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Original article

Symptomatic paradoxical low gradient severe aortic stenosis: A possible link to heart failure with preserved ejection fraction

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ABSTRACT

Background: There is an ongoing debate regarding optimal management of patients with paradoxical low gradient severe aortic stenosis (PLG-SAS). We hypothesized that the presence of symptoms is closely associated with future adverse outcome. We aimed to determine the relation between symptoms and outcome in patients with PLG-SAS.
Methods: We prospectively enrolled 222 patients with PLG-SAS. Left ventricular (LV) volumes, mass, and strain were measured by three-dimensional echocardiography. The primary end-point was cardiac events including cardiac death, ventricular fibrillation, and heart failure leading to hospitalization.
Results: There were 65 cases of symptomatic PLG-SAS and 157 cases of asymptomatic PLG-SAS. Patients with symptomatic PLG-SAS received beta-blockers, angiotensin blockers, and diuretics more frequently and showed higher levels of B-type natriuretic peptide than patients with asymptomatic PLG-SAS. Although LV chamber parameters were not different, patients with symptomatic PLG-SAS had significantly higher E-wave velocity and E/A ratio than patients with asymptomatic PLG-SAS. During the median follow-up of 18 months, 20 patients reached the primary end-point. Patients with symptomatic PLG-SAS had significantly worse prognosis than patients with asymptomatic PLG-SAS. A similar trend was observed while comparing with the propensity-score-matched cohort after adjusting for age, sex, stroke volume index, and severity of AS.
Conclusions: Symptomatic PLG-SAS is associated with poorer prognosis even after adjusting for flow status and severity of AS. Therefore, presence of symptoms is not always related to the severity of AS itself but might be related to the underlying comorbidities. Our results suggest a possible link between PLG-SAS and heart failure with preserved ejection fraction in some symptomatic patients.

Introduction

There is an ongoing debate regarding pathophysiology, optimal management, and prognosis of low gradient severe aortic stenosis with preserved left ventricular ejection fraction (LVEF), so-called paradoxical low gradient severe aortic stenosis (PLG-SAS) [1–9]. Current European Society of Cardiology guidelines recommended that "aortic valve replacement (AVR) should be considered in symptomatic patients with low flow, PLG-SAS only after careful confirmation of SAS" [10]. Although several imaging parameters could identify a high-risk group of patients with symptomatic PLG-SAS [11–13], discrepant results from each parameter could not help in making an appropriate decision.

Since PLG-SAS often shares similar clinical features with those of heart failure with preserved ejection fraction (HFpEF) [14,15],

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and reliable diagnosis of HFpEF is not always easy, whether existing symptoms in patients with PLG-SAS are solely related to the AS itself or are mainly linked with HFpEF is unclear. Previous studies have paid less attention to the symptomatic status during the prognosis of patients with PLG-SAS [5]. Therefore, it is important to compare the clinical characteristics and their prognosis of symptomatic and asymptomatic patients with PLG-SAS. A recent meta-analysis revealed that AVR is associated with favorable outcome in patients with PLG-SAS [16]. However, less information exists whether pressure gradient (PG) status remains constant or converts from low PG (LPG) to high PG (HPG) at the time of aortic valve surgery.

Accordingly, we aimed: (1) to compare clinical and echocardiography parameters between symptomatic and asymptomatic patients with PLG-SAS; (2) to determine their prognosis; and (3) to investigate the PG status at the time of aortic valve surgery and the impact of AVR on prognosis.

Materials and methods

Study patients

This study was a part of the prospective multicenter observational study in patients with aortic stenosis (AS) [Japanese Multicenter Aortic Stenosis Study, Prospective (JUST-P) registry]. From January 2013 to December 2014, we acquired transthoracic 3D echocardiography (3DE) datasets of patients with AS who underwent clinically indicated echocardiographic examinations in four Japanese cardiovascular centers. Of 618 AS patients enrolled during the study period, we excluded 396 patients due to poor echo image quality ($n = 36$), reduced LVEF ($n = 104$), mild to moderate AS ($n = 118$), HPG-SAS ($n = 137$), and whose follow-up data were not available ($n = 1$). The remaining 222 patients with PLG-SAS were considered as a final group of study subjects. LPG was defined as mean PG of $<$40 mmHg across the aortic valve on Doppler echocardiography. Stroke volume (SV) was calculated using 3DE. Flow status was divided into two groups [normal flow: stroke volume index (SVI) $\geq$ 35 mL/m^2, and low flow: SVI $<$ 35 mL/m^2]. Indexed aortic valve area (iAVA) was defined as SV measured by 3DE divided by the velocity time integral of peak aortic valve jet velocity indexed by body surface area. SAS was defined as iAVA of $<$0.6 cm^2/m^2. The study protocol was approved by the Ethics Committee of each hospital, and informed consent was obtained from all patients.

Clinical characteristics

At the time of echocardiographic examination, a cardiologist directly asked the patients regarding symptomatic status with chest pain, syncope, and dyspnea. Blood test reports within $<$3 months of indexed echocardiography were collected from the electronic medical records.

Echocardiography

Comprehensive transthoracic 2D echocardiography (2DE) and Doppler echocardiography were performed according to the American Society of Echocardiography guideline [17]. Aortic valve jet velocity was recorded in multiple transducer positions in order to obtain the highest jet velocity signal. Envelope of peak velocity was manually traced, yielding peak velocity, mean PG, and velocity time integral. LV inflow velocity was obtained at the tip of the mitral leaflets, and mitral annular velocity was recorded at the septal corner of the mitral annulus. E/e' was calculated. Maximum left atrial volume was measured by biplane Simpson's method. Systolic pulmonary arterial pressure was estimated by the formula: [4 $\times$ (peak velocity of tricuspid regurgitation)^2 + right atrial pressure]. Right atrial pressure was estimated based on the inferior vena cava diameter and its change during respiration [18].

Full-volume 3DE datasets were acquired using an apical approach with fully sampled matrix array transducers (iE33 with X5-1/3-1, Philips Healthcare, Andover, MA, USA; Vivid 7/E9 with 4 V, GE Healthcare, Horten, Norway). All echocardiography data were sent to the core laboratories (University of Occupational and Environmental Health for 3DE assessment, St Marianna University for 2DE and Doppler assessment) for the analysis. An independent examiner in each institution who did not know the patient's symptomatic status and outcome performed echocardiography analysis.

3DE measurements

3DE analysis was performed by speckle tracking software (4D LV analysis version 3.1.2, TomTec Imaging Systems, Unterschleissheim, Germany) by an experienced investigator. The methods have been described in detail in a previous report [12]. Briefly, endocardial border was semi-automatically delineated after 2-point clicks of a specific anatomical landmark. Manual adjustment of the endocardial border was performed, when required. The software performed a 3DE speckle tracking analysis throughout 1 cardiac cycle, and generated time domain LV volume curves, from which LV volumes, SV, and LVEF were calculated. The software also provided global longitudinal, circumferential, and radial strain (GLS, GCS, and GRS, respectively) values. GLS and GCS were presented as absolute values.

Follow ups

Patients were followed up regularly in an outpatient clinic. If patients were treated in other hospitals, we contacted patients, physicians, and next of kin. Final follow-up data were obtained from January 2016 to June 2016. The primary endpoint was cardiac events, including cardiac death, ventricular fibrillation/tachycardia, and development of heart failure requiring hospitalization. To determine natural history of PLG-SAS, patients who had surgical or trans-catheter AVR (SAVR/TAVR) were censored at the time of surgery.

The secondary endpoint was a composite of cardiac events and AVR. While comparing the cardiac events that occurred in the patients who received conservative treatment with those that occurred in patients who underwent AVR, follow-up duration was calculated from the time of surgery to the date when the cardiac event occurred or from the date of final follow up in patients who underwent AVR. In patients who underwent conservative treatment, follow-up duration was determined from the index echocardiography to the date of occurrence of cardiac events or the final follow-up date.

Observer variabilities

Intra-observer variability was assessed by having the observer repeat the measurement of 3DE SV and LVEF at 2 weeks apart in 20 randomly selected patients. Inter-observer variability was determined by employing a second observer to perform these measurements in the same 20 patients. The intra- and interobserver variability values were calculated as the absolute differences between the two corresponding measurements in percentages of their mean and intraclass correlation (ICC).

Statistical analysis

Continuous data were presented as mean $\pm$ SD or median and 25th to 75th percentile. Categorical data were expressed as

numbers or percentages. A *t*-test or Wilcoxon sum rank test was used to compare continuous variables between the two groups. Categorical variables were compared by Chi-square test. Survival analysis was conducted by Kaplan–Meier method, and group differences were determined by log-rank test. The prognostic value of echocardiography parameters was determined by univariable Cox proportional hazard analysis. To compare the predictive strengths of echocardiographic parameters and symptomatic status, which was usually graded as New York Heart Association (NYHA) class, receiver operating characteristic (ROC) curves for cardiac events were created. We conducted a pairwise comparison of the areas under the curve (AUC) using DeLong's test. A net reclassification improvement (NRI) analysis with and without NYHA class was also performed [19,20]. Furthermore, the robustness of symptomatic status was tested using progressive models. Echocardiographic parameters showing $p < 0.1$ of univariable analysis were used for the analysis. A logistic regression model was used to develop propensity score for the prediction of symptomatic status. To adjust the severity of AS, we included age, sex, heart rate, systolic blood pressure, mean PG, SVI, and iAVA. To generate propensity-score matched cohort, asymptomatic patients were matched with symptomatic patients by using the one-to-one matching technique. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed by using a commercial software (JMP 13.1.0, SAS Institute Inc., Cary, NC, USA; SPSS 24, Chicago, IL, USA; and R 3.4.3, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics

Among 222 patients with PLG-SAS, 65 patients manifested possible AS-related symptoms (29%), including chest pain in 22, syncope in 9, and dyspnea in 42 patients. Table 1 depicts clinical characteristics of patients with symptomatic and asymptomatic PLG-SAS. Patients with symptomatic PLG-SAS received beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and diuretics more frequently than patients with asymptomatic PLG-SAS. BNP level was significantly higher in the symptomatic group ($n = 47$) than in the asymptomatic group ($n = 87$, $p = 0.014$). Patients with chest pain had a higher prevalence of coronary artery disease (9/22, 41%) than those without chest pain (38/200, 19%, $p = 0.026$).

Echocardiography parameters between the two groups

Table 2 represents echocardiography parameters between the two groups. There were no significant differences in the LV volumes, LVEF, and LV mass index between both symptomatic PLG-SAS and asymptomatic PLG-SAS groups. Prevalence of low flow was also not different between the two groups. Regarding the parameters of LV diastolic function, patients with symptomatic PLG-SAS presented with significantly higher E-wave velocity, and E/A ratio than patients with asymptomatic PLG-SAS. Peak velocity, mean PG, iAVA, and systolic pulmonary arterial pressure were not different between the two groups.

Primary end points

During the median follow-up of 18 months, 20 patients reached the primary end-point, including cardiac deaths in 6; heart failure requiring hospitalization in 13; and ventricular fibrillation in 1 patient. Fig. 1A shows cardiac-event-free survival curve. Patients with symptomatic PLG-SAS had significantly worse prognosis than patients with asymptomatic PLG-SAS ($p = 0.003$). An estimated 2-year cardiac-event-free rate was $77 \pm 7\%$ in patients with symptomatic PLG-SAS, and $92 \pm 3\%$ in patients with asymptomatic

Table 1
Clinical characteristics in study population.

Variables	All ($n = 222$)	Symptomatic PLG-SAS ($n = 65$)	Asymptomatic PLG-SAS ($n = 157$)	p-Value
Age (year)	78 ± 9	78 ± 8	78 ± 9	0.93
Sex (male/female)	92/130	24/41	68/89	0.38
BSA (m^{-2})	1.53 ± 0.18	1.52 ± 0.17	1.53 ± 0.19	0.84
BMI	23.2 ± 3.5	23.6 ± 3.6	23.1 ± 3.5	0.37
Heart rate (bpm)	67 ± 11	69 ± 11	66 ± 11	0.074
Systolic blood pressure (mmHg)	141 ± 26	146 ± 28	140 ± 24	0.23
Diastolic blood pressure (mmHg)	73 ± 14	74 ± 14	72 ± 14	0.27
Hypertension (%)	168 (76)	53 (81)	115 (73)	0.18
Diabetes	70 (32)	25 (38)	45 (29)	0.16
Hypercholesterolemia	96 (43)	32 (49)	64 (41)	0.25
Chronic kidney disease	105 (47)	31 (48)	74 (47)	0.94
Coronary artery disease	47 (21)	18 (27)	29 (18)	0.13
Current smoking	27 (12)	6 (9)	21 (13)	0.31
COPD	23 (10)	10 (15)	13 (8)	0.13
CVA	28 (13)	13 (20)	15 (10)	0.040
Atrial fibrillation	32 (14)	11 (17)	21 (13)	0.50
Active malignancy	32 (14)	5 (8)	27 (17)	0.053
Frailty	37 (17)	15 (23)	22 (14)	0.11
Beta blocker	58 (26)	24 (37)	34 (22)	0.021
ACEI/ARB	114 (51)	41 (63)	73 (47)	0.024
Ca antagonists	107 (48)	32 (49)	75 (48)	0.84
Diuretics	46 (21)	20 (31)	26 (17)	0.021
Statin	75 (34)	25 (38)	50 (32)	0.35
SAVR/TAVR	59 (27)	23 (35)	36 (23)	0.060
Hemoglobin (g/dL)	12.1 ± 1.8	12.0 ± 1.7	12.2 ± 1.9	0.59
Creatinine (mg/mL)	0.81 (0.63–1.05)	0.88 (0.67–1.06)	0.8 (0.62–1.05)	0.53
eGFR (mL/min/1.73 m^2)	58 ± 24	56 ± 22	59 ± 24	0.39
hsCRP (mg/dL)	0.11 (0.04–0.47)	0.22 (0.05–0.50)	0.1 (0.04–0.46)	0.34
BNP (μg/mL)	101 (49–202)	114 (67–264)	91 (42–151)	0.014

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; PLG-SAS, paradoxical low gradient severe aortic stenosis, SAVR/TAVR, surgical aortic valve replacement/transcatheter aortic valve replacement.

Table 2
Echocardiography parameters in the study population.

Variables	All (n = 222)	Symptomatic PLG-SAS (n = 65)	Asymptomatic PLG-SAS (n = 157)	p-Value
LVEDVI (mL/m^2)	57.5 ± 12.3	58.2 ± 14.5	57.3 ± 11.3	0.60
LVESVI (mL/m^2)	23.6 ± 6.8	24.2 ± 7.8	23.3 ± 6.4	0.35
LVSVI (mL/m^2)	34.0 ± 6.8	34.0 ± 7.7	34.0 ± 6.4	0.99
Low flow (%)	123 (55%)	39 (60%)	84 (54%)	0.37
LVEF (%)	59.4 ± 5.3	58.8 ± 5.1	59.6 ± 5.4	0.32
LV mass index (g/m^2)	73 ± 17	72 ± 20	73 ± 15	0.75
Maximum LAVI (mL/m^2)	39.2 ± 17.7	41.9 ± 21.7	38.1 ± 15.7	0.15
E wave velocity (cm/s)	81 ± 27	88 ± 33	78 ± 23	0.015
A wave velocity (cm/s)	103 ± 29	101 ± 30	104 ± 28	0.39
E/A ratio	0.82 ± 0.42	0.92 ± 0.53	0.78 ± 0.35	0.041
e' (cm/s)	5.1 ± 1.9	5.1 ± 1.8	5.2 ± 1.9	0.69
E/e'	17.3 ± 7.4	18.2 ± 7.7	16.9 ± 7.3	0.23
Systolic PAP (mmHg)	33.4 ± 8.6	34.1 ± 9.6	33.0 ± 8.2	0.48
Peak velocity (m/s)	3.4 ± 0.5	3.5 ± 0.5	3.4 ± 0.5	0.12
Mean pressure gradient (mmHg)	26 ± 8	27 ± 7	26 ± 8	0.14
Index aortic valve area (cm^2/m^2)	0.46 ± 0.09	0.45 ± 0.09	0.46 ± 0.08	0.16
Zva (mmHg/mL/m^2)	5.07 ± 1.16	5.27 ± 1.32	4.99 ± 1.07	0.11
Global longitudinal strain (%)	15.6 ± 2.4	15.1 ± 2.4	15.8 ± 2.4	0.060
Global circumferential strain (%)	30.4 ± 4.1	30.4 ± 3.9	30.4 ± 4.2	0.99
Global radial strain (%)	37.8 ± 4.5	37.4 ± 4.4	37.9 ± 4.6	0.41
MR				
No-trivial/mild/moderate/severe	177/44/1/0	48/17/0/0	129/27/1/0	0.10
AR				
No-trivial/mild/moderate/severe	138/83/1/0	36/29/0/0	102/54/1/0	0.09

AR, aortic regurgitation; e', early diastolic mitral annular velocity; LAVI, left atrial volume index; LV, left ventricular; LVED(S)VI, left ventricular end-diastolic (end-systolic) volume index; LVEF, left ventricular ejection fraction; LVSVI, left ventricular stroke volume index; MR, mitral regurgitation; PAP, pulmonary arterial pressure; PLG-SAS, paradoxical low gradient severe aortic stenosis; Zva, valvuloarterial impedance.

PLG-SAS. Table 3 presents results of univariable analysis of clinical, echocardiographic, and blood examination parameters in predicting the occurrence of cardiac events. Presence of symptoms and NYHA class were significant predictors of future cardiac events. Among echocardiographic parameters, LV mass index, E-wave velocity, E/e', and GLS were significant predictors of future cardiac events. Hemoglobin, eGFR, high sensitivity CRP, and BNP were also significant predictors of future cardiac events.

Online Fig. 1 shows comparison of ROC curves between echocardiographic parameters and the corresponding parameters plus NYHA class. Addition of NYHA class increased AUC, but no statistically significant differences in AUC were noted. However, a reclassification analysis showed that addition of NYHA class significantly improved the classification for predicting outcome compared with each echocardiography parameter except E/e' (Online Table 1).

We further analyzed the robustness of NYHA class using progressive models. NYHA class significantly improved models based on LV mass index, E wave velocity, E/e', iAVA, and GLS (Table 4).

Among 64 paired propensity-score-matched cohort, patients with symptomatic PLG-SAS had still significantly worse prognosis than patients with asymptomatic PLG-SAS (p = 0.022) (Fig. 2A).

Secondary end points

During the follow-up period, AVR was performed in 59 patients (49 SAVR and 10 TAVR; 23 symptomatic and 36 asymptomatic patients). The number of isolated AVR, AVR + coronary bypass surgery, and AVR + the other valve surgery was 48, 8, and 3, respectively. Patients with symptomatic PLG-SAS showed a higher incidence of AVR than patients with asymptomatic PLG-SAS (31 ±

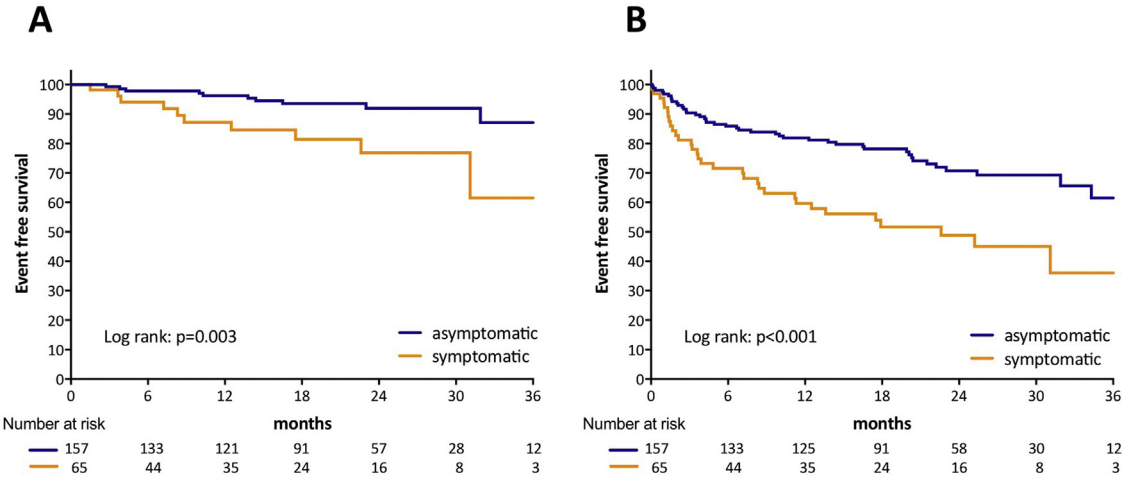

Fig. 1. Kaplan–Meier analysis for cardiac events (A) and a composite of cardiac events and SAVR/TAVR (B) between asymptomatic patients with PLG-SAS and symptomatic patients with PLG-SAS. PLG-SAS, paradoxical low gradient severe aortic stenosis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 3
Clinical and echocardiography parameters in patients with cardiac events and those without events and univariable Cox proportional analysis.

Variables	CE (+) ($n=20$)	CE (−) ($n=202$)	p-Value	Univariable analysis		
				HR	95% CI	p-Value
Age (years)	78 ± 7	78 ± 9	0.75	1.01	0.96–1.07	0.65
Female	9 (45%)	121 (60%)	0.20	0.58	0.24–1.41	0.23
BSA (m^{-2})	1.54 ± 0.18	1.53 ± 0.18	0.68	1.58	0.14–17.7	0.71
BMI	23.2 ± 3.5	23.2 ± 3.6	0.98	1.01	0.88–1.14	0.94
Symptom (yes)	10 (50%)	55 (27%)	0.041	3.43	1.42–8.27	0.006
NYHA class I/II/III/IV	10/6/2/2	159/40/2/1	0.004	3.03[a]	1.09–8.44	0.034
				24.9[b]	5.3–119	<0.001
				36.7[c]	7.4–182	<0.001
Hypertension (%)	14 (70%)	154 (76%)	0.54	0.75	0.28–1.95	0.55
Diabetes (%)	9 (45%)	61 (30%)	0.19	1.86	0.77–4.50	0.17
Hypercholesterolemia (%)	8 (40%)	88 (44%)	0.76	0.85	0.35–2.09	0.73
Chronic kidney disease (%)	14 (78%)	91 (45%)	0.032	2.49	0.96–6.49	0.061
Coronary artery disease (%)	6 (30%)	41 (20%)	0.33	1.59	0.61–4.14	0.34
Smoking (%)	4 (20%)	23 (11%)	0.33	2.37	0.73–7.61	0.15
COPD (%)	5 (25%)	18 (9%)	0.047	3.54	1.28–9.80	0.015
CVA (%)	7 (35%)	21 (10%)	0.006	4.19	1.67–10.5	0.002
Atrial fibrillation (%)	5 (25%)	27 (13%)	0.19	2.30	0.83–6.39	0.11
Active malignancy (%)	4 (20%)	28 (14%)	0.47	1.60	0.53–4.82	0.41
Frailty (%)	7 (35%)	30 (15%)	0.036	3.23	1.28–8.15	0.013
Heart rate (bpm)	69 ± 11	66 ± 11	0.30	1.03	0.99–1.07	0.18
Systolic blood pressure (mmHg)	131 ± 29	142 ± 25	0.014	0.98	0.97–1.00	0.063
Diastolic blood pressure (mmHg)	69 ± 12	73 ± 14	0.20	0.99	0.96–1.01	0.25
LVEDVI (mL/m^2)	57.0 ± 14.4	57.6 ± 12.1	0.84	1.00	0.97–1.04	0.87
LVSVI (mL/m^2)	33.1 ± 8.7	34.0 ± 6.6	0.54	0.99	0.92–1.06	0.69
LVEF (%)	58.0 ± 5.1	59.6 ± 5.3	0.22	0.93	0.86–1.02	0.12
LV mass index (g/m^2)	79 ± 18	72 ± 16	0.083	1.03	1.00–1.05	0.040
Maximum LAVI (mL/m^2)	43.1 ± 22.8	38.8 ± 17.1	0.29	1.02	0.99–1.04	0.17
E wave velocity (cm/s)	102 ± 39	79 ± 24	<0.001	1.03	1.01–1.04	<0.001
A wave velocity (cm/s)	111 ± 37	103 ± 28	0.26	1.01	0.99–1.03	0.18
E/A ratio	0.92 ± 0.49	0.81 ± 0.41	0.29	1.46	0.61–3.47	0.39
e' (cm/s)	5.3 ± 2.2	5.1 ± 1.8	0.68	1.04	0.83–1.30	0.75
E/e'	21.0 ± 10.8	16.9 ± 6.9	0.023	1.07	1.02–1.13	0.012
Systolic PAP (mmHg)	36.6 ± 9.8	33.0 ± 8.5	0.16	1.04	0.99–1.09	0.15
Peak velocity (m/s)	3.5 ± 0.5	3.4 ± 0.5	0.49	2.11	0.79–5.66	0.14
Mean pressure gradient (mmHg)	27 ± 8	26 ± 7	0.45	1.05	0.99–1.12	0.11
Index aortic valve area (cm^2/m^2)	0.43 ± 0.10	0.46 ± 0.08	0.16	0.01	0–1.37	0.066
Zva (mmHg/mL/m^2)	4.98 ± 1.07	5.08 ± 1.17	0.71	0.94	0.62–1.41	0.76
Global longitudinal strain (%)	14.1 ± 2.5	15.8 ± 2.4	0.003	0.69	0.56–0.84	<0.001
Global circumferential strain (%)	30.6 ± 3.6	30.4 ± 4.2	0.86	1.00	0.90–1.11	0.98
Global radial strain (%)	36.2 ± 4.5	37.9 ± 4.5	0.096	0.91	0.82–1.00	0.052
Hb (g/dL)	10.7 ± 1.6	12.3 ± 1.8	<0.001	0.65	0.51–0.82	<0.001
Creatinine (mg/dL)	1.15 (0.83–1.98)	0.8 (0.62–1.03)	0.002	1.19	0.99–1.41	0.056
eGFR ($mL/min/1.73\,m^2$)	41 ± 21	60 ± 23	<0.001	0.97	0.95–0.99	<0.001
hsCRP (mg/dL)	0.68 (0.37–2.36)	0.1 (0.03–0.35)	<0.001	1.23	1.09–1.40	0.001
Log BNP (μg/mL)	5.4 (4.2–6.2)	4.6 (3.8–5.1)	0.008	2.53	1.65–3.88	<0.001

95% CI, 95% of confidence interval; BMI, body mass index; BSA, body surface area; CE, cardiac event; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; e', early diastolic mitral annular velocity; Hb, hemoglobin; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; Log BNP, log-transformed brain natriuretic peptide; LAVI, left atrial volume index; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVSVI, left ventricular stroke volume index; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; Zva, valvuloarterial impedance.
[a] NHYA I vs. II.
[b] NYHA I vs. III.
[c] NYHA I vs. IV.

Table 4
Bivariable models for predicting cardiac events.

Model	Variables	Incremental value		
		χ^2	Comparison model	p
1	LV mass index	4.2	–	
2	LV mass index + NYHA class	66.2	1	<0.001
3	E	14.8	–	
4	E + NYHA class	63.8	3	0.019
5	E/e'	6.5	–	
6	E/e' + NYHA class	63.8	5	0.002
7	iAVA	3.4	–	
8	iAVA + NYHA class	63.7	7	<0.001
9	GLS	13.3	–	
10	GLS + NYHA class	75.3	9	<0.001

E, E wave velocity; iAVA, indexed aortic valve area; GLS, global longitudinal strain; LV, left ventricular; NYHA, New York Heart Association.

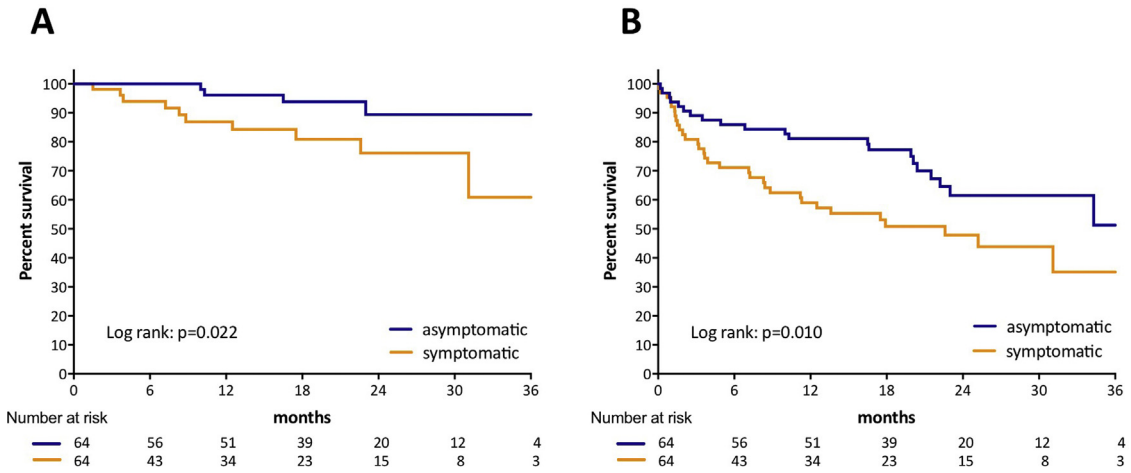

Fig. 2. Kaplan–Meier analysis for cardiac events (A) and a composite of cardiac events and SAVR/TAVR (B) between propensity score matched asymptomatic patients with PLG-SAS (n = 64) and symptomatic patients with PLG-SAS (n = 64). PLG-SAS, paradoxical low gradient severe aortic stenosis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

6% vs. 16 ± 3% at 1 year; 36 ± 6% vs. 24 ± 4% at 2 years; p = 0.013). Baseline echocardiography revealed that peak velocity (3.7 ± 0.3 m/s vs. 3.3 ± 0.5 m/s, $p < 0.001$) and mean PG (32 ± 5 mmHg vs. 24 ± 7 mmHg, $p < 0.001$) were significantly higher in patients who underwent AVR than in those without AVR. Kaplan–Meier analysis revealed that patients with symptomatic PLG-SAS had significantly lower event-free rate than patients with asymptomatic PLG-SAS (Fig. 1B). The same trend was also observed in the propensity-score-matched cohort (Fig. 2B).

We performed subgroup analysis of prognosis in the patients with low flow PLG-SAS (n = 123) and normal flow PLG-SAS (n = 99). Prevalence of symptoms was not different between the two groups (32% vs. 26%, p = 0.374). Cardiac event rate was similar between the two groups (11% vs. 10%, p = 0.909). However, secondary end-point rate was significantly lower in patients with low flow PLG-SAS (28%) than in patients with normal flow PLG-SAS (42%, p = 0.021). Thus, presence of symptoms was significantly associated with the future outcome, except for the occurrence of cardiac events, in patients with low-flow PLG-SAS (Online Fig. 2).

Among 23 patients with symptomatic PLG-SAS who underwent AVR, the median time-interval between the index echocardiography and the surgical treatment was 3.1 months. Seventeen patients (74%) underwent another echocardiographic examination before the surgery. Mean PG significantly increased from 32 ± 5 mmHg at baseline echocardiography to 42 ± 10 mmHg at echocardiography before the AVR, and 53% of patients (9/17) showed the conversion in their PG status from LPG to HPG (Fig. 3A).

Of 36 patients with asymptomatic PLG-SAS who underwent AVR, the median time-period from the index echocardiography to the surgery was 5.4 months. Reasons for opting for AVR were symptom-onset in 13 patients, attending physician's recommendation or patients' willingness in 12 patients, rapid disease progression in 5 patients, as concomitant cardiac surgery in 5 patients, and reduced LVEF in 1 patient. Twenty-nine patients (81%) underwent another echocardiographic examination before the surgery. Mean PG significantly increased from 32 ± 5 mmHg at baseline to 43 ± 7 mmHg at echocardiography before the AVR ($p < 0.001$), and 76% of patients (22/29) converted from LPG to HPG (Fig. 3B).

In patients who underwent AVR, there were 3 postoperative cardiac events, including 1 case of cardiac death early after the surgery, and 2 cases of heart failure late after the surgery. Online Fig. 3A shows cardiac-event-free rate between patients with symptomatic PLG-SAS who underwent AVR and those who were

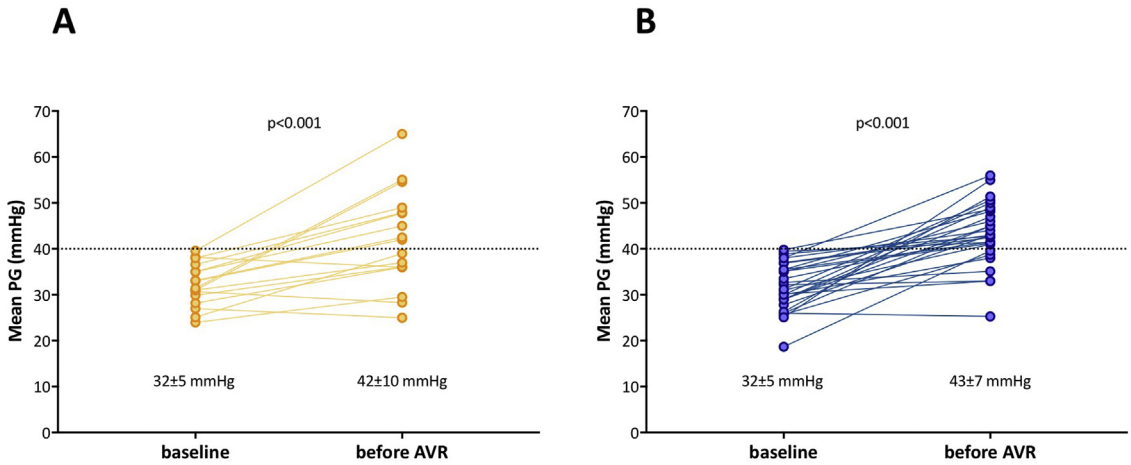

Fig. 3. Serial change in mean PG from baseline to before aortic valve replacement in symptomatic PLG-SAS (A) and asymptomatic PLG-SAS (B). AVR, aortic valve replacement; PG, pressure gradient.

managed conservatively. Event rates were higher in symptomatic patients who received conservative treatment than in those who underwent AVR but the difference did not reach statistical significance ($p = 0.087$). No significant differences were noted in the event rate between asymptomatic patients who received conservative treatment and those who underwent AVR (Online Fig. 3B).

Reliability of 3DE measurements

The intra-observer variability and ICC for the measurements of 3DE SV and LVEF were 5.9 ± 7.6% and 4.0 ± 3.1% and 0.94 and 0.91, respectively. The corresponding inter-observer variability and ICC values were 7.1 ± 9.4% and 6.7 ± 5.7%, 0.87 and 0.80, respectively.

Discussion

The main findings of this study are summarized as follows: (1) approximately 30% of patients with PLG-SAS were symptomatic; (2) symptomatic patients had a higher prevalence of the usage of beta-blockers, angiotensin blockers, and diuretics, and higher levels of BNP as compared to asymptomatic patients; (3) some diastolic function parameters showed more advanced stage of diastolic dysfunction in symptomatic patients; (4) prognosis was significantly worse in patients with symptomatic PLG-SAS than in patients with asymptomatic PLG-SAS, even after adjusting anthropometric factors, flow status, and the severity of AS; (5) PG increased significantly from that noted during the index echocardiographic examination to that noted during the echocardiography before the AVR.

Symptom and clinical characteristics of patients with LPG-SAS

Although history taking of AS-related symptoms is the initial step for proper management of patients with SAS, appropriate symptom evaluation is often difficult, because the existing comorbidities can limit physical activity in the elderly patients making them asymptomatic [21]. Even though patients are symptomatic, we are not sure whether the symptom is solely related to SAS itself. This is particularly important for the situations for which definite treatment guideline is not established, such as symptomatic PLG-SAS. Since results of previous studies revealed a higher prevalence of symptomatic PLG-SAS patients to be associated with worse prognosis [1,2,5–9], it is relevant to divide patients with PLG-SAS according to the symptoms in order to determine its functional properties and prognosis.

Symptomatic PLG-SAS was observed in 30% of patients in this study. Its prevalence was lower than that in some studies [1,2,6,7], but similar to that in other studies [5,8,9]. Patients with symptomatic PLG-SAS received beta-blockers, angiotensin blockers, and diuretics more frequently, and presented with higher BNP levels, all of which represent a possible association between PLG-SAS and HFpEF [15]. Although LV volumes and mass, and severity of AS were similar between both groups, E-wave velocity and E/A ratio were significantly higher in patients with symptomatic PLG-SAS, reflecting that patients with symptomatic PLS-SAS had a more advanced stage of diastolic dysfunction.

Symptom and prognosis in patients with PLG-SAS

Patients with symptomatic PLG-SAS had significantly worse prognosis than patients with asymptomatic PLG-SAS, which was in agreement with the previous studies [5,9]. In addition to the symptomatic status, several echocardiographic parameters remained as significant prognosticators in univariable analysis. A reclassification analysis revealed that NYHA class significantly improved reclassification over each echocardiographic parameter except E/e' (Online Table 1). We also found that NYHA class had a significant incremental value for future outcomes over several echocardiographic parameters using progressive model (Table 4). These results reinforced the close association between symptomatic status and prognosis in PLS-SAS. Echocardiographic parameters showing significant predictors in this study are also known as important predictors in patients with HFpEF. Even after propensity score matching, symptomatic PLG-SAS was still associated with a significantly worse outcome than asymptomatic PLG-SAS. These results suggest that the presence of symptoms is not closely associated with the severity of AS itself but can be related with the underlying comorbidities [15,22]. Some blood examination parameters, which had also been verified as significant predictors of SAS [4,23–26], were selected as significant univariable predictors of future cardiac events. All these blood examination parameters can be abnormal even in patients with HFpEF, since a high prevalence of comorbidities such as hypertension, diabetes, anemia, and chronic kidney disease can induce a systemic inflammatory state, resulting in myocardial hypertrophy and fibrosis. Both may contribute to high diastolic LV stiffness, resulting in elevated levels of BNP [27].

AVR in PLG-SAS

The finding that the AVR rate in patients with symptomatic PLG-SAS was 31% in the 1st year, and 36% in the 2nd year reflects that many attending physicians involved in this study may treat symptomatic patients with PLG-SAS as having symptomatic but moderate AS. Although AVR tended to be beneficial over conservative management for preventing cardiac events in patients with symptomatic PLG-SAS, no benefit was observed in patients with asymptomatic PLG-SAS. The prognostic impact of AVR in PLG-SAS is the subject of an ongoing debate. Our results underscored that PG status frequently changed at the time of AVR. PG across the aortic valve changes according to the progressive nature of AS [28] and LV function. In agreement with previous studies, our results demonstrate that PG increased according to the elapsed time, resulting in the conversion of the PG status from low gradient to high gradient in most patients with PLG-SAS [3,5]. This is another reason for the discrepant results of the impact of AVR on prognosis in patients with PLG-SAS.

Clinical implications

The presence of symptoms is important to stratify the high-risk patients with future adverse outcome in PLG-SAS. Asymptomatic patients with PLG-SAS can be managed medically with regular clinical and echocardiographic follow up, until symptoms develop, or pressure status converts to HPG-SAS. Symptomatic PLG-SAS has been a clinical dilemma, because it is often difficult to verify whether symptoms are related to AS itself or the existing comorbidities. In addition to risk-factor modification and searching for other potential pathology [22], AVR should be individualized after taking into consideration a number of abnormal findings that are closely related to poor prognosis, operative risk, cost, and expertise of the surgery.

Study limitations

Several limitations should be addressed in this study. First, AVR was performed at the discretion of the attending physician and as per the patient's approval, which might recall some bias. However, our results reflect the real world situation regarding how to manage patients with PLG-SAS. Second, not all patients with AVR underwent another echocardiographic examination before the

AVR. This might have affected the conversion rate from LPG to HPG. Third, PLG-SAS includes both normal-flow and low-flow patient populations. Although prognostic outcome in normal flow PLG-SAS has been reported to be better than that in other types of SAS [29], recent studies revealed that half of these patients manifest SAS; therefore, they may benefit from AVR when symptoms are presented [30,31]. Our results showed that cardiac event rate was similar between the two groups, and cardiac event plus AVR rate was higher in normal-flow PLG-SAS group. Finally, the number of cardiac events was small, and, thus, it precluded to perform extensive multivariable analysis. However, due to the progressive nature of the disease, AS-phenotype and LV geometry may change during longer follow-up period, and this change may affect the prognosis.

Conclusions

Since symptomatic PLG-SAS is associated with poorer prognosis even after adjusting for flow status and severity of AS, symptoms are not always caused by the severity of AS itself but might be associated with the underlying comorbidities. These results suggest a possible link between PLG-SAS and HFpEF in some patients.

Conflicts of interest

All authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.12.017.

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