

Long-Term Results (≤ 18 Years) of the Edge-to-Edge Mitral Valve Repair Without Annuloplasty in Degenerative Mitral Regurgitation

Implications for the Percutaneous Approach

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Background—To assess the long-term results of the edge-to-edge mitral repair performed without annuloplasty in degenerative mitral regurgitation (MR).

Methods and Results—From 1993 to 2002, 61 patients with degenerative MR were treated with an isolated edge-to-edge suture without any annuloplasty. Annuloplasty was omitted in 36 patients because of heavy annular calcification and in 25 for limited annular dilatation. A double-orifice repair was performed in 53 patients and a commissural edge-to-edge in 8. Hospital mortality was 1.6%. Follow-up was 100% complete (mean length, 9.2 ± 4.21 years; median, 9.7; longest, 18.1). Survival at 12 years was $51.3\pm 7.75\%$. At the last echocardiographic examination, MR $\geq 3+$ was demonstrated in 33 patients (55%). At 12 years, freedom from reoperation was $57.8\pm 7.21\%$ and freedom from recurrence of MR $\geq 3+$ was $43\pm 7.6\%$. Residual MR $>1+$ at hospital discharge was identified as a risk factor for recurrence of MR $\geq 3+$ (hazard ratio, 3.8; 95% confidence interval, 1.7–8.2; $P=0.001$). In patients with residual MR $\leq 1+$ immediately after surgery, freedom from MR $\geq 3+$ at 5 and 10 years was $80\pm 6\%$ and $64\pm 7.58\%$, respectively.

Conclusions—In degenerative MR, the overall long-term results of the surgical edge-to-edge technique without annuloplasty are not satisfactory. Early optimal competence (residual MR $\leq 1+$) was associated with higher freedom from recurrent severe regurgitation. (*Circulation*. 2014;130[suppl 1]:S19-S24.)

Key Word: mitral valve insufficiency

In degenerative mitral regurgitation (MR), annuloplasty is commonly recommended to complete mitral valve (MV) repair. Particularly when a prosthetic ring is used, repair durability is enhanced by increased leaflet coaptation and prevention of further dilatation of the mitral annulus.^{1–4} After the introduction of the MitraClip system, however, MR has been treated in many patients by applying a percutaneous ringless edge-to-edge (EE) procedure. Defining the long-term results of the surgical EE repair performed without annuloplasty may help to foresee, at least partially, the possible late results of this percutaneous technique. We have previously reported the midterm results of the surgical EE repair without annuloplasty in different clinical settings.^{5,6} Herein, we report the clinical and echocardiographic long-term results of our experience with the EE technique without annuloplasty in patients with severe degenerative MR.

Methods

Study Population

From November 1993 through December 2002, 548 patients with MV regurgitation were treated with the EE technique in our Institution. Out of them, for the purpose of this study, we selected 61 consecutive patients with degenerative MR, who underwent the procedure without the association of any sort of annuloplasty. Patients with pathogenesis of MR other than degenerative and those who received a rescue EE or other concomitant leaflet repair techniques were excluded. Patients who had the repair done with a robotic or minimally invasive approach were not included as well to avoid the influence of the learning curve of those specific surgical techniques. The Institutional Ethical Committee approved this study and waived individual consent for this retrospective analysis.

Data Collection

Preoperative, intraoperative, and postoperative data were collected through a hospital database and patients' records. Follow-up data were

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obtained by means of outpatient visit and TTE examination or by means of telephone interview with the patients and the referring cardiologists. At least 1 transthoracic echocardiography (TTE) was obtained at follow-up for all hospital survivors. For patients who underwent reoperation during the follow-up period, clinical and Doppler echocardiographic data refer to the latest findings available before reoperation.

Statistical Analysis

Calculations were performed using SPSS version 11.5 (SPSS Inc, Chicago, IL) for Windows (Microsoft Corp, Redmond, WA) software package and R 2.15.1 software (R Development Core Team [2011]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>). Continuous data were expressed as mean±SD or as median and interquartile range, and categorical data were reported as number and percentage. For continuous variables, differences were tested with the unpaired *t* test or nonparametric Mann–Whitney test, whereas for categorical variables, the χ^2 test or Fisher exact test were used. Time-to-event data (survival and freedom from events) were analyzed by Kaplan–Meier method, and differences among groups were evaluated with the log-rank test. Cox proportional-hazard regression was used to estimate the hazard ratios of potential predictors of MR $\geq 3+$ recurrence in univariate analysis

Results

The preoperative data of the final study population are reported in Table 1. At admission, 24 (39%) patients were in New York Heart Association (NYHA) class I or II, whereas 37 (61%) patients were in class III. Fifteen patients (24%) were in atrial fibrillation.

Mitral regurgitation degree was determined by means of a combination of color Doppler (color flow jet area and

vena contracta width) and pulmonary vein flow analysis and classified as mild (1+/4+), moderate (2+/4+), moderate to severe (3+/4+), and severe (4+/4+). Mitral regurgitation was severe (4+/4+) in 34 patients (34/61; 55.7%) and moderate to severe (3+/4+) in the remaining 27 patients (27/61; 44.2%).

Transesophageal echocardiography showed that the mechanism of MR was bileaflet prolapse in 28 patients (46%), anterior leaflet prolapse in 11 patients (18%), and a prolapse of the posterior leaflet in 22 patients (36%). Important annular calcification was found in 36 patients (59%).

Surgical Procedure

The MV was approached through a median sternotomy and a standard left atrial incision in all cases. According to the location of the main regurgitant jet, a double-orifice repair was performed in 53 (86.8%) patients and a commissural EE repair in the remaining 8 (13.1%). The paracommissural repair was posteriorly located in 6 patients and anteriorly located in 2 patients. A 4-0 polypropylene continuous suture without pledgets was used in most cases for leaflet approximation, unless the leaflets were thin. In these cases, a 5-0 suture was preferred.

In case of annular calcification, the rationale for adopting the EE technique was to correct leaflet lesions with no annular manipulation. Indeed, the main reason for annuloplasty omission was the presence of significantly/severely calcified annulus which was present in 36 patients (36/61; 59%). In the remaining 25 patients (41%), the EE was intentionally performed without a concomitant annuloplasty because the annulus was judged by the surgeon not to be significantly dilated. By avoiding annuloplasty in those cases, also the risk of inducing postoperative mitral stenosis was minimized. Several associated procedures were performed concomitantly with valve repair, including coronary artery revascularization (9 patients), tricuspid annuloplasty (7 patients), aortic valve replacement (3 patients), radiofrequency ablation of atrial fibrillation (4 patients), ascending aorta replacement (1 patient), atrial septal defect (2 patients), and patent foramen ovale closure (1 patient).

Hospital Mortality and Long-Term Survival

One patient died within 30 days of the operation of hemoperitoneum and hemorrhagic shock for a hospital mortality of 1.6%.

Follow-up was 100% complete. Mean clinical follow-up time was 9.2±4.21 years with a median (interquartile range) of 9.7 years (6.2–12.5 years). The mean duration of the echocardiographic follow-up was 7.4±3.4 years (median, 8 years). The longest duration of follow-up reached 18.1 years.

There were 25 late deaths for an overall survival at 12 years of 51±7%. At the last TTE performed before death, 12 of those 25 patients (12/25; 48%) had 3+ (5 patients) or 4+ (7 patients) MR. Cardiac-related deaths occurred in 9 patients (9/25; 36%) and were because of multiple organ failure after MV replacement (2 patients), acute myocardial infarction (2 patients), congestive heart failure (3 patients), stroke (1 patient), and sudden death (1 patient). Freedom from cardiac death at 12 years was 87±4.5% (Figure 1).

Table 1. Preoperative Clinical and Echocardiographic Data

Age, y, mean±SD	64±12.1
Male sex, n (%)	26 (42)
MR 3+/4+, n (%)	27 (44.2)
MR 4+/4+, n (%)	34 (55.7)
NYHA class, n (%)	
I–II	24 (39.3)
III	37 (60.6)
Previous cardiac operation, n (%)	3 (4.9)
AF at presentation, n (%)	15 (24)
Echocardiographic data	
LVEF, %, median (IQR)	60 (55–60)
LVEDD, mm, median (IQR)	63 (60–66)
LVESD, mm, median (IQR)	36 (35–38)
SPAP, mmHg, median (IQR)	42 (35–49)
Mechanism of MR, n (%)	
Flail/prolapse of both leaflets	28 (46)
Flail/prolapse of the anterior leaflet	11 (18)
Flail/prolapse of the posterior leaflet	22 (36)
Calcified annulus, n (%)	36 (59)
Noncalcified annulus, n (%)	25 (41)

AF indicates atrial fibrillation; IQR, interquartile range; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; New York Heart Association; and SPAP, systolic pulmonary artery pressure.

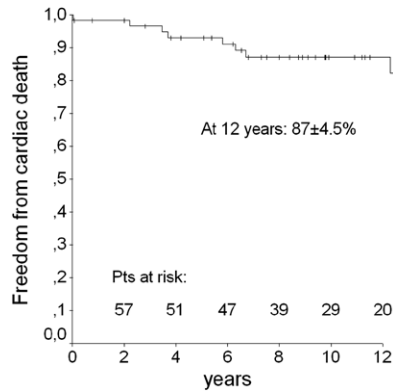


Figure 1. Freedom from cardiac death.

Reoperation

Twenty-one patients required reoperation during the follow-up period. All had undergone double orifice repair. The cause of reoperation was recurrent severe regurgitation in all cases. None of the 8 patients with paracommissural repair underwent reoperation during the follow-up period although 2 of them had recurrent MR $\geq 3+$ (1 patient with MR3+ was still in NYHA class II, and 1 patient with severe MR died before reoperation). Mitral valve replacement was performed in 19 cases (17 mechanical and 2 biological prostheses), and a successful rerepair (ring annuloplasty) was possible in 2 patients who had no annular calcification and in whom concomitant annuloplasty had been initially avoided on purpose. Overall freedom from reoperation was $57.8 \pm 7.21\%$ at 12 years (Figure 2). We assessed the freedom from reoperation according to the presence of annular calcification. Initially (≤ 4 years after surgery), patients without calcification had less events compared with those with annular calcification with a freedom from redo of $85 \pm 7.6\%$ versus $76 \pm 7.2\%$, respectively. However, beyond that time frame, an increasing number of reoperations was progressively recorded also in those patients who had an EE intentionally performed without annuloplasty. Therefore, the overall freedom from reoperation at 9 years in the no calcified annulus group was not significantly different from that registered in the calcified annulus group ($58.6 \pm 11.4\%$ versus $57.8 \pm 9.14\%$; $P=0.7$).

The results presented for the reoperation outcome do not change substantively when death is treated as a competing risk.

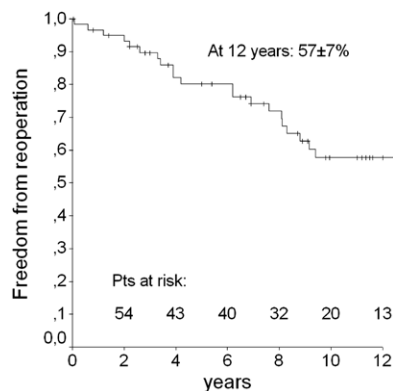


Figure 2. Freedom from reoperation.

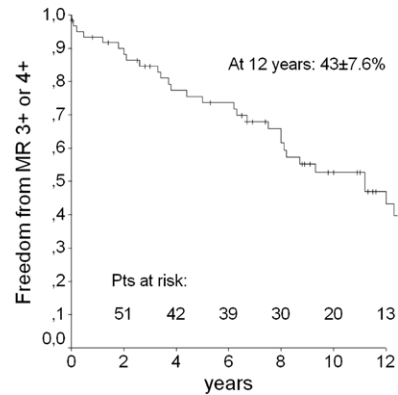


Figure 3. Freedom from recurrence of mitral regurgitation (MR) of grade 3 to 4+.

Echocardiographic Data and Recurrence of MR

At hospital discharge, residual MR was absent or mild in 48 patients (48/60; 80%), moderate (2+) in 10 patients (16.6%), and moderate to severe (3+) in 2 patients (3.3%). Of the 12 patients with residual MR $\geq 2+/4+$, 11 had massive annular calcification that precluded the possibility of performing a concomitant annuloplasty. Mitral stenosis was never detected either during the hospital stay or during follow-up. At the last echocardiographic assessment, 19 patients (19/60; 31.6%) had no or mild MR, 8 patients (13.3%) had moderate (2+) MR, 11 patients (18.3%) had moderate-to-severe (3+) MR, and 22 patients (36.6%) had severe MR. Therefore, 33 patients of 60 hospital survivors (54.9%) had MR $\geq 3+$. Freedom from MR $\geq 3+$ at 12 years was $43 \pm 7.6\%$ (Figure 3). Interestingly, as for the reoperation rate, patients without annular calcifications showed at midterm (≤ 4 years) a higher freedom from recurrent MR 3+ or 4+ ($81 \pm 8.4\%$) compared with those in whom annuloplasty was omitted for the presence of important calcification ($73 \pm 7.5\%$). With increased follow-up length, however, no statistically significant differences could be demonstrated between the 2 groups who had a similar freedom from this event at 9 years ($P=0.1$; Figure 4). As already mentioned, all patients with recurrent severe (4+/4+) MR were reoperated with the only exception of 1 patient who died before redo surgery. The reason for not reoperating the remaining 11 patients with moderately severe (3+/4+) MR was that they were still in NYHA functional class II, and most of them had

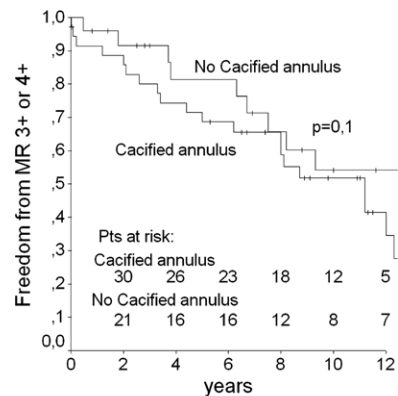


Figure 4. Freedom from recurrence of mitral regurgitation (MR) of grade 3 to 4+ in patients with and without annular calcification.

Table 2. Univariate HRs of Selected Baseline Variables and Recurrence of MR $\geq 3+$

	HR	95% CI	P Value
Age*	0.9	0.9–1.0	0.2
LVEF†	1.0	0.9–1.0	0.8
NYHA >2 ‡	0.6	0.3–1.3	0.2
Atrial fibrillation	1.2	0.5–2.6	0.6
Calcified annulus	1.8	0.8–3.8	0.1
Commissural EE vs DO	0.3	0.07–1.3	0.1
Associated procedures§	0.9	0.4–1.9	0.9
MR $>1+$ at discharge	3.8	1.7–8.2	0.001

CI indicates confidence interval; DO, double orifice; EE, edge-to-edge; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; and NYHA, New York Heart Association.

*Per year increase.

†Per % increase of LVEF.

‡Reference category was NYHA class 1 and 2 considered together.

§Coronary artery bypass grafting/aortic valve replacement/tricuspid valve annuloplasty/atrial fibrillation ablation.

severe annular calcification, which was already known from the previous operation to be a challenging issue to deal with. Therefore, a close clinical/echocardiographic follow-up was preferred for the time being.

As shown in Table 2, an initial suboptimal result with more than mild ($>1+/4+$) residual MR at hospital discharge was identified as a significant risk factor for recurrent MR $3+$ or $4+$ at follow-up. The prevalence of MR $\geq 3+/4+$ at follow-up was 83.3% (10/12) in the 12 patients who were discharged with MR $>1+$ and 47.9% (23/48) in those who left the hospital with no or mild MR ($\leq 1+$; $P=0.0001$). The proportional hazard assumption of the Cox model was checked with Schoenfeld residuals and associated statistic, resulting not violated ($P=0.844$). Freedom from MR $\geq 3+/4+$ in the patients with optimal initial result was $80\pm 6\%$ at 5 years, $64\pm 7.5\%$ at 10 years, and $50\pm 8\%$ at 12 years. Finally, freedom from recurrent MR $\geq 3+$ was calculated also for the best possible subgroup of patients, that is the one including only the 24 patients with intentionally avoided annuloplasty (no annular calcification) and with no or mild residual MR at hospital discharge. In those patients, freedom from this event was $62.8\pm 11.2\%$ at 9 years.

Clinical Status

At the latest follow-up, 20 patients (20/60; 33.3%) were in NYHA class I, 16 (26.6%) in class II, and 24 (40%) in class III. NYHA class was significantly higher in patients with recurrent MR $3+$ or $4+$ at follow-up. In particular, an NYHA class III was present in 60.5% of the patients with recurrent MR $\geq 3+/4+$ (20/33) compared with 14.8% (4/27) of those with MR $\leq 2+/4+$ ($P<0.0001$). Finally, as far as heart rhythm at follow-up is concerned, 41 patients (68.3%) were in sinus rhythm (including 2 with a pacemaker implanted) and 19 (31.6%) in atrial fibrillation.

Discussion

The main finding of this retrospective analysis is that, when the EE procedure is performed without a concomitant annuloplasty, long-term results are not satisfactory. The role of

annuloplasty in MV repair for degenerative MR is important. Particularly when a prosthetic ring is used, a concomitant annuloplasty, besides remodeling the annulus and forcing leaflet coaptation, stabilizes the repair over time preventing annular redilatation and reducing the risk of late failure. The benefits of annuloplasty in valve repair have been confirmed by several authors^{1–4} who found that the absence of annuloplasty was one of the most important risk factor for late failure of the repair. As far as the EE technique is concerned, in patients with degenerative MR, the long-term results of this procedure are excellent whenever an annuloplasty is concomitantly used.^{7,8} However, when annuloplasty is omitted and annular dilatation is not corrected, computational models have predicted higher stresses on the suture and on the leaflets, possibly leading to progressive degeneration of the reconstruction.⁹ In the clinical setting, we first reported a higher failure rate at 5 years for the EE technique without ring annuloplasty in 260 patients submitted to the double-orifice repair.¹⁰ In other 2 subsequent studies, we were able to confirm those preliminary findings, but, in addition, we demonstrated that midterm results (≤ 5 years) were suboptimal particularly in patients with calcified annulus and in those who were left with more than mild residual MR at hospital discharge.⁵ However, midterm outcomes were encouraging in patients in whom annuloplasty was intentionally avoided because of limited annular dilatation.⁶ However, besides the results at midterm (5 years) described in those 2 articles, no data at long-term have ever been published. Providing the long-term outcomes of the ringless EE technique was the aim of this retrospective analysis. After the introduction of the MitraClip system, $>13\,000$ patients have been submitted to a percutaneous transcatheter EE repair without concomitant annuloplasty.

Although the surgical EE and the Mitraclip therapy are not exactly the same, it is important to consider that, in the current clinical practice, >1 clip are often used in a significant number of patients, leading to a technical solution that is rather close to the surgical method. Therefore, we think that defining the results at long-term of the surgical ringless EE series might provide some important insights regarding the possible long-term outcomes of this percutaneous approach. In addition, the data reported here are rather unique because the EE technique was introduced by our group in 1991¹¹ and there are no other series available including patients with ringless EE repair followed for a median time of 9 years (≤ 18 years).

To try to eliminate as much confounding variables as possible, we focused just on patients with degenerative MR treated exclusively with an EE repair, in whom ring annuloplasty was omitted.

The omission of annuloplasty in the study population was because of specific situations such as the presence of annular calcification and small annulus. Those circumstances made the placement of the ring less desirable. In particular, important annular calcification was the most common condition precluding the possibility of a simultaneous annuloplasty.^{12–16} In a smaller number of patients, annuloplasty was intentionally avoided because of the presence of only mild annular dilatation/deformation. Although in our institution residual MR $>1+$ is not accepted after repair,¹⁷ we decided to tolerate this suboptimal result in a minority of patients included in this

series because they had massive annular calcification, and revision of the correction or valve replacement would have been high-risk procedures. Because annular calcification is a surgical challenge, treating type II lesions by acting only on the leaflets was considered an appealing approach in our clinical practice at the beginning of our experience. However, this study demonstrated that the long-term results of the EE repair without annuloplasty in this setting are poor, although one should consider that patients with calcified annulus and myxomatous disease represent high-risk patients with worse midterm and long-term outcomes because of the complexity of their disease.^{12–16} The reason why the EE technique failed in the calcified annulus is 2-fold. One reason is that we accepted suboptimal results at hospital discharge, which eventually progressed over time. The second explanation is that, by omitting annular remodeling, we left unchanged the overload on valve and annular tissues, predisposing to recurrent MR. Different considerations need to be made, however, for the patients in whom annuloplasty was intentionally avoided. Those patients showed at midterm (≤ 4 years) a higher freedom from reoperation and recurrence of MR ≥ 3 compared with those with calcified annulus. However, beyond this time frame, late progression of the disease was documented with recurrence of severe regurgitation and need for reoperation in a significant proportion of patients. Eventually, no statistically significant differences could be demonstrated between patients with and without calcified annulus. Those findings underline that the degenerative process is not arrested by the repair procedure and that, even in presence of apparently not significant annular dilatation, the progression of the disease might lead to further annular enlargement and recurrent MR (as shown by the 2 patients in whom rerepair was possible just by correcting late annular dilatation by ring annuloplasty). Considering the overall recurrence rate of MR, it is not surprising that 40% of the study patients were symptomatic (NYHA III) at follow-up and \approx one third of them were in permanent atrial fibrillation.

As shown previously,⁵ an initial optimal result does influence the durability of the repair. A more than mild ($>1+/4+$) residual MR at hospital discharge was identified as the only significant risk factor for recurrent MR ≥ 3 at follow-up. In patients with optimal initial result, freedom from MR $\geq 3+$ was 80% at 5 years. Unfortunately, at 12 years, this value decreased to only 50%. As a pure speculation, in the MitraClip perspective, a 5-year freedom from MR ≥ 3 of 80% might be considered an acceptable outcome in an old patient who has been considered otherwise inoperable or at high surgical risk. However, a procedure with a predicted 50% of failure at 12 years does not represent a good option in a normal surgical candidate in whom alternative techniques should be considered rather than a ringless EE repair. As a matter of fact, in our institution, the EE technique is nowadays always associated with a concomitant ring annuloplasty, and in patients with myxomatous valve disease and severe annular calcification, mitral replacement (with or without annular decalcification) is now considered the initial operation of choice. In selected patients, with less pronounced calcified annulus, decalcification is preferred followed by mitral repair with concomitant annuloplasty.

In conclusion, in degenerative MR, the overall long-term results of the surgical EE technique without annuloplasty are not satisfactory. In particular, the ringless EE technique is not effective in the challenging setting of extensively calcified annulus. In patients without annular calcification, in whom satisfactory midterm results had been previously documented, a high rate of repair failure and reoperation occurred at long-term. An early optimal competence is associated with higher freedom from recurrent severe MR. Those findings underline the need for appropriate patient selection for MitraClip therapy to minimize residual MR after the procedure. More important, they emphasize the need for a reliable annuloplasty to improve the long-term outcomes of the currently available transcatheter MV repair procedure.

Limitations

Data were retrospectively collected with all possible limitations related to this model of analysis. The study group was small and patients were selected to focus on degenerative MR. Therefore, the results cannot be extrapolated to functional MR. Considering that routine valve repair in our institution includes mitral annuloplasty, there was a bias of selection for the ringless annuloplasty in those patients with the most unfavorable anatomic conditions. In patients without calcified annulus, the exact reason for avoiding annuloplasty was not available for all patients. Because most of the patients were referred to our institution from remote geographical areas, most of the echocardiographic examinations and almost all reoperations were performed in other centers. Therefore, the exact mechanism of MR recurrence, as well as the intraoperative findings in case of reoperation, was not available in most of cases.

Finally, only 8 patients included in this series underwent commissural EE repair. Because the Mitraclip is currently used to reproduce a similar approach (zipping by clipping), we think that the long-term clinical and echocardiographic follow-up of those patients can still be of some interest. Nevertheless, we would like to emphasize that, because of such a small number, the overall results of the study remain substantially unchanged if they are removed from the analysis and only patients submitted to double-orifice technique are left.

Disclosures

None.

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