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Extent of Late Gadolinium Enhancement in Cardiovascular Magnetic Resonance and Its Relation With Left Ventricular Diastolic Function in Patients With Hypertrophic Cardiomyopathy

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Background The aim of this study was to determine whether the extent of late gadolinium enhancement (LGE) is associated with left ventricular (LV) function in patients with hypertrophic cardiomyopathy (HCM).
Methods and Results Forty-seven patients with HCM (35 males, mean age 53±14, 14 with LV outflow tract obstruction) underwent cardiovascular magnetic resonance imaging and comprehensive echocardiographic examination. The extent of LGE was expressed as LGE volume and LGE percentage of LV volume. LGE was present in 40 (85.1%) of 47 patients. The mean LGE volume was 36.5±36 cm^3, and the mean percentage of LV volume was 16.4±17%. Following adjustment for age, mitral regurgitation and LV mass index, LGE volume and percentage positively correlated with the left atrial volume index (r=0.388, p=0.009 and r=0.425, p=0.004, respectively). However, there was no significant association of functional class, ejection fraction, mitral flow, or annular velocities with the extent of LGE.
Conclusions In HCM patients, the extent of LGE positively correlated with the left atrial volume index, a surrogate marker of chronic diastolic burden. These findings suggest that myocardial scarring may be a pathologic substrate for chronic diastolic dysfunction in patients with HCM. (*Circ J* 2008; **72:** 1449 – 1453)

Key Words: Cardiovascular magnetic resonance; Diastolic function; Hypertrophic cardiomyopathy; Late gadolinium enhancement

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by a hypertrophied non-dilated left ventricle (LV).[1–3] Histologically, HCM is characterized by extensive myocardial disarray and various patterns of myocardial fibrosis.[4,5] Many of the clinical and pathophysiological features of HCM result from a complex disturbance of diastolic function.[6,7] Because myocardial fibrosis can lead to an increase in chamber stiffness and is an important determinant of passive diastolic dysfunction in patients with HCM,[8] evaluation of myocardial fibrosis in patients with HCM is important, but until recently, it was not possible to comprehensively quantify it in vivo.[9,10] A recent technique, late gadolinium enhancement (LGE), of cardiovascular magnetic resonance imaging (CMRI) enables in vivo quantification of myocardial fibrosis.[11,12] Upon injection of a gadolinium contrast agent, regions of increased myocardial fibrosis become apparent as LGE, allowing direct assessment of the underlying myocardial abnormality.[13] Previous studies in patients with ungenotyped HCM have shown correlations between the extent of LGE and both the clinical risk of sudden death and the presence of heart failure.[11,12,14] However, the relationship between the extent of LGE and LV function has not been investigated, so in the present study, we used cardiac MRI to evaluated LGE in patients with HCM and assess the impact of LGE on LV systolic and diastolic function. We hypothesized that the extent of LGE would correlate with LV functional parameters, especially diastolic function.

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Methods

Patients Population

Selected patients fulfilled the conventional criteria for HCM with LV hypertrophy ≥15 mm. Exclusion criteria included apical HCM, prior history of myocardial infarction and atrial fibrillation. The following clinical data were collected and analyzed: demographic data, blood pressure, heart rate, presence of angina-like symptoms, and New York Heart Association (NYHA) class. Study approval was obtained from the Internal Review Board of Yonsei University College of Medicine.

Echocardiography

Standard 2-dimensional (D) measurements of LV diastolic and systolic dimensions, ventricular septum and posterior wall thicknesses, left atrial (LA) volume, and LV outflow tract were obtained while the patient was in the left lateral position. The LV ejection fraction was calculated using the modified Quinones method.[15] Maximal thickness was determined at the beginning of the QRS complex on the parasternal short-axis view. LA dimensions were mea-

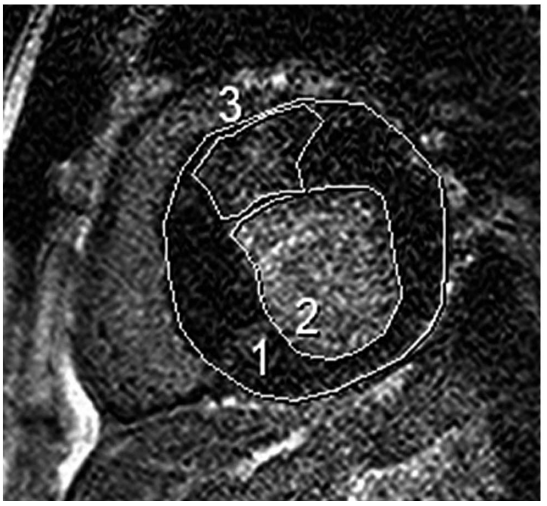

Fig 1. Defining and quantifying late gadolinium enhancement (LGE) in a patient with hypertrophic cardiomyopathy. LGE area was calculated as tracing area 3.

sured at end-systole. Mediolateral (ML) and supero-inferior (SI) dimensions of the LA were measured from the apical 4-chamber view and the anteroposterior (AP) dimension from the parasternal long-axis view. LA volume was calculated using the prolate ellipsoid model, which assumes that the LA can be adequately represented as a prolate ellipse with a volume of $4\pi/3$ (ML/2) (SI/2) (AP/2). The LA volume index was calculated as the LA volume divided by body surface area and is reported in ml/m^2. From the apical window, a 1–2-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities from 5–10 cardiac cycles were recorded. The mitral inflow velocities were traced, and the following variables were obtained: peak velocity of early (E) and late (A) filling, as well as deceleration time of the E-wave velocity. Tricuspid regurgitant jet velocity was also obtained to estimate pulmonary artery systolic pressure using continuous-wave Doppler, if measurable. Mitral annular velocity was measured by Doppler tissue imaging using the pulsed wave Doppler mode. The filter was set to exclude high-frequency signals, and the Nyquist limit was adjusted to a range of 15–20 cm/s. Gain and sample volume were minimized to provide a high signal to noise ratio. Early diastolic (E') and systolic (S') velocities of the mitral annulus were measured from the apical 4-chamber view with a 2- to 5-mm sample volume placed at the septal corner of the mitral annulus.

CMRI Protocol

Delayed enhancement image was acquired by using 1.5-T imaging unit (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands) 10–15 min after administration of 0.2 mmol/kg of a gadolinium-based contrast agent using an inversion recovery T1-weighted turbo field echo with the parameters of 10 mm slice thickness, typical TR/TE of 4.7/1.5 ms, flip angle of 15°, 36 cm field of view, NSA 2, and acquisition matrix 320/301.

Quantification of LGE

Analyses of CMRI were conducted by cardioradiologists who were unaware of the results of the other study. Quantification of LGE was performed by manually defining the areas of the LV and LGE on all short-axis slices (1 cm thickness) from the base to the apex at end-diastole (beginning of the QRS complex). Summing the areas yielded the total volume of LV and the LGE. The extent of LGE was expressed as absolute LGE volume and LGE percentage of the LV volume (Fig 1).

Table 1 Baseline Characteristics

Clinical data	
M/F	*35/12*
Age (years)	*53±14*
Hypertension	*20 (43%)*
Diabetes mellitus	*6 (13%)*
NYHA class	
1	*15 (32%)*
2	*20 (43%)*
3	*10 (21%)*
4	*2 (4%)*
LVOT obstruction	*14 (30%)*
SBP (mmHg)	*130±22*
DBP (mmHg)	*78±13*
HR (beats/min)	*67±15*
Echocardiographic data	
LVEDD (mm)	*46±5*
LVESD (mm)	*29±5*
LVEF (%)	*70±9*
LVMI (g/m^2)	*134±30*
LAVI (ml/m^2)	*38±17*
Maximal thickness (mm)	*21±4*
E (m/s)	*0.67±0.2*
A (m/s)	*0.62±0.3*
DT (ms)	*211±76*
S' (cm/s)	*6.2±1.4*
E' (cm/s)	*4.2±1.6*
A' (cm/s)	*6.8±2.2*
E/E'	*18.0±8.5*
Mitral regurgitation	
1	*11 (23%)*
2	*4 (9%)*
3	*2 (4%)*
4	*0 (0%)*
MRI data	
Presence of LGE	*40 (85.1%)*
LGE volume (cm^3)	*36.5±36.2*
LGE percentage to LV (%)	*16.4±17.1*

NYHA, New York Heart Association; LVOT, left ventricular outflow track; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; E, early diastolic mitral flow velocity; A, mitral flow velocity during atrial contraction; DT, deceleration time of E velocity; S', peak systolic myocardial velocity; E', peak early diastolic myocardial velocity; A', peak late diastolic myocardial velocity; MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; LV, left ventricular.

Statistical Analysis

Data are presented as mean ± SD. Pearson's partial correlations for confounding variables were performed to evaluate the association between the extent of LGE and both clinical and echocardiographic parameters. Patients were divided into tertiles according to the extent of LGE. The ANOVA test was used to compare results among groups, and post hoc analysis was performed using a Bonferroni test. A p value of ≤0.05 was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of the patients are given in

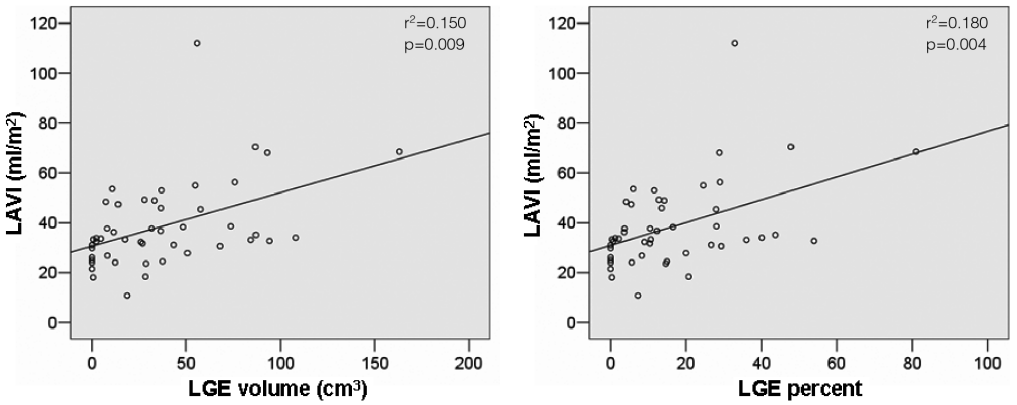

Fig 2. Correlation between the extent of late gadolinium enhancement (LGE) and the left atrial volume index (LAVI).

Table 2 Association Between LGE Volume and Clinical and Echocardiographic Parameters as Tertile

	1st tertile (n=15)	*2nd tertile (n=16)*	*3rd tertile (n=16)*	*p value*
Age (years)	*57±13*	*50±15*	*53±19*	*0.385*
NYHA class	*1.7±0.7*	*2.1±0.9*	*2.2±0.8*	*0.208*
Maximal thickness(mm)	*18±3*	*21±4*	*23±4*	*0.005*
LVEDD (mm)	*44±6*	*45±5*	*47±5*	*0.464*
LVEF (%)	*73±7*	*69±6*	*68±14*	*0.350*
LVMI (g/m²)	*121±28*	*144±26*	*134±30*	*0.089*
LAVI (ml/m²)	*31±10*	*34±12*	*48±22*	*0.009*
LVOT obstruction	*4 (27%)*	*4 (25%)*	*6 (38%)*	*0.705*
E (m/s)	*0.67±0.2*	*0.63±0.2*	*0.72±0.2*	*0.615*
A (m/s)	*0.75±0.2*	*0.54±0.1*	*0.51±0.2*	*0.002*
DT (ms)	*243±90*	*188±44*	*204±81*	*0.121*
S' (cm/s)	*6.8±1.1*	*6.2±1.7*	*5.8±1.3*	*0.198*
E' (cm/s)	*4.8±2.1*	*3.7±1.3*	*4.0±1.2*	*0.160*
E/E'	*16.1±9.4*	*17.9±5.4*	*19.7±10.2*	*0.516*

Abbreviations as in Table 1.

Table 3 Association Between LGE Percentage and Clinical and Echocardiographic Parameters as Tertile

	1st tertile (n=15)	*2nd tertile (n=16)*	*3rd tertile (n=16)*	*p value*
Age (years)	*57±13*	*48±15*	*55±12*	*0.138*
NYHA class	*1.7±0.8*	*2.0±0.9*	*2.2±0.8*	*0.333*
Maximal thickness (mm)	*18±2*	*22±5*	*23±4*	*0.002*
LVEDD (mm)	*45±6*	*45±6*	*46±5*	*0.829*
LVEF (%)	*71±8*	*70±7*	*69±13*	*0.852*
LVMI (g/m²)	*130±25*	*140±30*	*134±30*	*0.674*
LAVI (ml/m²)	*31±9*	*36±12*	*47±24*	*0.024*
LVOT obstruction	*4 (27%)*	*4 (25%)*	*6 (38%)*	*0.705*
E (m/s)	*0.69±0.3*	*0.64±0.2*	*0.69±0.3*	*0.765*
A (m/s)	*0.77±0.3*	*0.56±0.2*	*0.54±0.2*	*0.022*
DT (ms)	*233±71*	*191±81*	*211±75*	*0.3331*
S' (cm/s)	*6.5±1.1*	*6.3±1.7*	*5.8±1.3*	*0.315*
E' (cm/s)	*4.5±1.4*	*4.2±2.1*	*3.8±1.3*	*0.492*
E/E'	*16.8±9.3*	*17.3±5.7*	*19.6±10.3*	*0.650*

Abbreviations as in Table 1.

Table 1. A total of 47 patients were included (35 men, 12 women; mean [±SD] age 53±14 years). LV outflow tract obstruction was observed in 14 patients (30%); 20 patients (43%) had coexisting hypertension, and 6 patients (13%) had diabetes mellitus. According to the NYHA classification system, 15 patients were in class I (32%), 20 in class II (43%), 10 in class III (21%) and 2 in class IV (4%). By echocardiographic examination, LV end-diastolic and end-systolic dimensions, and ejection fraction were 46±5 mm, 29±5 mm, and 70±10%, respectively. LV systolic function was normal in all patients. The LV mass index was 134±30 g/m^2. Maximal thickness and LA volume index were 21±4 mm and 38±17 ml/m^2, respectively S', E', and A' were 6.2±1.4 cm/s, 4.2±1.6 cm/s and 6.8±2.2 cm/s, respectively. E/E' was 17.9±8.5. Mitral regurgitation greater than grade II was observed in 6 patients (13%). On CMRI, LGE was observed in 40 patients (85.1%). The LGE volume and LGE percentage of the LV volume were 38.3±38.0 cm^3 and 16.4±17.1%, respectively.

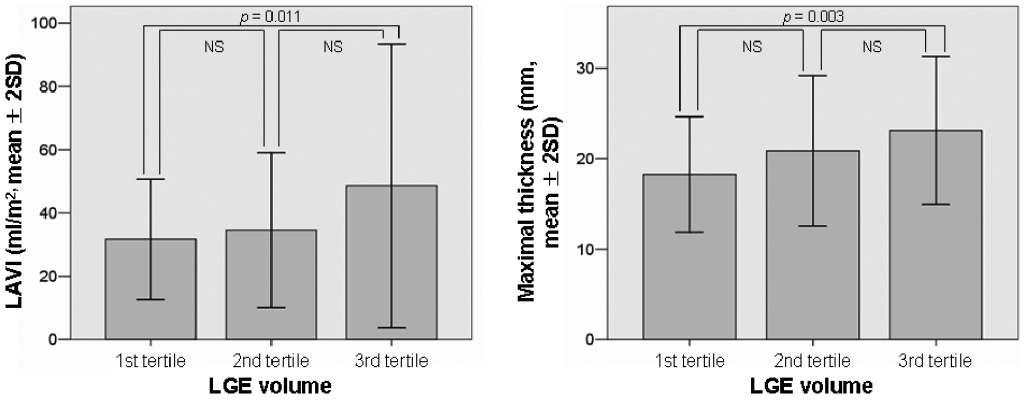

Fig 3. Left atrial volume index (LAVI) and maximal thickness as tertile. Both were significantly higher in the 3rd tertile than in the 1st tertile. LGE, late gadolinium enhancement.

Relationship Between LGE and Clinical/Echocardiographic Parameters

The LGE volume and percentage did not correlate with NYHA class, S', E', A', or the E/E' ratio. However, a significant age-, mitral regurgitation- and LV mass index-adjusted Pearson's partial correlation was noted between the LA volume index and the LGE volume (r=0.388, p=0.009) and the LGE percentage of the LV volume (r=0.425, p=0.004) (Fig 2). The LV mass index did not correlate with the LA volume index (p=0.204). When the patients were divided into tertiles according to the extent of LGE, there was no significant difference in age, sex, NYHA class, LV end-diastolic dimension, LV ejection fraction, LV mass index, presence of LV outflow tract obstruction, S', E' or E/E'. However, the LA volume index and maximal septal thickness were significantly larger in the 3rd tertile than in the 1st tertile (Tables 2,3, Fig 3). When patients were divided into 2 groups according to the presence of LV outflow tract obstruction and NYHA class (I & II vs III & IV), there was no significant difference in the extent of LGE (p=0.165 and 0.561 for LGE volume and p=0.227 and 0.533 for LGE percentage).

Discussion

Our results demonstrate that LGE is commonly observed in patients with HCM and that the extent of LGE correlates with the LA volume index, the surrogate marker of chronic LV diastolic burden.

The presence of LGE in 85.1% of the study population is consistent with results of previous studies[1,11,12,14] The LGE percentage of LV volume was 16.4% (range 0–81%) in our study. A previous study quantifying the extent of LGE using a similar method reported that the LGE percentage of LV volume was 10.9% (range 0–48%)[11] However, in that study, patients were younger (47±16) and less symptomatic (>90% of patients were in NYHA I & II) compared with the present patients.

Many clinical and pathophysiological features of HCM result from a complex disturbance of diastolic function[1,5,6,12,16–18] Collagen accumulation, which can lead to an increase in chamber stiffness, is an important determinant of passive diastolic dysfunction in patients with HCM[19] Clinically, gadolinium contrast media are inert extracellular agents that cannot cross intact sarcolemmal membranes[20] Therefore, LGE lesions represent areas of increased collagen or myocardial disarray. A recent study suggested that LGE lesions represent regions of increased myocardial collagen, but not disarray, and that segments containing ≥15% collagen were more likely to have LGE[13] In the present study the extent of LGE correlated significantly with the LA volume index. Because remodeling of the LA reflects a chronic increase in LV filling pressure, an enlarged LA could be a marker of chronic LV diastolic dysfunction[21] This study demonstrated that the extent of LGE was not associated with resting functional status; however, because remodeling of the LA is a reported predictor of functional capacity in patients with HCM[22] we speculate that there is a relationship between the extent of LGE and functional capacity, especially during exercise. Further studies are needed to verify this hypothesis.

Study Limitations

In this study, LA volume was calculated using 2-D echocardiography, which requires the geometric assumption of an ellipsoid model. Although Cine MRI measurement of LA volume on consecutive imaging slices covering the entire LA would be more accurate and reproducible, the LA was not included in the CMRI protocol used in our study. Therefore, the measurement of LA volume by CMRI was not feasible in this study.

In conclusion, LGE is a common abnormal observation in gadolinium-enhanced CMRI of patients with HCM. The extent of LGE, expressed as LGE volume and LGE percentage of LV volume, significantly correlates with the LA volume index as a representative marker of chronic LV diastolic dysfunction. This result suggests that myocardial scarring is a pathologic substrate for chronic LV diastolic dysfunction.

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