Recurrence of Mitral Valve Regurgitation After Mitral Valve Repair in Degenerative Valve Disease

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Background—Durability assessment of mitral valve repair for degenerative valve incompetence is actually limited to reoperation as the primary indicator, with valve-related risk factors for late death as a secondary indicator. We assessed serial echocardiographic follow-up of valve function as an indicator of the durability of mitral valve repair.

Methods and Results—In 242 patients who had undergone mitral valve repair for degenerative valve incompetence, echocardiographic follow-up of valve function, rate of reoperation, survival, and clinical outcome was studied. At 8 years after repair, clinical outcome was excellent, survival was 90.9±3.2%, freedom from reoperation was 94.2±2.3%, and freedom from anticoagulation bleeding and thromboembolic events was 90.4±2.7%. However, freedom from non-trivial mitral regurgitation (>1/4) was 94.3±1.6% at 1 month, 58.6±4.9% at 5 years, and 27.2±8.6% at 7 years. Freedom from severe mitral regurgitation (>2/4) was 98.3±0.9% at 1 month, 82.8±3.8% at 5 years and 71.1±7.4% at 7 years. The linearized recurrence rate of non-trivial mitral regurgitation (>1/4) was 8.3% per year and of severe mitral regurgitation (>2/4) was 3.7% per year. Inadequate surgical techniques (chordal shortening, no use of annuloplasty ring or sliding plasty) could only partially explain recurrence of regurgitation. In selected patients who did not have these risk factors, linearized recurrence rates were 6.9% per year and 2.5% per year, respectively.

Conclusion—The durability of a successful mitral reconstruction for degenerative mitral valve disease is not constant, and this should be taken into account when asymptomatic patients are offered early mitral valve repair. (Circulation. 2003;107:1609-1613.)

Key Words: echocardiography ▪ mitral valve ▪ follow-up studies ▪ valvuloplasty

Degenerative mitral valve disease is the leading cause of mitral regurgitation in the Western world.1 These diseased valves can be successfully repaired using a variety of surgical techniques. However, recent studies have demonstrated that myxomatous valve leaflets are structurally, biochemically, physically, and mechanically abnormal.2 Therefore, the question of long-term durability after valve repair is mandatory.

At first glance, abundant reports on highly successful repairs suggest that this consideration is irrelevant. Although these reports present up to 10-year follow-up results of survival, improved postoperative status, or freedom from reoperation, they do not describe echocardiographic follow-up of recurrence of mitral valve regurgitation.3-10

The goal of the present study is to analyze the recurrence of mitral regurgitation in terms of incidence and degree in a series of patients undergoing mitral valve repair for degenerative disease. All patients were operated on in the same institution, by the same surgeon, and with the use of standard repair techniques.

Myxomatous degeneration of the valve affects the leaflets as well as the subvalvular apparatus, and the extent of structural and mechanical changes differs between them.2 Therefore, besides overall progression of the valve disease, specific repair techniques may influence recurrence of regurgitation. For example, quadrangular resection of the billowing and degenerated portion of a posterior leaflet may fully exclude the sick part of the valve and can be expected to be more durable than shortening of elongated and severely affected chordae that are shortened but left in place. Therefore, an attempt is also made to identify possible predictive factors of recurrence of regurgitation from preoperative data and surgical techniques.

Methods

Patient Population
A group of 242 consecutive patients (mean age 62.7 years, 75% males) underwent mitral valve repair for degenerative disease. The majority of patients had a posterior leaflet prolapse (65%) and rupture of 1 or more chordae (69%). Mean ejection fraction was 66%, and average pulmonary artery pressure 40/16 mm Hg. The majority of patients (76%) were in sinus rhythm, 23% were in atrial fibrillation, and 0.8% had a pacemaker. Six percent of the patients were in New York Heart Association functional class I, 39% were in class II, 45% were in class III, and 10% were in class IV.

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Mitral Valve Characteristics
According to the preoperative echocardiographic analysis and the intraoperative findings, the valve pathology was identified and coded: location of the leaflet degeneration (anterior, posterior or both), leaflet integrity (normal, prolaps, perforation, calcification, cleft formation), annular integrity (normal, dilated, calcified), chordal integrity (normal, ruptured, elongated, retracted, fused), and papillary muscle integrity (normal, ruptured, elongated, fibrotic, necrotic).

We made an attempt to differentiate between Barlow disease and fibroelastic deficiency on the basis of gross macroscopical appearance; a valve with a distinct hood-like bulging of different parts of the anterior leaflet with excess tissue and multiple bulging posterior scallops with excess tissue as well was called Barlow Disease.

Surgical Techniques
All patients were operated by the same surgeon (W.F.). For repair, classical techniques described by Carpentier and others were used. Concomitant procedures were coronary artery bypass grafting (27% of patients, 1 to 6 grafts per patient), aortic valve replacement (1%), and tricuspid valve repair (4%). Leaflet excess tissue with prolapse and/or chordal rupture or with extensive billowing was treated with quadrangular (posterior leaflet) or triangular (anterior) resection. Quadrangular resection was usually combined with a sliding plasty of the posterior annulus when annular dilatation was present. In some cases, a plication of the posterior annulus was performed. Elongation of chordae, which was responsible for leaflet prolapse, was treated with chordal shortening, chordal transfer, or implantation of artificial polytetrafluoroethylene chordae. When the annulus was calcified, decalcification was performed, usually combined with a sliding plasty. Elongated papillary muscles were shortened. Most procedures were combined with the implantation of a complete prosthetic non-flexible Carpentier ring (90% of instances) or a complete non-movable prosthetic ring (10% of instances).

In every patient, the specific surgical repair techniques used were identified and coded, including intervention at the leaflet (none, quadrangular resection, triangular resection, plication, cleft closure), at the annulus (none, sliding plasty, plication, decalcification), at the chordae (none, shortening, transposition, artificial chordae), and at the papillary muscles (none, shortening, reimplantation, elongation), as well as the placement of an annuloplasty ring (yes or no).

Follow-Up
Clinical and echocardiographic follow-up were performed shortly before hospital discharge, at 1 month, and then every 6 months by the referring cardiologist. Survival, reoperation, cerebrovascular accidents, bleeding complications, anticoagulation therapy, New York Heart Association functional class, and cardiac rhythm were recorded. On echocardiography, mitral regurgitation was classified from 1 to 4.

Statistical Analysis
The Mann-Whitney U test, χ2 test, and Cox proportional hazards methods were used to analyze the data. For survival and follow-up of events, Kaplan-Meier techniques were used. For recurrence of mitral regurgitation, a classical Kaplan-Meier technique was used with the first echocardiographic follow-up date that demonstrated the recurrence of regurgitation as date of the event. Because the mitral regurgitation did in fact recur between the last echocardiogram without regurgitation (or the date of the operation if the echocardiogram before hospital discharge showed mitral regurgitation) and the first echocardiogram with regurgitation, an interval-censored survival curve using Turnbull’s algorithm was constructed additionally. For plotting the non-parametric maximum likelihood estimate based on interval-censored data, the mass was always placed at the at most right limit of the interval (for ease of making the graph).

Results
Survival and Reoperation Rate
Hospital mortality was 1.7%. Survival was 94.7±1.7% at 5 years and 90.9±3.2% at 8 years. Survival did not differ significantly between patients with or without associated coronary artery bypass graft (CABG) procedure (P>0.05). Freedom from reoperation at 5 years was 96.1±1.3% and at 8 years was 94.2±2.3%. Association of CABG procedures had no influence on freedom from reoperation (P>0.05).

Clinical Outcome and Morbidity
During the postoperative follow-up period, 91.3% of the patients improved at least one New York Heart Association functional class, 6.6% remained in class II, and 2.1% worsened (2 patients changed from class I to II, 1 from class II to III, and 2 from class III to IV). Postoperatively, 68.3% of the patients had sinus rhythm, 24.3% had atrial fibrillation, and 7.4% had a pacemaker (47% were preoperatively in sinus rhythm).

Anticoagulation (AC) therapy using coumarin (Marcumar, Roche Pharmaceuticals) was given during the follow-up period in 34.9% of the patients. Freedom from thromboembolic events up to 8 years after repair was higher, although not significantly so (P>0.05), in patients who received anticoagulation therapy than in those who did not (97.5±1.7% versus 89.9±3.6%). Freedom from thromboembolic events and/or major AC bleeding was 92.3±2.0% at 5 years and 90.4±2.7% at 8 years for the whole group. Freedom from thromboembolic events was significantly higher in patients who had sinus rhythm at their latest follow-up than in those who had not (P=0.009). The data at 8 years were 96.4±1.9% versus 84.2±5.8%.

Recurrent of Mitral Regurgitation
Postoperative echocardiography was performed at hospital discharge, at 1 month, and then serially at 6-month intervals. Operative success of the mitral valve repair was assessed by the echocardiographic examination of mitral valve function within the first 4 weeks postoperatively. Quality of the repair is considered successful when the early echocardiography showed only a trivial residual mitral valve regurgitation of 0 to 1/4, acceptable when the echo score was 1 to 2/4, and failed when the score was 3 to 4/4. Using this scoring system, 95% was successful.

Using the classical Kaplan-Meier approach, freedom from recurrence of non-trivial degrees of regurgitation (>1/4) was 94.3±1.6% at 1 month, 58.6±4.9% at 5 years, and only 27.2±8.6% at 7 years (Figure 1). Freedom from failing repair (regurgitation >2/4) was 98.3±0.9% at 1 month, 82.8±3.8% at 5 years, and 71.1±7.4% at 7 years (Figure 2). When the interval-censored Turnbull approach is used to calculate the freedom from recurrence of mitral incompetence, similar results are obtained (Figure 1 and Figure 2). The constant rate of recurrence of mitral regurgitation after the first month postoperatively was remarkable. When the classical Kaplan-Meier curves are restricted to the period 1 month until 7 years postoperatively, a highly linear regression can be made. Recurrence of mitral regurgitation >1/4 happens at a rate of 8.3% per year, and recurrence of mitral regurgitation >2/4 happens at a constant rate of 3.7% per year (Figure 3).
Predictive Factors of Recurrence of Mitral Valve Regurgitation After Repair

Using the Kaplan-Meier curves (Wilcoxon test for comparison of curves), the different forms of degenerative valve disease (ie, Barlow disease as identified by only gross macroscopical appearance [45 patients], Marfan disease [1 patient] and fibroelastic deficiency [remaining patients]) were also taken into account. In Barlow disease, recurrence of regurgitation after repair was somewhat more pronounced, but no statistically significant difference in recurrence of regurgitation was found ($P=0.059$ for $>1/4$ regurgitation and $P=0.063$ for $>2/4$ regurgitation).

The effect of association of CABG was also tested. No significant influence was found ($P=0.308$ for $>1/4$ regurgitation and $P=0.357$ for $>2/4$ regurgitation).

During the follow-up period, a subpopulation of 28 patients was identified who showed recurrence of significant mitral valve regurgitation ($>2/4$) and could be compared with the remaining 214 patients who did not. $\chi^2$ analysis revealed that the subpopulation showing recurrence of regurgitation was characterized by a higher incidence of bileaflet mitral valve degeneration ($P=0.03$) and a lower incidence of posterior annulus dilatation ($P<0.05$).

Specific surgical repair techniques also had a predictive value for recurrence of regurgitation; these included no use of an annuloplasty ring ($P<0.01$, $\chi^2$; $P=0.0025$, $t=4.34$, exponent beta=0.1427, Cox proportional hazard), the use of chordal shortening instead of artificial chordae or transposition ($P<0.03$, $\chi^2$) and no use of a sliding plasty in case of posterior annulus dilatation ($P<0.03$, $\chi^2$).

We separated the study population into 2 subgroups. The first bears the surgical risk factors as determined above (ie, no annuloplasty ring and/or chordal shortening and/or no use of sliding annuloplasty) and the second does not. We could define 2 significantly different reoccurrence rates of mitral regurgitation. The results are shown in the Table. Patients having the surgical risk factors had a recurrence rate of regurgitation $>1/4$ of 10.7% per year and of regurgitation $>2/4$ of 5.9% per year. However, patients not having these risk factors still had a recurrence rate of regurgitation $>1/4$ of 6.9% per year and of regurgitation of $>2/4$ of 2.5% per year. The differences between subgroups are statistically significant for regurgitation $>1/4$ as well as for $>2/4$ ($P=0.0361$ and $P=0.00001$, respectively).

The linear regression of freedom from mitral regurgitation in patients having the surgical risk factors had an intercept of 88.7% (Table). This means that in this subgroup, repair failed immediately or within 6 months after operation in about 10% of cases. This is in contrast to the second subgroup lacking the risk factors; the intercepts are at 94.8% and 99.5%, respectively, which means that the early postoperative results were excellent.
It has also been demonstrated\textsuperscript{16} that cells of the chordae of leaflets are more extensible and less stiff than normal valves. The results also suggest that repaired valves remain degenerative, and that their durability is limited. 

Although histological alterations in myxomatous valves have been well described in the past,\textsuperscript{12–15} only recently have the mechanical properties of myxomatous mitral valves been extensively studied,\textsuperscript{2} and it has been shown that myxoid leaflets are more extensible and less stiff than normal valves. It has also been demonstrated\textsuperscript{16} that cells of the chordae of myxomatous valves produce more glycoaminoglycans, giving them their characteristic thickening and gelatinous nature, which may account for their mechanical weakness.\textsuperscript{17}

All these pathophysiological findings may help to explain why a progressive incidence of mitral valve incompetence is found after initial adequate repair. Nevertheless, our results show that at 7 years after repair, the incidence of significant regurgitation remains low (29%). This is in concordance with the available clinical reports showing good clinical outcome and low reoperation rates after repair (93% to 96% freedom at 10 years).\textsuperscript{6} We also found a low reoperation rate at 8 years (5.8%) and an excellent clinical outcome. The discrepancy between reoperation rate and the incidence of significant mitral valve regurgitation indicates that not all patients having important valve incompetence late after repair undergo surgery again within the timeframe of the 10 year follow-up.

Recently, very long-term results (about 20 years) after repair for mitral valve prolapse were reported.\textsuperscript{18} It was shown that the reoperation rate was not different after repair or mitral valve replacement at 19 years. Furthermore, reoperation rate after repair constantly increased; it was at 7% at 5 years, 11% at 10 years, 16% at 15 years, and 20% at 19.5 years. Survival at 19.5 years was 30%. Our results show that, after highly successful repair, recurrence of mitral valve incompetence occurs at a constant rate during the following years. These results also suggest that repaired valves remain degenerative and that their durability is limited.

Factors Influencing Post-Repair Durability

Causes of recurrence of regurgitation after mitral valve repair may be classified as valve-related or procedure-related. Our study shows a constant rate of recurrence of mitral valve incompetence, suggesting that the underlying valve disease is the most important factor of post-repair failure. Also, the results of the multivariate analysis point in the same direction; advanced myxomatous changes with prolapse of both leaflets influence failure of valve repair. This was already recognized by others,\textsuperscript{6} as was the prevalence of failure after anterior leaflet prolapse.\textsuperscript{9,10} We could also show that patients having a dilated mitral annulus do better after repair than patients having a normal sized annulus in terms of recurrence of regurgitation. This, however, might be related to the surgical technique; none of the patients having a non-dilated annulus received an annular ring. No use of an annuloplasty ring is a known surgical risk factor for repair failure and is also recognized in this study.

Concerning surgical factors, our study revealed nothing new. The non-use of an annuloplasty ring, non-use of a sliding plasty, and the use of chordal shortening instead of transposition or artificial chordae were factors of recurrence of mitral valve incompetence, as already shown by others.\textsuperscript{7}

In a larger study, Gillinov et al\textsuperscript{6} demonstrated that the instantaneous risk of reoperation (hazard function) consists of 2 hazard phases: a peaking early hazard phase in the first year after the operation, followed by a slow rising late hazard phase of reoperation. He showed that patients with an isolated anterior leaflet prolapse had an increased early risk of reoperation. Also, chordal shortening increased the risk of early repair failure, and the use of ring annuloplasty and leaflet resection decreased the risk of reoperation in the late hazard phase. Nevertheless, most of these surgical factors are indirectly related to the process of valve degeneration, mainly in the chordae, which are severely structurally altered by the degenerative process.

Study Limitations

After hospital discharge, postoperative echocardiography was performed by the referring cardiologists. This may have influenced the quality of postoperative evaluation because...
echocardiographic assessment is observer-dependent. However, this observer-dependent variation will be small because only the in-hospital discharge echo can be done by a cardiologist other than the one doing the follow-up. Currently, more than 95% of patients show a normal functioning valve after repair. We made an attempt to differentiate between the different forms of degenerative valve disease, mainly Barlow disease and fibroelastic deficiency. Although the distinction between these entities is usually made on the basis of clinical and echocardiographic data, gross appearance, histology, and biochemistry, we feel that a clear distinction remains difficult. We used the somewhat pragmatic definition by Fasol and Mahdjoobian, which is based on gross appearance of the valve only. Therefore, our results cannot exclude the influence of valve pathology on post-repair recurrence of regurgitation. The differences in recurrence rate of regurgitation after repair between Barlow disease and fibroelastic deficiency were borderline \( P=0.059 \) and \( P=0.063 \), suggesting a less favorable outcome in Barlow disease.

Different techniques were used to correct a similar valve defect. For example, chordal elongation was treated by chordal shortening, chordal transposition, or implantation of artificial PTFE chordae. These techniques, however, were not randomized and were not always simultaneously available. This lack of randomization could be a limiting factor for result analysis.

Conclusion
This study reports for the first time on recurrence of mitral valve regurgitation after mitral valve repair for degenerative mitral valve disease. Serial echocardiographic follow-up assessment of mitral valve function allows identification of patients who had mitral valve regurgitation but did not undergo reoperation and shows that durability of repaired mitral valves is limited. This should be considered before early surgery is proposed to patients with mitral regurgitation due to valve degeneration.

References
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