Outcomes of Valve Repair for Degenerative Disease in Patients With Mitral Annular Calcification

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Background. The risk factors for the development of mitral annular calcification (MAC) in degenerative mitral valve disease and the effect it may have on patient-and valve-related outcomes require further evaluation.

Methods. Between January 2002 and December 2015, 627 patients underwent mitral valve operations for degenerative disease. MAC was seen in 75 patients (12%); 73 (97%) underwent valve repair (6 without annuloplasty ring implantation) and 2 (3%) underwent valve replacement after an unsuccessful repair attempt.

Results. MAC was linked to patient age, female sex, and degenerative disease subtype. Early mortality was comparable between patients with and without MAC (3 of 75 [4%] vs 10 of 552 [2%], $p = 0.20$]. In patients with MAC, one-third of the deaths were directly related to annular decalcification and reconstruction. Early repair failure was more common in patients with MAC (8 of 75 [11%] vs 17 of 552 [3%], $p = 0.006$). During follow-up, no differences in overall survival or freedom from late reintervention were observed. However, at 8 years after the operation, freedom from recurrent mitral regurgitation was worse in patients with MAC. In these patients, repair failure was linked to nonuse of ring annuloplasty. For patients with MAC in whom annular decalcification and annuloplasty were performed, repair durability was comparable to patients without MAC.

Conclusions. Mitral valve surgery in degenerative disease accompanied by MAC is safe. Optimal surgical strategy includes annular decalcification (when this would prevent implantation of an annuloplasty ring) and ring annuloplasty and will lead to results similar to patients without MAC. However, repair performance is hampered when the annulus is not addressed. For these patients, alternative repair techniques should be explored in the future.

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Mitral valve (MV) surgery in the presence of mitral annular calcification (MAC) presents a technical challenge. Although valve replacement in patients with MAC is already demanding, repairing a MV in the presence of MAC is even more challenging. Therefore, valve replacement will still often be performed primarily or after an unsuccessful repair attempt [1–5]. Theoretically, the best results are to be expected when complete annular decalcification is performed.

In patients with degenerative MV disease, MAC is rather commonly encountered [5–7]. The risk factors for the development of MAC in the setting of degenerative MV disease remain poorly understood. At the time of surgical intervention, several specific complications, including damage to the circumflex artery and disruption of the atrioventricular groove, may result from annular decalcification [4, 8]. Consequently, a modified surgical strategy with limited or even without annular decalcification is often chosen. This could lead to suboptimal results, especially in the case of valve repair without annuloplasty [9–12]. However, the effect of such technical modifications and outcomes of MV repair in patients with degenerative MV disease and MAC, in whom an aggressive repair-all strategy is advocated, remain insufficiently explored.

The aim of this study was to explore the risk factors for MAC in patients with degenerative MV disease, explore the effect of MAC on patient-related and valve-related outcomes, and determine the risk factors for repair failure in patients with MAC.

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Patients and Methods

Study Population

Between January 2002 and December 2015, 627 consecutive adult (aged ≥18 years) patients underwent surgical intervention for mitral regurgitation (MR) due to degenerative MV disease at our institution. Patients with active MV infective endocarditis or other etiologies were excluded. The presence and severity of MAC was based on intraoperative analysis and graded qualitatively. MAC was present in 75 (12%) of these patients. Mild MAC (calcification of less than one-third of the annulus circumference) was present in 30 patients (40%), moderate MAC in 27 (36%), and severe MAC (calcification of more than two-thirds of the annulus circumference) in 18 patients (24%). The distribution of MAC is shown in Figure 1.

Study Methods

The Leiden University Medical Center Medical Ethics Committee approved this study. Preoperative, intraoperative, and postoperative data were collected from our prospective computerized patient registry. Follow-up clinical and echocardiographic data were collected through clinical visits at our institution or affiliated clinics and hospitals and through patient questionnaires. Patient follow-up was closed in February 2017. Survival follow-up was 99% complete with a median duration of 6.4 years (interquartile range [IQR], 3.5 to 10.3) years. Follow-up on clinical events was 90% complete with a median duration of 5.9 years (IQR, 2.8 to 9.8 years), was 90% complete for patients with MAC with a median follow-up duration of 4.7 years (IQR, 2.1 to 8.5 years), and was 90% complete for patients without MAC with a median follow-up duration of 5.6 years (IQR, 2.6 to 9.9 years).

Surgical Procedure

MV repair was performed by experienced MV surgeons, and valve repair was attempted in all cases. The MV was carefully inspected to determine the site of leaflet prolapse and the presence and degree of MAC. In brief, the anterior MV leaflet prolapse was primarily addressed with chordal replacement. In the case of posterior MV leaflet involvement, leaflet resection, with or without annular plication (early study period) or leaflet sliding, was performed to address excessive leaflet tissue in width or height, or both. Residual prolapse was addressed with chordal replacement. Alternatively, shortening neochords were implanted to treat excessive posterior MV leaflet height. Commissural prolapse was addressed predominantly with papillary muscle head repositioning. Ring annuloplasty was considered in all patients, including patients with MAC.

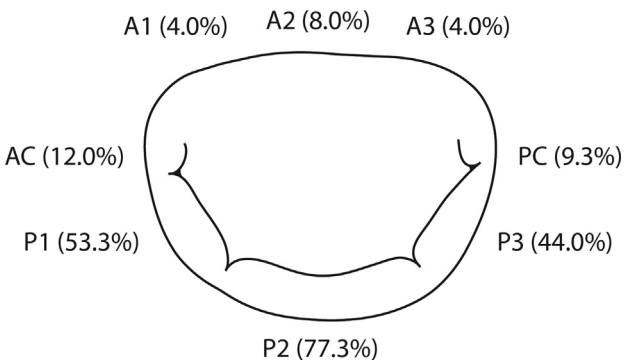

Fig 1. Distribution of mitral annular calcification.

In 14 patients (19%) with limited MAC, the presence of MAC was not expected to prevent annuloplasty ring implantation or influence leaflet mobility after repair, and no decalcification was performed. In 55 patients (73%) with MAC, en bloc decalcification of the calcified annulus was performed after leaflet detachment. Annular reconstruction was performed in patients with extensive annular decalcification by the "sliding atrium technique," or especially in cases of extensive MAC with extension into the left ventricular wall, by patch implantation to restore the continuity between the left atrium and ventricle and cover the exposed annular tissue and the underlying atrioventricular groove. BioGlue (CryoLife, Atlanta, GA) was used in 6 of the latter patients to reinforce the atrioventricular groove. The remnant of the leaflet was reattached to the "new" annulus; in case of the "sliding atrium technique," several millimeters into the left atrium, and in case of patch reconstruction of the posterior annulus, to the suture-line of the patch and left atrium. A ring was subsequently implanted just beyond the new leaflet insertion.

In 6 of 75 patients (8%) with MAC, no annular decalcification was performed despite the presence of severe MAC. These patients were typically older (mean age, 80.6 ± 2.1 years; range 77.2 to 83.3 years), with MAC usually expanding into the wall of the left ventricle. The decision not to perform annular decalcification was based on the presumable high risk of this maneuver that would also result in significant prolongation of the cardiopulmonary bypass and aortic cross-clamp times. Ring annuloplasty was not performed in these patients.

Study End Points

Postoperative mortality and morbidity end points were defined according to the joint Society of Thoracic Surgeons, American Association for Thoracic Surgery, and European Association for Cardio-Thoracic Surgery Guidelines [13]. Early mortality was defined as death within 30 days after the operation or during the index hospitalization. Residual and recurrent MR were defined as grade 2+ or more MR.

Statistical Analysis

Continuous data are presented as means ± SD for normally distributed data or as medians (IQRs) when not normally distributed. Categorical data are presented as counts and percentages. Comparisons between the two groups were performed using the χ^2 test or the Fisher exact test for categorical variables and Student *t* test or Mann-Whitney *U* test (skewed data) for continuous variables. Survival and events rates were summarized using

the Kaplan-Meier method and compared using the log-rank test. A multivariable regression and Cox proportional hazards regression analysis were used to analyze the risk factors for MAC and recurrent MR in patients with MAC, respectively. Variables were selected using a backward selection method. Variable retention in the model was set at a p value of 0.10. A double-sided p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 23.0 software (IBM, Armonk, NY) and GraphPad Prism software (GraphPad Software, La Jolla, CA).

Results

Risk Factors for MAC

Multivariable regression analysis demonstrated increasing patient age (odds ratio [OR], 1.032, 95% confidence interval [CI], 1.008 to 1.057; $p = 0.008$), female sex (OR, 2.105; 95% CI, 1.271 to 3.485; $p = 0.004$), and Barlow disease (OR, 2.117; 95% CI, 1.250 to 3.584; $p = 0.005$) as significant risk factors for MAC (Supplemental Material A). Surprisingly, in this specific group, systemic hypertension (OR, 0.583; 95% CI, 0.346 to 0.981; $p = 0.042$) demonstrated a protective effect against MAC. Notably, no link between renal impairment and MAC was observed.

Baseline Characteristics and Early Results

Baseline characteristics of the entire patient population are presented in Table 1. Patients with MAC were older, a higher proportion was women, and Barlow disease was more commonly seen.

In general, more postoperative complications were seen in patients with MAC (Table 2). There was no statistically significant difference in the early mortality rates between patients with and without MAC. Of the 3 early deaths in patients with MAC, 1 was directly related to annular decalcification. In this patient with left coronary artery dominance, postoperative compression of the left circumflex coronary artery resulted in fatal ventricular failure. Autopsy revealed hematoma formation under the pericardial patch that was used to reconstruct the posterior part of the annulus after decalcification. The 2 remaining patients died of multiorgan failure.

Early Repair Failure in Patients With MAC

Early repair failure was seen in 8 patients (11%) with MAC and in 17 patients (3%) without MAC ($p = 0.006$, Table 2). In patients with MAC, early repair failure occurred during the operation in 4 patients and was detected on postoperative echocardiography (with intraoperative echocardiography demonstrating ≤grade 1+ MR) in the remaining 4 patients (Table 3).

When the early results of valve repair in the 55 patients with MAC, in whom annular decalcification and annuloplasty were both performed, were compared with patients without MAC, no statistically significant difference in the early valve repair failure rate was observed (Table 4). Despite the lack of statistical significance, the incidence of valve repair failure was twice as high in the presence of MAC.

For 6 patients with MAC and no annuloplasty, residual MR was seen in 3 patients, and the remaining 3 patients were discharged with no residual MR (Table 5).

Table 1. Baseline Characteristics

Variables[a]	MAC (n = 75)	No MAC (n = 552)	p Value
Age, years	70.8 (63.3–77.4)	66.6 (58.2–74.2)	0.012
Female sex	42 (56)	190 (35)	<0.001
NYHA Functional Classification			0.69
I	21 (28)	155 (28)	
II	39 (52)	262 (48)	
III-IV	15 (20)	133 (24)	
Hypertension	28 (38)	272 (50)	0.058
Atrial fibrillation			0.10
Paroxysmal	16 (21)	100 (18)	
Chronic	19 (25)	92 (17)	
Renal impairment[b]			0.054
Moderate	35 (47)	264 (48)	
Severe	15 (20)	59 (11)	
Extracardiac arteriopathy	1 (1)	10 (2)	0.77
History of TIA or CVA	6 (8)	28 (5)	0.29
Diabetes mellitus	2 (3)	26 (5)	0.43
Chronic lung disease	9 (12)	47 (9)	0.31
Previous cardiac operation	2 (3)	19 (4)	0.73
Left ventricular			
Ejection fraction ≤0.60	18 (24)	149 (27)	0.57
End-diastolic diameter ≥45 mm	6 (8)	62 (6)	0.51
Pulmonary hypertension[c]	10 (13)	75 (14)	0.94
Etiology			0.024
FED/FED+	37 (49)	346 (63)	
Forme fruste/Barlow disease	38 (51)	204 (37)	
EuroSCORE II	2.15 (1.31–4.29)	1.86 (0.97–3.59)	0.043

[a] Continuous data are presented as the median (interquartile range) and categorical data as number (%). [b] Defined as moderate: creatinine clearance, 50–85 mL/min; severe: creatinine clearance <50 mL/min. [c] Defined as systolic pulmonary artery pressure >50 mm Hg.

CVA = cerebrovascular accident; EuroSCORE II = European System for Cardiac Operative Risk Evaluation 2011 revision; FED = fibroelastic deficiency; MAC = mitral annular calcification; NYHA = New York Heart Association; TIA = transient ischemic attack.

Late Results

During the follow-up period, 139 late deaths occurred, including 75 cardiac-related deaths. At 8 years after the operation, the overall survival rates were 69.2% (95% CI, 54.4% to 80.0%) for patients with MAC and 78.7% (95% CI 74.4% to 82.4%) for patients without MAC ($p = 0.093$, Fig 2). In patients with MAC, 16 late deaths occurred. The cause of death was cardiac-related in 14 patients: myocardial infarction in 1, heart failure with recurrent MR in 1, and sudden unexplained death in 12.

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Table 2. Early Results

Variables	MAC (n = 75) No. (%)	No MAC (n = 552) No. (%)	*p* Value
Mortality	3 (4)	10 (2)	0.20
Prolonged intubation	11 (15)	65 (12)	0.48
Surgical reexploration	13 (18)	42 (8)	0.006
Stroke	2 (3)	3 (1)	0.11
Renal failure	2 (3)	24 (4)	0.76
Failed repair	8 (11)	17 (3)	0.006
Valve replacement	2 (3)	7 (1)	0.30
Early reintervention	3 (4)	8 (2)	0.14
Residual MR (≥2+)	6 (8)	10 (2)	0.007

MAC = mitral annular calcification; MR = mitral regurgitation.

There were 19 (3%) late reinterventions, 1 (1%) in patients with MAC and 18 (3%) in patients without MAC. In the former patient, the indication for reoperation was recurrent MR, and upon reoperation, valve replacement was performed. The 8-year rates for freedom from MV reintervention were 98.3% (95% CI, 88.7% to 99.7%) for patients with MAC and 95.3% (95% CI, 92.2% to 97.2%) for patients without MAC ($p = 0.42$, Fig 3).

The median echocardiographic follow-up time was 3.8 years (IQR, 1.7 to 7.7 years), which was available for 92% of hospital survivors. Recurrent MR occurred in 74 patients (12%), 12 (18%) from the MAC and 62 (11%) from the no-MAC group. The 8-year rates for freedom from recurrent MR were 73.4% (95% CI, 54.5% to 85.4%) for patients with MAC and 84.7% (95% CI, 80.0% to 88.4%) for patients without MAC ($p = 0.044$, Fig 3).

MV Repair Performance in Patients With MAC

For patients with MAC, Cox proportional hazards regression analysis revealed nonuse of ring annuloplasty (hazard ratio, 17.092; 95% CI, 2.745 to 106.405; $p = 0.002$) and postoperative mild MR (hazard ratio, 6.291; 95% CI, 1.616 to 24.491; $p = 0.008$) as risk factors for recurrent MR (Supplemental Material B). For the 69 patients in whom annuloplasty was performed, no significant difference in valve repair durability was observed between patients in whom annular decalcification was and was not performed ($p = 0.64$, Fig 4).

For 3 patients with MAC in whom annuloplasty was not performed and no residual MR was seen on postoperative echocardiography, follow-up echocardiography was available for 2 patients. In both patients, recurrent MR occurred early after the initial operation, at 0.9 and 2.8 years (Table 5).

When the durability of valve repair in the 55 patients with MAC in whom annular decalcification and annuloplasty were both performed was compared with patients without MAC, no significant difference in the freedom from recurrent MR was observed ($p = 0.18$, Fig 4).

Comment

Risk factors for the development of MAC in the general population include patient age, female sex, systemic hypertension, and chronic kidney disease [14–16]. We did not observe a correlation between chronic kidney disease and MAC. This may be explained by the fact that chronic kidney disease was seldom present in our population. Our results suggest that the type of degenerative MV disease (Barlow disease vs fibroelastic deficiency) plays a role in the pathoetiology of MAC. This is contrary to the recent results by Fusini and colleagues [5]. As described by Carpentier and colleagues [17], development of MAC in degenerative MV disease is a prolonged, multiphase process of annular degeneration that is initiated by excess tension exerted on the MV annulus. Emerging evidence on the primary involvement of the MV annulus and the typical prolonged history of valve disease in patients with Barlow disease provide explanations for our findings.

The patients with MAC in our study were older, with a higher proportion of women. Both characteristics have been identified as risk factors for perioperative death in patients undergoing valve operations [18]. Despite this, perioperative death remained comparable between the groups. Of note, of 55 patients with MAC in whom annular decalcification was performed, 1 death was directly related to annular decalcification itself. Left coronary artery dominance was present, and fatal postoperative ischemia developed after an initial hemodynamically stable period without electrocardiographic or echocardiographic signs

Table 3. Details on Residual Mitral Regurgitation in Patients With Mitral Annular Calcification

Patient	Year of Operation	Age at Operation (years)	Residual MR Mechanism	Annuloplasty	Annular Decalcification	Early Reoperation
1	2002	71.8	Systolic anterior motion	Yes	No	Replacement
2	2002	83.3	Residual PMVL prolapse	No	No	Rerepair
3	2002	73.9	Mechanism not clear	Yes	No	…
4	2012	81.6	Lack of leaflet coaptation, intraoperative grade 2+ MR	No	No	…
5	2012	67.3	Residual PMVL prolapse	Yes	Yes	Rerepair
6	2013	79.1	Lack of leaflet coaptation, intraoperative grade 2+ MR	No	No	…

MR = mitral regurgitation; PMVL = posterior mitral valve leaflet.

Table 4. Early Valve Repair Results in Patients With Mitral Annular Calcification in Whom Annular Decalcification and Annuloplasty Were Performed

Variable	Decalcification (n = 55) No. (%)	No MAC (n = 552) No. (%)	*p* Value
Failed repair	3 (6)	17 (3)	0.42
Valve replacement	2 (4)	7 (1)	0.19
Early reintervention	1 (2)	8 (2)	0.58
Residual MR (≥2+)	1 (2)	10 (2)	1.00

MAC = mitral annular calcification; MR = mitral regurgitation.

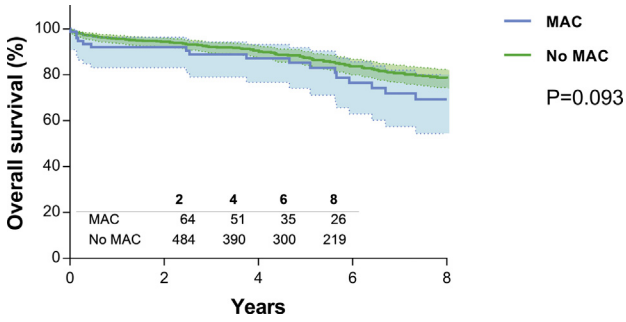

Fig 2. Overall survival in patients with and without mitral annular calcification (MAC). The shaded areas indicate the 95% confidence interval.

of ischemia. The delayed presentation was likely related to the fact that the circumflex artery was compromised by hematoma formation and not annuloplasty suture placement. Although damage to the circumflex artery after MV repair is relatively uncommon, a recent case series including 6 patients demonstrated the detrimental consequences of such an event, as severe left ventricular dysfunction developed in 4 of 6 patients [19]. Early recognition is of utmost importance to prevent serious complications and should, in case of annular decalcification, be suspected even when signs of ischemia are initially absent.

When valve repair is performed, only limited MAC, which does not compromise normal leaflet motion and the performance of annuloplasty, can be left in place with annuloplasty sutures passed around the calcified proportion of the annulus. Again, extra care should be taken to avoid circumflex artery injury, especially if unremoved MAC is present at the area of the anterolateral commissure where the artery lies in the vicinity [19].

In our experience, repair failure occurred more commonly in patients with MAC. Our results are similar to the results of a study by Chan and colleagues [6] of 625 patients with degenerative MV disease in whom MAC in various extent was present in 119 (19%). In their experience, intraoperative conversion to valve replacement was needed in 5 of 119 patients (4%) with MAC. However, technical difficulty of valve repair in these patients depends on the extent of MAC. On one hand, limited and even moderate MAC in these patients is a manageable problem that might not even necessitate annular decalcification. On the other hand, extensive MAC is linked to higher valve replacement rates, even in the setting of degenerative MV disease and, when left untreated, a technically imperfect repair.

When the freedom from MV reintervention rates was compared, no differences were observed between patients with and without MAC, but repair durability was worse in patients with MAC. This can only partially be explained by differences in patient characteristics, because female sex has previously been identified as a risk factor for recurrent MR after valve repair [20].

When exploring the results of valve repair in patients with MAC only, nonuse of ring annuloplasty emerged as the predominant risk factor for recurrent MR. Moreover, valve repair durability was not different between patients without MAC and patients with MAC in whom annular decalcification and annuloplasty were performed. On one hand, this suggest that should a technically sound repair be performed, valve repair durability in degenerative MV disease will not be hampered by the presence of MAC despite the technical challenges of annular decalcification that necessitates leaflet mobilization and reimplantation. On the other hand, this stresses the importance of annular remodeling and repair stabilization in these patients. An interesting observation was that when annuloplasty was performed in patients with MAC, repair durability did not differ between patients in whom

Table 5. Early and Late Results of Patients With Mitral Annular Calcification Who Underwent Mitral Valve Repair Without Annuloplasty[a]

Patient	Year of Operation	Age at Operation (years)	Early or Late Reoperation	Residual/Recurrent MR
1	2002	83.3	Early	Residual MR
2	2002	82.2	…	Recurrent MR (0.9 years)
3	2003	77.6	…	No follow-up echocardiography available
4	2007	79.8	…	Recurrent MR (2.8 years)
5	2012	81.6	…	Residual MR (intraoperative)
6	2013	79.1	…	Residual MR (intraoperative)

[a] No patients underwent annular decalcification.

MR = mitral regurgitation.

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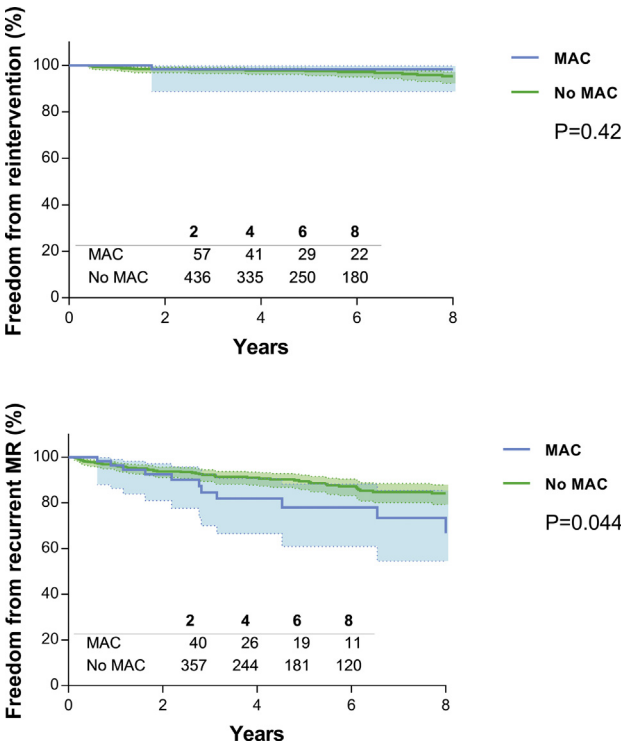

Fig 3. Freedom from (top panel) late mitral valve reintervention and (bottom panel) recurrent mitral regurgitation (MR) in patients with and without mitral annular calcification (MAC). The shaded areas indicate the 95% confidence interval.

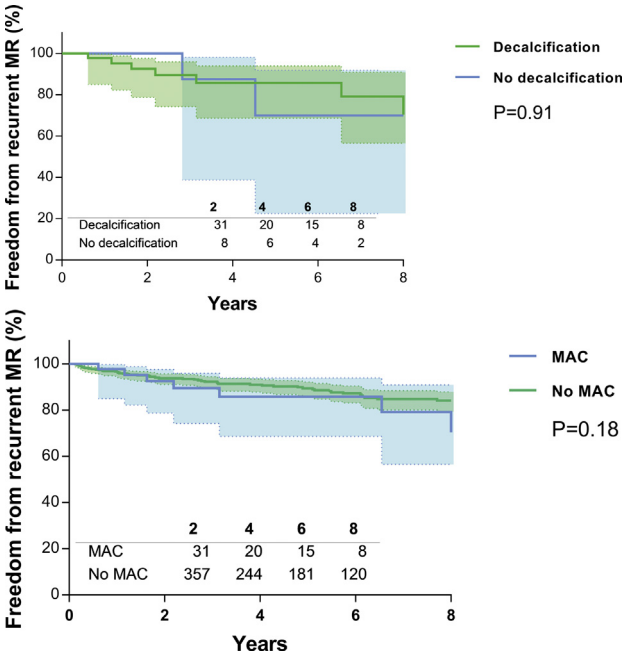

Fig 4. (Top panel) Freedom from recurrent mitral regurgitation (MR) in patients with mitral annular calcification (MAC) and annuloplasty ring implantation in whom annular calcification was or was not performed. (Bottom panel) Freedom from recurrent MR in patients without MAC and in patients with MAC in whom annular decalcification and annuloplasty were performed. The shaded areas indicate the 95% confidence interval.

annular decalcification was or was not performed. This suggests that mild MAC that does not hamper leaflet motion or annuloplasty ring implantation might be left in place.

When MAC is left untouched in a severely calcified annulus, progressive annular dilatation after repair is unlikely to occur. The high incidence of residual or recurrent MR seen in patients with valve repair without ring annuloplasty is likely to result from insufficient height of leaflet coaptation resulting from the absence of annular remodeling. To compensate for insufficient leaflet coaptation, anterior MV leaflet or posterior MV leaflet, or both, augmentation can be performed. Although a leaflet-only repair resulted in poor results in our experience and is related to poor results with the edge-to-edge technique in patients with MAC as well [9], leaflet augmentation resolves the shortage of leaflet coaptation that other repair techniques fail to address. Combined with a fixed, calcified annulus, this might result in a stable repair. As we learned about the poor results of valve repair without ring annuloplasty in MAC, we have started using this technique in selected patients with severe MAC in whom annular decalcification would be challenging to perform. The results of this repair technique will need to be explored in the future and should be seen as a repair alternative only in carefully selected patients.

MV replacement is a logical alternative in patients in whom annular decalcification is considered too risky and repair durability might be hampered. However, severe drawbacks should be acknowledged. Implanting a valve prosthesis in a nondecalcified annulus can be challenging and is likely to result in paravalvular leakage. Moreover, in the absence of decalcification, a smaller sized prosthesis is likely to be implanted, resulting in a risk of prosthesis-patient mismatch development. To partially compensate, the prosthesis can be implanted in an intraatrial position [12]; however, the high risk of paravalvular leakage will persist. In our experience, annular decalcification was considered too risky to perform only in older patients. To decrease the risk of prosthesis-patient mismatch development, a mechanical prosthesis (with larger orifice areas than bioprostheses of comparable size) would be preferred. The use of mechanical prostheses in elderly patients is linked to increased valve-related morbidity and death [21].

In patients with severe MAC in whom annular decalcification is undesirable, transcatheter MV implantation presents a less invasive alternative. Early experience in patients with MAC shows that this is linked to high early morbidity and mortality rates [22]. For the time being, transcatheter MV implantation in these patients should be seen as a bailout procedure to be reserved only for patients in whom surgical intervention is considered too high risk.

Limitations

This is a single-center study of a retrospective cohort of patients with limitations inherent to the study design. Considering that ring annuloplasty is performed

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routinely in patients with degenerative MV disease at our institution, the decision not to perform annuloplasty ring implantation was individually based.

Conclusion

MAC in patients with degenerative MV disease is linked to patient age, sex, and subtype of degenerative disease. In this selected population, MV intervention is reasonably safe to perform despite the presence of MAC. Early repair failure is more likely to occur and is predicted by nonuse of ring annuloplasty. Nevertheless, repair durability is comparable to patients without MAC when a technically sound repair is performed. New repair techniques should be explored in patients in whom annuloplasty ring implantation is not performed.

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