Degenerative diseases of the mitral valve (MV) are the most common cause of mitral regurgitation (MR) in North America, and myxomatous degeneration of the MV is the most common type of degenerative disease. The pathological spectrum of myxomatous degeneration is broad, and it ranges from mild changes in the central portion of the posterior leaflet to generalized involvement of the entire MV apparatus resulting in voluminous and thickened leaflets and chordae tendineae, and sometimes calcification of the annulus and even of the myocardium and papillary muscles.1,2 Myxomatous changes tend to be more severe in the medial half than in the lateral half of the MV. Another type of degenerative disease of the MV is the so-called fibroelastic deficiency, first described by Alain Carpentier,3 whereby the leaflets remain thin and transparent, and the chordae tendineae become attenuate and may rupture, causing leafllet prolapse and MR. Dystrophic calcification of the mitral annulus is also included in the group of degenerative diseases.2

Clinical Perspective on p 1492

MV repair is considered to be the ideal treatment for patients with symptomatic MR due to degenerative diseases.4,5 There has been no randomized trial on MV repair versus clinical observation in asymptomatic patients with severe MR,6 but several retrospective clinical outcomes and comparative studies on asymptomatic patients with severe MR have found that MV repair improves survival.7-11 Indeed, current guidelines indicate that MV repair should be considered in asymptomatic patients in whom the probability of successful repair is high, and the operative mortality and morbidity is low.4,5 During the past decade, two-thirds of our MV repairs were performed in asymptomatic or minimally symptomatic patients, and this is likely the case in most large referral centers. Despite this aggressive approach on the treatment of patients with degenerative MR, there has been limited information regarding echocardiographic evaluation of MV function late after repair.12-15

This study examines the clinical outcomes of MV repair for MR due to degenerative diseases in a large cohort of patients who were prospectively followed with clinical evaluations and echocardiographic assessment of MV function during the past 26 years.

Methods

Patients

From 1985 to 2004, 840 consecutive patients with MR due to degenerative diseases underwent MV repair and were followed prospectively at approximately biennial intervals up to 26 years, median of 10.4 years. Clinical, hemodynamic, and pathological variables were evaluated for their association with outcomes. Age, left ventricular ejection fraction, and functional class were predictors of late cardiac- and valve-related deaths by multivariable analysis. MV repair failed to restore life span to normal in patients with functional class IV. Thirty-eight patients had repeat MV surgery, and the probability of reoperation at 20 years was 5.9%. During the follow-up, recurrent severe MR developed in 37 patients, and moderate MR developed in 61. Age, isolated prolapse of the anterior leaflet, the degree of myxomatous changes in the MV, lack of mitral annuloplasty, and duration of cardiopulmonary bypass were associated with increased risk of recurrent MR. At 20 years, the freedom from recurrent severe MR was 90.7%, and the freedom from moderate or severe MR was 69.2%.

Conclusions—MV repair for degenerative MR restored life span to normal except in patients with symptoms at rest and impaired left ventricular function. Advanced age and complex mitral valve pathologies increased the risk of late recurrent MR. (Circulation. 2013;127:1485-1492.)

Key Words: degenerative disease of the mitral valve ■ mitral regurgitation ■ mitral valve repair

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Background—The pathological spectrum of degenerative diseases of the mitral valve (MV) that causes mitral regurgitation (MR) is broad, and there is limited information on late outcomes of MV repair in various subgroups of patients and pathologies. This study examines this issue.

Methods and Results—All 840 patients who had MV repair for MR due to degenerative diseases from 1985 to 2004 were prospectively followed with clinical and echocardiographic evaluations at biennial intervals up to 26 years, median of 10.4 years. Clinical, hemodynamic, and pathological variables were evaluated for their association with outcomes. Age, left ventricular ejection fraction, and functional class were predictors of late cardiac- and valve-related deaths by multivariable analysis. MV repair failed to restore life span to normal in patients with functional class IV. Thirty-eight patients had repeat MV surgery, and the probability of reoperation at 20 years was 5.9%. During the follow-up, recurrent severe MR developed in 37 patients, and moderate MR developed in 61. Age, isolated prolapse of the anterior leaflet, the degree of myxomatous changes in the MV, lack of mitral annuloplasty, and duration of cardiopulmonary bypass were associated with increased risk of recurrent MR. At 20 years, the freedom from recurrent severe MR was 90.7%, and the freedom from moderate or severe MR was 69.2%.

Conclusions—MV repair for degenerative MR restored life span to normal except in patients with symptoms at rest and impaired left ventricular function. Advanced age and complex mitral valve pathologies increased the risk of late recurrent MR. (Circulation. 2013;127:1485-1492.)

Key Words: degenerative disease of the mitral valve ■ mitral regurgitation ■ mitral valve repair

Testing
at risk. The degree of myxomatous changes in the MV was graded as none or mild, moderate, and severe after surgical inspection of the valve. It was defined as none or mild when the leaflets were thin, had fairly normal sizes, and were transparent, with the exception of the prolapsing segment, and the chordae tendineae were often thin and attenuated. This grading included Carpentier fibroelastic deficiency and cases with minimal myxomatous changes. Moderate degeneration was defined when the leaflets were opaque owing to obvious myxoid infiltration of the spongiosa, and the leaflets were increased in size but they were still elastic and not excessively thick (<3 mm in thickness), and the chordae tendineae also had myxoid infiltration. Severe myxomatous degeneration was defined when the leaflets were voluminous, aneurysmal, and thickened (≥3 mm); the annulus was massively dilated (eg, ≥40 mm) and often displayed posterior displacement of ≥5 mm; and the chordae tendineae were thick and obviously myxomatous.18

All operations were performed through a full or partial median sternotomy (minimal access surgery) by 1 surgeon (T.E.D.). Repair of prolapsed leaflets was initially accomplished by using techniques described by Carpentier,1 and, since 1990, we have used preferentially chordal replacement with fine Gore-Tex sutures (W.L. Gore & Associates, Inc). A mitral annuloplasty was added to the procedure in most patients. During the first decade of the study, no annuloplasty ring was used in patients with acute or subacute MR due to ruptured chordae tendineae and relatively normal or small leaflets and annulus (eg, fibroelastic deficiency). All patients received warfarin sodium postoperatively during the first 3 months if in sinus rhythm and permanently if in atrial fibrillation or flutter.

Patients were followed by the referring cardiologist and contacted by our research personnel every second year, and an echocardiogram was requested to assess MV valve function whenever possible. MR was initially classified as none, trivial, mild, moderate, and severe based on the length and area of the regurgitant jet17 and with the use of the guidelines of the American Society of Echocardiography since its publication in 2003.18 In addition to transesophageal echocardiography during the operation, every patient had a transthoracic study before hospital discharge and multiple studies thereafter. Approximately one-half of all late echocardiographic studies were performed in our institution, and the other half were performed by referring cardiologists. Whenever the report from an outside laboratory indicated severe MR, the images were reviewed in our clinical investigation unit, and, if appropriate, the study was repeated in our hospital. Adverse events were reported according to the guidelines set by cardiac surgical societies.19 The cause of death was determined by hospital charts review, death certificates, or information from the physician who was caring for the patient at that time. The follow-up for this study was closed on April 30, 2012 and extended from 0 to 26 years, median of 10.4 years, interquartile range of 7.4 to 13.7 years. Clinical follow-up was complete in 98.4% of the patients. The echocardiographic follow-up extended from 0 to 26 years, median 10.3 years, interquartile range of 7.5 to 13.3 years, and it was 94.9% complete. The proportion of patients who had valve function assessed at 5 to 10 years was 97%, at 10 to 15 years was 94%, at 15 to 20 years was 90%, and beyond 20 years was 76%. This study was approved by the Review Ethics Board of University Health Network.

Statistical Analyses

All variables in Tables 1 and 2 were examined as potential associated factors. Variables with rare frequencies (<2.5% or ≤20 events) were reported in the descriptive statistics but were either collapsed (when possible) or excluded from all risk factor analyses to avoid model overdetermination. Data are presented as means with standard deviations, median with interquartile range, and frequencies, as appropriate. Freedom from time-dependent outcomes was modeled in a parametric survival model, with the use of maximum likelihood estimates to resolve risk, which divide risk over time in up to 3 distinct phases of risk (early, constant, and late) by using standard mathematical algorithms from the hazard procedure (hazard function represents the rate of occurrence of a time-related event; http://www.clevelandclinic.org/heartcenter/hazard). The parametric survival models were combined in a competing risk model to obtain prevalence of mutually exclusive events (MV reoperation, death from valvular cause, death from cardiac nonvalvular cause, and death from other causes). Associations between patient and surgical characteristics and outcomes were included in a bootstrap bagging algorithm (500 resamples), variables with high reliability (>50%) (defined as percentage of resample in which a given variable is selected) were then included in a multivariable parametric survival regression model with backward selection of variables to obtain a final model. Only variables selected in the bootstrap resampling (ie, >50% reliability) were included in the backward selection. No variables were forced in the multivariable regression models as their nonselection from the bootstrap bagging indicate marginal association with outcome. All risk factor analyses were performed by using a unified phase of risk. We chose parametric hazard modeling instead of Cox regression because it can accommodate date for multiphased risk (rather than constant risk in Cox regression), it is better to handle risk factor analysis on rare outcomes and is necessary for bootstrap resampling. Life tables from the Province of Ontario from 2000 to 2002 period (available from Statistics Canada at http://www.statcan.gc.ca/pub/84-537-x/4064441-eng.htm) were used to estimate 20-year survival of the patient cohort according to age and sex distribution. These estimates were compared to actual patient survival stratified by New York Heart Association (NYHA) classes at the time of MV repair. With only 7 patients who underwent the operation twice, we were not able to perform a formal repeated-measure analysis; thus, those 7 reoperations were considered independent of the initial operation. Data collection was repeated before each operation (ie, as if it was a new patient), and a new variable was created to identify these patients with 2 entries to confirm that no potential confounding was introduced by our approach. Mean imputation was used to account for missing variables. All statistical analyses were performed by using SAS v9.3 (SAS statistical software, NC).

Results

Table 1 summarizes the clinical profile of all patients, and Table 2 summarizes the surgical pathology and operative procedures. The Society of Thoracic Surgery risk score was 1.5% for the entire cohort (95% confidence interval, 0.3%–5.5%).

Early and Late Mortality

There were 4 early (<31 days) and 179 late deaths (81 cardiac- or valve-related, 95 other causes, and 3 unknown) among 840 patients. The causes of late cardiac- and valve-related deaths were sudden death in 23 patients, congestive heart failure in 21, stroke in 11, myocardial infarction in 11, anticoagulation-related hemorrhage in 8, intracranial hemorrhage in patients without anticoagulation in 3, repeat cardiac surgery in 3, and gastrointestinal bleeding without anticoagulation in 1 patient. Figure 1 shows the survival of all patients and the competing risk of mortality and reoperation. Figure 2 shows the survival of patients according to their preoperative NYHA functional classes and compares their survival with that of the general population matched for age and sex. Table 3 lists the independent predictors of all-cause mortality, valve-related mortality, and cardiac-related mortality after MV repair by multivariable analysis. Table 4 shows survival estimates and freedom from adverse events at various times intervals.

Thromboembolic Events

Eighty-one patients experienced one or more thromboembolic events. Fifty-one patients had a stroke and 11 died. Thirty-eight patients had cerebral transient ischemic attacks. Figure 3 shows the freedom from thromboembolic complications and the competing risk. Table 4 shows the freedom from thromboembolic events at various times intervals. Age by 5-year
increments was the only independent risk factor for thromboemolic complications (Table 3).

**Infective Endocarditis**

Nine patients had an episode of infective endocarditis. Five patients were treated with antibiotics alone and 4 required surgery. All patients survived. The freedom from this complication at various times intervals is shown in Table 4. The number of events was too small to determine predictors of infective endocarditis.

**Anticoagulation-related Hemorrhage**

At the time of the latest contact, 174 patients were on warfarin sodium because of atrial fibrillation (AF), a previous thromboembolic event, or both. Thirty-eight patients experienced serious hemorrhagic complications resulting in death in 8.

**Reoperation on the MV**

Thirty-eight patients underwent repeat MV surgery. The indication for reoperation was recurrent MR in 24 patients, mitral stenosis due to pannus in annuloplasty ring and leaflets in 5, endocarditis in 4, and hemolytic anemia with moderate MR in 5. The MV was re-repaired in 8 patients and replaced in 30. Figure 4 shows the freedom from reoperation on the MV and the competing risk for this complication. Freedom from reoperation at various times intervals is shown in Table 4. Independent predictors of reoperation are shown in Table 3.
Recurrent MR

Only 3 patients were discharged from the hospital with moderate MR; the remaining patients had none, trivial, or mild MR. During the follow-up, 37 patients developed severe MR, and 61 patients developed moderate MR. Among 37 patients with severe MR, 18 had reoperations, 5 were alive (4 asymptomatic with normal ventricular function and 1 in class III and poor ventricular function), and 14 died (8 valve- or cardiac-related deaths and 6 noncardiac deaths). Among 61 patients with moderate MR, 11 had reoperation because of symptoms of MR or hemolysis, 28 were alive, and 22 died (10 valve- or cardiac-related deaths and 12 noncardiac deaths). Figure 5 shows the freedom from recurrent severe and severe or moderate MR. Table 4 shows the values at various times intervals. Independent predictors of recurrent moderate or severe MR are shown in Table 3.

Functional Class

At the most recent follow-up contact, 627 patients were alive and free from MV replacement: 433 (69%) patients were in NYHA functional class I, 138 (22%) in class II, and 56 (9%) in class III. Among patients in NYHA class III, 1 patient had severe MR and 5 patients had moderate MR.
Discussion

This study provides information on long-term clinical and echocardiographic outcomes on MV repair for MR due to degenerative diseases in a cohort of relatively low-risk patients, because the proportion with advanced age, poor ventricular function, coronary artery disease, and other comorbidities was small but certainly similar to other surgical series on patients with degenerative MR treated by means of MV repair.7,8,10–12,14,15,20

We found that several factors affected cardiac- and valve-related mortality by multivariable models as listed in Table 3. Asymptomatic patients and patients with minimal symptoms were younger and had fewer cardiac comorbidities than those with more advanced symptoms, but functional class was an independent predictor of cardiac- and valve-related death. Moreover, long-term survival of patients with more advanced symptoms (NYHA class IV) was below the expected survival for the general population matched for age and sex as shown in Figure 2. These findings support the recommendation of early surgical intervention in patients with asymptomatic severe MR and normal left ventricular function as proposed by the guidelines on the management of heart valve disease4,5 and other investigators.10,11 Kang and colleagues11 from South Korea published a retrospective study on 447 asymptomatic patients with isolated degenerative severe MR and normal ventricular function who were either treated with early surgery (161 patients) or

Table 4. Survival Estimates and Freedom From Adverse Events at Various Time Intervals From Competing Risk Models (Top) and From Parametric Survival Regression Models (Bottom)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1 y (95% CI)</th>
<th>5 y (95% CI)</th>
<th>10 y (95% CI)</th>
<th>15 y (95% CI)</th>
<th>20 y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competing risk*</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Valve-related death</td>
<td>0.3 (0.2–0.6)</td>
<td>1.7 (1.1–2.6)</td>
<td>3.7 (2.6–5.1)</td>
<td>6.7 (4.9–8.9)</td>
<td>11.3 (8.0–15.7)</td>
</tr>
<tr>
<td>Cardiac death (nonvalve)</td>
<td>0.3 (0.2–0.5)</td>
<td>1.3 (0.8–2.1)</td>
<td>2.8 (1.9–4.2)</td>
<td>5.0 (3.6–7.0)</td>
<td>7.8 (5.2–11.7)</td>
</tr>
<tr>
<td>Noncardiac death</td>
<td>0.4 (0.2–0.8)</td>
<td>2.6 (1.8–3.8)</td>
<td>7.4 (5.9–9.3)</td>
<td>14.8 (12.3–17.8)</td>
<td>23.7 (18.9–29.2)</td>
</tr>
<tr>
<td>Reoperation†</td>
<td>0.9 (0.7–1.3)</td>
<td>2.7 (1.9–3.6)</td>
<td>4.1 (3.0–5.6)</td>
<td>5.1 (3.8–7.0)</td>
<td>5.9 (4.3–8.0)</td>
</tr>
<tr>
<td>Alive and reoperation-free†</td>
<td>98.1 (97.2–98.7)</td>
<td>91.7 (88.2–94.2)</td>
<td>82.1 (76.5–86.5)</td>
<td>68.5 (61.2–75.0)</td>
<td>51.9 (43.0–60.6)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
*These are proportion of patients, freedom = 100 – (proportion of patients).
† Reoperation on the mitral valve.

Figure 3. Freedom from thromboembolic events (upper) and competing risk (lower). The dotted lines are the 95th confidence interval around the parameter estimates. MV indicates mitral valve.

Figure 4. Freedom from reoperation on the mitral valve. Dotted lines are the 95% confidence intervals. The dotted lines are the 95th confidence interval around the parameter estimates. MV indicates mitral valve.
pathology, the feasibility of MV repair, and the operative mortality and morbidity. The ideal candidate is relatively young and otherwise healthy with isolated prolapse of the central portion of the posterior leaflet. A poor candidate is an elderly patient with multiple comorbidities and advanced myxomatous degeneration with prolapse of multiple segments of the leaflets and dystrophic calcification of the mitral annulus. Unfortunately, most patients fall in between, and the decision to offer surgery must be individualized according to the surgeon’s expertise. Clearly, prospective randomized trials on MV repair versus observation on asymptomatic patients with appropriate stratification of multiple variables known to affect late survival are needed, and hopefully will be performed.6

Sudden death is a known complication of MV prolapse, and it has been estimated to occur in 1 of every 400 patients per year.24 Flail segment with severe MR, valves with advanced myxomatous changes, and impaired left ventricular function increase the risk of sudden death up to 2% per year.25–27 Several authors have suggested that early MV repair might decrease the risk of sudden cardiac death.7,27 Sudden death was the most common cause of cardiac deaths in our series of MV repair and was recorded in 23 of 81 deaths. This number of events was too small for robust multivariable models of factors associated with sudden death, but advancing age, associated congenital heart disease, and reduced left ventricular ejection fraction increased the risk of sudden death, and isolated anterior leaflet prolapse and advanced myxomatous degeneration of the MV decreased the risk of sudden death by univariate analysis. In a comparison of our data with historical controls,25–27 MV repair appears to reduce the risk of sudden death, but it does not abolish it. Further studies are clearly needed to clarify the relationships between sudden death and MV prolapse.

Patients who had MV repair had a small but constant risk of thromboembolic events as documented in our series. The highest risk of thromboembolism was during the first year after surgery, justifying the recommendation of oral anticoagulation during the 3 postoperative months, but oral anticoagulation probably should be extended to 6 months or longer. Age was the only predictor of thromboembolism. AF did not increase the risk of thromboembolism in this series by multivariable analysis, but all patients in AF were on oral anticoagulant. Instead, they were exposed to a risk of anticoagulation-related hemorrhage, which was a relatively common complication in this subgroup. AF did not have an independent effect on survival after MV repair; this finding is corroborated by other studies.28,29 We found the duration of follow-up and the degree of myxomatous degeneration was associated with risk of postoperative late AF in patients who did not have AF before surgery. The maze procedure was effective in reducing the risk of late AF in patients with preoperative AF. Thus, it appears reasonable to combine the maze procedure to MV repair in patients with preoperative AF.29

Infective endocarditis was rare in our series of MV repairs, and only 9 patients developed this complication. Unlike heart valve replacement, which is associated with a relatively higher risk of infective endocarditis early on after surgery,30 there was not a single event during the first year of follow-up in our series of MV repair.

MV repair does not cure the underlying degenerative process, and recurrent MR is a potential problem in these patients.
regardless of their symptomatic status at the time of surgery. Severe MR developed in 37 patients and moderate MR developed in 61 patients during a median echocardiographic follow-up of 10.3 years. This is equivalent to almost one-third of all patients developing significant recurrent MR by 20 years. At 20 years, the freedom from recurrent severe MR was 90.7%, and moderate or severe was 69.2%. We identified the pathology of the MV as an important predictor of recurrent MR. Isolated prolapse of the anterior leaflet and advanced myxomatous degeneration were independent predictors of recurrent MR. Other factors that also predicted the development of late MR were advancing age, lack of annuloplasty ring, and duration of cardiopulmonary bypass. Recurrent MR was the principal cause of reoperation on the MV in our series. Our results were better than in other studies that used echocardiography to assess MV function after surgery. The freedom from recurrent moderate or severe MR in those studies varied from 77% at 5 years,14 71% at 7 years,12 and 81% at 10 years.15 These differences are likely related to patients’ selection and the experience of the surgeons.32 In our hands, early failure was usually related to technical errors, and re-repair was often feasible, whereas late failure was usually related to progression of the degenerative process and valve replacement was often necessary. Thus, we believe that indications for surgery for late recurrent MR should be different than for the first operation in asymptomatic patients, because MV re-repair may not be feasible and MV replacement may not yield as good a survival as MV repair.

In our series of MV repairs, 78 patients did not have a mitral annuloplasty ring or band because we deemed the mitral annulus and leaflet to be relatively small (eg, cases of fibroelastic deficiency), and an annuloplasty could have caused stenosis. Those patients had a higher risk of recurrent moderate MR but not for reoperation by multivariable analysis. It seems that mitral annuloplasty is necessary in all patients with MR due to degenerative disease.32 The type of mitral annuloplasty (rigid ring such as Carpentier or flexible as Duran or simply a posterior band as Cosgrove) had no effect on late recurrent MR; however, we found that the Duran ring was a risk factor for reoperation on the MV largely because of 5 patients who developed mitral stenosis due to excessive pannus on the annuloplasty ring with extension into the leaflets.33 We did not encounter this problem with the Carpentier ring or the Cosgrove band in our patients.

The duration of cardiopulmonary bypass was also associated with increased risk of recurrent MR, but this finding may be a surrogate for more extensive and complex MV repair.

Freedom from reoperation on the MV underscored freedom from recurrent MR in our series, because some patients with recurrent MR remained asymptomatic with normal ventricular function, declined reoperation, or were not offered reoperation because of comorbidities. Thus, freedom from reoperation on the MV was not an accurate measurement of the durability of MV repair. Indeed, at 20 years, only 6% of our patients had a reoperation on the MV, and almost twice as many developed severe MR and ≈5 times more developed recurrent moderate MR.

This study has the inherent limitations of any observational study. The patients were followed in a fairly systematic fashion throughout the study with echocardiographic assessment of MV function, but the operations were performed by a single surgeon and the results may not be generalizable. In addition, MV function was assessed in multiple echocardiography laboratories, and the interpretation of the results may not have been consistent.

**Conclusion**

MV repair for degenerative MR restored the life span to normal, with the exception of patients who had advanced sympotmatology and impaired left ventricular function. The findings support the recommendation of early MV repair in patients with severe MR and normal ventricular function regardless of their symptomatic status. The degenerative process was not arrested by MV repair, but most patients had acceptable MV function by echocardiography up to 2 decades after surgery.

**Disclosures**

None.

**References**


CLINICAL PERSPECTIVE

This is a prospective study on 840 consecutive patients who had mitral valve repair for mitral regurgitation due to degenerative disease. Patients were followed at approximately biennial intervals with clinical and echocardiographic assessments from 0 to 26 years, median of 10.4 years. Although mitral valve repair restored life span to normal in most patients, the development of symptoms or minimal reduction in left ventricular ejection fraction was associated with increased risk of cardiac mortality by multivariable analysis. Thus, asymptomatic patients with severe mitral regurgitation due to degenerative disease should be considered for mitral valve repair before developing signs of left ventricular dysfunction. Patients who had mitral valve repair have a small but constant risk of thromboembolic complications. Mitral valve repair was associated with a 6% cumulative risk of reoperation on the mitral valve at 20 years of follow-up, but approximately one-third of the patients developed recurrent moderate or severe mitral regurgitation. Advancing age, isolated prolapse of the anterior leaflet, and advanced myxomatous degeneration of the mitral valve were associated with higher risk of recurrent mitral regurgitation.
Late Outcomes of Mitral Valve Repair for Mitral Regurgitation Due to Degenerative Disease
Tirone E. David, Susan Armstrong, Brian W. McCrindle and Cedric Manlhiot

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