



Extent of Late Gadolinium Enhancement on Cardiovascular Magnetic Resonance Imaging and Its Relation to Left Ventricular Longitudinal Functional Reserve During Exercise in Patients With Hypertrophic Cardiomyopathy

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Background: The aim of this study was to investigate whether the extent of late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging reflecting myocardial fibrosis correlates with left ventricular (LV) longitudinal function during exercise in hypertrophic cardiomyopathy (HCM).

Methods and Results: Mitral annular velocities (E' and S') were measured on echocardiography at rest and during graded bicycle exercise (25 W, 3-min increments) in 46 HCM patients (mean age, 53 years; 32 men). LV longitudinal diastolic and systolic functional reserve indices were calculated as $\Delta E' \times E'_{\text{base}}$ and $\Delta S' \times S'_{\text{base}}$, where $\Delta E'$ and $\Delta S'$ are the changes in E' and S' from baseline to 50 W of exercise, respectively. The patients were divided into 2 groups according to the extent of LGE (as "percentage of LV mass containing LGE": %LV with LGE; range, 0–37%; median, 6%): group 1 ($n=23$), %LV with LGE <6%, and group 2, %LV with LGE \geq 6%. Baseline echocardiographic parameters were similar between the 2 groups, but changes in E' and S' during exercise were smaller in group 2 ($\Delta E'$: 2.8 ± 1.8 cm/s vs. 1.5 ± 1.0 cm/s, $P=0.007$; $\Delta S'$: 2.2 ± 1.2 cm/s vs. 0.9 ± 0.8 cm/s, $P<0.0001$). LV functional reserve indices were also significantly lower in group 2 ($\Delta E' \times E'_{\text{base}}$: 12.8 ± 7.7 vs. 5.5 ± 3.4 , $P=0.001$; $\Delta S' \times S'_{\text{base}}$: 12.6 ± 7.4 vs. 4.7 ± 4.5 , $P<0.0001$).

Conclusions: LV longitudinal function during exercise is influenced by the extent of LGE in HCM. Myocardial fibrosis may represent a pathologic substrate that determines LV functional reserve in patients with HCM. (*Circ J* 2013; **77**: 1742–1749)

Key Words: Echocardiography; Exercise; Hypertrophic cardiomyopathy; Left ventricular function; Magnetic resonance imaging

Myocardial fibrosis, along with myocardial disarray, is a characteristic histological finding in hypertrophic cardiomyopathy (HCM).¹ It can lead to cardiac chamber stiffness, and its extent has been suggested to be an important determinant of systolic and diastolic dysfunction in HCM.^{2–4} The presence and the extent of myocardial fibrosis can now be non-invasively assessed with cardiovascular magnetic resonance imaging (CMRI) using late gadolinium enhancement (LGE).^{5,6} Several studies have shown that LGE is associated with non-sustained ventricular tachycardia as well

as with other risk factors for sudden cardiac death.^{3,7–9} Recent studies have further demonstrated that myocardial fibrosis as measured on CMRI is an independent predictor of all-cause and cardiac mortality even in low or asymptomatic HCM patients.^{7,10} Although the relationship between the presence and the extent of LGE and ventricular arrhythmias and sudden cardiac death has been well documented, few previous studies have evaluated the relationship between LGE and left ventricular (LV) functional reserve in HCM patients. In patients with HCM, already impaired myocardial relaxation does not aug-

Received November 7, 2012; revised manuscript received January 23, 2013; accepted February 19, 2013; released online April 2, 2013 Time for primary review: 28 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-12-1378

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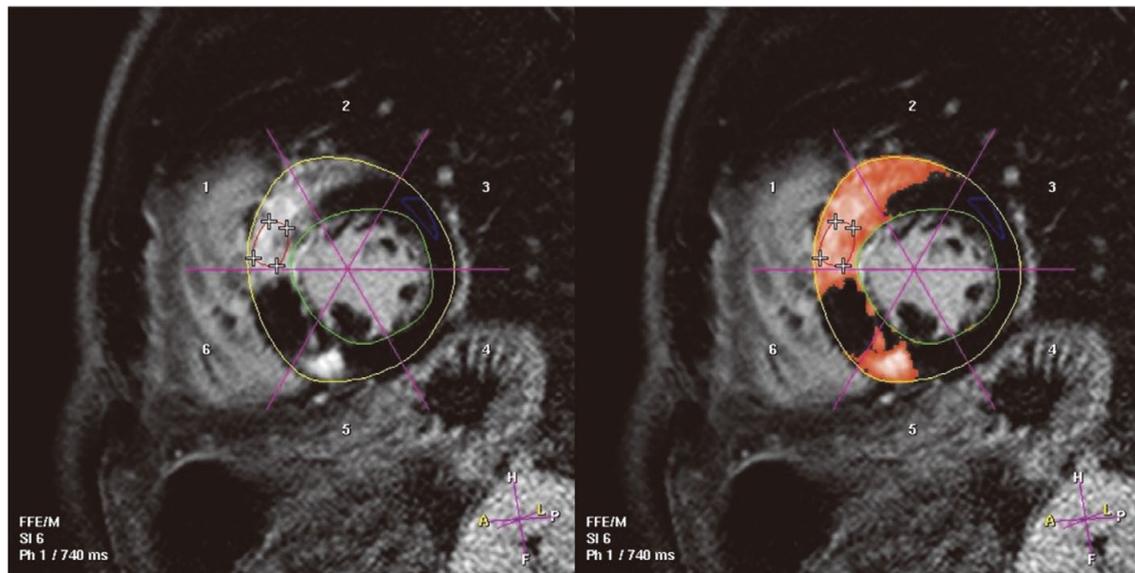


Figure 1. Quantification of late gadolinium enhancement (LGE) using the automatic thresholding software (ViewForum version 4.1; Philips Medical Systems, The Netherlands). Left ventricular (LV) myocardial mass was determined (g) and the extent of LGE was expressed as LGE mass (g) and percentage of LV mass containing LGE (%LV with LGE).

ment LV longitudinal function as much as seen in normal individuals during exercise.¹¹ The anatomic substrate of this lack of diastolic reserve during exercise, however, has not been explored before. In the present study, we hypothesized that the extent of myocardial fibrosis would correlate with the magnitude of augmentation in LV longitudinal function during exercise in patients with HCM.

Methods

Subjects

All 46 patients with HCM (mean age, 53 years; 32 men; 10 with LV outflow tract [LVOT] obstruction) were consecutively enrolled. The diagnosis of HCM was made according to the World Health Organization/International Society and Federation of Cardiology criteria.¹² Patients with apical HCM or atrial fibrillation were excluded. Patient who could not perform bicycle exercise for any reason or who had specific contraindications for CMRI such as implanted cardioverter-defibrillators or pacemakers, metallic fragments, known claustrophobia or renal insufficiency were also excluded. None of the patients had a history of alcohol septal ablation or surgical septal myectomy. CMRI and comprehensive echocardiography, including exercise Doppler evaluation, were performed in all patients. Prescribed medications, which were grossly similar between the 2 groups, were discontinued before exercise echocardiography. This study was approved by the institutional ethics committee. The study complies with the Declaration of Helsinki, and informed consent was obtained from all subjects.

2-D and Exercise Doppler Echocardiography (Diastolic Stress Echocardiography)

Diastolic stress echocardiography¹³ was performed as follows. Echocardiography was carried out using an ultrasound system (System 7, GE Vingmed, Horten, Norway) with 2.5-MHz trans-

ducer during rest and exercise. Standard 2-D measurements (LV end-diastolic and end-systolic dimensions, ventricular septum and posterior wall thickness, left atrial [LA] volume, and LVOT diameter) and Doppler parameters were obtained with the patient in the left lateral decubitus position. LV ejection fraction (EF) was calculated using the modified method of Quinones et al.¹⁴ LA volume was determined using the prolate ellipsoid formula and was indexed to body surface area.¹⁵ 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 to 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, and deceleration time of the E wave velocity. The peak instantaneous LV outflow gradient was estimated with continuous wave Doppler under basal conditions, and LVOT obstruction was defined as peak instantaneous outflow gradient ≥ 30 mmHg.^{16,17} Tricuspid regurgitant jet velocity was also obtained to estimate pulmonary artery systolic pressure using continuous wave Doppler, if measurable. After obtaining the rest images from the standard parasternal and apical views, a multistage supine bicycle exercise test was performed with a variable load bicycle ergometer (Medical Positioning, Kansas City, MO, USA). Patients pedaled at a constant rate beginning at a workload of 25 W with an increment of 25 W every 3 min. Mitral annular velocity was measured on Doppler tissue imaging (DTI) using the pulsed wave Doppler mode. The filter was set to exclude high-frequency signal, and the Nyquist limit was adjusted to a range of 15–20 cm/s. Gain and sample volume were minimized to allow a clear tissue signal with minimal background noise. Early diastolic (E') and systolic (S') velocities of the mitral annulus were measured on apical 4-chamber view with a 2–5-mm sample volume placed at the septal corner of the mitral annulus. These measurements were performed at baseline and at each stage of exercise in the same sequence.

	All (n=46)	Group 1 (extent of LGE <6%) (n=23)	Group 2 (extent of LGE ≥6%) (n=23)	P-value
Age (years)	53±11	50±12	55±8	0.075
Male	32 (70)	17 (74)	15 (66)	0.749
LVOT dynamic obstruction	10 (22)	5 (22)	5 (22)	1.000
CMRI findings				
LV mass (g)	177±69	171±68	182±71	0.576
LGE mass (g)	17±21	4±4	29±24	<0.0001
%LV with LGE (%)	8.9±9.9	2.2±1.9	15.5±10.2	<0.0001

Data given as n (%) or mean±SD. CMRI, cardiovascular magnetic resonance imaging; LGE, late gadolinium enhancement; LV, left ventricle/ventricular; %LV with LGE, percentage of LV volume containing LGE (ie, extent of LGE); LVOT, left ventricular outflow tract.

	Group 1 (extent of LGE <6%) (n=23)	Group 2 (extent of LGE ≥6%) (n=23)	P-value
LVEDD (mm)	48±4	45±6	0.052
LVESD (mm)	30±4	29±5	0.324
LVEF (%)	69±6	68±6	0.576
IVS (mm)	14±4	16±4	0.176
PW (mm)	11±2	11±2	0.889
Maximum wall thickness (mm)	19±4	20±4	0.667
LAVI (ml/m ²)	30±9	38±16	0.099
E (m/s)	0.62±0.16	0.57±0.23	0.343
A (m/s)	0.59±0.12	0.58±0.23	0.929
E/A	1.1±0.5	1.1±0.5	0.880
DT (ms)	189±36	230±75	0.023
TR (m/s)	2.3±0.3	2.3±0.3	0.762
E' (cm/s)	4.6±1.3	3.8±1.4	0.054
E/E'	14±5	17±8	0.150
S' (cm/s)	5.8±1.2	5.0±1.0	0.022
Longitudinal DFRI at 25W	7.0±5.5	4.0±4.7	0.060
Longitudinal DFRI at 50W	12.8±7.7	5.5±3.4	0.001
Longitudinal SFRI at 25W	3.7±6.2	2.6±3.5	0.475
Longitudinal SFRI at 50W	12.6±7.4	4.7±4.5	<0.0001

Data given as mean±SD. A, late diastolic mitral inflow; DFRI, diastolic functional reserve index; DT, deceleration time of E wave; E, early diastolic mitral inflow; E', early diastolic mitral annulus velocity; IVS, interventricular septum; LAVI, left atrial volume index; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; PW, posterior wall; S', systolic mitral annulus velocity; SFRI, systolic functional reserve index; TR, tricuspid regurgitation. Other abbreviations as in Table 1.

LV longitudinal diastolic and systolic functional reserve indices were calculated using the following formulas:^{18,19}

$$\text{diastolic functional reserve index} = \Delta E' \times E'_{\text{base}},$$

where $\Delta E'$ is the change in E' from baseline to 25 W or 50 W of exercise, and

$$\text{systolic functional reserve index} = \Delta S' \times S'_{\text{base}},$$

where $\Delta S'$ is the change in S' from baseline to 25 W or 50 W of exercise.

All data were digitally stored and analyzed by 2 experienced echocardiographers who were blinded to the clinical and CMRI data.

CMRI and LGE Quantification

LGE images were acquired with a 1.5-T CMRI unit (Gyrosan

Intera; Philips Medical Systems, Best, The Netherlands) 10–15 min after 0.2 mmol/kg of a gadolinium-based contrast media. Short-axis slices of the heart were obtained without any gaps, encompassing the entire LV. LGE was identified on a segmented inversion recovery T1-weighted turbo field-echo sequence with the following parameters (Look-Locker): slice thickness, 10 mm; typical repetition time, 5.3 ms; typical echo time, 1.6 ms; flip angle, 15°; field of view, 36 cm; number of signal averages, 2; acquisition matrix, 320×256; and reconstruction matrix, 512×512. Quantification of LGE was done using the automatic thresholding software (ViewForum, version 4.1; Philips Medical Systems) by 2 radiologists in consensus who were unaware of the patients' clinical and echocardiographic data (Figure 1). At first, raw image data were analyzed by each radiologist separately. After that, normal myocardium was designated on consensus and the dedicated soft-

	Group 1 (extent of LGE <6%) (n=23)	Group 2 (extent of LGE ≥6%) (n=23)	P-value
HR at rest (beats/min)	60±10	59±7	0.880
HR at 25W (beats/min)	87±15	93±14	0.160
HR at 50W (beats/min)	100±17	104±17	0.323
SBP at rest (mmHg)	128±19	119±17	0.063
SBP at 25W (mmHg)	148±25	145±21	0.709
SBP at 50W (mmHg)	154±27	152±21	0.729
DBP at rest (mmHg)	77±12	72±12	0.178
DBP at 25W (mmHg)	89±17	81±13	0.089
DBP at 50W (mmHg)	85±16	82±14	0.445
Exercise duration (min)	8±3	9±3	0.782

Data given as mean ± SD. DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure. Other abbreviations as in Table 1.

	β	t	P-value
$\Delta E' \times E'_{\text{base}}$ at 50W (Adjusted R square=0.096)			
%LV with LGE*	-0.360*	-2.396*	0.021*
Age	0.018	0.115	0.909
Male	0.175	1.147	0.258
LVOT dynamic obstruction	-0.140	-0.957	0.344
DT	-0.129	-0.757	0.453
$\Delta S' \times S'_{\text{base}}$ at 50W (Adjusted R square=0.061)			
%LV with LGE*	-0.318*	-2.045*	0.048*
Age	-0.204	-1.259	0.216
Male	0.135	0.854	0.398
LVOT dynamic obstruction	-0.124	-0.824	0.415
DT	-0.009	-0.052	0.958

*Independent predictor. DFRI, diastolic functional reserve index ($\Delta E' \times E'_{\text{base}}$); SFRI, systolic functional reserve index ($\Delta S' \times S'_{\text{base}}$). Other abbreviations as in Tables 1,2.

were determined the mean (μ) and standard deviation (σ) of pixel value of the area (ie, region of interest). After that, we defined the enhanced area (LGE) as signal intensity above the threshold T, where $T = \mu + 3\sigma$. LV mass was determined (g), and the extent of LGE was expressed as LGE mass (g) and percentage of LV mass containing LGE (%LV with LGE).

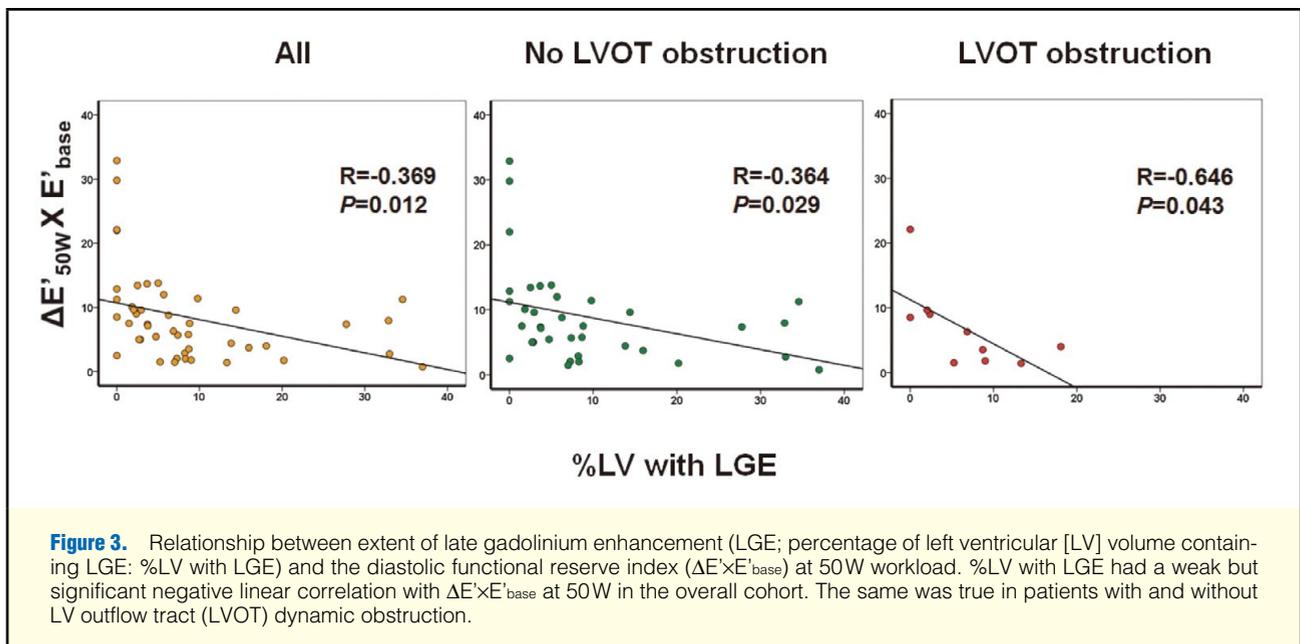
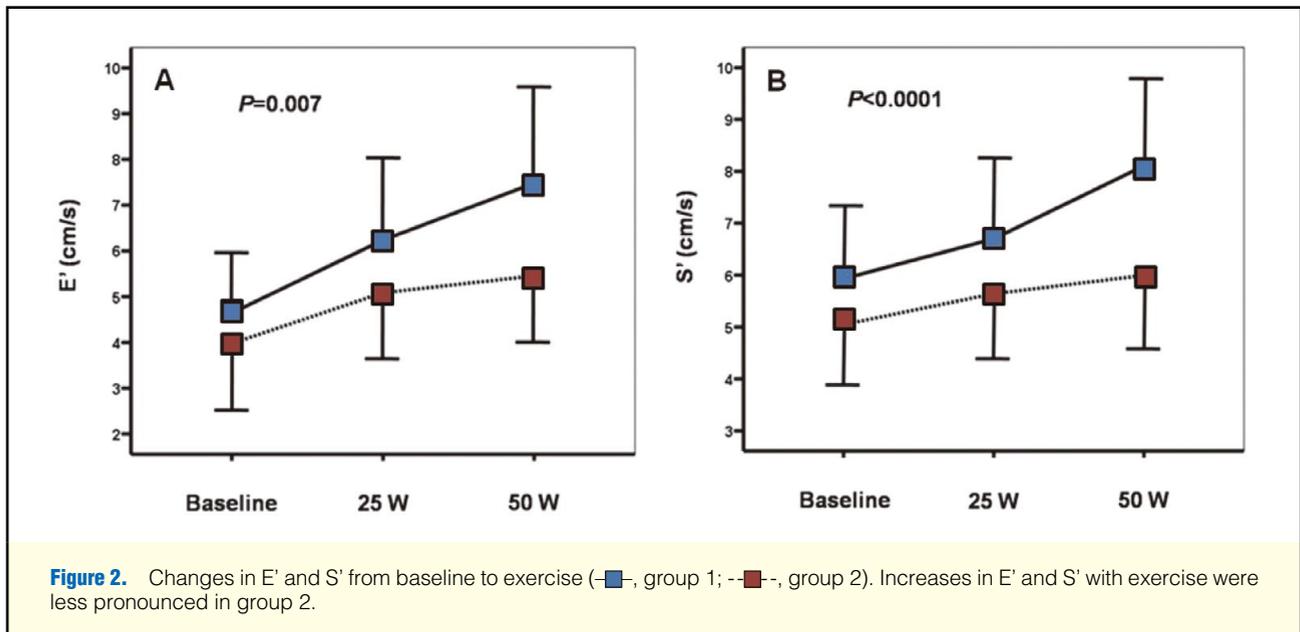
Statistical Analysis

Continuous data are expressed as mean ± SD, and normality tests were performed for each variable. Categorical variables were summarized as a percentage of the group total. The baseline characteristics of the 2 groups were compared using the 2-sample t-test for continuous variables, and chi-square test and Fisher's exact test for categorical variables. Differences in Doppler indexes between rest and exercise were compared using repeated measures analysis of variance. Pearson's bivariate correlation analysis was used to determine the correlation between variables. Multiple linear regression analysis was performed to test the association of diastolic/systolic functional reserve index with other parameters that were clinically meaningful or statistically significant including %LV with LGE. Intra- and interobserver variability for DTI measurement were calculated by analysis of 10 random images by 1 investigator blinded to the first analysis and additional analysis of images by a second observer who was unaware of the

results from the first observer. $P < 0.05$ was considered to be significant.

Results

LGE was observed in 38 of 46 patients (83%), but its degree was variable (%LV with LGE: range, 0–37%; median, 6%). Patients were divided into 2 groups according to the extent of LGE: group 1, %LV with LGE <6%; and group 2, %LV with LGE ≥6%. **Table 1** lists the clinical characteristics and CMRI findings of the patients. Demographic findings and LV mass assessed on CMRI were comparable between the 2 groups except the extent of LGE (**Table 1**). Echocardiographic findings are listed in **Table 2**. The baseline echocardiographic parameters were also similar between the 2 groups, except deceleration time of E wave and S'. LV longitudinal diastolic and systolic functional reserve indices at 25W were similar between the groups, but LV functional reserve indices at 50W were significantly lower in group 2 (**Table 2**). **Table 3** lists the hemodynamic responses during supine bicycle exercise. In both groups, heart rate, systolic and diastolic blood pressures increased during exercise compared with those at rest, but no significant differences were found between the 2 groups. Exercise duration was also similar between the 2 groups (**Table 3**). We analyzed the relationship between exercise du-



ration and LGE or LV longitudinal functional reserve and found that there was no significant correlation between these parameters (exercise duration and %LV with LGE, $R=0.069$, $P=0.650$; exercise duration with diastolic functional reserve index at 50 W, $R=0.149$, $P=0.322$; exercise duration with systolic functional reserve index at 50 W, $R=0.184$, $P=0.227$). Multiple linear regression analysis found that %LV with LGE was the only independent predictor of diastolic/systolic functional reserve index at 50 W workload even after age, gender, presence of LVOT obstruction and mitral DT were controlled for (Table 4).

The changes in LV performance are shown in Figure 2. At

rest, E' was smaller in group 2 ($P=0.054$), suggesting more impaired LV relaxation in those patients. In both groups, significant augmentation in E' was observed during exercise, but the increase in E' during exercise was less pronounced in group 2, and $\Delta E'$ at 50 W of exercise was significantly smaller in group 2 (Figure 2A). Similarly, the baseline S' was significantly smaller in group 2 ($P=0.022$), suggesting reduced longitudinal contraction in these subjects. During exercise, S' was significantly increased in both groups, but the magnitude of increase in S' during exercise and $\Delta S'$ at 50 W of exercise were smaller in group 2 when compared with group 1 (Figure 2B). In simple correlation analysis, the extent of LGE

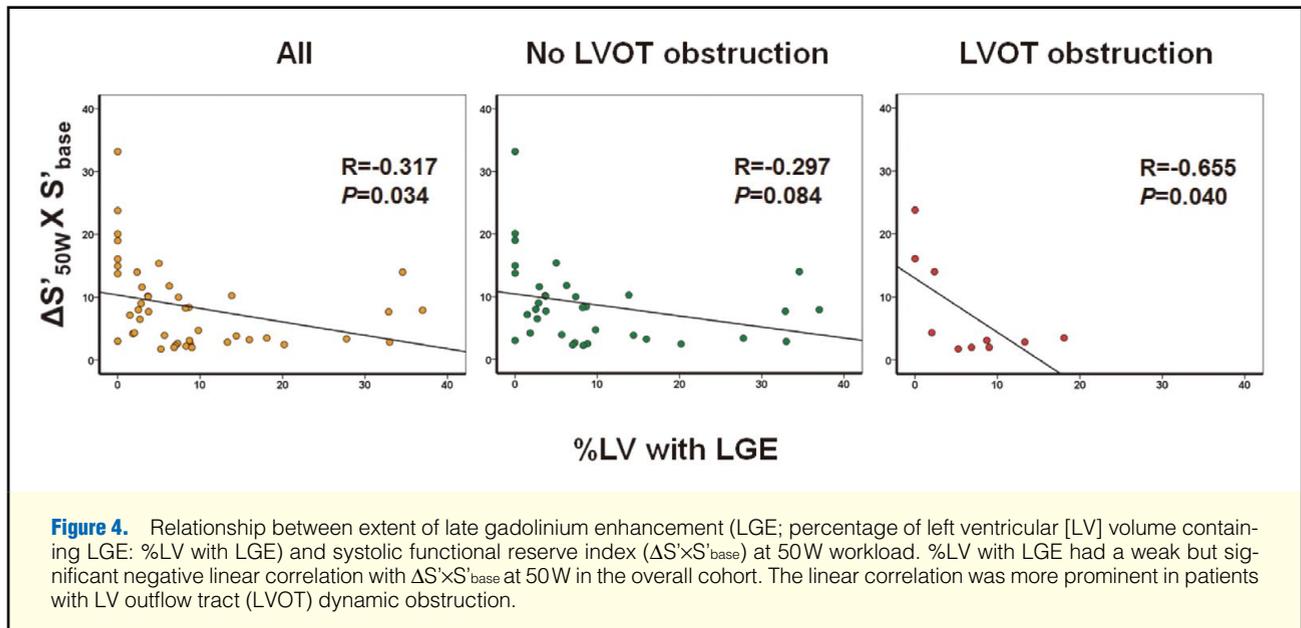


Figure 4. Relationship between extent of late gadolinium enhancement (LGE; percentage of left ventricular [LV] volume containing LGE: %LV with LGE) and systolic functional reserve index ($\Delta S' \times S'_{\text{base}}$) at 50W workload. %LV with LGE had a weak but significant negative linear correlation with $\Delta S' \times S'_{\text{base}}$ at 50W in the overall cohort. The linear correlation was more prominent in patients with LV outflow tract (LVOT) dynamic obstruction.

showed a significant inverse correlation with LV diastolic ($R=-0.369$, $P=0.012$; **Figure 3**) and systolic functional reserve indices ($R=-0.317$, $P=0.034$; **Figure 4**). Intra- and interobserver variability for DTI measurement were $5 \pm 3\%$ and $7 \pm 4\%$, respectively.

We additionally analyzed the changes in LV long-axis performance according to the location of LGE (ie, septal involvement of myocardial fibrosis), because we determined E' and S' only at the septal corner of mitral annulus. The augmentation of E' and S' during exercise (from baseline to 50W workload) was significantly blunted in patients who had LGE at the interventricular septum ($n=32$) than in patients without septal myocardial fibrosis ($n=14$; $P=0.001$ for E' and $P=0.030$ for S').

Discussion

We investigated the relationship between the extent of LGE on CMRI and LV functional reserve during exercise in patients with HCM and found that the augmentation of LV longitudinal function during exercise was more blunted in patients who had a larger extent of LGE. In addition, the magnitude of augmentation in LV long-axis movement was inversely correlated with the extent of LGE. The present study is the first to demonstrate the relationship between the burden of myocardial scar, non-invasively assessed on CMRI, and LV longitudinal functional reserve during exercise in patients with HCM.

Impaired Diastolic and Systolic Function in HCM

The cardinal pathophysiologic feature of HCM is diastolic dysfunction, which is seen in the majority of HCM patients.²⁰ Not only the diastolic function but also myocardial contractile property are known to be reduced in HCM, despite normal LVEF. Interestingly, even in the subclinical stage, mutation carriers have been found to have impaired myocardial relaxation and contractile property in the absence of myocardial hypertrophy.^{21,22} The assessment of LV long-axis movement is superior to classic echocardiographic parameters such as

LVEF because it is load independent and reflects subendocardial fiber function. The contraction and relaxation of LV are abnormal not only at rest²³ but also during exercise¹¹ in HCM. We have shown that LV longitudinal functional reserve was reduced in HCM patients when compared with age- and sex-matched normal control subjects¹¹ by assessing mitral annular velocity during exercise using DTI. The underlying histopathological substrate responsible for the abnormal LV functional reserve during exercise in HCM, however, is still unclear. The present results suggest that the extent of myocardial fibrosis may represent a pathological substrate which determines LV performance during exercise in patients with HCM.

Myocardial Fibrosis and LV Longitudinal Functional Reserve in HCM

Myocardial scarring has been considered in part to reflect the long-term consequence of myocyte death and replacement collagen accumulation as a repair process,²⁴ and thus the presence and the extent of LGE on CMRI have been reported to be associated with systolic and diastolic dysfunction in HCM patients.^{2-4,25} But even though LGE is regarded as a determinant of LV dysfunction in HCM, the relationship between the extent of LGE and the degree of LV dysfunction assessed at rest is relatively weak.^{3,8,26} In contrast, several current CMRI studies have nicely shown the correlation between LGE and impaired LV longitudinal function in patients with different kinds of cardiomyopathy.²⁷⁻²⁹ In the present study, we have further shown that the extent of myocardial fibrosis affects myocardial function during exercise in HCM patients. Although LV longitudinal movement was more depressed in patients with a larger volume of LGE even at rest, the augmentation in LV longitudinal function was more blunted in patients with a larger extent of LGE. The difference between group 1 and group 2 became greater as the intensity of exercise increased. The present results suggest that the presence and the extent of myocardial fibrosis may be determinants of exertional LV functional reserve in patients with HCM.

LGE on CMRI in Patients With HCM: Clinical Perspectives

In HCM, characteristic histological changes such as myocardial fibrosis, small vessel disease, and myocardial disarray are seen, which ultimately result in non-compliant LV and significant diastolic dysfunction. Moon et al have shown that regions of myocardial LGE on CMRI represent regions of increased myocardial collagen, which is a major component of myocardial fibrosis, but not disarray on histology of an explanted heart from an HCM patient.⁶ Therefore, CMRI with LGE is considered to be a robust imaging modality to quantitatively measure myocardial scar burden in various cardiac diseases including HCM. Previous investigations in ungenotyped HCM patients have shown a good correlation between the extent of LGE and both the clinical risk of sudden cardiac death and the presence of heart failure,^{5,30,31} and thus it was subsequently proposed as a prognostic factor.^{5,9,26} Based on the present results, we suggest that the extent of LGE on CMRI is a determinant of LV performance during exercise in HCM patients and that changes in LV long-axis movement may serve as a clinically useful complimentary tool to assess the early pathophysiologic changes in LV systolic or diastolic function, which are influenced by the burden of myocardial fibrosis.

Study Limitations

First, the current investigation had a small sample size, and the present subjects may not represent all HCM patients because Yonsei University Hospital is a tertiary referral center. Second, it would have been better to evaluate regional myocardial performance and changes during exercise with strain analysis, although it has technical limitations, particularly during faster heart rate with exercise. Third, some of the present patients had LVOT dynamic obstruction, which may have affected the loading condition of LV and the changes in LV longitudinal performances during exercise. The proportion of patients with LVOT dynamic obstruction, however, was not different between the 2 groups (22% vs. 22%, respectively), and, thus, its influence may not have been significant. Finally, although it would be better to evaluate the potential association between the severity of LVOT obstruction, instead of presence of LVOT obstruction, and burden of myocardial scar as in a recent study by Biagini et al,³² we did not have sufficient data for quantitative analysis of LVOT flow velocity during exercise for all patients.

Conclusion

Augmentation of LV longitudinal function during exercise is more blunted in HCM patients with greater extent of LGE on CMRI. The extent of myocardial fibrosis may represent a pathologic substrate that determines LV longitudinal functional reserve during exercise in patients with HCM.

Acknowledgments

We would like to thank the Research Affairs Department of Yonsei University College of Medicine for excellent assistance in statistical analysis. This work was supported by a grant from the Korean Science and Engineering Foundation (M10642120001-06N4212-00110).

Disclosures

None.

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