Impact of Ejection Fraction on Long-Term Outcome After Elective Aortic Valve Replacement in Octogenarians With Aortic Stenosis

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Background: Aortic stenosis (AS) is increasingly common in the elderly population. A recent invention of transcatheter aortic valve implantation tends to tilt the risk-benefit balance to favor earlier elective intervention for AS. Hence, decision making for elective intervention in octogenarians gradually becomes important. However, the outcome after elective aortic valve replacement (eAVR) has not been evaluated adequately. This study aimed to identify risk factors after eAVR in octogenarians and investigate their influence on long-term outcome.

Methods and Results: One hundred and thirty-seven consecutive Japanese octogenarians with AS who underwent eAVR were studied. The mean follow-up period was 35±22 (range, 0–88) months. Long-term overall survival rates after eAVR were 92.0%, 85.2% and 75.5% at 1, 3 and 5 years, respectively. Cox proportional hazards model identified age [hazard ratio (HR) 1.23; 95% confidence interval (CI) 1.07–1.43; P<0.01] and ejection fraction (EF) <50% (HR 3.38; 95%CI 1.34–8.52; P<0.01) as the risk factors of mortality. Post-eAVR survival rates in octogenarians with an EF ≥50% and <50% were 97.3% and 70.4% at 1 year, 90.1% and 65.3% at 3 years, and 84.3% and 39.2% at 5 years, respectively (P<0.0001).

Conclusions: Octogenarians with preserved LV systolic function before surgery have favorable long-term survival after eAVR. However, an EF <50% influences the mortality in octogenarian patients. Therefore, eAVR should be considered for octogenarians with AS before the progression of LV impairment. (Circ J 2012; 76: 1761–1767)

Key Words: Aortic stenosis; Echocardiography; Elderly; Left ventricular dysfunction; Surgery

In recent years, the continuous expansion of the elderly population in developed countries has resulted in a significant increase in the number of people aged over 80 years. Aortic stenosis (AS) is increasingly being diagnosed in octogenarians along with aging of the population and development of non-invasive diagnostic techniques, particularly 2-dimensional (2D) color Doppler echocardiography.1-4 The ACC/AHA guidelines states that the risk-benefit balance might change to favor earlier intervention for AS as improved valve substitutes are developed and methods of valve replacement become safer.5 The current trend thus suggests that decision making on elective intervention in elderly patients with AS is gradually becoming more important due to recent invention of transcatheter aortic valve implantation. However, decision making on surgical intervention in elderly patients with AS is often difficult, even as an elective procedure. A study estimated that surgery was denied in 33% of elderly patients with AS, for reasons such as advanced age and left ventricular (LV) systolic dysfunction [ejection fraction (EF) <50%].6 Surgical aortic valve replacement (AVR) in octogenarians has been performed with acceptable 5-year survival, which varied between 52% and 73% in selected individuals.7-14 In contrast, most of the previous studies included subjects who underwent non-elective procedures,7,11-13 which is known to be a strong risk factor of operative mortality in octogenarians.11,15,16 Therefore, the long-term outcome and risk factors of elective AVR (eAVR) in octogenarians have not been adequately evaluated. Furthermore, the subjects of most previous studies were American and European octogenarians. Because there are racial differences in cardiac size and function,17 these racial features need to be taken into consideration when considering surgical intervention in Japanese octogenarians with AS. The purpose of the present retrospective study was to identify risk factors associated with post-eAVR mortality and investigate how they affect the long-term outcome after eAVR in Japanese octogenarians with AS.

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Methods

Study Population
A retrospective study was conducted with 137 consecutive Japanese octogenarians who underwent eAVR for AS between July 2004 and October 2010 at the Department of Cardiovascular Surgery of the Sakakibara Heart Institute, Tokyo, Japan. Preoperative demographic and perioperative data were retrieved from our computerized database.

The primary end point was survival, which was obtained by reviewing inpatient records and follow-up records at outpatient clinics attended by discharged patients, and telephone interviews for a longer term outcome of 1 year or longer after surgery. This study was approved by the human ethics committee of the Sakakibara Heart Institute. Informed consent regarding participation in any clinical research was obtained from all subjects through the Sakakibara Heart Integrative Profile when patients were admitted to our hospital, and their data was available for this study.

Echocardiography
Comprehensive 2D and Doppler transthoracic echocardiography was performed at the Sakakibara Heart Institute in all patients within 2 months before and 1 week after AVR. A mid-term follow-up echocardiography was performed at random from 3 months to 1 year after hospital discharge. A long-term follow-up echocardiography was performed routinely at 1 year after and beyond.

Peak transaortic velocity (Vp) and mean transaortic pressure gradient (MPG) were measured by continuous wave Doppler using a multiwindow approach. The aortic valve area (AVA) and actual effective orifice area (EOA) were calculated by the continuity equation. Very severe AS was defined as Vp >5.0 m/s, MPG >60 mmHg, and AVA <0.60 cm². Indexed AVA and EOA were defined as AVA and prosthetic EOA, respectively, divided by body surface area (BSA), and prosthesis-patient mismatch (PPM) was classified as severe (Indexed EOA ≤0.60 cm²/m²), moderate (0.60 < Indexed EOA ≤0.85 cm²/m²) or non-significant (Indexed EOA >0.85 cm²/m²).²⁰-²⁶ The LV mass was calculated using the M-mode method by the following formula: 1.04×[(LV internal dimension+posterior LV wall thickness+interventricular septal thickness)³ – LV diastolic diameter]×0.8×0.6.²⁷ The LV end-diastolic volume, end-systolic volume and EF were calculated by using the biplane Simpson’s rule on 2D echocardiography. The peak mitral inflow velocity of the early rapid filling wave (E) was measured by pulsed wave Doppler. The peak mitral-annulus longitudinal velocity of the early diastolic wave (e’) was measured by tissue Doppler. The ratio between E and e’ (E/e’) was used as a parameter of LV diastolic function.

Surgical Procedures
All surgical records were reviewed to obtain information on the type and size of the aortic valve prosthesis and concomitant coronary artery bypass graft surgery (CABG) or valvular operations other than AVR.

eAVR was defined to be scheduled and to be performed more than 24 h after admission. In the present study, using bioprosthesis was indicated on the basis of the guideline. The patients who had a small aortic annulus (less than 18 mm) were excluded from selection of using bioprosthesis.

Anticoagulation After Operation
The patients with a mechanical prosthesis underwent permanent anticoagulation with warfarin therapy and the patients with a bioprosthesis underwent persistent anticoagulation for 3 months, in which both international normalized ratio (INR) were maintained from 2.0 to 3.0 according to the guideline.²⁹ Anticoagulation was used in patients with atrial fibrillation 3 months after their operation using bioprosthesis and beyond, in which the INR was also maintained from 2.0 to 3.0.

Statistical Analysis
Data are presented as mean±standard deviation for continuous variables, or as a number with percentage for categorical variables. To determine the predictors of mortality, the Cox proportional hazards model was used to estimate the risk for mortality associated with the following variables: age,⁴,¹¹,¹³ NYHA III or IV, diabetes mellitus,⁴,¹³ renal impairment (GFR <50 ml/min.),⁴,¹¹,¹³ chronic obstructive pulmonary disease,⁴,¹² EuroSCORE II,⁴,¹³ EF <50%,⁴,¹³,¹⁶,¹⁸,¹⁹,²⁰,²¹ CABG,²⁰,²¹ very severe AS (Vp >5.0 m/s, MPG >60 mmHg, and AVA <0.60 cm²),¹⁸,¹⁹ and PPM (severe: Indexed EOA ≤0.60 cm²/m², moderate or severe: Indexed EOA ≤0.85 cm²/m²).²⁰-²⁶ The variables with probability values less than 0.25 in univariate analyses were included in the multivariate analysis.³⁵

Follow-up survival curves were estimated by using the Kaplan-Meier method. For each patient included in this study, the corresponding mean age- and gender-specific annual mortality rate of the Japanese general population was obtained. These data were taken from Japanese life tables from 1962 to 2009, which were provided by the Ministry of Health, Labour and Welfare. On the basis of these mortality data, the probability of cumulative expected survival was determined for the beginning of each year, and plotted as an expected survival curve.

Two-tailed probability values less than 0.05 were considered statistically significant. Statistical analysis was performed using the SPSS17.0 software (SPSS Inc, Chicago, IL, USA).

Results

Clinical Characteristics
Baseline characteristics and operative and postoperative data are outlined in Tables 1.2. The mean age of the patients was 83±2 years (range, 80–93 years). Sixty-nine percent (n=95) of the patients were females. Careful medical interview and examination revealed some symptoms in all patients. The study population included patients who underwent a previous cardiac operation (5%, n=7), NYHA class III or IV (48%, n=66), moderate or severe aortic regurgitation (7%, n=9) and very severe AS (53%, n=72). The mean EuroSCORE II was 7.9±7.4%. Twenty-nine patients (21%) received a mechanical valve. Sixty-three (46%) had concomitant CABG, and 7 patients required CABG predominantly. Twenty (15%) had concomitant valvular operations other than AVR. After AVR, 59 patients (43%) had moderate or severe PPM, including 4 severe PPM (3%). Thirty-one patients (23%) had atrial fibrillation (AF), including 8 (6%) with new onset after AVR.

In-Hospital Mortality and Postsurgical Complications
In-hospital mortality and early postsurgical complications are listed in Table 3. In-hospital deaths occurred in 5 patients (4%). The 5 deaths included 4 cardiac deaths due to congestive heart failure in 3 patients (2%) and acute myocardial infarction in 1 patient (1%), and 1 non-cardiac death due to acute cholecystitis (1%). Of the 5 patients who died, 3 patients (2%) had combined AVR-CABG. Tachycardiac arrhythmias occurred in 14 patients (14%), 13 of whom had AF and 1 had ventricular tachycardia. Stroke occurred in 4 patients (3%) and cerebral hemorrhage in 1 patient (1%). Eighty-five patients (62%) had no postoperative complications.
Long-Term Outcome and Risk Factors of Mortality

Clinical follow-up data on the primary end point was available for all 137 patients (100%). During an estimated follow-up period of 35 ± 22 months (range, 0–88 months), a total of 18 patients had died after hospital discharge. Of these 18 patients, 5 patients (28%) died due to a cardiac cause, including 3 sudden deaths, 5 patients (28%) due to a cerebrovascular cause (3 strokes, 1 subdural hematoma due to falling and 1 subarachnoid hemorrhage) and 8 patients (44%) due to miscellaneous causes (3 malignancies, 2 chronic renal failures, 2 infections and 1 senility). The estimated overall survival after eAVR was 92.0% at 1 year, 85.2% at 3 years, and 75.5% at 5 years (Figure 1), which was similar to the expected survival curve.

Table 4 shows the results of univariate and multivariate analyses of risk factors for mortality. The Cox proportional hazards model revealed that age [per 1-year increment: hazard ratio (HR) 1.23; 95% confidence interval (CI) 1.07–1.43; P<0.01] and EF <50% (HR 3.38; 95% CI 1.34–8.52; P<0.01; Figure 2) were independent negative predictors for long-term survival. Survival rates following eAVR in octogenarians with EF ≥50% (n=110) and <50% (n=27) were 97.3% and 70.4% at 1 year, 90.1% and 65.3% at 3 years, and 84.3% and 39.2% at 5 years, respectively (P<0.0001).

**Serial Echocardiographic Data**

All 137 patients completed echocardiography within 2 months before and 1 week after AVR (100%). Mid- and long-term follow-up echocardiographic data were available for 88 pa-
patients (64%) and 110 patients (80%), respectively (Table 5).

The preoperative echocardiographic data [mean±standard deviation (range)] showed an EF of 58±11% (24–80%), LV mass of 198±54 (80–341), E/e’ of 1.34–7.91, AVA of 0.59±0.19 cm² (0.21–1.0 cm²), Vp of 5.1±1.1 m/s (2.3–7.6 m/s) and a MPG of 60±26 mmHg (11–148 mmHg). Although the mean EF did not change significantly 1 week after AVR compared to baseline, it increased significantly at follow up. Of 22 patients with an EF <50% at the performed follow-up echocardiography, all patients had improved LV systolic function at follow up, with 17 patients (77%) showing an improvement by 10% or more. The mean LV volume, mean LV mass, mean Vp, mean MPG and mean RVSP were significantly reduced 1 week after AVR and the improvements were maintained at follow up. The mean E/e’ did not change at follow up compared to baseline.

**Discussion**

Accompanying the continuous expansion of the elderly population, AS has become an increasingly common cardiovascular disease in octogenarians.1–4 Because the risk-benefit balance

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**Table 4. Univariate and Multivariate Analyses of Risk Factors for Mortality**

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95%CI]</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.19 [1.04–1.37]</td>
<td>0.01</td>
</tr>
<tr>
<td>NYHA III-IV</td>
<td>2.38 [0.99–5.66]</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.26 [1.34–7.91]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Renal impairment (GFR &lt;50 ml)</td>
<td>1.38 [0.58–3.25]</td>
<td>0.47</td>
</tr>
<tr>
<td>COPD</td>
<td>0.53 [0.07–3.98]</td>
<td>0.54</td>
</tr>
<tr>
<td>EuroSCORE II</td>
<td>1.05 [1.01–1.09]</td>
<td>0.04</td>
</tr>
<tr>
<td>EF &lt;50%</td>
<td>4.70 [2.07–10.70]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>1.49 [0.65–3.37]</td>
<td>0.34</td>
</tr>
<tr>
<td>Very severe AS</td>
<td>0.47 [0.18–1.28]</td>
<td>0.14</td>
</tr>
<tr>
<td>PPM</td>
<td>1.83 [0.42–8.02]</td>
<td>0.42</td>
</tr>
<tr>
<td>Severe</td>
<td>1.11 [0.49–2.52]</td>
<td>0.81</td>
</tr>
</tbody>
</table>

The definition of very severe AS: Vp >5.0 m/s, MPG >60 mmHg, and AVA <0.60 cm².
The definition of severe PPM: Indexed EOA ≤0.60 cm²/m², and moderate or severe PPM: Indexed EOA ≤0.85 cm²/m².
HR, hazard ratio; CI, confidence interval; EOA, effective orifice area. Other abbreviations as in Tables 1,2.
might change to favor earlier elective intervention in octogenarians with AS due to the development of valve intervention, decision making on elective intervention in octogenarians is gradually becoming more important. Furthermore, the subjects in most of the previous studies were American and European octogenarians, and it is necessary to address racial differences when making a decision of eAVR in Japanese octogenarians with AS. The purpose of the present retrospective study was to identify risk factors associated with eAVR and investigate how they affect the long-term outcome after eAVR in Japanese octogenarians with AS.

Long-Term Outcome After eAVR
The overall survival rates in this study were 92.0%, 85.2%, and 75.5% at 1, 3 and 5 years, respectively. These rates were slightly higher than many previous reports on AVR in octogenarians.
narians, which ranged from 52% to 73% at 5 years.7–14 The survival rate depends largely on the prevalence of risk factors in the study population. The difference from previous studies might be due to the fact that our study evaluated only elective procedures while past studies included also non-elective surgeries (6–56%).7–11,13 Kolh et al14 reported survival rates after elective surgery of 88.1%, 84.3% and 78.1% at 1, 3 and 5 years respectively, which were similar to our results. However, their study did not evaluate the risk factors of eAVR in octogenarians because their study population included non-elective surgeries. To the best of our knowledge, our report is the first to identify risk factors and long-term outcome of eAVR in octogenarians with AS. One study on 36 Japanese elderly patients reported that the survival rates at 1, 3 and 5 years after AVR were 93.6%, 79.6% and 79.6%, respectively, but that study included only 5 octogenarians.15 Moreover, the follow-up period was short and the number of patients was too low for multivariate analysis in that report.

A total of 18 deaths occurred after hospital discharge in our study, but there were only 5 cardiac deaths (28%). In previous reports, cardiac deaths occupied less than one-third of all deaths after hospital discharge in octogenarians who underwent AVR.11,12 Non-cardiac causes, such as cerebrovascular disease, chronic kidney disease (CKD), malignant disease and infection, had a strong influence on long-term outcome after AVR in octogenarians with AS. The relationship between LV systolic dysfunction and stroke was reported in a previous study.13 Therefore, it was thought that stroke increased when a low EF was present. It was reported that systolic heart failure worsened kidney function and was associated with increased mortality.24 Hence, LV systolic dysfunction might increase the mortality after eAVR due to CKD. However, we have no data to indicate the relationship between malignancy and low EF or between infection and low EF.

Prognostic Factors for Mortality

Our study identified an EF <50% and age as the risk factors for mortality after eAVR for octogenarians with AS, and demonstrated that LV systolic dysfunction in octogenarians undergoing eAVR had an unfavorable impact on long-term survival (Figure 2).

Age is one of the strong risk factors of long-term outcome after AVR in octogenarians.6,11–13 However, age is not a predictor of poor long-term outcome compared with the corresponding age-matched expected survival.35–36 Therefore, the ACC/AHA guideline describes that all elderly patients with symptomatic AS might be considered for AVR and that the decision to proceed with surgery depends on many factors other than old age.5

The ACC/AHA guideline states that the survival outcome is similar in symptomatic patients with normal LV function and in those with moderate depression of contractile function.5 However, most previous studies in octogenarians reported LV dysfunction as a strong predictor of mortality after AVR5,16 and some reports revealed that even a slight decrease in EF might be a risk factor.9,11 Therefore, particularly in an advanced aged population, even mild LV dysfunction might strongly influence long-term outcome after AVR.

Kita et al15 recommended early intervention for very severe AS because these patients had a significantly poorer natural history than those with severe AS. In octogenarians who underwent eAVR for AS, we demonstrated that very severe AS before surgery was not a risk factor of mortality. Therefore, our result supports the proposal of early elective intervention in octogenarians with very severe AS.

PPM was not significantly associated with mortality in our study. Although controversy remains over the impact of PPM in the elderly, Moon et al24 demonstrated that PPM did not influence long-term survival after AVR in patients older than 70 years. Our result in Japanese octogenarians was in agreement with theirs.

Serial Changes in Echocardiographic Parameters

In our study, preoperative LV chamber size and LV mass, which were larger than normal, decreased significantly toward the normal values at follow up.17 Previous studies have shown significant regression of LV dimensions after AVR,37,38 and a 20–30% decrease in LV mass index within the first year was reported.39 Our result was consistent with these studies. We also studied the serial changes of LV systolic and diastolic function on echocardiography. LV systolic function improved significantly in most of the patients with depressed LV systolic function before surgery, as was also shown by other studies.39–41 In contrast, LV diastolic function did not change significantly at follow up. It has been reported that advanced diastolic dysfunction indirectly reflects non-reversible structural myocardial abnormalities, although a reduced LV systolic function often reflects the after load excess in patients with AS.42 We speculate that diastolic function deteriorates with old age, and that diastolic dysfunction in octogenarians with AS might reflect non-reversible myocardial impairment in our study.

Racial Differences Between Japanese and Other Developed Countries’ Octogenarian Patients

Japanese octogenarians in this study (n=137, female 69%) have a significantly smaller mean BSA (1.5 m²) and mean body mass index (BMI) (23 kg/m²) than European octogenarians who underwent AVR for AS in a previous study (n=149, female 54%), in whom a mean BSA was 1.8 m² and a mean BMI was 28 kg/m².26 The percentage of PPM in this study (43%) was not larger than in previous American and European elderly studies, which varied between 60% and 63%.24–26 Therefore, PPM is not the inherent problem, particularly in Japanese octogenarians.

Study Limitations

Our study has several limitations. First, the number of patients was low and the follow-up period was short. However, regarding the validity of the Cox proportional hazards model, the estimated P values and CIs for the 2 risk factors should be valid because there were 23 post-AVR deaths among 137 octogenarians in the present study. Second, the mechanism underlying the association between a slight decrease in EF and long-term survival is not clear because of the low number of deaths. Finally, there was no control group in this study, which limits our ability to assess the efficacy of surgical intervention. From an ethical standpoint, a therapeutic decision for each individual patient has to be made by the attending physician according to current practice guidelines.

Conclusion

Japanese octogenarians with AS and preserved LV systolic function have favorable long-term survival after eAVR. However, an EF less than 50% is a risk factor for mortality after eAVR in octogenarian patients. Therefore, eAVR should be considered for octogenarians with AS before the progression of LV impairment.
Disclosures

None.

References


