Noninvasive estimate of left ventricular filling pressure correlated with early and midterm postoperative cardiovascular events after isolated aortic valve replacement in patients with severe aortic stenosis

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Objectives: The aim of this study was to investigate whether preoperative estimated left ventricular filling pressure predicts the postoperative outcome in patients with severe aortic stenosis.

Methods: Two hundred ten patients who underwent isolated aortic valve replacement because of severe aortic stenosis were analyzed. Left ventricular filling pressure was noninvasively assessed based on the ratio between early diastolic mitral inflow and mitral annular velocity (E/E'), which was calculated based on results of mitral inflow and mitral annular tissue Doppler scanning. Early postoperative hospital events were reviewed. Postoperative mortality and morbidity were searched and compared according to left ventricular filling pressure.

Results: Preoperative functional class was associated with increased E/E' values. Postoperative hospital events were higher in patients with increased preoperative E/E' values. Midterm mortality of the overall population was very low after aortic valve replacement (2%). Cardiovascular event-free survival, including hospital visits caused by heart failure symptoms, embolic cerebral infarction, and sudden cardiac death, was significantly lower in the patients with increased left ventricular filling pressure and E/E' values of greater than 12 ($P = .03$). Multivariable analysis showed a high hazard ratio of increased E/E' values of greater than 12 (hazard ratio, 41; $P < .001$).

Conclusions: The incidence of postoperative mortality after isolated aortic valve replacement caused by severe aortic stenosis is relatively low in the current era. E/E' representing diastolic filling pressure is the most important preoperative predictor of risk of early postoperative hospital course and postoperative morbidity. (J Thorac Cardiovasc Surg 2010;140:1361-6)

Prolonged pressure overload in patients with severe aortic stenosis (AS) induces remodeling of the left ventricle and alteration of both systolic and diastolic function. As a result, left ventricular (LV) filling pressure is commonly increased in patients with severe AS.^{1,2} The increased filling pressure results in pulmonary hypertension and dyspnea² in this patient population. However, most patients with increased LV filling pressure in the setting of severe AS have a normal left ventricular ejection fraction (LVEF). It is also likely that the increased filling pressure is partly related to superimposed diastolic dysfunction independent of se-

vere AS. After aortic valve replacement (AVR), LV afterload rapidly decreases and LV function improves, but LV filling pressure can remain increased in some patients for years after surgical intervention and affects postoperative outcomes.^{3,4}

Increased LV filling pressure is associated with diastolic dysfunction and hence is a reliable parameter to evaluate LV diastolic dysfunction.⁵ Previous reports suggested that diastolic dysfunction,⁶ pulmonary hypertension,⁷ and more severe functional class⁴ were associated with poor patient outcomes, and all of these factors can be explained by increased LV filling pressure. Therefore the single parameter of LV filling pressure might predict postoperative outcomes after AVR because of severe AS.

The velocity of mitral annular motion can be easily measured online by using echocardiography with the Doppler tissue-imaging technique. Because early diastolic velocity of the mitral annulus is a relatively load-independent index of LV relaxation and early mitral inflow velocity is associated with relaxation and LV filling pressure, the simple ratio between early diastolic mitral inflow and mitral annular velocity (E/E') has been shown to be a reliable method for noninvasive estimation of LV filling pressure.^{8,9} It is now routinely used in clinical practice, including in patients with moderate-to-severe AS.¹⁰ The primary aim of this study

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Abbreviations and Acronyms

AS	= aortic stenosis
AVR	= aortic valve replacement
E/E'	= Ratio between early diastolic mitral inflow and mitral annular velocity
LA	= left atrial
LV	= left ventricular
LVEF	= left ventricular ejection fraction

was to investigate whether preoperative E/E' values (noninvasively estimated LV filling pressure) predict postoperative adverse outcomes in patients with severe AS.

MATERIALS AND METHODS**Study Population**

Two hundred forty-eight patients who underwent isolated AVR for degenerative severe AS from January 2003 to December 2008 in Samsung Medical Center were retrospectively reviewed. Patients who had rheumatic AS, other severe valve diseases requiring a valve operation, and a history of previous cardiac surgery or recent myocardial infarction in the last 6 months were excluded from this study. Patients who presented with acute coronary syndrome with left main disease or multivessel disease were also excluded. Of the 248 patients, 210 who had complete preoperative echocardiographic analysis, including tissue Doppler parameters, were our study subjects. Hospital records were reviewed, and clinical variables, including age, sex, cardiovascular risk factors, and/or other variables regarding AVR, were investigated.

Echocardiographic Examination

Preoperative echocardiographic parameters were acquired from our electronic medical database. Preoperative echocardiographic analysis was usually performed within 2 weeks before the operation. As a routine protocol, our laboratory measures LV systolic and diastolic dimensions, end-diastolic LV wall thickness, LVEF, and pulsed-wave Doppler velocities of mitral inflow. The LV mass index was calculated based on M-mode echocardiographic analysis, as previously described,¹¹ and the left atrial (LA) volume index was calculated with the prolate-ellipsoid biplane method.¹² Peak early (E) and late (A) diastolic velocities of mitral inflow were measured by using pulsed-wave Doppler scanning at the tip of the mitral valve leaflets. Peak early (E') and late (A') diastolic mitral annular velocities were acquired at the septum in the apical 4-chamber view. Aortic valve mean and peak transvalvular gradients were calculated from the peak aortic valve Doppler velocities interrogated from multiple transducer locations. Aortic valve area was calculated by using the continuity equation.¹³

Outcome Measures

The postoperative hospital course was reviewed regarding in-hospital cardiovascular events. In-hospital complications were divided into surgical and cardiovascular complications. The former included wound problems, including infection or bleeding and redo operations caused by technical failure. Cardiovascular complications were defined as cerebral embolism, cardiopulmonary resuscitation, and arrhythmia requiring cardioversion or pacemaker insertion before discharge. If a cardiovascular complication was associated with a surgical complication, that event was excluded from the cardiovascular events. Early postoperative mortality was defined as death within 30 days after AVR.

Postoperative outcomes and events after discharge were acquired from the review of medical records, direct telephone interviews with patients or

their families, and national registry of birth and death data. Cause of death was classified as cardiac (sudden death, heart failure, or myocardial infarction) or noncardiac. Cardiovascular events were defined as heart failure requiring hospital admission or an early hospital visit, embolic cerebral infarction, or cardiac death during the follow-up period. This study protocol for retrospective review and follow-up analysis was approved by our institutional review committee (Samsung Medical Center).

Statistical Analysis

Continuous variables are expressed as means $\pm$ standard deviations. Time variables were expressed as medians $\pm$ interquartile ranges. Categorical variables are expressed as numbers and percentages. For comparison between 2 groups, the χ^2 test or Fisher's exact test was used for categorical variables, and the independent *t* test or Mann-Whitney test was applied for continuous variables, where appropriate, according to normality. The optimal cutoff value of E/E' to predict postoperative morbidity was determined by using receiver operating characteristic curve analysis. Postoperative clinical outcomes were demonstrated by using the curve derived from the Kaplan-Meier estimation method and were compared by with the log-rank test. For multivariable analysis for cardiovascular events, the proportional hazard assumption was tested with Schoenfeld residuals and the Supremum test for proportional hazards assumption. Possible predictors were tested by using Cox proportional hazard regression with the bootstrapping method. Each proportional hazards model was subjected to 1000 bootstrap replications by using random samples generated from and consisting of the same number of patients as the original model. Bootstrap estimates of hazard ratios and 95% confidence intervals were calculated by using a bias-corrected method derived from the 1000 replications. All statistical analyses were performed with the Statistical Analysis Software package (SAS version 9.1, SAS Institute, Inc, Cary, NC).

RESULTS**Patient Characteristics**

Clinical and echocardiographic characteristics of the 210 patients are summarized in Table 1. The ethnicity of all the patients was Korean. Severe dyspnea with New York Heart Association functional class 3 or 4 was present in 22% of the patients before AVR. LVEF was less than 50% in 18% of the patients. The mean E/E' value was increased at 16.8 ± 8.6 , and the LV mass index was increased at 151 g/m^2 . E/E' values were correlated with LVEF ($r = -0.34$, $P < .001$), aortic valve area ($r = -0.24$, $P = .001$), LV mass index ($r = 0.23$, $P < .001$), LA volume index ($r = 0.42$, $P < .001$), pulmonary hypertension ($r = 0.48$, $P < .001$), and the functional class of the patients ($r = 0.30$, $P < .001$). A history of coronary artery disease was presented in 17% of the patients, and coronary artery bypass grafting during AVR was performed in 11% of the patients.

Postoperative Hospital Course

None of the patients experienced early postoperative death within 30 days after AVR. Postoperative ventilator time was 11.0 ± 8.3 hours. Mean postoperative intensive cardiac unit and hospital stays after valve surgery were 1.0 ± 1.0 days and 8.0 ± 3.0 days, respectively.

Postoperative surgical complications were present in 5 (2.3%) patients, and in-hospital cardiovascular complications were present in 13 (6.2%) patients (embolic cerebral

TABLE 1. Characteristics of the study population

	Values (n = 210)
Age, y	64.6 ± 10.0
Male sex, n (%)	136 (64.8)
Body surface area, m ²	1.7 ± 0.2
NYHA functional class	2.1 ± 0.7
NYHA class III or IV, n (%)	46 (21.9)
Hypertension, n (%)	92 (43.8)
Diabetes mellitus, n (%)	36 (17.1)
Smoking, n (%)	79 (37.6)
History of CAD, n (%)	36 (17.1)
End-systolic dimension, mm	33.9 ± 8.6
End-diastolic dimension, mm	54.0 ± 7.4
Left ventricular ejection fraction (%)	60.4 ± 11.7
Left ventricular ejection fraction <50%, n (%)	37 (17.6)
Left ventricular mass index, g/m ²	151.4 ± 43.0
LA volume index, mL/m ²	38.6 ± 14.6
E/E'	16.8 ± 8.6
Peak systolic pulmonary artery pressure, mm Hg*	39.6 ± 11.4
Valve morphology	
Tricuspid/bicuspid/unicuspid	69 (32.9)/141 (67.1)/0 (0)
Aortic valve area, cm ²	0.71 ± 0.16
Mean transvalvular gradient, mm Hg	57.1 ± 17.0
Aortic prosthesis type, n (%)	
Mechanical	71 (33.8)
Bioprosthesis	139 (66.2)
Aortic prosthetic size, mm	22.3 ± 1.8
Associated coronary artery bypass graft, n (%)	22 (10.5)
Preoperative medication, n (%)	
Statin	82 (39.0)
ACE inhibitor or ARB	70 (33.3)
β-Blocker	60 (28.6)
Calcium-channel blocker	43 (20.5)

NYHA, New York Heart Association; CAD, coronary artery disease; LA, left atrial; E/E', ratio between early diastolic mitral inflow and mitral annular velocity; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. *Peak systolic pulmonary arterial pressure was available only in 163 patients because reliable tracing of tricuspid regurgitation Doppler scanning was impossible.

infarction in 2, transient ischemic accident in 1, intraoperative intra-arterial balloon pump in 1, cardiopulmonary resuscitation or cardioversion caused by clinically significant arrhythmia resulting in sudden collapse in 7, pacemaker insertion during surgical intervention caused by atrioventricular block in 1, and pericardiocentesis caused by pericardial effusion in 1). Cardiovascular complications were more prevalent in patients with preoperative E/E' values of greater than 12 (Figure 1).

Midterm Morbidity and Mortality

All-cause mortality was confirmed in the entire study population as follows. Telephone or outpatient interviews were performed with 97.1% (n = 204) of the patients or their first-degree relatives to confirm the mortality and morbidity of the

FIGURE 1. In-hospital cardiovascular complications according to the ratio between early diastolic mitral inflow and mitral annular velocity (E/E'). Postoperative cardiovascular complications, including embolic cerebral infarction, cardiopulmonary resuscitation, and arrhythmia requiring cardioversion or pacemaker insertion, occurred in patients with E/E' values of greater than 12 (P < .05), suggesting increased left ventricular filling pressure before surgical intervention.

patients. The mortality of the rest of the patients (2.9%, n = 6), who could not be reached by telephone, was confirmed by using national registry of death and survival data.

The median follow-up duration was 25.39 ± 16.2 months. Four (1.8%) patients died during follow-up (Figure 2). Among them, cardiovascular mortality occurred in 2 patients. Cardiovascular events were more prevalent in the patients with high E/E' values in the overall study population (Figure 3, A). Fourteen (10.1%) of the patients with E/E' values of greater than 12 (n = 72) had morbidity of cardiovascular events, but only 2 (2.8%) of the patients with E/E' values of 12 or less (n = 138) had cardiovascular events during the follow-up period (P = .03; Figure 3, A). This finding persisted among the patients with preserved LVEF (LVEF >50%, P = .04; Figure 3, B). Multivariable analysis using Cox proportional hazard regression with the bootstrapping method also showed a significantly high hazard ratio with increased E/E' values of greater than 12 (Table 2).

DISCUSSION

In this study postoperative outcome of isolated AVR because of severe AS was excellent, with a very low mortality rate. Average preoperatively estimated LV filling pressure, as determined by means of Doppler echocardiographic analysis, was increased in patients with severe AS. Midterm mortality was excellent, but postoperative cardiovascular

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FIGURE 2. Survival curve after aortic valve replacement (AVR). The Kaplan-Meier survival curve shows excellent postoperative outcome with very low midterm mortality (median follow-up duration, 25.39 ± 16.2 months). Only 4 (1.8%) patients died during follow-up.

events were more common in the patients with increased preoperative LV filling pressures ($E/E' > 12$). On the other hand, early postoperative outcomes were not related to the preoperative aortic valve gradients or area.

Outcome of Isolated AVR in Patients With Degenerative AS

Early postoperative mortality has decreased¹⁴ with improvement in surgical techniques and perioperative care. In-hospital mortality of isolated AVR varies according to the study group, but it is usually less than 5%,¹⁵⁻¹⁷ and midterm mortality has been reported to be less than 10%.¹⁸ In our clinical experience there was no in-hospital mortality, and the midterm mortality was only 3% of overall patients. Our excellent postoperative outcome can be explained by the characteristics of our study population, all of whom are Korean. Our study population is younger, and the percentage of bicuspid aortic valve was higher than in other previous studies,³ which were mainly reported from Western countries. Moreover, the prevalence of coronary artery disease is much lower than that of other previous studies^{16,18} because of less prevalent atherosclerosis in the Asian population.¹⁹

Preoperative LV Filling Pressure as a Risk for Postoperative Outcomes

LVEF and cardiac symptoms have been used to determine the timing of valvular surgery, especially in patients with AS.²⁰ This guideline is easy to use and supported by much clinical data.^{21,22} Still, there are debates on the right timing of AVR. Even though the presence of symptoms is a definite predictor of poor outcome,²³ patients might not be aware of the fact that they are limited clinically, and fur-

A

B

FIGURE 3. Event-free survival after aortic valve replacement (AVR). A, The cardiovascular event-free survival curve shows a significantly higher incidence of cardiovascular events with an increased ratio between early diastolic mitral inflow and mitral annular velocity (E/E') values. B, Differences in event-free survival according to the estimated left ventricular filling pressure was also observed in the patients with preserved left ventricular ejection fractions.

thermore, symptoms are not specific. Moreover, symptoms are sometimes insidious and are not easily elicited by physicians. We might need to perform exercise testing to assess the patient's functional status.²⁴ Even when AVR is performed according to the guidelines, persistent or recurrent heart failure can be observed after successful AVR, and persistent heart failure has been reported to be present in 10% of patients 5 years after AVR.⁴ Therefore we need more objective parameters to discriminate the high-risk patients who are at risk of postoperative heart failure.

Increased LV filling pressure is a common pathophysiology of pulmonary congestion in patients with heart failure,⁵

TABLE 2. Preoperative risk factors for postoperative cardiovascular events

Variables	Hazard ratio	95% CI	P value
Age, y	1.0	0.96–1.07	.63
Aortic valve area, cm ²	17.0	0.96–300.2	.06
LV ejection fraction, %	1.0	0.94–1.08	.53
LV mass index, g/m ²	1.0	0.98–1.00	.11
E/E' >12	40.8	39.00–41.68	<.001

CI, Confidence interval; LV, left ventricle; E/Et, ratio between early diastolic mitral in-flow and mitral annular velocity.

including patients with AS.² Increased LV filling pressure has been shown to be positively correlated with the functional class of the patients and the development of pulmonary hypertension,² which was also demonstrated in our study population. A prolonged increase in LV filling pressure promotes LA remodeling,²⁵ which can be a substrate of atrial fibrillation and a source of embolism.²⁶ Furthermore, myocardial fibrosis is an important pathology of the myocardium with diastolic dysfunction and LV filling pressure, and it can be a substrate for ventricular arrhythmia or conduction abnormality. In our study subjects fatal arrhythmias were more common in the patients with increased preoperative LV filling pressure, which can be associated with increased LV fibrosis and LA remodeling. The fact that E/E' values were not well correlated with the severity of AS using aortic valve pressure gradient and aortic valve area suggests that the increased preoperative LV filling pressure in patients with severe AS is not all from AS but also from independent, superimposed diastolic dysfunction. Increased LV filling pressure has been predictive of poor long-term outcome in patients with other conditions, such as diastolic heart failure, systolic heart failure, and acute myocardial infarction.²⁷ In our study population cardiovascular events, including arrhythmia requiring resuscitation and embolic cerebral infarction, were more common in the patients with preoperatively increased LV filling pressure. After discharge, recurrent heart failure was more common in patients with preoperatively increased LV filling pressure. This phenomenon was also found in patients with preserved LVEF before AVR.

From our results, preoperative LV filling pressure did not affect the mortality of the patients undergoing isolated AVR but was associated with postoperative hospital course and postoperative morbidity. We also suggest that noninvasive measurements of LV filling pressure preoperatively can be a prognostic indicator of midterm cardiovascular events after isolated AVR in patients with severe AS, even in the setting of preserved LVEF. Postoperative E/E' values would be beneficial also for follow-up of longer-term outcome of the patients after AVR, which requires further study. The usefulness of LV filling pressure to determine the timing of the AVR in asymptomatic patients with severe AS is beyond our scope, but from our results, LV filling pressure deserves a serious consideration as a marker to identify the high-risk

group in future clinical investigations of valvular heart diseases.

Study Limitations

Our study has several limitations. First, the preoperative and perioperative characteristics of our study population were collected in a retrospective manner, but our echocardiographic performance has been standardized since 2003 and recorded in an electronic database, which minimizes possible errors in data collection.

Second, our study population, all of whom are Korean, has relatively low risk compared with those of other previous studies from Western countries²⁸; our data were not powered to address any association with mortality, and the effect of LV filling pressure on morbidity after AVR might not be generalized. However, the predictive value of E/E' has been validated in other conditions in other ethnic populations.

Third, LV filling pressure was not acquired by means of invasive cardiac catheterization but assumed based on E/E' values by using echocardiographic analysis. E/E' values can be influenced by LA pressure²⁹ or LV systolic and diastolic pressure^{30,31} and thus have the possibility of being confounded. However, LV filling pressure in patients with AS has been reported to be well correlated with LV filling pressure measured by means of invasive methods.^{10,32} Moreover, although cardiac catheterization is relatively safe, it remains an invasive procedure and is associated with measurable risk. In this context noninvasive measurement of LV filling pressure might be a safer method in routine clinical practice.

CONCLUSIONS

The incidence of early postoperative and midterm mortality after isolated AVR caused by severe AS is relatively low in the current era. Still, increased LV filling pressure measured by using echocardiographic analysis is associated with increased preoperative symptoms and early postoperative morbidity in patients with severe AS. Increased LV filling pressure did not increase mortality after AVR but was associated with midterm cardiovascular events. The aortic valve gradient and area were not related to the preoperative symptoms and postoperative clinical outcomes in patients with severe AS.

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