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Original article

Preoperative left atrial minimum volume as a surrogate marker of postoperative symptoms in senile patients with aortic stenosis who underwent surgical aortic valve replacement

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ABSTRACT

Background: Previous reports have shown that postoperative symptoms despite successful surgical aortic valve replacement (AVR) are not uncommon depending on severity of myocardial fibrosis in patients with aortic stenosis (AS). Left atrial minimum volume (LAV_{min}) at end-diastole determined by direct exposure of left ventricular end-diastolic pressure may be useful as a surrogate marker of postoperative symptoms in patients with AS undergoing AVR.

Methods and results: We studied 75 patients with AS who underwent AVR and were followed up to 600 days after AVR. We examined the postoperative symptomatic status which occurred between 60 days to 600 days after AVR. The study patients were divided into 2 groups: 19 patients (25%) with postoperative symptoms (symptomatic group) and 56 without symptoms (asymptomatic group). There were no significant differences in preoperative left ventricular volumes and ejection fraction and AS severity by echocardiography between the two groups. There were significant differences in preoperative echocardiographic LAV_{min} index ($LAVI_{min}$) between symptomatic group and asymptomatic group (45 ± 15 vs. 28 ± 11 ml/m^2). Using receiver operating characteristic curve analysis, $LAVI_{min} \geq 30$ ml/m^2 detected postoperative symptoms with the large area under the curve (0.84) (sensitivity 94% and specificity 68%). In the multivariate analysis, preoperative $LAVI_{min}$ was the independent predictor of the postoperative symptomatic status after AVR (odds ratio: 1.11; 95% CI: 1.04–1.18).

Conclusions: The preoperative echocardiographic $LAVI_{min}$ measurement is useful as a surrogate marker of symptomatic status after AVR in patients with AS.

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Introduction

Severe aortic stenosis (AS) mainly affects the elderly, with a prevalence ranging from less than 2% of those under the age of 65 years to nearly 8% of those over the age of 80 years [1,2]. The prevalence of AS is strongly correlated with age, and the most common cause of AS is degenerative aortic valve [1–3]. From the 1990s, the clinical management of patients with severe AS was based generally on the assessment of symptoms and left ventricular ejection fraction (LVEF) [4,5]. However, despite successful surgery, from 23% to 56% of patients experienced symptomatic status during 6 months to 1 year of follow-up after surgical aortic valve replacement (AVR) [6–9].

In patients with AS, diastolic dysfunction dominates and precedes changes in myocardial contractility [10,11], and with

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worsening of fibrosis and myocyte degeneration, left ventricular end-diastolic pressure (LVEDP) increases and later LVEF decreases [12]. Most patients with severe left ventricular (LV) myocardial fibrosis reported symptoms after AVR despite normal preoperative LVEF [9]. Thus, preoperative evaluation of LV fibrosis or LVEDP appears to provide more accurate information to decide the timing of AVR than LVEF. However, these parameters are too invasive and expensive to repeat follow-up to decide the timing of surgery, especially in senile patients.

Several studies have shown that the echocardiographic measurement of left atrial minimum volume (LAV_{min}) at end-diastole determined by direct exposure of LVEDP provides information on LVEDP or LV diastolic dysfunction [13–15]. Preoperative LAV_{min} measurement may be useful as a surrogate marker of postoperative symptoms in patients with AS. Thus, we attempted to examine the ability of preoperative LAV_{min} index ($LAVI_{min}$) as a surrogate marker of symptomatic status after AVR in patients with AS.

Methods

Study population

We studied retrospectively 219 consecutive patients with AS who underwent AVR at our hospital from April 2008 to March 2015. Exclusion criteria were: a history of coronary artery disease (CAD) varying from silent ischemia, stable angina pectoris, or old myocardial infarction to prior coronary artery bypass graft surgery or percutaneous coronary intervention, significant mitral and/or tricuspid valve disease, atrial fibrillation rhythm and/or pacemaker rhythm at the timing of preoperative echocardiography, congenital heart diseases, infectious endocarditis, and inadequate echocardiographic images (Fig. 1). The institutional medical ethics committee of Wakayama Medical University approved the study protocol, and opt-out consent method was given.

Symptomatic status

A clinical examination assessing symptoms and signs of heart failure was performed before surgery and repeated follow-up for 600 days after AVR. Assessment of New York Heart Association (NYHA) functional class was performed retrospectively by review of the medical records in all cases. We defined the postoperative symptomatic status as the symptom of NYHA functional class II to IV between 60 days to 600 days after AVR.

Echocardiographic assessment

Echocardiographic studies were performed and analyzed on Vivid E9 and 7 ultrasound machine (GE Vingmed Ultrasound AS, Horten, Norway), and EPIQ and iE33 ultrasound machine (Philips Ultrasound, Bothell, WA, USA) before surgery. The echocardiographic data were analyzed blinded to all clinical information. Aortic valve area (AVA) was estimated with quantitative Doppler using the continuity equation. AVA was indexed by body surface area (BSA) and abbreviated as AVAI. Peak and mean aortic valve pressure gradient (AV-PG) were obtained by placing the continuous wave Doppler cursor as parallel as possible with the flow across the valve. LVEF was estimated by the bi-apical Simpson method [16].

The E- and A-wave and deceleration time (Dct) were measured by mitral inflow profile assessed in the apical 4-chamber view using pulsed-wave Doppler echocardiography with the sample volume paced at the tips of mitral leaflets during diastole. The e' velocity from septal and lateral mitral valve annulus was measured by Doppler tissue imaging of the mitral annulus in the apical 4-chamber view. The mean E/e' ratio was calculated by them. LV mass was estimated using Devereux's method [16]. Measurements for LV mass were indexed by BSA and abbreviated as LVMI. Pulmonary artery systolic pressure (PASP) was measured from the maximal continuous-wave Doppler velocity of the tricuspid regurgitant jet using the systolic transtricuspid pressure calculated by the modified Bernoulli equation. Diastolic dysfunction grade (grade 0–3) was determined using the ASE and the European Society of Cardiovascular Imaging (ASE/EACVI) diastolic dysfunction grading system [17]. Right atrial pressure was estimated from the inferior vena cava diameter and collapsibility [18].

LAVs were measured using biplane method of disks at end-systole just before mitral valve opening (LAV_{max}) and end-diastole just before mitral valve closure (LAV_{min}). In each view, the LA wall was traced, excluding the LA appendage and pulmonary veins. LAV_{max} and LAV_{min} were indexed by BSA ($LAVI_{max}$ and $LAVI_{min}$). Left atrial emptying fraction (LAEF) was defined as fractional volume changes as the following formula: $\{[(LAV_{max} - LAV_{min})/LAV_{max}] \times 100\%\}$ [19].

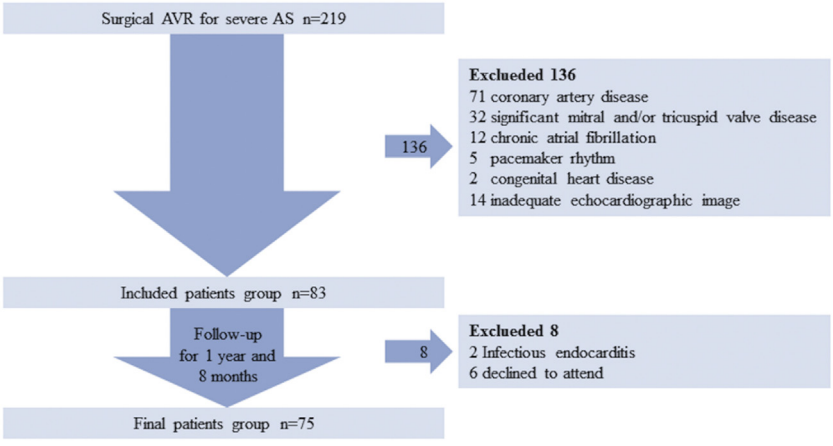


Fig. 1. Study flow chart. In total, 219 patients who underwent surgical aortic valve replacement (AVR) for aortic stenosis (AS) were screened at our institution (Wakayama Medical University Hospital, Wakayama, Japan), and 136 patients were excluded [coronary artery disease ($n = 71$), significant mitral and tricuspid valve disease ($n = 32$), chronic atrial fibrillation ($n = 12$), pacemaker rhythm ($n = 5$), congenital heart diseases ($n = 2$), and inadequate echocardiographic images ($n = 14$)]. During follow-up, there were 2 patients with infectious endocarditis, and 6 patients declined follow-up. 75 patients were included in the final data set.

Reproducibility

Reproducibility of LAV_{max} and LAV_{min} measurement was assessed in 10 randomly selected patients. The LAV_{max} and LAV_{min} were remeasured by the original reader and by a second reader in a blinded fashion. Intra-observer variability was calculated as the absolute difference between the first and second determination for a single observer and expressed as a percentage of the average value. Inter-observer variability was calculated as the absolute difference between the measurements of two observers and expressed as a percentage of the average value.

Statistical analysis

Data are presented as mean ± SD, number (percentage), and median (interquartile range), respectively. Fisher's exact test (categorical variables) or Student *t* test (continuous variables) was used for differences between two groups. Differences between groups were tested by Mann–Whitney *U* test for non-normally distributed continuous variables (serum biomarker). The statistical analyses including intra-class correlation coefficients (ICC) were performed with JMP® 13 (SAS Institute, Cary, NC, USA). The diagnostic accuracy to predict postoperative symptoms in patients with AS after AVR was determined by receiver operating characteristic (ROC) analysis with JMP® 13. Their precision was calculated by EZR version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). The area under the curve (AUC) for each parameter was compared. The comparison between ROC curves was performed with Benjamini–Hochberg method for multiple testing correction based on false discovery rate with R software version 3.5.0 (R Foundation for Statistical Computing). All *p*-values ≤0.05 were considered statistically significant. We used a multivariate logistic regression model that involved the following variables: age, sex, body mass index (BMI), chronic obstructive pulmonary disease (COPD), hemoglobin, which clinically relevant potential confounding factors of symptomatic status, and preoperative echocardiographic parameter which was identified by the ROC analysis. These analyses were performed with JMP® 13.

Results

Baseline patient characteristics

In total, 219 patients who underwent AVR for AS were screened, and 136 patients were excluded [CAD (n = 71), significant mitral and/or tricuspid valve disease (n = 32), chronic atrial fibrillation (n = 12), pacemaker rhythm (n = 5), congenital heart diseases (n = 2), inadequate echocardiographic images (n = 14)]. During follow-up, there were 2 patients with infectious endocarditis, and 6 patients declined follow-up. A total of 75 patients were included in the final data set (Fig. 1). In the final data set, there was no patient who died during 600 days of follow-up. The baseline characteristics of all 75 patients are listed in Table 1. The median age was 75 years, and 46 of 75 (61.3%) patients in this study were female; 16 patients (21.3%) had no symptoms before AVR, and all of them were asymptomatic after AVR. During follow-up, 19 patients (25.3%) developed postoperative symptoms. Among them, 4 patients (5.3%) experienced hospital readmission due to congestive heart failure during 600-days of follow-up after AVR. The final study patients were divided into 2 groups according to presence or absence of postoperative symptoms. Age, NYHA functional class, and serum brain natriuretic peptide were significantly different between the two groups. Sex, COPD, and diabetes mellitus were also different although they were non-significant. BSA, BMI, cigarette smoking, hypertension, dyslipidemia, diabetes mellitus, serum hemoglobin, and serum creatinine were similar between the two groups.

Preoperative echocardiographic data

The preoperative echocardiographic variables are shown in Table 2. There were significant differences in E/A, mean E/e',

Table 1
Baseline characteristics of the study population.

Characteristics	All patients (n = 75)	Postoperative symptomatic group (n = 19)	Postoperative asymptomatic group (n = 56)	p-Value
Age (years)	75.3 ± 6.7	77.9 ± 5.1	74.4 ± 7.0	**0.05**
Sex (female)	46 (61.3)	14 (73.7)	32 (57.1)	0.28
Body surface area (m^2)	1.5 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	0.52
Body mass index (kg/m^2)	22 ± 4	23 ± 5	22 ± 4	0.39
Clinical history				
COPD	9 (12.0)	4 (21.1)	5 (8.9)	0.22
Cigarette smoker	19 (25.3)	5 (26.3)	14 (25.0)	1.00
Hypertension	54 (72.0)	14 (73.7)	40 (71.4)	0.77
Dyslipidemia	41 (54.7)	9 (47.4)	32 (57.1)	0.60
Diabetes mellitus	20 (26.7)	8 (42.1)	12 (21.4)	0.13
NYHA[a] I	16 (21.3)	0 (0)	16 (28.6)	<**0.01**
NYHA[a] II	24 (32.0)	5 (26.3)	19 (33.9)	
NYHA[a] III	17 (22.7)	11 (57.9)	6 (10.7)	
NYHA[a] IV	18 (24.0)	3 (15.8)	15 (26.8)	
NYHA[a] III-IV	35 (46.7)	14 (73.7)	21 (37.5)	<**0.01**
Laboratory results				
Serum hemoglobin (g/dL)	11.3 ± 1.6	10.9 ± 1.2	11.5 ± 1.7	0.12
Serum creatinine (mg/dL)	1.1 ± 1.6	1.2 ± 1.4	1.1 ± 1.6	0.76
Serum BNP (pg/ml)	151 (62–602)	602 (158–1089)	127 (49–468)	<**0.01**
Surgical techniques				
Mechanical prosthesis	6 (8.0)	1 (5.3)	5 (8.9)	1.00
Prosthetic valve size (mm)	19 (19–21)	19 (19–19)	19 (19–21)	0.19

Values are median ± SD, n (%), or median (interquartile range). **Bold** p-value is statistically significant.
COPD, chronic obstructive pulmonary disease; BNP, brain natriuretic peptide; NYHA, New York Heart Association.
[a] NYHA functional class was documented at the preoperative time.

Table 2
Preoperative echocardiographic data.

Characteristics	All patients ($n = 75$)	Postoperative symptomatic group ($n = 19$)	Postoperative asymptomatic group ($n = 56$)	p-Value
AVAI (cm^2)	0.49 ± 0.09	0.50 ± 0.10	0.48 ± 0.09	0.69
Peak aortic valve pressure gradient (mmHg)	93.2 ± 23.1	89.5 ± 30.1	94.5 ± 20.4	0.42
Mean aortic valve pressure gradient (mmHg)	57.1 ± 15.9	54.3 ± 19.8	58.0 ± 14.5	0.39
LVEDVI (ml/m^2)	63.4 ± 17.5	61.8 ± 12.8	63.9 ± 18.9	0.66
LVESVI (ml/m^2)	27.9 ± 15.1	26.7 ± 12.5	28.3 ± 16.0	0.69
LVEF (%)	57.8 ± 11.4	58.1 ± 12.1	57.7 ± 11.2	0.89
E/A ratio	0.78 ± 0.28	0.95 ± 0.32	0.72 ± 0.24	<**0.01**
Dct (ms)	270.6 ± 90.6	258.1 ± 98.1	275.0 ± 88.4	0.49
Mean E/e' ratio	19.9 ± 10.9	24.9 ± 2.5	18.2 ± 1.5	**0.02**
LVMI (g/m^2)	117.2 ± 26.6	112.3 ± 21.1	118.8 ± 28.1	0.34
$LAVI_{max}$ (ml/m^2)	50.2 ± 15.7	59.8 ± 14.8	46.8 ± 14.6	<**0.01**
LAVImin (ml/m^2)	32.0 ± 14.0	44.9 ± 14.6	27.6 ± 10.8	<**0.01**
LAEF (%)	38.6 ± 12.4	28.7 ± 12.4	42.0 ± 10.5	<**0.01**
PASP (mmHg)	34.7 ± 12.3	43.9 ± 16.6	32.0 ± 9.4	<**0.01**
Diastolic dysfunction grade I	29 (41)	4 (22)	25 (47)	0.10
Diastolic dysfunction grade II	42 (59)	14 (78)	28 (53)	
Diastolic dysfunction grade III	0 (0)	0 (0)	0 (0)	
RVFAC (%)	49.6 ± 11.0	48.3 ± 11.6	50.0 ± 10.9	0.59

Values are median ± SD, or n (%). **Bold** p-values are statistically significant.
AVAI, aortic valve area index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; E/A ratio, ratio of early to late ventricular filling velocities; Dct, deceleration time; e', peak early diastolic velocity of the mitral annulus displacement; LVMI, left ventricular mass index; $LAVI_{max}$, left atrial maximum volume index; $LAVI_{min}$, left atrial minimum volume index; LAEF, left atrial emptying fraction; PASP, pulmonary artery systolic pressure; RVFAC, right ventricular fractional area change.

$LAVI_{max}$, $LAVI_{min}$, LAEF, and PASP between the patients with and without postoperative symptoms. There were no significant differences in AVAI, AV-PG, LVEDVI, LVESVI, LVEF, Dct, LVMI, and RVFAC between the two groups.

ROC analyses

Fig. 2 demonstrates ROC curves of the ability of the echocardiographic variables with significant differences between the two groups to identify patients with postoperative symptomatic status. $LAVI_{min} \geq 30$ ml/m^2 predicted postoperative symptoms with the largest AUC (0.84) among all echocardiographic parameters. The sensitivity and specificity of $LAVI_{min} \geq 30$ ml/m^2 were 94% (95% CI 71.3%, 99.9%) and 68% (95% CI 53.3%, 80.5%). Comparison of ROC curves showed that $LAVI_{min}$ was significantly better for identifying postoperative symptomatic status than mean E/e' ($p < 0.01$) and LVEF ($p < 0.05$).

Predictors of postoperative symptomatic status after AVR

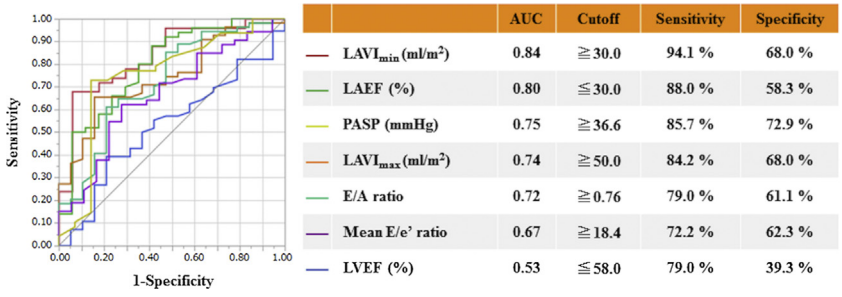
The following variables: age, sex, BMI, COPD, hemoglobin, and $LAVI_{min}$ were retained for multivariate analysis. Preoperative $LAVI_{min}$ was the independent predictor of the postoperative symptomatic status during 600 days of follow-up after AVR [odds ratio (OR): 1.11; 95% CI: 1.04–1.18].

Reproducibility of LA volumes

The intra-observer variability for the measurement was LAV_{max} (10.7 ± 7.7%) and LAV_{min} (9.6 ± 6.6%). The intra-observer ICC was 0.96 (95% CI, 0.85–0.99) for LAV_{max} and 0.93 (95% CI, 0.72–0.98) for LAV_{min}. The inter-observer variability for the measurement was LAV_{max} (11.2 ± 6.6%) and LAV_{min} (14.4 ± 6.9%). Inter-observer ICC was 0.93 (95% CI, 0.71–0.98) for LAV_{max} and 0.89 (95% CI, 0.59–0.97) for LAV_{min}.

Discussion

In the present study, we showed that preoperative $LAVI_{min}$ was closely associated with the postoperative symptomatic status in senile patients with AS. In addition, $LAVI_{min}$ independently predicts postoperative symptoms in the present study patients. To the best of our knowledge, this is the first study to examine the ability of preoperative $LAVI_{min}$ for the prediction of symptomatic status after AVR in patients with AS.



	AUC	Cutoff	Sensitivity	Specificity
$LAVI_{min}$ (ml/m^2)	0.84	≧30.0	94.1 %	68.0 %
LAEF (%)	0.80	≦30.0	88.0 %	58.3 %
PASP (mmHg)	0.75	≧36.6	85.7 %	72.9 %
$LAVI_{max}$ (ml/m^2)	0.74	≧50.0	84.2 %	68.0 %
E/A ratio	0.72	≧0.76	79.0 %	61.1 %
Mean E/e' ratio	0.67	≧18.4	72.2 %	62.3 %
LVEF (%)	0.53	≦58.0	79.0 %	39.3 %

Fig. 2. Receiver-operating characteristic curves comparing the relationship of left atrial minimum volume index ($LAVI_{min}$), left atrial ejection fraction (LAEF), pulmonary artery systolic pressure (PASP), left atrial maximum volume index ($LAVI_{max}$), E/A ratio, mean E/e' ratio, left ventricular ejection fraction (LVEF), and symptomatic status after aortic valve replacement. AUC, area under the curve.

Value of preoperative LAV measurement for the prediction of postoperative symptomatic status

The close correlation between the left atrial size and LV filling pressures measured by cardiac catheterization was demonstrated in a previous study [13]. Increase in LA size and reduction in LAEF are induced by chronic increase in LV end-diastolic pressure because LA is directly exposed to the LV pressure during diastole and affected by increased LV pressure. Previous studies showed that LAV_{min} and LAEF had better correlation with LV diastolic function in comparison with LAV_{max} [14,15]. Although LAV_{max} measured at end-systole has been generally used as the index for LA function, LAV_{min} may be a more sensitive marker of diastolic dysfunction compared with LAV_{max} [14].

The present study showed preoperative $LAVI_{min} \geq 30$ ml/m^2 yielded the largest AUC (0.84) (sensitivity 94% and specificity 68%) to detect the postoperative symptomatic status among all echocardiographic indexes for diastolic function although there were significant differences in the other indexes between the two groups. $LAVI_{min}$ was measured just at end-diastole directly exposed to the LVEDP while the other parameters including E/A, $LAVI_{max}$, and PASP were not measured at end-diastole. Therefore, increased $LAVI_{min}$ as the most sensitive sensor of increased LVEDP was most closely associated with postoperative symptomatic status in patients with AS in this study.

In addition, we found that preoperative LAEF $\leq$ 30% had the second larger AUC (0.80) for the prediction of postoperative symptomatic status with the sensitivity of 88% and the specificity of 58%. The cut-off value of LAEF for the prediction of postoperative symptoms in this study was similar to the optimal LAEF threshold for predicting increased LV filling pressure (LAEF $\leq$ 30%) [15] or that of elevated LVEDP (LAEF $\leq$ 35%) [20]. Preoperative LAEF which is estimated from both LAV_{max} and LAV_{min} may also be a robust marker of the postoperative symptomatic status in severe AS.

Study limitations

The main limitation of this study was that the evaluation of clinical outcome was assessed only by qualitative assessment by NYHA functional class. Six-minute walking test or cardiopulmonary exercise test would allow a more precise quantification of exercise capacity after AVR. Second, our sample size, especially number of patients with postoperative symptomatic status was relatively small. Our results need to be confirmed in larger and prospective studies. Third, the study population in this study excluded subjects with CAD, significant mitral valve or tricuspid valve disease to eliminate the effect of these comorbidities. Thus, our results may not fully apply to every patient with AS. In fact, there were no patients who required a prolonged stay in an intensive care unit after AVR or who died during follow-up. Value of LAV_{min} for the prediction of postoperative symptoms may be limited to the patients without significant CAD or other valvular diseases. Fourth, 2D echocardiographic measurement of LAV may not be accurate in some cases because of the inability to obtain adequate cross-sections or the complexity of LA shape [21] although 2D echocardiography is currently standard method for LAV measurement [16]. Previous studies have shown LAV_{min} assessed by 3D echocardiography is a better correlate of LV diastolic function [14]. If 3D echocardiography is available, it may be ideal for the measurement of LAVs. The prospective study using 3D echocardiography may be necessary in the future. Finally, this study showed that $LAVI_{min} \geq 30$ ml/m^2 was very sensitive (sensitivity 94%) but not so specific (specificity 68%) for the prediction of postoperative symptomatic status. It suggests that reverse remodeling of large left atrium can occur after AVR [22]. Postoperative large $LAVI_{min}$ or postoperative change of large LAVI may be an important parameter of postoperative symptomatic status. The value of these postoperative indexes should be evaluated in the next study including more patients.

Conclusion

The preoperative echocardiographic $LAVI_{min}$ measurement is useful as a surrogate marker of symptomatic status after AVR in patients with AS.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

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