

# Predictors of early restenosis after intracardiac echocardiography guided antegrade balloon aortic valvuloplasty in high-risk or inoperable patients

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Received: 17 June 2016 / Accepted: 20 December 2016 / Published online: 20 January 2017  
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**Abstract** Antegrade balloon aortic valvuloplasty (BAV) may be more effective than retrograde BAV. However, early restenosis is found inconstantly within three months after BAV. To evaluate the factor of ER after intracardiac echocardiogram (ICE) guided Antegrade BAV, fifty patients with severe aortic stenosis (AS) underwent BAV procedures with ICE. ER was defined as mean aortic valve pressure gradient (PG) >40 mmHg. During one-year follow-up period, 6 patients died and 2 patients underwent aortic valve replacement. ER was present in 13 patients (26%) at three months after BAV. Procedural, clinical, and hemodynamic data were collected. The mean age of the patient population was  $85.4 \pm 7.6$  years; the mean STS score and EuroSCORE were  $7.8 \pm 1.1$  and  $14.6 \pm 4.1$ , respectively. The mean aortic valve PG decreased from  $63.4 \pm 19.8$  to  $28.5 \pm 10.1$  mmHg ( $p < 0.0001$ ). Baseline characteristics were similar between the two groups. There is no significant difference of mean aortic valve PG immediate after BAV (ER;  $29 \pm 8.8$  mmHg, nonER;  $21 \pm 6.1$  mmHg,  $p = ns$ ). Univariate analysis showed patients with ER group had significantly higher rate of left ventricular hypertrophy, pulmonary hypertension, and high mean aortic valve PG at admission. Multivariate analysis revealed high mean aortic valve PG at admission as independent predictors of ER. Antegrade BAV may be effective for severe AS. Left ventricular hypertrophy, pulmonary hypertension and high mean PG were predictor

of early restenosis. Early intervention should be considered for these patients.

**Keywords** Aortic stenosis · Antegrade balloon valvuloplasty · Intracardiac echocardiography · Early restenosis

## Introduction

Balloon aortic valvuloplasty has previously been used as a palliative procedure but has possibly been underused in patients with symptomatic aortic stenosis not suitable for surgical aortic valve replacement (AVR) [1]. Recently, BAV has been reconsidered as a bridge to surgical AVR or transcatheter aortic valve implantation (TAVI). Previous reports have shown that immediate adverse outcomes of BAV were not trivial, ranging from 15 to 43% for major procedural complications and from 1.6 to 10% for procedural and in-hospital mortality [2–10]. These reports described the results of the retrograde BAV procedure, and there remain few reports of antegrade transseptal BAV, mainly because this is considered to be a complex procedure.

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have been used for guidance of intervention procedure. However, both modalities require an additional operator and their risk for radiation exposure is an important consideration. Despite this, TEE remains useful for transseptal puncture and monitoring of aortic valve dilation, aortic regurgitation, and pericardial effusion. In addition, TEE is also sometimes used invasive for severe aortic stenosis and when prolonged or general anesthesia is needed.

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Recently, ICE has resolved many of these limitations and is increasingly used during cardiac interventions [11]. An ICE catheter positioned in the right atrium can provide a clear visualization of the interatrial septum and fossa ovalis. ICE can be used to guide transseptal puncture repeatedly without complications, even in inexperienced hands [12].

In addition, the antegrade approach resulted in 20% increase in aortic valve area (AVA) compared to the group treated by the retrograde approach [13].

However, early restenosis (ER) is found inconstantly within three month after BAV. The aim of study was to evaluate the factor of ER after intracardiac echocardiogram (ICE) guided antegrade BAV.

## Methods

### Patient populations

From March 2012 to March 2015, data from 50 antegrade transseptal BAV procedures with symptomatic severe AS were obtained. The mean age was  $85.4 \pm 7.6$  years and 27 pts (54%) of patients were female. The mean STS and Euro score was  $7.8 \pm 1.1$  and  $14.6 \pm 4.1$ . For all patients, a discussion was held regarding surgical aortic valve replacement. Surgical aortic valve replacement was refused by 32 (64%) patients and their families due to advanced age and comorbidity. The reasons for BAV as palliative treatment were: advanced age (>90 years; 13 patients, 26%), cancer (9 patients, 18%), previous cardiovascular surgery (3 patients, 6%), bridge to non-cardiac surgery (5 patients, 10%), and severe cerebrovascular disease (2 patients, 4%). Twenty-six patients (52%) had clinical symptoms of heart failure NYHA class III or IV. All patients had severe AS, as confirmed by transthoracic echocardiography at rest or dobutamine stress echocardiography. The STS score and the logistic EuroSCORE II (European System for Cardiac Operative Risk Evaluation) were calculated for all patients.

### Valvuloplasty

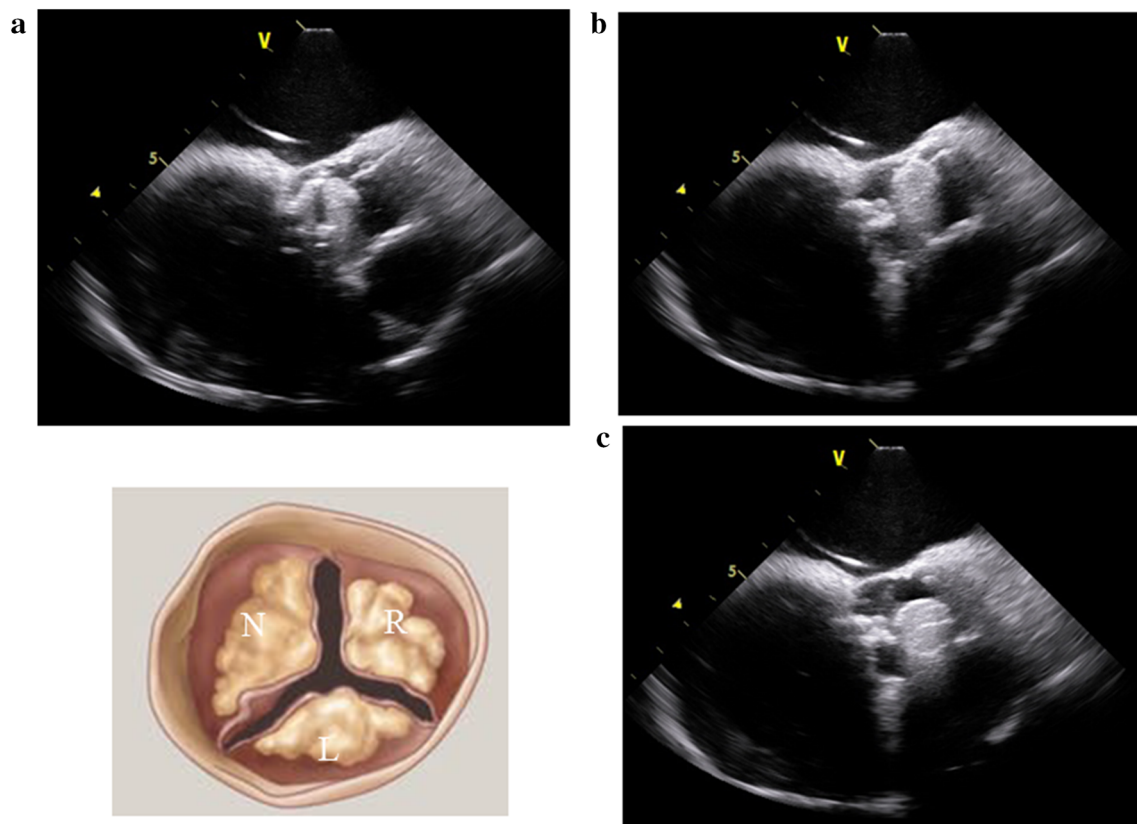
#### *Computed tomography*

Patients underwent cardiac CT assessment using a 320-row detector CT scanner (Aquilion ONE, Toshiba Medical Systems, Tochigi, Japan). The CT protocol consisted of rest coronary CTA followed by cardiac CT. Cardiac CT was performed to exclude thrombus in patients with atrial fibrillation or a dilated ventricle. Right femoral venous, left femoral arterial, left femoral venous, and right radial artery access were obtained. The size of the aortic valve annulus

was calculated from the traced annulus area and also the perimeter by CT. However, all patients did not undergo CT with contrast for reasons of renal function and congestive heart failure. These patients underwent plain CT.

#### *Procedure*

Coronary angiography via a 6Fr left femoral artery long sheath was obtained if coronary stenosis was suspected by coronary CTA. Systemic pressure was then used to monitor the same sheath. A 6Fr thermodilution pulmonary catheter was advanced from the 14Fr right femoral vein long sheath and the hemodynamics was measured. ICE was performed via a 8 or 9Fr left femoral vein long sheath. Pacing lead was placed in right ventricular apex via a 5Fr left femoral long sheath in preparation for bradycardia or the need for rapid pacing. Heparin was administered to maintain an activated coagulation time between 250 and 350 s. Standard transseptal puncture was performed using ICE and a 8Fr Mullins sheath was advanced to the left atrium. Pre-operative transaortic valve peak and mean pressure gradient were measured. Stenotic AVA was calculated from pressure tracing and cardiac output by the Gorlin formula. A 6 Fr balloon-tipped catheter was advanced from the Mullins sheath through the left atrium and left ventricle. A left ventricular loop was formed using Inoue wire and a hydrophilic 260 cm 0.035 inch angled wire. After the guide wire passed across the aortic valve, the balloon-tipped catheter was advanced into the descending aorta. The balloon-tipped catheter was then snared by a 15 mm snare catheter from a 6Fr left femoral artery long sheath. Hydrophilic 0.035 inch angled wire was subsequently exchanged for a 260 cm extra stiff 0.032 inch wire. The distal part of this wire was also snared and tied up at the descending aorta. Pig tail catheter was placed valsalva sinus for root shot. The Inoue balloon was prepared at 2 mm under size calculated annular diameter. Inoue balloon was advanced from 14Fr right femoral vein long sheath to the aortic valve along the guide wire loop. The Inoue balloon was then dilated step-by-step. Aortic and mitral valve regurgitation, left ventricular motion, and pericardial effusion were monitored by ICE. The final balloon size was determined using the annular diameter calculated by CT area and ICE image. After final dilation, the postoperative transaortic valve peak and mean pressure gradient were measured. Our goal was to achieve a mean aortic valve pressure gradient <40 mmHg or a calculated aortic valve area over  $1 \text{ cm}^2$ . If a suboptimal result occurred, additional balloon dilation was performed. We attempted to dilate each commissure of aortic valve by changing the guide wire loop formation via guided ICE (Fig. 1). Half of our patients were performed this strategy successfully.



**Fig. 1** Dilatation of each commissure. Balloon was dilated each commissure of aortic valve by changing the guide wire loop formation via guided ICE. **a** Balloon started to dilate non-coronary

cusps and left coronary cusp. **b** Same situation of non-coronary cusp and right coronary cusp. **c** Same situation of right coronary cusp and left coronary cusp

### Echocardiography

An experienced ultrasonographer utilizing commercially available ultrasound systems performed comprehensive examinations on all patients before and after BAV. The AVA was calculated with the continuity equation. Peak and mean aortic valve pressure gradients were also measured. Left ventricular hypertrophy was defined as interventricular septum (IVS) + posterior wall (PW). ER was defined as mean aortic valve pressure gradient (PG) >40 mmHg within three months after BAV.

### Definitions

#### Procedural complication

Major adverse cardiac events were defined as perioperative death, neurological event, respirator use, hemodynamic complication (prolonged hypotension cardiopulmonary resuscitation required, pulmonary edema, cardiac tamponade, IABP use, acute mitral or aortic valvular insufficiency, cardiogenic shock), arrhythmia, tamponade, permanent pacemaker, vascular complication (transfusion required), and ischemia.

### In-hospital and mid-term outcome

In-hospital and mid-term clinical events were determined from a review of medical records. The median duration of follow-up was  $11.6 \pm 6.1$  month. TAVI was not approved early phase of this series. All patients were considered indication of TAVI. After approval for TAVI, 14 patients were treated by TAVI.

### Statistical analysis

Differences between continuous variables were assessed by the Student's *t* test. Paired tests were analyzed by paired Student's *t* test. Categorical variables were compared using the  $\chi^2$  test or Fisher's exact test as indicated. Significance was set at  $p < 0.05$ . The receiver-operating characteristic (ROC) curve was determined to evaluate the predictable performance of ER. Optimal cut-off points for the ER were chosen when sensitivity and specificity were maximized. Statistical significance was defined as  $p < 0.05$ . All statistical analyses were performed using SPSS 18.0 (IBM SPSS Statistics, IBM Corp.) software.

## Results

### Hemodynamic and valve area change

Average mean aortic valve pressure gradients improved from  $60.4 \pm 19.8$  to  $24.8 \pm 10.1$  mmHg ( $p < 0.0001$ ) immediately after BAV. Aortic valve area increased from  $0.580 \pm 0.22$  to  $1.090 \pm 0.34$  cm<sup>2</sup> ( $p < 0.001$ ). There is no significant difference of final balloon size (ER:  $21.4 \pm 1.25$  mm vs  $21.3 \pm 1.33$ ,  $p = 0.88$ ).

### Procedural complications

The median hospital duration after BAV was  $7.4 \pm 7.1$  days [interquartile range (IQR): in days]. First 20 cases were longer than last 30 cases ( $10.5 \pm 8.7$  vs  $5.2 \pm 4.3$ ,  $p < 0.05$ ). There were no cases of perioperative deaths, arrhythmia, ischemic complications, or heart failure. However, transient speech disturbance was reported by one patient. The patient fully recovered after a few weeks. One vascular complication (2%) necessary for transfusion occurred. One patient (2%) died due to pneumonia caused by myeloma. Two hemodynamic complications (4%) also occurred, and both involved prolonged hypotension, lasting a few minutes until the wire loop was released. However, there was no cardiopulmonary resuscitation, intubation, requirement for cardioversion, shock, pulmonary edema, cardiac tamponade, IABP or PCPS use, acute mitral or aortic valvular insufficiency, cardiogenic shock or permanent pacemaker (Table 1). A distinct learning curve was found in our series evidenced by the observation that the first 20 cases had a longer catheter laboratory stay time than last 30 cases ( $107 \pm 34$  vs  $87 \pm 21$  min,  $p < 0.05$ ).

### Outcome

After discharge, no patient deaths were reported in the following 30 days. However, during this nearly one year follow-up period, 6 patients (12%) died and 2 patients (4%)

**Table 1** Procedural complications

Complication	N (%)
Cardiac death	0
Patients with any complication	5 (12.8%)
Hemodynamic (prolonged hypotension within 5 min)	2 (5.1%)
Neurological (temporary focal neurological event)	1 (2.6%)
Respiratory	0
Arrhythmia	0
Vascular (transfusion required)	1 (2.6%)
Ischemic	0
Other severe complications (pneumonia)	1 (2.6%)

underwent aortic valve replacement. Reasons for deaths were 2 cardiac, 2 pneumonia, 1 cancer, and 1 stroke. Two cardiac deaths were caused by congestive heart failure due to severe aortic stenosis. They denied repeat BAV. In our cohort, ER patients without re-intervention were considered too sick and no indication for TAVI by heart team conference.

### Restenosis

ER was present in 13 patients (26%) at three months after BAV. Baseline characteristics showed ER group obtained high frequency of female and pulmonary hypertension (Table 2).

In ER patients, one patient died for CHF, two patients were repeated with BAV. However, admission of heart failure within 1 year after BAV was in 7 patients (14%), including 3 patients without restenosis. There is no significant difference of mean aortic valve PG immediate after BAV (ER;  $29 \pm 8.8$  mmHg, non ER;  $21 \pm 6.1$  mmHg,  $p = ns$ ). Univariate analysis showed patients with ER group had significantly higher rate of left ventricular hypertrophy (IVS + PW;  $27.5 \pm 2.5$  vs  $24.4 \pm 4.4$ ,  $p < 0.05$ ), pulmonary hypertension ( $44.9 \pm 4.7$  vs  $35.4 \pm 2.4$ ,  $p < 0.05$ ), and high mean aortic valve PG at admission ( $63.1 \pm 4.1$  vs  $44.6 \pm 3.7$ ,  $p < 0.00005$ ). Multivariate analysis revealed high mean aortic valve PG at admission as independent predictors of ER (Table 3). The ROC curve of independent predictors of ER was analyzed. The area under the ROC curves of pulmonary artery systolic pressure (PAP) was 0.606 (95% CI 0.397–0.815,  $p = 0.033$ ), left ventricular hypertrophy (LVH) was 0.738 (95% CI 0.559–0.917,  $p = 0.028$ ), and mean aortic valve PG (m-PG) at admission was 0.842 (95% CI 0.691–0.993,  $p = 0.002$ ). Optimal cut-off value of each parameter to

**Table 2** Baseline characteristics

	ER (n = 13)	nonER (n = 37)
Age (years)	$85.2 \pm 6.2$	$86.2 \pm 8.3$
Sex (female)	11 (84%) <sup>#</sup>	16 (43%)
STS score	$6.661 \pm 2.353$	$9.748 \pm 3.636$
Euro score	$12.195 \pm 4.589$	$17.068 \pm 8.272$
NYHA >II	10 (76.9%)	32 (86.5%)
Coronary artery disease	5 (38.5%)	11 (29.8%)
Diabetes mellitus	5 (38.5%)	10 (27.0%)
Pulmonary hypertension	10 (76.9%) <sup>#</sup>	12 (32.4%)
LVH(IVS + PW) (mm)	$27.5 \pm 2.5$ <sup>#</sup>	$24.4 \pm 4.4$
Pulmonary pressure (mmHg)	$44.9 \pm 4.7$ <sup>#</sup>	$35.4 \pm 2.4$
mean pressure gradient on admission (mmHg)	$63.1 \pm 4.1$ <sup>#</sup>	$44.6 \pm 3.7$

<sup>#</sup>  $p < 0.05$

**Table 3** Univariate and multivariate analysis

Factor	OR	95% CI	<i>p</i> value	
Univariate analysis				
LVH(IVS + PW)	1.254	0.99	1.590	0.0340
PH >40 mmHg	5.560	1.078	28.639	0.0460
Pre-procedural mean gradient	1.097	1.029	1.170	0.0047
Multivariate analysis				
Pre-procedural mean gradient	1.124	1.014	1.247	0.0267

detect ER was PAP; 41.5 mmHg, LVH; 25.5 mm and m-PG; 56.5 mmHg (Fig. 2). Sensitivity and specificity of m-PG >56.5 were 84.6 and 89.2%.

## Discussion

This study identified three independent predictors of early restenosis in patients undergoing BAV, namely PAP, LVH, m-PG. Our data also confirmed the safety and utility of ICE-guided antegrade BAV in high-risk or inoperable patients. Recently reported retrograde BAV data showed an incidence of serious adverse events of 15.6 and 1.6% of perioperative death [3]. In contrast, our data showed no serious cardiovascular adverse events and no perioperative death. Only one (2.6%) transient speech disturbance occurred and the symptoms disappeared after a few weeks.

These findings were led by antegrade BAV methods and continuous monitoring of ICE. Sakata et al. [13] reported that the advantages of this approach were a reduction of the risk of arterial complications and utilization of the Inoue balloon, which has a potentially more efficient profile for the dilating degenerated and densely calcific aortic valve with a greater effect of fracturing the calcific nodules on the valve. In addition, the use of the Inoue balloon, which is also easier to position, has a more rapid inflation–deflation profile and is more stable in the aortic valve. However, the technical disadvantages of this approach are need for transseptal puncture, difficulty of wire loop formation inside the left ventricle, and mechanical stress of mitral apparatus and left ventricle. The problem of this loop is stress of cardiac conduction system near the right and non-coronary cusp and mitral valve or subvalvular apparatus. These disadvantages were solved by the use of ICE. Transseptal puncture is relatively easy to achieve by ICE-guided fossa ovalis view, while monitoring the mitral regurgitation is possible by left ventricular long axis view. The left ventricular long axis view is thought to be helpful for detecting the existence of wire loop stress. In addition,

pericardial effusion, aortic or mitral regurgitation, and left appendage thrombus are also visible by this view. Useful information of aortic valve dilation was provided by short axis aortic view. In our experience, it is necessary to add dilations due to suboptimal result of aortic valve area increase or pressure gradient reduction. It is noteworthy that we tried to control the wire loop and dilate each of the aortic valve commissure. Based on early experience, this procedure has a high complication rate. NHLBI Balloon Valvuloplasty Registry Participants [9] showed a mortality incidence of 3 and a 25% incidence of any severe complications within 24 h of the valvuloplasty procedure. The in-hospital stay mortality rate was 10%, with an incidence of any occurrence of severe complications of 61%. Khawaja [14] in a recent report of 423 patients with severe aortic stenosis (mean age, 80.9 years), found an acceptable outcome with a 6.3% procedural complication rate, and 2.4% intraprocedural death rate. However, the 13.8% of 30-day mortality rate was clearly not considered to be low. In our cohort, cardiovascular death (congestive heart failure) developed 2 patients (4%). Antegrade BAV may provide better outcome of these high-risk patients. Factor of poor prognosis were previously reported, that younger age and a lower left ventricular ejection fraction contributed for independent adverse prognostic information [15].

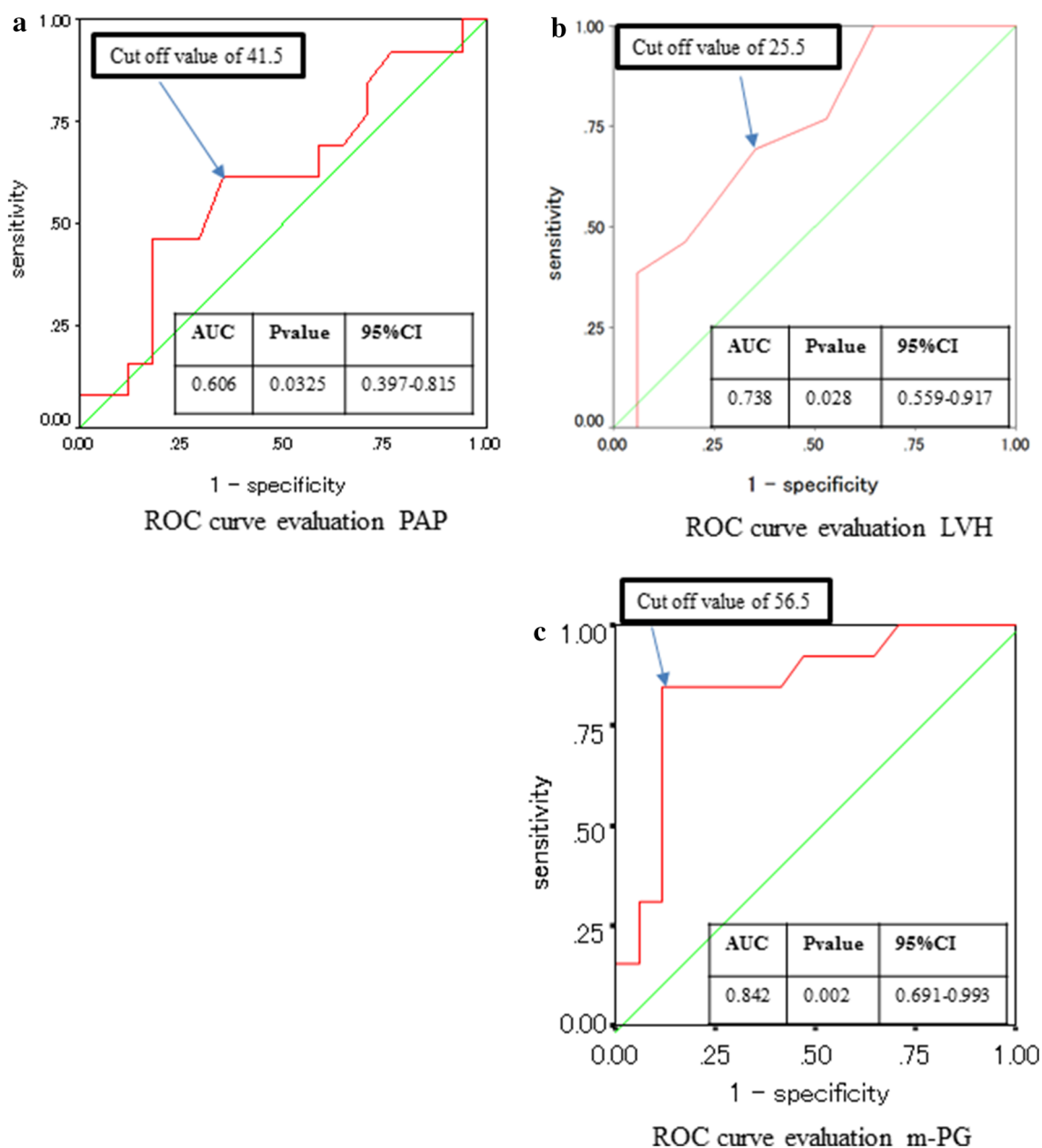
Our data thus confirm a low complication rate, better in-hospital outcomes, and improved 30-day mortality rate and mid-term outcome than previously reported. However, restenosis may affect not only mid-term outcome but also in-hospital or long-term outcome.

Early restenosis occurred about 26% of all patients. Three predictors of ER (higher rate of left ventricular hypertrophy, pulmonary hypertension, and high mean aortic valve PG at admission) mean pre-BAV severity of aortic stenosis. Predictors of restenosis after BAV were reported only congenital aortic stenosis. Aortic valve morphology of these patients was not same as that of high-age adult patients. According to our result, these patients with restenosis predictor should be considered early intervention (AVR or TAVI).

## Study limitations

This study was a retrospective, observational report with several limitations including a small sample size and lack of randomization. Most importantly, there were no procedural deaths or severe cardiovascular complications. Further investigation of ICE-guided antegrade BAV in high-risk or inoperable patients utilizing a larger patient sample





**Fig. 2** Receiver-operating characteristic (ROC) curve evaluating pre-operative systolic pulmonary pressure, left ventricular hypertrophy (IVS + PW), and pre-operative mean aortic valve pressure gradient for prediction of early restenosis (ER). ROC curve identified the threshold PAP of 41.5 mmHg, LVH of 22.5 mm, and mean PG of

56.5 mmHg for prediction of ER. **a** AUC of PAP was 0.606,  $p = 0.0325$  (95% CI 0.397–0.815). **b** AUC of LVH was 0.738,  $p = 0.028$  (95% CI 0.559–0.917). **c** AUC of pre-operative mean PG was 0.842,  $p = 0.002$  (95% CI 0.691–0.993)

size and a prospective, randomized study design is therefore warranted.

## Conclusions

ICE-guided antegrade BAV is feasible, safe, and associated with better short and mid-term outcomes than previously reported for conventional BAV. However, ER occurred

about one quarter patients. Left ventricular hypertrophy, pulmonary hypertension, and high mean PG at admission were predictor of ER. Early intervention should be considered for these patients.

## Compliance with ethical standards

This study complied with the Declaration of Helsinki in regard to investigation in humans and was approved by the institutional ethics committees at Tokushima red cross Hospital. There was no industry

involvement in the design, conduct, financial support, or analysis of this study.

**Conflict of interest** I have no disclosures/support grants and potential conflicts of interest.

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