Iranian Heart Journal; 2020; 21 (4)

Original Article

Incremental Values of Cardiac Mechanics in Systolic and Diastolic Heart Failure in Hypertrophic Cardiomyopathy

Anita Sadeghpour[1], MD; Nasrin Ghadakkar[1*], MD; Behshid Ghadrdoost[1], PhD; Hooman Bakhshandeh[2], MD; Hamid Reza Pouraliakbar[3], MD; Mohammad Mehdi Peighambari[3], MD; Nahid Rezaeian[2], MD

ABSTRACT

Background: The early diagnosis of heart failure in patients with hypertrophic cardiomyopathy (HCM) remains a challenge. In this study, we sought to evaluate cardiac mechanics in patients with HCM.

Methods: Sixty patients (60% men, mean age = 45.8 ± 17 y) with documented HCM were identified from an ongoing clinical registry.

Results: The values of maximal left ventricular (LV) wall thickness, the ejection fraction (EF), global the longitudinal strain (GLS), and the global circumferential strain (GCS) were 2.2 ± 0.5 cm, 54.1 ± 6.5%, −15.3 ± 4.5%, and −26.9 ± 7.5, consecutively. Cardiovascular magnetic resonance imaging (CMR) data on 34 patients were included in the analysis. Nearly half of the patients had obstructive HCM; and in comparison with nonobstructive HCM, there were no significant differences in terms of GLS, GCS, EF, and the New York Heart Association Functional Class (NYHA FC). EF was similar between the 2 NYHA FC groups (I and II vs III and IV). GLS had a meaningful difference between the NYHA FC groups. In patients with a late gadolinium enhancement (LGE) value of equal to or greater than 15%, EF, GLS, and GCS were correlated and reduced. Additionally, in those with an LGE value of between 5% and 15%, EF was preserved with a reduced GLS. GLS was worse in patients with an E/average E′ ratio of equal to or greater than 14.

Conclusions: Our study showed that an increased LV wall thickness and/or a reduced LV end-diastolic volume, with better GCS, maintained a normal EF despite a reduced GLS. GLS had a better correlation with NYHA FC and LGE in CMR than EF alone. ***(Iranian Heart Journal 2020; 21(4): 43-59)***

KEYWORDS: Hypertrophic cardiomyopathy, Strain, Late gadolinium enhancement

[1] Echocardiography Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
[2] Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Science, Tehran, IR Iran.
[3] Heart Valve Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.

***Corresponding Author:** Nasrin Ghadakkar, MD; Echocardiography Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
Email: drghadakkar@gmail.com **Tel:** +989128162435

Received: September 17, 2019 **Accepted:** December 23, 2019

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy (about 1/200 in the general population) and is associated with increased cardiovascular morbidity and mortality. Particularly, patients with HCM experience more frequent sudden cardiac death and death because of heart failure (HF).[1, 2]

Nevertheless, risk stratification in patients with HCM remains a formidable challenge. The current approach toward risk stratification in patients with HCM is mainly focused on sudden cardiac death due to ventricular arrhythmias and advocates for a combination of clinical and echocardiographic parameters. [3, 4] Those parameters are, however, known to have limited sensitivity and specificity, particularly in predicting cardiovascular events other than sudden cardiac death (eg, HF-related morbidity and mortality). [4] Therefore, research has focused on identifying other potential indicators with a view to optimizing the management of patients suffering from HCM. [4-8] This is because the left ventricular ejection fraction (LVEF) cannot discriminate subclinical LV dysfunction from normal systolic function. Technological advances in echocardiography have bolstered the capacity of the longitudinal strain analysis for the early detection of LV contraction abnormalities in patients with a preserved EF. [9] HCM is associated with low values of regional and global longitudinal myocardial deformations. Increased wall thickness and/or a diminished LV end-diastolic volume can increase EF and, thus, maintain a normal EF despite reduced shortening. [10] Left ventricular global longitudinal strain (GLS) forms a part of the cardiac mechanic analysis and is known to be of higher prognostic values than LVEF in various cardiomyopathies. [11] Moreover, a few studies have posited that it may be a good independent prognostic indicator in patients with HCM. [12, 13]

Late gadolinium enhancement (LGE) by contrast-enhanced cardiovascular magnetic resonance imaging (CMR) is frequently observed in patients with HCM [14-16] and allows an in vivo quantification of myocardial fibrosis. [15,16] Previous studies have demonstrated that the extent of LGE is correlated with LV systolic and diastolic dysfunction as well as adverse cardiac events such as sudden cardiac death, fatal arrhythmias, and worsening HF in patients with HCM. [15] Some previous studies have also reported that regional myocardial strain and wall thickening are affected by regional myocardial fibrosis in patients suffering from HCM. [16, 17]

The present study aimed to evaluate cardiac mechanics through the measurement of GLS, left ventricular global circumferential strain (GCS), and EF, in addition to their relationship with LGE in CMR, among patients with HCM.

METHODS

Patient Population

The study population consisted of patients with HCM, defined according to the current guidelines: maximal wall thickness (MWT) of equal to or greater than 15 mm in the absence of any other cardiac or systemic diseases capable of producing a similar magnitude of hypertrophy confirmed by echocardiography or CMR. [4] Patients were identified from an ongoing clinical registry. The exclusion criteria were comprised of age under 16 years, poor image quality, a history of surgical septal myectomy, and septal alcohol ablation. Data were collected cross-sectionally in the Echo Lab of Rajaie Cardiovascular Medical and Research Center and included the following information: demographic characteristics, New York Heart Association Functional Class (NYHA FC), a history of hypertension, and the currently adopted risk factors for sudden

cardiac death (ie, unexplained syncope and a positive family history of sudden cardiac death at a young age [< 50 y] in the first- or second-degree relatives). Furthermore, comprehensive transthoracic echocardiography was performed in all the patients upon the first visit at the outpatient clinic.

The diagnosis of HCM was initially established via echocardiography and CMR imaging parameters based on the latest guidelines; however, CMR data were included if CMR had been performed within the recent year.

The study protocol was approved by the institutional review board, and informed written consent was obtained from all the patients.

Echocardiography

Standard transthoracic 2D echocardiography was performed using a commercially available ultrasound machine (Philips EPIQ 7). The images were digitally stored and analyzed offline (QLab software). LV volumes, LVEF, and left atrial volumes were measured via the Simpson method and indexed for the body surface area. [18] The septal and posterior wall thickness was measured in the parasternal long-axis view via the 2D method, while MWT was assessed in the short-axis view in 3 different levels of basal, mid, and apical. LV diastolic function was assessed mainly using peak pulsed Doppler velocities to determine the early (E) and late (A) diastolic flow across the mitral valve, the mitral inflow peak velocities of E divided by the peak early diastolic velocity (E′) of the septal and lateral mitral annuli via tissue Doppler imaging, yielding the E/average E′ ratio, the left atrial volume index, and the tricuspid regurgitation jet velocity. [19] Diastolic function was determined in only 46 (76.7%) patients, and the other 14 (23.3%) patients had more-than-moderate mitral regurgitation or atrial fibrillation rhythms, which precluded a precise estimation of diastolic function. The presence of systolic anterior movement of the mitral valve was assessed in the parasternal long-axis view, as well as the apical 3- and 5-chamber views. The resting peak gradient of the left ventricular outflow tract (LVOT) was quantified via continuous-wave Doppler. The presence and grade of mitral regurgitation were assessed through a multi-parametric approach in accordance with the existing guidelines. [20]

GLS was measured via the speckle-tracking analysis in the standard apical views (ie, 2-, 3-, and 4-chamber views), and GLS was measured via the speckle-tracking analysis in the standard parasternal short-axis views (ie, apical, mid, and base) acquired at a frame rate of 40 to 90 Hz (mean = 60 fps). The region of interest was automatically created and manually adjusted, when necessary, to fit the entire wall thickness. GLS and GCS were then calculated by averaging the peak longitudinal and circumferential strain in 17 segments separately from 6 different views (3 apical and 3 parasternal short-axis views).

Cardiovascular Magnetic Resonance Imaging and Image Analysis

CMR data were accepted provided that they had been obtained in our center within the 1-year period leading to the echocardiographic examinations (if the clinical situation did not change significantly during this indexed time). Accordingly, CMR data on 34 patients were included in our analysis. The CMR studies were performed using a Siemens MAGNETOM Avanto (Siemens, Germany) 1.5 T whole-body scanner with dedicated cardiac coils. Breath-hold cine images were acquired in multiple short-axis and long-axis views with steady-state free precession sequences. Images for LGE diagnostics were acquired 10 minutes after the injection of gadoterate meglumine (Dotarem; 0.2 mmol/kg) with breath-hold

segmented inversion-recovery sequences acquired in the same views as function views. In patients with cardiac arrhythmias, single-shot inversion recovery sequences were acquired. Ventricular coverage was achieved with contiguous 8-mm thick slices (no gap). The inversion time was individually acquired using a Look–Locker inversion-recovery sequence. The LV mass at end-diastole and the extent of the total enhanced volume (%LGE volume/total LV volume) were semi-automatically calculated on the basis of the Simpson rule using a workstation (CMR 42, Canada). Semiautomated algorithms identified high-signal intensity LGE pixels and the number of standard deviations above the mean signal intensity within a remote region containing normal "nulled" myocardium. In addition, the presence and myocardial wall distribution of LGE were visually analyzed in a 17-segment model according to previous reports. [21, 22] The LV mass was normalized to the body surface area. The myocardial tissue with LGE was defined as an area with a signal intensity of greater than 5 standard deviations from the mean of the remote myocardium.

Statistical Analysis

The continuous variables were expressed as the mean ± the standard deviation and/or the median (with the interquartile range) and compared using ANOVA (normal distributions) or the Mann–Whitney *U* test (non-normal distributions), as appropriate. The categorical variables were presented as absolute numbers and percentages. The differences in the baseline characteristics between the patients were assessed using the Student *t*-test, the Mann–Whitney *U*-test, or the χ^2 test, when appropriate. The receiver operating characteristic (ROC) curve was analyzed for some parameters in order to assess the best cutoff values of GLS in the study population, in addition to analysis according to the median value among the population of the study (−15.3%), while the normal cutoff value for the general population is about −18% for GLS and −22% for GLS. [23, 24] The cutoff values for all the echocardiographic data were determined in accordance with the recommendations of the latest guidelines. [18] A *P*-value of less than 0.05 was considered statistically significant. The statistical analyses were performed using the SPSS software, version 11.5, (SPSS Inc, Chicago, IL).

The intra- and interobserver agreements for strain measurements were tested in 10 randomly selected cases. The Pearson *r* was used to test the correlation, and the Bland–Altman plot was employed to assess the agreement between the observers. Kappa statistics were applied to test the consistency between readers and intraclass correlation coefficients for inter- and intraobserver variabilities.

RESULTS

Patient Population

Totally, 60 patients with a guideline-based diagnosis of HCM (60% men, mean age = 45.8 ± 17 y) were included. The demographic, clinical, and echocardiographic data of the study population are shown in Table 1 and Table 2. The mean EF was 54.1% ± 6.5%, the mean GLS was −15.3 ± 4.6%, and the mean GCS was −26.9 ± 7.5%. Among the patient population, 51.6% had LVOT obstruction (LVOT gradient > 30 mm Hg at rest or with provocative maneuvers), and 30% were hypertensive. Gender analysis showed a higher GLS absolute value in female patients than in their male counterparts (−16.6 ± 4.2% and −14.4 ± 4.6%; *P* = 0.05). In contrast, EF and GCS did not show significant differences between the 2 sexes (Table 1). Eight (13.3%) patients had a history of unexplained syncope; there was

no significant difference in terms of GLS between the patients with and without syncope (−15.5 ± 4.5% vs −15.3 ± 4.7%; *P* = 0.8). Forty-one (68.3%) patients had a positive family history of HCM; however, there were no meaningful differences apropos of GLS, GCS, and EF between the relatives (first- or second-degree) or the groups with a positive or negative family history.

Inter- and Intraobserver Variabilities

The Bland–Altman method showed no statistically significant differences between the measured GLS and GCS by 2 observers. The mean of the differences in GLS and GCS for the 2 observers was −0.5 ± 0.39 and −0.53 ± 0.38, respectively. The agreement between GLS and GLS measured by the 2 observers was as follows: intraclass correlation coefficient of 0.985 (95% CI: 0.946 to 0.983) and intraclass correlation coefficient of 0.974 (95% CI: 0.938 to 0.975), respectively.

The interobserver variabilities for GLS and GCS were measured by 2 echocardiologists. The results showed that the smallest intraobserver variabilities for GLS and GCS were an intraclass correlation coefficient of 0.93 (95% CI: 0.961 to 0.980) for GLS and an intraclass correlation coefficient of 0.92 (95% CI: 0.951 to 0.972) for GCS.

Clinical and Echocardiographic Data

Between the study groups, normal or increased GLS values were found in patients with EF of equal to or greater than 60% (Table 1 and Table 2). All 7 patients in the burned-out group (EF < 50%) had the worst GLS values (−12.5 ± 3.7%). After the exclusion of patients with atrial fibrillation rhythms and those who had more-than-moderate mitral regurgitation, the diastolic function of 46 (76.6%) patients was measured. No more result was obtained in a different GLS cutoff analysis according to the suggested cutoff point by the ROC curve. Still, the E/average E′ ratio, the tricuspid regurgitation velocity, and the left atrial volume index were determined as the markers of diastolic function in all the patients. The GLS analysis showed no more results in these groups. The exception was that the E/average E′ ratio was statistically meaningful in the GLS cutoff value of −11.5 (obtained from the ROC curve, with 70% sensitivity and 30% specificity). It means that most of the patients with an E/average E′ ratio of less than 14 had absolute GLS values of greater than −11.5 (*P* = 0.043).

When emphasis was placed upon GLS, GCS, EF, and NYHA FC, no statistically significant differences were observed between obstructive and nonobstructive HCM. Further, with respect to both the location of most of the hypertrophied segments (ie, basal, mid, and apical) and the different anatomic patterns of HCM (ie, reverse curvature, apical, and atypical), there were no significant differences in GLS, GCS, and EF.

Table 1: Demographic and clinical data of the study population

	Overall (N = 60)	Mean LVEF	*P*-value	Mean LVGLS	*P*-value	Mean LVGCS	*P*-value
Age, y	45.8 ± 17						
Gender, n(%)							
Male	36 (60)	54.4 ± 6.1	**0.8**	-14.4 ± 4.6	**0.05**	-26.5 ± 7.1	**0.67**
Female	24 (40)	53.8 ± 6.9		-16.6 ± 4.4		-27.1 ± 7.9	

HTN, n (%)							
Yes	18 (30)	53.3 ± 6.2	**0.65**	-15.3 ± 3.8	**0.9**	-26.4 ± 8.2	**0.8**
No	42 (70)	54.5 ± 5.9		-15.2 ± 5		-27.1 ± 7.5	
NYHA FC class, n %							
I, II	31 (51.7)	55.4 ± 4.8	**0.85**	-16.7 ± 4.7	**0.03**	-28.1 ± 7.5	**0.08**
III, IV	29 (48.3)	53.6 ± 5.7		-14.2 ± 2.6		-24.8 ± 7.2	
Unexplained syncope, n(%)							
yes	8 (13.3)	53.1 ± 4.9	**0.65**	-15.5 ± 4	**0.8**	-23.2 ± 7.4	**0.14**
no	52 (86.7)	54.3 ± 6.6		-15.2 ± 4.7		-27.4 ± 7.5	
Family history of HCM, n(%)	41 (68.3)						
First-degree	33 (80)	54.6 ± 6	**0.7**	-16.1 ± 3.8	**0.45**	-25.8 ± 6.8	**0.9**
Second-degree	8 (20)	53.6 ± 6		-13.3 ± 6.5		-28.5 ± 9.3	
None	19 (31.7)	54.8 ± 4.8		-15.5 ± 4.2		-28.4 ± 7.1	
Family history of SCD, n (%)							
Yes	3 (5)	54.1 ± 4.2	**0.8**	-15.1 ± 3.1	**0.7**	-25.3 ± 6.9	**0.5**
No	57 (95)	54.1 ± 6.7		-15.4 ± 4.5		27 ± 6.7	
ICD insertion, n (%)							
Yes	8 (13.3)	51.5 ± 6.8	**0.019**	-14.9 ± 3.6	**0.4**	-24.9 ± 7.8	**0.3**
No	52 (86.7)	54.8 ± 6.7		-15.6 ± 4.6		-27.2 ± 8.6	

LVEF, Left ventricular ejection fraction; LV-GLS, Left ventricular global longitudinal strain; LV-GCS, Left ventricular global circumferential strain; HTN, Hypertension; NYHA FC, New York Heart Association Functional Class; SCD, Sudden cardiac death; HCM, Hypertrophic cardiomyopathy; ICD, Implantable cardioverter-defibrillator

Table 2: Echocardiographic data

	Overall (N = 60)	Mean EF	*P*-value	Mean GLS	*P*-value	Mean GCS	*P*-value
LVEF (%)		54.1±6.5					
<50	7(11.7)			-12.4±3.7	**0.04**	-19.9±7.2	**0.017**
50-55	13(21.7)			-15.1±3.8		-25.1±6.8	
55-60	26(43.3)			-15.1±5.3		-28±7.8	
≥60	14(23.3)			-18±2.8		-30.2±5.7	
Maximal wall thickness	2.2±0.5						
<3	55(91.7)	55.6±4.4	**0.1**	-15.6±4.4	**0.02**	-26.4±6.7	**0.08**
≥3	5(3.3)	53.6±3.4		-11.8±3.5		-31.1±12	
LVEDI ml/m2	36.4±4.2						
Small	4(6.6)	55	**0.58**	-6.4±1.9	**0.01**	-23.3±2.6	**0.3**
Normal	56(93.4)	54±5.5		-15.8± 4.4		-27±7.5	
Diastolic dysfunction, n (%)	46(76.7)						
Mild	22(47.8)	54.9±6.4	**0.55**	-15.7±4.6	**0.7**	-28±7.6	**0.9**
Moderate	19(41.3)	52.9±5.2		-15.4 ±4.4		-27±7.1	
Severe	5(8.4)	53±3.2		-12.5±5.6		28.3±11.8	
TR velocity cm/s), n (%)	2.6±0.6						
<2.8	40(66.7)	54±6.8	**0.4**	-15±4.8	**0.56**	-26.8±8.1	**0.98**
≥2.8	20(33.3)	54.6±5.6		-15.8± 4.3		-26.9±6.4	

LAVI cc/m^2, n (%)	42.1±10.2						
<34	16(26.7)	55.7±3.2	**0.008**	-15.2±3.6	**0.6**	-24±4.5	**0.1**
34-42	16(26.7)	54.6±5.5		-15±4.2		-29 ± 7.2	
42-48	14(23.3)	49.9±4.4		-15.6±3.6		-26.5±8.3	
≥48	14(23.3)	45.3±5.6		-15.2±3.8		-28.1±7.4	
E/average e' #	14.2±3.6						
<14	26(43.3)	54.2±6.1	**0.6**	-16.7±4.6	**0.1**	-27.5±9.6	**0.46**
≥14	34(56.7)	53.8±5.7		-14.2±6.8		-26.1±8.4	
Obstructive vs non obstructive, n (%)							
Obstructive	31(51.6)	54.3±5.7	**0.29**	-15.4±4	**0.8**	-26.9±8.2	**0.9**
Nonobstructive	29(48.4)	54±6.4		-15.2±5.2		-26.9±7	
LVOT G (mm Hg) in the obstructive group	69±9.7						
30-50	1(3.2)	55	**0.6**	-8	**0.39**	-22.7	**0.7**
50-100	26(83.9)	54.5±5.8		-15.8±3.3		-27.6±9.4	
≥100	4(12.9)	53±5.2		-15.8±1.3		-22.7±5.3	
MR, n (%)							
<Moderate	37(61.7)	53.1±6.5	**0.2**	-15.8±4.1	**0.33**	-28.7±9.6	**0.44**
≥Moderate	23(38.3)	50.3±6.2		-14.4±3.1		-23.9±8.5	
GLS (%)	-15.3±4.5						
<15.3	24(40)	51.4±7.4	**0.05**			-26.2± 9.5	**0.85**
≥15.3	36(60)	55.9±4.9				-27.1±7.6	
GCS (%)	26.9±7.5						
<26.9	28(46.7)	51.4±4.7	**0.017**	-13.2±4.6	**0.05**		
≥26.9	32(53.3)	55.9±5.5		-16.8±3.5			
Type of anatomic HCM							
Reverse curvature, n (%)	52(86.6)	54.2±7.5	**0.53**	-15.1±3.5	**0.48**	-27.8±8.6	**0.6**
Apical, n (%)	7(11.7)	52.1± 5.6		-15.9±1.7		-25.7±6.9	
Atypical, n (%)	1(1.7)	56		-15.3		-28	
Most hypertrophied segment location							
Basal, n (%)	26(43.3)	54.5±4.6	**0.2**	-15.5±5.6	**0.6**	-26.9±8.1	**0.54**
Mid, n (%)	27(45)	54.3±5.7		-14.9±4		-27.1±8.5	
Apical, n (%)	7(1.7)	52.1±5.6		-15.9±1.7		-25.7±6.9	
LGE (%)							
≥15	4(6.7)	41.2±11	**0.08**	-12.7±3.1	**0.29**	-13.2±1.7	**0.03**
5-15	6(17.6)	54.8±3.1		-13.9±6.3		-28.6±10.8	
<5	24(70.7)	55.1±5.6		-15.9±3.8		-26.9±6.1	

LVEF, Left ventricular ejection fraction; LV-GLS, Left ventricular global longitudinal strain; LV-GCS, Left ventricular global circumferential strain; HTN, Hypertension; NYHA FC, New York Heart Association Functional Class; SCD, Sudden cardiac death; HCM, Hypertrophic cardiomyopathy; LVEDVI, Left ventricular end diastolic volume index; TR, Tricuspid regurgitation; LAVI, Left atrial volume index; LVOT G, Left ventricular outflow tract gradient; MR, Mitral regurgitation; LGE, Late gadolinium enhancement

E/ average e' was not statistically meaningful for the mean GLS, but it had a significant difference with a GLS cutoff value of -11.5% (*P* = 0.046).

DISCUSSION

In the present study, we found that GLS had an incremental value in determining subclinical systolic dysfunction in patients with EF of between 50% and 60%. Those with EF of 60% or greater had near-normal GLS (−18 ± 2.7%), and patients who had burned-out HCM had reduced EF and absolute values of GLS. Still, in patients with EF of between 50% and 60%, GLS determined the presence of any systolic dysfunction. The average GLS in the current study was −15.3%. Those with EF of between 50% and 60% and GLS absolute values of below this cutoff point had worse NYHA FC groups (Fig. 1). GLS is, thus, a more valuable and sensitive marker in distinguishing the early stage of systolic dysfunction in HCM.

In our patients suffering from HF with preserved EF due to significant diastolic dysfunction, the best GLS cutoff value was −11.5%, bearing in mind that most patients with significant diastolic dysfunction or increased E/E' ratios have GLS absolute values of less than −11.5%.

GLS is correlated with LGE in CMR and is useful in the early detection of systolic function impairment. When LGE is still lower than 15%, EF is still preserved, but the GLS absolute value is less than −15.3.

In our patients with MWT of equal to or greater than 3 cm, higher wall thickness was associated with preserved EF but with systolic dysfunction due to lower GLS (GLS mostly < −11.5). LGE was not noticeable in 75% of these patients. Increased LV wall thickness and/or a reduced LV end-diastolic volume, concomitant with better circumferential deformation, maintained a normal EF despite a reduced GLS.

Heart failure: a neglected component in the risk stratification of hypertrophic cardiomyopathy

The major causes of death in HCM are sudden cardiac death, HF, and stroke. Since 1980, the natural course, mortality rate, and causes of HCM have changed significantly. In the first reports in 1980, the HCM mortality rate was reported to range between 4% and 6% per year (mostly due to sudden cardiac death). In subsequent reports in the year 2000, this statistic dropped to 1.5% (51% due to sudden cardiac death, 36% due to HF, and 13% due to stroke). Finally, in recent years, the mortality rate of HCM has decreased to 0.5% (50% due to sudden cardiac death, 50% due to HF, and < 1% due to stroke). [25-32] The current risk stratification for HCM mostly focuses on arrhythmic events and sudden cardiac death. Considering this holistic attention to arrhythmias, advanced HF has emerged as a significant problem in many patients with HCM due to improvements in sudden cardiac death risk stratification in clinical cardiology practice. [32]

In a multicenter study on 1101 patients with HCM, Maron et al [33] reported that 273 (25%) patients had LVOT obstruction at rest with a peak gradient of equal to or greater than 30 mm Hg. The authors also reported that at a mean follow-up of 6 years, 127 (12%) patients died and 216 (20%) surviving patients had progression to the NYHA FC III or IV HF. In a subsequent report on 526 consecutive patients with HCM, Bernabo et al [34] reported that 141 (27%) patients had LVOT obstruction and noted that the prognostic value of LVOT obstruction varied with the severity of symptoms during a mean follow-up of 4.5 years. In their investigation, at initial evaluation, LVOT obstruction was a significant predictor of mortality among patients with no or mild symptoms at presentation (adjusted HR = 2.4); nonetheless, after the onset of severe symptoms, the NYHA FC became the dominant marker of the prognosis independent of the LVOT gradient.

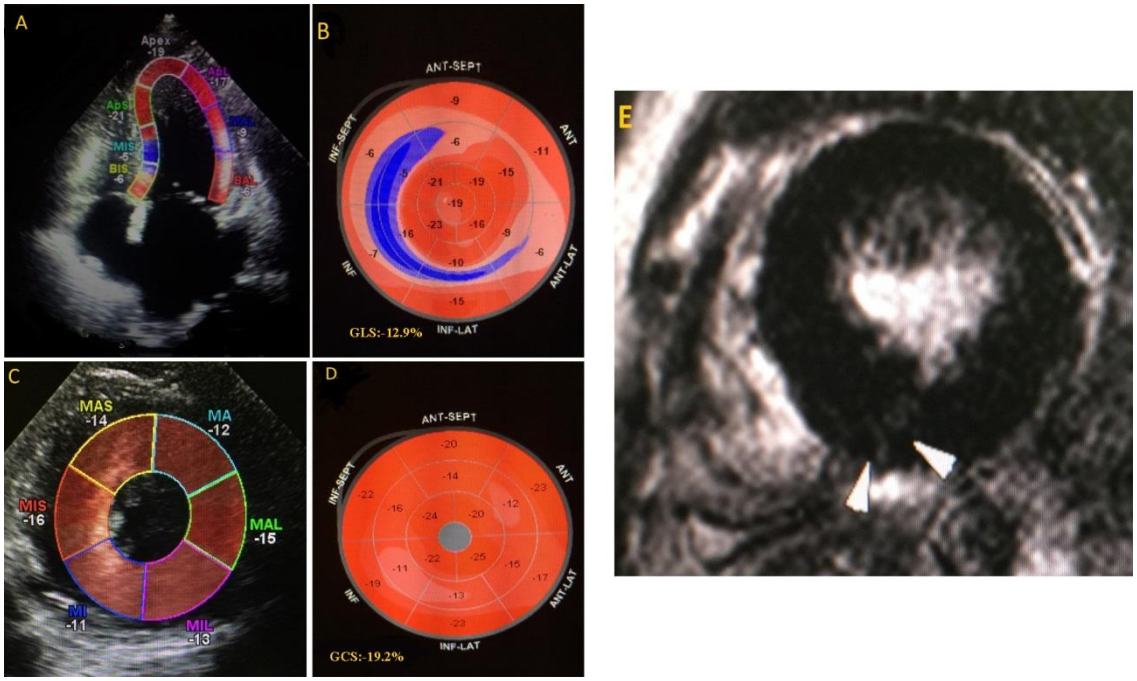

Figure 1: A 60-year-old woman with obstructive hypertrophic cardiomyopathy and an ejection fraction of between 50% and 55% was admitted with pulmonary edema. (A): Two-dimensional speckle-tracking transthoracic echocardiography (TTE) in the 4-chamber view shows reduced segmental longitudinal strain, especially in the base and mid of the inferoseptal (most hypertrophied segments) portions. (B): Two-dimensional TTE global longitudinal strain (GLS) bulls' eye shows reduced GLS (−12.9%). (C): Two-dimensional speckle-tracking echocardiography in the mid-short-axis view shows reduced circumferential strain in the mid-segments of the left ventricle. (D) Two-dimensional TTE global circumferential strain (GCS) bulls' eye shows reduced GCS (−19.2%). E: Cardiac magnetic resonance imaging late gadolinium enhancement (LGE) shows small fibrosis with low percentage LGE (2%–3%).

Rowin et al [35] in a cohort study on 2100 patients suffering from nonobstructive HCM in 2 referral centers showed that 2.2% of this population had advanced HF requiring heart transplantation. Among these patients, 1.1% had burned-out HCM and 1% had HF with a preserved LVEF. Melacini et al [36] followed 293 patients with HCM for almost 6 years to evaluate progression to HF and reported that 17% of their study population progressed to advanced HF. Among these patients, 30% progressed to burned-out HCM, 22% had HF owing to obstructive HCM, and 48% suffered from nonobstructive HCM and had HF with a preserved EF.

In our study, 29 (48.6%) patients had progressive HF symptoms (NYHA FC III and IV). Among these patients, 7 (24.1%) had burned-out HCM, 14 (48.3%) had HF secondary to obstructive HCM, and 8 (27.6%) had HF with a preserved EF. Our HCM registry center is a tertiary referral center and is one of the few centers with expertise in surgical septal myectomy and heart transplantation in Iran, which could be a sound rationale for the significantly worse condition of our study population by comparison with the previous studies insofar as our center admits more complicated patients in need of additive care or surgical procedures.

Another scintillating point in our study is that while only 8 (13.3%) patients had implantable cardioverter-defibrillators or a history of presyncope, 48.6% of the patients had advanced HF symptoms, which underscores the significance of HF over arrhythmic events.

Left ventricular global longitudinal strain as a risk marker

In the majority of patients with HCM, visual assessment of LV systolic function is normal and often hyperdynamic. The emergence of novel echocardiographic techniques such as myocardial strain has provided an opportunity to assess intrinsic regional and global myocardial mechanics and function. [13, 29] GLS is now deemed one of the most robust of these techniques, and a number of studies have demonstrated abnormal GLS values in HCM, suggesting that impaired myocardial contractile function is present in this disease despite a normal EF. [37,38] However, the precise role of GLS in broad populations of patients with HCM remains to be clarified. Hiemstra et al [13, 39] in a large cohort study on 427 patients with HCM (nonobstructive) showed that absolute GLS values of less than −15% had a significant incremental value over clinical and standard echocardiographic parameters in the determination of all-cause mortality, heart transplantation, sudden cardiac death, and appropriate implantable cardioverter-defibrillator therapy during a 6.7-year follow-up. Their investigations included patients with atrial fibrillation rhythms, and the results revealed that worse GLS values were associated with a greater likelihood of new or progressive HF. In a study where patients with atrial fibrillation rhythms were excluded, Reant et al [40] showed an association between GLS and the combined endpoint of cardiac death, HF admission, and appropriate implantable cardioverter-defibrillator therapy in a large cohort of 472 patients with HCM. In their study, patients with GLS absolute values of less than −15.6% showed higher risks of cardiac events. In addition, the prognostic value of GLS was demonstrated for the hard endpoint of all-cause mortality and appropriate implantable cardioverter-defibrillator therapy. Tower-Rader et al [41] in a large observational study on 1019 patients suffering from obstructive HCM with a composite endpoint of cardiac death and appropriate internal defibrillator discharge at an average follow-up of 9.4 years showed that patients with GLS absolute values of greater than −14% had excellent 5-year event-free survival. Moreover, the risk of events continuously increased when GLS worsened below −14%, and there was an exponential rise when GLS worsened below −7%, irrespective of surgery.

In the current study, the average GLS was −15.3%, which is close to the figures in other studies, specifically in the investigations by Hiemstra et al and Reant et al. Chiming in with previous research, in our study, patients with absolute GLS values of higher than the average cutoff point had a better clinical condition (mostly the NYHA FC I and II) and those with absolute GLS values of lower than the average cutoff point had worse NYHA FC groups. After we made adjustments for other factors such as obstructive and nonobstructive HCM, LVEF, and MWT, patients with absolute GLS values of less than −11.5% had a significantly higher filling pressure together with worse symptoms. In concordance with the previous investigations, in our study, patients who needed implantable cardioverter-defibrillators had absolute LV-GLS values below the average cutoff point, although it was not statistically meaningful, probably due to our small sample volume (GLS = −14.9. ± 3.6%; $P = 0.3$).

Relationships between late gadolinium enhancement, global longitudinal strain, global circumferential strain, and left ventricular ejection fraction

Approximately half the patients suffering from HCM may have LGE with a characteristic pattern of patchy involvement, particularly at right ventricular septal insertion sites and walls with the greatest hypertrophy. [42] In the latest HCM guideline, only extensive LGE (≥

15%) has been considered for prophylactic implantable cardioverter-defibrillators due to an increased sudden cardiac death risk. [3] Absent or focal LGE denotes a lower risk, as does LGE localized to the junctional areas of the right ventricular attachment to the septum. [43] Nonetheless, a meta-analysis of 5 studies involving 2993 patients with a median follow-up of 3 years demonstrated that just the presence of LGE was associated with a 3.4-fold increase in the risk for sudden cardiac death, a 1.8-fold increase in all-cause mortality, a 2.9-fold increase in cardiovascular mortality, and a trend to increase in HF deaths. [44] Several studies have revealed a correlation between prognosis and GLS, segmental longitudinal strain, and LGE in patients with HCM. [43-45] Satio et al [45] in a study on 48 patients with HCM showed that GLS in patients with LGE was significantly lower than that in those without LGE (−11.8 ± 2.8% vs 15.0 ± 1.7%; P = 0.001). During their follow-up (42 ± 12 mon), patients with GLS values worse than the average (−12.9%) had a worse outcome. The authors also reported that there was no relationship between LGE and EF in their study population. Ruvio et al [46] studied 61 patients suffering from HCM with a mean GLS of −15.6% and a mean GCS of −18.3% and showed that worse GLS, GCS, and EF values well correlated with an increased LGE value and more fibrosis and, consequently, arrhythmic events.

In the current study, when LGE was more than 15%, all systolic markers (ie, EF, GLS, and GCS absolute values) were reduced. Nonetheless, when LGE was between 5% and 15%, EF and GCS were preserved, while GLS was reduced (EF = 41.2 ± 11% vs 54.9 ± 5%; GLS: −12.7 ± 3.1% vs −13.9 ± 6.3%; and GCS: −13.2 ± 1.7% vs −28.6 ± 10.6%). Nevertheless, in contrast to GLS, GLS was normal when LGE was between 5% and 15% (−28.6 ± 10%), indicating that GLS is a more sensitive marker in detecting systolic dysfunction early even with low degrees of fibrosis.

The important point in the study by Satio et al [45] in comparison with our study is that they defined LGE as an area with a signal intensity of greater than 2 standard deviations from the mean of the remote myocardium, whereas we defined it as an area with a signal intensity of greater than 5 standard deviations from the mean of the remote myocardium. In addition, while we analyzed GLS and EF with categorized LGE (< 5%, 5–15%, and ≥ 15%), Satio and coworkers analyzed GLS and EF in terms of LGE but not LGE. Moreover, our results showed a significant relationship between LGE and EF, where Satio and colleagues reported no relationship between them. Additionally, whereas Satio et al reported a good correlation between GLS and LGE, we found that this relationship was weak and present in patients with LGE values of greater than 15%. Finally, our findings are closer to those reported by Ruvio et al [46] in terms of the correlations between LGE and EF, GLS, and GCS, although Ruvio and colleagues did not perform an LGE categorized analysis and reported LGE as segments in lieu of percentages.

Global longitudinal strain, global circumferential strain, left ventricular end-diastolic volume index, and maximal wall thickness

EF remains preserved in HCM until the end stages of the disease, while GLS and deformation are reduced. The mechanism behind a normal EF in patients suffering from HCM with a reduced systolic function is not comprehensively described. A possible explanation is that increased wall thickness results in lower volumes and alters the equation for EF (end-diastolic volume − end-systolic volume)/end-diastolic volume). [47, 49] Haland et al [47] in a cross-sectional study on 180 patients showed that those with HCM and left ventricular hypertrophy (HCM/LVH+)

had smaller cardiac volumes, which could explain the preserved EF, despite a worse GLS closely related to MWT. Those with HCM/LVH− had reduced cardiac volumes and subtle changes in GLS compared with the healthy individuals, indicating that there was a continuum of both volumetric and systolic changes before increased MWT. Stoke et al [48] via a mathematic model showed that the paradox of reduced myocardial shortening in the presence of a preserved EF could be explained mathematically through geometric factors, where EF could be constant for a large variation in shortening if other geometric factors were altered to compensate. Increased wall thickness and/or reduced end-diastolic volume can augment EF and, therefore, maintain a normal EF despite reduced shortening. EF is quadratically dependent on circumferential shortening and only linearly dependent on longitudinal shortening; hence, EF is less sensitive to a reduction in longitudinal shortening. Our findings suggest that strain measurements reflect systolic function better than EF in patients with a preserved EF.

In the current study, in patients with MWT of equal to or greater than 3 cm, EF remained normal despite a significantly reduced GLS because GCS was increased and compensated for the reduction in GLS. Consequently, there was no significant difference in EF between patients with MWT of equal to or greater than 3 and those with less thickness (GLS = −11.8 ± 3.5 vs −15.6 ± 4.4%; P = 0.02; GCS = −31.2 ± 12.9 vs −26.1 ± 8.4%; P = 0.08; and EF = 53.6 ± 3.4 vs 55.6 ± 4.4%; P = 0.1, correspondingly).

When LV size was normal in our study population, EF and GLS were correlated (54 ± 5.5% and −5.8 ± 4.6%, r = 0.34; P = 0.01); however, when LV size was small despite a normal LVEF, the absolute GLS value was significantly reduced (55%, −6.4 ± 1.9%, r = −0.8; P = 0.05) and GLS had no statistically significant difference between the 2 groups with different wall thickness, although it was worse in the small thickness group (−23.3 ± 2.6% vs 27 ± 7.5). In our study, GLS well correlated with EF and MWT. When EF was greater than 50%, GLS compensatory to a reduced GLS was increased; nevertheless, when EF fell below 50%, GCS dropped significantly (28.8 ± 8.6 vs 19.9 ± 7.2, r = 0.38; P = 0.017). Our study findings are in line with the foregoing study.

Study Limitations

First and foremost among the limitations of the present study is its small sample group and, thus, relatively weak statistical power. More clinical studies with larger sample volumes need to be done to confirm the validity of GLS as a marker for subtle systolic dysfunction and its influence on clinical conditions. The cross-sectional design of this study precluded a follow-up, which could have bolstered our evaluation of GLS vis-à-vis patient prognosis. The other possible weakness of this single-center study could be the administration of the echocardiographic equipment of Philips as the only piece of equipment for research. Accordingly, the results should be interpreted with caution when compared with those obtained on equipment from other vendors. The European Association of Cardiovascular Imaging and the American Society of Echocardiography recently set up a task force to evaluate the intervendor variability and reported that GLS had variabilities of less than 10% between different vendors, which is comparable to the standard echocardiographic measurements currently used. [50]

CONCLUSIONS

The present study on cardiac mechanics and their relationship with clinical conditions is the first of its kind among Iranian patients with HCM. We hope that our results will contribute to a better understanding of cardiac mechanics and their role in clinical practice in HCM.

Both forms of HCM, obstructive and nonobstructive, can be treated successfully in the early stage of the disease before the establishment of overt HF. Consequently, progression to advanced HF can be prevented if patients with subtle systolic dysfunction together with a reduced GLS have been identified and treated with appropriate medical treatment plans in both obstructive and nonobstructive forms and with septal myectomy (surgically or with alcohol ablation) in the obstructive form. In our study, patients with a GLS value of greater than −15.3% had better NYHA FC after adjustments were made for other confounding factors such as EF and obstructive or nonobstructive form. In addition, for the early detection of systolic dysfunction, the measurement of GLS is an easy, accessible, and affordable method in comparison with the determination of LGE by CMR. This is because while the role of LGE values of greater than 15% is clear, an LGE value of less than 15% has an unclear role in clinical decision-making. However, our results showed that even when LGE was less than 15% (particularly between 5% and 15%), there was systolic function impairment due to a reduced GLS- despite a good or preserved EF, which was temporarily compensated for by an increased GCS. This is a crucial stage in an appropriate treatment plan so as to prevent progression to irreversible changes in the myocardium and advanced HF. Further, the results of the current study demonstrated that when MWT was greater than 3 cm, a good EF might mask an impaired systolic function, created by a diminished GLS: this is another benefit of the measurement of GLS in patients with HCM. Patients with a small LV cavity had the lowest GLS values, which was an alarm for progression to overt systolic dysfunction despite a deceptively good EF. Finally, in the current study, patients with a higher NYHA FC had worse GLS values than those with an average cutoff value (−15.3%) even with a good EF. We, therefore, suggest that GLS be measured in all patients with a good or preserved EF, even when the other factors appear to be acceptable.

Conflict of Interest: None

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