimate for that particular time point. On average, there were less than one such disagreements across the time points for each pair of survival curves. For each 6-month time interval along the survival curves, log hazard ratios and their variances were estimated using the method of Parmar et al. when only the survival curves were available [14]. This method assumes uniform censoring across the entire curve. However, when numbers of subjects at risk were available at various points along the curve, censoring rates were adjusted analogous to the method proposed by Williamson et al. [15]. This method effectively adjusts for varying rates of censoring across the survival curve but still assumes that censoring is uniform within the intervals defined by the numbers at risk. Overall log hazard ratios using inverse variances as weights were then calculated for each study, reflecting the likelihood of mortality associated with mitral valve replacement relative to repair. These estimates, as well as those for the short-term mortality, were then examined using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ, USA) [16]. Heterogeneity was examined using Cochran’s Q as well as the \( I^2 \) statistic [17]. Fixed models were used to calculate the summary statistics and their 95% confidence intervals (CIs). Funnel plots were inspected to assess the potential of publication bias [18]. Meta-analyses results are displayed in forest plots.

3. Results

A literature search was performed using PubMed using the following search terms in the title/abstract field: 'ischemic mitral regurgitation' and 'repair or replacement or annuloplasty or reconstruction'. This provided a total of 290 articles for review (Fig. 1). After exclusion of 58 non-English publications, the abstracts of the remaining 232 articles were assessed using the exclusion criteria outlined in the 'Methods' section to eliminate clearly irrelevant studies. In addition, the full text and references of all review articles were examined in detail to further identify other relevant publications. A total of 184 articles were eliminated based on the exclusion criteria. The remaining 48 articles were reviewed in full text because the abstract did not provide sufficient information to make a decision. Of these, 14 were excluded because they focused on either repair or replacement but did not provide a direct comparison between the two techniques; and 15 articles were excluded because the etiology of the MR was ischemic only in a subset of the patients and repair versus replacement outcomes was not specifically provided for the ischemic subset. Ten additional articles were eliminated for various reasons as outlined in Table 1. Of these, nine articles were eliminated because >10% of the repair group received either no annuloplasty or suture annuloplasty or annuloplasty with a Teflon or pericardial strip [19–27]. One article was excluded because 20% of the patients were hemodynamically unstable and the etiology of MR was ischemic in only 38% of the patients [28]. Nine articles were selected for the final analysis [29–37].

Selected details of each study, including availability of short-term and long-term data, proportion of patients undergoing concomitant coronary artery bypass graft (CABG), as well as inclusion and exclusion criteria are presented in Table 2. The vast majority of patients underwent concomitant CABG. All studies excluded patients with degenerative mitral valve disease. In addition, most studies excluded patients with cardiogenic shock (either explicitly stated or implied by exclusion of patients with emergent or salvage status).
The preoperative patient characteristics are shown in Table 3. All studies were retrospective and included a relatively small number of patients, ranging from 27 to 416 for the repair group and 14 to 184 for the replacement group. Five out of the nine studies included less than 100 patients in both the repair and the replacement groups. All patients were relatively young with mean or median age in the 60s for both the groups across studies. There were no significant differences with respect to age except for two studies in which the replacement patients were 5—6 years older than the repair patients. In general, there were more males than females in both the repair and the replacement groups. There was no significant difference with respect to gender across studies with the exception of one in which there were significantly more males in the replacement group compared to the repair group. In addition, the two groups were similar with respect to hypertension (HTN), diabetes, chronic renal insufficiency, and the New York Heart Association (NYHA) class. Of note, where differences in comorbidities were statistically significant between groups, higher percentages of patients with comorbidities were in the repair group compared to the replacement group. The number of patients with atrial fibrillation was not consistently reported. However, in the four studies in which this information was included, the two groups were similar (20—27% for the repair group and 12—29% for the replacement group).

The ventricular function of patients in the repair versus replacement group across studies is presented in Table 4. Six of the nine studies reported mean or median ejection fraction (EF). In two of these studies, there was a statistically significant difference between the two groups with the lower EFs present in the patients with repair. In addition, six studies included data on severe ventricular dysfunction. Although the exact EF cutoff value for the definition of severe ventricular dysfunction differed slightly between studies, the repair and replacement groups were similar with respect to the proportion of patients with severe ventricular dysfunction in each group.

The details of the mitral valve replacement patients across studies are depicted in Table 5. Six of the studies included data on the type of prosthesis used for mitral valve replacement. With the exception of one study, the majority of patients received a mechanical valve. In addition, the vast majority of mitral valve replacements were performed with preservation of the subvalvular apparatus (either total or partial).

### 3.1. Short-term results

The short-term results are shown in Fig. 2. Eight studies provided information on short-term mortality. Typically, this is categorized as in-hospital/30-day mortality. Odds ratios comparing the repair and replacement groups within each study were obtained. The odds ratios in the study ranged from 0.88 to 17.24 (see Fig. 2). While there appeared to be greater variability in the odds ratios, the assessment of heterogeneity among the studies yielded similar findings to those for the long-term measures: Cochran’s $Q = 8.71$ and
with respect to the amount of variability due to heterogeneity, $I^2 = 19.6\%$; therefore, about 20% of the variability between the studies would be considered due to heterogeneity. This still tends to be considered a relatively low level of heterogeneity. The summary odds ratio was 2.66 (95% CI 1.86–3.82), $p = 0.001$, indicating that odds of early mortality were more than 2.5 times greater in the replacement group than in the repair group.

### 3.2. Long-term results

The long-term results are depicted in Fig. 3. Eight studies provided usable information on long-term survival. Overall hazard ratios for each study were calculated by estimating the hazard ratios for 6-month intervals across the available

Table 2. Study characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Long-term data</th>
<th>Short-term data</th>
<th>Concomitant CABG %</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magne et al. [29]</td>
<td>Yes</td>
<td>Yes</td>
<td>89</td>
<td>Chronic ischemic MR with or without CABG</td>
<td>(1) Acute ischemic MR; (2) nonischemic dilated cardiomyopathy; (3) concomitant organic MR; (4) aortic or pulmonary valve stenosis or regurgitation more than mild; (5) severe tricuspid regurgitation; (6) previous mitral valve surgery; (7) concomitant surgery on another valve than mitral</td>
</tr>
<tr>
<td>Micovic et al. [30]</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>Ischemic MR (ischemic etiology identified based on preoperative and intra-operative records)</td>
<td>(1) Nonischemic MR; (2) concomitant surgery on another valve than mitral; (3) previous mitral valve surgery; (4) repair of postinfarct ventricular septal defect or papillary muscle rupture; (5) ventricular aneurysm repair or restoration</td>
</tr>
<tr>
<td>Milano et al. [31]</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>CABG with IMR (based on the preoperative or intra-operative studies or documented in the operative note with normal leaflet motion and chordal morphology)</td>
<td>(1) Previous MV surgery; (2) floppy or rheumatic valve</td>
</tr>
<tr>
<td>Ngaage et al. [32]</td>
<td>Yes</td>
<td>No</td>
<td>85</td>
<td>IMR with LVEF ≤ 35% (ischemic etiology based on the presence of prior transmural myocardial infarction OR prior coronary artery bypass grafting (CABG) OR &gt; 50% stenosis affecting two or more coronary arteries, with grossly normal mitral leaflets on echocardiography and/or at surgery</td>
<td>(1) Previous MV surgery; (2) previous MV surgery</td>
</tr>
<tr>
<td>Silberman et al. [33]</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>NA</td>
<td>(1) Previous MV surgery; (2) cardiogenic shock (including acutely ruptured papillary muscle)</td>
</tr>
<tr>
<td>Al-Radi et al. [34]</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>IMR defined as chronic MR resulting from papillary muscle infarction/ elongation/dysfunction/rupture, leaflet tethering by LV dysfunction or aneurysm, annular dilatation alone with no evidence of associated degenerative valve disease</td>
<td>(1) Previous MV surgery; (2) any additional cardiac procedures other than CABG</td>
</tr>
<tr>
<td>Mantovani et al. [35]</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>Combined CABG and mitral valve surgery for chronic ischemic mitral regurgitation (grades 2–4)</td>
<td>(1) Nonischemic MR associated with CAD; (2) recent myocardial infarction (&lt; 21 days); (3) presence of significant tricuspid regurgitation; (4) any additional cardiac procedures other than CABG</td>
</tr>
<tr>
<td>Reece et al. [36]</td>
<td>No</td>
<td>Yes</td>
<td>100</td>
<td>Combined CABG and mitral valve surgery</td>
<td>(1) Cardiogenic shock; (2) acute papillary muscle rupture requiring emergent MVR; (3) previous cardiac surgery; (4) postinfarct ventricular septal defect</td>
</tr>
<tr>
<td>Hickey et al. [37]</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>Combined CABG and mitral valve surgery for moderate and severe MR</td>
<td>(1) Congenital heart disease; (2) primary valve disease; (3) previous cardiac surgery; (4) postinfarction ventricular septal defect</td>
</tr>
</tbody>
</table>

$\text{Fig. 2: Short-term survival across studies. The odds of experiencing short-term mortality for patients in the replacement group were 2.5 times greater than for those in the repair group.}$
survival curves. The study hazard ratios ranged from 0.67 to 3.21 (see Fig. 1). In assessing potential heterogeneity among the studies, Cochran’s Q = 7.43 and \( p = 0.386 \), which reflects no statistically significant heterogeneity. Further, \( I^2 = 5.8\% \), indicating that only about 6% of the variability between the studies, is due to heterogeneity. This tends to be considered a low level of heterogeneity [38]. The summary hazard ratio was 1.35 (95% CI 1.13–1.62), \( p = 0.001 \), reflecting a 35% increased risk of death in the replacement group as compared to the repair group.

### 4. Discussion

To the best of our knowledge, our report is the first meta-analysis focusing specifically on repair versus replacement in
patients with IMR. One previous meta-analysis has examined the clinical outcomes of mitral valve repair versus replacement, reporting data on four subsets of patients based on the etiology of mitral valve disease: degenerative/myxomatous, ischemic, mixed, and rheumatic [39]. The ischemic subset was relatively small and included a total of six publications [39]. Although all of these publications were initially identified by our literature search, only two of them were selected for final inclusion [35,36]. The other four were eliminated because they included a large percentage of patients without ring annuloplasty in the repair group, reflecting former and not current surgical practice [19,21,25,26]. Our report overcomes some (but not all) of the limitations of the previously published meta-analysis and provides a more contemporary review of the current literature.

Because of the poor long-term prognosis of patients with IMR, some have advocated the routine implantation of bioprosthetic valves in this patient subset in order to avoid the bleeding and thrombo-embolic complications associated with mechanical valves. According to data from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, there has been a dramatic decline in the use of mechanical valves for mitral valve replacement in favor of bioprostheses in the last 8 years [40]. Although eight of the nine articles in our meta-analysis were published in 2004–2009, in more than half of the studies, the majority of patients in the replacement group received a mechanical prosthesis. Since the long-term survival of patients with bioprosthetic versus mechanical valve replacement in the mitral position has been found to be similar in multiple reports, it is unlikely that the large proportion of mechanical prostheses in the replacement group across studies had a negative influence on short-term and long-term outcomes [41–44].

The superiority of mitral valve repair over replacement is well established for patients with degenerative mitral valve disease. The advantages of mitral valve repair include lower operative mortality, improved long-term survival, better preservation of both early and late ventricular function, fewer valve-related complications, including thromboembolism, endocarditis, anticoagulation-related bleeding events, and late prosthetic dysfunction [45–52]. In agreement with these reports, our meta-analysis of nine studies comparing mitral valve repair versus replacement in patients with IMR shows improved short-term and long-term survival with mitral valve repair. The studies included in our meta-analysis are representative of the contemporary surgical practice in which there is lack of uniform preservation of both the anterior and the posterior leaflets in patients undergoing mitral valve replacement. Therefore, the advantage of repair over replacement may have been influenced by this and other factors that are not possible to capture using meta-analysis of retrospective data, including the algorithm for selection of repair versus replacement by the treating physician.

4.1. Strengths

When comparing mitral valve repair with replacement, one commonly raised argument is that there is an intrinsic selection bias such that patients undergoing valve replacement are sicker and often have more advanced ventricular dysfunction. This was not the case in our study. On the contrary, with the exception of the replacement patients being older in two of the studies, the repair patients more often had HTN, diabetes, and lower EF. In addition, the proportion of patients with severe ventricular dysfunction was similar between the two groups across all studies that reported data on that subset of patients (six out of nine studies).

All studies selected for our meta-analysis used rigorous inclusion and exclusion criteria. Consequently, patients with degenerative mitral valve disease or dilated cardiomyopathy were excluded. As expected, the majority of the patients underwent concomitant CABG. Therefore, the results of our study truly reflect the management of patients with chronic IMR. In addition, by excluding the patients in cardiogenic shock (often due to ruptured papillary muscles and therefore much more likely to undergo replacement), we have eliminated a potential bias for worse outcomes in the replacement group [25].

The lack of annuloplasty has been identified as a risk factor for mitral valve repair failure [53–56]. In addition, the advantages of ring annuloplasty over suture or bovine pericardium annuloplasty have been established in several series [53–56]. For IMR, ring annuloplasty is the mainstay of mitral valve repair. Therefore, to make the comparison between repair and replacement more meaningful and applicable to current surgical practice, we excluded articles that had >10% lack of annuloplasty ring (i.e., used suture annuloplasty and/or Teflon or pericardial strips).

The survival benefit of mitral valve repair over replacement for patients with degenerative disease has been explained in part with preservation of the subvalvular apparatus and the subsequent salutatory effects on ventricular function. Although initial mitral valve replacement was carried out with resection of the valve leaflets and chordae tendinae, the concept of preservation of the posterior subvalvular apparatus has been around for quite some time since first introduced by Lillehei et al. in 1964 [57]. Since then, a large body of literature has established the contribution of the subvalvular apparatus to postoperative ventricular function [58–60]. More recently, preservation of both the anterior and the posterior leaflets was found to confer a greater benefit compared with preservation of the posterior leaflet alone with respect to reducing LV chamber
size and systolic afterload, and improving ventricular performance [61,62]. Although some concerns have been raised with respect to preservation of both leaflets, including the potential interference with prosthesis motion, the need to undersize the mitral prosthesis, and the possibility of creating an LV outflow tract obstruction, the majority of these concerns do not apply to patients with ischemic mitral valve disease who have normal leaflet morphology and are quite amenable to total subvalvular preservation [62,63]. Of note, the vast majority of mitral valve replacements in our meta-analysis were performed with preservation of either the total or at least the posterior subvalvular apparatus and therefore reflected contemporary surgical practice. This adds to the validity of our results with respect to short-term and long-term survival following repair compared with replacement in patients with IMR.

4.2. Limitations

Our study has several limitations. The publications included in the meta-analysis were relatively small observational studies with the inherent biases of retrospective reviews. Inspection of funnel plots revealed fairly symmetric distributions and did not raise any major concerns about the potential of publication bias. However, given the small number of studies included in the meta-analysis, the possibility of such bias still exists and should be taken into account when considering the results.

The established technique for mitral valve repair of ischemic etiology is an undersized ring annuloplasty. However, ring placement alone does not result in durable repair in 15–39% of the patients [64–67]. A major limitation of our meta-analysis is the lack of long-term data on repair durability. However, adjunctive repair techniques in addition to ring annuloplasty were used in a number of patients across studies. Moreover, assuming there was a fair number of MR recurrences in patients with repair, long-term survival was still higher for the repair group compared with the replacement group. Therefore, further improvement in outcomes could be expected by addressing known risk factors for failure of mitral valve repair in IMR. These include preoperative LV end-diastolic diameter ≥70 mm, coaptation depth at discharge ≥5 mm, severe bileaflet tethering, higher annular diameter, higher tethering area, higher MR grade, preoperative posterior leaflet angle, and interapillary distance [53,68–71]. These sophisticated echocardiographic parameters were not available in most of the studies included in our meta-analysis. In addition, the following information was not presented in many of the studies: (1) ventricular chamber size, (2) preoperative MR grade (moderate vs severe), (3) timing of surgery with respect to recent MI, and (4) the presence or absence of residual MR in the repair group at the end of the procedure.

Another major limitation of our report is the fact that strict criteria for performing repair versus replacement were not laid out in any of the studies. As common in clinical practice, the decision to repair or replace the valve is based on the individual surgeon’s judgment and includes information regarding patient characteristics and valuable intraoperative information. Therefore, although the question of which patients should benefit from repair and which should be replaced cannot be addressed in this study, individualized consideration should be given to mitral valve repair in this setting of IMR.

5. Conclusion

Based on the meta-analysis of the current relevant literature, mitral valve repair for IMR is associated with better short-term and long-term survival compared with mitral valve replacement. Our conclusion should be interpreted in the context of the inherent limitations of a meta-analysis of retrospective studies including heterogeneity of patient characteristics, which may have influenced the physician’s decision to perform mitral valve repair or replacement. Prospective randomized trials are needed to definitively settle this controversy. Until then, mitral procedure selection should be individualized. An appropriate patient selection based on specific echocardiographic criteria to minimize the risks of persistent and/or recurrent MR would likely lead to even further improvement in outcomes with mitral valve repair for patients with IMR.

References


