Long-term clinical outcome of mitral valve repair in asymptomatic severe mitral regurgitation§§

Fabien Chenot 1, Patrick Montant 1, David Vancraeynest, Agnès Pasquet, Bernhard Gerber, Philippe Henri Noirhomme, Gébrine El Khoury, Jean-Louis Vanoverschelde*

Division of Cardiology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Avenue Hippocrate 10-2881, B-1200 Brussels, Belgium

Received 1 September 2008; received in revised form 20 February 2009; accepted 24 February 2009; Available online 25 July 2009

Abstract

Objective: To assess the long-term survival, the incidence of cardiac complications and the factors that predict outcome in asymptomatic patients with severe degenerative mitral regurgitation (MR) undergoing mitral valve repair. Methods: Up to 143 asymptomatic patients (mean age 63 ± 12 years) with severe degenerative MR who underwent mitral valve repair between 1990 and 2001 were subsequently followed up for a median of 8 years. The study population was subdivided into three subgroups: patients with left ventricular (LV) dysfunction and/or dilatation (n = 18), patients with atrial fibrillation and/or pulmonary hypertension (n = 44) and patients without MR-related complications (n = 81). Results: For the patients, 10-year overall and cardiovascular survival was 82 ± 4% and 90 ± 3%. At 10 years, patients without preoperative MR-related complications had significantly better overall survival than patients with preoperative LV dysfunction and/or dilatation (89 ± 4% vs 57 ± 13%, log rank p = 0.001). Patients without preoperative MR-related complications also tended to have a better 10-year overall and cardiovascular survival than patients with atrial fibrillation and/or pulmonary hypertension (overall survival of 79 ± 8%), although this did not reach statistical significance (log rank p = 0.17). Cox regression analysis identified the baseline left ventricular ejection fraction and age as the sole independent predictors of outcome. Conclusion: Our data indicate that in asymptomatic patients with severe degenerative MR, mitral valve repair is associated with an excellent long-term prognosis. Nonetheless, the presence of preoperative MR-related complications, in particular LV dysfunction and/or dilatation, greatly attenuates the benefits of surgery. This suggests that mitral valve repair should be performed early, before any MR-related complications ensue.

© 2009 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Mitral valve; Mitral regurgitation; Early surgery

1. Introduction

Degenerative mitral regurgitation (MR) is the second most frequently encountered valvular disease in Western countries and is often discovered fortuitously in still asymptomatic patients [1,2].

The timing of surgery in asymptomatic patients remains controversial. With the advent of conservative mitral valve surgery, the management of severe MR has changed significantly [3]. These operations indeed have a low operative mortality as well as good long-term durability; they provide the patient with a better long-term outcome than valve replacement [4]. Accordingly, a number of authors have suggested that if the mitral valve is both severely regurgitant and repairable, postponing surgery would expose the patient to unnecessary risk [5]. Thus, they recommend early surgery in such patients. On the other hand, other authors have advocated for postponing surgery until the end points in the guidelines are met [6]. They argue that, according to most database reports, operative mortality remains relatively high [1], that the long-term durability of an initially successful mitral reconstruction is not constant [7], and that the majority of patients who undergo mitral valve surgery ultimately receive a mitral prosthesis [1,8,9].

In view of this controversy, the purpose of the present study was to assess the long-term survival, the incidence of cardiac complications and the factors that predict the outcome in asymptomatic patients with severe degenerative MR undergoing mitral valve repair. In particular, we sought to...
Table 1
Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 81)</th>
<th>Group 2 (n = 44)</th>
<th>Group 3 (n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 13</td>
<td>67 ± 11</td>
<td>69 ± 12</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>73</td>
<td>68</td>
<td>94</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 ± 0.08</td>
<td>1.72 ± 0.09</td>
<td>1.73 ± 0.08</td>
<td>0.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ± 11</td>
<td>72 ± 16</td>
<td>76 ± 13</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>9</td>
<td>9</td>
<td>17</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>29</td>
<td>41</td>
<td>33</td>
<td>0.4</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>18</td>
<td>18</td>
<td>39</td>
<td>0.10</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>218 ± 34</td>
<td>216 ± 40</td>
<td>228 ± 44</td>
<td>0.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.95/0.27</td>
<td>1.07/0.26</td>
<td>1.11/0.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Prolapse type (%)</td>
<td>64/11/24</td>
<td>73/14/14</td>
<td>89/11/0</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>60 ± 8</td>
<td>58 ± 7</td>
<td>62 ± 8</td>
<td>0.4</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>36 ± 5</td>
<td>36 ± 5</td>
<td>44 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>70 ± 7</td>
<td>68 ± 7</td>
<td>53 ± 4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>48 ± 8</td>
<td>51 ± 10</td>
<td>54 ± 10</td>
<td>0.10</td>
</tr>
<tr>
<td>AF</td>
<td>0%</td>
<td>68%</td>
<td>11%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic tricuspid gradient (mmHg)</td>
<td>28 ± 8</td>
<td>42 ± 14</td>
<td>40 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%With systolic tricuspid gradient &gt;40 mmHg</td>
<td>0%</td>
<td>41%</td>
<td>16%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; prolapse type: posterior/anterior/bileaflet.

To determine the influence of preoperative MR-related complications (LV dilatation or dysfunction, atrial fibrillation (AF) or pulmonary hypertension) on the long-term prognosis.

2. Materials and methods

2.1. Study population

Between 1 January 1990, and 31 December 2001, 143 consecutive asymptomatic patients with severe (i.e., grade 3) degenerative MR underwent mitral valve repair at our institution. Exclusion criteria were age >85 years, associated mitral valve stenosis, previous valve surgery and associated congenital heart disease. Patients who had coronary artery disease or had undergone bypass grafting were not excluded. Information on postoperative events was obtained for all patients between December 2006 and April 2007. Cardiac events and causes of death were ascertained by contacting the patients' physicians and reviewing death certificates, coroners' reports or autopsy records.

2.2. Operative procedures

The techniques of mitral valve repair used in this series were basically those described by Carpentier, but certain modifications were introduced over the years as, for instance, the use of expanded polytetrafluoroethylene (ePTFE) sutures to reinforce or replace chordae tendineae (introduced in 1996). Most procedures were combined with the implantation of a complete prosthetic semi-rigid or non-flexible ring (>90% of the cases).

2.3. Statistical analysis

All analyses were conducted using the SPSS software (version 15.0, SPSS Corp., Chicago, IL, USA). Continuous variables were expressed as mean ± 1 standard deviation (SD), categorical variables as counts and percentages and follow-up times as median and range. Differences between groups were analysed with a one-way analysis of variance or a chi-square test where appropriate. A probability value of <0.05 was considered indicative of a statistically significant difference.

Overall, cardiovascular and event-free survival functions were computed with the Kaplan–Meier method and compared using the log rank chi-square test. Cardiac events were defined as cardiac death, need for mitral surgery (including re-operation), mitral endocarditis, complete atrio-ventricular block, non-fatal stroke and acute coronary syndrome. For each patient included in the study, the corresponding average age- and gender-specific annual mortality rates of the Belgian general population were obtained. The expected survival was determined and an expected survival curve was constructed.

All clinical and echocardiographic variables were also proposed for inclusion into a Cox’s proportional-hazards survival model for the determination of the factors independently associated with the outcome. For this purpose, an interactive step-wise selection procedure employing the maximum partial likelihood ratio chi-square statistic ($\chi^2$ test) to enter (<0.05 level) or to remove (>0.05 level) a covariate into the model was used. Variables were entered until no F-to-enter statistics were significant at the 5% level and until the mean squared error reached a minimum.

3. Results

3.1. Baseline characteristics

The baseline clinical characteristics of the 143 patients who met the inclusion criteria are shown in Table 1. Patients were separated into three groups according to the presence

of preoperative MR-related complications. Group 1 consisted of 81 patients free of any MR-related complications, group 2 of 44 patients with preoperative AF and/or PHT (defined as pulmonary artery systolic pressure above 40 mmHg) and group 3 of 18 patients with LV dysfunction (defined as a left ventricular ejection fraction (LVEF) <60%) and/or dilatation (defined as a left ventricular end-systolic dimension >45 mmHg). Thirty-two patients underwent concomitant coronary artery bypass graft surgery (CABG).

At follow-up, all patients who were initially free of any MR complications were in New York Heart Association (NYHA) classification I or II (72% in class I and 28% in class II). Among patients with preoperative AF or PHT, 68% were in NYHA class I at follow-up and 32% in class II. Finally, in patients with preoperative LV dysfunction, only one (8%) was in NYHA class III at follow-up. The other patients were either in class I (59%) or II (33%).

3.2. Overall and cardiovascular survival

During a median follow-up of 8 years, 21 patients died, seven (8%) in group 1, seven (16%) in group 2 and seven (39%) in group 3. The cause of death was cardiac in 13 of them (operative death in three, intractable heart failure in three, sudden cardiac death in five, thrombo-embolic stroke in one and abdominal aortic aneurysm rupture in one). At 30 days, two patients from group 3 and one patient from group 2 died. No patients died among group 1. On average, 30-day mortality was thus 2% (3/143 patients). During follow-up, an additional 18 patients died. At 10 years, the overall survival was 82 ± 4% and cardiovascular survival was 90 ± 3% (Fig. 1).

Fig. 2A and B shows the overall and cardiovascular free survival in the three subgroups of patients. Ten-year overall and cardiovascular survival was significantly better in group 1 and group 2 than in group 3 (overall survival: 89 ± 4%, 79 ± 8% and 57 ± 13%; log rank \( p = 0.005 \); cardiovascular survival: 96 ± 2%, 86 ± 6% and 68 ± 13%, log rank \( p = 0.005 \)). Because 32 patients underwent combined CABG and mitral valve repair, we also evaluated the impact of adding CABG to mitral repair on survival. After 10 years of follow-up, patients who underwent combined mitral repair and CABG had a poorer overall and cardiovascular survival (54 ± 11% and 70 ± 10%, respectively) than patients undergoing mitral valve repair alone (90 ± 3% and 95 ± 2%, respectively, both log rank \( p < 0.0001 \)). Fig. 3 shows the overall, cardiovascular and event-free survival in patients undergoing mitral repair alone.

3.3. Cardiovascular events

In addition to overall and cardiovascular mortality, during follow-up, seven patients needed also a re-operation, five because of recurrent severe MR (moderate 2+ MR in two and severe 3+ MR in three), one because of mitral stenosis and another because of a voluminous atrial thrombus. Nine additional non-fatal cardiac events occurred as well (four strokes, four complete atrio-ventricular blocks and one acute coronary syndrome). As shown in Fig. 2C, groups 1 and 2 tended to have a better 10-year event-free survival than group 3 (83 ± 4%, 75 ± 8% vs 57 ± 13% respectively) although this did not reach the statistical significance (log rank \( p = 0.12 \)).

3.4. Cox’s proportional-hazards survival analysis

To assess the factors potentially associated with 10-year overall and cardiovascular survival, two different Cox’s survival models were built for which all the clinical and echocardiographic parameters available were proposed for inclusion. Among these variables, age was the sole independent predictor of global mortality while age and LV ejection fraction were independently associated with the time to cardiac death (see Table 2).

4. Discussion

The results of the present study can be summarised as follows:

1. The overall and cardiovascular outcome of asymptomatic patients undergoing mitral valve repair is excellent, with
the overall 10-year survival being 82% and cardiovascular survival being 90%.

2. The long-term outcome of asymptomatic patients undergoing mitral valve repair depends on the presence of preoperative MR-related complications. Patients free from any MR-related complications have the best 10-year overall and cardiovascular survival. In these patients, overall survival is at least as good as that of the age- and gender-matched Belgian population.

3. The presence of preoperative AF or PHT appears to slightly but non-significantly reduce the overall and cardiovascular survival.

4. The presence of preoperative LV dysfunction or dilatation is accompanied by a significantly poorer overall and cardiovascular outcome.

Mitral valve surgery is the only acceptable treatment option in patients with severe degenerative mitral regurgitation. In the past, the operative mortality of mitral valve replacement was undoubtedly too high to consider surgery in asymptomatic patients [3]. However, with the advent of mitral valve repair, operative mortality has considerably decreased. As early as in 1996, Sousa et al. reported surgical results on a series of asymptomatic or mildly symptomatic patients who underwent mitral valve repair for severe MR [10]. The overall operative mortality in these patients was 1.7%. More recently, Ling et al., [11] Smolens et al. [9] and David et al [12] reported very similar results, with operative mortality ranging from 0 to 0.5%. The results of the present study confirm and extend these previous findings. In our study also, overall 30-day mortality was low and accounted only for 2%. Interestingly, the three case fatalities only occurred in the presence of preoperative MR-related complications. No deaths were noted in patients free from any of these complications. Taken together, these observations suggest that, in asymptomatic patients without any MR-related complications, mitral valve repair is an extremely safe procedure.

Besides the immediate risk of repair procedures, their long-term durability is also an important parameter to consider before an early surgical approach can be proposed to asymptomatic patients without any MR-related complications. Although, innovations in mitral repair techniques, an improved understanding of the functional anatomy of the mitral valve, as well as an increased awareness of the mechanisms leading to MR have allowed the improvement of the durability of repair procedures, some authors have reported a high incidence of recurrent MR during follow-up [7,13]. In 242 patients who had undergone mitral valve repair for degenerative valve incompetence, Flameng et al. reported a rate of non-trivial MR recurrence of 6% at 1 month, 41% at 5 years and 73% at 7 years. Based on these
findings, these authors recommended the use of caution before proposing 'preventive' early surgery to every patient with asymptomatic severe MR [7]. Although the results of Flameng et al. share some concerns about the durability of mitral repair procedures, it is important to emphasise that in most cases, the severity of recurrent MR in their study was mild to moderate and that only a minority of patients developed recurrent severe MR during follow-up. This probably explains why both the overall survival and the rate of re-operation in their patients remained excellent throughout the study period (91% and 6% at 8 years, respectively). Similarly good long-term clinical outcomes were also reported by other authors, overall 5-year survival ranging from 90% to 100% [11,12]. The present results are thus in agreement with those earlier reports. Indeed, on average, the 10-year survival of our patients was 80%. Our data nonetheless show that the presence of any MR-related complication, in particular LV dysfunction and/or dilatation, greatly reduces the beneficial long-term effects of mitral valve repair. Although the current ESC guidelines only recommend mitral valve repair as a class I indication for asymptomatic patients with severe degenerative MR once LV ejection fraction decreases below 60%, [14] our current results would suggest that it is unwise to wait for LV function to deteriorate before proposing surgery to an asymptomatic patient. We therefore believe that the excellent 10-year overall survival of mitral valve repair is a strong incentive to propose an early surgical strategy in these patients. In our point of view, such a strategy offers several important advantages over the more conservative, watchful waiting approach proven by Rosenheck et al. [6] First, early mitral repair surgery solves the patient’s clinical problem once and for all; it does not require the patient to comply with a regular and quite strict clinical and echocardiographic follow-up. In view of the poor spontaneous prognosis of patients with severe degenerative MR, [5] any effective, safe and definite treatment of this condition is indeed welcome.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>p value</th>
<th>Multivariate analysis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;60%</td>
<td>3.8 (1.5; 9.9)</td>
<td>0.005</td>
<td>1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.02; 1.15)</td>
<td>0.005</td>
<td>(1.02; 1.14)</td>
<td></td>
</tr>
<tr>
<td>LVEDD &gt;45 mm</td>
<td>3.8 (1.2; 11)</td>
<td>0.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;60%</td>
<td>5.8 (1.9; 17.9)</td>
<td>0.002</td>
<td>3.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>1.13 (1.03; 1.2)</td>
<td>0.007</td>
<td>1.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.1 (1.1; 9.3)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Kaplan—Meier curves for overall (panel A), cardiovascular (panel B) and event-free (panel C) survival for asymptomatic patients without any MR-related complications (solid line), patients with preoperative atrial fibrillation or pulmonary hypertension (dashed line) and patients with preoperative LV dysfunction or dilatation (dashed-dotted line) after exclusion of concomitant CABG pts. Numbers at bottom indicate patients at risk.
Second, it protects the patient against the occurrence of sudden cardiac death, a frequent and devastating complication in asymptomatic patients with severe MR [15]. Finally, it allows operating upon patients before the usual MR-related complications, such as LV dysfunction, atrial fibrillation and pulmonary hypertension develop and hence negatively impact the postoperative prognosis [11,16].

4.1. Limitations to the study

There are several limitations to this study that should be acknowledged. First, despite the completeness of our follow-up data and the prospective nature of the database from which the data were retrieved, our study has a retrospective design. We cannot exclude the possibility that unaccounted confounding factors contributed to our results. Second, patients were deemed asymptomatic or mildly symptomatic on the basis of the NYHA functional classification, which has obvious intrinsic limitations. Ideally, patients should have been classified according to the results of an exercise test. Unfortunately, because of the retrospective design of our study, these data were unavailable in a large majority of our patients. Finally, because no systematic echocardiographic follow-up data was obtained, the exact rate of asymptomatic MR recurrence could not be assessed.

4.2. Conclusions

Our data demonstrate that mitral valve repair in asymptomatic patients with severe degenerative MR is usually associated with an excellent prognosis, except in the presence of preoperative MR-related complications. This suggests that mitral valve repair should be performed early in the presence of severe MR, before the development of any MR-related complications.

References

only survival. Did you assess the quality of life and the symptoms in these patients?

Dr Glineur: We did not have a specific questionnaire on quality of life, but I guess it would be an excellent idea, yes. But we did not do it.

Dr Glineur: Well, in fact it is a retrospective study, so we went back into the files of 1990, and of course, like every retrospective study, we did not have for all patients effort tests. So we based it mainly on the questionnaire that we could find in these files.

Dr M. Antunes (Coimbra, Portugal): Well, I also tend to agree that one should go earlier rather than late, and I am not sure that being asymptomatic is a contraindication to surgery. I understand the problems in these retrospective studies, but we should be careful about it.