Does moderate mitral regurgitation impact early or mid-term clinical outcome in patients undergoing isolated aortic valve replacement for aortic stenosis?

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Abstract

Objective: The early and mid-term impact of functional mitral regurgitation (MR) in patients undergoing isolated aortic valve replacement (AVR) for aortic stenosis remains unresolved. Method: Through our institutional database, using a case-match study, we identified 58 patients with MR grades 0–1 and 58 patients with MR grades 2–3 (patients matched for sex, age, ejection fraction (EF), NYHA, diabetes, and CVA). Data were collected prospectively (mean duration of follow-up: 3.2 ± 2.4 years). Results: Perioperative morbidity (re-operation for bleeding, low cardiac output, CVA, renal failure) was comparable among groups. Difference in mortality between the two groups was non-significant (7.0 vs. 3.5%, \( P = 0.67 \) in groups MR 2–3 vs. 0–1, respectively). At early echocardiographic follow-up, 7/58 patients (12.1%) within group MR grades 0–1 increased their MR to grades 2–3; among which only two remained with MR grades 2–3 at mid-term follow-up. Within MR group 2–3, 18/58 (31.0%) remained with MR grades 2–3 among which 7/18 (38.9%) decreased of at least one grade at follow-up. Eight year actuarial survival was comparable in both groups: MR grades 0–1 = 60.9% vs. MR grades 2–3 = 55.0%; \( P = 0.1 \). Actuarial survival of patients with MR grades 2–3 postoperatively was similar to patients with MR grades 0–1 (MR grades 0–1 = 59.0%, MR grades 2–3 = 58.9%, \( P = NS \)). Conclusions: Presence of preoperative moderate functional MR (grades 2–3) in patients undergoing isolated AVR for aortic stenosis regresses in the majority of patients postoperatively and has no significant impact on perioperative morbidity or mortality, nor mid-term survival. Thus, moderate functional MR should be treated conservatively in the majority of patients especially in the elderly subjected to isolated AVR for aortic stenosis.

Keywords: Cardiac surgery; Aortic valve; Mitral regurgitation; Survival; Echocardiography

1. Introduction

Mild to moderate mitral regurgitation (MR) often coexists with severe aortic stenosis and has been reported to be present in up to 2/3 patients requiring aortic valve replacement (AVR) [1]. The mechanism underlying MR in such circumstances is probably multifactorial. MR in patients with aortic stenosis is often functional in nature although organic mitral disease may coexist. Increased afterload and LV remodelling have been implicated to explain the functional MR in patients with aortic stenosis. Furthermore, remodelling observed after AVR may impact the outcome of MR postoperatively [2,3,6,7]. However, the natural history and early clinical impact of mild to moderate MR in patients with severe aortic stenosis submitted to AVR remains unsettled. In addition, the clinical outcome of persistent MR after AVR is uninvestigated. On the other hand, concomitant replacement of the aortic and mitral valves is associated to an increased morbidity and mortality compared to an isolated AVR [4]. The purpose of the present study is to evaluate the early and mid-term clinical impact of moderate MR (grades 2–3) in patients undergoing isolated AVR for aortic stenosis. In addition, clinical outcome of persistent moderate MR after AVR is further investigated.
2. Material and methods

2.1. Patients

To assess the early and mid-term impact of moderate MR, we established a case-match study through our institutional databank. Follow-up of our institutional databank is over 98% complete and compromises data of yearly clinical visits and annual echocardiography. During follow-up, all readmissions are reviewed and assessed regarding valve related events. Between January 1992 and December 2000, 623 patients underwent a first operation for isolated AVR at the Quebec Heart Institute. Current practice in our institution, throughout the years, was to treat conservatively functional grades 2–3 MR in patients undergoing isolated AVR for aortic stenosis. In presence of MR grade 4, mitral repair or replacement was performed. Patients with echocardiographic criteria of organic MR (ischemic, rheumatic, or degenerative etiologies) were excluded from the present study. Furthermore, charts of all patients with moderate functional MR were reviewed to assess etiology and were included in the present study, once the functional nature of MR was confirmed. Patients with concomitant coronary artery disease were excluded. Fifty-eight patients with preoperative functional MR grades 2 or 3 were identified. Each patient was matched for sex, age, NYHA, ejection fraction (EF) lower than 40%, diabetes, and history of stroke with a patient submitted to isolated AVR but with MR grades 0 or 1 preoperatively.

Patient characteristics are listed in Table 1. All patients of both groups had an aortic stenosis secondary to a bicuspid or senile degeneration aortic valve. All patients underwent an isolated AVR. Stented or stentless aortic bioprosthesis were implanted in all patients.

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>MR 0–1 (n = 58)</th>
<th>MR 2–3 (n = 58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.7 ± 6.6</td>
<td>74.8 ± 7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex male (%)</td>
<td>43.1</td>
<td>43.1</td>
<td>NS</td>
</tr>
<tr>
<td>EF &lt; 40% (%)</td>
<td>15.5</td>
<td>15.5</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA III–IV (%)</td>
<td>82.8</td>
<td>82.8</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>15.5</td>
<td>15.5</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>8.6</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>51.7</td>
<td>68.9</td>
<td>0.09</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>27.6</td>
<td>36.2</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>9.0</td>
<td>22.4</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>72.2</td>
<td>73.9</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>12.1</td>
<td>13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative gradient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max (mmHg)</td>
<td>72.3 ± 23.5</td>
<td>87.4 ± 27.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean (mmHg)</td>
<td>45.2 ± 15.0</td>
<td>53.3 ± 17.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Parsonnet score</td>
<td>16.6 ± 7.8</td>
<td>22.0 ± 8.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

MR, mitral regurgitation; EF, ejection fraction; COPD, chronic obstructive pulmonary disease.

Perioperative variables analyzed were type of valve implanted, cardiopulmonary bypass and cross-clamp times, prolonged intubation defined as intubation > 24 h, cardiogenic shock defined as cardiac index < 2.2 l/m²/min or inotropic support or intraaortic balloon counterpulsation for more than 24 h and renal failure as defined as a creatinin > 150 μmol/l or an increase > 20% from baseline. Event-free survival was defined by the absence of one of the following events at follow-up: pulmonary edema, myocardi- dal infarction, reoperation, or death of all causes. Survival and event-free survival were plotted in regards of both preoperative groups but also in terms of presence or absence of moderate MR at postoperative echocardiographic follow-up.

2.2. Pre and postoperative transthoracic echocardiography

All patients had a complete M-mode, 2D, pulsed, continuous wave, and colour Doppler study preoperatively, within 3 months postoperatively and yearly subsequently.

MR grading was established according to the semi-quantitative method [5]. More specifically, grading of MR was assessed by colour jet characteristics including jet width and area and mitral and pulmonary vein flow pattern by pulsed wave Doppler. Grade 1 regurgitation was characterized by a high continuous wave Doppler signal and a small colour Doppler area. Grade 2 regurgitation was identified by a continuous wave Doppler signal of intermediate intensity and a normal vein flow pattern. Grades 3 and 4 regurgitation were characterized by a high continuous Doppler intensity, a large Doppler area, and by blunted or reversed systolic pulmonary vein flow pattern. Moderate MR was defined as grades 2 or 3 regurgitation.

2.3. Data collection and analysis

Results of quantitative and nominal variables were expressed with mean ± SD and percentage, respectively. One-way analysis of variance (ANOVA) was performed to carry out analyses for comparison between MR grades 0–1 and 2–3. The normality assumption was verified with the Shapiro–Wilk test and the Brown and Forsythe’s variation of the Levene’s test statistic was used to verify the homogeneity of variances. When these assumptions were not fulfilled for some parameters, an alternative procedure that does not depend on these assumptions was done. The procedure performed was to replace the observations by their rank, called rank transformation, and applying the ordinary F-test from one-way ANOVA. This technique is an approximate procedure result, but one that has good statistical properties when compared to the Kruskal–Wallis test. Categorical variables were analyzed with the Fisher’s exact tests. Product-limit analyses (also called Kaplan–Meier analyses) were performed to examine the time-dependent cumulative probabilities of the outcomes. The plots of the negative log of the survival function vs. time revealed that...
exponential model were not appropriated for the survival data. Consequently, the log rank tests with associated Chi-square were used to test the hypothesis that there was no difference in survival functions between both groups. The results were considered significant if P-values were ≤ 0.05. The data were analyzed using the statistical package program SAS (SAS Institute Inc., Cary, NC).

3. Results

3.1. Operative data and postoperative mortality and morbidity

(Tables 2 and 3) Operative data showed comparable X-clamp time and duration of cardiopulmonary bypass in both groups. Valve types were similar among both groups (Table 2). Two patients with MR 0–1 died in the first 30 days, postoperatively. Within MR groups 2–3, four patients died within 30 days of the operation. Postoperative complications were comparable among both study groups (Table 3).

3.2. Echocardiography follow-up

Patients were followed through an annual clinical visit for a mean of 3.2 ± 2.4 years. A mean of 3.6 ± 1.6 echocardiography were performed for each patient during the follow-up period. Within groups MR 0–1 preoperatively, 7/58 (12.1%) increased to MR grades 2–3 within the first 6 months, postoperatively. However, after 1 year, only two patients (3.4%) remained with MR grades 2 or 3. Among patients with MR 2–3 preoperatively, 40/58 (69%) decreased to an MR grades of 0–1 within 6 months of the operation. Among the 18 patients with a residual MR 2–3, seven decreased of at least one MR grade after 1 year of follow-up. At 1 year postoperatively, 15 patients demonstrated persistent MR 2–3 and were considered as the postoperative MR 2–3 groups.

Maximal and mean preoperative echocardiography aortic gradients were significantly higher in groups 2–3 compared to groups 0–1 (maximal gradient: groups 0–1, 72.3 ± 23.5 mmHg vs. groups 2–3, 87.4 ± 27.9 mmHg, P = 0.02; mean gradient: groups 0–1, 45.2 ± 15.0 mmHg vs. groups 2–3, 53.3 ± 17.6 mmHg, P = 0.04). Within the early postoperative period, the indexed effective orifice area (IEOA) and mean and maximal aortic gradients were comparable among patients with early postoperative MR grades 0–1 and MR grades 2–3 (IEOA: groups 0–1, 0.88 ± 0.22 cm²/m² vs. groups 2–3, 0.82 ± 0.19 cm²/m², P = 0.21; maximal gradient: groups 0–1, 24.6 ± 12.5 mmHg vs. groups 2–3, 26.5 ± 14.1 mmHg, P = 0.46; mean gradient: groups 0–1, 12.5 ± 7.1 mmHg vs. groups 2–3, 14.2 ± 7.8 mmHg, P = 0.33).

3.3. Survival and event-free survival

(Figs. 1 and 2) Eight year actuarial survival for MR groups 0–1 and 2–3 preoperatively were comparable (groups 0–1: 60.9% vs. groups 2–3: 55.0%, P = 0.10) (Fig. 1). Within MR group 0–1, in addition to the two perioperative deaths, seven patients died at follow-up with one death being cardiac related owing to heart failure in a patient with renal failure and severe chronic obstructive pulmonary disease supervening 89 months postoperatively. Within MR group 2–3, four patients died perioperatively and one patient died of heart failure (MR at last follow-up 2/4) 13 months postoperatively. Furthermore, nine patients died from non-cardiac related causes at follow-up.

Event-free survival was comparable for both preoperative groups (groups 0–1: 55.3%; groups 2–3: 40.4%; P = 0.20) (Fig. 2). Four patients required reoperation at follow-up. Within group 1, three patients necessitated reoperation: two patients for prosthetic endocarditis, 2 and 9 months after AVR and one patient for prosthetic dysfunction 77 months after surgery. One patient of MR groups 2–3 was reoperated 26 months after AVR for a ventricular septal defect. Owing to an MR grade 3, decision was made to replace the mitral valve concomitantly.

Results were comparable when assessing survival for patients with MR grades 2–3 postoperatively compared to patients with MR grades 0–1 (groups 0–1: 59.0%, groups 2–3: 58.9%; P = NS) (Fig. 3). Similarly, no significant difference was observed in event-free survival between the
postoperative groups with or without moderate MR (groups 0–1: 42.1%; groups 2–3: 55.7%; \( P = NS \)) (Fig. 4).

4. Discussion

MR and coronary artery disease often coexist with aortic stenosis. Presence of combined valvular disease may render evaluation and treatment selection difficult. MR in patients with aortic stenosis may be secondary to intrinsic mitral valve disease, to the increased afterload of the aortic stenosis or the presence of left ventricular dysfunction. We have excluded patients with intrinsic mitral valve disease and limited our study to patients with functional MR without associated coronary artery disease. The effect of increased afterload as a contributory mechanism for MR in patients with aortic stenosis is suggested by the increased preoperative gradient in the moderate MR group observed in our study. Such a relationship has also been reported by Brener and colleagues [6]. Schulman and colleagues have suggested that presence of mild MR in patients with aortic stenosis is a marker of impaired left ventricular performance [7]. However, within our study, close to 70% of patients with moderate regurgitation decreased at least one grade early postoperatively, suggesting that the reduction in intraventricular pressure with the AVR seems the most important mechanism related to the preoperative MR. Moreover, EF albeit a crude evaluation of left ventricular performance, was similar within both groups. On the other hand, mean aortic gradient and effective valve orifice area were comparable in patients with or without moderate MR postoperatively suggesting other mechanisms such as changes in ventricular morphology to explain the MR. Interestingly, Harris and colleagues have observed a significant reduction in left atrial size and mitral annular area after AVR and was linked to a decrease in MR [8]. Such a mechanism was observed principally in patients with large left atrial size preoperatively suggesting left atrial size as a predictor of
MR improvement after AVR. Improvement of MR after AVR has already been suggested by other authors [9,10]. The present study confirms, within a case–control study, that the majority of cases with moderate MR diminish following AVR for aortic stenosis. Perioperative morbidity and mortality did not show any significant difference between patients with or without moderate MR preoperatively. Mid-term and event-free survivals were comparable for the two groups. Interestingly, seven patients among the MR groups 0–1 increased their MR to moderate early postoperatively although only two remained in the moderate grade at longer follow-up. Changes in left ventricular geometry or hemodynamic conditions during echocardiography may partly explain presence of moderate MR in these patients. However, mid-term and event-free survivals of patients with postoperative moderate MR was comparable to patients without moderate MR.

Although this study clearly demonstrates the high level of resolution of moderate MR after AVR and the lack of clinical impact of moderate MR, limitations have to be expressed. Our study population was elderly patients with a significant number of deaths being non-cardiac related. The poor mid-term outcome mainly related to non-cardiac deaths in our elderly population further stresses a conservative approach toward the management of the presence of moderate MR in elderly patients with aortic stenosis submitted to AVR. Moreover, operative mortality and morbidity related to combined aortic and mitral valve replacement in this population is especially high [11]. However, extrapolating these results to a younger more active age group may not be appropriate. Longer follow-up in a larger population without co-morbidities may show different results. Moreover, the present study specifically addressed patients with predominant aortic stenosis and may not be transposed to patients with a predominant regurgitant component. Furthermore, although our patients are followed prospectively in our databank, the present study has inherent limitations of a retrospective study. Confirmation of such
results in a well-designed and powered prospective study should be investigated. Such a study should take into account a standardized postoperative medication regimen, which could impact overall results on MR outcome. We further stress the importance of evaluating the mitral valve to exclude any structural abnormality which may portend a different prognosis than functional MR. Patients with combined aortic stenosis and coronary artery disease may have a different outcome considering the possible ischemic component of the MR. The clinical impact of moderate ischemic MR remains controversial [12]. Furthermore, no data to our knowledge has demonstrated that repairing moderate ischemic MR may increase long-term outcome.

In conclusion, the present study confirms that moderate functional MR associated to isolated aortic stenosis regresses following AVR in most circumstances. Furthermore, presence of moderate functional MR preoperatively does not impact perioperative and mid-term outcome after AVR. Moreover, presence of moderate MR postoperatively does not seem to influence mid-term outcome. Thus moderate functional MR in patients submitted to isolated AVR should be treated conservatively especially in the elderly population.

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References


Appendix A. Conference discussion

Dr A. El Sayed (Khartoum, Sudan): We have a totally different subgroup of patients, who are the youn rheumatics, with pretty much the same problem. We did reach the same conclusions that you did, but I think for absolutely different reasons. The question I put to you is, I find that hypertension is significantly much more in your patients, group 2. Now, we found that in these patients with moderate MR, we do not replace the mitral valve but we put them on a significantly high dose of ACE inhibitors, which tends to stabilize moderate MR. So I wonder if you are doing the same thing, putting your moderate MR group on ACE inhibitors to treat their hypertension and so that is why you are getting these results?

Dr Absil: Yes, sure, we do use a little bit of inhibitors.

Dr M. Emsara (Cairo, Egypt): Did you do anything for the left atrial size and the pulmonary hypertension, because in the place where I am practicing we have lots of rheumatic heart disease and we face this problem very often? We cannot let the the mitral regurg without treatment if I have a sizable left atrium and pulmonary hypertension. What do you do?

Dr Absil: The first thing, we spoke about functional moderate MR. Then that excludes rheumatic valve disease, That is the first point. And your question is?

Dr Emsara: The size of the left atrium, you didn’t tell me anything about the size of moderate mitral regurg. What was your left atrial size and your pulmonary artery pressure?

Dr Absil: Concerning the size of oth the atrium, we think that atrial size is important and they can give atrial fibrillation, but, this fact doesn’t change our procedure.

Dr C. Yankah (Berlin, Germany): In your patient characteristics you didn’t show any existing history of coronary artery disease or angina. But you had a very high perioperative mortality and patients with low cardiac output. Did you find coexistent coronary artery disease in those patients which could cause second or third grade mitral regurgitation?

Dr Absil: No. It was a case match study, and we made sure to exclude patients with coronary artery disease, In the case of a patient present coronary artery disease, we reconsider the situation and it is sure that our surgical procedure will change.

Dr M. Josa (Barcelona, Spain): In 25 patients mitral regurgitation did not improve or it was worse. Could you characterize factors which may influence this lack of improvement or define the patients that worsened versus the ones that did not so that we could identify preoperatively a group of them at risk of not improving their mitral regurgitation?

Dr Absil: Some of the patients don’t improve their moderate MR in the postoperative period. I think in these patients we can explain the percentage of moderate MR by the correction of afterload. Then I think in these patients it is another problem, like ventricular remodeling of anything can explain the percentage of moderate MR after the procedure, after aortic valve replacement.