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ORIGINAL ARTICLE

Left Atrial Reservoir Strain-Based Left Ventricular Diastolic Function Grading and Incident Heart Failure in Hypertrophic Cardiomyopathy

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BACKGROUND: The echocardiographic assessment of left ventricular (LV) diastolic dysfunction (LVDD) in patients with hypertrophic cardiomyopathy is complex and not well-established. We investigated whether the left atrial reservoir strain (LARS) could be used to categorize LVDD and whether this grading is predictive of heart failure (HF) events in hypertrophic cardiomyopathy.

METHODS: A total of 414 patients with hypertrophic cardiomyopathy (aged 58.3±12.8 years; 65.7% male) were categorized using LARS-defined LVDD (LARS-DD) grades: ≥35% (grade 0), ≥24% to <35%, ≥19% to <24%, and <19% (grade 3). Patients were followed for a median of 6.9 years to assess hospitalization for HF or HF-related death.

RESULTS: An increase in LARS-DD grade was associated with worse conventional echocardiographic parameters of LVDD, such as lower e′, higher E/e′ ratio, greater maximum tricuspid regurgitation velocity, and restrictive mitral inflow pattern. Higher LARS-DD grade was also associated with parameters reflecting increased LV filling pressure, such as greater LV wall thickness, greater extent of fibrosis, obstructive physiology, and decreased LV longitudinal strain. Furthermore, higher LARS-DD grade was associated with worse HF-free survival (log-rank P<0.001). Patients with LARS-DD grades 0, 1, 2, and 3 showed 10-year HF-free survival of 100%, 91.6%, 84.1%, and 67.5%, respectively. LARS-DD grade was an independent predictor of HF events after adjusting for clinical and echocardiographic variables (hazard ratio, 1.53 [95% CI, 1.03–2.28], per 1-grade increase). The LARS-DD grade also had incremental prognostic value for incident HF events over the traditional echocardiographic LVDD parameters and grading system. The prognostic value of advanced LARS-DD grade was consistent in sensitivity analyses and various patient subgroups.

CONCLUSIONS: LARS can be used as a simple single or supplemental index to categorize LV diastolic function and predict HF events in hypertrophic cardiomyopathy.

Key Words: diastole ■ echocardiography ■ fibrosis ■ heart failure ■ hypertrophic cardiomyopathy ■ prognosis

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In patients with hypertrophic cardiomyopathy (HCM), left ventricular (LV) hypertrophy with associated fibrosis leads to LV diastolic dysfunction (LVDD) and development of heart failure (HF).[1] While LVDD is an important pathophysiological mechanism underlying HF in patients with HCM, the noninvasive estimation of LVDD is not well-established.[2] The guidelines recommend multiple echocardiography-based parameters be used for the assessment of LVDD, which can be cumbersome to acquire and are often discrepant causing difficulty in interpretation.

LVDD is related to left atrial (LA) remodeling with LA dilatation and dysfunction.[3] LA enlargement reflects LVDD

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CLINICAL PERSPECTIVE

The noninvasive echocardiographic assessment of left ventricular (LV) diastolic function in patients with hypertrophic cardiomyopathy (HCM) is challenging and not well-established. The current guidelines recommend that multiple echocardiography-based parameters be taken into account for optimal assessment of LV diastolic function in HCM; however, acquiring all parameters is not always possible, and parameters are often discrepant causing inconclusive grading. Recently, the single measurement of left atrial reservoir strain (LARS) was suggested as a simple index for grading LV diastolic function (LARS-DD grade) and predicting heart failure in the general population. We demonstrated in patients with HCM that higher LARS-DD grades were associated with worse traditional echocardiographic diastolic parameters, as well as greater LV hypertrophy and fibrosis. The LARS-DD grade provided good discrimination of heart failure-free survival and was an independent predictor of heart failure events. It also showed incremental prognostic value over traditional echocardiographic LV diastolic function parameters. Thus, the LARS-DD grade can used as a simple index to categorize LV diastolic function and predict heart failure events in HCM. LARS measurement should be incorporated into the assessment of LV diastolic function and prognosis in HCM.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ASE	American Society of Echocardiography
AUC	area under the curve
HCM	hypertrophic cardiomyopathy
HF	heart failure
HR	hazard ratio
LA	left atrial
LARS	left atrial reservoir strain
LARS-DD grade	LARS-defined left ventricular diastolic dysfunction grade
LAVI	left ventricular volume index
LV	left ventricular
LVDD	left ventricular diastolic dysfunction
LVEF	left ventricular ejection fraction
LV-GLS	left ventricular global longitudinal strain
MR	mitral regurgitation
SCD	sudden cardiac death
TR	tricuspid regurgitation

and chronic elevation of LA pressure in the absence of other causes such as mitral valve disease.[3] LA strain is a more sensitive measure of LV filling pressure than LA volume,[4,5] and thus is useful for the early detection of preclinical LVDD.[5] Recently, LA strain measurement using speckle tracking echocardiography was reported to change progressively with the severity of LVDD, and the grade of LVDD based on the American Society of Echocardiography (ASE) guidelines as reference could be categorized accurately using distinct cutoffs of LA reservoir strain (LARS).[6] LVDD grading defined with LARS cutoffs (LARS-DD grade) was reported to be a strong predictor of HF development in the general population.[7] In patients with HCM, myocardial hypertrophy is predominantly observed in the ventricles and does not directly involve the atrial wall.[8] However, the left atrium dilates and its function decreases as a chronic secondary change caused by LVDD in HCM, and thus it is conceivable that LVDD can be assessed with LA strain analysis.

With this background, we investigated whether the LARS is a promising simple index for grading LV diastolic function and whether the LARS-DD grade can predict HF-related outcomes in patients with HCM.

METHODS

Study Population

This study was a retrospective analysis of data from a cohort of patients with HCM who underwent initial evaluation between January 2007 and June 2019 at Seoul National University Hospital. HCM was diagnosed by echocardiography defined by increased end-diastolic LV wall thickness ≥15 mm (or ≥13 mm in patients with a family history of HCM),[1] with the magnitude and distribution of LV hypertrophy unexplained by abnormal loading conditions such as hypertension or aortic stenosis. Apical HCM was defined as pathological LV hypertrophy involving only apical segments. Details of exclusion criteria and data collection are available in Methods in the Supplemental Material. The 5-year sudden cardiac death (SCD) risk score was calculated.[9] The study was approved by the institutional review board, and written informed consent was waived due its retrospective nature. Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Cardiac Imaging and LARS-DD Grading

Echocardiography and cardiac magnetic resonance were performed (Methods in the Supplemental Material). LV and LA strain were measured using the speckle-tracking technique with vendor-independent postprocessing software (Imaging Arena 4.6, TomTec Imaging Systems) by 2 independent investigators blinded to the clinical information.[10] In short, the LA endocardial borders were traced manually on the end-systolic frame from the nonforeshortened apical 4-chamber view, and tracked throughout the cardiac cycle, generating a composite LA longitudinal strain curve. LARS was measured at end-systole just before mitral valve opening (Figure S1).[11] In patients in sinus rhythm, LA contraction strain was measured at the onset of atrial contraction, and LA conduit strain was calculated as the difference between LARS and LA contraction strain. For patients in atrial fibrillation (AF), strain measurements were averaged over three cardiac cycles. LARS was used to categorize LV diastolic function (LARS-DD grade) based on previously validated cutoff values[6,7]: ≥35% (grade 0), 24≤35% (grade 1), 19%≤24% (grade 2), and <19% (grade 3).

The LVDD categorization for HCM patients in 2016 ASE guideline (ASE-LVDD grade) was used for comparison (Figure S2).[2]

Clinical Outcomes

The primary end point was HF events, defined as a composite of hospitalization for HF and HF-related death. The secondary end point was a composite of hospitalization for HF and all-cause death. HF was diagnosed clinically based on aggravation of dyspnea with signs of congestion and administration of diuretics and exclusion of noncardiac causes.[12] Outcomes were assessed by review of medical records until January 2021, and the deaths and their causes were further confirmed by data from the National Death Registration Records.

Statistical Analysis

Characteristics were compared between the groups using one-way ANOVA, Kruskal-Wallis test, or the χ^2 test, as appropriate (Details in the Supplemental Material). The prognostic value of diastolic function parameters and grading systems to predict HF events at 10 years was assessed by area under the curve (AUC) calculated using time-dependent receiver operating characteristic curve analysis. Kaplan-Meier survival curves with log-rank tests were used to compare event-free survival according to the LVDD grade. Cox proportional-hazards regression analyses were used to assess the associational effects on the end points, and effect sizes were expressed as hazard ratios (HRs) with 95% CIs. Variables with $P<0.010$ in the univariable analysis or with clinical significance were included in the multivariable analysis, and the final multivariable model was constructed with the stepwise backward selection method. For the main analysis, LARS-DD was used to represent LVDD, and other traditional echocardiographic parameters of LV diastolic function were not included. Exploratory analysis including traditional echocardiographic parameters of LV diastolic function and the LARS-DD grade was also performed. The LA diameter was used to adjust for LA size in the main multivariable analysis as LA volume index (LAVI) was not available for all patients. The potential incremental value of adding LARS-DD grade to other important variables for predicting HF events was explored using the global χ^2 score with the likelihood ratio test, and the net reclassification index. Sensitivity analyses were performed adjusting for LAVI instead of LA diameter and excluding patients with baseline AF. Tests for interaction were conducted to evaluate statistically significant subgroup differences.

RESULTS

Study Population

Data from a total of 414 patients with HCM (mean age 58.3±12.8 years; male 65.7%; apical HCM 105 [25.4%]) were analyzed. The mean LARS was 23.3%±10.1%. Most patients (98.1%) had preserved LV ejection fraction (LVEF) defined as >50%. LAVI was not measured routinely in the early years, and the un-foreshortened apical 2-chamber view of the LA was not available in 56 patients; thus, the LAVI was measured in 358 (86.5%). At baseline, 60 patients (14.5%) had AF, of whom 37 were in AF during the index echocardiography. Cardiac magnetic resonance was performed in 326 patients (78.7%) at a median interval of 6.6 (interquartile range, 0.6–29) months from the index echocardiography.

Agreement of LA Strain Measurements

Bland–Altman plots for LA strain measurements are presented in Figure S3. The intraclass correlation coefficients of intraobserver variability and interobserver variability were excellent for LARS, being 0.95 (95% CI, 0.90–0.98) and 0.90 (95% CI, 0.81–0.95), respectively.

Clinical and Echocardiographic Characteristics According to LARS-DD Grade

According to the LARS-DD categorization, there were 49 (11.8%) patients with grade 0, 135 (32.6%) with grade 1, 78 (18.8%) with grade 2, and 152 (36.7%) with grade 3 LARS-DD. Clinical variables associated with higher LARS-DD grade included older age, higher 5-year SCD risk score, and greater prevalence of nonsustained ventricular tachycardia, hypertension, and AF (Table 1).

There was no difference in blood pressure or heart rate among the LARS-DD groups at the time of index echocardiography (Table 2). Patients with higher LARS-DD grades had greater LA diameter and LAVI. Higher LARS-DD grade was associated with more advanced parameters of LVDD, such as lower e′, higher E/e′ ratio, greater maximum tricuspid regurgitation (TR) velocity, and more restrictive mitral inflow pattern. Higher LARS-DD grade was also associated with a greater maximum LV wall thickness, obstructive physiology, and decreased LV global longitudinal strain (LV-GLS), although there was no difference in LVEF between the groups. Only 6 patients (1.4%) had moderate mitral regurgitation (MR), while none had severe MR; all patients with significant MR (moderate or severe) were in the LARS-DD grade 3 group. In patients who underwent cardiac magnetic resonance, higher LARS-DD grade was associated with a greater extent of late gadolinium enhancement.

Outcomes

The study population was followed for a median of 6.9 (interquartile range, 3.7–10.0) years. The primary end point occurred in 51 (12.3%) patients, including 43 hospitalizations for HF and 11 HF-related deaths. The secondary end point occurred in 73 patients (17.6%),

Table 1. Clinical Characteristics According to LARS-DD Grade

	Grade 0 (n=49)	Grade 1 (n=135)	Grade 2 (n=78)	Grade 3 (n=152)	*P* value*
Age, y	51.9±13.2	56.4±12.5	56.9±12.5	62.6±11.8	<0.001
Male	38 (77.6)	90 (66.7)	51 (65.4)	93 (61.2)	0.213
NYHA class ≥3	1 (2.0)	6 (4.4)	3 (3.8)	16 (10.5)	0.052
5-year SCD risk score (%)	2.3±1.5	2.8±2.3	3.4±2.6	3.5±3.3	0.010
Family history of SCD	3 (6.1)	21 (15.6)	6 (7.8)	18 (11.9)	0.205
Nonsustained VT	4 (8.3)	29 (21.5)	27 (34.6)	47 (31.1)	0.003
Syncope	11 (22.4)	28 (20.7)	16 (20.8)	33 (21.9)	0.991
Hypertension	15 (30.6)	51 (37.8)	37 (47.4)	76 (50.0)	0.042
Diabetes	15 (26.5)	25 (18.5)	11 (14.1)	34 (22.4)	0.294
Ischemic heart disease	7 (14.3)	26 (19.3)	14 (17.9)	28 (18.4)	0.893
Atrial fibrillation	0 (0.0)	4 (3.0)	5 (6.4)	51 (33.6)	<0.001
Chronic kidney disease	3 (6.1)	5 (3.7)	3 (3.8)	4 (2.6)	0.725
Use of β-blockers	18 (36.7)	62 (45.9)	30 (38.5)	77 (50.7)	0.195

LARS-DD indicates left atrial reservoir strain-defined left ventricular diastolic dysfunction; NYHA, New York Heart Association; SCD, sudden cardiac death; and VT, ventricular tachycardia.

*Calculated using the 1-way ANOVA for normally distributed continuous variables and the χ^2 test for categorical variables.

including 39 all-cause deaths. Hospitalization for HF was related to arrhythmia in 16 cases, of which 7 were acute newly diagnosed AF; 13 cases showed reduced LVEF (EF ≤50%), of which 11 had newly progressed; 5 cases showed significant dynamic LVOT obstruction.

Echocardiographic Diastolic Parameters for Predicting HF Events

The time-dependent receiver operating characteristic curves for HF events and AUC at 10-years were estimated for diastolic function parameters and diastolic function grading systems to assess their accuracy for identifying patients with incident HF events (Table 3, Figure S4). Among the dichotomized diastolic parameters, LARS <24% showed the highest AUC (AUC=0.676), which was significantly higher than that of maximum TR velocity ≥2.8 m/s, E/A ≥2, and septal e′ ≥7 cm/s. The AUC for LARS-DD grade was comparable to that of the ASE-LVDD grade (AUC, 0.734 versus 0.708, respectively).

HF-Free Survival According to LARS-DD Grade

Higher LARS-DD grade was significantly associated with worse HF-free survival (log-rank *P*<0.001; Figure 1A). Notably, in patients with LARS-DD grade 0, no HF events were observed at 10 years. Each 1-grade increase in LARS-DD grade was associated with progressively higher HF events, and patients with LARS-DD grade 1, 2, and 3 showed a 10-year HF-free survival of 91.6% (95% CI, 85.4–98.2), 84.1% (95% CI, 74.2–95.3), and 67.5% (95% CI, 57.9–78.7), respectively. Similarly, higher LARS-DD grade was associated with worse event-free survival for the secondary end point (log-rank *P*<0.001; Figure 1B).

Independent Prognostic Value of LARS-DD Grade for HF Events

Variables associated with the primary end point on univariable analysis included age, SCD risk score, hypertension, baseline AF, diastolic function parameters (ie, E/e′ ratio, maximum TR velocity, LAVI, LA diameter, and E/A ≥2), systolic function parameters (ie, LVEF and LV-GLS), significant MR, nonapical HCM, extent of late gadolinium enhancement, and LA strain parameters including LARS and a higher LARS-DD grade (Table S1). After multivariable analysis adjusting for significant clinical and echocardiographic variables, LARS as a continuous variable was independently associated with the primary end point (Table S2).

Higher LARS-DD grade was also independently associated with HF events after adjustment for significant clinical variables including age, SCD risk score, hypertension, and AF (HR, 1.79 [95% CI, 1.22–2.63] per 1-grade increase; Model 1), as well as echocardiographic variables including maximum LV wall thickness, maximum LV outflow tract gradient, LVEF, LV-GLS, LA diameter, significant MR, and apical HCM (HR, 1.67 [95% CI, 1.13–2.49]; model 2). LARS-DD grade remained significantly associated with incident HF events (HR, 1.55 [95% CI, 1.04–2.30]) in the final multivariable model constructed using a stepwise selection method, with other variables including female sex, AF, LVEF, LA diameter, significant MR, and apical HCM (model 3) and was also significant after further adjustment for the SCD risk score (HR, 1.53 [95% CI, 1.03–2.28]; model 4; Table 4).

Further adjustment for traditional diastolic function parameters was performed in patients without missing E/e′ or TR velocity measurements (n=262, total 37 events; Table S3), and higher LARS-DD grade remained

Table 2. Imaging Characteristics According to LARS-DD Grade

	Grade 0 (n=49)	Grade 1 (n=135)	Grade 2 (n=78)	Grade 3 (n=152)	*P* value*
Systolic blood pressure, mmHg	125±12	128±14	127±18	126±15	0.409
Diastolic blood pressure, mmHg	75±9	77±10	75±11	75±10	0.496
Heart rate, BPM	70±16	70±13	69±10	68±15	0.634
LV end-diastolic dimension, mm	45.2±4.6	46.8±5.0	47.1±5.5	47.0±5.6	0.187
LV end-systolic dimension, mm	27.0±4.0	28.3±4.1	28.0±4.8	28.3±4.6	0.291
LV ejection fraction, %	64.7±5.3	63.5±6.0	65.0±6.2	63.5±7.4	0.272
LV ejection fraction ≤50%	0 (0)	2 (1.5)	1 (1.3)	5 (3.3)	0.430
LA diameter, mm	40.2±5.0	43.4±5.5	45.3±5.5	49.2±7.6	<0.001
LA volume index, mL/m^2 (n=358)	32.6±9.1	38.0±12.0	43.8±12.9	56.9±22.2	<0.001
E, m/s	0.61±0.17	0.59±0.21	0.61±0.19	0.64±0.22	0.208
E/A†	1.07±0.51	0.98±0.57	1.10±0.51	1.12±0.67	0.236
E/A ≥2†	4 (8.2%)	4 (3.0%)	2 (2.6%)	14 (12.0%)	0.013
Septal e′, cm/s (n=409)	5.7±1.7	5.0±1.4	4.6±1.4	4.4±1.8	<0.001
Septal E/e′ (n=409)	11.5±4.5	12.9±6.6	14.9±6.3	16.3±7.6	<0.001
Maximum TR velocity, m/s (n=267)	2.1±0.2	2.2±0.3	2.4±0.3	2.4±0.4	<0.001
Maximum LV wall thickness, mm	17.4±3.2	18.6±4.2	19.8±4.4	19.4±3.5	0.002
Maximum LVOT gradient, mm Hg	5.3 [4.2 to 7.0]	5.0 [4.0 to 7.9]	5.7 [3.8 to 9.0]	5.6 [3.6 to 13.0]	0.916
Obstructive type, ≥30 mm Hg	3 (6.1)	7 (5.2)	9 (11.5)	22 (14.5)	0.047
MR severity ≥moderate	0 (0)	0 (0)	0 (0)	6 (3.9)	0.015
Apical HCM	17 (34.7)	39 (28.9)	18 (23.1)	31 (20.4)	0.149
LV global longitudinal strain (n=413)	−18.0±4.5	−16.9±4.5	−16.0±4.4	−14.5±4.3	<0.001
LARS, %	42.2±8.1	28.3±2.8	21.5±1.4	13.6±3.8	<0.001
LA conduit strain, %†	25.0±8.4	16.1±5.0	12.7±4.4	7.7±3.5	<0.001
LA contraction strain, %†	17.1±6.0	12.2±4.8	8.8±4.2	6.9±3.3	<0.001
LGE, %‡	3.1 [1.5 to 5.9]	3.3 [1.0 to 7.2]	2.8 [1.1 to 9.1]	5.2 [1.4 to 14.1]	0.033
Extensive LGE (≥15%)‡	3 (7.7)	8 (7.4)	9 (14.1)	22 (21.4)	0.018

BPM indicates beats per minute; HCM, hypertrophic cardiomyopathy; LA, left atrial; LARS, LA reservoir strain; LARS-DD, LARS-defined left ventricular diastolic dysfunction; LGE, late gadolinium enhancement; LV, left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; and TR, tricuspid regurgitation.

*Calculated using the 1-way ANOVA and Kruskal-Wallis test for normally and non-normally distributed continuous variables, respectively, and the χ^2 test for categorical variables.

†In patients in sinus rhythm during echocardiography (n=377).

‡In patients with cardiac magnetic resonance (n=326).

associated with the primary end point independent of E/e′ and TR velocity.

Univariable and multivariable analyses for the secondary end point are shown in the Tables S4–S5. Higher LARS-DD grade remained independently associated with the secondary end point in the final multivariable model (HR, 1.63 [95% CI, 1.18–2.25]; model 3 in Table S5).

Incremental Prognostic Value of LARS-DD Grade for HF Events

The model including the SCD risk score, AF, LVEF, significant MR, and HCM type showed significant increase in the predictive value for HF events with the addition of LA dimension and the LARS-DD grade (global χ^2 77.9 versus 89.5 versus 91.5, respectively, all *P*<0.050; Figure 2A). The LARS-DD grade also showed incremental prognostic value over the models including traditional diastolic function parameters and the ASE-LVDD grade (Figure 2B). The addition of LARS-DD grade to other important variables also significantly improved risk classification for 10-year HF events assessed by the net reclassification index (Table S6).

Sensitivity Analyses

Sensitivity analyses were performed for the primary end point: (1) adjusting for LAVI instead of LA diameter in patients with LAVI measurements (n=358, total 43 events; Table S7); and (2) in patients without baseline AF (n=354, total 29 events; Table S8). In all sensitivity analyses, higher LARS-DD grade consistently remained associated with the outcome.

Subgroup Analysis

LARS-DD grade ≥2 (LARS <24%) was significantly associated with HF events (HR, 4.88 [95% CI,

Table 3. Comparison of Individual Diastolic Function Parameters and Diastolic Function Grading Systems for the Prediction of Incident Heart Failure Events

	Cutoff	AUC at 10 y (95% CI)*	*P* value for comparison of AUC*
Dichotomized diastolic function parameters			
LARS (%; n=414)	24	0.676 (0.599–0.752)	(ref)
Septal E/e′ ratio (n=409)	15	0.630 (0.541–0.719)	0.420
Left atrial volume index (mL/m²; n=358)	34	0.588 (0.509–0.668)	0.094
Left atrial diameter (mm; n=414)	40	0.586 (0.528–0.645)	0.052
Maximum TR velocity (m/s; n=267)	2.8	0.589 (0.517–0.662)	0.010
E/A (n=377)	2	0.553 (0.495–0.611)	0.028
Septal e′ (cm/s; n=409)	7	0.506 (0.452–0.560)	<0.001
Diastolic function grading systems			
LARS-DD grade (n=414)		0.734 (0.654–0.815)	(ref)
ASE-LVDD grade (n=298)		0.708 (0.593–0.822)	0.366

ASE-LVDD indicates LVDD grading in the American Society of Echocardiography guideline; AUC, area under the curve; LARS, left atrial reservoir strain; LARS-DD, LARS-defined LVDD; LVDD, left ventricular diastolic dysfunction; and TR, tricuspid regurgitation.
*Calculated using timeROC R package.

2.29–10.4]) compared with grades 0 or 1. There was no significant interaction in the association of advanced LARS-DD grade with incident HF events in subgroups stratified by age, sex, presence of AF, LA size, E/e′ ratio, LV-GLS, maximum LV wall thickness, and 5-year SCD risk (all *P* values for interaction >0.05; Figure 3).

DISCUSSION

We demonstrated in patients with HCM that a novel and simple classification system based on LARS can be used to categorize LV diastolic function and predict HF events (Figure 4). Higher LARS-DD grades were associated with worse traditional echocardiographic diastolic Doppler parameters and greater LA size, as well as greater LV hypertrophy and fibrosis. The LARS-DD grade provided good discrimination of HF-free survival. Higher LARS-DD grade was an independent predictor of HF events, even after adjustment for clinical and echocardiographic variables, and also had incremental prognostic value over traditional echocardiographic LVDD parameters and the ASE-LVDD grade. The prognostic value of higher LARS-DD grade for predicting HF events was consistent in sensitivity analyses and various subgroups, suggesting its utility in a broad range of HCM patients.

The assessment of LVDD grade is of particular interest in patients with HCM, as LVDD is the main pathophysiologic mechanism explaining symptoms and

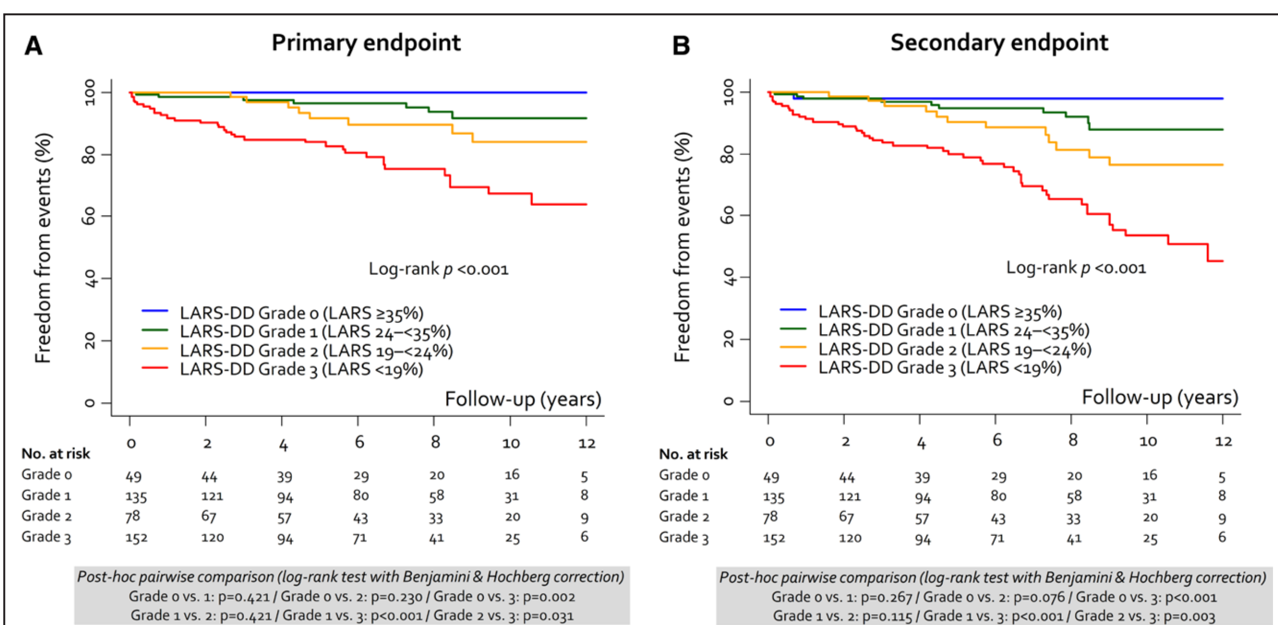

Figure 1. Event-free survival according to left atrial reservoir strain-defined left ventricular diastolic dysfunction (LARS-DD) grade. Kaplan-Meier analyses for the (**A**) primary and (**B**) secondary end points are presented.

Table 4. Predictors of the Primary End Point: Multivariable Cox Regression Models

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LARS-DD (per 1-grade increase)	1.79 (1.22–2.63)	0.003	1.67 (1.13–2.49)	0.001	1.55 (1.04–2.30)	0.032	1.53 (1.03–2.28)	0.037
Clinical variables								
Age, y	1.01 (0.98–1.04)	0.581	…	…	…	…	…	…
Sudden cardiac death risk score, %	1.08 (1.01–1.16)	0.030	…	…	…	…	1.02 (0.95–1.10)	0.532
Hypertension	1.41 (0.78–2.52)	0.255	…	…	…	…	…	…
Atrial fibrillation	3.20 (1.71–5.99)	<0.001	…	…	2.27 (1.13–4.58)	0.021	2.42 (1.17–4.98)	0.017
Echocardiographic variables								
Maximum LV wall thickness, mm	…	…	1.03 (0.96–1.10)	0.432	…	…	…	…
Maximum LVOT gradient, mm Hg	…	…	1.00 (0.99–1.01)	0.671	…	…	…	…
LV ejection fraction, %	…	…	0.95 (0.91–0.99)	0.007	0.95 (0.92–0.99)	0.015	0.95 (0.92–0.99)	0.018
LV global longitudinal strain, %	…	…	1.01 (0.94–1.08)	0.770	…	…	…	…
Left atrial diameter, mm	…	…	1.08 (1.03–1.12)	<0.001	1.06 (1.01–1.10)	0.013	1.05 (1.01–1.10)	0.028
Mitral regurgitation severity ≥moderate	…	…	2.15 (0.43–10.7)	0.349	3.22 (0.96–10.8)	0.058	3.38 (1.00–11.5)	0.050
Apical hypertrophic cardiomyopathy	…	…	0.52 (0.22–1.25)	0.145	0.48 (0.20–1.15)	0.098	0.50 (0.21-1.18)	0.114

Model 1 is adjusted for important clinical variables and Model 2 for important echocardiographic variables. Model 3 was constructed with stepwise backward selection from variables presented in the first column. Model 4 further adjusts Model 3 for the sudden cardiac death risk score.

HR indicates hazard ratio; LARS-DD, left atrial reservoir strain-defined LV diastolic dysfunction; LV, left ventricular; and LVOT, LV outflow tract.

HF events; however, the noninvasive estimation of LV diastolic function is complex and not well-established. Individual echocardiographic parameters showed, at best, modest correlations with LV filling pressures in HCM, which is likely related to the heterogeneity in LV muscle mass, interstitial fibrosis, myofiber disarray, and ischemia.[2] The guidelines recommend that a conglomeration of E/e′ ratio, LAVI, pulmonary vein atrial reversal velocity, maximum TR velocity, E/A, and e′ should be considered for the assessment of LV diastolic function in HCM[2]; however, these parameters are often discrepant causing difficulty in interpretation, and acquiring all parameters are sometimes impossible in routine practice.

The LA structure and function reflect the degree of LVDD[3]; while LA volume reflects the duration and severity of LVDD, LA function begins to decrease starting in the earliest stages of LVDD.[3,5] Elevated LV filling pressure is the afterload of the LA and thus, can lead to a reduced LA reservoir function by causing mechanical stress on the LA. A chronic increase in LV filling pressures leads to LA dilatation with fibrosis, which is also associated with decreased LA strain.[13] LARS was shown to have a strong inverse correlation with invasively measured

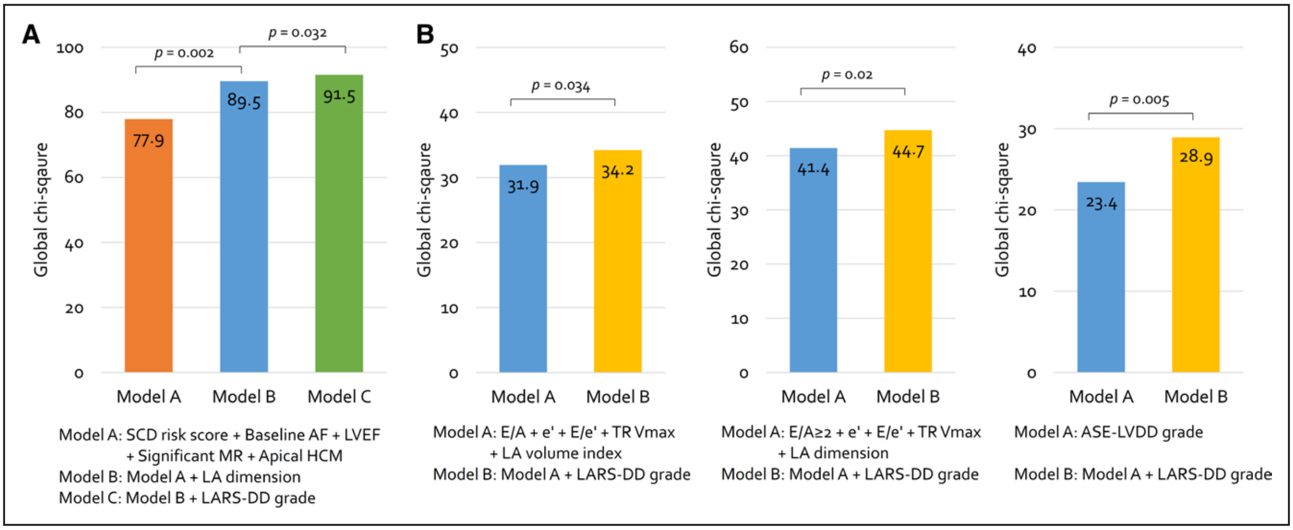

Figure 2. Incremental prognostic value of left atrial reservoir strain-defined left ventricular diastolic dysfunction (LARS-DD) grade for the primary end point.

AF indicates atrial fibrillation; ASE-LVDD, LV diastolic dysfunction grading in American Society of Echocardiography guideline; HCM, hypertrophic cardiomyopathy; LA, left atrial; LVEF, LV ejection fraction; MR, mitral regurgitation; SCD, sudden cardiac death; and TR, tricuspid regurgitation.

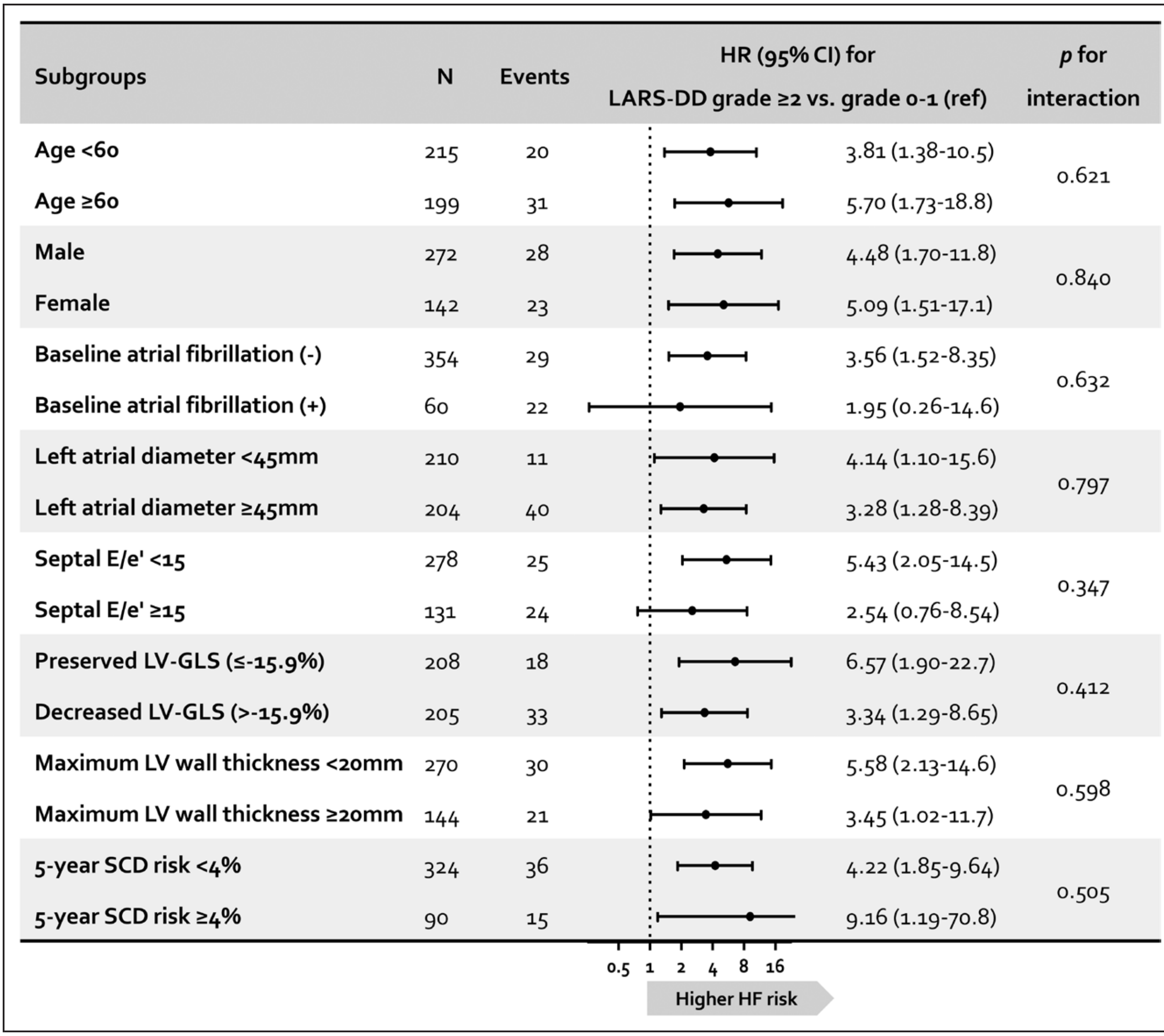

Figure 3. Predictive value of left atrial reservoir strain-defined left ventricular diastolic dysfunction (LARS-DD) grade for the primary end point in various subgroups.
HF indicates heart failure; HR, hazard ratio; LV-GLS, left ventricular global longitudinal strain; and SCD, sudden cardiac death.

LV filling pressure (r=−0.80, P<0.001)[14] and was more strongly correlated with invasively measured LV filling pressure than the E/e′ ratio,[15,16] a surrogate marker of LV filling pressure.[17] A multi-center study showed that LARS had the strongest correlation with LV filling pressure (r=−0.52, P<0.001), and LARS <18% predicted elevated LV filling pressure better than other conventional Doppler parameters.[18] Furthermore, LA strain showed an inverse relationship to the E/e′ ratio and the degree of LVDD determined by echocardiography.[6,19] More recently, categorizing LV diastolic function using the LARS as a single index was shown to be accurate and prognostic.[6,7] These observations support the theoretical background of a LARS-based categorization of LVDD.

Here, we demonstrated that the single measurement of LARS using speckle-tracking echocardiography may reliably and efficiently categorize LV diastolic function in patients with HCM. With increased LARS-DD grade, there was a progressive worsening of conventional echocardiographic diastolic parameters. Moreover, greater LV hypertrophy, myocardial fibrosis, and subclinical LV systolic dysfunction were noted with higher LARS-DD grades. LVDD causes increased atrial afterload and atrial wall stress[20] and is closely related to the development and persistence of AF.[21,22] In line with this, we observed that the prevalence of AF progressively rose with increasing LARS-DD grade.

More importantly, we noted that the LARS-DD grade was a strong predictor of HF events in HCM patients in the short-term as well as in the long-term. This is in line with previous smaller studies showing that LA strain was predictive of composite outcomes including HF events.[23–25] LARS had the highest predictive value for HF development in 250 patients with HCM followed-up

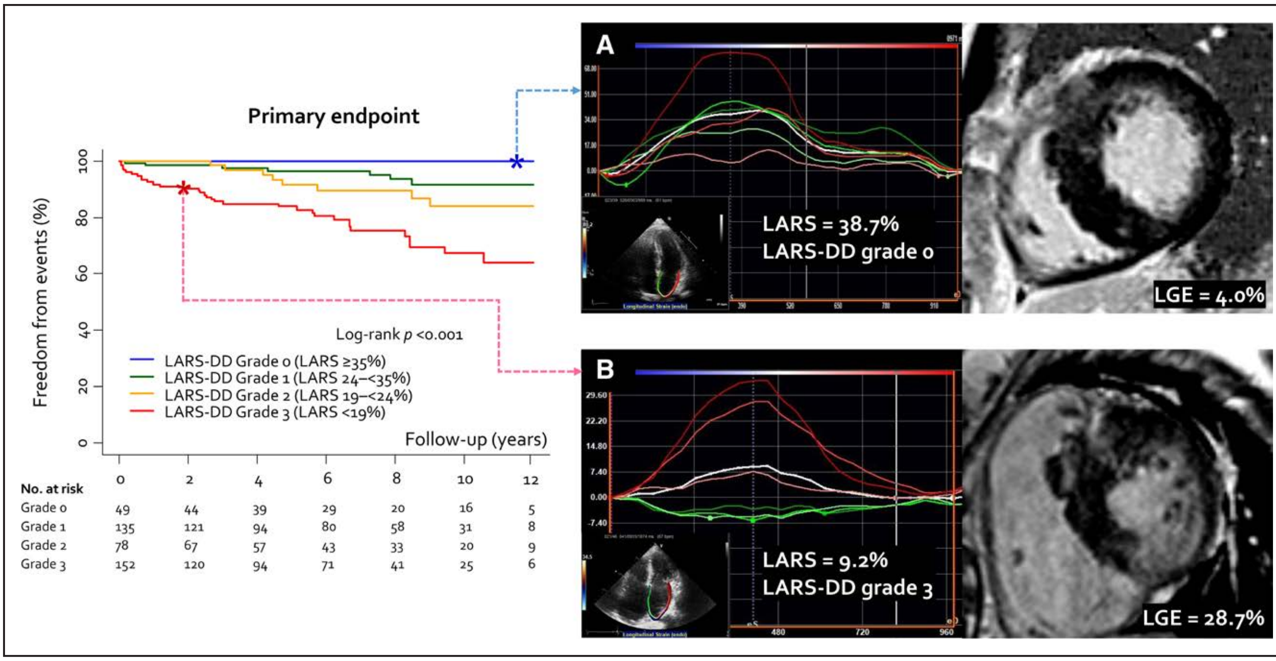

Figure 4. Representative examples.

A, A 56-year old man with septal hypertrophic cardiomyopathy (HCM) and mild fibrosis had left atrial reservoir strain (LARS) of 38.7% and remained event-free. **B**, A 75-year old woman with septal HCM and extensive fibrosis had LARS of 9.2% and was admitted for heart failure 1.9 y after the index exam. LARS-DD indicates left atrial reservoir strain defined left ventricular diastolic dysfunction; and LGE, late gadolinium enhancement.

over 2.5 years, compared with LVEF or LV-GLS.[26] To the best of our knowledge, our study is the largest regarding LA strain to focus on HF events as the primary end point, and the first to show that the LARS-DD grade had clinical value in HCM. Notably, we observed that patients with LARS-DD grade 0 had a 10-year HF-free survival similar to the general population,[27] and thus could be regarded as a very low-risk group, while patients with LARS-DD grade 3 had a 10-year HF-free survival of only 67.5%.

LARS is affected not only by LVDD and subsequent increase in LA pressure, but also by AF and MR. The predictive value of the LARS-DD grade was significant after adjusting for the presence of AF and significant MR. Furthermore, the LARS-DD grade had independent and incremental prognostic value for HF events over variables including LVEF and HCM type, and other traditional diastolic function parameters including LA size, E/e′ and maximum TR velocity. Moreover, the LARS-DD grade using LARS as a single measure of LV diastolic function had predictive value for HF events comparable to the ASE-LVDD grade, without generating inconclusive grading. According to the ASE-LVDD grading algorithm, 21% had inconclusive grading; most of them due to unmeasurable TR velocity while having discrepant septal E/e′ and LAVI values. Our study also suggests that the ASE-LVDD grading algorithm may be improved with the incorporation of LARS, especially by separating patients with LVDD grade 0 who are at very low risk of HF events, and also further categorizing LVDD grade in patients with inconclusive LVDD grading.

Some limitations merit attention. First, this is a single-center longitudinal cohort study of HCM patients referred to a tertiary center; thus, selection bias cannot be fully excluded. Second, as the number of patients who underwent cardiac catheterization was small, we could not analyze the direct relationship between invasively measured LV filling pressures and LARS. Instead, we used echocardiographic parameters as surrogates, as the current standard of care is to assess diastolic function using the noninvasive modality of Doppler echocardiography. Third, the LA-focused apical 2-chamber view was not available in all patients; thus, we did not measure biplane LA strain. However, the current consensus guidelines recommend using LA strain values obtained from the single apical 4-chamber view,[11] and reference values have been provided with this method.[28] Fourth, the prognostic value of the LARS-DD grade was consistent in various subgroups, but the sample sizes for subgroup analyses may not have reached sufficient power to detect meaningful differences in effect size. Lastly, considering our sample size and number of events, some other positive relationships may have been missed.

In conclusion, LARS is a simple single or supplemental echocardiographic index for detecting and categorizing LVDD in patients with HCM, and LARS-DD grading was independently associated with HF outcomes. LARS measurement should be incorporated into the assessment of LV diastolic function and prognosis in HCM.

ARTICLE INFORMATION

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Supplemental Material

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