The International Journal of Cardiovascular Imaging (2019) 35:1241–1247
https://doi.org/10.1007/s10554-019-01565-1

ORIGINAL PAPER

Predictive value of exercise stress echocardiography in asymptomatic patients with severe aortic regurgitation and preserved left ventricular systolic function without LV dilatation

Su Yeon Lee[1] · Sung-Ji Park[1,2,5] · Eun Kyoung Kim[1,2] · Sung-A Chang[1,2] · Sang-Chol Lee[1,2] · Joong Hyun Ahn[3] · Keumhee Carriere[3,4] · Seung Woo Park[1,2]

Received: 18 October 2018 / Accepted: 15 February 2019 / Published online: 28 February 2019

Abstract

The management of asymptomatic patients with severe aortic regurgitation (AR) and preserved left ventricular (LV) systolic function remains controversial. We evaluated the predictive value of exercise stress echocardiography (ESE) in asymptomatic severe AR with preserved LV systolic function for identifying high risk patients who might benefit from early referral for surgery. Symptom-limited treadmill ESE was performed in 67 asymptomatic patients with severe AR (effective regurgitant orifice area > 30 mm^2, regurgitant volume > 60 ml) and preserved LV systolic function without LV dilatation [ejection fraction (EF) ≥ 50% and LV end-systolic diameter ≤ 50 mm]. A post-exercise EF increase of > 4% was defined as presence of contractile reserve (CR). The primary outcome was defined as the composite of symptoms development, deterioration in LV function (EF < 50% in echocardiography) and aortic valve replacement (AVR) at follow-up. Operations performed within 60 days of ESE were excluded. Twenty-eight patients were CR (+) and 39 patients were CR (−). Compared with the CR (+) group, the CR (−) group was older (52.0 ± 14.0 years vs. 43.8 ± 10.6 years, p = 0.011) and had higher Ln N-terminal natriuretic peptide (NT-proBNP) [5.2 (4.5–5.7) vs. 4.1 (3.7–5.1), p = 0.001]. The CR (−) group showed lower exercise time than the CR (+) group (576 ± 159 s vs. 671 ± 108 s, p = 0.008). Otherwise, there were no differences in demographics and imaging data between the two groups. During a follow-up duration of 46 ± 23 months, the primary outcome occurred in 17 patients (25%) including development of symptoms (n = 9), new-onset LV systolic dysfunction (n = 1) and AVR (n = 7). Fourteen of 17 were CR (−) group patients. The survival rate during follow-up was significantly lower in the CR (−) group than in the CR (+) group of asymptomatic severe AR patients (log-rank p = 0.035). The absence of CR in ESE is independently associated with deterioration of symptoms or LV systolic function in asymptomatic patients with severe AR and preserved LV systolic function. It can further risk stratify asymptomatic patients with severe AR and preserved LV systolic function and may influence the optimal timing of AVR.

Keywords Aortic regurgitation · Exercise stress echocardiography · Asymptomatic

✉ Sung-Ji Park
tyche.park@gmail.com

[1] Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[2] Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[3] Statistics and Data Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[4] Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, Canada

[5] Division of Cardiology, Department of Medicine, Cardiovascular Imaging Center, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea

Introduction

The management of asymptomatic severe aortic regurgitation (AR) and normal left ventricular (LV) systolic function remains controversial. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, aortic valve surgery is reasonable for asymptomatic patients with severe AR and normal LV systolic function [ejection fraction (EF) ≥ 50%] but with severe LV dilatation [LV end-systolic dimension (LVESD) > 50 mm or indexed LVESD > 25 mm/m^2] (class IIa indication, level of evidence B) [1]. In the recently released European Society of Cardiology (ESC) guidelines, surgery should be considered in asymptomatic patients with resting EF ≥ 50% with severe LV dilatation: LV end-diastolic dimension (LVEDD) > 70 mm or LVESD > 50 mm [or LVESD > 25 mm/m^2 body surface area (BSA) in patients with small body size] (class IIa indication, level of evidence B) [2]. However, these parameters have limitations in detecting early LV subclinical dysfunction. In severe AR, even asymptomatic, chronic volume overload status can cause LV remodeling and fibrosis. This leads to irreversible dilatation and progressive deterioration in myocardial contractility [3]. More reliable indications of AVR are needed to detect subclinical LV dysfunction and prevent irreversible LV dysfunction in asymptomatic patients with severe AR and preserved LVEF.

Our group demonstrated although contractile reserve (CR) is best related to baseline resting indexed LVESD, one-third of patients were found to have discordance between the presence of CR and the LV dimension recommended for AVR in minimally symptomatic patients with severe AR. It suggested that exercise test may be able to further stratify the current guideline for AVR [4]. In this study, we evaluated the value of exercise stress echocardiography (ESE) in asymptomatic severe AR patients with preserved LV function and without LV dilatation (LVEF ≥ 50% and LVESD ≤ 50 mm) who were not indicated for AVR according to the current guidelines, as predicting high risk patients who might benefit from early referral for surgery.

Methods

Study population

Study subjects were selected patients with significant AR diagnosed by two-dimensional (2-D) echocardiography and referred to ESE for discrepancy between symptom and AR severity between November 2009 and December 2016. Sixty-seven asymptomatic severe AR patients with preserved LV systolic function and without LV dilatation (LVEF ≥ 50% and LVESD ≤ 50 mm) were enrolled. Quantitative and qualitative measures of AR severity were taken according to the American Society of Echocardiography guidelines [1, 5]. The severity of AR was derived using a multi-parametric approach. Jet size (including vena contracta), descending thoracic and abdominal aortic flow reversal, jet density, pressure half-time, and LV function were all used in this process.

To classify asymptomatic status, all initial symptoms assessed by the primary physician in the medical records were carefully reviewed by one cardiologist (S.Y.L). Patient information was carefully collected including baseline demographic characteristics, underlying medical history, laboratory data, and echocardiographic data at rest and during exercise.

We included severe AR patients with preserved LV systolic function and without LV dilation (LVEF ≥ 50% and LVESD ≤ 50 mm) who denied cardiovascular symptoms assessed by New York Heart Association classification grade ≤ 1. Exclusion criteria were other concomitant valvular heart disease of moderate or severe severity, significant coronary artery disease, history of percutaneous coronary intervention or coronary artery bypass graft, and suboptimal imaging. Significant coronary artery disease was defined as one or more lesions with > 50% stenosis (diameter reduction) by coronary angiography or coronary computed tomography angiography. Subjects with LV dilatation (LVESD > 50 mm) who were indicated for AVR in common based on current ACC/AHA [1] and ESC guidelines [2] were excluded. This study was approved by our institutional ethnic committee and informed consent was obtained.

Baseline and ESE

2-D echocardiography was performed using commercially available equipment (Vivid 7, GE Medical Systems, Milwaukee, WI). In all patients, LVEDD and LVESD were obtained from parasternal views according to standard guidelines. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were calculated from 2-D recordings using the modified biplane Simpson's method, which was chosen to allow comparison of pre-exercise and post-exercise LV volume [6]. Pulse-wave Doppler transmitral inflow velocity was obtained from the apical four-chamber view for assessment of diastolic function in accordance with the current guidelines using a combination of echocardiographic variables; mitral inflow velocity of the early phase (E) and late phase (A) during diastole, deceleration time, and pulsed-wave Doppler-derived mitral annular velocity imaging in septal wall (e′). Quantitative and qualitative measurements of AR severity were taken according to the American Society of Echocardiography guidelines. AR severity was determined using an integrated approach that included the size of the regurgitant jet in the LV cavity, the proximal regurgitant jet width, the jet deceleration rate, the magnitude of diastolic flow reversal in the descending aorta, the regurgitant volume (RV) and effective regurgitant orifice area (ERO). Severe AR based on vena contracta width > 0.6 cm (semiquantitative parameter), ERO ≥ 0.30 cm^2 (quantitative parameter), RV ≥ 60 ml (quantitative parameter) and presence of prominent holodiastolic flow reversal in the descending thoracic and abdominal aorta (qualitative parameter) [5, 7]. Additionally, off-line speckle tracking analysis was performed by one independent researcher who was blinded to the data using customized software (EchoPAC PC 7.05, GE Medical System) at two-, three-, and four chamber views. Frame rate for speckled tracking echocardiography was maintained at 60–100 frames/s. Global longitudinal strain for the LV was automatically provided as the average value of the regional peak systolic longitudinal strain of the three apical views.

All patients underwent a symptom-limited treadmill exercise echocardiography with the Bruce protocol. Twelve-lead electrocardiography was performed with the use of conventional chest lead positioning before exercise, after each stage, and after stress. Blood pressure was recorded every 2 min. Exercise was terminated if marked dyspnea, fatigue, chest discomfort, or > 2-mm ST depression occurred, and on patient request. At rest and after peak exercise within 1 min, echocardiographic images were obtained. Images were stored digitally and analyzed offline using a standard GE analysis package (EchoPac PC version 7.05, GE Medical Systems) by an investigator blinded to clinical data. All echocardiography measurements were averaged from three to five cardiac cycles [8–10].

Clinical outcome and definitions

Data were obtained until June 2017 from regular visits to the outpatient clinic. All patients were followed with 2-D echocardiography for at least 1 year. In ESE, the difference between the resting and post-exercise EF was used to define CR. Patients with an increase of ≥ 4% were defined as being CR+ [11]. The composite of development of symptoms such as dyspnea or chest tightness, new-onset LV dysfunction (EF < 50% in 2-D echocardiography during follow-up) and AVR were defined as the primary outcome. Primary outcome reflected only the first events if patients had more than one event. Operations performed within 60 days of ESE were excluded.

Interobserver and intraobserver variability for measurements of CR

Interobserver measurement variability was determined by a second independent blinded observer who measured resting EF and postexercise EF in 10 randomly selected patients. Intraobserver variability was determined by having the first observer who measured the data in all patients remeasure CR in 10 patients 1 month apart. Interobserver and intraobserver variability were calculated as the absolute difference between the corresponding repeated measurements as a percent of their mean.

Statistical analysis

All analysis was conducted with SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as percentages and comparison between groups was performed using χ^2 test or Fisher exact test. Continuous variables were expressed as mean with standard deviations or median with interquartile range. They were compared using the Student's *t* test or Mann–Whitney U test, as appropriate. Event free survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. All p values were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Among asymptomatic patients with severe AR with preserved LV systolic function (LVEF ≥ 50%) (n = 91) who underwent ESE, 67 subjects were eligible for this study. The total population included 67 patients with 48 men (72%), and a mean age of 48.6 ± 13.8 years (Fig. 1). The mean duration from diagnosis of AR was 17.7 ± 28.0 months.

The study population was divided into two groups based on presence of CR. CR (+) was noted in 28 and CR (−) in 39 patients. Baseline characteristics of CR (+) and CR

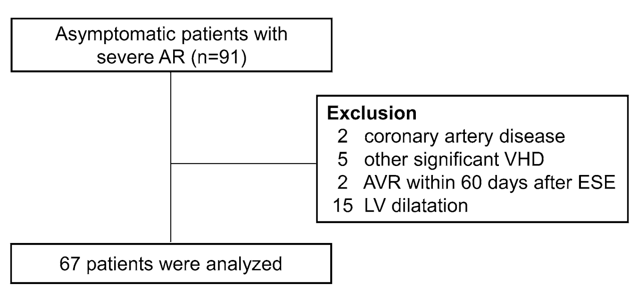

Fig. 1 Patient flow chart. *AR* aortic regurgitation, *AVR* aortic valve replacement, *ESE* exercise stress echocardiography, *LV* left ventricle, *VH*D valvular heart disease

Table 1 Baseline characteristics

	Total (n = 67)	Without CR (n = 39)	With CR (n = 28)	p-value
Age, years	48.6 ± 13.3	52.0 ± 14.0	43.8 ± 10.6	0.011
Male	48 (72%)	26 (67%)	22 (79%)	0.411
Diabetes	4 (6%)	3 (8%)	1 (4%)	0.635
Hypertension	55 (82%)	33 (85%)	22 (79%)	0.748
BSA, m^2	1.75 ± 0.19	1.74 ± 0.21	1.76 ± 0.17	0.629
SBP, mmHg	121.4 ± 15.9	122.9 ± 17.6	119.3 ± 13.1	0.360
DBP, mmHg	61.0 ± 8.1	62.6 ± 7.7	58.9 ± 8.2	0.066
Heart rate, beat/min	79.8 ± 14.3	78.4 ± 12.8	81.8 ± 16.0	0.339
Laboratory findings				
Creatinine, mg/dl	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.635
Ln NT-proBNP	4.6 (4.0–5.5)	5.2 (4.5–5.7)	4.1 (3.7–5.1)	0.001
Medication				
Beta blocker	24 (36%)	14 (36%)	10 (36%)	1.000
ACEi/ARB	41 (61%)	27 (69%)	14 (50%)	0.133
Diuretics	28 (42%)	19 (49%)	9 (32%)	0.214

Data are presented as n (%), mean ± SD or median with interquartile range

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor antagonist, *BSA* body surface area, *DBP* diastolic blood pressure, *NT-proBNP* N-terminal pro-B type natriuretic peptide, *SBP* systolic blood pressure

Table 2 Echocardiography and ESE data

	Total (n = 67)	Without CR (n = 39)	With CR (n = 28)	p-value
Echocardiography				
EF, %	59.9 ± 4.8	59.3 ± 4.6	60.7 ± 5.0	0.247
LVEDD, mm	64.7 ± 5.7	64.1 ± 5.8	64.7 ± 5.3	0.936
LVESD, mm	40.8 ± 4.8	40.9 ± 4.9	40.7 ± 4.7	0.871
ERO, mm^2	24.8 ± 20.0	24.6 ± 21.0	25.0 ± 18.8	0.937
Regurgitation volume, ml	79.5 ± 31.6	81.7 ± 33.9	76.8 ± 29.2	0.607
Exercise echocardiography				
Exercise time, seconds	616 ± 147	576 ± 159	671 ± 108	0.008
METs	11.8 ± 2.1	11.3 ± 2.3	12.6 ± 1.5	0.010
Max heart rate, beat/min	157.2 ± 18.2	154.7 ± 17.8	160.8 ± 18.5	0.205
Max SBP, mmHg	193.7 ± 23.0	194.8 ± 24.6	192.1 ± 20.9	0.633
Max DBP, mmHg	73.4 ± 16.2	75.5 ± 16.6	70.5 ± 15.5	0.212
Pre-exercise EF, %	59.3 ± 4.3	59.5 ± 4.6	59.0 ± 3.8	0.650
Post-exercise EF, %	61.3 ± 7.7	57.6 ± 7.5	66.4 ± 4.4	< 0.001
Pre-exercise LVEDV, ml	230.0 ± 52.1	225.9 ± 55.1	235.7 ± 48.0	0.454
Post-exercise LVEDV, ml	176.0 ± 38.6	178.0 ± 42.1	173.1 ± 33.7	0.609
Pre-exercise LVESV, ml	94.4 ± 24.2	92.8 ± 26.5	96.5 ± 21.1	0.539
Post-exercise LVESV, ml	68.9 ± 24.8	76.6 ± 27.8	58.2 ± 14.4	0.001
Pre-exercise GLS, %	− 18.5 ± 2.2	− 18.3 ± 2.0	− 18.8 ± 2.5	0.335
Post-exercise GLS, %	− 18.7 ± 2.6	− 18.1 ± 2.6	− 19.5 ± 2.5	0.036

Data are presented as n (%), mean ± SD or median with interquartile range

Abbreviations as in Table 1

EF ejection fraction, *ERO* effective regurgitant orifice, *GLS* global longitudinal strain, *LVEDD* left ventricular end-diastolic diameter, *LVEDV* left ventricular end-systolic volume, *LVESD* left ventricular end-systolic diameter, *LVESV* left ventricular end-systolic volume, *METs* metabolic equivalent

(−) groups were shown in Tables 1 and 2. Compared to patients with CR, those without CR were older (52.0 ± 14.0 vs. 43.8 ± 10.6, p = 0.011) and had higher Ln NT-proBNP [5.2 (4.5–5.7) vs. 4.1 (3.7–5.1), p = 0.001]. On ESE, the CR (−) group showed shorter exercise time than the CR (+) group (576 ± 159 s vs. 671 ± 108 s, p = 0.008). Both groups had similar value of global longitudinal strain (GLS) at rest (− 18.3 ± 2.0% vs. − 18.8 ± 2.5%, p = 0.335). Otherwise, there were no other significant differences between the two groups with regard to clinical features, laboratory data, and imaging data. Since there were no differences representing AR severity including ERO and RV, Ln NT-proBNP, exercise time on ESE, and global longitudinal strain at peak exercise were presumed to reflect the presence of CR.

During the median follow-up duration of 46 months, 17 participants experienced the primary outcome. Nine patients developed symptoms associated with AR and one patient experienced deterioration in LV function. After that about half of them (five out of 10 patients) underwent AVR. And seven patients underwent AVR for increased dimensions accepted as the basis for AVR. There was no cardiac death or death from all causes (Fig. 2). Fourteen of seventeen (82%) patients were CR (−). Cox regression analysis for time to primary end-point, could not be applied due to the relatively small number of events. However, it showed a significant survival advantage in patients who had CR (log-rank p = 0.035) on the Kaplan–Meier survival curve for primary outcomes by the presence of CR in the total population (Fig. 3). Though we did not show, there was no significant relationship between GLS and clinical outcomes, when we analyzed association of the difference of GLS and clinical outcomes.

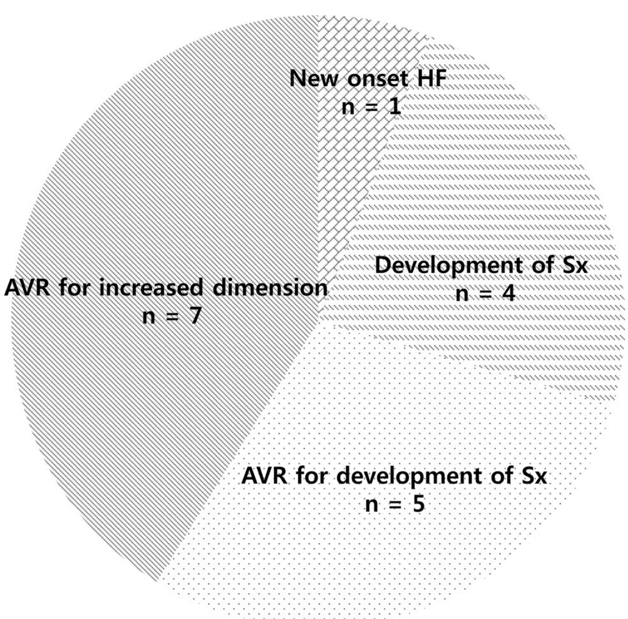

Fig. 2 Primary outcomes. Nine patients developed symptoms associated with AR and about half of them underwent AVR. One patient experienced deterioration in LV function; seven patients underwent AVR for increased dimensions accepted as the basis for AVR. *AVR* aortic valve replacement, *HF* heart failure, *Sx* symptoms

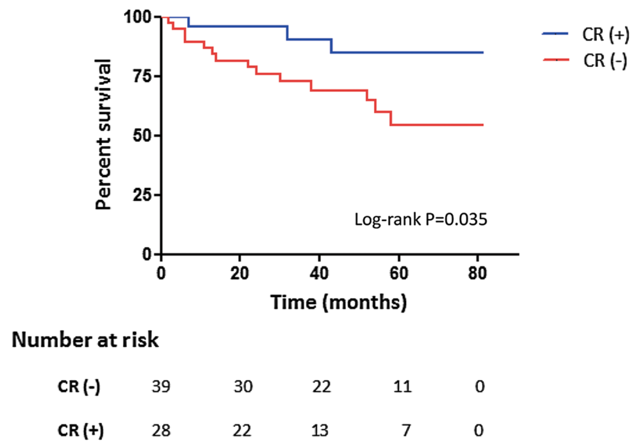

Fig. 3 Kaplan–Meier survival curves in asymptomatic severe AR patients according to the presence of CR. The survival rate during follow-up was significantly lower in the CR (−) group than in the CR (+) group of AR patients (log-rank p = 0.035)

Measurement variability

The interobserver variability was r = 0.908 for resting EF and r = 0.912 for postexercise EF. Intraobserver variability showed r = 0.901 for resting EF, and r = 0.892 for postexercise EF.

Discussion

The main finding of our study was that in asymptomatic severe AR patients with preserved LV systolic function and without LV dilatation (LVEF ≥ 50% and LVESD ≤ 50 mm), presence of CR on ESE demonstrated significant survival advantage. In this study, we investigated the predictor of AVR in asymptomatic patients with severe AR who were not recommended for AVR according to current guidelines. CR on ESE could predict development of LV function deterioration and symptoms, which are indications for AVR. Since the number of patients and events was relatively small, we could not apply Cox regression analysis for time to primary end-point. However, the Kaplan–Meier survival curve showed that the survival rate for a primary outcome during follow-up was significantly lower in the CR (−) group than the CR (+) group in asymptomatic severe AR patients with preserved LV systolic function and without LV dilatation (LVEF ≥ 50% and LVESD ≤ 50 mm).

AVR is recommended for asymptomatic patients with severe AR with LV systolic dysfunction at rest or with severe

LV dilatation [1, 2]. However, LV systolic dysfunction or severe LV dilatation such as EF or LV dimension have limitations for predicting early LV dysfunction in asymptomatic patients with chronic severe AR. Detection of early LV dysfunction is very important for decision making. However, significant LV dilatation and remodeling occur in severe AR patients who are clinically well compensated. The optimal management of patients who are not included in guidelines for AVR is not clear. Although long-term increase in load results in slowly progressive LV dilatation and dysfunction in asymptomatic severe AR, it is challenging to know when to operate to prevent irreversible LV dysfunction [3].

For these reasons, more reliable methods such as ESE are needed to detect early LV dysfunction in asymptomatic patients with severe chronic AR. Some studies have suggested that an exercise induced decrease in LVEF is a predictor of poor outcome that warrants surgery [4, 12–14]. However, most of these studies included patients who already had symptoms, LV dilation, or LV dysfunction at rest [4, 12, 13]. Wahi et al. revealed that CR on ESE was a better predictor of LV decompensation than resting indices in asymptomatic patients with severe AR with preserved LVEF and without LV dilatation [14]. However, the sample size of that study was small ($n=35$) and other clinical outcomes such as new development of symptoms or heart failure (HF) were not evaluated.

Our findings were consistent with previous studies that CR on ESE provided important benefit of clinical determinant. However, our study group was isolated and homogenous based on strict criteria : (1) totally asymptomatic, (2) severe AR based on vena contracta width >0.6 cm (semiquantitative parameter), ERO ≥ 0.30 cm^2 (quantitative parameter), RV ≥ 60 ml (quantitative parameter) and presence of prominent holodiastolic flow reversal in the descending thoracic and abdominal aorta (qualitative parameter), (3) preserved LV systolic function and without LV dilatation (EF $\geq 50\%$ and LV-end systolic dimension ≤ 50 mm). Also, the sample size was larger than previous study. Primary outcome was defined as newly developed symptoms or HF, which were indications for AVR, as well as AVR.

Our group suggested that ESE may be able to further stratify the current guideline for AVR [4]. In present study, we evaluated the value of CR on ESE in asymptomatic severe AR patients with preserved LV function and without LV dilatation (LVEF $\geq 50\%$ and LVESD ≤ 50 mm) who were not indicated for AVR according to the current guidelines. In this regard, CR on ESE might help identify high risk patients with asymptomatic severe AR with preserved LV systolic function and without LV dilatation (LVEF $\geq 50\%$ and LVESD ≤ 50 mm) who would benefit from early referral for surgery.

GLS is a more sensitive marker of incipient LV dysfunction in many valvular diseases, including patients with chronic AR. However, previous studies using GLS in chronic AR have had a short follow-up duration and have used a variety of endpoints including 1-year survival, need for AVR, changes in LV dimensions, and improvement of symptoms. As such, whether GLS might provide superior risk discrimination in patients with chronic AR and preserved LVEF regarding the timing for aortic valve intervention remains unclear. Even when only patients with preserved LVEF are considered, GLS values show marked heterogeneity, perhaps reflecting the preload and afterload dependence of GLS [15]. In recently announced study, worsening GLS was associated with long-term mortality, providing incremental prognostic value and improved reclassification in 1,063 asymptomatic patients with severe AR with preserved LV systolic function [16]. However, there was similar values of baseline GLS according to the presence of CR in this study, furthermore, change of GLS between at rest and at peak did not have significant relationship to clinical outcomes. It might be influenced by small sample size ($n=67$) and events due to strict criteria of enrolment for asymptomatic patients with severe AR and preserved LV systolic function without LV dilation. Further large, multicenter, prospective, randomized, controlled trial is needed to evaluate the association between change of GLS according to exercise and clinical outcomes in asymptomatic patients with severe AR and preserved LV systolic function without LV dilation.

Limitations

This study has several limitations. First, it was performed retrospectively at a single center, and thus our series might not represent the characteristics of asymptomatic severe AR in the general population. Second, the sample size was relatively small, and the population that reached the primary outcome was heterogeneous and very small, which inhibited detailed analysis. However, the study population was an isolated and homogenous group (LVEF $\geq 50\%$ and LVESD ≤ 50 mm) and it was meaningful that CR was a significant parameter predicting outcomes in this situation. Therefore, ESE could be valuable for helping to define subsets of asymptomatic patients with severe AR and preserved LV systolic function and without LV dilatation in whom earlier treatment should be considered. Further large-scale multicenter prospective studies are needed to clarify the additive prognostic implications.

Conclusions

In asymptomatic severe AR patients with preserved LV systolic function and without LV dilatation in whom AVR is not indicated based on the current guidelines, the absence of CR on ESE was independently associated with worsening symptoms or deteriorating LV systolic function. It can further risk stratify asymptomatic patients with severe AR and preserved LV systolic function and may influence the optimal timing of AVR.

Acknowledgements We would like to acknowledge the echocardiographers at Samsung Medical Center- Ae-Young Yun, Jung-Eun Song, Seol-Hwa Kim, and Yung-Joo Lee-who performed exercise stress echocardiography for this study.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Nishimura RA, Otto CM, Bonow RO et al (2014) 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 63(22):e57–e185
2. Baumgartner H, Falk V, Bax JJ et al (2017) 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 38(36):2739–2791
3. Bekeredjian R, Grayburn PA (2005) Valvular heart disease: aortic regurgitation. Circulation 112(1):125–134
4. Park SJ, Enriquez-Sarano M, Song JE et al (2013) Contractile reserve determined on exercise echocardiography in patients with severe aortic regurgitation. Circ J 77(9):2390–2398
5. Zoghbi WA, Adams D, Bonow RO et al (2017) Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 30(4):303–371
6. Lang RM, Bierig M, Devereux RB et al (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18(12):1440–1463
7. Zoghbi WA, Enriquez-Sarano M, Foster E et al (2003) Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 16(7):777–802
8. Stewart RA, Kittelson J, Kay IP (2000) Statistical methods to improve the precision of the treadmill exercise test. J Am Coll Cardiol 36(4):1274–1279
9. Gibbons RJ, Balady GJ, Beasley JW et al (1997) ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 30(1):260–311
10. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of Echocardiography (2007) American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 20(9):1021–1041
11. Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH (2005) Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. Heart 91(11):1407–1412
12. Goldman ME, Packer M, Horowitz SF et al (1984) Relation between exercise-induced changes in ejection fraction and systolic loading conditions at rest in aortic regurgitation. J Am Coll Cardiol 3(4):924–929
13. Greenberg B, Massie B, Thomas D et al (1985) Association between the exercise ejection fraction response and systolic wall stress in patients with chronic aortic insufficiency. Circulation 71(3):458–465
14. Wahi S, Haluska B, Pasquet A, Case C, Rimmerman CM, Marwick TH (2000) Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. Heart 84(6):606–614
15. Cavalcante JL (2018) Global longitudinal strain in asymptomatic chronic aortic regurgitation: the missing piece for the watchful waiting puzzle? JACC Cardiovasc Imaging 11(5):683–685
16. Alashi A, Mentias A, Abdallah A et al (2018) Incremental prognostic utility of left ventricular global longitudinal strain in asymptomatic patients with significant chronic aortic regurgitation and preserved left ventricular ejection fraction. JACC Cardiovasc Imaging 11(5):673–682