Negative impact of atrial fibrillation and pulmonary hypertension after mitral valve surgery in asymptomatic patients with severe mitral regurgitation: a 20-year follow-up

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Abstract

OBJECTIVES: The timing for mitral valve (MV) surgery in asymptomatic patients with severe mitral regurgitation (MR) and preserved left ventricular (LV) function remains controversial. We aimed at analysing the long-term outcome of asymptomatic patients with atrial fibrillation (AF) and/or pulmonary hypertension (PHT) after successful MV repair.

METHODS: From January 1992 to December 2012, 382 patients with severe degenerative MR, with no or mild symptoms, preserved LV function (ejection fraction > 60%) and LV systolic dimensions < 45 mm were submitted to surgery and followed up for up to 22 years (3209 patient-years). Patients with associated surgeries, other than tricuspid repair, were excluded. Patients with AF and/or PHT (Group A; n = 106, 24.4%) were compared with patients without these comorbidities (Group B; n = 276, 63.6%). Propensity-score matching (for preoperative variables) was performed obtaining 102 patients in each arm. Survival and event-free survival [major cardiac and cerebrovascular events (MACCEs); freedom from mitral reoperation and recurrent moderate and severe MR] were analysed.

RESULTS: MV repair was performed in 98.2% of cases and tricuspid annuloplasty in 6.9%. Overall 30-day mortality was 0.8%, not different between groups, and absent in patients with isolated posterior leaflet prolapse (n = 211). Patients with AF/PHT had worse late survival by comparison with Group B patients (67.0 ± 7.4 vs 86.5 ± 3.9% at 15 years, P < 0.001), survival free from MACCE (52.7 ± 8.7 vs 74.5 ± 5.0%, P < 0.001), from recurrent moderate and severe MR (65.1 ± 10.3 vs 87.0 ± 3.8%, P = 0.002) and from mitral reoperation during the follow-up (87.3 ± 6.3 vs 94.2 ± 2.7%, P = 0.04). These differences were confirmed in the propensity score-matched population. Patients from Group A also displayed a lesser degree of reverse remodelling. There was a significant reduction in the systolic pulmonary artery pressure (SPAP) after surgery, more pronounced in Group A patients; nonetheless, the mean SPAP at late follow-up was higher in these patients (45 vs 30 mmHg).

CONCLUSIONS: MV repair can be achieved in the majority of patients with degenerative regurgitation, with low mortality (<1%). Asymptomatic or mildly symptomatic patients with severe MR, preserved LV function and AF/PHT had poorer long-term survival and event-free survival even after a successful surgery. The durability of MV repair was also compromised in these patients, which indicates that they should have been operated earlier.

Keywords: Degenerative mitral regurgitation • Asymptomatic patients • Pulmonary hypertension • Atrial fibrillation • Long-term outcomes

INTRODUCTION

Primary degenerative mitral regurgitation (MR) has become the main form of presentation of mitral valve (MV) disease in western countries and MV repair is the procedure of choice whenever it is feasible and expected to be durable. The current trend to intervene earlier in the natural history of the disease, already included in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery [1] and American College of Cardiology/American Heart Association [2] guidelines, has been driven by the high rates of MV repair and the very low mortality (<1%) reported from centres of reference [3, 4].

Pulmonary hypertension (PHT) and atrial fibrillation (AF) are common in patients referred for MV surgery for chronic MR [5, 6]. Both factors have been identified as negative prognostic markers of poor outcome after MV surgery and the available data have shown that a reasonable percentage of patients will remain with PHT and/or AF, even after a successful MV repair or replacement [7–9].
The impact of the presence of PHT and AF in asymptomatic patients with preserved left ventricular (LV) function at the time of MV surgery is poorly defined and the existing information is remarkably scanty and generally originating from small series [10, 11]. The current guidelines only recommend or consider reasonable (class IIa, level of evidence C) to perform MV surgery in the setting of new-onset AF and PHT [defined as a systolic pulmonary artery pressure (SPAP) >50 mmHg].

We hypothesize that asymptomatic patients with severe MR, preserved LV function and AF and/or PHT have compromised survival even after successful MV repair. Therefore, the primary aim of this study was to evaluate the long-term survival of this subset of patients by comparison with those without these negative markers. As a secondary end point, we sought to examine other relevant clinical outcomes, such as adverse cardiovascular events and freedom from moderate and severe MR/MV reoperation after MV repair.

MATERIALS AND METHODS

Patient population and surgical technique

From January 1992 to December 2012, 1437 patients were submitted to MV surgery for severe degenerative MR, 434 of whom were asymptomatic or mildly symptomatic [New York Heart Association (NYHA) functional class I or II], with preserved left ventricular ejection fraction (LVEF > 60%). Of these, 382 also had conserved LV dimensions (defined as a LV end-systolic internal diameter <45 mm) and constituted the study population. Primary indication for surgery was severe MR in all patients.

In the interest of most precisely examining the impact of PHT/AF after MV surgery, we have only included patients with isolated mitral surgery, with or without concomitant tricuspid valve annuloplasty for functional regurgitation. Thus, patients in NYHA class III or IV, EF ≤ 60% and LV end-systolic diameter ≥45 mm, and with patients with other associated procedures, including coronary artery disease, aortic valve disease, hypertrophic cardiomyopathy, ascending aortic aneurysms and with previous mitral and other cardiac surgeries, were excluded.

The clinical characteristics of the 382 patients who met the inclusion criteria are given in Table 1. Patients were divided into two groups, according to the presence (n = 106, 24.4%—Group A) or absence (n = 276, 63.6%—Group B of AF and/or PHT). In order to homogenize both groups for comparison, a propensity-score analysis was performed, obtaining 102 comparable patients for each group. In general, patients from Group A were significantly older, with more comorbidities. Preoperative echocardiographic data were not significantly different between groups, except for the larger left atrium (LA) diameters and the higher prevalence of tricuspid regurgitation in patients with AF/PHT. After propensity-score matching, the two groups were perfectly matched with the exception of the LA dimensions and presence and degree of tricuspid regurgitation.

The operation was standardized for all patients, including cardiopulmonary bypass with moderate hypothermia (28–30°C) and intermittent antegrade cold crystalloid cardioplegia through the aortic root. LV exposure was via left atriotomy, posterior to the Waterston’s groove in the majority of cases. In some cases, the valve was reached through the right atrium and interatrial septum. During the ‘first decade’ of the study (1992–2002), the classical Carpentier techniques (chordal shortening and transfer, leaflet resection) were more frequently employed, and is, of late, being replaced by the use of artificial neochordae, which has become the standard of care for correcting anterior leaflet prolapse and, in the more recent years, also for posterior leaflet prolapse. Two-thirds (68.3%) of the enrolled patients were operated on in the last decade. Nevertheless, there was no statistical significant difference regarding the MV repair rates between the two decades of the study (99.2 vs 97.7%, P = 0.318).

All patients gave informed consent for surgery and had previously granted permission for the use of their medical records for research purposes.

Echocardiographic analysis

All patients had a comprehensive preoperative transthoracic echocardiogram (TTE) documentering severe MR. The standard TTE included M-mode, two-dimensional (2D), spectral and colour Doppler, obtaining the usual planes (long and short parasternal axis, apical 3, 4 and 5 chamber planes). Anatomic and Doppler measurements (LV and LA diameters, EF and fractional shortening) were performed as recommended [12]. Transoesophageal echocardiograms were performed intraoperatively in all cases for the purpose of evaluating the final result of the repair with regard to persistence of MR only. TTE was performed in all patients after surgery, before discharge from the hospital, and repeated during the follow-up. The median follow-up echocardiogram time (after discharge) was 7.9 years [Interquartile range (IQR) range: 5.9–12.6 years].

Although quantitative assessment of the degree of MR has recently become part of our clinical practice, over the course of the entire study period MR grade was determined semi-quantitatively. To be consistent with the follow-up echocardiography reports,

### Table 1: Baseline characteristics of the overall population, comparing patients with pulmonary hypertension (PHT) and/or atrial fibrillation (AF; Group A) with those without (Group B)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group A (n = 106)</th>
<th>Group B (n = 276)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.2 ± 11.9</td>
<td>52.8 ± 13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>29 (27.4%)</td>
<td>77 (26.8%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Previous CVA/TIA</td>
<td>5 (4.7%)</td>
<td>8 (2.9%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43 (40.6%)</td>
<td>73 (26.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (8.5%)</td>
<td>4 (1.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (5.7%)</td>
<td>11 (4.0%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>67 (63.2%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PHT (SPAP &gt; 50 mmHg)</td>
<td>69 (65.1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tricuspid valve pathology</td>
<td>29 (27.4%)</td>
<td>7 (2.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>56.1 ± 9.1</td>
<td>48.6 ± 7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>37.4 ± 4.5</td>
<td>37.4 ± 4.5</td>
<td>0.91</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>62.3 ± 6.8</td>
<td>62.1 ± 6.7</td>
<td>0.86</td>
</tr>
<tr>
<td>LV shortening fraction (%)</td>
<td>39.4 ± 5.4</td>
<td>39.7 ± 5.8</td>
<td>0.66</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>69.2 ± 9.1</td>
<td>68.0 ± 8.0</td>
<td>0.56</td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>57.3 ± 16.2</td>
<td>37.1 ± 8.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Figures in bold indicate statistical significance.

CVA/TIA: cerebrovascular accident/transitory ischaemic accident; COPD: chronic obstructive pulmonary disease; PHT: pulmonary hypertension; SPAP: systolic pulmonary artery pressure; LA: left atrium; LV: left ventricle.
the severity of MR was graded as follows: none (0), trivial (1), mild (2), moderate (3) and severe (4). Preoperative SPAP (or right ventricle systolic pressure) was obtained from preoperative catheterization if available and, if not, by echocardiography using the simplified Bernoulli’s equation. Whenever there was discrepancy of values of SPAP obtained by the two methods, the right catheterization value prevailed.

Data collection, follow-up and outcome events

All preoperative data, both clinical and echocardiographic, operative and postoperative records, including intensive care unit information and complications, were prospectively introduced in a dedicated database.

The follow-up information was collected during a 3-month period ending in December 2013. This was done through a mailed questionnaire or by a telephone interview with surviving patients, family members or the patient’s personal physician. The follow-up data included information about the level of activity, current symptoms and occurrence of late cardiac and non-cardiac events. The echocardiographic follow-up was obtained by querying the institutional echocardiographic database (Cardiology Department), patient records and correspondence to and from referring cardiologists.

The total duration of the follow-up for the entire cohort extended from 1 to 21 years for a total of 3209 patient-years, with a median of 6.9 years (IQR: 3.8–11.5 years) and was complete for 98% of the patients.

Mortality and morbidity were reported according to the latest guidelines for reporting mortality and morbidity after cardiac valve interventions [13]. Early mortality was defined as death in hospital or within 30 days. A composite cardiac and cerebrovascular outcome [major adverse cardiac and cerebrovascular events (MACCEs)] was used and included: cardiac-related mortality (sudden, unexplained death included), all cardiac and valve-related morbidity [thromboembolic events (cerebrovascular accident/transitory ischaemic accident); bleeding events; endocarditis and reoperation] and need for hospital readmission for congestive heart failure.

Statistical analysis

Continuous variables were reported as means and standard deviation and compared by Student’s t-test. Values obtained from pre- and postoperative data were compared by a paired t-test. Categorical variables were reported as percentages and were compared using χ² tests. Actuarial survival and event-free survival were plotted using the Kaplan–Meier method and comparison was made by the log-rank test.

Multivariate analysis to identify risk factors for survival was performed using Cox regression models, calculating hazard ratios (HRs) and 95% confidence intervals (95% CIs). All variables with a P-value of <0.1 in the univariate analysis entered the multivariate analysis, and in the final model we have only included those variables with a P-value of <0.05.

Since patients from Group A (with AF and/or PHT) were presented as a single covariate, AF and PHT were not included separately in the multivariate analysis to exclude multicollinearity effect. Moderate/severe MR at the follow-up was analysed as a time-dependent variable and also compared between groups with the Kaplan–Meier method (log-rank test).

To reduce the effect of selection bias and potential confounding in this observational study, we performed a rigorous adjustment in baseline characteristics (age, gender, body surface, diabetes, hypertension, chronic pulmonary obstructive disease, chronic renal disease, previous cerebrovascular accident/transient ischaemic accident and myocardial infarction) using propensity-score matching, obtaining 102 comparable pairs. The propensity scores (Ps) were estimated without regard to outcome variables, using multivariable logistic regression analysis. Patients were matched according to the Ps previously calculated, by the ‘nearest neighbour matching’ technique, using a calliper of 0.2. Each patient was matched to a single patient (no-replacement).

Statistical significance was defined as a two-tailed probability value of <0.05. The data were analysed using the statistical package programme SPSS (version 20) and the STATA software (version 11).

RESULTS

Operative data

Thirty-day mortality was 0.8% and, notably, the mortality rate for patients with isolated posterior leaflet prolapse (n = 211) was 0%. There were no significant differences between the two groups with regard to operative procedures, as well as in-hospital mortality and morbidity (Table 2).

MV repair was performed by four surgeons and achieved in 98.2% of the patients. The more demanding repairs, such as Barlow’s valves, bileaflet prolapses were more frequently done by the senior surgeon (M.A.) and the repair rate of this surgeon was 99.2%.

Patients from Group B had a greater myxomatous involvement (77.2 vs 22.8%, P < 0.001) and Barlow’s disease was present in 59 patients from this group (21.4%) against 6 patients from Group A (5.7%, P < 0.001). Isolated posterior prolapse and bileaflet prolapse was observed in 51 patients (48.1%) and 25 (23.6%) from Group A, respectively, and in 160 (58.0%) and 77 (27.9%) from Group B (P = NS), respectively.

Long-term survival and event-free survival

There were 38 late deaths during the late follow-up: 21 (2.68%/patient/year) from Group A (patients with AF/PHT) and 17 (0.75%/patient/year) from Group B (P < 0.001). Separate analysis of both markers showed a negative impact on survival on patients having either one. Patients with higher degrees of SPAP exhibited lower survival rates (P = 0.01) and this was more notable in those with a SPAP ≥ 50 mmHg (Fig. 1). Fifteen-year survival was 84.5 ± 5.3% for patients with mild degrees or absence of PHT (SPAP < 40 mmHg), 83.7 ± 9.1% for those with SPAP between 40 and 49 mmHg, 67.0 ± 12.2% for those with SPAP between 50 and 59 mmHg, and 62.4 ± 12.4% for those with SPAP ≥ 60 mmHg. Patients with AF were also at increased risk for late mortality, with an overall survival at 15 years of 59.9 ± 9.3%, compared with 86.5 ± 3.9%, P < 0.001) for those without AF (Fig. 2).

Patients with both AF and PHT (Group A) had an adjusted survival at 1, 5 and 15 years of 96.1 ± 1.9, 88.9 ± 3.4 and 67.0 ± 7.4%, respectively, compared with 99.6 ± 0.4, 97.4 ± 1.0 and 86.5 ± 3.9% for Group B patients (Fig. 3A; P < 0.001), respectively. These results were replicated in the propensity-matched population (Fig. 3B; P = 0.04).
Cox proportional hazards analysis revealed age (HR: 1.08; 95% CI: 1.04–1.12, P < 0.01), AF/PHT (HR: 2.32; 95% CI: 1.13–4.78, P = 0.02), chronic obstructive pulmonary disease (HR: 4.38; 95% CI: 1.61–11.93, P < 0.001) and preoperative renal dysfunction (HR: 8.39; 95% CI: 1.11–63.6, P = 0.04) as independent predictors of late mortality.

A composite index of MACCEs, as defined above, was further analysed. Patients from Group A incurred a greater risk of having an adverse event during the follow-up, with freedom from MACCE at 5, 10 and 15 years of 87.7 ± 3.5, 68.8 ± 6.1 and 52.7 ± 8.7%, respectively, vs 95.7 ± 1.3, 91.4 ± 2.2 and 74.5 ± 5.0%, respectively in Group B (P < 0.001) (Fig. 4A). This effect persisted in the propensity-
score analysed population, with a 15-year freedom from MACCE of 58.6 ± 7.3% in Group A and 80.5 ± 7.0% for Group B (P = 0.02) (Fig. 4B).

**Mitral valve reoperation and freedom from moderate and severe mitral regurgitation**

There were two early (in-hospital) failures of the MV repair (suture and ring dehiscence) and we were able to re-repair and preserve the valve in both cases.

Ten patients (2.6%; 5 patients in each group) required MV reoperation for significant MR late after the primary procedure. The mean time from the first surgery to reoperation was 8.6 ± 5.1 years. It was possible to re-repair the MV in 2 cases. The main intraoperative findings were as follows: marked posterior leaflet retraction conditioning lack of central coaptation, ring dehiscence, rupture of native and artificial chordae, endocarditis with severe leaflet and chordal destruction and leaflet calcification.

Freedom from mitral reoperation at 5, 10 and 15 years was 97.9 ± 1.5, 92.4 ± 4.0 and 87.3 ± 6.3%, respectively for Group A patients, and 100%, 97.5 ± 1.4 and 94.2 ± 2.7%, respectively, for Group B patients (P = 0.04). In the propensity-score matched (Ps) population, patients without AF/PHT maintained a longer period free from mitral reoperation (95.7 ± 3.0 vs 86.2 ± 6.9%), but this was not statistically significant (P = 0.24).

The degree of MR decreased substantially in both groups immediately after surgery and was maintained during the follow-up (P < 0.001). However, the mean MR was higher in...
patients from Group A (2.16 vs 1.54, P = 0.03). Freedom from recurrent moderate and severe MR was substantially lower in patients with AF/PHT (Fig. 5). At 15 years, only 65.1 ± 10.3% of these latter patients were free from relevant MR against 87.0 ± 3.8% in patients without these negative markers (P = 0.002). This finding was sustained in the Ps analysis, although it did not reach statistical significance (62.6 ± 10.9 vs 79.5 ± 9.5%, P = 0.1).

Several factors were identified on the Cox analysis to independently predict the risk of reoperation, namely P2 prolapse (HR: 0.06, 95% CI: 0.008–0.51, P = 0.03), myxomatous valves (HR: 0.07, 95% CI: 0.008–0.62, P = 0.01), shortening of chordae tendineae (HR: 9.09, 95% CI: 1.16–18.12, P = 0.04) and patients with AF/PHT (HR: 4.20, 95% CI: 1.10–11.20, P = 0.03).

Functional status and cardiac remodelling

The majority of patients remained asymptomatic or mildly symptomatic after surgery, with only 8% of the living patients being in NYHA ≥ 3 at the end of the follow-up (no difference between groups).

Both groups experienced reverse cardiac remodelling, but this effect was more evident in the group without AF/PHT (Table 3). Patients from this group had a mean decrease in the LV dimensions (diastole/systole) of 12.0 ± 7.9 and 2.7 ± 7.2 mm, respectively. In Group A, the decrease was also significant with regard to LV end-diastolic diameter, albeit less important (7.4 ± 10.1 mm), but there was an increase of LV end-systolic dimension during the follow-up (2.26 mm). The mean reduction of the LA dimension was statistically significant in both groups (P < 0.05). Both groups have also exhibited an important reduction of the mean SPAP, but the mean SPAP in Group A was near 45 mmHg, while it was 30 mmHg in Group B (P = 0.01).

LV function [EF and shortening fraction (SF)] suffered an important reduction in the early postoperative period in both groups, by comparison with preoperative levels, with a mean decrease in EF of 7.0 ± 14.7% in Group B and 11.0 ± 17.7% in Group A (P < 0.001).

Over the course of time, patients had a recovery of the LVEF; however, patients with AF/PHT displayed globally a mild LV dysfunction (EF ≤ 60%).

DISCUSSION

Our policy when approaching the MV is that every valve is potentially amenable to repair, irrespective of the pathology. We have been performing MV repair for over 30 years in over 3000 patients, which has enabled us to standardize and simplify the operative procedure, thus reducing the surgical times and improve results, as expressed in the results of the current work.

Recently, we reported the long-term outcomes of surgery for severe degenerative MR and preserved LV function in patients with no symptoms or mildly symptomatic, with a MV repair rate greater than 98% and a mortality <1%, and a long-term survival equal to the expected survival of an age- and sex-matched general population [14]. In that work, patients with AF and/or PHT were shown to be at increased risk for late survival and mitral reoperation. These results triggered a deeper evaluation of this subset of patients, which is the aim of the current analysis.

AF is the most common arrhythmia and is associated with adverse prognosis [15]. Its association with valvular heart disease is widely recognized and the relationship with MR is of utmost importance due to the high incidence of this pathology in the general population, and because MR leads to dilatation of the LA, a possible precursor of AF. Patients with degenerative MR, and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>MR (mean)</td>
<td>1.84</td>
<td>1.35, 2.33</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>7.36</td>
<td>0.49, 14.23</td>
</tr>
<tr>
<td>LVED (mm)</td>
<td>7.46</td>
<td>1.39, 13.53</td>
</tr>
<tr>
<td>LVES (mm)</td>
<td>−1.33</td>
<td>−9.91, 7.24</td>
</tr>
<tr>
<td>LVSF (%)</td>
<td>4.87</td>
<td>−4.79, 14.54</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>11</td>
<td>4.87, 32.91</td>
</tr>
<tr>
<td>SPAP (%)</td>
<td>17.78</td>
<td>1.11, 34.45</td>
</tr>
</tbody>
</table>

*Figures in bold indicate statistical significance.

MD: mean difference; CI: confidence interval; LA: left atrium; LVED: left ventricular end-diastolic diameter; LVES: left ventricular end-systolic diameter; SPAP: systolic pulmonary artery pressure.
sinus rhythm at diagnosis may develop AF in 48% of the cases at 10 years, with a linearized rate of 5% per year. Additionally, after onset of AF, an increase in cardiac mortality and morbidity are observed under conservative management [16]. Thus, the onset of AF has been considered to be a turning point in the course of MR and a useful marker of disease progression [17].

PHT has also been considered an important prognostic marker in patients with severe MR, and is usually associated with the chronic nature of the mitral disease. Preoperative PHT has also been identified as a powerful predictor of early and late survival after MV surgery and even modest increases in SPAP have been associated with adverse outcomes [18].

Both factors are included in the current guidelines as class Ila recommendation for surgery in asymptomatic patients with severe MR and preserved LV function. However, this is based on expert opinion (Level C) and supported by scarce reports [1, 2]. Our study has shown that the presence of AF and PHT in this setting, either separately or in conjunction (Group A), is associated with decreased late survival and event-free survival when compared with patients without these markers, even after successful MV repair with full restoration of competence. Notably, this effect persisted in the propensity-matched population.

Late survival also correlated with the degree of SPAP; patients with moderate or severe PHT having poorer survival. Ghoreishi et al. [19] have also recently demonstrated this relationship, but in their study even a mild PHT carried a worse prognosis. However, their study included aetiologies other than degenerative mitral disease, 57% of patients were in NYHA class III and IV and the mean EF was 52%, which means that the impact on survival could possibly not be solely attributed to the degree of PHT. In the Cox proportional analysis, patients from Group A in our study had a near two-and-half-fold increased risk of late mortality (HR: 2.32) compared with patients without AF/PHT. Of note, those patients have also experienced more relevant adverse events, integrated in the composite outcome MACCE, with nearly half of patients having at least one major event 15 years after MV surgery.

Operating on asymptomatic patients implies a greater responsibility and, for this reason, complete assessment of the durability of MV repair and of the need for mitral reoperation for recurrent MR is of paramount importance. Excellent freedom from reoperation and from moderate or severe MR at the late follow-up was seen in our patients in sinus rhythm and without severe PHT (94 and 87%, respectively) by comparison with patients with AF/PHT (87 and 65%, respectively).

AF has been considered a possible promoter of significant MR, secondary to isolated annular dilatation and atrial remodelling [19]. In a different study, we have also demonstrated that preoperative AF is a risk factor for persistence of MR in patients with moderate MR submitted to aortic valve replacement. Hence, patients in AF should also have their MV repaired in this context [20]. Shimokawa et al. [21] have also recognized AF as an independent predictor (HR: 1.67) of recurrent MR after MV repair for mitral prolapse. By contrast, AF did not affect the durability of mitral repair in a series reported by Lim et al. [17]. However, their mean follow-up time was rather short (2.8 years), which could be responsible for that conclusion. In our study, patients from both groups also had similar rates of recurrent moderate and severe MR in the first years after surgery. Nevertheless, 5 years after MV surgery, patients with AF/PHT had already shown a slight tendency for higher rates of recurrent MR and that difference became significant at 10 years after surgery. This finding was also evident in the matched population (freedom from moderate and severe MR at 15 years was 62.6 vs 79.5% in Group B).

The majority of patients remained asymptomatic or only mildly symptomatic after surgery and we might speculate that this early surgery strategy permitted preservation of a good functional capacity. Despite being a highly selected population, since all patients had ‘preserved’ LV function (EF > 60%) without signs of LV dilatation (LV < 45 mm) preoperatively, the burden of recurrent MR after surgery would prevent reverse remodelling and would favour LV dilatation and consequently LV dysfunction. Both groups exhibited a beneficial remodelling with decrease of the LV and LA dimensions. Nonetheless, this was less notorious in Group A patients. In these patients, the systolic LV dimensions actually increased comparatively to baseline values, which could be an indirect effect of the higher percentage of patients with recurrent moderate or severe MR during the follow-up, precluding reverse remodelling.

As could have been expected, patients in Group A showed a more significant reduction of SPAP, as they started with higher values. However, at the last follow-up visit, the mean SPAP was close to 45 mmHg, which means that an important number of patients maintained a relevant degree of PHT. By contrast, patients without preoperative AF/PHT had a mean SPAP on the follow-up of only 30 mmHg.

Regarding LV function, both groups experienced a significant reduction of EF and SF immediately after surgery, as is usually observed after correction of MR due to elimination of the regurgitant backflow, unveiling certain cases of preoperative LV dysfunction. This has been recently mentioned in a report by Quintana et al. [22] as the fallacy of ‘normal’ preoperative myocardial function in the presence of severe MR. LV dysfunction could persist after MV repair, impairing recovery of LV size, function and survival. These authors concluded that mitral repair should be considered before the onset of LV dilatation or PHT, even in patients with preserved EF. Varghese et al. [23] found that the presence of preoperative AF and PHT in patients undergoing MV repair increased the risk of early postoperative LV dysfunction by almost 2-fold. We have also observed a greater reduction of EF in the discharge echocardiogram in patients with AF/PHT compared with those without these prognostic markers.

STUDY LIMITATIONS

The lack of randomization is always subjected to the appearance of unmeasured confounding factors and to selection bias. We have tried to minimize this by restricting the study to patients without important symptoms (classes I and II of the NYHA) and without signs of LV deterioration, in addition to performing propensity-score matching.

Likewise, patients were deemed asymptomatic or mildly symptomatic according to the NYHA functional classification (class I or II), which has obvious intrinsic limitations. Preferably, patients should have been classified on the basis of the results of an exercise test.

CONCLUSION

We believe that our study vindicates an early surgery policy in patients with severe MR, independently of having AF/PHT. However, we have to acknowledge that this rationale may not be ‘universally’ applicable, because of the broad variability of results. In a landmark study, Rosenhek et al. [24] have elegantly demonstrated that asymptomatic patients with severe MR can be safely followed until either symptoms occur or currently recommended triggers are reached. The discussion triggered by their work is very
important because the rate of MV repair is highly variable among different centres and on average is far from the 90–95% rate of MV repair considered ideal in the guidelines for this type of patients.

The detrimental effects of AF/PHT revealed in this study in a wide set of relevant outcomes (survival, event-free survival, durability of MV repair and cardiac remodelling) question the actual guidelines. These patients represent a distinct risk cluster compared with those patients in sinus rhythm and without PHT, in whom the probability of a successful and durable repair is high with an expected mortality rate of <1% when performed at a ‘heart valve centre of excellence’. In our opinion, a class IIa indication for surgery in these patients leads to a late intervention with negative consequences. Hence, they should probably be ‘reclassified’ to a Class I recommendation.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr O. Alfieri (Milan, Italy): The problem of pulmonary hypertension is intriguing because it is having a very bad impact on the survival and the natural history. I would like to ask you whether you have criteria to know if these patients are expected to have persistent pulmonary hypertension after surgery? Also, I would like to know whether you consider pulmonary hypertension a possible contraindication in mitral valve surgery?

Dr Coutinho: In this particular setting we are talking about asymptomatic patients with preserved left ventricular function, so the probability to have irreversible severe pulmonary hypertension is less than if you have a patient with rheumatic mitral valve pathology or uncontrolled chronic MR. The interesting fact was that, even after being able to repair the valve successfully, those patients with pulmonary hypertension at the time of surgery, showed even mild to moderate degrees of pulmonary hypertension during late follow-up.

We are used to thinking that after surgery, pulmonary hypertension will reverse, but this study has shown that there are several patients in whom it did not occur. I don’t know if there is a cutoff value to not operate these patients, but if those doubts are of concern, you can always perform a right catheterization with vasoactives and see if it reverses or not. However, this is a very specific population, so we didn’t find any patients in that condition.

Dr Alfieri: And certainly the survival is lower in these patients with pulmonary hypertension. Can you tell us the mode of death, why they die and how they die?

Dr Coutinho: Unfortunately we don’t have data regarding the causes of death, namely if it was a cardiac or a noncardiac death. Therefore, we have only used overall survival. Nevertheless we can speculate that there is a high percentage of patients that could have died from cardiac causes.
Dr M. Solinas (Massa, Italy): You say that we don’t have to wait in a symptomatic patient for the onset of atrial fibrillation or pulmonary hypertension. So we need other indicators, really early indicators, of significant mitral regurg. That could be BNP, the size of the left atrium. Are there some of those indicators that are used in your daily practice to give the indication for surgery?

Dr Coutinho: Those indicators are recent ones. We are talking about a population that was operated during the last 20 years, until 2012. But I agree completely with you. We should use more indicators like BNP, left atrium volume, and even an exercise test to check the pulmonary hypertension during exercise, all of which are very important.

Another important aspect of this study is that these patients with AF and pulmonary hypertension have shown lesser durability of mitral valve repair, and this was strange for us, because we were not expecting that result, and that needs further evaluation. This study reinforces that these patients should go promptly to surgery to avoid these negative events.