Original Article

Systolic Global Longitudinal Strain: A Novel Predictor of Myocardial Fibrosis Extent in Patients with Hypertrophic Cardiomyopathy

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Abstract

Introduction: Myocardial fibrosis is a marker of adverse prognosis in hypertrophic cardiomyopathy (HCM). It can be assessed with cardiac magnetic resonance (CMR) using late gadolinium enhancement (LGE) as a gold standard. New echocardiographic parameters have ability to determine degree of myocardial fibrosis in patients with coronary heart disease. However, the relationship between these two imaging methods in identifying myocardial fibrosis in patient with HCM is still limited

Objectives: To evaluate the correlation of peak systolic global longitudinal strain (GLS) using 2D-speckle tracking echocardiogram (2D-STE) and the extent of LGE by CMR.

Methods: Adult patients with diagnosis of HCM at Thammasat University Hospital during January 2011 to December 2020 were identified if both comprehensive echocardiogram and CMR studies were performed less than 1 year apart. Standard echocardiographic parameters including GLS by 2D-STE were retrospectively measured. %LGE by CMR ≥15% was defined as extensive LGE.

Results: Ninety-six patients with HCM were included (age = 67 ± 14, female 54%, GLS -14.2 ± 3.7%, extensive LGE 37.5%). GLS and maximal LV wall thickness were significantly correlated with %LGE in univariate analysis (r = 0.526, $P \leq .001$ and r = 0.431, $P \leq .001$, respectively). In multivariate linear regression analysis, both were independent predictors of %LGE (standard coefficient 0.418, $P = .002$ and standard coefficient 0.309, $P = .017$, respectively). GLS was an independent predictor of extensive LGE [(OR 1.2 (95% CI 1.04 - 1.46)*,* $P = .013$]. ROC analysis of GLS had demonstrated a best cutoff of -15% for prediction of extensive LGE (AUC of 0.68, sensitivity 74%, specificity 53%)

Conclusions: GLS was independently correlated with extent of LGE. 2D-STE strain analysis may be a potential tool for initial risk stratification in HCM.

Keywords: Hypertrophic cardiomyopathy, Myocardial fibrosis, Cardiac magnetic resonance (CMR) imaging, Global longitudinal strain

Volume 2023, Issue 1, Page 59-68

https://asianmedjam.com/

Received: 29 March 2022 **Revised: 1 November 2022** **Accepted: 14 November 2022**

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Introduction

Hypertrophic cardiomyopathy (HCM) is one of common genetic heart diseases in clinical practice with estimated prevalence of 1 in 500 in general population.[1] It's inherited in autosomal dominant pattern. HCM is structurally associated with LV systolic and diastolic dysfunction, dynamic LV outflow tract or intra-cavitary obstruction leading to reduced functional capacity and symptomatic heart failure. Furthermore, it has increasing risks of atrial fibrillation (AF), ventricular arrythmias (VA). Hence, patients with HCM can present with syncope or even sudden cardiac death (SCD). HCM is also the most common cause of SCD in young athletes.[2]

Primary prevention of SCD is essential strategy in HCM patients care. The current standard guidelines[3-5] have provided clinical risks of SCD in HCM as followings; family history of SCD, unexplained syncope, massive LVH, LVEF <30%, LV apical aneurysm, non-sustained VT and presence of extensive left ventricular myocardial fibrosis on cardiac magnetic resonance imaging (CMR). These factors are major determinants for consideration of implantable cardioverter defibrillator (ICD) implantation.[4,5] In addition to clinical assessment and diagnosis of HCM, CMR also provides information about degree of myocardial fibrosis (i.e. late gadolinium enhancement -LGE) and is an emerging tool for SCD risk stratification in HCM. Percent of LGE(%LGE), quantified to percentage of total LV myocardial mass or volume, is associated with increasing risk of SCD, ventricular arrhythmias (VA) and heart failure.[6-9] Presence of LGE in patients with HCM has 3.6X higher risk of SCD. Every 10-point of %LGE increased is associated with 1.36X higher risk of SCD.[8] The %LGE more than 15 has been defined as extensive LGE since the risk of SCD is markedly increased and ICD should be considered.[7,10] Unfortunately, few HCM patients were referred for CMR study due to limited accessibility, availability or financial issues.

Echocardiography, a standard frontline investigation in HCM,[5] provides important information about geometry and function as well as mechanics of diseased heart. With new imaging techniques such as 2D speckle-tracking echocardiography (2D-STE), LV myocardial deformation during systole can be determined using parameter of peak systolic global longitudinal strain (GLS). The GLS has ability in detecting subtle LV systolic dysfunction and myocardial fibrosis due to coronary heart disease. However, knowledge gap exists as the correlation of GLS and degree of myocardial fibrosis in patients with HCM are limited to small studies.[10-16] We specifically aimed to assess 1) the correlation of GLS and %LGE and 2) predictive value of GLS for extensive LGE (>15%).

Methods

Study Population

Adults patients with HCM at Thammasat University Hospital during January 2011 to December 2020, were identified from CMR database and reviewing medical records, by both echocardiogram and CMR studies were performed less than 1 year apart. Inclusion criteria were age more than 15 years, diagnosed with HCM based on CMR study, defined by LV wall thickness equal or more than 15 mm in one or more LV myocardial segments that is not explained solely by abnormal loading conditions. In lesser degree of LV thickness (13 - 14 mm), diagnosis of HCM required other findings such as septal to free wall thickness ratio more than 1.3 and the presence of abnormal papillary muscle or mitral valve apparatus typical seen in HCM. We included all subtypes of HCM.

Patient was excluded if any of followings was present; post-septal myectomy or septal alcohol ablation, moderate or severe degree any valvular heart disease or presence of prosthetic heart valve, congenital heart disease, previously received systemic chemotherapy or thoracic radiation therapy and patients with significant coronary artery stenosis (>50% coronary artery stenosis on coronary angiogram/CTA coronary or ischemic scar pattern on CMR) and suboptimal echocardiographic study. The latter included suboptimal echocardiographic view, high resting heart rate (>70/min), poor or incomplete standard apical view.

The study protocol was approved by the Ethics Committee of Faculty of Medicine, Thammasat University.

Cardiac Magnetic Resonance Protocol and Image Analysis

CMR was performed using Philips and Siemens 1.5-T scanner [Philips Achieva -Philips Healthcare, Best, The Netherlands] or Siemens Magnetom Aera [Siemens Health Care, Erlangen,

Germany] using steady-state, free-precession (SSFP) breath-hold cines in short-axis slices from base to apex of LV and 3 long-axis planes with ECG-gating. LGE image was acquired 10 - 20 minutes after intravenous administration of 0.2 mmol/kg Gadolinium-DTPA with breath-hold 2-dimensional segmented phase-sensitive inversion-recovery sequences in identical planes as cine images. The LV volume, LV mass, and EF were measured by the commercial software (syngo.via VB30A). LV endocardial and epicardial borders on cine images were semi-automatically planimetered to define the myocardium with excluding papillary muscles.

LV short-axis stack of LGE images was analyzed by manually adjusting a gray-scale threshold to define area of visually identified LGE. These areas were summed to obtain a total volume of LGE, then expressed as a total LV myocardium (% LGE). Visual quantitation method used gray-scale threshold method of >6 SDs exceeding the mean of normal myocardium. The value of high gray-scale threshold >6 SDs has been well validated by histopathology and provided the best total fibrosis burden as shown in prior studies.[17,18] Quantification of LGE was performed by using the same commercial software to manually trace area of LGE with >6 SDs on sequential short-axis slices (8 mm of thickness) at end-diastole from base to apex of LV, then expressed as total LGE volume and percentage of LGE per total LV myocardial volume (as % LGE). Extensive LGE was defined as LGE% ≥15%.[5, 7] All CMR data was analyzed by 1 experienced CMR specialist (I.A.) blinded from echocardiographic results. Figure 1 shows two representative examples of two-dimensional speckled tracking echocardiography in apical four-chamber view with bull's eye map of longitudinal strain and LGE measured with cardiac MR in short axis cardiac view.

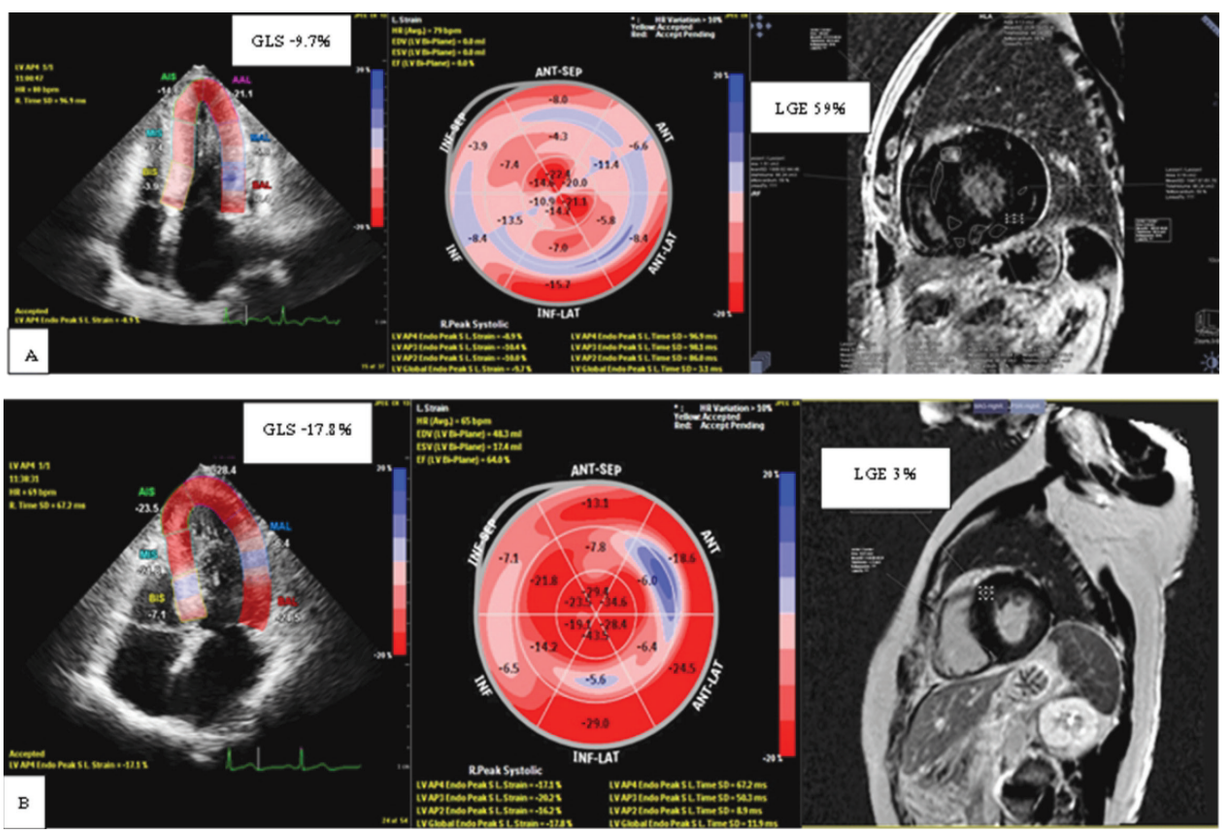

Figure 1 Example of two-dimensional speckled tracking echocardiography in apical four-chamber view with bull's eye maps of longitudinal strain and LGE measurement in short axis view. Large amount of LGE (A) and small amount of LGE (B) were depicted. Abbreviations as in Table 1.

Table 1 Clinical characteristics of HCM subjects

	Total N = 96	**Non-extensive %LGE** N = 60	**Extensive %LGE*** N = 36	***P*-value****
Age (years)	67.9 ± 13.9	69.2 ± 14.0	63.8 ± 11.5	.055
Female (%)	52 (54)	38 (63)	14 (39)	.034
HT (%)	66 (69)	45 (75)	21 (58)	.113
DM (%)	21 (22)	15 (25)	6 (17)	.447
AF (%)	20 (21)	14 (23)	6 (17)	.605
History of VA (%)	3 (3)	0 (0)	3 (8)	.050
History of syncope (%)	2 (2)	2 (3)	0 (0)	.526
LV mass index (g/m^2)	148 ± 55	141 ± 48	158 ± 64	.154
LVEDd (cm)	4.8 ± 4.1	5.0 ± 5.2	4.5 ± 0.8	.521
LVESd (cm)	2.5 ± 0.9	2.6 ± 0.9	2.5 ± 0.9	.648
LV maximal wall thickness (cm)	1.8 ± 0.4	1.7 ± 0.3	1.9 ± 0.5	.020
LVEF (%)	67 ± 9	68 ± 9	66 ± 9	.243
E/A	1.0 ± 0.7	1.0 ± 0.7	1.1 ± 0.7	.551
Septal E velocity (cm/s)	5.0 ± 2.8	5.1 ± 3.3	4.8 ± 1.9	.636
Lateral E velocity (cm/s)	6.1 ± 2.2	6.2 ± 2.2	6.0 ± 2.3	.601
Average E/e’	17.0 ± 7.1	16.8 ± 6.8	17.2 ± 7.7	.800
LAVI (ml/m^2)	49 ± 28	44 ± 18	59 ± 38	.058
LV intra-cavitary with PG ≥ 30 mmHg (%)	17 (18)	11 (18)	6 (17)	1.000
Apical HCM (%)	9 (9.4)	5 (8)	4 (7)	.724
LV aneurysm (%)	3 (3.1)	1 (2)	2 (6)	.554
GLS (%)	-14.2 ± 3.7	-15.2 ± 3.4	-12.7 ± 3.7	.030
LGE% (%)	15.9 ± 14.9	7.8 ± 3.4	29.5 ± 16.9	N/A

Data given as mean±SD or n (%).
*Extensive LGE = %LGE ≥15%. **The *P*-value comparison between non-extensive LGE and extensive LGE group.
AF, atrial fibrillation; DM, diabetes mellitus; HT, hypertension; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LV, left ventricular; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; PG, pressure gradient; VA, ventricular arrhythmias; E, early diastolic mitral flow velocity; A, mitral flow velocity during atrial contraction; e’, peak early diastolic mitral annular velocity; GLS, peak systolic global longitudinal strain; N/A= not applicable.

Transthoracic Echocardiography and Speckled Tracking Echocardiography

We retrospectively reviewed echocardiographic studies using iE33 ultrasound machine (Philips Medical Imaging, Andover, MA). Standard two-dimensional, Doppler and M-mode echocardiographic measurements were thoroughly assessed. Geometry and function of left ventricle (LV) and left atrium (LA) were measured to derived LV dimensions/volumes LV mass index, maximal LV wall thickness, LVEF (Simpson’s method). LV diastolic parameters were obtained (MV inflow E and A velocities, medial and lateral tissue Doppler velocities and left atrial volume index-LAVI). Tricuspid annulus systolic excursion (TAPSE), maximal TR velocity, maximal resting LVOT or intracavitary gradient were recorded. Significant resting LVOT or intra-cavitary gradient defined as pressure gradient >30 mmHg. All mentioned parameters were previously measured according to standardized protocol of Thammasat echocardiography lab.

Two-dimensional LV GLS by speckle-tracking echocardiography was obtained by averaging GLS data from three standard apical views (i.e. three-, four and two-chamber view) and 16

LV-segment model according to standard recommendation[19]. This strain analysis was performed semi-automatically on Xcelera workstation (QLAB11, Philips). Peak systolic global longitudinal strain (GLS) was defined as the highest averaged strain value (absolute) during systole (before aortic valve closure). Reproducibility tests of GLS analysis were performed at different time frame (2-week apart) by 2 independent researchers (A.B. and P.W.) and blinded from CMR results to obtain inter-observer and intra-observer variability.

Statistical Analysis

Data were expressed as mean and standard deviation or frequency (%) and between-group comparison with student t-test or Fisher's exact test as appropriate. Correlations between echocardiographic parameters and %LGE were assessed with Pearson's correlation and observed for collinearity. Univariate logistic regression analysis was used to identify echocardiographic predictor for extensive LGE. Multivariable logistic regression analysis was then performed with independent parameters including age and only echocardiographic variables with $P < 0.1$ from previous univariate analysis. This was to find the independent predictor for extensive LGE. Receiver operator characteristic (ROC) curve was created to obtain optimal cut-off value and its sensitivity and specificity for extensive LGE. The inter-observer and intra-observer analysis for GLS measurement were expressed as the coefficient of variation. Statistical analyses were performed using SPSS 26.0 software. Two-sided values of $P < .05$ were considered statistically significant.

Results

Clinical Characteristics of Studied Population

Patient clinical characteristics were summarized in Table 1. Ninety-six HCM patients were included (mean age 67 ± 14 years, female 54%). Hypertension and diabetes were present in 68.8% and 21.9%, respectively. Prevalence of atrial fibrillation was 20.8%. Three patients had history of ventricular arrhythmias (2 NSVT and 1 VT arrest) and 2 patients had history of syncope.

Important echocardiographic data were as follows; LVMI 148 ± 55g/m^2, maximal LV wall thickness was 1.75 ± 0.4 cm. LVEF was 67 ± 9%. Averaged E/e' was 17 ± 7 and LAVI was 49 ± 28 ml/m^2. Significant LV intra-cavitary pressure gradient was found in 17 patients (18%). Nine patients had apical type HCM. Averaged GLS of the whole group was low (-14.2 ± 3.7%).

LGE by CMR was present in all patients. Mean %LGE was 15.9± 14.9%. Extensive %LGE was observed in 36 patients (37.5%).

Correlations Between Echocardiographic Parameters and Extent of LGE

GLS and LV maximal wall thickness but not other echocardiographic parameters were modestly correlated with %LGE (r = 0.526, $P < .001$ and r = 0.431, $P < .001$, respectively) (Table 2). No collinearity was observed between GLS and LV wall thickness. Multivariate linear regression analysis among these two parameters and age had shown that GLS was more predictive of %LGE (standard coefficient = 0.418, *P*-value = .002) than LV maximal thickness (standard coefficient = 0.309, *P*-value = .017).

Predictors for Extensive LGE

Clinical characteristics of non-extensive and extensive LGE groups were shown in Table 1. History of VA was only observed in Extensive LGE. Mean %LGE in extensive LGE and non-extensive LGE groups were 29.5 ± 16.9% and 7.8 ± 3.4%, respectively. For between-group comparisons, patients in extensive LGE group had higher maximal LV wall thickness (1.9 ± 0.5 cm vs. 1.7 ± 0.3 cm, $P = .02$) and significantly reduced GLS (-12.7 ± 3.4% vs. -15.2 ± 3.4%, $P = .03$).

In univariate logistic regression analysis, both GLS and LV maximal wall thickness were significant predictors for extensive LGE (Table 3). However, only GLS was an independent predictor for extensive LGE in multivariate logistic regression analysis when adjusted with age, sex, HT, and DM.

GLS as a Screening Tool for Extensive LGE

GLS had an area under the receiver operating characteristic (AUROC) of 0.680 ($P = .007$) (Figure 2). The best GLS cut-off value for prediction of extensive LGE was -15% (sensitivity 74% and specificity 53%).

Reproducibility of GLS Measurement

We randomly selected 10 patients (around 10% of total studied population) to assess

variability of GLS measurement. The variabilities were assessed by the difference and percent difference between the two measurements along with their 95% limit of agreement (LOA). The intra-observer variability for GLS was 0.5% (95% CI -0.3 to 0.6%) (95% LOA -0.5 to 1.1%). The inter-observer variability for GLS was 0.9% (95% CI -0.2 to 1.3%) (95% LOA -0.7 to 1.4%).

Table 2 Correlation between each echocardiographic parameter and %LGE

Echocardiographic parameters	**r**	***P*-value**
LV mass index	0.205	.054
LV maximal wall thickness	0.431	<.001
LVEF	-0.188	.071
Septal E velocity	-0.009	.932
Average E/e’	0.144	.178
LAVI	0.071	.601
GLS	0.526	<.001

Abbreviations as in Table 1.

Table 3 Echocardiographic parameters and prediction of extensive LGE

	Univariate logistic regression		**Multivariate logistic regression**	
	OR (95%CI)	***P*-value**	**OR (95%CI)**	***P*-value**
LV mass index	1.01 (0.98 - 1.0)	.160		
LV maximal wall thickness	5.2 (1.6 - 16.9)	.007	3.2 (0.8 - 13.8)	.117
LVEF	0.9 (0.96 - 1.01)	.241		
Septal E velocity	0.9 (0.8 - 1.1)	.636		
Average E/e’	1.0 (0.9 - 1.1)	.797		
LAVI	1.0 (0.9 - 1.0)	.087		
GLS%	1.2 (1.1 - 1.4)	.006	1.24 (1.05 - 1.46)	.013

Abbreviations as in Table 1. Multivariate logistic regression adjusted with age, sex, HT, and DM

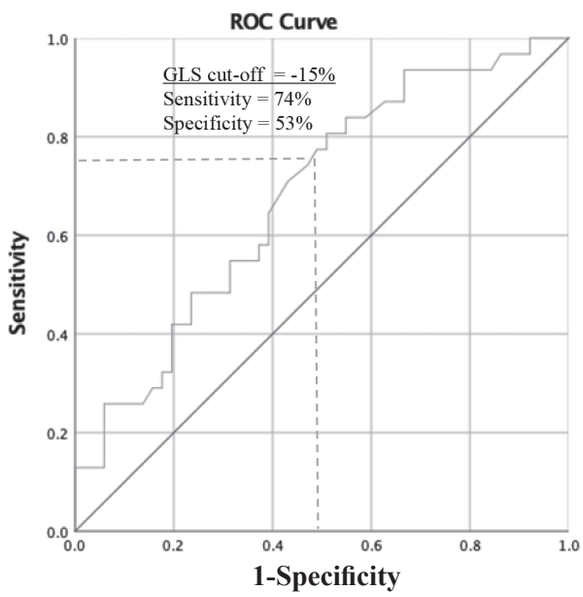

Figure 2 ROC curve of GLS for prediction of extensive LGE.
AUROC = 0.680 [95%CI 0.562 - 0.797] (*P* = .007)

Discussion

We have demonstrated that GLS and LV maximal wall thickness were both significantly correlated with extent of myocardial fibrosis (%LGE). Furthermore, only GLS was an independent predictor for extensive LGE.

Myocardial fibrosis is a hallmark finding in HCM. Mechanism of myocardial fibrosis in HCM is not well established. Premature death of cardiomyocyte may be common final pathway. It is caused by sarcomere gene mutations, microvascular dysfunction due to small vessel disease or mechanic effect of intracavitary obstruction.[23] Myocardial fibrosis in HCM is arrhythmogenic and associated with higher risk of SCD and heart failure.[7,24-26] It can be non-invasively detected with LGE CMR imaging which has been well validated with myocardial pathology.[18] The prevalence of LGE and extensive LGE were in range of 33 - 86% and 8 - 24%, respectively.[8,20-22] Presence of extensive LGE (i.e. LGE ≥15% of LV mass) in HCM had shown to increase SCD risk by 2-fold in patients who were considered to be at lower risk by other clinical factors.[7] In our study, LGE was present in all patients. Of these, thirty-six patients (37.5%) had extensive LGE. The latter were at higher risk of future cardiac event. Possible explanations of high prevalence of LGE in our study are relatively older patients and higher co-morbidities (mean age of 67 years, HT 69%, DM 22%, and AF 21%). The largest meta-analysis of LGE-HCM study (n = 2,993) had a mean age of 55 years, 6-13% with diabetes and AF 3-16% with AF.[8]

The pattern of LGE in HCM is non-specific with patchy mid-wall and non-coronary distribution. It's often found at RV insertion point and in hypertrophic segments. Severity of LV wall thickness was related with increased %LGE.[20] Our study was in accordance with these findings as increasing LV thickness was associated with degree of %LGE.

Presence of LVH, myocardial disarrays and fibrosis results in diastolic dysfunction in HCM. In our study, the medial and lateral mitral annulus velocities and other diastolic parameters including LAVI, mitral E/A were mostly abnormal. LVOT or intracavitary pressure gradient is dynamic and not only influenced by LV wall thickness but also heart rate, loading condition and abnormal mitral valve apparatus. Therefore, these conventional echocardiographic parameters had limited role in predicting wide-range of %LGE (fibrosis).

Global longitudinal strain (GLS), a new parameter of myocardial deformation, derived from two-dimension speckle tracking echocardiogram (2D-STE) has been demonstrated as a sensitive tool to detect subtle LV systolic dysfunction despite normal LVEF.[27-29] LVEF is not a good parameter for systolic function in HCM as it is usually maintained until patients reach advanced stage of disease. Our study had shown that GLS in HCM was significantly correlated with %LGE, even adjusted with LV wall thickness and LVEF. These findings were in line with prior studies that GLS varied with degree of myocardial fibrosis and independent of regional LV wall thickness.[14]

The latest HCM clinical guideline[5] has given an important role of LGE quantified by CMR in SCD risk stratification. It suggests that ICD should be considered if extensive LGE is present. Several previous studies had attempted to predict extensive LGE by using conventional echocardiographic and clinical parameters. However, the results were less satisfactory or inconsistent. A group of researchers had shown that reduced LVEF, LV pressure gradient < 30 mmHg, and increased LV maximal wall thickness were independent factors associated with extensive LGE (defined as extent LGE ≥ 4/17 in LV 17-segment model).[30] Another study proposed LGE-Score including LVEF, history of non-sustained ventricular tachycardia, atrial fibrillation, LV maximal wall thickness and significant LVOT to predict extensive LGE.[21] We have demonstrated in our study that GLS was correlated with degree of LGE and more importantly, an independent predictor of extensive LGE. In addition, GLS (as a strong predictor of %LGE) was associated with subsequent cardiac events (unexpected death, fatal arrhythmias, and hospitalization) in a recent study.[29] We selected a GLS cut-off point less than 15% (absolute number) which had the sensitivity 74% and the specificity 53% for extensive LGE in our patient population. This GLS cut-off value is reasonably appropriate when considered with other clinical parameters such as LV wall thickness. It may be used as initial risk stratification during assessment of patient with HCM.

GLS was independently correlated with extent of LGE. Routine integration of 2D-STE strain analysis into standard 2D echocardiography may play an important role for initial risk stratification in patients with HCM.

Study Limitations

First, this study was a retrospective design and relatively small number of patients. The latter was partly due to exclusion of some patients with limited 2D-echo image quality and missing data. Second, GLS by 2D-STE was affected by age of patients, heart rate and loading conditions (preload, afterload). However, with careful and thorough reviews of echocardiographic study, this limitation was reduced. As GLS measurement is semi-automated, the author has practiced procedure with an expert to assure best GLS analysis as later shown as having good reproducibility. Third, compared with previous studies, present study had high prevalence of LGE in HCM. This was likely due to selection bias as we identify case of HCM with CMR study. However, it's provided an opportunity to study GLS specifically in patient with extensive LGE. Although time difference between cMR study and echocardiogram was allowed to the maximum of 1-year, actual difference was only 4 months. This was unlikely to have significant impact on both cMR and echocardiographic measurement.

Clinical Implications

CMR is the current gold standard for LGE assessment. However, the main limiting factors of CMR procedure are its availability, duration of study and cost. As our study has shown that GLS was related to extensiveness of %LGE, it should be a routine measured parameter during echocardiographic study in patient with HCM. This may help in selecting patients who are at high probability of severe myocardial fibrosis to receive prioritized proper management.

Acknowledgments

Financial support. This study was supported by Faculty of Medicine, Thammasat University, Thailand.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

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