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ORIGINAL RESEARCH

Prediction of Deterioration of Left Ventricular Function Using 3-Dimensional Speckle-Tracking Echocardiography in Patients With Left Bundle-Branch Block

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BACKGROUND: Previous studies have demonstrated that 2-dimensional (2D) global longitudinal strain (GLS) is associated with cardiovascular outcomes in patients with left bundle-branch block. However, the predictive value of 3-dimensional (3D) speckle-tracking echocardiography has not yet been investigated in these patients.

METHODS AND RESULTS: The authors retrospectively identified 290 patients with left bundle-branch block who underwent echocardiography more than twice. Using speckle-tracking echocardiography, 2D-GLS, 3D-GLS, 3D-global circumferential strain, 3D global radial strain, and 3D global area strain were acquired. The association between 2D and 3D strains and the follow-up left ventricular (LV) ejection fraction (LVEF) was analyzed. The study population was divided into 2 sets: a group with preserved LVEF (baseline LVEF ≥40%) and a group with reduced LVEF (baseline LVEF <40%). After a median follow-up of 29.1 months (interquartile range, 13.1–53.0 months), 14.9% of patients progressed to LV dysfunction in the group with preserved LVEF, and 51.0% of patients showed improved LV function in the group with reduced LVEF. Multivariable analysis of 2D and 3D strains revealed that higher 2D-GLS (odds ratio [OR], 0.65 [95% CI, 0.54–0.78], P<0.001) was highly associated with maintaining LVEF in patients with preserved LVEF. However, a lower 3D-global circumferential strain (OR, 0.61 [95% CI, 0.47–0.78], P<0.001) showed a strong association with persistently reduced LVEF in patients with reduced LVEF.

CONCLUSIONS: Although 2D-GLS showed a powerful predictive value for the deterioration of LV function in the preserved LVEF group, 3D strain, especially 3D-global circumferential strain, can be helpful to predict consistent LV dysfunction in patients with left bundle-branch block who have reduced LVEF.

Key Words: 3D echocardiography ■ left bundle-branch block ■ speckle-tracking echocardiography

Recently, 2-dimensional (2D) speckle-tracking echocardiography (STE), an innovative imaging technique used for the evaluation of left ventricular (LV) function, has shown benefits over ejection fraction (EF) evaluation in the diagnosis, prognosis, and management of diverse cardiovascular diseases.[1–8] However, 2D-STE tracks speckles moving only in 2 spatial planes, while speckles move in a 3-dimensional (3D) pattern in reality. Therefore, a limited portion of the real motion can be analyzed using 2D-STE. Three-dimensional echocardiography is a more advanced myocardial imaging technique for evaluating LV function using volumetric measurements and is devoid of foreshortening and geometrical assumptions. This implies that 3D-STE can overcome the "out-of-plane" limitation of 2D-STE and, thus, can be more accurate and reproducible.[9–13] However, there are

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CLINICAL PERSPECTIVE

What Is New?

- In patients with left bundle-branch block who have preserved left ventricular ejection fraction (LVEF), higher 2-dimensional global longitudinal strain was highly associated with maintaining the LVEF.
- Three-dimensional strain, especially lower 3-dimensional global circumferential strain, showed a strong association with persistently reduced LVEF in patients with left bundle-branch block with reduced LVEF.

What Are the Clinical Implications?

- Measurement of 3-dimensional strain can be helpful in the prediction of left ventricular function deterioration for patients with left bundle-branch block who have reduced LVEF.

Nonstandard Abbreviations and Acronyms

2D	2-dimensional
3D	3-dimensional
GCS	global circumferential strain
GLS	global longitudinal strain
pEF	preserved ejection fraction
rEF	reduced ejection fraction
STE	speckle-tracking echocardiography

limited clinical data available on the merits of 3D-STE, and the technique has not been used as a routine tool for cardiac function assessment.

Left bundle-branch block (LBBB) is a disorder caused by the interruption of electrical activity in the His–Purkinje system. It is associated with dyssynchronous LV activation, leading to reduced efficiency of LV contraction, which, in turn, contributes to LV systolic and diastolic dysfunction. The LBBB is an independent predictor of mortality in patients with various cardiovascular diseases. Moreover, the adverse effects of LBBB are more pronounced in patients with heart failure (HF).[14–16] Previous studies have demonstrated that 2D global longitudinal strain (GLS) can provide better risk prediction of cardiovascular ailments than LVEF or other echocardiographic parameters.[5] However, the prognostic implications of 3D-STE have not been studied in patients with LBBB. Therefore, our aim was to study the association between strain values obtained from 2D- and 3D-STE and the deterioration of LV function in a cohort of patients with LBBB.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We retrospectively identified 386 consecutive patients with LBBB who underwent 2D and 3D echocardiography and in whom the obtained image quality was good enough to analyze STE at least twice between June 2009 and January 2021. Among the 386 patients, those who underwent cardiac resynchronization therapy (n=47) had poor image quality for the measurement of 2D and 3D strain (n=44), and those who underwent follow-up echocardiography within 3 months (n=5) were excluded from the study. A total of 290 patients were included in the final analysis and were divided into 2 groups based on baseline 2D LVEF: a group with preserved LVEF (baseline 2D LVEF ≥40%; group with preserved EF [pEF], n=194) and a group with reduced LVEF (baseline 2D LVEF <40%; group with reduced EF [rEF], n=96). Each group was further subdivided into preserved follow-up LVEF (follow-up 2D LVEF ≥40%) and reduced follow-up LVEF (follow-up 2D LVEF <40%) (Figure 1). The causes of of LBBB were divided into "ischemic" or "nonischemic." Ischemic cause of LBBB was defined as any presence of significant (≥70% in the epicardial arteries or ≥50% in the left main/proximal left anterior descending artery) stenosis of coronary arteries detected by invasive coronary angiography, coronary computed tomographic angiography, or a perfusion defect on myocardial perfusion imaging, or a history of percutaneous coronary intervention or coronary artery bypass surgery. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Institute of Seoul National University Bundang Hospital and Seoul National University Hospital. The requirement for informed consent was waived because of the retrospective study design.

Echocardiography

Two-dimensional transthoracic echocardiography was performed using commercially available equipment (Vivid E9, GE Medical Systems). The quantitative analysis of the left ventricle was performed as recommended.[17] LV end-diastolic volume, LV end-systolic volume, and LVEF were calculated according to the biplane Simpson method. The LV mass index was calculated using the Devereux formula. LV diastolic function was assessed via pulsed-wave Doppler transmitral flow. Peak early (E) and late (A) diastolic mitral inflow velocities and deceleration times were

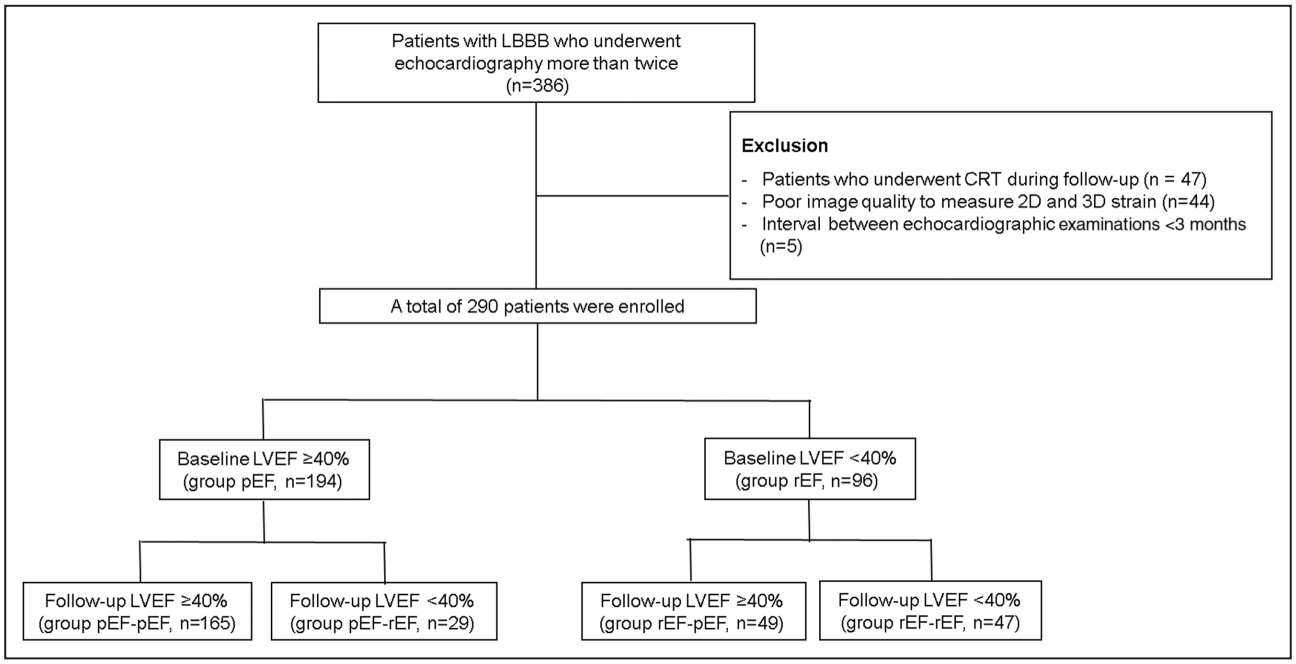

Figure 1. Study flowchart showing patient enrollment.
2D indicates 2-dimensional; 3D, 3-dimensional; CRT, cardiac resynchronization therapy; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; pEF, preserved ejection fraction; and rEF, reduced ejection fraction.

measured. Peak systolic (s'), early (e'), and late diastolic (a') velocities at the septal mitral annulus were also recorded. Left atrial volumes were determined using the biplane area-length method, and the left atrial volume index was calculated as left atrial volume divided by the body surface area. Right ventricular systolic pressure was estimated using the peak velocity of tricuspid regurgitation.

Real-time 3D echocardiography imaging was performed with a 4V-D probe (1.5–4.0 MHz, GE Healthcare). Volumetric data were acquired from the apical 4-chamber view using the full-volume mode through which sequential acquisition of narrow subvolumes was performed for 6 consecutive heartbeats during breath-holding. These subvolumes were subsequently stitched together to form an entire data set. The minimum frame rate was no <40% of the heart rate. Reproducibility in the measurement of 3D echocardiography was evaluated in 20 randomly selected patients using the interclass correlation coefficient. The interclass correlation coefficients for intraobserver and interobserver variability were 0.936 to 0.988 and 0.956 to 0.991, respectively (Table S1).

Strain Analysis

EchoPAC analysis software (version 204, GE Medical Systems) was used for the analysis of the 2D-STE and 3D-STE images. The LV endocardium was traced semiautomatically with manual adjustment in the apical 4-chamber, apical 3-chamber, and apical 2-chamber views for 2D-GLS analysis. Peak strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. The 2D-GLS was calculated as the average of the peak values of the 3 apical views. Three-dimensional strain measurements were performed using a 3D image obtained with a 4V-D probe. The system automatically delineated the endocardium and epicardium of the left ventricle, and refinements were made by manual adjustments. After generating an LV 3D cast, the software automatically calculated the 3D LV end-diastolic volume, ESV, and EF. The left ventricle was further divided into 17 segments, and the software calculated 3D-GLS, 3D global circumferential strain (GCS), 3D global radial strain, and 3D global area strain. To avoid confusion regarding the magnitude relationships, 2D and 3D strain values were expressed as absolute values.

Statistical Analysis

Continuous variables are expressed as mean±SD, and categorical variables are expressed as numbers and percentages. Patient characteristics were compared between groups (pEF-pEF versus pEF-rEF, and rEF-pEF versus rEF-rEF) using Pearson chi-square test for categorical variables and Student *t*-test for continuous variables. Multivariable logistic regression analysis with a forward selection method was performed to determine the independent variables associated with follow-up LVEF <40% in the pEF and rEF groups. To overcome collinearity between strain value, we

compared strain parameters with separate logistic regression. Multivariable analyses with age, sex, hypertension, diabetes, cause, QRS width, and cardiovascular medications (including renin-angiotensin system blocker and β-blocker) were conducted. To determine the prediction accuracy of the 2D and 3D strains, original data were divided into 2 data sets: training data and test data. It is well known that to validate the prediction performance of a statistical model, one should consider an independent test set. Then, the prediction model should be constructed using training data, and the model is validated using test data. Therefore, we randomly selected training data and test data at a ratio of 2:1, and the test data were used to evaluate the prediction performance of the model. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and area under the curve were presented to compare the predictive performance of each strain. To analyze the relationship between 2D and 3D strains and follow-up LVEF, we computed odds and confidence limits for LVEF <40% from the logistic regression. To do that, we first fit the 2D or 3D strain using a continuous restricted cubic spline method, and then we computed odds according to the strain value. All statistical analyses were performed using SPSS version 22.0 (SPSS Institute Inc.), and the restricted cubic spline was graphed using R programming software, version 3.6.1 (The R Foundation for Statistical Computing). Statistical significance was set at $P<0.05$.

RESULTS

Baseline Clinical Characteristics

A total of 290 patients were enrolled in this study, and the baseline characteristics of the study groups are listed in Table 1. The mean age of the study population was 68.5±11.3 years, and 45.2% of the patients were men. Seventy-five (25.9%) patients had LBBB of ischemic cause. After a median of 29.1 months (interquartile range, 13.1–53.0 months), LVEF was changed from 56.2±8.7% to 53.3±12.7% and from 28.7±7.0% to 38.9±13.7% in the pEF and rEF groups, respectively (Table 2 and Table S2). Among the patients with preserved LVEF (group pEF, n=194), 29 (14.9%) patients showed reduced LVEF (EF <40%) on a follow-up echocardiogram. There were no significant differences in terms of demographic parameters, cause of LBBB, or medication used between the subgroups (follow-up LVEF ≥40% [group pEF-pEF] versus follow-up LVEF <40% [group pEF-rEF]); however, the prevalence of diabetes was higher in the pEF-rEF group. In patients with reduced LVEF (n=96), improvement in LVEF was shown in 49 (51.0%) patients after a median follow-up duration of 29.1 months. No significant differences

Table 1. Baseline Characteristics According to Groups

	Baseline LVEF ≥40% (pEF)			Baseline LVEF <40% (rEF)		
	Follow-up LVEF ≥40% (pEF-pEF, n=165)	Follow-up LVEF <40% (pEF-rEF, n=29)	*P* value*	Follow-up LVEF ≥40% (rEF-pEF, n=49)	Follow-up LVEF <40% (rEF-rEF, n=47)	*P* value†
Demographics						
Age, y	68.6±10.8	68.6±11.9	0.998	67.4±13.4	69.6±10.1	0.367
Men, n (%)	71 (43.0)	15 (51.7)	0.385	18 (36.7)	27 (57.4)	0.042
Height	159.6±8.5	160.6±8.1	0.523	159.5±10.3	160.0±8.7	0.817
Weight	62.2±9.4	61.5±11.0	0.713	61.4±11.0	60.7±10.7	0.730
Body surface area, m^2	1.7±0.3	1.7±0.2	0.662	1.6±0.2	1.6±0.2	0.798
Underlying diseases, n (%)						
Hypertension	98 (59.4)	15 (51.7)	0.440	18 (36.7)	23 (48.9)	0.227
Diabetes	36 (21.8)	14 (48.3)	0.003	12 (24.5)	8 (17.0)	0.368
Cause of LBBB, n (%)						
Ischemic	46 (27.9)	10 (34.5)	0.469	7 (14.3)	12 (25.5)	0.167
Nonischemic	119 (72.1)	19 (65.5)		42 (85.7)	35 (74.5)	
Medication, n (%)						
RAS blocker	108 (80.6)	26 (92.9)	0.119	45 (95.7)	39 (92.9)	0.555
β-Blocker	90 (72.6)	20 (74.1)	0.874	40 (88.9)	34 (77.3)	0.143
Diuretics	68 (56.7)	20 (74.1)	0.095	41 (87.2)	32 (72.7)	0.083
QRS duration	134.5±27.5	136.3±27.1	0.752	146.0±22.6	152.3±22.1	0.172

LBBB indicates left ventricular bundle-branch block; LVEF, left ventricular ejection fraction; and RAS, renin-angiotensin system.
*P value between the preserved ejection fraction (pEF)-pEF and pEF-reduced ejection fraction (rEF) groups.
†P value between the rEF-pEF and rEF-rEF groups.

were noted in the prevalence of underlying diseases, cause of LBBB, and cardiovascular medication between groups according to the follow-up LVEF data (group rEF-pEF versus group rEF-rEF).

Two-dimensional and 3D Echocardiographic Characteristics

Comparisons of echocardiographic parameters according to the patient groups are presented in Table 2. The mean LV end-diastolic dimension was higher in the pEF-rEF group than in the pEF-pEF group. No significant differences were noted in other 2D-derived echocardiographic parameters, including LVEF and LV end-diastolic volume, between the pEF-pEF and pEF-rEF groups. However, the 3D-derived LVEF was lower and the LV end-systolic volume was larger in the pEF-rEF group than in the pEF-pEF group.

In the rEF group, there was no significant difference in the 2D-derived LVEF between the subgroups, but the LV cavity size and volume were larger in the rEF-rEF group than in the rEF-pEF group. In addition, significant differences were found in 3D-derived LV size and LVEF between the subgroups. Three-dimensional–derived LV volume was larger and LVEF was lower in the rEF-rEF group than in the rEF-pEF group.

Relationship Between 2D and 3D Strain and Follow-Up Echocardiographic Parameters

Two-dimensional GLS and 3D-derived strain, including GLS, GCS, global radial strain, and global area strain, were significantly impaired in the reduced LVEF group compared with those in the preserved LVEF group at the follow-up examination (Table 2, Figure 2). A nonlinear association between strain and follow-up LVEF <40% was demonstrated in the pEF and rEF groups and the total population (Figures 3 and 4, and Figure S1). The odds of LVEF <40% on follow-up showed a similar tendency with values that were low and static until a certain point, after which a positive linear association emerged. In the pEF group, this trend of a low and static odds until a certain point was most pronounced for 2D-GLS (Figure 3). However, in the rEF group, the 3D strain showed a more pronounced association (Figure 4).

In the pEF group, 2D-GLS, 3D LVEF, and 3D-derived strain were significantly associated with reduced follow-up LVEF (LVEF <40%) (Table 3). In the multivariable analysis, 2D-GLS showed the lowest value of odds ratio (OR) among 2D and 3D strains, indicating that 2D-GLS (OR, 0.65 [95% CI, 0.54–0.78]; $P<0.001$) had a strong association with the deterioration of LV function. However, in the rEF group, 3D-GCS (OR, 0.61 [95% CI, 0.47–0.78]; $P<0.001$) showed a strong association with consistently reduced LVEF, followed by 3D-GLS (OR, 0.69 [95% CI, 0.56–0.85]; $P<0.001$) (Figure 5). Although 3D EF was identified as an independent parameter associated with LV function in the univariate analysis, 2D and 3D EFs were not reported to be associated with LVEF on follow-up in the multivariable analysis. To support these results, we created 7 separate regression models for the logistic analysis considering the multicollinearity of EF and strain values. Each regression model included age, sex, hypertension, diabetes, cause, and cardiovascular medications, including renin-angiotensin system blockers and β-blockers. Comparisons between the 7 models for regression analysis also revealed that 2D-GLS in the pEF group and 3D-GCS in the rEF group showed the best prediction performance for the deterioration of LV function (Table 4).

When patients were classified by baseline and follow-up 3D LVEF data, the results were not significantly different compared with the results of grouping by 2D LVEF, except for 2D-GLS, in patients with preserved 3D LVEF (Table S3).

DISCUSSION

In this study, we demonstrated that impaired 2D and 3D myocardial strain has a significant and independent association with the deterioration of LV function regardless of baseline LVEF in patients with LBBB. In patients with preserved LVEF, 2D-GLS had a strong predictive value for the deterioration of LV function, whereas in patients with reduced LVEF, 3D strain, especially lower 3D-GCS, showed a higher tendency to predict LV dysfunction than 2D strain. These results suggest that although 2D-GLS provides sufficient prognostic information in patients with LBBB who have preserved LVEF, measurement of 3D strain can be helpful to predict prognosis of LV dysfunction in patients with LBBB who have reduced LVEF.

In patients with LBBB, the ventricular septum is activated during isovolumic contraction, whereas the posterior and lateral walls are activated later in systole. This dyssynchronous motion prolongs the isovolumic contraction and relaxation time, ultimately affecting the efficiency of LV contraction.[18] Abnormal pattern of ventricular depolarization can induce systolic and diastolic dysfunction and lead to redistribution of circumferential shortening and myocardial blood flow, resulting in the development of ventricular remodeling.[19–21] Further, Calle et al proposed a classification suggesting a pathophysiological continuum of LBBB-induced LV remodeling via speckle tracking–based strain imaging of LBBB-induced dyssynchrony.[22] According to the previous studies, 24.4% of patients whose baseline LVEF >50% had a significant drop in LVEF at a

Table 2. Baseline Echocardiographic Parameters

	Baseline LVEF ≥40% (pEF)				Baseline LVEF <40% (rEF)			
	Total (N=194)	Follow-up LVEF ≥40% (pEF-pEF, n=165)	Follow-up LVEF <40% (pEF-rEF, n=29)	*P* value*	Total (N=96)	Follow-up LVEF ≥40% (rEF-pEF, n=49)	Follow-up LVEF <40% (rEF-rEF, n=47)	*P* value†
LVEDD, mm	47.5±5.6	47.1±5.3	49.8±6.5	0.017	58.4±7.6	56.5±6.4	60.4±8.4	0.011
LVESD, mm	32.2±6.5	32.0±6.1	33.8±8.5	0.166	48.7±8.1	46.5±6.6	51.0±9.1	0.007
LVEDV, mL	84.9±29.1	82.7±26.5	97.6±38.8	0.055	152.7±50.0	141.7±39.5	164.3±57.1	0.028
LVESV, mL	36.2±18.1	37.2±17.2	43.8±21.9	0.130	110.8±43.5	100.3±33.2	121.9±50.3	0.016
LVEF, %	56.2±8.7	56.2±8.5	56.0±9.5	0.934	28.7±7.0	29.9±6.4	27.5±7.4	0.078
LV mass index, g/m^2	107.2±29.3	105.4±28.3	116.9±33.3	0.052	146.8±38.6	142.2±30.2	151.5±45.7	0.248
LA volume index, mL/m^2	36.2±12.0	35.9±12.0	37.8±12.1	0.452	52.7±21.1	55.1±23.8	50.2±17.8	0.261
Mitral inflow E-wave velocity, m/s	0.6±0.2	0.6±0.2	0.7±0.4	0.185	0.7±0.3	0.7±0.3	0.7±0.3	0.673
Mitral inflow A-wave velocity, m/s	0.9±0.2	0.9±0.2	0.9±0.4	0.467	0.9±0.2	0.9±0.2	0.8±0.2	0.093
Mitral annular e' velocity, cm/s	5.5±1.9	5.4±1.8	5.6±2.2	0.581	4.2±1.6	4.3±1.8	4.2±1.5	0.723
Mitral annular a' velocity, cm/s	8.9±2.1	8.9±2.1	8.6±2.6	0.466	7.6±2.2	7.9±2.3	7.2±2.0	0.141
Mitral annular s' velocity, cm/s	6.3±1.7	6.3±1.7	6.2±1.5	0.734	4.7±1.5	4.8±1.4	4.7±1.5	0.654
Mitral annular E/e' ratio	12.8±5.9	12.6±5.4	13.8±8.2	0.347	17.3±9.0	18.0±10.6	16.4±7.1	0.433
PASP, mm Hg	27.7±9.8	28.0±9.3	26.1±12.3	0.383	32.3±13.2	32.4±11.9	32.2±14.4	0.947
3D LVEDV, mL	105.0±63.4	101.4±65.8	125.4±43.1	0.061	152.0±47.4	137.1±42.5	167.2±47.6	0.002
3D LVESV, mL	53.0±25.7	48.5±19.3	78.3±40.0	<0.001	96.8±8.1	82.7±36.8	111.5±34.0	<0.001
3D LVEF, %	49.4±10.4	51.0±9.3	39.7±11.4	<0.001	36.8±9.4	40.4±9.8	33.3±7.4	<0.001
2D-GLS, %	14.6±3.4	15.2±2.9	10.8±3.7	<0.001	9.9±2.9	10.5±2.9	9.2±2.7	0.016
3D-GLS, %	10.2±3.3	10.6±3.1	7.6±3.2	<0.001	7.1±2.9	8.1±2.7	6.1±2.7	<0.001
3D-GCS, %	10.9±3.9	11.5±3.6	7.8±4.0	<0.001	7.0±3.4	8.3±3.7	5.6±2.4	<0.001
3D-GRS, %	26.4±10.3	27.7±9.8	18.7±9.4	<0.001	16.6±7.9	19.3±7.2	13.7±7.7	<0.001
3D-GAS, %	19.0±6.0	19.9±5.5	13.8±5.8	<0.001	12.7±4.9	14.7±4.7	10.7±4.2	<0.001

The absolute value |x| of strain is used. 2D indicates 2-dimensional; 3D, 3-dimensional; ESD, end-systolic dimension; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; and PASP, pulmonary artery systolic pressure.

**P* value between the preserved ejection fraction (pEF)-pEF and pEF-reduced ejection fraction (rEF) groups.

†*P* value between the rEF-pEF and rEF-rEF groups.

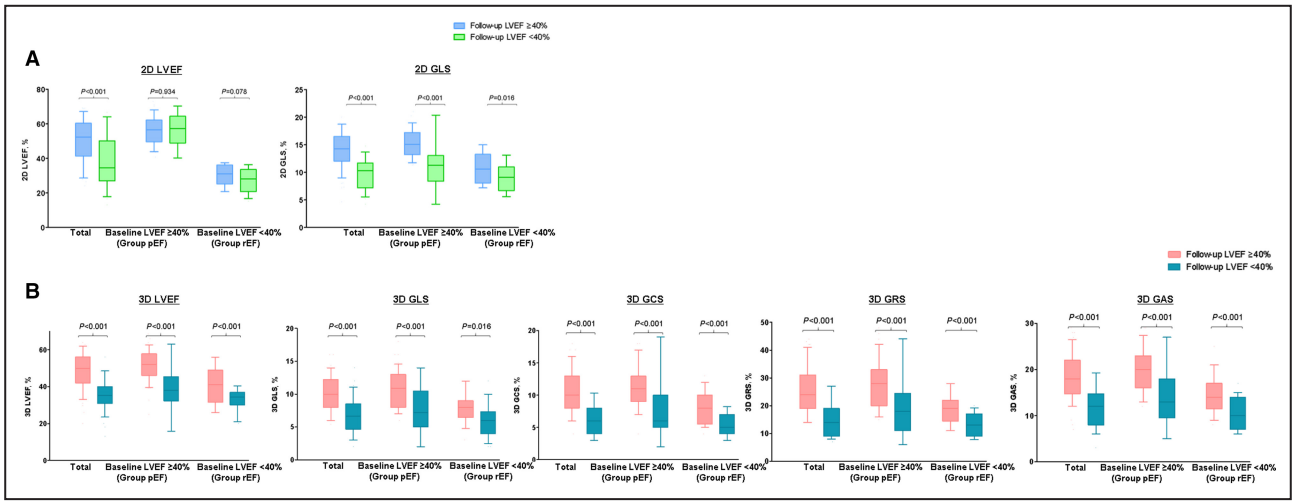

Figure 2. Changes in serial echocardiographic measurements based on groups.
A, 2D LVEF and 2D GCS. **B**, 3D LVEF, 3D GLS, 3D-GCS, 3D GRS, and 3D GAS. 2D indicates 2-dimensional; 3D, 3-dimensional; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; pEF, preserved ejection fraction; and rEF, reduced ejection fraction.

follow-up echocardiogram,[23] and the relative risk for LV systolic dysfunction in LBBB was reported as 3.78.[24] Based on these findings, it can be assumed that dyssynchrony in LBBB can induce LV systolic dysfunction over time. Data derived from several studies suggest that the risk of cardiovascular events, including cardiovascular death, myocardial infarction, and heart failure is significantly elevated in patients with LBBB who are >50 years.[20,25,26] Indeed, according to the existing literature, about 25% of patients with heart failure had LBBB pattern on ECG,[27] which is significantly higher than the estimated 1.5% prevalence of LBBB in the general population. In this study, 96 (33.1%) of 290 patients showed reduced LVEF at baseline, of whom 51.0% demonstrated improved LVEF. Among patients with pEF, 14.9% showed newly developed reduced LVEF after a median follow-up time of 29.1 months. These findings suggest that periodic observation and close monitoring of patients with LBBB are necessary; however, the appropriate period or examination methods have not been expounded. Conventional echocardiography is the most common and convenient imaging modality for diagnosing LV dysfunction, but LVEF determined using 2D conventional

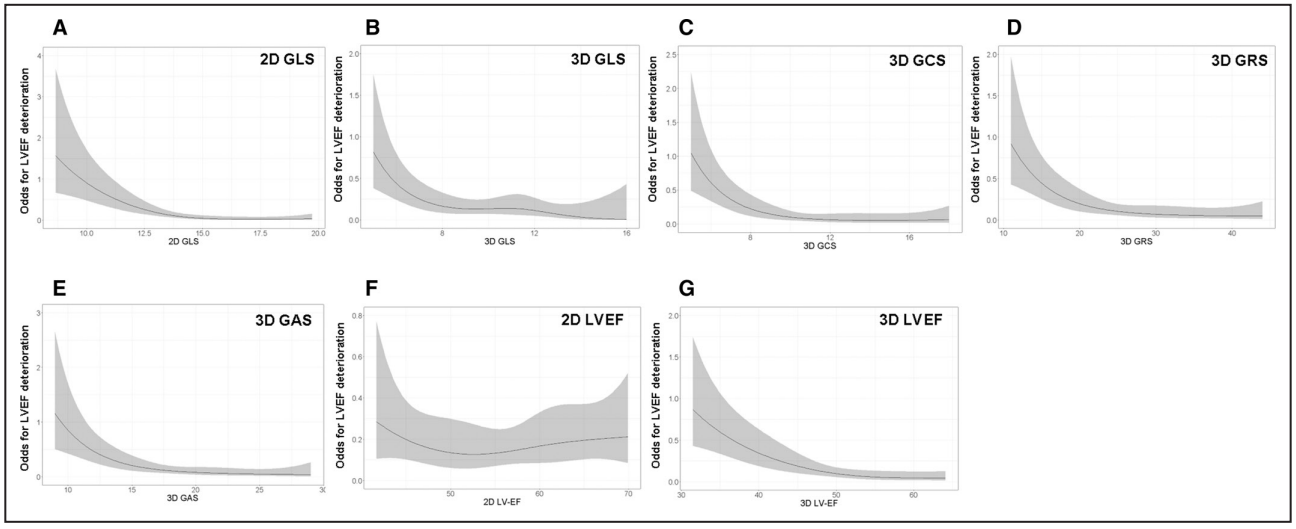

Figure 3. Cubic spline analysis showing changes in the odds ratio for LVEF deterioration in patients with preserved LVEF (group pEF).
A, 2D GLS, **B**, 3D GLS, **C**, 3D GCS, **D**, 3D GRS, **E**, 3D GAS, **F**, 2D LVEF, and **G**, 3D LVEF. 2D indicates 2-dimensional; 3D, 3-dimensional; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; and pEF, preserved ejection fraction.

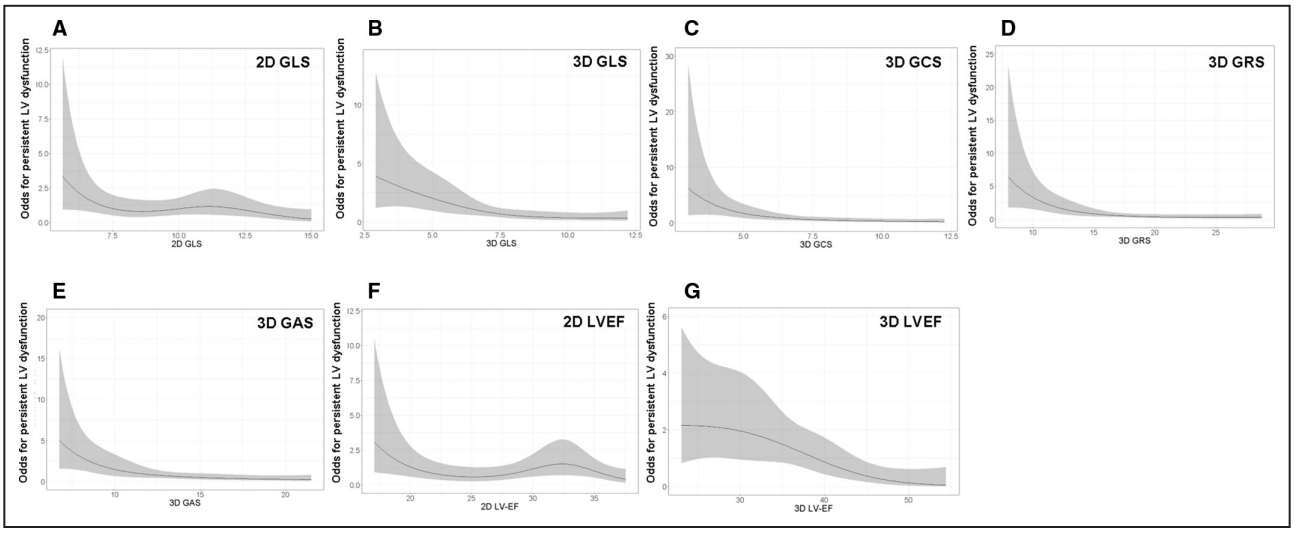

Figure 4. Cubic spline analysis showing changes in the odds ratio for persistent LV dysfunction in patients with reduced LVEF (group rEF).
A, 2D GLS, **B**, 3D GLS, **C**, 3D GCS, **D**, 3D GRS, **E**, 3D GAS, **F**, 2D LVEF, and **G**, 3D LVEF. 2D indicates 2-dimensional; 3D, 3-dimensional; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; and rEF, reduced ejection fraction.

echocardiography is unable to effectively detect subtle and subclinical changes in LV function. Compared with 2D echocardiography, 3D echocardiography showed higher accuracy in quantifying LV size and function, as it is based on volumetric measurement without geometric assumption.[11] Previous studies have proven that 3D LVEF has a better prognostic value than 2D LVEF.[28,29] In fact, in our study, 3D LVEF showed significant differences between the subgroups, whereas 2D LVEF did not. There was no difference in baseline 2D LVEF, but there was a difference in 3D LVEF between the pEF-pEF and pEF-rEF groups. This finding suggests that systolic function is already deteriorated in the pEF-rEF group, and this cannot be detected with

Table 3. Independent Association of 2D and 3D Strain With Follow-Up LVEF<40%

	Univariable		Multivariable	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Baseline LVEF ≥40% (pEF)				
2D LVEF, %	1.00 (0.95–1.05)	0.933	…	…
3D LVEF, %	0.90 (0.86–0.94)	<0.001	0.90 (0.86–0.94)	<0.001
2D-GLS, %	0.63 (0.53–0.75)	<0.001	0.65 (0.54–0.78)	<0.001
3D-GLS, %	0.72 (0.62–0.84)	<0.001	0.75 (0.64–0.88)	<0.001
3D-GCS, %	0.73 (0.63–0.84)	<0.001	0.74 (0.63–0.86)	<0.001
3D-GRS, %	0.89 (0.84–0.94)	<0.001	0.90 (0.85–0.95)	<0.001
3D-GAS, %	0.81 (0.74–0.89)	<0.001	0.83 (0.75–0.91)	<0.001
Baseline LVEF <40% (rEF)				
2D LVEF, %	0.95 (0.89–1.01)	0.08	…	…
3D LVEF, %	0.91 (0.86–0.96)	0.001	…	…
2D-GLS, %	0.84 (0.72–0.97)	0.018	0.74 (0.61–0.89)	0.002
3D-GLS, %	0.75 (0.63–0.89)	0.001	0.69 (0.56–0.85)	<0.001
3D-GCS, %	0.70 (0.58–0.85)	<0.001	0.61 (0.47–0.78)	<0.001
3D-GRS, %	0.89 (0.82–0.95)	0.001	0.80 (0.71–0.89)	<0.001
3D-GAS, %	0.81 (0.72–0.90)	<0.001	0.74 (0.64–0.86)	<0001

Multivariable analysis with age, sex, hypertension, diabetes, cause, QRS width, cardiovascular medications, including renin-angiotensin system blocker and β-blocker.

The absolute value |x| of strain is used in this analysis. 2D indicates 2-dimensional; 3D, 3-dimensional; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; OR, odds ratio; pEF, preserved ejection fraction; and rEF, reduced ejection fraction.

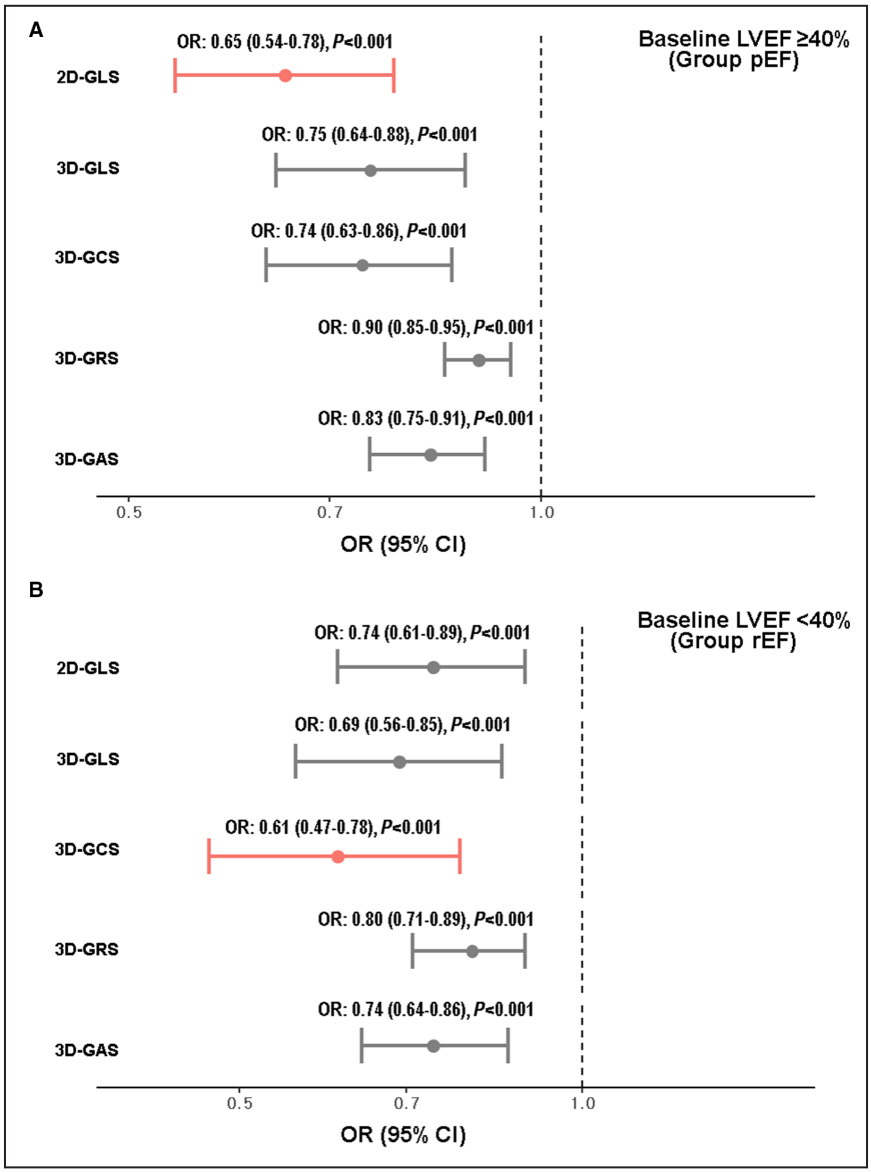

Figure 5. Adjusted OR for follow-up LVEF <40%.
A, Baseline LVEF ≥40% (group pEF) and **B**, baseline LVEF <40% (group rEF). LVEF indicates left ventricular ejection fraction; OR, odds ratio; pEF, preserved ejection fraction; and rEF, reduced ejection fraction.

2D images. In addition, lower 3D LVEF was a predictor of the deterioration of LV function in the univariate analysis, suggesting that 3D LVEF is more sensitive than 2D LVEF in detecting the deterioration of LV function.

However, both 2D-GLS and 3D strains showed a higher tendency to predict follow-up LV dysfunction than 3D LVEF in the present study. A previous study has already demonstrated that among several prognostic parameters, 2D-GLS provided better prognostic power for patients with LBBB than the conventional echocardiographic parameter, LVEF.[5] Our study revealed that all 3D strains, including GLS, GCS, global radial strain, and global area strain, were significantly associated with follow-up LV dysfunction in patients with LBBB. In particular, the 3D strain showed a tendency of a strong association with the prognosis of patients with reduced LVEF. It is measured by tracking speckles in 3 dimensions, overcoming the limitation of 2D strain "out-of-plane" motion. Two-dimensional GLS was estimated from different cardiac cycles of apical 4-chamber, 3-chamber, and 2-chamber views, but the 3D strain is acquired in the same cycle and position.[13] In addition, existing literature shows that 3D strain can overcome LV rotation and twisting effects; thus, it might provide more reliable data.[30,31] Taken together, a possible reason for the higher tendency of

Table 4. Prediction Performance of LVEF and Strain for Follow-Up LVEF <40%

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	AUC
Baseline LVEF ≥40% (pEF)						
Model 1: 2D LVEF+clinical factors	0.982	0.000	0.889	0.000	0.875	0.602
Model 2: 3D LVEF+clinical factors	0.947	0.286	0.915	0.400	0.875	0.787
Model 3: 2D-GLS+clinical factors	0.946	0.571	0.946	0.571	0.905	0.814
Model 4: 3D-GLS+clinical factors	0.929	0.571	0.946	0.500	0.890	0.677
Model 5: 3D-GCS+clinical factors	0.965	0.286	0.917	0.500	0.890	0.782
Model 6: 3D-GRS+clinical factors	0.947	0.286	0.916	0.400	0.875	0.749
Model 7: 3D-GAS+clinical factors	0.947	0.428	0.931	0.500	0.891	0.762
Baseline LVEF <40% (rEF)						
Model 1: 2D LVEF+clinical factors	0.615	0.579	0.500	0.688	0.539	0.595
Model 2: 3D LVEF+clinical factors	0.846	0.579	0.579	0.846	0.688	0.721
Model 3: 2D-GLS+clinical factors	0.769	0.579	0.556	0.786	0.656	0.721
Model 4: 3D-GLS+clinical factors	0.692	0.474	0.474	0.692	0.562	0.656
Model 5: 3D-GCS+clinical factors	1.000	0.632	0.650	1.000	0.781	0.806
Model 6: 3D-GRS+clinical factors	0.847	0.684	0.647	0.867	0.750	0.765
Model 7: 3D-GAS+clinical factors	0.847	0.632	0.611	0.857	0.719	0.765

Clinical factors: age, sex, hypertension, diabetes, cause, QRS width cardiovascular medications, including renin-angiotensin system blocker and β-blocker. 2D indicates 2-dimensional; 3D, 3-dimensional; AUC, area under the curve; EF, ejection fraction; GAS, global area strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LVEF, left ventricular ejection fraction; pEF, preserved ejection fraction; and rEF, reduced ejection fraction.

the predictive value of 3D-STE than that of 2D-STE in reduced LVEF may be related to the ability to display all myocardial segments simultaneously and offer a more comprehensive evaluation of the entire myocardial performance. Our results suggest that the prognosis of patients with LBBB who have preserved LV function is sufficiently predicted using 2D-GLS; however, for patients with LBBB patients who have reduced EF, the possibility of improved LVEF might be higher if the 3D strain value is maintained well.

Among 3D strain values, 3D-GCS tended to show a strong association with follow-up LV dysfunction in patients with reduced LVEF in our study. In previous studies regarding 2D strain, mostly 2D-GLS, rather than GCS and global radial strain, was shown to be a predictor of cardiovascular outcomes in diverse cardiac diseases. It has been inferred that 2D-GLS can detect subtler and minor LV dysfunction because longitudinal myocardial function is impaired earlier than circular function owing to its subendocardial localization.[32,33] In other words, GLS is the best prognostic marker in cardiac diseases in patients with preserved LV function. GCS is based on the contraction of circumferential fibers, which maintain contractility during early LV dysfunction and play an important role in endocardial thickening.[34,35] A previous study has shown that a reduced circumferential strain is an important determinant of LV dilatation. Furthermore, given that the circumferential function plays a key role in maintaining LV structure and tensile strength, preserved GCS might inhibit further deterioration of LV function.[35] Additionally, in patients with ischemic cardiomyopathy, the ischemic effects are more pronounced on the circumferential movement than on the longitudinal movement; thus, decrement in circumferential strain suggests a more advanced stage of ischemia.[36] In nonischemic cardiomyopathy, midwall fibrosis in cardiac magnetic resonance is a known predictor of cardiac morbidity and mortality.[37] Among the strain values, GCS has the maximum association with midwall fibrosis in cardiac magnetic resonance.[38] Considering these facts, it can be stated that GCS may be helpful in predicting the prognosis for patients who have an already progressed LV dysfunction.

This study has some limitations that need to be addressed. First, 3D strain images have low temporal and spatial resolution and require the sequential acquisition of 6 consecutive heartbeats; thus, a better acoustic window without arrhythmia is required. However, they have the advantage of being able to measure LV volume, LVEF, and 3D strain simultaneously. Second, this was a single-center retrospective study and included a relatively small number of patients; thus, the results of the present study should be interpreted with caution. In this study, the cardiac resynchronization therapy implementation rate was low because of to cultural proscriptions and strict insurance coverage criteria in Korea, and the LV reverse

remodeling rate in the rEF group was relatively higher compared with that in other studies, probably attributable to a high proportion of nonischemic patients with LBBB. Therefore, considering different characteristics of ischemic and nonischemic LBBB, we performed a multivariable regression analysis adjusted with variables, including LBBB cause. Third, the timing of follow-up echocardiography was different for each patient. However, we excluded patients whose duration of follow-up echocardiography was <3 months and who had a median follow-up duration longer than 1 year, which was a sufficient time for improvement of LVEF in patients with heart failure with reduced EF with medication.[39] Fourth, we focused on changes in LVEF and did not investigate hard end points. Given that a decrease in LVEF is directly proportional to the risk of hospitalization or cardiac death,[40] LVEF could be an outcome of this study.

CONCLUSION

In patients with LBBB who had preserved LVEF, 2D-GLS showed a strong association with the deterioration of LV function. However, in patients with LBBB who had reduced LVEF, 3D strain, especially lower 3D-GCS, showed a higher tendency to predict persistent LV dysfunction. Thus, it can be concluded that 3D-GCS can be helpful for prediction of LV function deterioration in patients with LBBB who have reduced LVEF.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1-S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Inter-observer and intra-observer variability of 3D echocardiography

	Inter-observer	95% CI	Intra-observer	95% CI
3D EF	0.936	0.859–0.971	0.956	0.869–0.985
3D GLS	0.988	0.975–0.995	0.982	0.948–0.994
3D GCS	0.981	0.959–0.991	0.990	0.970–0.997
3D GAS	0.986	0.970–0.994	0.991	0.973–0997
3D GRS	0.948	0.887–0.976	0.982	0.947–0.994

Abbreviations: 3D, three-dimensional; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; GAS, global area strain.

Table S2. Follow-up echocardiographic parameters

	Baseline LV-EF≥40% (pEF)			P value*	Baseline LV-EF<40% (rEF)			P value †
	Total (N=194)	Follow-up LV-EF≥40% (pEF-pEF, N=165)	Follow-up LV-EF<40% (pEF-rEF, N=29)		Total (N=96)	Follow-up LV-EF≥40% (rEF-pEF, N=49)	Follow-up LV-EF<40% (rEF-rEF, N=47)	
LV-EDV (mL)	90.1±34.2	82.3±24.1	134.5±47.6	<0.001	129.4±46.8	103.8±33.7	156.1±47.8	<0.001
LV-ESV (mL)	44.7±29.3	35.7±14.3	96.2±38.7	<0.001	83.2±46.2	51.7±19.1	116.1±43.2	<0.001
LV-EF (%)	53.3±12.7	57.6±7.7	29.1±7.3	<0.001	38.9±13.7	50.7±5.4	26.7±7.5	<0.001

*P value between pEF-pEF and pEF-rEF group. †P value between rEF-pEF and rEF-rEF group.

Abbreviations: LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

Table S3. Independent association of 2D and 3D strain with follow-up 3D LV-EF<40%

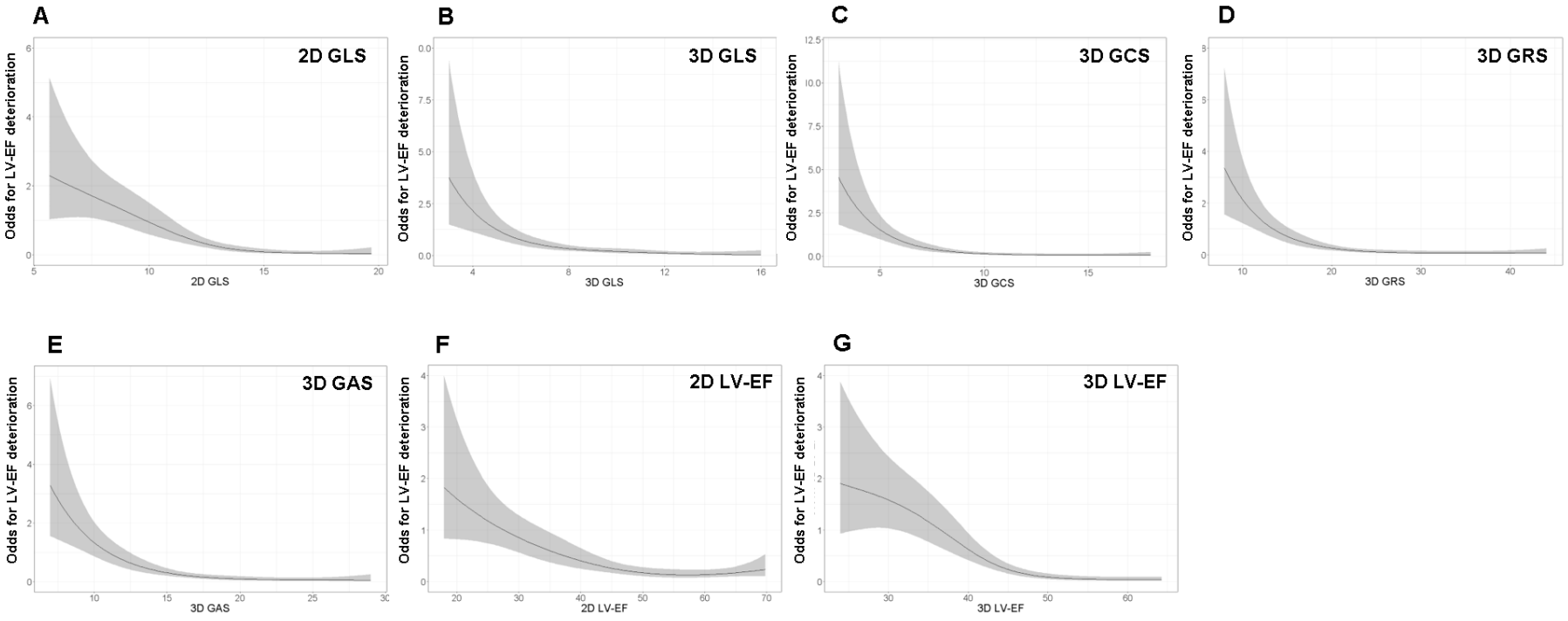
	Univariable		Multivariable	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Baseline 3D EF≥40% (p3DEF)				
2D LV-EF (%)	0.98 (0.94-1.02)	0.338	-	-
3D LV-EF (%)	0.88 (0.81-0.95)	0.003	0.90 (0.81-1.00)	0.039
2D-GLS (%)	0.84 (0.72-1.00)	0.044	-	-
3D-GLS (%)	0.78(0.64-0.95)	0.015	0.74 (0.57-0.97)	0.032
3D-GCS (%)	0.78 (0.65-0.95)	0.011	0.68 (0.50-0.92)	0.011
3D-GRS (%)	0.91 (0.84-0.98)	0.012	0.85 (0.74-0.97)	0.015
3D-GAS (%)	0.83 (0.73-0.95)	0.006	0.78 (0.64-0.95)	0.013
Baseline 3D EF<40% (r3DEF)				
2D LV-EF (%)	0.98 (0.95-1.01)	0.176	-	-
3D LV-EF (%)	0.98 (0.91-1.06)	0.561	-	-
2D-GLS (%)	0.82 (0.70-0.96)	0.015	0.81 (0.68-0.95)	0.009
3D-GLS (%)	0.85 (0.73-1.00)	0.045	0.83 (0.71-0.98)	0.025
3D-GCS (%)	0.79 (0.66-0.95)	0.010	0.73 (0.60-0.89)	0.002
3D-GRS (%)	0.90 (0.84-0.97)	0.008	0.89 (0.82-0.96)	0.002
3D-GAS (%)	0.85 (0.76-0.95)	0.005	0.84 (0.74-0.94)	0.002

Multivariable analysis with age, sex, hypertension, diabetes, etiology, QRS width, cardiovascular medications including renin-angiotensin system blocker, beta blocker.

The absolute value |x| of strain is used in this analysis.

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; LV, left ventricular; EF, ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; GAS, global area strain.

Figure S1. Cubic spline analysis showing changes in the odds ratio for LV-EF deterioration in the total study population



(A) 2D GLS, (B) 3D GLS, (C) 3D GCS, (D) 3D GRS, (E) 3D GAS. (F) 2D LV-EF, and (G) 3D LV-EF