N-terminal pro-B-type natriuretic peptide measurement is useful in predicting left ventricular hypertrophy regression after aortic valve replacement in patients with severe aortic stenosis

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ABSTRACT

Background The predictive factors for early left ventricular hypertrophy (LVH) regression after aortic valve replacement (AVR) have not been fully elucidated. This study was conducted to investigate which preoperative parameters predict early LVH regression after AVR.

Methods and results 87 consecutive patients who underwent AVR due to isolated severe aortic stenosis (AS) were analysed. Patients with ejection fraction <50% or concomitant coronary artery disease were excluded from the analysis. Preoperative evaluation including echocardiography and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement was performed and midterm follow-up echocardiography was done at a median of 9 months after AVR. The presence of complete regression of LVH at the midterm follow-up was determined. In multivariate analysis, including preoperative echocardiographic parameters, only E/e' ratio was associated with midterm LVH regression (OR 1.11, 95% CI 1.01 to 1.22; $p=0.035$). When preoperative NT-proBNP was added to the analysis, logNT-proBNP was found to be the single significant predictor of midterm LVH regression (OR 2.00, 95% CI 1.08 to 3.71; $p=0.028$). By receiver operating characteristic curve analysis, a cut-off value of 440 pg/mL for NT-proBNP yielded a sensitivity of 72% and a specificity of 77% for the prediction of LVH regression after AVR.

Conclusions Preoperative NT-proBNP was an independent predictor for early LVH regression after AVR in patients with isolated severe AS.

which can predict complete regression (CR) of LVH after AVR have not yet been elucidated.

Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) was found to be related to the development of symptoms and the severity of stenosis, and to the degree of LVH in patients with AS.^{12–14} Like LVH, NT-proBNP values have been reported to decrease after AVR and to be closely related to the long-term prognosis of severe AS.^{15 16} The relation of preoperative NT-proBNP concentration with LVH regression after AVR, however, has not been fully evaluated. Therefore, we investigated which preoperative findings, including both NT-proBNP values and echocardiographic parameters, could predict early regression of LVH after AVR in patients with isolated severe AS.

METHODS

Study population

Study patients were recruited from the institutional electronic database of valvular heart disease. Two-hundred and thirty-one consecutive patients who underwent AVR due to severe AS (estimated aortic valve area (AVA) <1 cm² or mean transvalvular pressure gradient >50 mm Hg) at Samsung Medical Center between January 2006 and December 2009 were eligible for inclusion in this study. Among these, 131 were excluded for the following reasons (figure 1): (1) ≥ moderate grade valvular dysfunction other than AS; (2) concomitant coronary artery disease (CAD) proven by coronary angiography with ≥50% stenosis before AVR, history of previous percutaneous coronary intervention, or previous coronary artery bypass grafting; (3) LV dysfunction with LV ejection fraction (LVEF) <50%; (4) atrial fibrillation; (5) a plasma creatinine value ≥2 mg/dL; (6) previous cardiac surgery; (7) patient–prosthesis mismatch (aortic valve area index (AVAI) <0.8 cm²/m²) or paravalvular leakage after AVR; (8) infective endocarditis; or (9) not having LVH on preoperative evaluation. LVH was defined as an LV mass index (LVMI) ≥102 g/m² in men and ≥88 g/m² in woman.¹⁷ Of the remaining 100 patients, 13 patients who had no midterm echocardiography were additionally excluded, leaving 87 patients. LVMI was calculated on a midterm follow-up echocardiographic evaluation performed between 6–18 months after AVR. Based on the presence of LVH on follow-up echocardiography, patients were classified into two groups: CR or non-CR of LVH.

INTRODUCTION

In aortic stenosis (AS), left ventricular (LV) pressure overload results in LV hypertrophy (LVH) accompanied by myocardial fibrosis.^{1 2} Subsequently, LVH and myocardial fibrosis cause LV diastolic dysfunction and symptoms in patients with AS before development of LV systolic dysfunction.^{3–6} Although regression of LVH and improvement of LV diastolic function may occur after aortic valve replacement (AVR), these reversible processes are frequently incomplete, and LVH or LV diastolic dysfunction can persist for several years after AVR in patients with severe AS.^{7–9} LVH regression has been reported to occur mostly within 1–2 years after AVR, and incomplete regression of LVH after AVR is associated with a poor long-term prognosis.^{7 10 11} However, the clinical characteristics

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Figure 1 Flow diagram of the study population showing the number of patients enrolled and excluded. AVR, aortic valve replacement; EF, ejection fraction; LVH, left ventricular hypertrophy.

CR was defined as having an LVMI of less than the LVH criteria on the mid-term evaluation. Follow-up data of the study patients were obtained from direct interviews or telephone interviews, and mortality data from the national registry. This study was approved by the institutional review board of our institute, and informed consent was waived.

Echocardiographic examination and plasma NT-proBNP

Comprehensive echocardiographic evaluations including two-dimensional and tissue Doppler study were performed on every patient before AVR and at the midterm evaluation according to the guidelines of the American Society of Echocardiography.¹⁸ Preoperative echocardiography was performed in the 2 weeks before operation. LVEF, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), interventricular septum thickness (IVST), and LV posterior wall thickness (LVPWT) were obtained in diastole and LV mass was estimated using the Devereux formula $(0.8 \times (1.04 \times [LVEDD + LVPWT + IVST]^3 - [LVEDD]^3) + 0.6 \text{ g})$.¹⁹ Relative wall thickness (RWT) was calculated as $2 \times LVPWT / LVEDD$ and regarded as having increased if ≥ 0.42 .¹⁷ Left atrial (LA) volume was calculated using the prolate-ellipsoid biplane method.²⁰ LA volume and LV mass were indexed to body surface area. Diastolic mitral inflow E and A velocities and annular e' velocity were also measured. AVA was calculated using the continuity equation, and AVAI was also calculated.²¹ Plasma NT-proBNP concentrations were measured using an Elecsys proBNP reagent kit (Roche Diagnostics, Indianapolis, Indiana, USA).

Statistical analysis

Continuous variables are expressed as mean $\pm$ SDs or median (IQR), and categorical variables as numbers and percentages. The χ^2 or Fisher's exact test was used for comparison of categorical variables, and the independent t test or Mann-Whitney test was used for continuous variables according to the results of a normality test. For comparison between preoperative and follow-up data, a paired t test or Wilcoxon's signed rank test was used for continuous variables. Logarithmic transformation was performed for the analysis of NT-proBNP. Univariate

logistic regression analyses were carried out for all clinical, laboratory and echocardiographic variables. For multivariate logistic regression analyses, variables with significant p values on univariate analyses as well as other clinically important variables were included in the models to identify independent predictors of postoperative regression of LVH. Pearson's correlation test or Spearman's correlation test were performed for calculation of linear correlations between preoperative logNT-proBNP and echocardiographic parameters. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic concentration of NT-proBNP and to identify the optimal cut-off value of NT-proBNP for prediction of LVH regression. Statistical analyses were performed using SPSS (V19.0, SPSS Inc, Chicago, Illinois, USA) and values of $p < 0.05$ were regarded as significant.

RESULTS

Patients and clinical characteristics

Of the 87 patients, 34 (39%) patients (CR group) showed complete LVH regression on midterm follow-up echocardiography, while the other 53 (61%) patients (non-CR group) still had LVH (figure 1). Follow-up echocardiography was performed at a median of 8 (IQR 7–11) months and 9 (IQR 7–11) months after AVR in the CR group and the non-CR group, respectively ($p=0.396$). The mean follow-up duration after AVR was 37 ± 15 months, and one patient died of lung cancer during follow-up. Preoperative clinical and laboratory findings are summarised in table 1. There were no significant differences in age, gender, body surface area, blood pressure, New York Heart Association (NYHA) functional class, comorbidity or medication between the two groups. Preoperative heart rates were significantly different between the CR group and the non-CR group (65 ± 7 beats/min (bpm) vs 70 ± 12 bpm, $p=0.027$). Although not statistically significant, in the CR group a significant proportion of patients had the bicuspid aortic valve. Concomitant operation of the proximal aorta was more frequently performed in the non-CR group compared to the CR group (25 (47%) vs 8 (24%), $p=0.027$).

Table 1 Patient characteristics

	CR (N=34)	Non-CR (N=53)	p Value
Age (years)	65±8	67±10	0.484
Male gender (%)	22 (65)	32 (60)	0.685
Body surface area (m ²)	1.7±0.2	1.7±0.2	0.846
Systolic blood pressure (mm Hg)	119±15	123±15	0.232
Diastolic blood pressure (mm Hg)	69±8	70±11	0.546
Heart rate (beats/min)	65±7	70±12	0.027
NYHA class III/IV* (%)	6 (18)	8 (15)	0.752
Comorbidity			
Diabetes (%)	9 (27)	9 (17)	0.286
Hypertension (%)	16 (47)	29 (55)	0.486
Stroke (%)	0 (0)	1 (1.9)	0.999
Smoking (%)	15 (44)	16 (30)	0.186
Hyperlipidaemia (%)	9 (27)	13 (25)	0.839
Operative findings			
Bicuspid aortic valve (%)	22 (65)	24 (45)	0.077
Mechanical prosthesis (%)	15 (44)	18 (34)	0.341
Valve size (mm)	22±2	22±2	0.636
Concomitant aortic operation (%)	8 (24)	25 (47)	0.027
Medication			
ACE inhibitor or ARB (%)	13 (38)	19 (36)	0.822
β-blocker (%)	10 (29)	16 (33)	0.754
Calcium channel blocker (%)	6 (18)	14 (39)	0.252
Diuretics (%)	8 (24)	17 (35)	0.276
Statin (%)	9 (27)	18 (37)	0.326

*There were no patients with NYHA functional class IV.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CR, complete regression; NYHA, New York Heart Association.

Preoperative echocardiographic findings and NT-proBNP values

Preoperative echocardiographic findings and NT-proBNP values are summarised in [table 2](#). The CR group had higher LVEF (66±6% vs 63±6%, p=0.008), smaller LVESD (29±4 mm vs

Table 2 Preoperative echocardiographic data and NT-proBNP

	CR (N=34)	Non-CR (N=53)	p Value
LVEF (%)	66±6	63±6	0.008
LVEDD (mm)	51±4	52±6	0.131
LVESD (mm)	29±4	32±5	0.019
IVST (mm)	11±1	12±2	<0.001
LVPWT (mm)	11±1	12±2	0.029
RWT	0.44±0.06	0.45±0.08	0.364
LVMI (g/m ²)	131±18	155±36	<0.001
LAVI (mL/m ²)	32±12	38±13	0.013
E/A	0.74±0.26	0.91±0.68	0.167
Deceleration time (ms)	282±80	275±65	0.654
E/e'	12.8±5.6	16.6±6.5	0.006
Aortic valve area (cm ²)	0.71±0.17	0.71±0.17	0.958
Mean pressure gradient (mm Hg)	57±14	63±19	0.137
NT-proBNP* (pg/mL)	226 (122–439)	685 (378–1419)	<0.001
LogNT-proBNP	5.4±0.9	6.4±1.1	<0.001

*Expressed as median (IQR) due to non-Gaussian distribution.

CR, complete regression; IVST, interventricular septum thickness; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RWT, relative wall thickness.

32±5 mm, p=0.019), thinner IVST and LVPWT (11±1 mm vs 12±2 mm, p<0.001; 11±1 mm vs 12±2 mm, p=0.029, respectively), and lower LVMI (131±18 g/m² vs 155±36 g/m², p<0.001). LVEDD and RWT were not significantly different. Among the parameters of diastolic function, the CR group had smaller LA volume index and E/e' ratio compared to the non-CR group (32±12 mL/m² vs 38±13 mL/m², p=0.013; 12.8±5.6 vs 16.6±6.5, p=0.006, respectively). There were no differences in E/A ratio or deceleration time of E velocity. Neither AVA nor the mean pressure gradient across the aortic valve were different between the two groups. The non-CR group had significantly higher logNT-proBNP than the CR group (6.4±1.1 vs 5.4±0.9, p<0.001).

Echocardiographic findings at follow-up evaluation

Echocardiographic findings and medication status at midterm evaluation are shown in [table 3](#). LVEF and mean pressure gradient across the aortic valve were not different between the two groups at midterm evaluation. When those echocardiographic parameters not related to LV wall thickness (IVST, LVPWT, RWT, and mass index) were compared, the CR group showed smaller LVEDD (46±4 mm vs 49±4 mm, p=0.002), LVESD (28±3 mm vs 30±4 mm, p=0.016), LA volume index (29±9 mL/m² vs 33±9 mL/m², p=0.045), and E/e' ratio (11.4±4.0 vs 16.1±6.5, p=0.001).

Independent predictors for LVH regression

The multivariate model analyses for the prediction of early LVH regression are summarised in [table 4](#). To identify the independent predictors among echocardiographic parameters, with the exception of LVMI, model 1 included age, gender, LVEF, LVESD, LA volume index, and E/e'. E/e' was a significant independent predictor of LVH regression (OR 1.11, 95% CI 1.01 to 1.22; p=0.035). When logNT-proBNP and LVMI were added into model 1 (model 2), logNT-proBNP was the sole independent predictor of early LVH regression (OR 2.00, 95% CI 1.08 to 3.71; p=0.028). In model 3, including age, gender, LVMI, E/e', AVA, and logNT-proBNP, logNT-proBNP was still the only independent predictor of early LVH regression (OR 2.56, 95% CI 1.31 to 4.98; p=0.002). The correlations between preoperative logNT-proBNP and preoperative echocardiographic parameters are shown in [figure 2](#). Preoperative logNT-proBNP was

Table 3 Postoperative follow-up echocardiographic data

	CR (N=34)	Non-CR (N=53)	p Value
LVEF (%)	65±5	64±7	0.502
LVEDD (mm)	46±4	49±4	0.002
LVESD (mm)	28±3	30±4	0.016
IVST	9±1	11±2	<0.001
LVPWT	9±1	10±1	<0.001
RWT	0.39±0.07	0.43±0.06	0.012
LVMI (g/m ²)	84±11	118±18	<0.001
LAVI (mL/m ²)	29±9	33±9	0.045
E/A	0.87±0.26	0.89±0.39	0.821
Deceleration time (ms)	250±58	271±68	0.178
E/e'	11.4±4.0	16.1±6.5	0.001
Mean pressure gradient (mm Hg)	11±5	13±4	0.100

CR, complete regression; IVST, interventricular septum thickness; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; RWT, relative wall thickness.

Table 4 Multivariable analyses for prediction of left ventricular hypertrophy regression at midterm evaluation

Variable	Model 1			Model 2			Model 3		
	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
Age, years	0.98	0.93 to 1.04	0.488	0.99	0.93 to 1.06	0.830	0.99	0.93 to 1.06	0.771
Male gender	1.27	0.41 to 3.91	0.678	1.29	0.39 to 4.25	0.678	1.14	0.36 to 3.66	0.825
LVEF (%)	0.91	0.80 to 1.04	0.152	0.89	0.77 to 1.03	0.129			
LVESD (mm)	1.01	0.85 to 1.19	0.907	0.90	0.73 to 1.10	0.299			
LVMI (g/m ²)				1.03	0.99 to 1.06	0.115	1.02	1.00 to 1.05	0.089
LAVI (mL/m ²)	1.04	1.00 to 1.09	0.086	1.03	0.98 to 1.08	0.316			
E/e'	1.11	1.01 to 1.22	0.035	1.07	0.97 to 1.18	0.174	1.08	0.98 to 1.19	0.119
AVA (cm ²)							127.39	0.50 to 32 431.18	0.086
LogNT-proBNP				2.00	1.08 to 3.71	0.028	2.56	1.31 to 4.98	0.002

AVA, aortic valve area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

significantly correlated with preoperative LVEF ($r=-0.40$, $p<0.001$), LVMI ($r=0.48$, $p<0.001$), LVESD ($r=0.36$, $p<0.001$), LA volume index ($r=0.23$, $p=0.034$), E/e' ratio ($r=0.43$, $p<0.001$), and AVA ($r=-0.40$, $p<0.001$), but the degree of correlation was only modest. ROC curve analysis was performed to evaluate the predictive value of NT-proBNP for early LVH regression (figure 3). The optimal cut-off value of NT-proBNP was 440 pg/mL, showing a sensitivity of 72% and a specificity of 77% for predicting LVH regression (area under curve 0.78, 95% CI 0.69 to 0.88; $p<0.001$).

DISCUSSION

In the present study, CR of LVH was seen in about 40% patients with isolated severe AS at the time of midterm evaluation after

AVR. Among the echocardiographic parameters, preoperative E/e' was independently associated with midterm LVH regression. In multivariate analysis, including both echocardiographic variables and natriuretic peptide values, NT-proBNP was the only independent predictor for CR of LVH at midterm.

Recent improvements in diagnostic and surgical techniques and perioperative care have significantly reduced early post-operative and midterm mortality after AVR.^{22–24} There were 12 (4%) cardiac deaths in 313 patients over a mean 43-month follow-up in a study by Tasca *et al.*²³ and only one (1%) death in 95 patients over a mean 44-month follow-up in a study by Iwahashi *et al.*²⁴ Likewise, mortality after AVR was very low in our study population, and there was only one non-cardiac death among 87 patients over a follow-up period of 37 ± 15 months.

Figure 2 Preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) values correlated with preoperative echocardiographic parameters showing all significant correlations with left ventricular ejection fraction (LVEF), LV mass index (LVMI), LV end-systolic diameter (LVESD), left atrial volume index (LAVI), E/e' ratio, and aortic valve area (AVA).

Figure 3 Receiver operating characteristic (ROC) curve of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for regression of left ventricular hypertrophy. AUC, area under the ROC curve.

Although short-term outcomes after AVR have improved, incomplete resolution of LVH and subsequent LV diastolic dysfunction are still frequently observed and are the main causes of morbidity in these patients.^{7 11 25} In other words, incomplete regression of LVH may limit quality of life and leave a substrate for increased mortality and morbidity in the long term after AVR.^{26 27} In addition, Lund *et al* found that incomplete regression of LVH at a 1.5-year follow-up was associated with higher mortality 10 years after AVR.¹¹ Petrov *et al* also showed that faster regression of LVH after AVR in AS was associated with less myocardial fibrosis.²⁸ In this regard, the presence of LVH at midterm evaluation could be a good parameter for evaluating the postoperative status of patients undergoing AVR. However, there have been few studies that examined the preoperative predictors for LVH regression after AVR for severe AS. A recent study reported that preoperative natriuretic peptide value had a positive correlation with LVMI both early and late after AVR.²⁴ The current study showed that preoperative NT-proBNP is the most powerful predictor for early LVH regression after AVR among laboratory and echocardiographic parameters.

Since, unlike most other studies, we excluded patients with CAD, LV dysfunction, or other significant valvular heart disease on preoperative evaluation, the NT-proBNP value in our patients might purely reflect LV wall stress resulting from pressure overload by severe AS. Although preoperative logNT-proBNP showed a significant correlation with echocardiographic variables related to systolic and diastolic function, the degree of correlation was not strong. These findings are similar to those of previous reports showing correlations between natriuretic peptide and echocardiographic parameters in patients with AS.^{24 29 30} Despite having similar AVA and mean pressure gradient as well as demographic characteristics, the non-CR group

had significantly higher NT-proBNP and LVMI (table 2). Both systolic function (LVEF) and diastolic function (LAVI and E/e') were also significantly decreased in the non-CR group compared with those in the CR group. Therefore, we felt that the non-CR group might be in a more advanced disease state despite similar AVA.

Although current guidelines for the management of severe AS generally recommend delaying AVR until symptoms develop, the management of asymptomatic patients with severe AS remains controversial.^{31 32} The same guidelines also recommend considering surgery for patients with asymptomatic severe AS if they have extremely severe AS or excessive LVH. A recent study reported that early operation in patients with asymptomatic severe AS improved long-term survival.³³ This present study showed that LVH regression after AVR was better predicted by NT-proBNP than by AVA or LVMI. Another study conducted on patients with severe AS demonstrated that NT-proBNP concentration was associated with symptom-free survival in initially asymptomatic patients and with postoperative survival in symptomatic patients undergoing AVR.¹⁶ These data, together with our findings, suggest that measurement of natriuretic peptide is useful for identifying patients for whom early surgical intervention is warranted. The present study suggests that the optimal cut-off value of preoperative NT-proBNP for predicting midterm LVH regression is 440 pg/mL. However, the role of natriuretic peptide in determining the timing of AVR in severe AS requires further study.

Our study has several limitations. First, the study population was relatively small, especially for the multivariate analysis, which included both clinical and echocardiographic parameters. Second, although we demonstrated NT-proBNP threshold to predict early regression of LVH after AVR, we could not show any association between NT-proBNP concentration and cardiac events in this study. Third, we included consecutive patients with severe AS in a prospective manner, but analyses were performed retrospectively, and thus this study may suffer from the biases which are intrinsic to retrospective studies. In addition, although follow-up evaluation of echocardiography and NT-proBNP were usually performed 8–9 months after AVR, the range was relatively wide. Lastly, as only a limited number of patients underwent regular follow-up echocardiography after the midterm evaluation, we are unable to provide data on the long-term regression of LVH.

CONCLUSION

NT-proBNP was the most important predictor for LVH regression after AVR in patients with isolated severe AS and preserved LV systolic function.

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Competing interests None declared.

Patient consent Waived. The institutional review board of our institute waived informed consent as this study was retrospective and the data were collected by electronic chart review. Risk to the study patients was minimal and the study did not affect patient management.

Ethics approval The institutional review board of Samsung Medical Center.

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