



Cardiac Magnetic Resonance Feature Tracking in Aortic Stenosis: Exploration of Strain Parameters and Prognostic Value in Asymptomatic Patients with Preserved Ejection Fraction

Moon Young Kim, MD, MS^{1,2}, Eun-Ah Park, MD, PhD¹, Whal Lee, MD, PhD¹, Seung-Pyo Lee, MD, PhD³

Departments of ¹Radiology and ³Internal Medicine, Cardiology Division, Seoul National University Hospital, Seoul, Korea; ²Department of Radiology, SNU-SMG Boramae Medical Center, Seoul, Korea

Objective: To determine the most valuable cardiac magnetic resonance feature tracking (CMR-FT) parameters for evaluating aortic stenosis (AS) and determine whether they can predict the prognosis in asymptomatic AS patients with preserved ejection fraction (pEF).

Materials and Methods: A prospective cohort of 123 moderate to severe AS patients (60 males, 68.6 ± 9.2 years) and 32 control subjects (14 males, 67.9 ± 4.4 years) underwent echocardiography and 3T CMR imaging from 2011–2015. CMR cine images were analyzed using CMR-FT to assess the left ventricular radial, circumferential, and longitudinal peak strain (PS) in 2- and 3-dimensions. The primary endpoints were clinical cardiac events (CCEs), including cardiac death, heart failure, and AS-associated symptom development. For statistical analysis, logistic regression and log-rank tests were used.

Results: Global PSs differed between AS patients and controls and between severe and moderate AS patients ($p < 0.05$). Two-dimensional (2D) global radial and longitudinal PSs changed gradually with the severity of AS groups ($p < 0.001$). Twenty-two of 67 asymptomatic AS patients with pEF experienced CCEs during the follow-up (median: 31.1 months). 2D global longitudinal PS (GLPS) was the single risk factor for CCE ($p = 0.017$). The relative risk for CCE was 3.9 ($p = 0.016$, 95% confidence interval: 1.2–11.9) based on 2D GLPS with a cutoff of -17.9% according to receiver operating characteristic curve analysis. Survival analysis demonstrated that asymptomatic AS patients with pEF having impaired 2D GLPS experienced worse event-free survival than the others ($p = 0.041$).

Conclusion: 2D global longitudinal and radial PSs may reflect cardiac dysfunction according to the degree of AS. 2D GLPS might be a prognostic predictor of CCEs in asymptomatic AS patients with pEF.

Keywords: Cardiac magnetic resonance; Feature tracking; Strain; Aortic stenosis; Event-free survival

INTRODUCTION

Despite the fatal natural history of symptomatic patients

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Corresponding author: Eun-Ah Park, MD, PhD, Department of Radiology, Seoul National University Hospital, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea.

• Tel: (822) 2072-0187 • Fax: (822) 743-6385

• E-mail: iameuna1@gmail.com

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with severe aortic stenosis (AS), the benefits of a surgical strategy are well established in these patients. However, the management of asymptomatic AS patients remains disputed; wide variation in individual outcomes, the potential risk of complications related to the prosthetic valve, and the risk of valve surgery make it difficult to decide whether to operate (1). Currently, aortic valve replacement has been limitedly applied to patients: those undergoing surgery for coronary artery or concomitant valve disease or aorta or those with associated significantly obstructed coronary artery disease, left ventricle (LV) dysfunction, or progressive decline of LV ejection fraction (LVEF). Although LVEF is well established as an independent predictor of adverse outcome in heart

failure, reduced EF is often a late consequence of valve dysfunction. Recent studies suggest that strain imaging reflecting myocardial deformation may identify myocardial injury at an earlier stage before decline in EF (2).

Cardiac magnetic resonance feature tracking (CMR-FT) enable us to evaluate myocardial strain, using routinely acquired CMR cine images. CMR-FT has been validated against speckle-tracking echocardiography, and CMR myocardial tagging techniques, which need sophisticated additional imaging sequences, and burdensome post-processing (3-5). Furthermore, clinical applicability of CMR-FT has been demonstrated in diverse cardiovascular diseases (3, 6, 7).

Therefore, the purpose of this study was to determine the most valuable CMR strain parameters for evaluating AS, and to assess whether they predict clinical cardiac events (CCEs) in asymptomatic AS patients with preserved EF (pEF).

MATERIALS AND METHODS

Patient Population

The protocol for this prospective cohort study was

approved by Institutional Review Board, and all subjects gave written informed consent for the study. Out of the 137 patients with moderate or severe AS enrolled to the prospective registry, 14 patients were excluded for the following reasons: more than a moderate degree of concomitant aortic regurgitation (n = 6), a previous history of cardiac surgery (n = 1), myocardial infarction (n = 7), and suboptimal CMR quality (n = 4). Four subjects had overlapping exclusion criteria. Finally, patients with moderate or severe AS (123 in total; 60 males, mean age, 68 years [range, 31–87 years]; 63 females, mean age, 69 years [range, 42–86 years]) were included in this study (8) (Fig. 1). Patients underwent echocardiography, and CMR imaging within a month. Moderate to severe AS was defined with echocardiography as a maximal transaortic velocity higher than 3 m/sec or a mean transaortic pressure gradient of more than 30 mmHg and an aortic valve area of up to 1.5 cm² (9). In addition, 32 healthy volunteers (mean age of males, 68 years [range, 61–74 years]; mean age of females, 68 years [range, 60–76 years]) without cardiovascular disease or risk factors, were enrolled prospectively in the control group. The control subjects were matched for age,

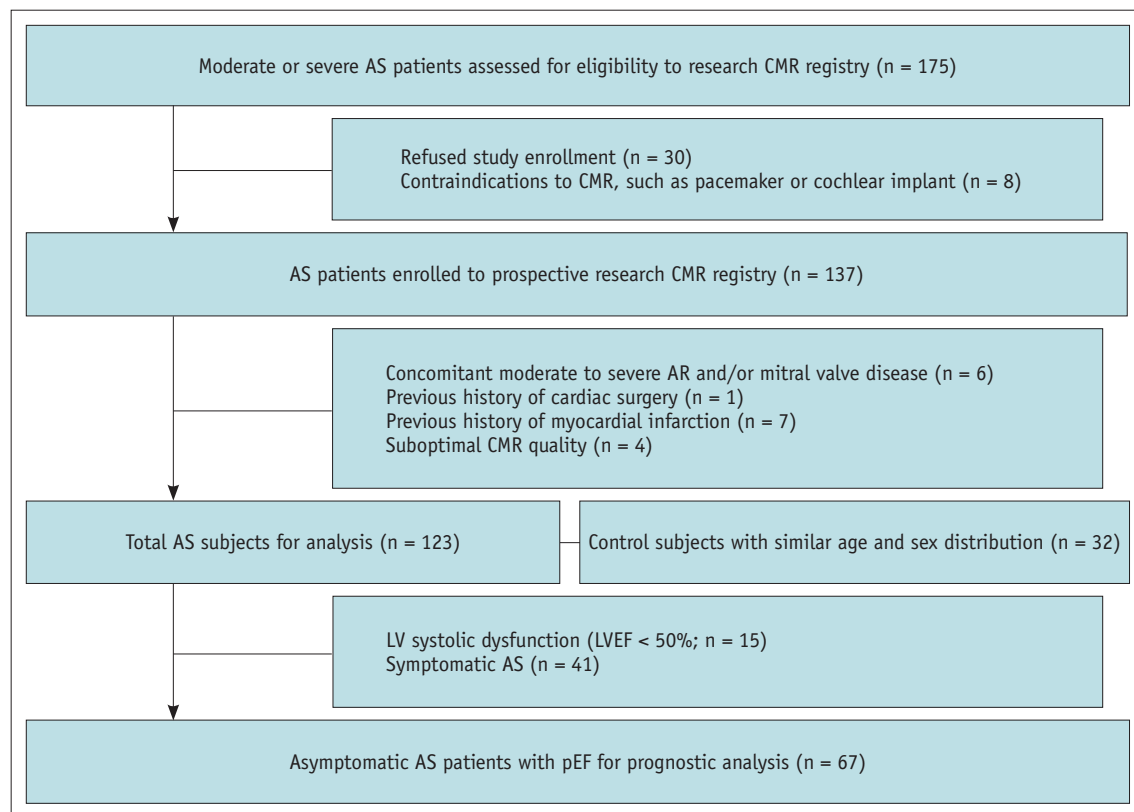


Fig. 1. Flowchart of study population enrollment. AR = aortic regurgitation, AS = aortic stenosis, CMR = cardiac magnetic resonance, EF = ejection fraction, LV = left ventricle, pEF = preserved EF

sex, and body surface area (BSA) with AS patients (10).

Follow-Up

For analysis of the prognostic value of CMR-FT strain parameters in asymptomatic AS patients with pEF, 56 of 123 patients were excluded for the following reasons: 1) patients with LVEF of less than 50% at CMR imaging ($n = 15$); and 2) patients with dyspnea or other symptoms of heart failure (class III or IV according to the New York Heart Association functional classification system), and patients with typical exertional chest pain or syncope ($n = 41$) (Fig. 1). Finally, 67 asymptomatic AS patients with pEF were followed-up. The primary endpoint was a composite of CCEs, defined as cardiovascular death, heart failure, and AS-associated symptom development (11, 12).

Echocardiographic Examination

Detailed methods are described in the Supplementary Materials.

CMR Imaging Acquisition and Analysis

CMR imaging was performed using a 3T imager (Trio, Siemens, Erlangen, Germany) equipped with six-channel phased-array coils using standard protocols (13). After acquiring cine images, T1 mapping sequences were obtained. Detailed image acquisition, and analysis can be found in the Supplementary Materials.

CMR-FT Analysis

CMR-FT analyses were performed using a dedicated software (cvi42 version 5, Circle Cardiovascular Imaging Inc., Calgary, Canada). Two-, three-, and four-chamber, and short axis images were used to reconstruct a three-dimensional (3D) model that is used for analyses of LV strain. The preferred images were loaded into the analysis/viewer frame of the software, and analyzed in a random order by two blinded investigators (17 years and 5 years of CMR experience) in consensus.

FT analysis was manually performed by drawing the endocardial and epicardial surfaces in the end-diastolic and end-systolic phases (reference phases), using short axis and long axis cines. Three horizontal long-axis cines including four-chamber, two-chamber, and three-chamber views were tracked to derive longitudinal strain, while short-axis cines were used to derive radial and circumferential strains. Reference points were manually delineated at the right ventricle upper and lower septal insertions into the

LV for regional and global analysis of strain and for the generation of polar map views. Cvi42 software interpolated the myocardial contour from the endocardial and epicardial contours of the reference phases and traced its myocardium voxel points throughout the remainder of the cardiac cycle. Strain parameters including peak strain (PS) were obtained automatically in all slices in two-dimensional (2D) as well as 3D manners. A seventeen-segment model was used for assessments of regional and global myocardial mechanics (Fig. 2) (14). 3D longitudinal, radial, and circumferential strain components were derived from averaging the 17-segmental strain curves separately.

Statistical Analysis

Continuous variables are presented as means \pm standard deviations and compared using Student's *t* test. Dichotomous variables are presented as number (percentage) and compared by using the chi square (χ^2) test. Bivariate correlation analysis between the various CMR and echocardiographic parameters was performed, using either the linear or the quadratic equation. The strength of correlation is presented as a Pearson correlation coefficient. The cutoff value of CMR strain parameters in discriminating a prognostic effect was determined using receiver operating characteristic (ROC) curve analysis. The prognostic factor of CCE in asymptomatic AS patients with pEF was chosen by logistic regression. The multicollinearity of variables in multivariate analysis was evaluated with colinearity statistics tolerance. The cut-off value of variance inflation factor for detecting multicollinearity was greater than 10 (15). For survival analysis, a log-rank test was performed. Analysis was conducted with SPSS version 23.0 software (IBM Corp., Armonk, NY, USA), with the exception of ROC curve analysis (MedCalc version 9.3.1, MedCalc Software, Mariakerke, Belgium). A two-tailed *p* value of less than 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics

The entire AS population was categorized according to the degree of AS. None of the clinical characteristics described in Table 1 were significantly different between moderate and severe AS groups. In 32 control subjects with 14 males (45%), mean age was 67.9 ± 4.4 years and mean BSA was 1.64 ± 0.13 m².

Echocardiographic and CMR Parameters

The measurements from echocardiography and CMR are listed in Table 2. The mean LVEF and the mean LV mass index (LVMI) by CMR of the entire AS population were

$62.1 \pm 14.0\%$ and $96.2 \pm 35.9 \text{ g/m}^2$, respectively. The LVEF estimated by CMR in the moderate AS group was significantly higher than that in the severe AS group, in contrast to the insignificant result in echocardiographic

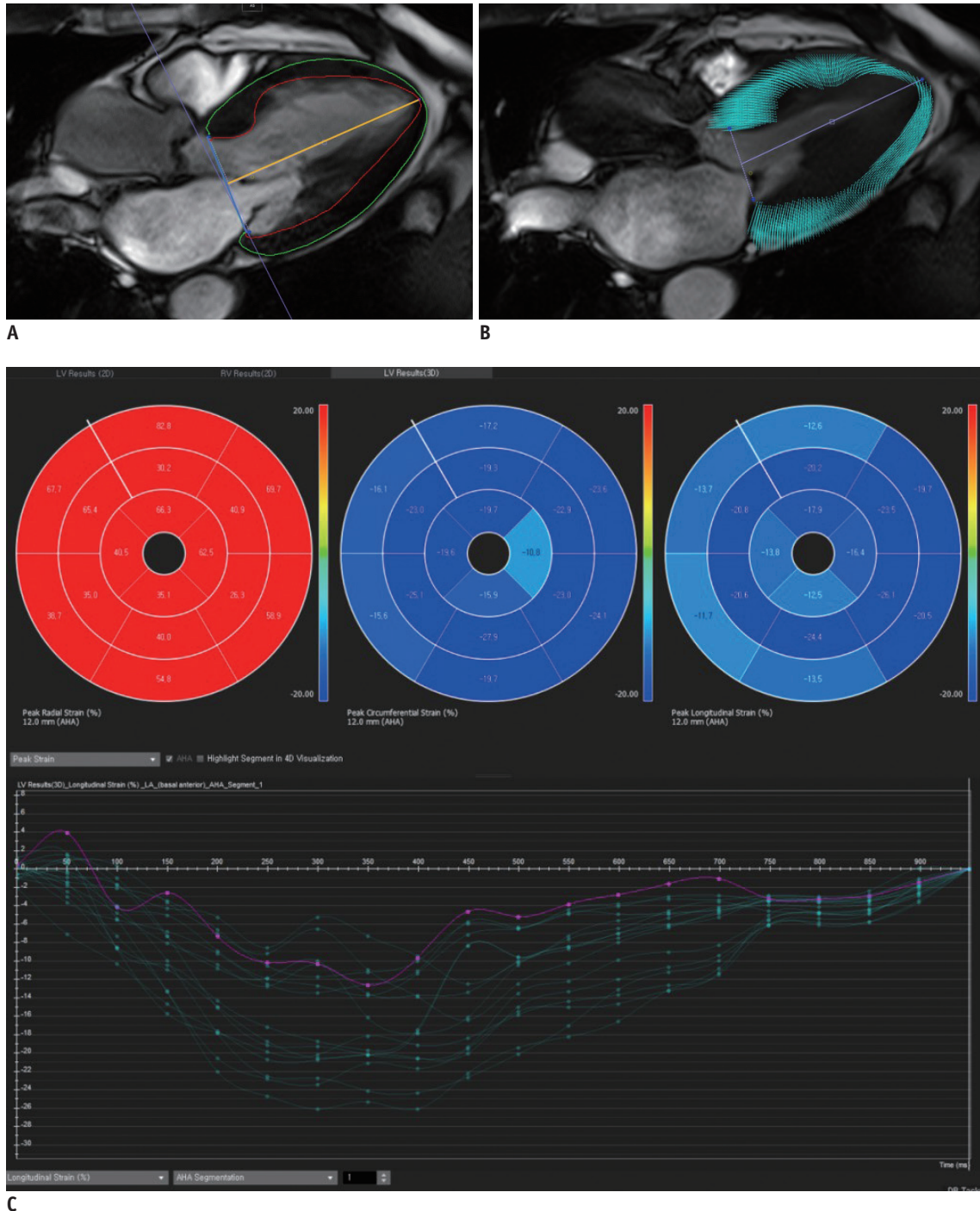


Fig. 2. Assessment of left ventricular myocardial strain using CMR feature tracking software in 72-year-old male with severe AS. **A.** First step for assessing myocardial strain is defining axis of LV (yellow line), and drawing endocardial (red line) and epicardial (green line) contours on end-diastolic and end-systolic phases, respectively. Phase shown is end-diastolic. **B.** Second step is visualization of automatic process of myocardial strain measurement. Myocardial points in each slice are connected by visualizing motion lines from end-diastolic to end systolic phases on static systolic 3-chamber-view cine image. **C.** Third step is automatically obtaining global and segmental strain values (polar maps) and phasic graphs.

LVEF. Echocardiographic and CMR LVMI in the severe AS group were higher than those in the moderate AS group. There were significant differences between moderate and

severe AS groups in the following echocardiographic and CMR parameters: echocardiography, interventricular septal thickness, posterior wall thickness, e' velocity, transaortic

Table 1. Clinical Characteristics according to AS Subgroups

Parameter	Total AS Subjects (n = 123)	Moderate AS (n = 45)	Severe AS (n = 78)	P
Number of men	60 (49)	19 (42)	41 (53)	0.273
Age (years)	68.6 ± 9.2	66.2 ± 11.7	70.0 ± 7.2	0.055
Body surface area (m ²)	1.67 ± 0.15	1.68 ± 0.15	1.66 ± 0.15	0.463
Systolic blood pressure	130 ± 18	130 ± 17	130 ± 19	0.958
Diastolic blood pressure	71 ± 11	73 ± 11	70 ± 11	0.176
Hypertension medication	82 (67)	28 (62)	54 (69)	0.435
Beta-blockers	40 (33)	14 (31)	26 (33)	0.844
Renin angiotensin system blockers	61 (50)	25 (56)	36 (46)	0.353
Calcium channel blockers	30 (24)	7 (16)	23 (29)	0.126
Diuretics	32 (26)	7 (16)	25 (32)	0.499
Diabetes mellitus	34 (28)	15 (33)	19 (24)	0.302
Dyslipidemia	35 (28)	16 (36)	19 (24)	0.216
Current smoker	7 (6)	2 (4)	5 (6)	0.494
Atrial fibrillation	14 (11)	4 (9)	10 (13)	0.571
Serum creatinine level (mg/dL)	0.96 ± 0.74	0.84 ± 0.17	1.03 ± 0.91	0.171
Follow-up duration (months)	28 ± 13.9	29 ± 13.7	27 ± 13.9	0.311
Subjects with CCE	34 (28)	14 (31)	20 (26)	0.536

Continuous variables are presented as means ± standard deviations, and dichotomous variables are presented as numbers of patients, with percentages in parentheses. Each parameter was compared by using either Student's *t* test or χ^2 test, as appropriate. AS = aortic stenosis, CCE = clinical cardiac event

Table 2. Echocardiographic and CMR Parameters of Moderate and Severe as Subgroups

Parameter	Moderate AS (n = 45)	Severe AS (n = 78)	P
Echocardiography			
LVEF (%)	61.4 ± 6.5	60.2 ± 10.5	0.467
LV end-diastolic diameter (mm)	48.8 ± 6.3	50.0 ± 6.2	0.308
LV end-systolic diameter (mm)	30.3 ± 6.1	31.6 ± 7.7	0.144
LV mass index (mL/m ²)	107.9 ± 36.9	138.7 ± 37.3	< 0.001*
Interventricular septal thickness (mm)	10.2 ± 1.6	11.9 ± 1.2	< 0.001*
Posterior wall thickness (mm)	10.2 ± 1.7	11.5 ± 1.9	< 0.001*
E velocity (m/sec)	0.75 ± 0.31	0.70 ± 0.24	0.336
Deceleration time (msec)	222 ± 86	250 ± 78	0.074
e' velocity (cm/sec)	4.7 ± 1.4	4.1 ± 1.3	0.031*
Transaortic peak velocity (m/sec)	3.7 ± 0.5	4.9 ± 0.7	< 0.001*
Transaortic mean pressure gradient (mm Hg)	32.0 ± 9.5	57.7 ± 17.3	< 0.001*
Aortic valve area (cm ²)	1.02 ± 0.21	0.69 ± 0.16	< 0.001*
Indexed aortic valve area (cm ² /m ²)	0.61 ± 0.14	0.41 ± 0.09	< 0.001*
CMR			
LVEF (%)	65.3 ± 10.3	60.3 ± 15.4	0.034*
LV end-diastolic volume index (mL/m ²)	85.6 ± 27.1	104.8 ± 35.3	0.001*
LV end-systolic volume index (mL/m ²)	32.0 ± 21.6	45.5 ± 32.3	0.007*
LV mass index (mL/m ²)	76.2 ± 22.6	107.4 ± 37.2	< 0.001*
Heart rate (beats per minute)	67.4 ± 11.4	66.6 ± 13.0	0.741
Noncontrast T1 (msec)	1217 ± 62	1240 ± 46	0.019*

Continuous variables are presented as means ± standard deviations. Each parameter was compared by using Student's *t* test. **p* < 0.05. CMR = cardiac magnetic resonance, EF = ejection fraction, LV = left ventricle

peak velocity, mean pressure gradient, aortic valve area, CMR:LV end diastolic and systolic volume indices, and non-contrast T1 ($p < 0.05$ for all the parameters).

Association between AS and CMR Strain Parameters

The absolute mean values of global radial, circumferential, and longitudinal PS were significantly reduced in both 2D and 3D measurements in AS patients compared to the controls ($p < 0.05$ for all) (Table 3). Severe AS patients showed more impaired global PS values than moderate AS patients did ($p < 0.05$). All 2D and 3D segmental strain parameters showed no significant differences between subgroups ($p > 0.05$ for all parameters). Trend analysis of control, moderate AS, and severe AS subgroups was performed with a Jonckheere-Terpstra test. The post-hoc analysis demonstrated that the absolute mean values of 2D global radial and longitudinal PSs revealed a significant gradual decreasing trend in the order of control, moderate, and severe AS groups ($p < 0.001$).

Correlation of Strain Parameters and Other Imaging Indices

There were significant linear correlations between the global PSs, and various other cardiac imaging indices ($p < 0.05$) (Table 4). All global strain parameters showed significant linear correlations with all of the CMR measurements including EF, LVMI, LV end-diastolic and end-systolic volume indices, and non-contrast T1 and echocardiographic EF, LVMI, LV end-diastolic and end-systolic diameters, deceleration time, left atrial (LA) diameter, and (indexed) aortic valve area. Especially, EF on CMR and echocardiography, CMR LVMI, and

echocardiographic LV end-systolic diameter had moderate to strong linear correlations with all global PSs.

Prognostic Value of Strain Parameters in Asymptomatic AS Patients with pEF

Among total AS patients, 67 asymptomatic patients with pEF were analyzed to find the effective and predictive parameters for prognosis. Their mean age was 68.4 ± 9.6 years. The mean LVEF and LVMI by CMR were $69.0 \pm 6.7\%$ and 89.3 ± 32.6 g/m², respectively. The median follow-up period was 31.1 months (interquartile range, 17.8–41.7). Twenty-two of the 67 patients experienced CCEs during the follow-up period (cumulative event rate 32.8%). Two patients died due to cardiac causes. Heart failure occurred in nine patients. Twenty patients developed AS-associated symptoms, such as chest pain, syncope, and dyspnea. Eight patients suffered from more than one CCE.

Clinical and imaging data of asymptomatic AS patients with pEF are listed in Supplementary Table 1, in terms of presence or absence of CCE. There were significant statistical differences between two groups by using student *t* test or χ^2 test in following: history of diabetes mellitus (DM), echocardiographic LVMI, interventricular septal and posterior wall thickness, *e'* velocity, transaortic peak velocity and mean pressure gradient, CMR EF, LV end-diastolic/systolic volume indices, LVMI, non-contrast T1, and all global PS parameters ($p < 0.05$ for all parameters).

The univariate logistic regression revealed that history of DM ($p = 0.015$), and all global PSs, except 2D global circumferential PS ($p = 0.065$), were determined as predictors of CCEs among all clinical and imaging variables (Table 5). Multivariate logistic regression analysis was

Table 3. Differences of CMR Feature Tracking Global Peak Strains between Control and AS Subjects and between Moderate and Severe AS Subjects

Global Peak Strain Parameters (%)	Control	AS	<i>P</i>	Moderate AS	Severe AS	<i>P</i>	<i>P</i> Value for Trend
2D							
Longitudinal	-18.97 ± 2.33	-14.96 ± 4.04	< 0.001*	-16.47 ± 3.15	-14.09 ± 4.23	0.001*	< 0.001 [†] (6.38)
Radial	36.29 ± 7.77	26.60 ± 9.58	< 0.001*	29.75 ± 7.51	24.79 ± 10.15	0.003*	< 0.001 [†] (-6.10)
Circumferential	-21.07 ± 2.69	-19.38 ± 4.09	0.008*	-20.43 ± 3.38	-18.78 ± 4.33	0.031*	0.028 (2.60)
3D							
Longitudinal	-17.98 ± 2.25	-15.88 ± 3.83	< 0.001*	-16.79 ± 3.51	-15.36 ± 3.91	0.045*	0.002 (3.46)
Radial	47.64 ± 10.78	42.84 ± 15.04	0.046*	47.28 ± 13.23	40.27 ± 15.41	0.013*	0.012 (-2.89)
Circumferential	-20.07 ± 2.13	-18.18 ± 4.06	0.001*	-19.34 ± 3.37	-17.51 ± 4.27	0.016*	0.006 (3.14)

Continuous variables are presented as means ± standard deviations. * $p < 0.05$. *p* values for trend are derived from trend analysis of Jonckheere-Terpstra test among control group and moderate and severe AS subgroups with Z statistic in parentheses, [†]Means there were significant statistical differences in each 2-subgroup combination among all 3 subgroups in post-hoc analysis. 2D = two-dimensional, 3D = three-dimensional

Table 4. Linear Correlation (Pearson Correlation Coefficient) between Global Peak Strain Parameters and Echocardiographic and CMR Functional Indices in AS

Global Peak Strain Parameters	Longitudinal		Radial		Circumferential	
	2D	3D	2D	3D	2D	3D
Echocardiography						
LVEF (%)	-0.635 [†]	-0.714 [†]	0.598 [†]	0.571 [†]	-0.662 [†]	-0.703 [†]
LV end-diastolic diameter (mm)	0.294 [†]	0.443 [†]	-0.297 [†]	-0.314 [†]	0.383 [†]	0.446 [†]
LV end-systolic diameter (mm)	0.522 [†]	0.666 [†]	-0.504 [†]	-0.519 [†]	0.628 [†]	0.671 [†]
LV mass index (mL/m ²)	0.401 [†]	0.380 [†]	-0.411 [†]	-0.428 [†]	0.337 [†]	0.435 [†]
Interventricular septal thickness (mm)	0.271*	0.062	-0.285*	-0.188*	0.060	0.122
Posterior wall thickness (mm)	0.299 [†]	0.164	-0.312 [†]	-0.247*	0.190*	0.204*
E velocity (m/sec)	0.075	0.051	-0.040	0.066	-0.059	0.039
Deceleration time (msec)	-0.238*	-0.336 [†]	0.248*	0.237*	-0.257*	-0.236*
e' velocity (cm/sec)	-0.261*	-0.186*	0.274*	0.262*	-0.228*	-0.144
E velocity/e' velocity ratio	0.235*	0.194*	-0.221*	-0.200*	0.094	0.140
Left atrial diameter	0.354 [†]	0.282 [†]	-0.335 [†]	-0.208*	0.239 [†]	0.242 [†]
Transaortic peak velocity (m/sec)	0.191*	0.002	-0.228*	-0.142	0.044	0.047
Transaortic mean pressure gradient (mm Hg)	0.213*	0.082	-0.247*	-0.198*	0.105	0.116
Aortic valve area (cm ²)	-0.394 [†]	-0.316 [†]	0.392 [†]	0.363 [†]	-0.294 [†]	-0.302 [†]
Indexed aortic valve area (cm ² /m ²)	-0.422 [†]	-0.339 [†]	0.428 [†]	0.347 [†]	-0.323 [†]	-0.315 [†]
CMR						
LVEF (%)	-0.645 [†]	-0.714 [†]	0.604 [†]	0.650 [†]	-0.648 [†]	-0.759 [†]
LV end-diastolic volume index (mL/m ²)	0.453 [†]	0.364 [†]	-0.461 [†]	-0.491 [†]	0.433 [†]	0.455 [†]
LV end-systolic volume index (mL/m ²)	0.407 [†]	0.445 [†]	-0.396 [†]	-0.434 [†]	0.421 [†]	0.528 [†]
LV mass index (mL/m ²)	0.623 [†]	0.676 [†]	-0.583 [†]	-0.615 [†]	0.661 [†]	0.749 [†]
Noncontrast T1 (msec)	0.451 [†]	0.422 [†]	-0.432 [†]	-0.352 [†]	0.297 [†]	0.391 [†]

Statistically significant corresponding *p* value to each Pearson correlation coefficient was indicated by following symbols. **p* < 0.05, [†]*p* < 0.001

performed using those predictors for evaluating the prognostic factors for CCE. As a result, the 2D global longitudinal PS (GLPS) remained as a single independent risk factor for CCE {odds ratio = 4.3 (95% confidence interval [CI] = 1.8–10.3), *p* = 0.017} (Table 6).

ROC curve analysis for 2D GLPS prediction of CCE revealed an area under the ROC curve of 0.656 and an associated criterion of -17.9%, with a sensitivity of 54.6% and specificity of 76.3% (Fig. 3). The relative risk for CCE was 3.9 (*p* = 0.016, 95% CI: 1.2–11.9) based on 2D GLPS with a cutoff of -17.9% from which a Kaplan-Meier graph was derived. Kaplan-Meier survival curves demonstrated that if the asymptomatic AS patients with pEF had an impaired value for 2D GLPS, they experienced worse event-free survival than those without impaired values (*p* = 0.041 by log-rank test) (Fig. 4).

DISCUSSION

The major findings of this study were that 1) 2D global longitudinal and radial PSs were significantly correlated to

the degree of AS; 2) global PSs showed linear correlations with cardiac imaging functional indices; and 3) impaired 2D GLPS was associated with increased risk of CCEs.

2D global longitudinal and radial PSs showed increasing impairment from control to moderate AS to severe AS groups. This indicates that subtle changes in longitudinal and radial deformation progress gradually from mild to severe AS. Our result was similar to that using speckle-tracking echocardiography, which also showed a gradual decrease in global longitudinal strain as the severity of AS increases despite an unchanged LVEF (16). Previous studies in severe AS patients using echocardiography or CMR tissue tagging also revealed a significant reduction in circumferential and longitudinal function, even in patients who had no or only mild symptoms (17, 18). Thus, objective change in myocardial strain can be more sensitive than observable symptoms in detecting functional abnormality in AS.

On the other hand, all 3D strain parameters, even longitudinal ones, showed no statistical significance for predicting prognosis in asymptomatic AS subjects with

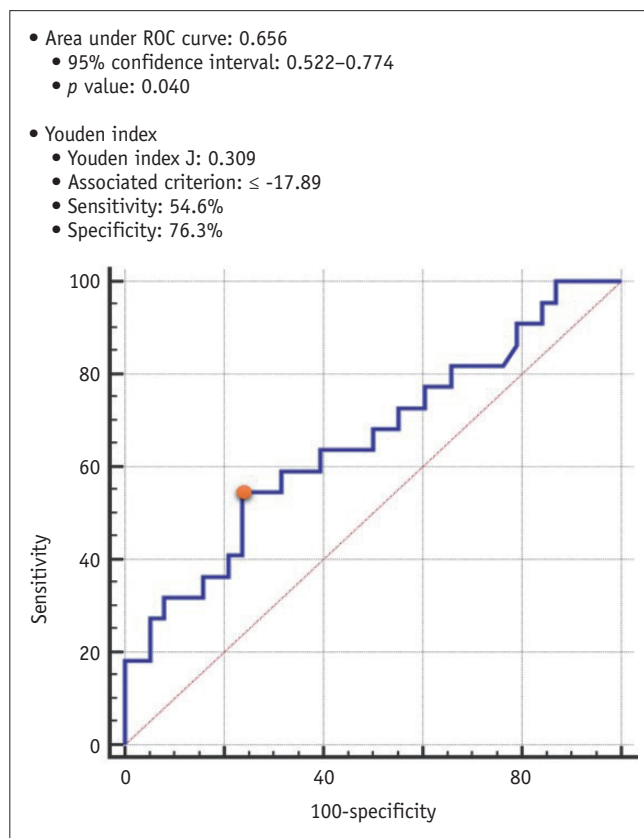
Table 5. Univariate Logistic Regression Analysis for Predicting CCEs in Asymptomatic AS with pEF

Variables	Univariate Analysis			
	Odd Ratio	95% Confidence Interval		P
Clinical Characteristics				
Male	0.865	0.308	2.43	0.865
Age (years)	1.03	0.975	1.10	0.269
Body surface area (m ²)	0.830	0.024	28.2	0.918
Systolic blood pressure	1.04	0.108	10.1	0.150
Diastolic blood pressure	1.02	0.975	1.08	0.350
Hypertension medication	0.366	0.106	1.26	0.112
Beta-blockers	0.618	0.203	1.88	0.397
Renin angiotensin system blockers	0.797	0.287	2.22	0.664
Calcium channel blockers	0.809	0.245	2.68	0.728
Diuretics	0.857	0.199	3.69	0.836
Diabetes mellitus	4.50	1.34	15.1	0.015*
Dyslipidemia	1.87	0.587	5.94	0.290
Current smoker	0.667	0.065	6.80	0.732
Atrial fibrillation	0.800	0.142	4.49	0.800
Serum creatinine level (mg/dL)	1.28	0.116	14.1	0.839
Follow-up duration (months)	1.03	0.990	1.69	0.151
Echocardiography				
LVEF (%)	1.04	0.940	1.16	0.430
LV end-diastolic diameter (mm)	1.01	0.901	1.12	0.929
LV end-systolic diameter (mm)	1.03	0.921	1.15	0.612
LV mass index (mL/m ²)	1.01	0.992	1.02	0.374
Interventricular septal thickness (mm)	1.04	0.833	1.30	0.724
Posterior wall thickness (mm)	1.11	0.857	1.44	0.430
E velocity (m/sec)	1.74	0.191	15.9	0.623
Deceleration time (msec)	1.00	0.997	1.01	0.275
e' velocity (cm/sec)	1.01	0.724	1.40	0.970
Transaortic peak velocity (m/sec)	0.660	0.365	1.19	0.168
Transaortic mean pressure gradient (mm Hg)	0.987	0.961	1.01	0.335
Aortic valve area (cm ²)	1.14	0.123	10.5	0.909
Indexed aortic valve area (cm ² /m ²)	1.33	0.041	42.7	0.873
CMR				
LVEF (%)	0.959	0.886	1.04	0.301
LV end-diastolic volume index (mL/m ²)	0.991	0.968	1.02	0.453
LV end-systolic volume index (mL/m ²)	1.01	0.970	1.06	0.561
LV mass index (mL/m ²)	0.984	0.964	1.00	0.113
Noncontrast T1 (msec)	1.00	0.992	1.01	0.783
Global peak strain parameters				
2D				
Longitudinal	3.41	2.80	4.31	0.023*
Radial	3.00	1.10	8.18	0.032*
Circumferential	0.836	0.690	1.01	0.065
3D				
Longitudinal	3.14	2.57	4.01	0.017*
Radial	1.05	1.00	1.10	0.031*
Circumferential	3.67	2.82	5.11	0.024*

*p < 0.05. pEF = preserved EF

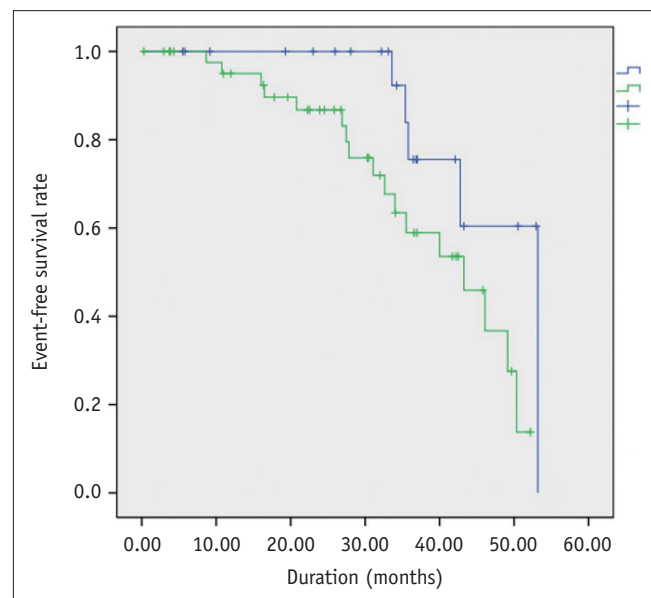
Table 6. Multivariate Logistic Regression Analysis for Predicting CCEs in Asymptomatic AS with pEF Using Univariate Predictors

Variables	Multivariate Analysis			
	Odd Ratio	95% Confidence Interval	P	
Clinical characteristics				
Diabetes mellitus	6.17	0.423	89.9	0.183
Global peak strain parameters				
2D				
Longitudinal	4.27	1.77	10.3	0.017*
Radial	1.28	0.990	1.65	0.060
3D				
Longitudinal	6.44	0.705	58.8	0.099
Radial	0.160	0.024	1.08	0.059
Circumferential	6.17	0.423	89.9	0.183

* $p < 0.05$ **Fig. 3. ROC curve of 2D global longitudinal peak strain for predicting clinical cardiac event in asymptomatic AS patients with pEF.** ROC = receiver operating characteristic, 2D = two-dimensional

pEF. This may be explained by dilution of each significant directional component in the data because the 3D strain parameters were derived from various segmental 2D measurements by software-dependent calculation with limited reliability validation (19).

We found significant linear correlations between global PSs. and other traditionally important cardiac indices on CMR

**Fig. 4. Kaplan-Meier event-free survival curves were stratified by 2D global longitudinal peak strain in asymptomatic AS patients with pEF.** For more than -17.9% ($n = 22$, blue line), median event-free survival period was 53.0 months, while for the others ($n = 45$, green line), median event-free survival period was 43.3 months ($p = 0.041$).

and echocardiography in AS. EF showed the best correlation with the strain parameters which themselves reflected the dimensional change in different vectors during LV contraction. EF is a well-established prognostic factor of AS (20). A high LVMI was found to be independently associated with increased cardiovascular mortality in mild to severe AS (21). In AS, LA enlargement could suggest chronically elevated LV filling pressure. The LA diameter was reported to predict the occurrence of symptoms and mortality in severe AS (22). The non-contrast T1 value is known to indicate the degree of myocardial fibrosis as the anatomical change (23). CMR-FT and myocardial fibrosis determined by non-contrast

T1 value were well-correlated (24). Considering those facts together, the strain parameters of CMR-FT may be useful outcome parameters of AS without additional T1 mapping or tagging sequences.

We confirmed that an impaired 2D GLPS was an independent predictor of worse clinical outcome in asymptomatic AS patients with pEF, but the other echocardiographic and CMR parameters, including the maximum velocity and mean pressure gradient of aortic valve, LVMI, and non-contrast T1 value were not. This result indicated that assessing the 2D GLPS using CMR-FT in AS patients may provide a further risk stratification over known predictors of clinical outcome. Several recent studies also demonstrated the significant role of longitudinal strain as a prognostic factor of preoperative or postoperative outcome (24, 25). In a large meta-analysis, global longitudinal strain, assessed by echocardiography, was shown to be more predictive of mortality than was EF in patients with LV dysfunction (26). Taken together, impaired longitudinal strain with equivalent subclinical dysfunction or borderline symptoms should be handled cautiously to avoid adverse delays in intervention (17).

The LV wall is not homogenous and is composed of endocardial, mid-myocardial, and epicardial layers (27). LV function is determined by the sum of contraction and relaxation in these three layers (28). The early stage of myocardial fibrosis in the progression of AS can develop from subendocardial layers. Only longitudinal function could detect the early progression of myocardial fibrosis. It has been reported that circumferential and radial strains cannot detect the early stage of fibrosis progression because they are related to mid wall function (24). Strain imaging has been demonstrated to be the most appropriate method to evaluate LV myocardial contractility properties and myocardial deformation, as strain may enable detection of subtle changes in LV performance in severe AS patients (29).

CMR-tagging has become the reference standard for the evaluation of myocardial strain, and may help to identify patients before the onset of overt myocardial dysfunction (30-32). However, CMR-tagging requires specialized tagging sequences and lengthy breath-holds, and the post-processing procedure is laborious and time-consuming (33). It may suffer from progressive attenuation of the tag signal during the cardiac cycle (34). Meanwhile, CMR-FT is available for previously obtained CMR including basic steady-state free precession cine images, and useful for coherent follow-up for the strain parameters. It is also promising to assess strain

especially in patients with suboptimal echocardiography quality (24). CMR is free from operator-dependency in contrast to the echocardiography (35).

CMR-FT has some technical limitations in clinical use. First, the FT software algorithm tracks pixels frame-by-frame at the tissue-cavity interface and tracks intra-myocardial pixels. However, the myocardium on CMR is homogeneous, and intrinsically lacks features (36). The second limitation is the temporal resolution, which may not be able to resolve short-lived phases of cardiac motion in CMR. The frame rate depends on the patient's heart rate and various acquisition parameters. Since CMR acquisitions obtain data over several heart beats, minor beat-to-beat differences are smoothed out, which in combination with suboptimal temporal resolution, will obscure rapid iso-volumic phases and might lead to an underestimation of displacement and strain values (30, 31, 37).

The major limitation of this study is that it is a single center study with a small number of patients. Second, we didn't compare CMR-FT with CMR tagging, which is still considered as the gold standard for strain analysis for research purposes. However previous studies showed reasonable agreement between CMR-FT and CMR tagging in healthy subjects and different diseases including AS (37-39). On the other hand, there is no standard reference for CMR-FT. Third, several known risk factors such as age, aortic valve area, and LV systolic function were not demonstrated as the prognostic factors in asymptomatic AS patients with pEF of this study. Because our study population was a heterogeneous mixture of asymptomatic moderate to severe AS patients, it is possible that some parameters that reached borderline significance would predict outcome in a subgroup analysis. Nevertheless, the population size of our final subgroup study was quite small, making further stratified analysis difficult. Lastly, our primary endpoint including the development of AS-associated symptoms was relatively subjective, in contrast to other studies using endpoints covering overt manifestations, such as mortality and heart failure (8). Because the aim of our study focused on early finding suggesting myocardial dysfunction and worse prognosis, the endpoint was designed to measure the subtlest change detectable in a clinical setting (17).

In conclusion, 2D global longitudinal and radial PSs are correlated with the degree of AS and can reflect cardiac dysfunction. 2D GLPS may be one of the most potent predictive factors for CCE in asymptomatic AS patients with pEF. If the asymptomatic AS patients with pEF show the

absolute value of 2D GLPS less than 17.9%, they might have worse prognosis compared to the other asymptomatic AS patients with pEF.

Supplementary Materials

The Data Supplement is available with this article at <https://doi.org/10.3348/kjr.2019.0441>.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Eun-Ah Park

<https://orcid.org/0000-0001-6203-1070>

Moon Young Kim

<https://orcid.org/0000-0003-3025-0409>

Whal Lee

<https://orcid.org/0000-0003-1285-5033>

Seung-Pyo Lee

<https://orcid.org/0000-0002-5502-3977>

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