Role of global longitudinal strain in discriminating variant forms of left ventricular hypertrophy and predicting mortality

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Abstract

Objective: In this study, we aimed to compare the functional adaptations of the left ventricle in variant forms of left ventricular hypertrophy (LVH) and to evaluate the use of two-dimensional speckle tracking echocardiography (2D-STE) in differential diagnosis and prognosis.

Methods: This was a prospective cohort study of 68 patients with LVH, including 20 patients with non-obstructive hypertrophic cardiomyopathy (HCM), 23 competitive top-level athletes free of cardiovascular disease, and 25 patients with hypertensive heart disease (HHD). All the subjects underwent 2D transthoracic echocardiography (TTE) and 2D-STE. The primary endpoint was all-cause mortality. Global longitudinal strain (GLS) below –12.5% was defined as severely reduced strain, –12.5% to –17.9% as mildly reduced strain, and above –18% as normal strain.

Results: The mean LV-GLS value was higher in athletes than in patients with HCM and HHD with the lowest value being in the HCM group (HCM: –11.4±2.2%; HHD: –13.6±2.6%; and athletes: –15.5±2.1%; p<0.001 among groups). LV-GLS below –12.5% distinguished HCM from others with 65% sensitivity and 77% specificity [area under curve (AUC)=0.808, 95% confidence interval (CI): 0.699–0.917, p<0.001]. The median follow-up duration was 6.4±1.1 years. Overall, 11 patients (16%) died. Seven of these were in the HHD group, and four were in the HCM group. The mean GLS value in patients who died was –11.8±1.5%. LV-GLS was significantly associated with mortality after adjusting age and sex via multiple analysis (RR=0.723, 95% CI: 0.537–0.974, p=0.033). Patients with GLS below –12.5% had a higher risk of all-cause mortality compared with that of patients with GLS above –12.5% according to Kaplan-Meier survival analysis for 7 years (29% vs. 9%; p=0.032). The LV-GLS value predicts mortality with 64% sensitivity and 70% specificity with a cut-off value of –12.5 (AUC=0.740, 95% CI: 0.617-0.863, p=0.012).

Conclusion: The 2D-STE provides important information about the longitudinal systolic function of the myocardium. It may enable differentiation variable forms of LVH and predict prognosis.

Keywords: left ventricular hypertrophy, hypertension, hypertrophic cardiomyopathy, athlete's heart, speckle-tracking echocardiography

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Introduction

Left ventricular hypertrophy (LVH) may present physiologically in a highly trained athlete or pathologically in cases of hypertension (HTN), valvular heart disease, or cardiomyopathy (1, 2). LVH is a cardiovascular risk factor that causes an increase in cardiovascular morbidity and mortality (3).

HTN is the most common cause of LVH in daily practice. In hypertensive heart disease (HHD), increased arterial stiffness, increased pressure load in the LV, and neurohormonal factors

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HIGHLIGHTS

- Left ventricular global longitudinal strain (LV-GLS) may help identify patients with pathological left ventricular hypertrophy (LVH).
- An athlete's heart with severely reduced LV-GLS should be evaluated for pathological LVH.
- Severely reduced LV-GLS was associated with poor outcomes in patients with LVH.

increase the size of myocytes, and leads to LVH (4, 5). In addition, perivascular and myocardial fibrosis have also been observed in chronic HTN (4).

However, there are benefits to consider the rare cases of LVH. Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited heart muscle disease caused by mutations in sarcomere protein genes (6). The main pathological changes associated with HCM are myocardial hypertrophy, contractile protein dysfunction, muscle cell disorder, and interstitial fibrosis (7). Diagnosing HCM is of great importance because it is one of the most common causes of sudden death in young people (8, 9). Clinical diagnosis is often based on the presence of unexplained LVH (2, 6).

Athlete's heart refers to cardiac structural and functional adaptations to exercise training. LV increases the diameter and wall thickness to compensate for the elevated cardiac output (10, 11). The physiological LVH in athletes is usually mild. However, significant hypertrophy in an athlete requires a differential diagnosis with HCM. HCM, with a prevalence of 1 in 500, is the most common cause of pathological LVH in young athletes (12, 13).

Differentiation between variant forms of LVH is very important as the final diagnosis can significantly impact an individual's life. LVH in HHD and HCM is associated with sudden cardiac death, arrhythmias, diastolic dysfunction, heart failure, coronary artery disease, and mortality; however, the hypertrophy in athlete's heart is thought to be a benign, physiologic response (14, 15). However, it is not always easy to distinguish the type and cause of LVH. Conventional echocardiographic parameters may be insufficient, especially in the presence of a normal LV ejection fraction (LVEF) (16). More sensitive earlier markers of impaired LV function may be useful to identify variant forms of LVH and prognosis. Myocardial strain imaging with 2D speckle tracking echocardiography (2D-STE) objectively measures myocardial deformation globally and regionally and characterizes contractile function (17). Global longitudinal strain of the LV (LV-GLS) was identified as a better predictor of mortality than the conventional parameters of LV (18). In this study, we aimed to compare functional adaptations of the LV in variant forms of LVH using conventional echocardiographic methods and 2D-STE and to determine prognosis.

Methods

This prospective cohort study included 20 patients with non-obstructive HCM, 23 highly trained athletes free of cardiovascular disease, and 25 patients with HHD, who were admitted to the İstanbul University İstanbul Faculty of Medicine between July 2013 and September 2014 and were clinically indicated for echocardiography.

Patients with poor image quality and suboptimal imaging, abnormal regional or global systolic function (LVEF <55%), moderate to severe valvular heart disease, prior infarction or known obstructive coronary artery disease, atrial fibrillation, restrictive cardiomyopathy, inflammatory or systemic disease, obstructive HCM (peak gradient LV outflow tract ≥30 mm Hg), and apical HCM were excluded. The inclusion criteria for pathological LVH were as follows: HCM - patients with known familial HCM and/or unexplained LVH with septal wall thickness >15 mm and septal to posterior wall thickness ratio >1.3, in the absence of a cardiac or systemic cause; and HHD - patients with known HTN with a systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or current pharmacological treatment for HTN exhibiting at least moderate LVH (septal or posterior wall thickness >13 mm). All the athletes included were highly trained elite football players engaged in high-intensity endurance as well as isometric exercise training.

The primary outcome was all-cause mortality. The vital statuses of all the patients were collected from the national death records. The study was approved by the İstanbul Faculty of Medicine Ethics Board. All the patients provided informed consent.

Two-dimensional transthoracic echocardiography

Two-dimensional transthoracic echocardiography (2D TTE) was performed in all the subjects using an X5 transducer with Philips IE33 (Philips Healthcare, Inc., Andover, MA, USA) to evaluate parasternal and apical images (2D, M-mode, Doppler echocardiography), with the patient placed in the left lateral decubitus position. A single echocardiographer examined the patients. All the data were recorded digitally, analyzed, and averaged over at least 3 cardiac cycles for each echocardiographic imaging. Images were obtained using the techniques recommended by the European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE) guidelines (19).

Conventional echocardiographic analysis

Measurements were obtained using parasternal and apical views. The LV dimensions used an average of 5 M-mode measurements and included end-diastolic (LVEDD) and end-systolic (LVESD) diameters, diastolic thickness of the interventricular septum (IVS), and posterior wall (PW) from the parasternal long-axis view. LV mass was calculated from the parasternal view based on Devereux's formula. LVH was diagnosed according to the formula for estimation of LV mass index and was indexed to

body surface area (cutoff values for LV mass index were >115 g/m^2 for men and >95 g/m^2 for women). LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and LVEF were measured using the biplane Simpson method. From the apical 4-chamber view, mitral inflow velocities were traced using pulsed Doppler, and the following variables were obtained: peak velocity of early diastolic mitral inflow (E), late diastolic mitral inflow (A), and deceleration time (DT) of the E velocity. Color-coded tissue Doppler imaging (TDI) from the apical 4-chamber view was used to determine the septal annular velocities, including early diastolic mitral annular velocity (e'), with a 2- to 5-mm sample volume placed at the septal corner of the mitral annulus. LV diastolic function was estimated using the ratio of E to A and the ratio of E to e'. Normal filling was defined as a deceleration time (DT) of 140–240 ms and an E/A of >1, abnormal relaxation as an E/A ratio of <1, and a DT of ≥240 ms; pseudonormal filling as a DT of 140–240 ms, an E/A ratio of >1, and an E/A ratio of >15, and restrictive filling as a DT of <140 ms and an E/A of >2 (20). The left atrial (LA) diameter was measured from the parasternal long-axis view at end-systole.

Speckle-tracking echocardiographic analysis

The 2D-STE was performed according to the recommendations of the ASE and the European Association of Cardiovascular Imaging (21). The images were analyzed at 50 to 70 frames/second in apical 2-, 3-, and 4-chamber views using Philips IE33 with the QLAB-CMQ software. First, for each view, the operator placed 3 points (2 points at the base of the LV and 1 point at the apex) at the end of diastole. The endocardial and epicardial borders were automatically traced using the software. The region of interest option was the mid-wall strain with optimal manual adjustments. Aortic valve closure (AVC) time was calculated using the automatic ECG timing. Systolic longitudinal strain values were calculated at the AVC time by averaging the values of all segments for the assessment of LV global longitudinal strain (LV-GLS). Each wall of the LV was segmented into 3 (base, mid, and apical) equal parts automatically, and 17 segmental strain curves were obtained to give the so-called bull's-eye plots (Fig. 1). If it was not feasible to track one or more segments, that case was excluded. LV-GLS below –12.5% was defined as severely reduced strain, –12.5% to –17.9 % as mildly reduced strain and –18% and above –18% as normal strain (22).

Statistical analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences version 26.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to analyze the normality of the data. Continuous data are expressed as mean ± standard deviation (SD), and categorical data are expressed as number and percentages. The chi-squared or Fisher's exact test was used to assess the differences in categorical variables between the groups. The primary analysis used analysis of variance with Tukey's post-hoc test to compare all reported data for normally distributed continuous variables, whereas the Kruskal–Wallis test followed by a post-hoc analysis Dunn's pairwise test was used for comparison among non-normally distributed variables between the groups. A Student's t-test or the Mann–Whitney U test was used to compare independent samples as needed. Cumulative survival curves were derived according to the Kaplan–Meier method. For the echocardiographic parameters, receiver operating characteristic (ROC) curves were obtained, and the optimal values

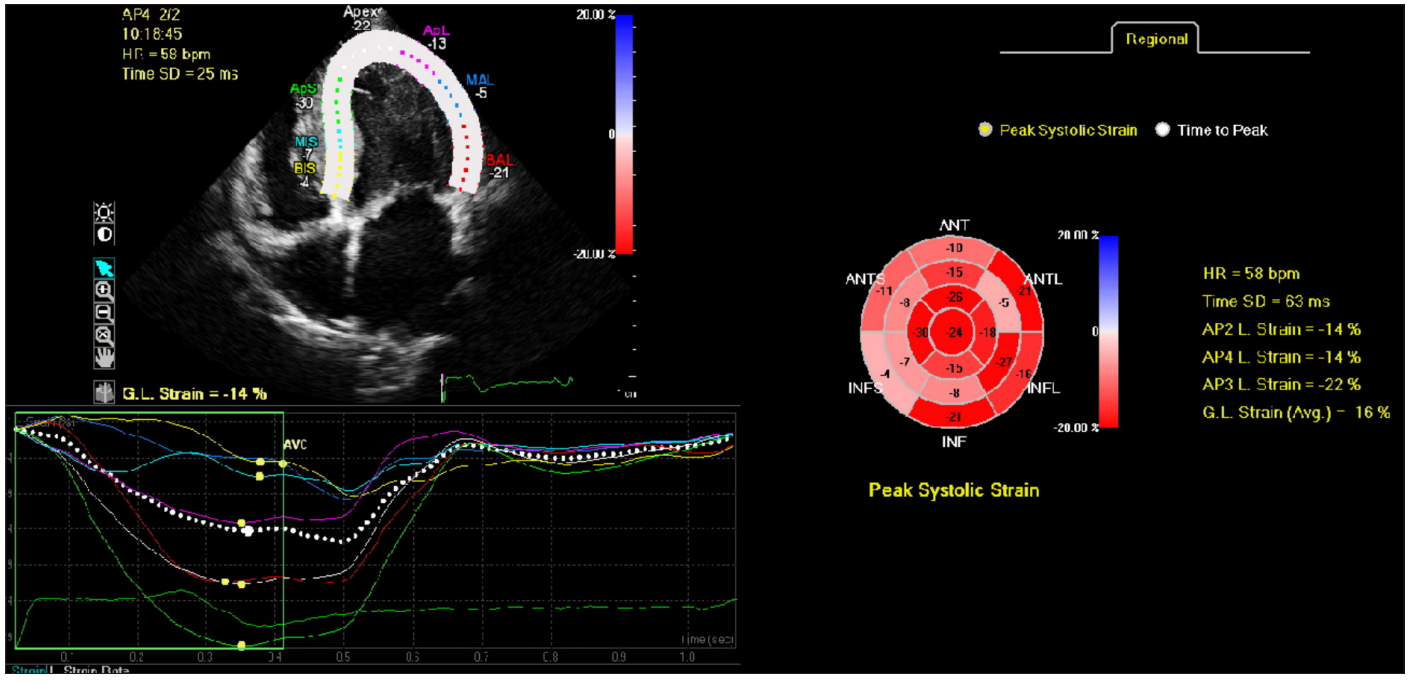

Figure 1. Bull's eye image of left ventricular global longitudinal strain

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with the greatest total sensitivity and specificity in the differentiation of HCM or athlete's heart were selected. Again, ROC curve was obtained for LV-GLS and the optimal values with the greatest total sensitivity and specificity in the prediction of mortality were selected. Univariate and multiple logistic regression analyses were used to identify the independent variables of mortality. After performing univariate analysis, the stepwise method was used to select significant prognostic variables for use in the multiple logistic regression analysis. The results of the univariate and multiple regression analyses were presented as odds ratios with 95% confidence intervals (CIs). Significance was assumed as a two-sided p<0.05.

Results

The average age of subjects was 22.7±3 years for athletes, 43.3±10.6 years in HCM, and 54.8±10.6 years in HHD groups; and there was a statistically significant difference among the 3 groups (p<0.001 among groups; p=0.032 between HHD and HCM; p<0.001 between HHD and athletes; and p<0.001 between HCM and athletes). The athletes were younger than those in the HCM and HHD groups, and the oldest group was HHD (p=0.032 between HHD and HCM; p<0.001 between HHD and athletes; and p<0.001 between HCM and athletes). Male gender was dominant in all the groups (76% of HHD; 70% of HCM; 91% of athletes; p=0.197 among groups). All the groups were similar in terms of sex, body mass index (kg/m^2), and systolic and diastolic blood pressures (mm Hg). However, the heart rate (HR) was significantly lower in athletes than in individuals in the HCM (p<0.001) and HHD (p<0.001) groups (55.5±6.6 vs. 73.3±8.6 vs. 70.7±9.2, respectively)

LVEF was higher in the HCM group than in the HHD (p<0.001) and the athlete (p=0.023) (74.6±6.3 vs. 67.1±4.1 vs. 70±4.8, respectively; p<0.001 among groups) groups. LVEDD (mm), LVESD (mm), LVEDV (mL), and LVESV (mL) were significantly higher in athletes compared with those in the HCM and HHD groups (p<0.001 for each).

In ROC analysis, LVEDD >5.3 cm predicts athletes heart with 91% sensitivity and 96% specificity (AUC=0.982, 95% CI: 0.957–1.0, p<0.001). LVESD >3.3 cm predicts athletes heart with 83% sensitivity and 82% specificity (AUC=0.891, 95% CI: 0.815–0.968, p<0.001).

IVS thickness of the HCM, HHD, and athlete groups were 1.9±0.2, 1.5±0.1, and 1.3±0.1, respectively; and there was a statistically significant difference among the 3 groups (p<0.001 among groups; p=0.001 between HHD and HCM; p<0.001 between HHD and athletes; p<0.001 between HCM and athletes). PW thickness was higher in HHD group compared with that in the HCM (p=0.001) group and athletes (p<0.001) (1.4±0.1 vs. 1.3±0.2 vs. 1.2±0, respectively; p<0.001 among groups). IVS/PW ratio was higher in HCM group compared that in the HHD group (p<0.001) and athletes (p<0.001) (1.5±0.2 vs. 1.1±0.1 vs. 1±0.1, respectively; p<0.001 among groups). In ROC analysis, IVS >1.65 cm predicts HCM with 80% sensitivity and 96% specificity (AUC=0.951, 95% CI: 0.900–1.0; p<0.001). IVS/PW ratio >1.35 predicts HCM with 80% sensitivity and 99% specificity (AUC=0.979, 95% CI: 0.942–1.000, p<0.001).

When the diastolic function parameters were evaluated, E velocity was lower in HHD group compared with that of the HCM group (p=0.005) and athletes (p=0.005) (60.9±18.5 vs.76.6±21.1 vs. 76.6±8.9, respectively; p=0.001 among groups) and septal e' velocity was higher in athletes compared with that of the HCM (p<0.001) and HHD (p<0.001) groups (10.7±1.5 vs. 5.2±1.4 vs. 6.4±1.8, respectively; p<0.001 among groups). E/A ratio was lower in HHD group compared with that in the HCM group (p=0.010) and athletes (p<0.001) (0.8±0.3 vs. 1.1±0.5 vs. 1.2±0.2, respectively; p=0.002 among groups). E/e' ratio of the HCM, HHD, and athlete groups were 16.3±8.4, 10±4, 7.2±0.9, respectively; and there was a statistically significant difference among the 3 groups (p<0.001 among groups; p=0.001 between HHD and HCM; p<0.001 between HHD and athletes; p<0.001 between HCM and athletes). In ROC analysis, E/e' ratio >11 identified HCM from others with 80% sensitivity and 79% specificity. Septal e' >9 cm/sn identified athlete's heart from others with 91% sensitivity and 87% specificity (AUC=0.977, 95% CI: 0.949–1.0, p<0.001).

The LV-GLS values of the HCM, HHD, and athlete groups were –11.4±2.2%; –13.6±2.6%; and –15.5±2.1%, respectively; and there was a statistically significant difference among the 3 groups (p<0.001 among groups; p=0.015 between HHD and HCM; p=0.016 between HHD and athletes; and p<0.001 between HCM and athletes).

In ROC analysis, LV-GLS value below –12.5% predicts HCM with 65% sensitivity and 77% specificity (AUC=0.808, 95% CI: 0.699–0.917, p<0.001).

The demographic characteristics and echocardiographic findings of the groups are presented in Table 1. The performance of echocardiographic criteria in differentiating athlete's heart or HCM by ROC analysis is presented in Tables 2 and 3.

The median follow-up duration was 6.4±1.1 years. Overall, 11 (16%) patients died, 7 of them (28%) in the HHD group and 4 of them (20%) in the HCM group. No athlete died during follow-up. The mean LV-GLS value in patients who had died was –11.8±1.5%. According to Kaplan–Meier survival analysis for 7 years, the patients with HCM and HHD with LV-GLS below –12.5% have higher risk for all-cause mortality than patients with LV-GLS above –12.5% (29% vs. 9%; p=0.032) (Fig. 2). One-year mortality rates were 4% for patients with LV-GLS above –12.5% and 10% for patients with LV-GLS below –12.5%. LV-GLS below –12.5% was significantly associated with mortality after adjusting age and sex via multiple analysis (RR=0.723, 95% CI: 0.537–0.974, p=0.033).

We evaluated the specificity and sensitivity of the LV-GLS value that was significant in the multiple analysis with ROC analysis to predict all-cause mortality. The blue line represents LV-GLS. LV-GLS predicts mortality with 64% sensitivity and 70% specificity with a cut-off value of –12.5% (AUC=0.740, 95% CI: 0.617–0.863, p=0.012) (Fig. 3).

Table 1. Demographic characteristics and echocardiographic findings of HHD, HCM, and athlete groups

Variables	Total (n=68)	HHD (n=25)	HCM (n=20)	Athlete (n=23)	ANOVA *P*-value	Tukey's test *p1*	*p2*	*p3*
Age (year)	40.6±16.2	54.8±10.6[b]	43.3±10.6[c]	22.7±3[b,c]	<0.001*	0.032	<0.001	<0.001
Sex, Male, n (%)	54 (80%)	19 (76%)	14 (70%)	21 (91%)	0.197	0.314	0.098	0.062
Female, n (%)	14 (20%)	6 (24%)	6 (30%)	2 (9%)				
HR (bpm)	66.3±11.3	70.7±9.2[b]	73.3±8.6[c]	55.5±6.6[b,c]	<0,001*	0.552	<0.001	<0.001
BMI (kg/m^2)	25±1.9	25.2±2.3	24.8±2.4	25±0.8	0.693	0.562	0.792	0.502
SBP (mm Hg)	118.5±10.4	119.6±12	120.8±9.4	115.2±8.9	0.195	0.247	0.174	0.155
DBP (mm Hg)	72.7±5.6	73.6±5.9	70.8±5.7	73.3±5.1	0.202	0.388	0.642	0.586
Deaths, n (%)	11 (16.2%)	7 (28%)[b]	4 (20%)[c]	0 (0%)[b,c]	0.027*	0.472	0.009	0.078
Follow-up (years)	6.4±1.1	6.3±1.1	6.6±1.2	6.4±1.1	0.257	0.324	0.188	0.256
LVEF (%)	70.3±5.8	67.1±4.1[a]	74.6±6.3[a,c]	70±4.8[c]	<0.001*	<0.001	0.092	0.023
LVEDD (cm)	4.8±0.6	4.6±0.4[a,b]	4.2±0.6[a,c]	5.4±0.2[b,c]	<0.001*	0.001	<0.001	<0.001
LVESD (cm)	3±0.5	2.9±0.4[a,b]	2.5±0.4[a,c]	3.4±0.2[b,c]	<0.001*	0.003	<0.001	<0.001
LVEDV (mL)	108.6±32.3	100.4±18.1[a,b]	79.2±25.4[a,c]	143.2±12.3[b,c]	<0.001*	0.001	<0.001	<0.001
LVESV (mL)	35.1±13	33.2±11[a,b]	24.1±8.8[a,c]	46.7±8[b,c]	<0.001*	0.012	<0.001	<0.001
LVMI (mL/m^2)	189.6±34.6	199.1±33.1	184.3±44.6	183±26	0.062	0.044	0.030	0.472
IVS (cm)	1.5±0.3	1.5±0.1[a,b]	1.9±0.2[a,c]	1.3±0.1[b,c]	<0.001*	0.001	<0.001	<0.001
PW (cm)	1.3±0.1	1.4±0.1[a,b]	1.3±0.2[a]	1.2±0[b]	<0.001*	0.001	<0.001	0.133
IVS/PW ratio	1.2±0.2	1.1±0.1[a,b]	1.5±0.2[a]	1±0.1[b]	<0.001*	<0.001	0.041	<0.001
LA (cm)	4.1±0.4	4.1±0.3	4±0.3	4.1±0.4	0.474	0.478	0.784	0.466
Mitral E (cm/s)	70.6±18	60.9±18.5[a,b]	76.6±21.1[a]	76.6±8.9[b]	0.001*	0.005	0.005	0.988
Septal e′ (cm/s)	7.7±2.8	6.4±1,8[b]	5.2±1.4[c]	10.7±1.5[b,c]	<0.001*	0.273	<0.001	<0.001
E/A ratio	1±0.4	0.8±0.3[a,b]	1.1±0.5[a]	1.2±0.2[b]	0.002*	0.010	<0.001	0.488
E/e′ ratio	10.7±6.1	10±4[a,b]	16.3±8.4[a,c]	7.2±0.9[b,c]	<0.001*	0.001	<0.001	<0.001
DT (msn)	168.6±37.6	155±46.8[a]	192.8±35.8[a,c]	165.4±11.2[c]	0.004*	0.003	0.562	0.045
LV-GLS (%)	–13.7±2.8	–13.6±2.6[a,b]	–11.4±2.2[a,c]	–15.5±2.1[b,c]	<0.001*	0.015	0.016	<0.001

* [a]*P*<0.05 between HHD and HCM groups, [b]*P*<0.05 between HHD and athlete groups, [c]*P*<0.05 between HCM and athlete groups (ANOVA test)
p1: between HHD and HCM groups, *p2*: between HHD athlete groups, *p3*: between HCM and athlete groups (Tukey's test)
ANOVA - analysis of variance; BMI - body mass index; DT - deceleration time; DBP - diastolic blood pressure; HCM - hypertrophic cardiomyopathy; HHD - hypertensive heart disease; HR - heart rate; IVS - interventricular septum; LA - left atrial; LVEF - left ventricular ejection fraction; LVEDD - left ventricular end diastolic diameter; LVESD - left ventricular end systolic diameter; PW- posterior wall; LVEDV - left ventricular end diastolic volume; LVESV - left ventricular end systolic volume; LV-GLS - left ventricular global longitudinal strain; LVMI - left ventricular mass index; E - early diastolic velocity of mitral valve inflow; A - late diastolic velocity of mitral valve inflow; Septal e′ - early diastolic velocity at basal mitral annulus, SBP - systolic blood pressure

Table 2. Performance of echocardiographic criteria in differentiating athlete's heart

	Sensitivity	Specificity	AUC	95% CI
LVEDD >5.3 cm	91	96	0.982	0.957–1.000
LVESD >3.3 cm	83	82	0.891	0.815–0.968
Septal e′ >9 cm/sn	91	87	0.977	0.949–1.000
Mitral E >75 cm/sn	65	64	0.658	0.531–0.786

AUC - area under curve; CI - confidence interval; LVEDD - left ventricular end diastolic diameter; LVESD - left ventricular end systolic diameter; Mitral E - early diastolic velocity of mitral valve inflow, Septal e′ - early diastolic velocity at basal mitral annulus

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Table 3. Performance of echocardiographic criteria in differentiating hypertrophic cardiomyopathy

	Sensitivity	Specificity	AUC	95% CI
IVS >1.65 cm	80	96	0.951	0.900–1.000
IVS/PW ratio >1.35	80	99	0.979	0.942–1.000
LV-GLS below –12.5	65	77	0.808	0.699–0.917
E/e′ ratio >11	80	79	0.865	0.776–0.953

AUC - area under curve; CI - confidence interval; IVS - interventricular septum; LV-GLS - left ventricular global longitudinal strain; Mitral E - early diastolic velocity of mitral valve inflow; PW - posterior wall; Septal e′ - early diastolic velocity at basal mitral annulus

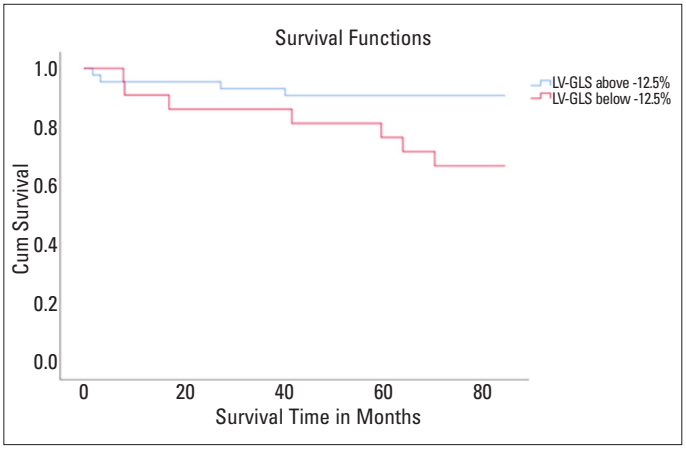

Figure 2. Kaplan-Meier survival curves for mortality during follow-up. Seven-year mortality rates were 9% (n=4) for left ventricular global longitudinal strain (LV-GLS) above –12.5% and 29% (n=7) for LV-GLS below –12.5% (*P*=0.032)

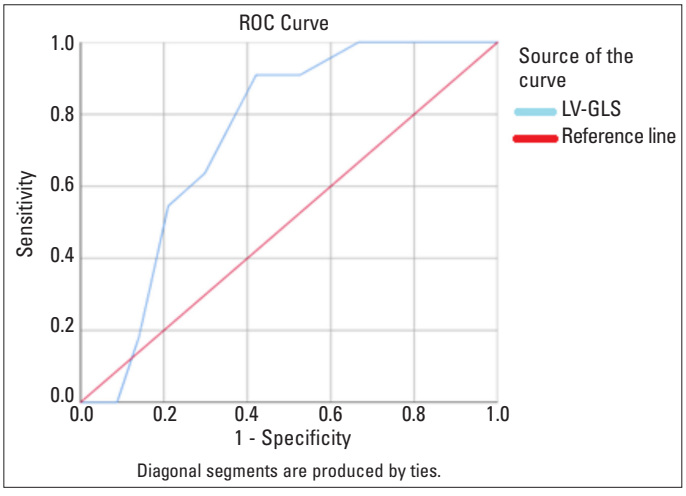

Figure 3. Receiver operating characteristic curve analysis showing the specificity and sensitivity of left ventricular global longitudinal strain in predicting mortality

Discussion

To the best of our knowledge, this is one of the first studies to use combined and comprehensive conventional echocardiographic analysis as well as 2D-STE strain analysis for differentiating between pathologic and physiologic variant forms of LVH with a long-term follow-up. We studied 68 subjects, 20 patients with non-obstructive HCM, 23 competitive top-level athletes free of cardiovascular disease, and 25 patients with HHD. This study demonstrated the important role of LV-GLS in evaluating global function, echocardiographic discrimination, and predicting outcomes in HCM, HHD, and athletes. Our results show that LV-GLS was higher in athletes than in patients with HCM and HHD, with the lowest LV-GLS value in the HCM group; and severely reduced LV-GLS was associated with all-cause mortality, with convincing sensitivity and specificity.

It is not always possible to differentiate variant forms of LVH in daily practice, causing diagnostic difficulties. Criteria proposed for distinguishing between physiologic and pathologic hypertrophy include LV cavity size, LV diastolic dysfunction, an increase in LV wall thickness, and an increase in the ratio of IVS to PW end-diastolic diameter (23, 24). LV cavity size is a well-established discriminator between physiological LVH and HCM. HCM is characterized by a mismatch between the magnitude of the LVH and LV cavity size. In contrast, concomitant enlargement of the LV cavity with physiological LVH can be observed in athletes. Pelliccia et al. (24) evaluated 947 elite athletes who participated in various sports. Sixteen (1.7%) athletes had a wall thickness of >13 mm. All the athletes with IVS ≥13 mm also had enlarged LVEDDs (55–63 mm). They suggested that athletes with an IVS >16 mm and a nondilated LV cavity are likely to have primary forms of pathologic hypertrophy, such as HCM. In our study, athletes had larger LV cavities than patients with HCM and HHD with the smallest LV cavities observed in the HCM cohort.

In previous studies, mitral valve inflow Doppler measurements and pulsed TDI at the level of the septal mitral valve annulus were used to distinguish HCM from others (25, 26). This may be clinically important because it is sometimes problematic to determine the significance of hypertrophy using other methods. A septal e′ velocity of <9 cm/s favored pathological LVH in previous studies, with a sensitivity of 90%. In addition, the E/e′ ratio may also be useful in differentiating physiological LVH from HCM and HHD (26, 27). An E/e′ ratio of >12 is an indicator of high left atrial filling pressure, which is a well-known feature of HCM (28). However, most trained athletes exhibited E/e′ <8 (27). These findings were confirmed by our study. HHD and HCM subsets had lower septal e′ velocity than athletes with the lowest diastolic velocities observed in the HCM cohort. None of the patients with HCM had a septal e′ >8 cm/sn. Patients with HCM had a higher E/e′ ratio than those in the other groups.

The structure and function of the LV are usually evaluated using echocardiography, but it is insufficient to evaluate the deformation movements of myocardial fibers. Speckle tracking imaging, unlike TDI, is a new imaging modality that objectively measures the strain of the myocardium globally and regionally, regardless of the imaging angle or cardiac translational movements (29). The IVS receives subendocardial fibers arranged longitudinally from the LV and right ventricle. These fibers are thought to play an important role in ventricular long axis motion to help assess LV function.

In pathological LVH, increased myocardial demand and decreased coronary resistance and dilatation ability resulted in decreased perfusion of the subendocardium. Subendocardial fibrosis and reduced compliance, which are potential mechanisms for the failure of the hypertrophic myocardium, are associated with pathological LVH (30). A significant decrease in GLS in both HCM and HHD groups with normal EF has been demonstrated in the literature (31, 32). In our study, the mean LV-GLS value was higher in athletes than in patients with HCM and HHD. Patients with the lowest mean LV-GLS were in the HCM group. LV-GLS below –12.5% distinguished HCM from others with 65% sensitivity and 77% specificity. In a study, Afonso et al. (33) compared HCM, HHD, athletes, and control groups. They observed that patients with HCM had significantly lower average peak systolic GLS compared with controls and other forms of LVH. They did not follow the patients' clinical outcomes. In addition, it is unclear whether the mean GLS was similar between the HHD, athletes, and control groups in that study. In our study, GLS was lower in patients with HHD than in athletes. Whether poor perfusion, myocyte dysfunction, or fibrosis in HHD may be responsible for the decreased strain parameters uncovered in our study. Furthermore, as GLS above –18% was defined as normal strain, it can be concluded that the mean GLS value was mildly reduced in athletes in our study despite the absence of a control group. There are studies using 2D-STE to evaluate adult athletes' hearts. Richand et al. (34) analyzed 29 professional soccer players, 26 patients with HCM, and 17 controls. They found that athletes had higher GLS values than patients with HCM, but lower values compared to controls. Thus, the authors believed this might be an indication of a specific myocardial adaptation to exercise-induced excessive volume overload. In addition, the authors suggested that a longitudinal basal septal strain value of –11% identified HCM from physiological LVH with 60% sensitivity and 96% specificity. Recently, Caselli et al. (35) confirmed these findings in Olympic athletes, demonstrating that LV-GLS was mildly lower than that of controls. Charfeddine et al. (36) studied football players and controls. A mildly lower LV-GLS was found in young athletes than in controls. Conversely, further studies showed minimal or no differences in LV-GLS in athletes compared with healthy controls (37, 38). In an athlete's heart, it is crucial to determine whether hypertrophy is physiologic or pathologic. Therefore, 2D-STE can be considered a useful, fast, and helpful method in daily practice to differentiate between physiological and pathological LVH. Thus, athletes who present with a severe reduction of LV-GLS should be carefully evaluated, especially in the presence of significant hypertrophy.

A pathological hypertrophy is a risk factor for morbidity and mortality, we followed the patients' prognosis. The median follow-up duration was 6.4±1.1 years. Overall, 11 patients (16%) died. No athlete died during follow-up. The mean LV-GLS value in patients who died was –11.8±1.5%. Unlike LVEF, reduced LV-GLS appears to be of particular prognostic interest. LV-GLS was significantly associated with mortality via multiple analysis, independent of age and sex. According to Kaplan–Meier survival analysis for 7 years, patients with HCM and HHD with GLS below –12.5% had a higher risk of all-cause mortality. LV-GLS predicts mortality with 64% sensitivity and 70% specificity with a cutoff value of –12.5%. The prognostic significance of LV-GLS in coronary artery disease, heart failure, and valvular heart disease has previously been demonstrated. Park et al. (39) observed that patients with heart failure with a GLS below –12.5% had a higher risk of 5-year all-cause mortality. Our results are also consistent with the few studies published to date in the field. Saito et al. (40) showed that GLS below –12.9% was a predictor of cardiac events in patients with HCM.

Our data are based on the average LV-GLS derived from 17 segments with 2D-STE as a factor associated with the differentiation of variant forms of LVH and clinical outcomes. This is the only follow-up study evaluating LV-GLS in patients with HCM and HHD in addition to athletes in a head-to-head comparative analysis.

Study limitations

This study had several limitations. Despite our best attempts to match groups for LVH grades, a methodological limitation of this study was the disparity in IVS thickness in cohorts. In fact, this was not possible owing to the nature of the groups, similar to the fact that the average ages were not similar. Asymptomatic coronary artery disease may be present in the HHD group because of the high average age, which may contribute to mortality. The reproducibility of deformation imaging could not be discussed as the measurements were evaluated by a single echocardiographer. Moreover, the sample size was small. Finally, our findings cannot be generalized to patients with a decreased EF.

Conclusion

In the setting of preserved LVEF, GLS obtained by 2D-STE revealed subclinical systolic involvement in the myocardium in variant forms of LVH. GLS is a useful and sensitive method in daily practice and can be used as a differential and prognostic tool in various forms of LVH.

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