Pre-operative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation

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Aims To examine the impact of pre-operative atrial fibrillation (AF) on the outcome of mitral valve repair (MVR) for degenerative mitral regurgitation (MR).

Methods and results Among 392 patients with moderate to severe MR who underwent MVR between 1991 and 2002, 283 patients with isolated degenerative MR were followed for 4.7 ± 3.3 years. Of 27 deaths, nine were due to cardioembolic events and four were due to left ventricular (LV) dysfunction. When compared with patients with pre-operative AF, those with sinus rhythm (SR) had better survival (96 ± 2.1 vs. 87 ± 3.2% at 5 years, P = 0.002) and higher cardiac event-free rates (96 ± 2.0 vs. 75 ± 4.4% at 5 years, P < 0.001). In patients with pre-operative SR, observed and expected survival were similar (P = 0.811). Cox multivariable regression analysis confirmed AF [P = 0.027, adjusted hazard ratio (AHR) 2.9] and age as independently predictive of survival, and AF (P = 0.002, AHR 3.1), New York Heart Association Class, and LV fractional shortening as independently predictive of cardiac event.

Conclusion Death due to LV dysfunction was not frequent and cardioembolic events due to AF were the leading cause for cardiac death. Pre-operative AF became a strong independent predictor of survival and morbidity. Patients with pre-operative SR had excellent prognosis. The benefits of preventing cardioembolic events due to AF validate the indication of MVR for patients with high risk for AF.

KEYWORDS
Atrial fibrillation; Echocardiography; Mitral valve repair

Introduction

The ACC/AHA guidelines designate mitral valve surgery in non-ischaemic mitral regurgitation (MR) for patients with even slight symptoms and patients with mild left ventricular (LV) dysfunction as class I indication. In the meantime, there has been a consensus without obvious evidence that onset of episodic or chronic atrial fibrillation (AF) is an indication for surgery. Recent studies on the natural history of degenerative MR have clarified the significance of AF in conservative management of MR and reinforced this consensus.

However, previous studies on the outcome of mitral valve repair (MVR) for MR did not find significant difference in survival between patients with pre-operative sinus rhythm (SR) and AF, and even recent studies on the influence of AF were not able to demonstrate the independent significance of AF for survival. All these studies on AF included patients with ischaemic MR. The aetiology of MR is known to be important in the analysis of outcome of MVR. As patients with ischaemic MR have poor LV function and poor prognosis, there is a possibility that the influence of LV function on survival is overestimated.

Our recent study on LV function after MVR for degenerative MR again clarified the ability of the evolved and matured technique of MVR to preserve post-operative LV function. Considering the aforementioned facts, the influence of preservation of LV function by MVR and the absence of prosthetic valve on the importance of pre-operative AF should be examined.

In this study, we focused on a series of MVRs for isolated degenerative MR conducted after 1991 and investigated the significance of AF on the outcome of MVR. On the basis of these results, we propose the optimal timing of MVR for degenerative MR.

Methods

Patients

Among 406 consecutive patients aged ≥20 with moderate to severe MR without concomitant mitral stenosis who underwent surgery for...
MR at our institution between 1 October 1991 and 30 September 2002, 392 (96.6%) patients underwent MVR. The aetiologies of regurgitation were as follows: degenerative (including fibroelastic deficiency, billowing valves, and healed infective endocarditis) in 331, rheumatic in 19, ischaemic in 16, dilated cardiomyopathy in five, active infectious endocarditis in four, congenital in six, trauma in four, others in two, and secondary repair after the previous MVR in five.

Among 331 patients with MR due to degenerative pathology, 34 patients were excluded because of concomitant surgical procedures comprising aortic valve replacement or plasty, coronary artery bypass grafting, closure of atrial septum defects, closure of ventricular septum defects, Bentall’s procedure, and ligation of patent ductus arteriosus (17, 7, 5, 2, 2, and 1 patients, respectively).

Among the remaining 297 patients, 14 patients (4.7%) were confirmed to be unsuitable for MVR intraoperatively and converted to mitral valve replacement. Finally, 283 patients comprised our study population. Partial analyses of part of this population have been published previously.11,13

Follow-up
Follow-up data were collected through review of the medical records of our institution and telephone contact with the referring physicians and/or patients. The follow-up rate until 30 September 2002 or death was 100% for a median of 4.1 years (interquartile range, 2.0–7.3).

We assessed overall mortality, cardiac events, recurrence of severe MR (MR area >8.0 cm²), and AF after surgery.

The histories of cardioembolic events were based on the diagnosis in clinical records of our hospital or the referral institute, and were cerebral infarction confirmed by diagnostic imaging in all cases. The histories of major haemorrhage were defined as haemorrhage requiring hospitalization, and were due to gastrointestinal bleeding in all cases.

Death due to LV dysfunction was defined as death due to congestive heart failure or sudden death of unknown aetiology. Valve-related complication was defined as cardioembolic events, major haemorrhage related to anticoagulation or infective endocarditis. Cardiac death was defined as death due to LV dysfunction or valve-related complications. Cardiac event was defined as cardiac death, re-operation, valve-related complication, and hospitalization due to congestive heart failure.

Of the 27 deaths, the cause of 24 deaths was confirmed with the clinical records of our hospital or the referral institute, the cause of two deaths was confirmed with history taken from the family because of destruction of clinical records due to expiration of the preservation period, and one sudden death of unknown origin was classified as death due to LV dysfunction in order not to underestimate the number of deaths due to LV dysfunction.

Surgical procedures
Prolapse of the posterior leaflet was repaired with sliding plasty or leaflet resection in most cases and some required chordal replacement with expanded polytetrafluoroethylene (ePTFE) sutures. Most cases of prolapse of the anterior leaflet were managed with ePTFE sutures.14 The majority of patients also had a ring or band annuloplasty. Since February 1996, we have performed physiological remodelling annuloplasty that we developed to retain the shape of the anterior leaflet.15 Since 1993, intraoperative transoesophageal echocardiography has been performed routinely, and repair was redone when more than mild regurgitation was detected.

Echocardiographic examinations
All patients had transthoracic echocardiography before surgery. LV and left atrial dimensions were obtained by using M-mode echocardiography, guided by two-dimensional imaging. Estimated right ventricular systolic pressure was calculated as the sum of tricuspid jet gradient calculated using a modified Bernoulli equation with 10 mmHg added for the estimated right atrial pressure.16 For those patients who underwent re-operation during the follow-up period, the latest echocardiogram data before the secondary surgical intervention were used.

Statistical analysis
All data are expressed as means ± SD. Comparison of variables between patients with SR and AF before surgery was performed by unpaired Student’s t-test. The difference in incidence between two groups was evaluated using Fisher’s exact test. For overall mortality and cardiac event-free rate, the Kaplan–Meier method was used to estimate the absolute risk, the length of time to a first event was compared with use of the two-sample log-rank test, and the relative risk was calculated with the Cox proportional-hazards model. Observed survival was compared with expected survival based on age- and sex-matched actual data from the 1996 Japanese population and tested with the one-sample log-rank test.

Cox regression analysis was used to assess the effect of pre-operative variables on overall mortality and cardiac event-free rate. The accelerated failure-time model17,18 with Weibull distribution, implemented with the LIFEREG procedure (SAS), which allowed the direct incorporation of interval-censored data, was used to predict post-operative cardiac rhythm using pre-operative variables and to analyse the relationship between pre-operative AF and recurrence of MR.

Age, New York Heart Association (NYHA) Class, cardiac rhythm, LV fractional shortening, LV end-diastolic diameter, LV end-systolic diameter, left atrial diameter (LAD), and right ventricular systolic pressure were included in the multivariable model building. Score statistic selection was used to find the best model in all the possible 2^k (~236) multivariable models of Cox regression analysis. Backward elimination of non-significant variables was conducted in multivariable models of the accelerated failure-time analysis, where P < 0.05 was regarded significant.

To assess the assumption of proportional hazards in Cox regression analysis, we divided the population into two groups according to each variable and produced the graphs of −log(log(survival)) against log(time). To assess the linearity assumption for continuous variables, we divided the population into five categories according to each continuous variable and constructed the graphs of hazard ratio (HR) and its 95% confidence interval (CI) among these five categories. None of the graphs contradicted the assumptions.

All comparisons were two-tailed. The accelerated failure-time analysis and Cox regression analysis were performed with SAS statistical software (SAS Institute Inc. release 8.02) and the other analyses were performed with SPSS statistical software (SPSS Inc. release 11.0.1J).

Results
Patient characteristics
The age was 55 ± 14 (range 21–82 years), and 180 (64%) of the patients were men. Before surgery, 79% of patients were in NYHA Class I–II, the LV fractional shortening was 37 ± 7.2% and 33 (12%) patients had LV fractional shortening of <29%.

Comparison of patients with SR and AF before surgery
Before surgery, 154 (54%) patients were in SR. The sex distribution was similar in both groups. Patients with AF were older, had more severe symptoms, had greater dilatation of left atrium and LV, and had more severe LV dysfunction and pulmonary hypertension (Table 1).
Patient survival

There were 27 deaths (Table 2). Among five (1.8%) hospital deaths occurring within 90 days after the procedures, one (0.6%) death among 154 patients with pre-operative SR was due to septic shock and four (3.1%) deaths among 129 patients with pre-operative AF were due to pneumonia. Among 22 late deaths, five had pre-operative SR; and the causes of death were malignant disease in two deaths, infective endocarditis in one, congestive heart failure in one, and pneumonia in one. The remaining 17 deaths had pre-operative AF; the causes of death were cardioembolic events in nine, malignant disease in four, congestive heart failure in two, sepsis in one, and sudden death of unknown aetiology in one. Of the nine patients who died of cardioembolic events, eight had AF and one was in junctional rhythm at the last follow-up. Of the eight patients with AF, six patients received coumarin and two received aspirin. The patient in junctional rhythm did not receive anticoagulation because of gastrointestinal bleeding. As to the prescription at the time of last follow-up of the whole population, 74 patients received coumarin, 64 patients received aspirin, and 12 patients received antiarrhythmic drugs. Of the 12 patients taking antiarrhythmic drugs, three patients still had paroxysmal AF.

The overall survival rate was 92 ± 1.9% at 5 years and 81 ± 3.9% at 10 years. A significant difference in survival was observed between patients with pre-operative SR (96 ± 2.1% at 5 years and 88 ± 5.8% at 10 years) and AF (87 ± 3.2% at 5 years and 74 ± 5.5% at 10 years) (P = 0.002, HR 3.8) (Figure 1). When compared with their respective expected survivals, no significant difference was observed in patients with pre-operative SR (standardized mortality ratio 0.91, P = 0.811), whereas for those with pre-operative AF, excess mortality was noted (standardized mortality ratio 2.35, P < 0.001) (Figure 2).

The results of univariate and multivariable analyses on predictors of survival are presented in Table 3. By multivariable analysis, pre-operative AF (adjusted HR (AHR) 2.9, 95% CI 1.1–7.2) and age (P = 0.009, AHR per 5 year increment 1.3, 95% CI 1.1–1.6) were identified as independent predictors. For reference, when multivariable analysis was performed, including also NYHA and LV fractional shortening which were demonstrated to be independent predictors of survival in reports that included mitral valve replacement for degenerative MR, age (P = 0.008, AHR per 5 year increment 1.3), AF

Table 1  Characteristics of patients

<table>
<thead>
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<th>SR</th>
<th>AF</th>
<th>P-value</th>
<th>Overall</th>
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<tr>
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<td>154</td>
<td>129</td>
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<td>283</td>
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<tr>
<td>Age (years)</td>
<td>52 ± 14</td>
<td>59 ± 13</td>
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<td>55 ± 14</td>
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<td>Sex distribution (% male)</td>
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<td>79</td>
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<td>LV fractional shortening (%)</td>
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<td>LV diastolic diameter (mm)</td>
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<td>LAD (mm)</td>
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<td>53 ± 10</td>
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<td>48 ± 9.7</td>
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<tr>
<td>Right ventricular systolic pressure (mmHg)</td>
<td>38 ± 15</td>
<td>42 ± 14</td>
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Table 2  Causes of death

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<td>Late mortality</td>
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<tr>
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Figure 1  Survival.
(P = 0.080, AHR 2.4), LVFS (P = 0.177, AHR per 5% increment 0.94), and NYHA (P = 0.642, AHR 1.2) were the best multivariable model. When the nine deaths due to cardioembolic events were eliminated, no significant difference in survival was observed between patients with pre-operative SR and those with AF (P = 0.109).

**Re-operation**

Five patients required repeat MVR and 12 patients underwent mitral valve replacement. Freedom from re-operation was 94 ± 1.9% at 5 years and 87 ± 3.3% at 10 years. Of the 17 cases of re-operation, four were patients with pre-operative SR. A significant difference in freedom from re-operation was observed between patients with pre-operative SR (98 ± 1.5% at 5 years and 94 ± 3.3% at 10 years) and those with AF (89 ± 3.5% at 5 years and 80 ± 5.3% at 10 years) (P = 0.022, HR 3.4, 95% CI 1.1–10.5).

**Cardiac events**

Sixteen patients with pre-operative AF had cardioembolic events. One patient with pre-operative SR had a cardioembolic event due to infective endocarditis. Major haemorrhage related to anticoagulation occurred in five patients, all occurred in patients with pre-operative AF and none was fatal. A significant difference in freedom from valve-related complication was observed between patients with pre-operative SR (100% at 5 year and 95 ± 4.7% at 10 years) and those with AF (85 ± 3.6% at 5 years and 77 ± 5.1% at 10 years) (P < 0.001, HR 23, 95% CI 3.1–171).

Eight patients with pre-operative AF and six patients with pre-operative SR needed hospitalization due to congestive heart failure. No significant difference in freedom from hospitalization due to congestive heart failure was observed between patients with pre-operative SR (98 ± 1.3% at 5 years and 86 ± 7.0% at 10 years) and those with AF.
Cardiac event-free rates were 86\% + 4.2\% at 5 years and 75\% + 4.4\% at 10 years. A significant difference in cardiac event-free rate was observed between patients with pre-operative SR (96\% + 2.0\% at 5 years and 78\% + 8.3\% at 10 years) and AF (75\% + 6.2\% at 5 years and 57\% + 6.2\% at 10 years) (P = 0.001, HR 4.0, 95\% CI 2.0–8.2) (Figure 3). The results of univariate and multivariable analyses on predictors of cardiac events are presented in Table 3. By multivariable analysis, pre-operative AF (P = 0.002, AHR 3.1, 95\% CI 1.5–6.5), NYHA (P = 0.013, AHR 2.1, 95\% CI 1.2–3.9), and LV fractional shortening (P = 0.036, AHR per 5\% increment 0.82, 95\% CI 0.68–0.99) showed significant correlation.

Post-operative cardiac rhythm

Before surgery, 154 patients were in SR, 20 had intermittent AF, and the remaining 109 had chronic AF. After excluding 16 patients who underwent maze procedure or cryosurgery and six patients who died within 6 months after operation, 261 patients were included in the analysis of post-operative cardiac rhythm. The rate of maintaining SR in patients with pre-operative SR was 87\% (132/152) and the rate of reversion to SR was 53\% (10/19) in patients with intermittent AF and was 19\% (17/90) in patients with chronic AF during a mean of 4.4 ± 3.1 years after surgery.

By multivariable analysis, independent association of pre-operative LAD, pre-operative AF, and age with post-operative AF was demonstrated (Table 4). The estimated acceleration factor of 5 mm increment of LAD after adjustment for pre-operative AF and age was 11 (P = 0.001, 95\% CI 2.6–44).

Figure 4 shows that when pre-operative LAD exceeds 45 mm, the rate of SR after surgery was significantly lower when compared with patients with LAD ≤ 45 mm (58 vs. 20\%, P < 0.001).

Post-operative echocardiogram

After surgery, 153 patients with pre-operative SR and 122 patients with pre-operative AF had echocardiographic data at a median of 2.5 years (interquartile range 0.9–5.4) after operation. The rate of freedom from severe MR and re-operation was 96\% in patients with pre-operative SR and 87\% in patients with pre-operative AF. By univariate analysis, the estimated acceleration factor of pre-operative AF for the recurrence of severe MR or re-operation was 4.2 (P = 0.035, 95\% CI 1.1–16).

After excluding those without post-operative echocardiographic data at least 6 months after operation and those who underwent re-operation within 6 months after operation, 227 patients with post-operative echocardiographic data at a median of 3.6 years (interquartile range 1.8–5.8) after operation were included in the analysis of LV fractional shortening. Pre-operative and post-operative LV fractional shortenings were 38 ± 7.2 and 33 ± 7.8\%, respectively.

Discussion

The present study showed improved survival and morbidity when surgery was performed for the patients in SR.
Furthermore, AF was the most significant factor affecting survival and morbidity in a multivariable analysis, adjusting for all independent predictors. Remarkably, this advantage was confirmed in comparison with expected survival, showing no excess post-operative mortality for patients with pre-operative SR, in contrast to excess mortality for patients with pre-operative AF. Cardiac event-free rate was also excellent in patients with pre-operative SR. These data suggest that the timing of MVR should be during SR. However, previous studies on mitral valve surgery for non-ischaemic MR demonstrated that LV ejection fraction or NYHA Class to be the most significant factor affecting survival in multivariable analysis. The background of this discrepancy should be considered.

The difference between previous studies and our study

Our previous report demonstrated that earlier timing of MVR, which is superior to mitral valve replacement in preservation of LV function, successfully avoided post-operative LV dysfunction. Consistent with this report, only four out of 14 cardiac deaths were due to LV dysfunction. Moreover, nine were due to cardioembolic events, all of which occurred in patients with pre-operative AF.

When compared with the report by Enriquez-Sarano et al., which followed 409 patients who underwent MVR or replacement for non-ischaemic MR for ~5 years and described in detail both the causes of death and the predictors of post-operative survival, death due to LV dysfunction was markedly lower in our study: four (1.4%) patients in our study and 39 (9.5%) patients in their study, and death due to valve-related complication was lower in our study: nine (3.2%) patients in our study and 28 (6.8%) patients in their study. As a result, the contribution of cardioembolic events to mortality increased in our study (Table 5). The results of their sub-study, focusing on 195 patients who had MVR yielded almost intermediate findings: nine (4.6%) died of LV dysfunction and eight (4.1%) died of valve-related complication during a mean follow-up of ~4 years (Table 5).

Consistent with a previous report on predictors of post-operative congestive heart failure, pre-operative AF did not show correlation with post-operative congestive heart failure but showed significant correlation with post-operative cardioembolic events. These data suggested that effective avoidance of death due to LV dysfunction enabled the excellent prognosis of patients with pre-operative SR and increased impact of cardioembolic events on post-operative survival. In addition, because of the absence of a prosthetic valve, AF was the leading cause of cardioembolic events. These observations explain the reason why pre-operative AF became the key determinant of survival and morbidity after MVR.

Rationale for MVR for patients with high risk for AF

Having successfully avoided post-operative LV dysfunction and prosthetic valve-related complications, it is important to identify effective methods to prevent cardioembolic events through prevention of post-operative AF.

The role of mitral valve surgery in preventing development of new AF has been reported. Considering the low possibility of reversion to SR after surgery, which is consistent with previous reports, our study demonstrated that the onset of AF is not effective to prevent post-operative AF. As suggested in previous reports using logistic regression analysis, our multivariable analysis with direct incorporation of interval-censored data of post-operative cardiac rhythm also identified pre-operative LAD as the optimal indicator to avoid post-operative AF.

According to our study, our study reported no excess mortality when compared with the general population was observed. Survival and cardiac event-free rates at 5 years were as high as 96 ± 2.1 and 96 ± 2.0%, respectively, valve-related complication occurred in only one (0.7%) patient and cardiac death occurred in only two (1.3%) patients during a mean of 4.5 ± 3.1 years. Good estimation of feasibility with echocardiography and low operative mortality for MVR has also been reported.

According to the outcome of conservative management of patients in SR with moderate to severe MR, high rate of developing AF; 5% per year or 30–48% at 10 years, the independent association between LAD and new onset of AF, and independent significance of LAD and onset of AF on cardiac mortality and morbidity have been reported.

All the aforementioned arguments concerning surgical and conservative management of moderate to severe MR demonstrated a strong incentive to perform MVR for patients with high risk for AF, which can be estimated with LAD.

Limitation

Some reports have indicated the effectiveness of the maze procedure in preserving SR after surgery. However, we did not study the prognosis of the maze procedure. The effect of maze procedure on the prognosis of MVR in patients with AF should be examined.

From the aspect of freedom from severe MR and re-operation, significantly better durability of MVR in patients with pre-operative SR was observed. Though this difference could be because of preserved morphology of...
mitral valve by earlier surgery, a prospective study with periodic echocardiography is needed to clarify the detail. We found that an LAD ≥ 45 mm in Japanese patients predicts a lower possibility of post-operative SR, and this value is lower than previous reports. 4,5 Echocardiographic measurements in Japanese patients may not be applied directly to patients in other countries because the normal size of the heart may be different.

Conclusion
Post-operative LV function was preserved with MVR and death due to LV dysfunction after MVR was effectively avoided. Consequently, increased significance of pre-operative AF, the major cause of cardioembolic events in patients without prosthetic valve, has been demonstrated. Taking into consideration the high incidence of AF and worse prognosis after the onset of AF in conservative management, low possibility of reversion to SR after surgery, and no excess post-operative mortality for patients with pre-operative SR, the benefits of preventing cardioembolic events due to AF validate the indication of MVR for patients with high risk for AF, which can be estimated by LAD.

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References