Mitral valve repair versus replacement in patients with ischaemic mitral regurgitation and depressed ejection fraction: risk factors for early and mid-term mortality†

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Abstract

OBJECTIVES: Mitral valve (MV) surgery for ischaemic mitral regurgitation (IMR) in patients with depressed left ventricular ejection fraction (LVEF) is associated with poor outcomes. The optimal surgical strategy for IMR in these patients remains controversial. The objective of this study was to compare the early mortality and mid-term survival of MV repair versus MV replacement in patients with IMR and depressed LVEF undergoing coronary artery bypass grafting (CABG).

METHODS: A retrospective, observational, cohort study was undertaken of prospectively collected data on 126 consecutive CABG patients with IMR and LVEF <40% undergoing either MV repair (n = 98, 78%) or MV replacement (n = 28, 22%) between July 2002 and February 2011.

RESULTS: The overall mortality rate was 7.9% (n = 10). MV replacement was associated with a 4-fold increase in the risk of death compared with MV repair [17.9%, n = 5 vs 5.1%, n = 5; odds ratio (OR) 4.04, 95% confidence interval (CI) 1.08–15.1, P = 0.04]. However, after adjusting for preoperative risk factors, the type of surgical procedure was not an independent risk factor for early mortality (OR 0.1, 95% CI 0.01–31, P = 0.7). Multivariable analysis showed that preoperative LVEF (OR 0.8, 95% CI 0.6–0.9, P = 0.018), preoperative B-type natriuretic peptide (BNP) levels (OR 1.01, 95% CI 1.01–1.02, P = 0.025), preoperative left ventricle end-systolic diameter (OR 0.8, 95% CI 0.7–1.0, P = 0.05) and preoperative left atrial diameter (OR 1.3, 95% CI 1.0–1.6, P = 0.015) were independent risk factors of early mortality. At the median follow-up of 45 months (interquartile range 20–68 months), the mid-term survival rate was 74% in the MV repair group and 70% in the MV replacement group (P = 0.08). At follow-up, predictors of worse survival were BNP levels [hazard ratio (HR) 1.0, 95% CI 1.0–1.01, P = 0.047], preoperative renal failure (HR 4.6, 95% CI 1.1–20.3, P = 0.039) and preoperative atrial fibrillation (HR 3.3, 95% CI 1.1–10, P = 0.032).

CONCLUSIONS: MV repair in CABG patients with IMR and depressed LVEF is not superior to MV replacement with regard to operative early mortality and mid-term survival.

Keywords: Ischaemic mitral regurgitation • Mitral valve surgery • Left ventricular dysfunction

INTRODUCTION

Ischaemic mitral regurgitation (IMR) complicates 13–50% of the cases of acute myocardial infarction and is associated with poor outcomes, and worse long-term survival and functional status than coronary disease without IMR [1, 2]. The basic mechanism of IMR is the remodelling of the left ventricle (LV), which may lead to annular dilatation and displacement of the papillary muscles with leaflet tethering [3].

The benefit of mitral valve repair (MVRp) compared with mitral valve replacement (MVR) has been well established for degenerative mitral regurgitation; however, the optimal surgical strategy for the management of IMR remains a subject of debate, especially in the presence of LV dysfunction [2–7].

The objective of this study is to compare the early mortality and mid-term survival of MVRp compared with MVR in patients undergoing coronary artery bypass grafting surgery (CABG) with IMR and depressed left ventricular ejection fraction (LVEF).

MATERIALS AND METHODS

Patient selection and data collection

A retrospective, observational, cohort study was undertaken of prospectively collective data on consecutive patients with chronic IMR and coronary artery disease with an LVEF <40% who

†This paper was read at the 2012 Annual Meeting of the American College of Cardiology.
underwent MV surgery and CABG between July 2002 and February 2011. The study was approved by the local ethical committee and individual consent was waived. The data collection form was entered in a local database and included several sections that were filled by the anaesthetists, cardiac surgeons and perfusionists involved in the care of the patients. The sample consisted of 126 patients: 98 (78%) underwent MVRp plus CABG and 28 (22%) underwent MVR plus CABG. The primary end-points were early mortality, defined as any death occurring within 30 days of operation or before discharge from the hospital, and mid-term survival.

Mid-term outcomes were determined from clinical records when available or from direct patient contact with telephone interviews when necessary. The median duration of the follow-up for survival was 45 months [interquartile range 20–68 months]. Follow-up was 90% complete.

**Echocardiography and laboratory data**

All patients had a preoperative transthoracic echocardiography. The severity of mitral regurgitation was graded following the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery recommendations: mitral regurgitation was defined severe in the presence of an effective regurgitant orifice area ≥20 mm² and a regurgitant volume ≥30 ml/beat [8]. Preoperative left ventricular tele-systolic and tele-diastolic diameters, and preoperative left atrial diameter were recorded. Left ventricular volumes (end-diastolic and end-systolic) were measured according to the biapical Simpson disk method, and LVEF was calculated.

Blood samples for B-type natriuretic peptide (BNP) measurement were collected preoperatively into disposable polypropylene tubes containing ethylenediaminetetraacetic acid (1 mg/ml of plasma). Plasma samples were rapidly separated by centrifugation for 15 min at 4°C and then assayed as soon as possible (no more than 4 h after blood withdrawal).

Plasma BNP was measured by an automated Access platform (Triage BNP reagents, ACCESS Immunoassay Systems, REF 98200; Beckman Coulter, Inc., Fullerton, CA, USA). This fully automated immunoassay uses as antigens the intact BNP 1–32 peptide and the same mouse anti-human BNP antibodies. The capture antibody (Scios) recognizes the peptide ring, whereas the detection antibody (Biosite) recognizes an epitope between amino acids 5 and 10 at the NH₂ terminus.

**Surgical technique**

All patients underwent surgery through a midline sternotomy, with the use of cardiopulmonary bypass, mild systemic hypothermia and blood cardioplegia. The decision to perform repair or replacement was at the surgeon’s discretion. However, MVR was performed in the presence of a coaptation depth of mitral leaflets >10 mm. In these cases, abnormalities in the subvalvular apparatus prevent proper coaptation of mitral leaflets, causing residual mitral regurgitation (MR) [9].

Downsizing ring annuloplasty was performed for all patients who underwent MVRp: the ring size was selected by measuring the inter-commissural distance of the MV and positioned to cover the surface of the stretched middle scallop of the anterior leaflet: a ring undersized by two sizes was then inserted. MVR was performed with preservation of the subvalvular apparatus. Concomitant CABG was performed on main coronary vessels or branches that displayed luminal stenoses of 70% or more on preoperative angiography.

**Statistical analysis**

Continuous data were expressed as mean ± standard deviation or median with the interquartile range and categorical data as percentages. Preoperative data were compared between the two groups using t-test, χ² test or Fisher’s exact test as appropriate. Cumulative survival was evaluated with the Kaplan–Meier method, and the log-rank test was used to compare the groups. Univariate and multivariate analyses were performed to determine risk factors for early mortality. Clinically relevant variables with P < 0.2 on univariate analysis were incorporated into the multivariate models. Stepwise logistic regression and Cox proportional hazards regression analyses were performed to identify independent predictors of early mortality and mid-term survival, respectively. Results were reported as effect sizes [odds ratios (ORs) or hazard ratios (HRs)] with 95% confidence intervals (CIs). All reported P values were two-sided, and P values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, IL, USA).

**RESULTS**

**Patients’ characteristics and operative data**

Baseline characteristics of the 126 patients are shown in Table 1. Patients in the MVR group were older and more likely to have a higher NYHA functional class, higher percentage of redo operation (7.1%) and pulmonary hypertension (32.1%). There was no difference in diabetes, hypertension, chronic obstructive pulmonary disease (COPD), extracardiac arteriopathy and extent of coronary disease.

The operative variables for all patients are listed in Table 2. In the MVR group, the choice of the prostheses was determined on the basis of the patient’s age, special request and comorbidities: 10 mechanical and 18 bioprosthetic valves were implanted. In the MVRp group, closed semi-rigid rings were implanted in 62 patients and open rigid rings in 36. No flexible ring was used.

The extent of surgical revascularization was similar in both groups (number of grafts, 2.5 ± 0.9 in MVRp vs 2.2 ± 0.9 in MVR, P = 0.47).

Every patient received a postoperative echocardiography at discharge: in the MVRp group, residual mitral regurgitation was trivial in 24 patients (27.6%) and mild in 7 (8%).

**Early mortality**

The overall rate of mortality was 7.9% (10 of 126). MVR was associated with a 4-fold increase in the risk of death compared with MVRp (17.9 vs 5.1%; OR 4.04, 95% CI 1.08–15.1, P = 0.04). On univariate analysis, the predictors of early mortality were pulmonary hypertension (OR 4.5, 95% CI 1.2–17, P = 0.02), LVEF (OR 0.9, 95% CI 0.8–1.0, P = 0.008), LV end-systolic diameter (OR 0.9, 95% CI 0.8–1.0, P = 0.023), LV end-diastolic diameter (OR 0.9, 95% CI 0.8–1.0, P = 0.048) and BNP levels (OR 1.01, 95% CI 1.0–1.02, P = 0.028). However, after adjusting for preoperative risk factors, the type of
surgical procedure (MVRp or MVR) was not an independent risk factor for early mortality (OR 0.1, 95% CI 0.01–31, P = 0.7). Multivariable analysis showed that preoperative LVEF (OR 0.8, 95% CI 0.6–0.9, P = 0.018), preoperative BNP levels (OR 1.01, 95% CI 1–1.02, P = 0.025), preoperative LV end-systolic diameter (OR 0.8, 95% CI 0.7–1.0, P = 0.05) and preoperative left atrium diameter (OR 1.3, 95% CI 0.6–1.6, P = 0.015) were independent predictors of early mortality (Table 3).

**Mid-term survival**

At a median follow-up of 45 months (interquartile range 20–68 months) the mid-term survival rate was 74% in the MVRp group and 70% in the MVR group (P = 0.08). On univariate analysis, the predictors of late mortality were age (HR 1.09, 95% CI 1.03–1.16, P = 0.03), LV end-systolic diameter (HR 0.93, 95% CI 0.88–0.98, P = 0.017), preoperative chronic renal failure (HR 4.2, 95% CI 1.2–14.1, P = 0.02), atrial fibrillation (HR 3.3, 95% CI 1.4–7.7, P = 0.006) and BNP levels (HR 1.0, 95% CI 1.0–1.01, P = 0.0001). Multivariable analysis showed that BNP levels (HR 1.0, 95% CI 1.0–1.01, P = 0.047), preoperative renal failure (HR 4.6, 95% CI 1.1–20.3, P = 0.039) and preoperative atrial fibrillation (HR 3.3, 95% CI 1.1–10, P = 0.032) were independently associated with worse survival. The type of surgical procedure was not a significant predictor of mortality (HR 0.98, 95% CI 0.3–2.9, P = 0.97) (Table 4). At follow-up, 2 patients (2%) in the MVRp group were reoperated for MV regurgitation.

**DISCUSSION**

The main finding of this study is that, in patients with IMR and depressed LVEF, there is no evidence that MVRp provides better results in terms of operative early mortality compared with MVR. We found that preoperative LVEF, preoperative BNP levels, preoperative left ventricular tele-systolic diameter and preoperative left atrial diameter were associated with increased risk of early mortality. Moreover, no difference was found regarding late mortality in the MVR group compared with the MVRp group. At follow-up, preoperative atrial fibrillation, preoperative BNP levels and preoperative renal failure were predictors of worse survival. IMR is a major source of patient morbidity and mortality, with a strong association with heart failure and poor outcomes [1, 2]. In this setting, the joint European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines define severe MR in the presence of 20 mm² for effective regurgitant orifice area and 30 ml for regurgitant volume, as these values are associated with poor outcomes [8]. According to that, severe MR should always be corrected at the time of bypass surgery (Class I, Level C). However, there is continuing debate whether MVRp is superior to

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**Table 1: Preoperative data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>MV repair (n = 98)</th>
<th>MV replacement (n = 28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>64.8 ± 10.5</td>
<td>69.7 ± 10</td>
<td>0.029</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>26 (26.5)</td>
<td>11 (39.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>NYHA class (3–4), n (%)</td>
<td>60 (61.2)</td>
<td>20 (71.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>34 (34.7)</td>
<td>9 (32.1)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>79 (80.6)</td>
<td>25 (89.3)</td>
<td>0.43</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>14 (14.3)</td>
<td>4 (14.2)</td>
<td>1</td>
</tr>
<tr>
<td>Extracardiac arteriopathy, n (%)</td>
<td>19 (19.4)</td>
<td>6 (21.4)</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32.1 ± 6.7</td>
<td>34.1 ± 7.1</td>
<td>0.18</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm ± SD</td>
<td>47 ± 7.1</td>
<td>44.8 ± 10</td>
<td>0.21</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm ± SD</td>
<td>61.6 ± 6.3</td>
<td>58.6 ± 9.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Left atrium diameter, mm ± SD</td>
<td>45.3 ± 5.1</td>
<td>44 ± 6.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Previous operations (%)</td>
<td>0 (0)</td>
<td>2 (7.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Critical preoperative state (%)</td>
<td>7 (7.1)</td>
<td>7 (25)</td>
<td>0.021</td>
</tr>
<tr>
<td>Recent myocardial infarction (%)</td>
<td>14 (14.3)</td>
<td>15 (57.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Preoperative intra-aortic balloon pump, n (%)</td>
<td>18 (18.4)</td>
<td>10 (35.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>17 (17.3)</td>
<td>9 (32.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of coronary lesions, n ± SD</td>
<td>2.6 ± 0.7</td>
<td>2.4 ± 0.7</td>
<td>0.52</td>
</tr>
<tr>
<td>BNP levels, ng/ml (interquartile range)</td>
<td>966.5 (658–1307)</td>
<td>964.5 (734–2036)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; LV: left ventricle; MV: mitral valve; NYHA: New York Heart Association; SD: standard deviation; BNP: B-type natriuretic peptide.

**Table 2: Operative data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>MV repair (n = 98)</th>
<th>MV replacement (n = 28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB time (min ± SD)</td>
<td>156 ± 46</td>
<td>180 ± 79</td>
<td>0.10</td>
</tr>
<tr>
<td>Cross-clamp time (min ± SD)</td>
<td>107 ± 29</td>
<td>132 ± 47</td>
<td>0.002</td>
</tr>
<tr>
<td>CABG (no. of grafts)</td>
<td>2.5 ± 0.9</td>
<td>2.2 ± 0.9</td>
<td>0.47</td>
</tr>
<tr>
<td>Prosthesis type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical, n (%)</td>
<td>10 (36)</td>
<td>18 (64)</td>
<td></td>
</tr>
<tr>
<td>Bioprosthesis, n (%)</td>
<td>10 (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ring type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open ring, n (%)</td>
<td>36 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closed ring, n (%)</td>
<td>62 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid ring, n (%)</td>
<td>36 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-rigid ring, n (%)</td>
<td>62 (63)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; MV: mitral valve; SD: standard deviation.
MVR in patients with severe IMR undergoing CABG, especially in the presence of left ventricular dysfunction.

Since its introduction in 1995, undersized annuloplasty for treatment of IMR has shown good results in terms of mitral regurgitation correction and improvement of outcomes [10, 11]. Despite these good results, a high incidence of residual and recurrent mitral regurgitation has been reported with mitral annuloplasty [12]. In previous studies, better results in terms of early and late survival in low-risk MVRp patients compared with MVR have been reported [5, 6, 13]. De Bonis et al. [14] documented higher survival rates for the repair group compared with the replacement group, though persistent or recurrent moderate (2+/4+) MR was documented in 14.4% of patients and severe MR in 7.2% of the cases at the 2-year follow-up. On the contrary, several studies comparing MVRp and MVR have documented no benefit in high-risk cases, with poor survival in both groups [3, 5, 7]. Furthermore, the presence of persistent or recurrent MR is associated with markedly worse outcomes, regardless of the degree of severity [7, 15, 16]. A meta-analysis focusing specifically on MVRp versus MVR in patients with IMR showed improved short-term and long-term survival with MVRp [17]. However, this conclusion was based on retrospective studies and, in the MVR group, there was no uniform preservation of the subvalvular apparatus. Conversely, in a recent meta-analysis, Dayan et al. have shown that no difference existed between MVRp and MVR.
Regarding long-term survival, although MVRp was associated with lower operative mortality [18].

Similarly, in a randomized trial comparing chordal-sparing MVR and repair in IMR, Acker et al. [19] have not observed significant differences between the two groups in terms of left ventricular reverse remodelling and rate of major adverse cardiac or cerebrovascular events at 12 months. Our study reached similar conclusions; in our multivariable analysis, surgical procedure was excluded as a potential independent risk factor of early and late mortality. In the multivariable analysis, preoperative LVEF, preoperative left ventricular tele-systolic diameter, left atrial diameter and BNP levels were independent risk factors for early mortality, whereas preoperative atrial fibrillation, preoperative BNP levels and preoperative renal failure were predictors of worse mid-term survival.

Left ventricular size is a factor independently associated with increased mortality in mitral surgery [20]. Particularly, in the setting of IMR, left ventricular dimensions are an important predictor of reverse remodelling after restrictive mitral annuloplasty. In patients with a left ventricular end-diastolic dimension exceeding 65 mm, reverse remodelling of the LV does not occur, with a high risk of residual or recurrent MR and therefore associated with worse outcome [21]. The association between left atrial diameter and increased operative mortality has probably to be related to the increased incidence of atrial fibrillation in patients with a larger left atrium; atrial fibrillation is a well-known negative prognostic factor in cardiac surgery [22], and our Cox hazard multivariate analysis confirmed these data.

BNP is another important prognostic indicator of various manifestations of myocardial dysfunction that makes it useful as an indicator of cardiovascular prognosis in many contexts. Preoperative BNP determination could be useful in predicting some adverse outcomes after cardiac surgery [23, 24]. Particularly, elevated BNP levels have been associated with atrial fibrillation and postoperative low cardiac output [25]. Our study confirms this strong association between BNP levels and adverse outcomes, showing that increased levels of BNP are associated with higher early mortality in patients with IMR undergoing cardiac surgery. Furthermore, in our series, a strong association between BNP level and long-term mortality was found, highlighting the importance of BNP as a predictive marker of worse outcomes, encouraging an early surgical approach in IMR.

Finally, another important item of data of our series is the low rate of reoperation in MVR group at follow-up (2%). This result is probably due to the criteria used to decide whether to repair or replace the mitral valve. Calafiore et al. [9] have shown that in the presence of a coaptation depth more than 10 mm, the mitral valve should be replaced as a repair is associated with a high risk of residual or recurrent MR due to excessive leaflet movement restriction. According to this, we have used this cut-off in the surgical planning, with good results at the follow-up.

Study limitations

This study has several limitations. It is based on the retrospective analysis of our institutional, observational, prospectively collected database. Although multivariable analysis was performed to exclude potential confounding factors, it is still subject to bias by unmeasured confounders. Furthermore, our study is limited by the small sample size and this might explain the lack of statistical significance among different preoperative variables. We confirm that patients undergoing MVRp were worse in terms of ejection fraction and, consequently, had larger end-systolic or end-diastolic diameters. On the other hand, NYHA class was higher in the MVR group. However, NYHA class may be affected by other factors such as pulmonary hypertension, medical treatment, recent myocardial infarction causing pulmonary oedema and pulmonary disease (not only COPD, but also fibrosis). In Table 1, patients in the MVR had a higher incidence of pulmonary hypertension and critical preoperative state. Unfortunately, we do not have additional information on medical therapy, pulmonary disease (other than COPD) or if the patient had pulmonary oedema.

An important factor that may influence the outcome of patients with ischaemic disease and IMR is the amount of myocardium that can be saved through revascularization; however, no study was performed to assess myocardial viability.

In patients who underwent MVRp, postoperative echocardiography described only the degree of residual mitral regurgitation, but not other parameters such as length of coaptation of mitral leaflets or gradients across the mitral valve. Finally, we did not report postoperative echocardiographic data at follow-up; however, the objective of our study was to evaluate the early mortality and mid-term survival of these cohorts of patients.

CONCLUSION

Our retrospective study indicates that MVRp in CABG patients with IMR and depressed LVEF did not confer any benefit compared with MVR in terms of operative early mortality and mid-term survival. Therefore, MVR remains a valuable surgical option for patients with IMR and LV dysfunction.

REFERENCES

References

[1] Lio A, Miceli A, Varone E, Canarutto D, Di Stefano G, Della Pina F et al. Mitral valve repair versus replacement in patients with ischaemic mitral regurgitation and depressed ejection fraction. They obtained invaluable scientific data from the study. These results can be represented with a stronger level of evidence by utilizing a robust statistical method called ‘bootstrapping’.

A confidence interval (CI) gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data. Confidence intervals are needed because there is variation in nature, nearly all information gained from humans varies to a greater or lesser extent. There are two important factors that affect the width of a CI: the sample size and the amount of variation in the population. Classically, CIs are calculated with formulas developed on the assumptions of normality and the central limit theorem which were developed when there were no computers, and analytical methods were needed in the absence of computational power.

How do we know how much sample statistics vary, if we only have one sample? The answer lies in the term ‘bootstrapping’. In essence you use the sample data to take large numbers of random samples and examine the distribution of these samples. You can do it by re-using the data from your one actual study over and over again. The term ‘bootstrapping’ is an allusion to the expression ‘pulling oneself up by one’s bootstraps’, in this case using the sample data as a population from which repeated samples are drawn. Over the years, the bootstrap procedure has become an accepted way to get reliable estimates of standard errors (SE) and confidence intervals for almost anything you can calculate from your data [2]. Nowadays bootstrapping is often considered the gold standard method to determine SEs and CIs. Bootstrap techniques are heavily dependent upon computer calculations. As a widely used programme for statistical analysis in medicine, SPSS 18 and newer versions afford bootstrap methods for standard use.

Bootstrap based approaches for statistical estimation and determination of the properties of the estimator are being increasingly realized in modern methods of data analysis. As a result it is time to revise our statistical habits.

Conflict of interest: none declared.

References
