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Original article

Prognostic value of global left ventricular strain for conservatively treated patients with symptomatic aortic stenosis

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ABSTRACT

Aims: Impaired left ventricular (LV) strain is associated with an increased risk of cardiac events in asymptomatic severe aortic stenosis (AS). We aimed to evaluate the prognostic value of global LV strain in conservatively treated patients with symptomatic AS.
Methods and results: This cohort study retrospectively reviewed symptomatic AS patients who were treated conservatively or surgically between July 2007 and April 2010. We measured their global longitudinal strain (GLS) and global circumferential strain (GCS). Clinical events were defined as readmission for heart failure or all-cause death for 2 years. GLS and GCS could predict a worse outcome in the conservatively treated group at cut-offs of =−16.5% (77% sensitivity and 67% specificity) and =−22.2% (92% sensitivity and 83% specificity), respectively. By univariate Cox regression analysis, age, logistic EuroSCORE, aortic valve area, GLS, and GCS were significant predictors. When adjusted for age, logistic EuroSCORE, and aortic valve area, impaired GLS and GCS were independently associated with a higher risk of clinical events.
Conclusion: In conservatively treated patients with symptomatic AS, impaired GLS and GCS were associated with an increased risk of cardiac events during a 2-year follow-up. Global LV strain may help to define a higher risk subset; therefore, a larger and prospective observation study would be necessary.

Introduction

Previous studies have demonstrated that patients with severe aortic stenosis (AS) and a preserved left ventricular (LV) ejection fraction have impaired global longitudinal strain (GLS), and that the impairment of GLS improves after aortic valve replacement [1–5]. In patients with asymptomatic severe AS, impaired GLS was reported to be associated with a poor prognosis [6]. Clinically, up to 30% of patients with symptomatic AS are treated conservatively [7–9]. The role of strain parameters in the prognosis of symptomatic AS patients who are treated conservatively remains unclear. Accordingly, the aims of this study were to assess global LV strain in patients with symptomatic AS and a preserved LV ejection fraction who were treated conservatively, and to evaluate the prognostic value of strain parameters in these patients.

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Methods

Patients

This cohort study retrospectively reviewed symptomatic AS patients who were treated conservatively or surgically between July 2007 and April 2010. Patients were excluded from the analysis if they were not in sinus rhythm or had a LV ejection fraction <50%. Patients with a previous valve replacement, severe aortic or mitral regurgitation, and unsuitable two-dimensional imaging quality for speckle-tracking analysis were also excluded from the study. Patients were included after their first symptomatic presentation of angina, dyspnea, or both. Patients who did not undergo aortic valve replacement were conservatively treated patients [10]. The predominant reasons included high estimated surgical risk and patient refusal. If patients were not managed surgically, medications including aspirin (35%), statin (19%), beta-blocker (26%), and renin–angiotensin system blocker (48%) were given. The study group consisted of 31 conservatively treated patients who met these criteria; these patients were divided into 2 subgroups according to the occurrence of clinical events (patients with or without clinical events within 2 years). The clinical events were defined as all-cause death or readmission for heart failure, which were

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determined by evaluation of medical records. Additionally, we enrolled a control (surgical) group of 31 patients who met the above criteria but were treated with aortic valve replacement for the comparison of clinical outcome with the conservatively treated group. All echocardiographic measurements were performed by an experienced research personnel blinded to other clinical characteristics.

The study complies with the Declaration of Helsinki. The research protocol was approved by the local Institutional Review Board.

Echocardiography

Conventional 2-dimensional echocardiography was performed using commercially available equipment (Vivid 7, GE, Horten, Norway) with a 3.5-MHz transducer. LV ejection fraction was determined by the biplane Simpson's method. LV mass was calculated using the formula proposed by Devereux et al. [11], and was corrected by body surface area to derive the LV mass index. Measurements of LV diastolic filling included the mitral early (E)-velocity, mitral late (A)-velocity, and the E/A ratio [10]. In addition, tissue Doppler echocardiography was performed with the peak early diastolic velocity (E') measured at the basal septal segment in the apical 4-chamber view and the E/E' ratio was calculated [12]. The maximum transaortic pressure gradient was calculated using the Bernoulli equation, and mean transaortic pressure gradient was calculated by averaging the instantaneous gradients over the ejection period on the continuous-wave Doppler recordings [13]. The aortic valve area (AVA) was calculated with the continuity equation as previously described [14–17].

Strain analysis

Two-dimensional speckle-tracking strain analysis was performed offline by using a commercially available program (EchoPAC version 110.0, GE) [18–20]. The frame rate for this study was between 50 and 80 Hz. Longitudinal strain was obtained from the apical 4-chamber, 2-chamber, and long-axis views in an 18-segment LV model [21,22]. Circumferential strain was calculated from the parasternal short-axis view in the basal-, mid-, and apical-LV levels. If 2 or more segments were inadequately tracked, we excluded the data because the images were not useable for speckle-tracking analysis [19]. Three patients (2 conservatively treated; 1 surgically treated) were excluded from the analysis due to inadequate imaging quality. Subsequently, peak longitudinal strain and peak circumferential strain of all 18 LV segments were averaged to assess the GLS and global circumferential strain (GCS).

Statistical analysis

Data are presented as mean ± standard deviation or as a count (percentage). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) statistical software, version 18 for Windows. To compare each parameter between the groups, the chi-square test and Fisher's exact test were used for categorical variables, as appropriate, and the 2-sample t test and Mann–Whitney U-test were used for continuous variables. A Cox proportional hazards model was used for multivariate analysis to investigate which prognostic factors identified using univariate analysis were significantly associated with clinical events. Receiver operating characteristic curve (ROC) analysis was used to determine the optimal cut-off value of strain parameters for the prediction of clinical events. Event-free survival between the groups and subgroups was compared using a log-rank test, and representative Kaplan–Meier survival curves were constructed. The effect of different variables on event-free survival was investigated using the Cox proportional hazard model. For all analyses, a p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics for the study patients are shown in Table 1. The mean age was 70.2 ± 12.4 years and approximately half of the patients were male. No significant differences were found in age, gender, risk factors of coronary artery disease, percentage of coronary artery disease, LV mass, and LV ejection fraction between the conservatively treated group and the surgical control group. There were significant differences in logistic EuroSCORE, maximal transaortic pressure gradient, mean transaortic pressure gradient, and AVA between the 2 groups. In the conservatively treated group, the GLS and GLS rate were $-16.1 \pm 3.2\%$ and $-0.86 \pm 0.20\ s^{-1}$, respectively; the GCS and GCS rate were $-22.7 \pm 5.2\%$ and $-1.32 \pm 0.38\ s^{-1}$, respectively.

Clinical events and event-free survival

Four patients (6%) were admitted for heart failure and 12 patients (19%) died during the follow-up period. The cause of death

Table 1
Baseline characteristics.

	Total (n = 62)	Conservatively treated (n = 31)	AVR (n = 31)	p-Value
Age (years)	70.2 ± 12.4	72.9 ± 14.5	67.4 ± 9.2	0.08
Male, n (%)	30 (48)	15 (48)	15 (48)	1.00
Hypertension, n (%)	35 (56)	16 (52)	19 (61)	0.44
Dyslipidemia, n (%)	13 (21)	4 (13)	9 (29)	0.12
Smoking, n (%)	8 (13)	4 (13)	4 (13)	1.00
Diabetes mellitus, n (%)	16 (26)	10 (32)	6 (19)	0.25
Coronary artery disease, n (%)	12 (19)	5 (16)	7 (23)	0.52
Logistic EuroSCORE	10.4 ± 10.7	14.3 ± 12.1	6.5 ± 7.5	0.003
LV ejection fraction (%)	72.1 ± 9.1	71.4 ± 8.7	72.8 ± 9.7	0.53
LV mass index (g/m^2)	172.9 ± 67.9	171.6 ± 66.1	174.2 ± 71.0	0.89
Maximal PG (mmHg)	66.8 ± 23.9	56.1 ± 20.6	77.4 ± 22.3	0.001
Mean PG (mmHg)	39.3 ± 18.2	32.5 ± 13.5	53.5 ± 18.7	0.001
E/A	0.88 ± 0.23	0.99 ± 0.53	0.86 ± 0.39	0.29
E/E'	20.3 ± 7.0	21.7 ± 7.6	18.8 ± 6.1	0.11
Aortic valve area (cm^2)	0.88 ± 0.23	0.95 ± 0.21	0.81 ± 0.23	0.01
Death	12 (19)	9 (29)	3 (10)	0.12
Readmission for heart failure	4 (11)	4 (13)	0 (0)	0.32

AVR, aortic valve replacement; E/A, the ratio between early diastolic mitral inflow velocity and late inflow velocity; E/E', the ratio between early diastolic inflow velocity and early diastolic tissue velocity; LV, left ventricular; PG, pressure gradient.

Table 2
Comparisons between conservatively treated patients with and without clinical events.

	Events ($n = 13$)	No event ($n = 18$)	p-Value
Age (years)	81.6 ± 5.2	66.7 ± 16.0	0.01
Male, n (%)	17 (55)	14 (45)	0.61
Hypertension, n (%)	9 (69)	7 (39)	0.10
Dyslipidemia, n (%)	1 (8)	3 (17)	0.62
Smoking, n (%)	3 (23)	1 (6)	0.28
Diabetes mellitus, n (%)	6 (46)	4 (22)	0.25
Coronary artery disease, n (%)	4 (31)	1 (6)	0.13
Logistic EuroSCORE	19.6 ± 11.6	10.4 ± 11.1	0.04
LV ejection fraction (%)	68.0 ± 8.9	73.5 ± 8.1	0.17
Stroke volume (ml)	70.8 ± 26.8	72.5 ± 18.8	0.39
Relative wall thickness (mm)	0.6 ± 0.1	0.6 ± 0.1	0.93
LV mass index (g/m^2)	205.8 ± 73.6	147.0 ± 48.5	0.08
Maximal PG (mmHg)	63.6 ± 23.1	50.7 ± 17.3	0.10
Mean PG (mmHg)	38.0 ± 14.2	28.4 ± 11.8	0.03
Aortic valve area (cm^2)	0.9 ± 0.2	1.0 ± 0.2	0.009
E/A	1.08 ± 0.75	0.92 ± 0.29	0.79
E/E'	23.7 ± 7.6	20.2 ± 7.5	0.11

E/A, the ratio between early diastolic mitral inflow velocity and late inflow velocity; E/E', the ratio between early diastolic inflow velocity and early diastolic tissue velocity; LV, left ventricular; PG, pressure gradient.

Table 3
Comparisons of global left ventricular strain between AVR group and patients with/without events in the conservatively treated group.

	AVR group	Conservatively treated group	
		Events ($n = 13$)	No event ($n = 18$)
GLS (%)	−15.2 ± 3.8	−13.7 ± 3.8	−17.8 ± 2.0$^{*,\#}$
GCS (%)	−20.3 ± 5.7	−19.2 ± 4.9	−25.4 ± 4.0$^{*,\#}$

AVR, aortic valve replacement; GCS, global circumferential strain; GLS, global longitudinal strain.
* $p < 0.05$ events vs. no events in the conservatively treated patients.
\# $p < 0.05$, AVR group vs. no events in the conservatively treated patients.

was noncardiac in 2 (1 gastrointestinal bleeding, 1 septic shock). The 10 cardiac deaths were due to congestive heart failure (5), myocardial infarction (3), and sudden cardiac death (2). The clinical event rate over 2 years was significantly greater in the conservatively treated group than in the surgical group (42% vs. 10%, $p = 0.008$). In the conservatively treated group, there were significant differences in age, logistic EuroSCORE, LV mass index, mean transaortic pressure gradient, AVA, GLS, and GCS between patients with and without clinical events (Tables 2 and 3). In the surgical group, there were no significant differences in those baseline characteristics and LV strain between patients with and without events. There were significant differences in GCS and GLS between the aortic valve replacement group and patients without events in the conservatively treated group, but no significant differences in GCS and GLS between the aortic valve replacement group and patients with events in the conservatively treated group (Table 3). In the ROC curve analysis for the prediction of 2-year clinical events, several indices including age, logistic EuroScore, mean pressure gradient, stroke volume, ejection fraction, AVA, GLS, GCS, and combined GLS and GCS were analyzed. Among these prognostic factors, GCS or GLS were the most valuable factors for the patients with symptomatic AS who were treated conservatively (Fig. 1). Both GLS and GCS had an area under the curve (AUC) that was greater than the line of no information (AUC = 0.838, $p = 0.002$ for GLS; AUC = 0.865, $p = 0.001$ for GCS). Of note, GLS and GCS could differentiate between patients with or without clinical events in the conservatively treated group (cut-off value = −16.5% for GLS, 76.9% sensitivity, 66.7% specificity; cut-off value = −22.2% for GCS, 92.3% sensitivity, 83.3% specificity).

The conservatively treated patients had a worse outcome compared with the surgical group [hazard ratio (HR): 2.31, 95% confidence interval (CI): 1.23–4.33]. In the conservatively treated patients, the event-free survival was worse in patients with impaired LV strain than in those with relatively preserved LV strain (HR: 4.67, 95% CI: 1.27–17.09 for GLS ≥ −16.5% vs. GLS < −16.5%; HR: 22.03, 95% CI: 2.84–170.99 for GCS ≥ −22.2% vs. GCS < −22.2%; Fig. 2). There was no significant difference in event-free survival between the surgical group and the conservatively treated patients with preserved LV strain. By using the Cox regression analysis to predict the event-free survival, age, logistic EuroSCORE, AVA, GLS, and GCS were significant predictors according to the univariate analysis (Table 4). When adjusted for age, logistic EuroSCORE, and

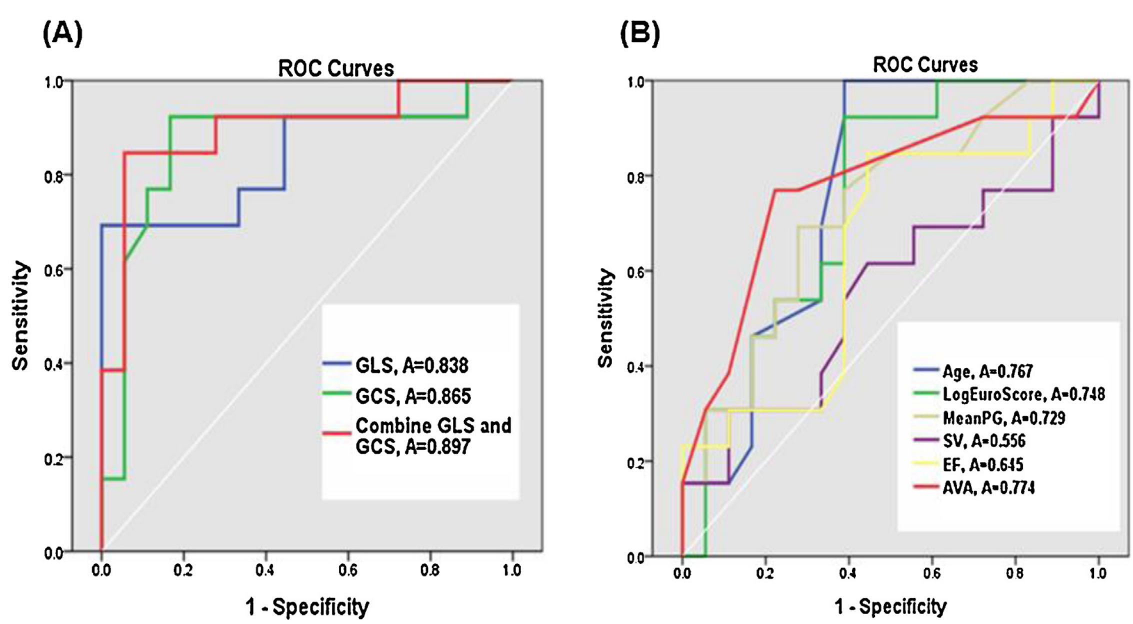

Fig. 1. Receiver operating characteristic (ROC) curve analysis for the prediction of 2-year clinical events including: (A) global longitudinal strain (GLS), global circumferential strain (GCS), and combination of GLS and GCS and (B) age, logistic EuroScore, mean pressure gradient (PG), stroke volume (SV), ejection fraction (EF), and aortic valve area (AVA).

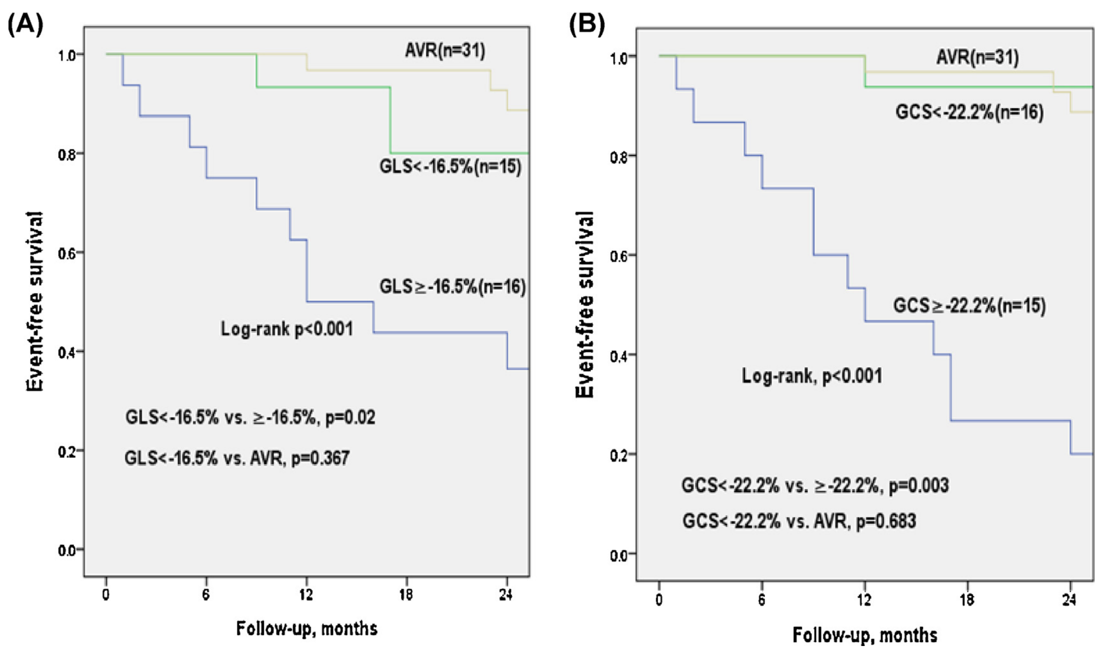

Fig. 2. Kaplan–Meyer analysis for event-free survival in patients with symptomatic aortic stenosis. Conservatively treated patients with impaired global longitudinal strain (GLS) or impaired global circumferential strain (GCS) had a worse outcome than patients with preserved strain or patients who underwent aortic valve replacement (AVR).

AVA, impaired GLS and GCS were independently associated with a higher risk of clinical events over 2 years.

Discussion

We demonstrated the value of global LV strain in the prediction of outcome for symptomatic AS patients who had to be treated surgically but conservatively. Importantly, not all symptomatic AS patients without AVR had poor prognosis, but the outcome of conservatively treated patients with preserved LV strain was not inferior to those with aortic valve replacement. Among the echocardiographic variables that were evaluated, only GLS and GCS were independent predictors for 2-year clinical events in conservatively treated patients with symptomatic AS.

Previous studies have shown that impaired GLS is associated with abnormal exercise response and an increased risk of cardiac events in patients with asymptomatic severe AS [23,24]. In the present study, not only GLS but also GCS could predict clinical outcome in symptomatic AS patients who were treated conservatively. In patients with severe AS, LV hypertrophy and the small effective orifice of the aortic valve impair coronary flow reserve, which renders the myocardium susceptible to ischemic injury, especially in the subendocardium [25–28]. The subendocardium mainly consists of longitudinal fibers; thus, longitudinal shortening is the first measurement to decrease in patients with AS [23,24,29,30]. Circumferential shortening is initially increased to compensate for the decrease in longitudinal shortening and to maintain normal LV ejection [4,31]. Hence, a decrease in circumferential shortening reflects more extensive myocardial injury and the loss of LV compensation [31–33]. This may explain the findings in the present study indicating that GLS and GCS are significant prognostic factors in symptomatic AS patients.

Symptomatic severe AS is an indication for aortic valve replacement [34]. However, some patients are denied intervention due to perceived high operative risk, their symptoms being regarded as mild stenosis, or patient preference [7–9]. Since the long-term outcome after aortic valve replacement is worse when the LV ejection fraction is impaired [35,36], it is imperative that patients are referred for intervention before the LV ejection fraction is reduced. Previous studies have shown that LV strain analysis could provide a better characterization of subtle LV dysfunction than the LV ejection fraction [17,18,37]. The present study demonstrated that GLS and GCS were useful in risk stratification of symptomatic AS patients who had a preserved ejection fraction and were treated conservatively, and could identify patients with poor outcome. Additionally, the recent development of transcatheter aortic valve

Table 4
Cox-regression hazard ratio in univariate and multivariate analyses for predicting cardiac events in conservatively treated patients.

	Univariate analysis		Multivariate analysis (model 1)		Multivariate analysis (model 2)	
	HR	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (years)	1.13	0.01	1.14 (0.99–1.30)	0.05	1.29 (1.07–1.57)	0.009
Logistic EuroSCORE	1.05	0.02	1.02 (0.96–1.08)	0.62	1.02 (0.96–1.08)	0.62
LV ejection fraction (%)	0.95	0.11				
Maximal pressure gradient (mmHg)	1.02	0.14				
Mean pressure gradient (mmHg)	1.03	0.08				
Aortic valve area (cm^2)	0.04	0.02	0.41 (0.02–8.36)	0.56	0.16 (0.004–6.77)	0.33
E/A	1.60	0.36				
E/E'	1.04	0.16				
Global longitudinal strain (%)	1.35	<0.001	1.30 (1.06–1.58)	0.01		
Global circumferential strain (%)	1.24	0.001			1.28 (1.10–1.49)	0.001

CI, confidence interval; E/A, the ratio between early diastolic mitral inflow velocity and late inflow velocity; E/E', the ratio between early diastolic inflow velocity and early diastolic tissue velocity; HR, hazard ratio; LV, left ventricular.

replacement treatment offers an effective treatment for symptomatic severe AS patients who decline surgery due to high surgical risk for aortic valve replacement [38].

Apart from the intrinsic limitations associated with a retrospective study, the other limitations were this work being a single-center study, a small sample size, and a heterogeneous study population that included patients with coronary artery disease and hypertension. However, coronary artery disease and hypertension are frequently associated co-morbidities in patients with symptomatic AS, and the exclusion of these conditions may mask the clinical spectrum of the disease. The inclusion of these patients yields a realistic view of what is observed in daily clinical practice. More severe AS was demonstrated in the surgical group compared to the conservatively treated group in our study population. That could be explained by the fact that the severity of AS could affect our treatment strategy for AS patients although they were all symptomatic. However, the therapeutic decision-making should be based on whether clinical symptoms were present [34]. We had taken the AS severity into account and found that it was not an independent predictor of clinical events. A recent study indicated that aging results in a decrease in GLS [39]. The present study also demonstrated that age was an independent predictor of clinical events. As our study population mostly comprised elderly patients, additional studies evaluating a younger population could provide more specific information in this regard. Our study also demonstrated a real-world elderly patient population with symptomatic severe AS not undergoing aortic valve replacement due to age (i.e. life expectancy) and comorbidities. The observed high surgical risk (logistic EuroScore 19%) was similar to that of the patients having transcatheter aortic valve replacement [40]. Global LV strain may help identify these high-risk patients who were treated conservatively as potential candidates for transcatheter aortic valve replacement.

In conclusion, speckle-tracking strain analysis could detect myocardial deformation abnormalities and is useful for the prediction of clinical outcome in symptomatic AS patients who are treated conservatively. The outcome of conservatively treated patients with preserved LV strain was not inferior to those with aortic valve replacement. Global LV strain may help to define a higher risk subset; therefore, a larger and prospective observational study would be necessary.

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