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# Layer-specific longitudinal strain predicts left ventricular maximum wall thickness in patients with hypertrophic cardiomyopathy

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## Abstract

**Aims:** The aim of this study was (a) to clarify the detailed mechanisms of structural and functional abnormalities of myocardial tissue in hypertrophic cardiomyopathy (HCM) using layer-specific strain (LSS) and compare it with healthy subjects (b) to investigate the diagnostic accuracy of LSS for HCM.

**Methods and Results:** Forty-one patients with HCM and preserved left ventricular ejection fraction (LVEF; 66% male, 52 ± 18 years, LVEF 62.9% ± 3.7%) and 41 controls matched for age and sex (66% male, 52 ± 20 years, LVEF 63.5% ± 8.2%) underwent 2D-speckle tracking echocardiography. Absolute values of LSS were globally lower and the ratio of endocardial/epicardial layer (End/Epi ratio) was higher in HCM. LSS gradually increased from the epicardial toward the endocardial layer at all chamber views and at all levels of the LV. LSS and End/Epi ratio at the apex were higher than those at the middle or basal level of the LV. End/Epi ratio was correlated with LV maximal wall thickness both controls ($r = .35$, $P = .03$) and HCM ($r = .81$, $P < .001$). End/Epi ratio was an independent factor associated with LV maximal wall thickness ($\beta = 0.96$, $P < .001$). A higher End/Epi ratio (≥1.31) was associated with diagnostic criteria for HCM (sensitivity 98%, specificity 95%, area under the curve 0.99, $P < .001$).

**Conclusion:** LSS has the potential for unraveling the mechanism of impaired LV wall motion in HCM and to accurately detect HCM.

KEYWORDS

hypertrophic cardiomyopathy, 2D echocardiography, multilayer strain, speckle tracking echocardiography, segmental deformation

## 1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness caused by mutations in sarcomeric contractile proteins. European Society of Cardiology Guidelines states that LV wall thickness is an important parameter for the diagnosis of HCM[1] and is also associated with long-term clinical outcome in HCM patients.[1,2] Accurate assessment of cardiac anatomy by computed tomography, cardiac magnetic resonance, or 2D-transthoracic echocardiography is crucial in HCM.[1] However, conventional tools are not sensitive enough to analyze the mechanisms of structural and functional abnormalities that occur at the cellular level in hypertrophied myocardium. The LV wall has a complex architecture and consists of circumferential fibers in the midwall layer and longitudinal fibers in the endocardial and the epicardial layers.[3-5] Recently, technological progression of 2D-speckle tracking

  

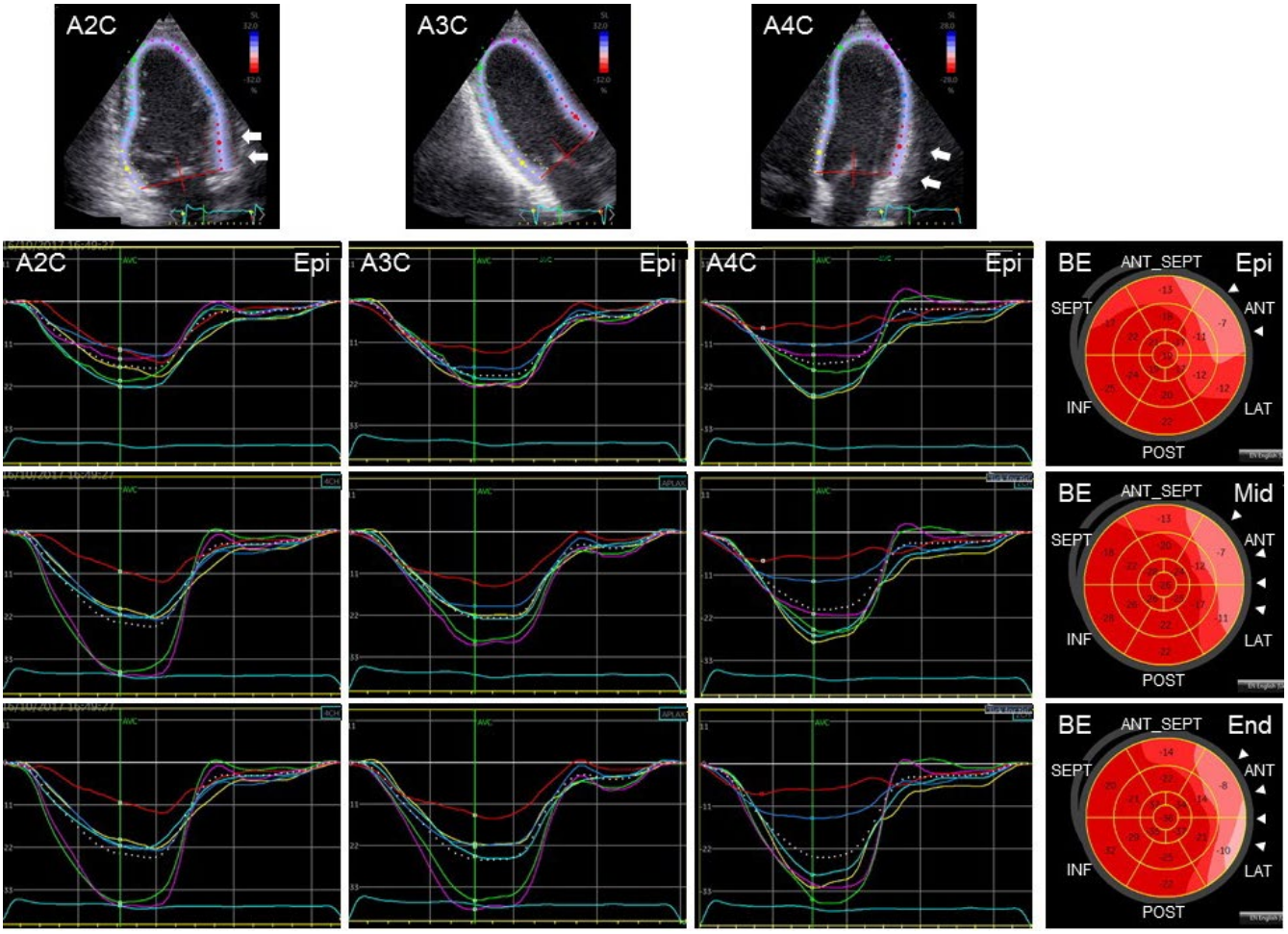


**FIGURE 1** Example of layer-specific strain curves measurement by 2D-speckle tracking echocardiography in a hypertrophic cardiomyopathy patient with mild thickening (15 mm) at the anterior and lateral segments of the left ventricular wall (arrow). At the bull's eye (right panel), all layers strain values (arrowhead), which are corresponding to mild thickened area. A2C, apical 2-chamber; A3C, apical 3-chamber; A4C, apical 4-chamber; BE, bull's eye of the layer-specific strain; End, endocardial strain; Epi, epicardial strain; Mid, mid-myocardial strain

echocardiography has enabled the evaluation of layer-specific strain (LSS), such as epicardial, mid-myocardial, and endocardial longitudinal strain, respectively. LSS may have the potential to elucidate the detailed mechanisms of myocardial dysfunction.

The present study aimed (a) to clarify the detailed mechanisms of structural and functional abnormalities of myocardial tissue in HCM using LSS by comparing with healthy subjects (b) to investigate the diagnostic accuracy of LSS for HCM.

## 2 | METHODS

### 2.1 | Patient population

A total of 56 clinically stable outpatients with HCM who regularly visited our heart valve clinic from January 2013 to February 2019 were retrospectively evaluated. The local ethics committee approved the study protocol. The definition of HCM was based on the presence of LV wall thickness ≥15 mm in one or more LV myocardial segments that were not explained by loading conditions.[1] Patients with more than mild valve disease, ischemic heart disease, significant arrhythmias including atrial fibrillation, previous myomectomy, and/or alcohol ablation were excluded. Fifteen patients were excluded for suboptimal quality of 2D-speckle tracking echocardiography image analysis. The final study population consisted of 41 patients. The control group included 41 patients matched for age and sex who were extracted from a total of 734 healthy European subjects.[6-8]

### 2.2 | Echocardiographic examination

2D-transthoracic echocardiography examination was performed using a Vivid ultrasound system (GE Vivid E9 or E95; Vingmed Ultrasound, Horten, Norway). Conventional echocardiographic measurements were performed in accordance with the guidelines.[9] In order to acquire the LV strain curves, grayscale imaging of apical 2-, 3-, and 4-chamber views with a frame 70-90 Hz, and recordings were processed with acoustic-tracking software (EchoPAC, version 203, GE Healthcare),

allowing offline semi-automated speckle-based strain analysis. Lines were first manually traced along the LV endocardium, and then an additional epicardial line was automatically generated by the software to create a region of interest (ROI). After manually adjusting the ROI shape, the software divides the LV region into six segments and generated longitudinal strain curve. LSS values were obtained by averaging the peak longitudinal strain of 17 segments (Figure 1) and expressed as an absolute value. Categorization of basal, middle, or apical segments of the LV was assessed on the basis of Bull's eye.

We defined quantitative indices for epicardial and endocardial strain as the following formula: End/Epi ratio = endocardial strain/epicardial strain.

### 2.3 | Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). The 95% confidence interval was calculated as ±1.96 SDs from the mean. Differences between groups were analyzed for statistical significance with the unpaired *t* test for normally distributed continuous variables. Comparison of continuous variables according to age groups was done with one-way ANOVA test. When a significant difference was found, post hoc testing with Bonferroni comparisons to identify specific group differences was used. The correlation between continuous variables was performed using the Pearson correlation test. Multivariable linear regression analyses were performed to examine the independent correlates between LSS and baseline parameters. The receiver operating characteristic curve and its area under the curve (AUC) were estimated using the Mann–Whitney *U* test. A *P*-value under the null hypothesis corresponded to the AUC of 0.5 (H0: AUC = 0.5). Cutoff values showing the best combination of sensitivity and specificity were identified for each continuous variable. $P < .05$ was considered statistically significant. All statistical analyses were performed using JMP 11.0 statistical software (SAS Institute).

## 3 | RESULTS

### 3.1 | Demographic data

Table 1 summarizes the demographic data of controls and HCM populations analyzed in the present study. A total of 41 controls (mean age 52 ± 18 years) and 41 HCM (mean age 52 ± 20 years) were included. The most frequent hypertrophic type according to the Maron's classification[10] was type II (n = 24, 59%), followed by type IV (n = 7, 17%), type I (n = 5, 12%), and type III (n = 5, 12%), while type V (apical HCM) was not seen. There were no significant differences between controls and HCM for age, body surface area, systolic blood pressure, diastolic blood pressure, heart rate, and LVEF. LV wall thickness, including the interventricular septum thickness, posterior wall thickness, and maximum wall thickness, LV mass index, and relative wall thickness were significantly higher in HCM.

**TABLE 1** Baseline characteristics and echocardiographic results in controls and HCM

| Parameters | Control (n = 41) | HCM (n = 41) | *P*-value |
|---|---|---|---|
| Age (years) | 52 ± 18 | 52 ± 20 | 1.00 |
| Male, n (%) | 27 (66) | 27 (66) | |
| Height (cm) | 170 ± 10 | 173 ± 11 | .24 |
| Weight (kg) | 69 ± 10 | 76 ± 18 | .04 |
| Body mass index (kg/m$^2$) | 23.7 ± 2.3 | 25.2 ± 5.0 | .10 |
| Body surface area (m$^2$) | 1.8 ± 0.2 | 1.9 ± 0.3 | .09 |
| Systolic blood pressure (mmHg) | 122 ± 13 | 130 ± 20 | .05 |
| Diastolic blood pressure (mmHg) | 76 ± 9 | 72 ± 11 | .11 |
| Heart Rate (beats/min) | 64 ± 9 | 65 ± 14 | .64 |
| Maron type (I/II/III/IV/V) | | 5/24/5/7/0 | |
| Interventricular septum thickness (mm) | 10.6 ± 11.2 | 18.9 ± 5.0 | <.001 |
| Posterior wall thickness (mm) | 10.3 ± 11.2 | 11.5 ± 2.5 | <.001 |
| Maximum wall thickness (mm) | 9.3 ± 1.7 | 20.1 ± 4.3 | <.001 |
| LA dimension (mm) | 34.2 ± 4.0 | 40.3 ± 6.0 | <.001 |
| LA atrial volume index (mL/m$^2$) | 29.0 ± 7.5 | 39.5 ± 17.1 | <.001 |
| LV end-diastolic dimension (mm) | 45.0 ± 4.0 | 41.2 ± 6.1 | <.001 |
| LV end-systolic dimension (mm) | 31.2 ± 3.9 | 26.7 ± 6.9 | <.001 |
| LV ejection fraction (%) | 62.9 ± 3.7 | 63.5 ± 8.2 | .66 |
| LV mass (g) | 129.0 ± 31.8 | 250.2 ± 78.4 | <.001 |
| LV mass index (g/m$^2$) | 70.8 ± 13.4 | 134.1 ± 43.8 | <.001 |
| Relative wall thickness | 0.4 ± 0.1 | 0.6 ± 0.2 | <.001 |
| E (cm/s) | 68.5 ± 14.6 | 75.8 ± 21.8 | .08 |
| A (cm/s) | 56.4 ± 13.7 | 64.7 ± 24.7 | .07 |
| E/A ratio | 1.3 ± 0.4 | 1.2 ± 0.6 | .70 |
| E' (cm/s) | 11.4 ± 3.2 | 7.5 ± 2.6 | <.001 |
| E/E' ratio | 6.3 ± 1.7 | 10.9 ± 5.0 | <.001 |

Abbreviations: HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricular.

*P*-value differences between HCM patients and controls.

### 3.2 | Relationship between LSS at apical 2-, 3-, and 4-chamber views

Relationships between LSS at all chamber views (apical 2-, 3-, and 4-chamber view) are shown in Table 2 and Figure 2. In all apical chamber views, LSS was significantly lower in HCM, and LSS gradually increased from the epicardial toward the endocardial

layer in both controls and HCM. End/Epi ratio was significantly higher in HCM (Controls vs. HCM; 2-chamber, 1.18 ± 0.07 vs. 1.45 ± 0.22; 3-chamber, 1.25 ± 0.09 vs. 1.51 ± 0.18; 4-chamber, 1.21 ± 0.05 vs. 1.45 ± 0.24, $P$ <.001, respectively). Furthermore, End-Epi ratio did not differ between controls and HCM in any chamber views.

### 3.3 | Relationship between LSS at basal, middle, and apical levels of the LV

Relationships between absolute LSS at basal, middle, and apical levels of the LV are shown in Table 3 and Figure 3. In all levels of the LV, LSS was significantly lower in HCM, and LSS gradually increased from the epicardial toward the endocardial layer in both controls and HCM; these results were similar to those of the previous apical chamber view classification. Notably, End/Epi ratio did not differ significantly at the basal level between controls and HCM, but it increased from middle toward apical levels to a greater extent in HCM compared with control (Controls vs. HCM; base, 1.08 ± 0.04 vs. 1.07 ± 0.16, $P$ = .53; middle, 1.11 ± 0.05 vs. 1.27 ± 0.17. $P$ < .001; apex, 1.48 ± 0.12 vs. 2.33 ± 0.87, $P$ < .001).

### 3.4 | Correlations between LV maximal wall thickness and 2DE parameters

End/Epi ratio was correlated with LV maximum wall thickness in both controls and HCM. The correlation coefficient was weak in controls (r = .35, $P$ =.03), but powerful in HCM (r = .81, $P$ < .001) (Figure 4). Multivariable analysis for LSS showed that End/Epi ratio was the strongest factor of LV maximum wall thickness (β-coefficient = 1.46, $P$ = .007) (Table 4). Receiver operating characteristic analysis revealed that a higher End/Epi ratio (≥1.31) was the strongest factor associated with the diagnostic criteria for HCM (maximum LV wall thickness ≥15 mm) (area under the curve 0.99, $P$ < .001, sensitivity 98%, specificity 95%; Figure 5).

## 4 | DISCUSSION

The present study highlights the following findings. In HCM patients with preserved LVEF, (a) LSS was lower and End/Epi ratio was higher than controls; (b) LSS increased gradually from the epicardial toward the endocardial layer at all chamber views or any level of the LV; (c) LSS, End/Epi ratio at the apex was significantly higher than the middle or basal levels of the LV; and (d) End/Epi

**TABLE 2** Absolute value of layer-specific strain at apical 2-, 3-, and 4-chamber in controls and HCM

| | Control (n = 41) | | HCM (n = 41) | | *P*-value |
|---|---|---|---|---|---|
| Variables | Mean ± SD | 95% CI | Mean ± SD | 95% CI | |
| A2C | | | | | |
| Epi (%) | 20.2 ± 2.5 | 19.4-21.0 | 13.4 ± 3.3 | 12.3-14.4 | <.001 |
| Mid (%) | 21.9 ± 2.7 | 21.0-22.7 | 16.0 ± 3.5 | 14.9-17.1 | <.001 |
| End (%) | 23.8 ± 3.0 | 22.8-24.7 | 19.1 ± 4.2 | 17.8-20.5 | <.001 |
| Average (%) | 21.9 ± 2.7 | 21.1-22.8 | 16.2 ± 3.5 | 15.0-17.3 | <.001 |
| End/Epi ratio | 1.18 ± 0.07 | 1.16-1.20 | 1.45 ± 0.22 | 1.38-1.52 | <.001 |
| A3C | | | | | |
| Epi (%) | 19.0 ± 2.4 | 18.3-19.8 | 12.6 ± 3.5 | 11.4-13.7 | <.001 |
| Mid (%) | 21.2 ± 2.5 | 20.4-22.0 | 15.4 ± 4.1 | 14.1-16.7 | <.001 |
| End (%) | 23.7 ± 2.8 | 22.8-24.6 | 18.7 ± 4.7 | 17.2-20.2 | <.001 |
| Average (%) | 21.3 ± 2.5 | 20.5-22.1 | 15.5 ± 4.1 | 14.2-16.8 | <.001 |
| End/Epi ratio | 1.25 ± 0.09 | 1.22-1.28 | 1.51 ± 0.18 | 1.45-1.57 | <.001 |
| A4C | | | | | |
| Epi (%) | 19.1 ± 1.5 | 18.7-19.6 | 13.3 ± 3.5 | 12.1-14.4 | <.001 |
| Mid (%) | 21.0 ± 1.6 | 20.5-21.5 | 15.9 ± 3.9 | 14.7-17.2 | <.001 |
| End (%) | 23.2 ± 1.8 | 22.6-23.8 | 19.0 ± 4.7 | 17.4-20.5 | <.001 |
| Average (%) | 21.1 ± 1.6 | 20.6-21.6 | 16.0 ± 4.0 | 14.8-17.3 | <.001 |
| End/Epi ratio | 1.21 ± 0.05 | 1.20-1.23 | 1.45 ± 0.24 | 1.37-1.53 | <.001 |

Abbreviations: A2C, apical 2-chamber view; A3C, apical 3-chamber view; A4C, apical 4-chamber view; CI, confidence interval; End, the absolute value of the endocardial strain; Epi, absolute value of epicardial strain; HCM, hypertrophic cardiomyopathy; Mid, absolute value of mid-myocardial strain; SD, standard deviation.

*P*-value differences between HCM and controls.

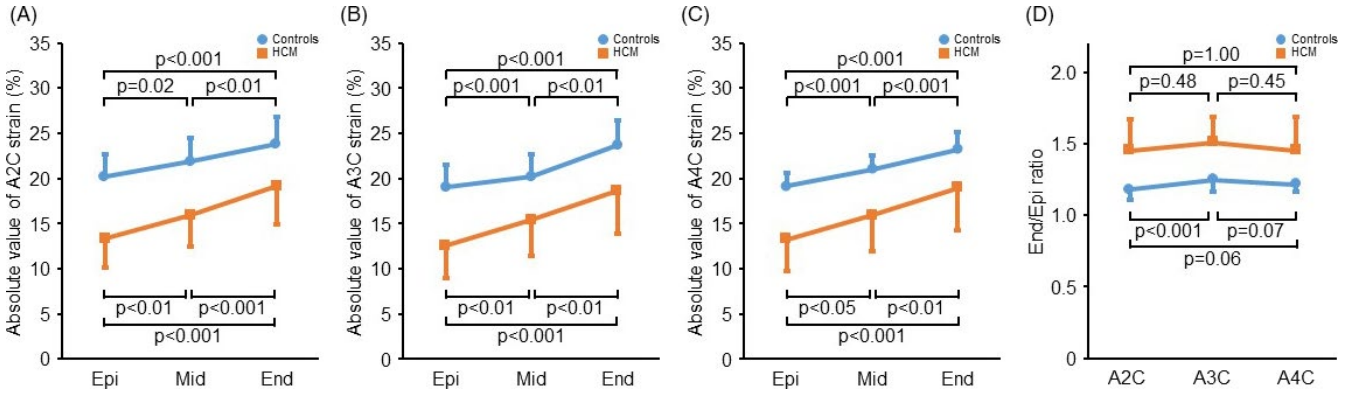


**FIGURE 2** Layer-specific strain values at (A) A2C, (B) A3C, and (C) A4C. (D) End/Epi ratio. Other abbreviations as in Figure 1

**TABLE 3** Absolute value of layer-specific strain at the basal, middle, and apical levels of left ventricle in controls and HCM

| Variables | Control (n = 41) | | HCM (n = 41) | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | 95% CI | Mean ± SD | 95% CI | |
| Base | | | | | |
| Epi (%) | 18.6 ± 1.6 | 18.1-19.1 | 11.8 ± 3.5 | 10.7-13.0 | <.001 |
| Mid (%) | 19.4 ± 1.8 | 18.8-20.0 | 12.3 ± 3.6 | 11.2-13.5 | <.001 |
| End (%) | 20.2 ± 2.0 | 19.6-20.8 | 12.5 ± 4.0 | 11.2-13.8 | <.001 |
| Average (%) | 19.4 ± 1.8 | 18.9-20.0 | 11.9 ± 4.1 | 10.6-13.2 | <.001 |
| End/Epi ratio | 1.08 ± 0.04 | 1.07-1.10 | 1.07 ± 0.16 | 1.02-1.12 | .53 |
| Mid | | | | | |
| Epi (%) | 19.7 ± 1.7 | 19.2-20.2 | 12.7 ± 3.5 | 11.6-19.2 | <.001 |
| Mid (%) | 20.5 ± 1.9 | 19.9-21.1 | 14.4 ± 3.9 | 13.2-15.6 | <.001 |
| End (%) | 21.9 ± 1.9 | 21.3-22.5 | 16.3 ± 4.7 | 14.8-17.8 | <.001 |
| Average (%) | 20.7 ± 1.7 | 20.2-21.2 | 14.1 ± 4.5 | 12.7-15.5 | <.001 |
| End/Epi ratio | 1.11 ± 0.05 | 1.10-1.13 | 1.27 ± 0.17 | 1.21-1.33 | <.001 |
| Apex | | | | | |
| Epi (%) | 20.3 ± 2.5 | 19.5-21.1 | 13.1 ± 4.4 | 11.7-14.5 | <.001 |
| Mid (%) | 24.4 ± 2.8 | 23.5-25.3 | 18.1 ± 8.8 | 15.3-20.9 | <.001 |
| End (%) | 30.0 ± 3.6 | 28.9-31.2 | 28.7 ± 7.4 | 26.4-31.1 | <.001 |
| Average (%) | 24.9 ± 2.9 | 24.0-25.8 | 19.5 ± 6.3 | 17.5-21.5 | <.001 |
| End/Epi ratio | 1.48 ± 0.12 | 1.45-1.52 | 2.33 ± 0.87 | 2.05-2.61 | <.001 |

Abbreviations: A2C, apical 2-chamber view; A3C, apical 3-chamber view; A4C, apical 4-chamber view; CI, confidence interval; End, the absolute value of the endocardial strain; Epi, absolute value of epicardial strain; HCM, hypertrophic cardiomyopathy; Mid, absolute value of mid-myocardial strain; SD, standard deviation.

ratio was correlated with LV maximum wall thickness, and the value above 1.31 was the strongest factor associated with abnormal LV wall thickness in HCM.

All values of LSS were lower in HCM, and these values increased gradually from the epicardial toward the endocardial layer in both controls and HCM. These results are consistent with previous studies,[11-13] but detailed mechanisms of structural and functional abnormalities of myocardial tissue in HCM remains to be established.

In apical 2-, 3-, or 4-chamber view, End/Epi ratio was significantly higher at all views in HCM compared with controls. This result may be attributable to a decrease in the circumferential strain value in the mid-myocardial and epicardial layers due to myocardial disarray and fibrosis.[13] In the present study, the patients with Maron's classification type I, II, and III showing hypertrophic lesions in the LV septal segments accounted for 83% of the enrolled patients, while it was not present in the remaining 17%. Thus, hypertrophic lesions were heterogeneously distributed, but End/Epi ratio was elevated uniformly in all of 2-, 3-, and 4-chamber views in HCM compared with controls. In hypertrophic lesions, interstitial fibrosis and myocardial disarray are mainly seen pathological findings. Furthermore, interstitial fibrosis which was reported to be associated with a reduction in LSS is

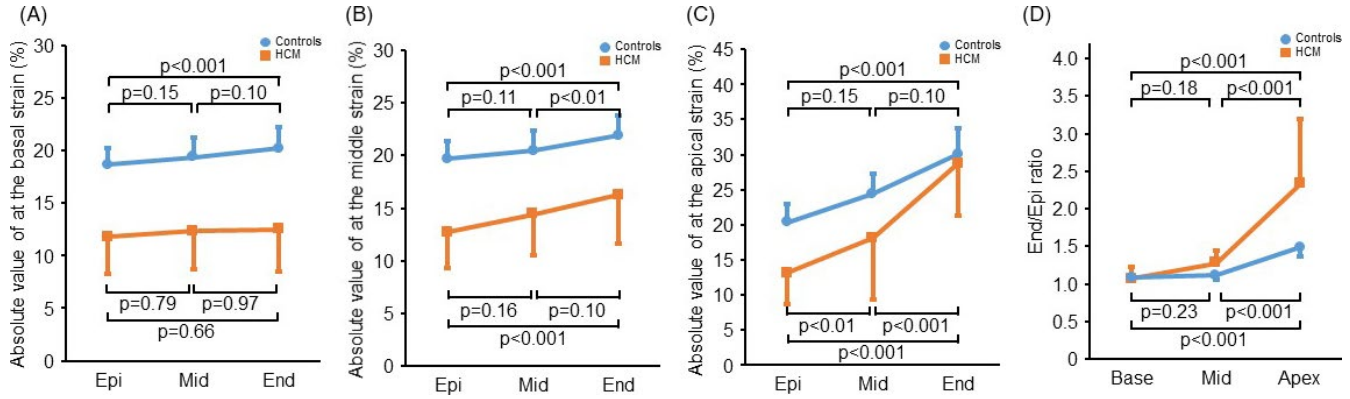


**FIGURE 3** Layer-specific strain values at (A) base, (B) middle, and (C) apex. (D) End/Epi ratio at each level of the LV. Other abbreviations as in Figure 1

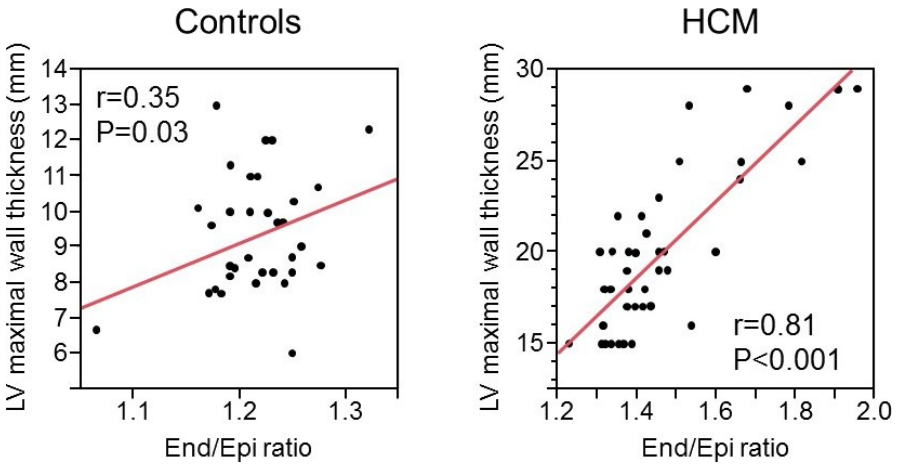


**FIGURE 4** Relationship between End/epi ratio and left ventricular maximal wall thickness in controls and HCM

**TABLE 4** Univariable and multivariable predictors of left ventricular maximal wall thickness in HCM

| | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | *t* value | *P*-value | β | 95% CI | *t* value | *P*-value |
| Age | −0.0094 | −0.07 to 0.07 | −0.06 | .95 | | | | |
| Sex | −0.13 | −4.07 to 1.70 | −0.83 | .41 | | | | |
| BMI | −0.52 | −0.67 to −0.20 | −3.75 | .0006 | | | | |
| SBP | −0.075 | −0.09 to 0.05 | −0.47 | .64 | | | | |
| DBP | −0.15 | −0.19 −0.07 | −0.93 | .36 | | | | |
| LVEF | 0.14 | −0.10 to 0.24 | 0.88 | .38 | | | | |
| Epi | 0.38 | 0.11 to 0.99 | 2.51 | .02 | | | | |
| Mid | 0.19 | −0.17 to 0.67 | 1.21 | .23 | −7.26 | −15.9 to 2.4 | −2.77 | .01 |
| End | 0.015 | −0.35 to 0.39 | 0.09 | .93 | 5.25 | 1.24 to 10.1 | 2.62 | .01 |
| End/Epi ratio | 0.81 | 15.96 to 25.85 | 8.56 | <.001 | 1.46 | 11.4 to 64.0 | 2.94 | .007 |

Abbreviations: A2C, apical 2-chamber view; A3C, apical 3-chamber view; A4C, apical 4-chamber view; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; End, the absolute value of the endocardial strain; Epi, absolute value of epicardial strain; HCM, hypertrophic cardiomyopathy; LVEF left ventricular ejection fraction; Mid, absolute value of mid-myocardial strain; SBP, systolic blood pressure; SD, standard deviation.

heterogeneously distributed in all myocardial layers[14] and myocardial disarray is mainly distributed in mid-myocardial layer but its relationship with LSS is unknown.[15] In nonhypertrophic lesions, there is no macroscopically abnormal LV wall structure, but LSS is lower than in normal heart.[14] Therefore, LSS may have the potential to detect immature functional changes or subclinical dysfunction in nonhypertrophic

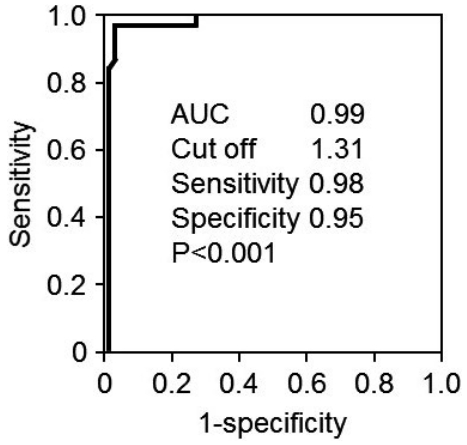


**FIGURE 5** Receiver operating curve of the End/Epi ratio for predicting diagnostic criteria for HCM

segments, and reduction in LSS in nonhypertrophic lesions may have resulted in a uniform reduction in all apical views.

In basal, middle, or apical levels of the LV, absolute LSS increased gradually from the epicardial toward the endocardial layer in both controls and HCM. Whereas this increase in LSS from epicardial toward the endocardial layer was not significant at the basal level, it was prominent at apical level in HCM (Figure 3A,C). As a result, End/Epi ratio was significantly higher at apex than those at middle or basal LSS, especially in HCM (Figure 3D,E). The preserved endocardial strain at apex cannot be explained by the previously reported HCM-related pathological findings such as a heterogeneous distribution of interstitial fibrosis or predominant distribution of myocardial disarray in mid-myocardial layer. Although its mechanism remains unknown, this feature might be an important factor in differentiating other hypertrophic heart disease, such as hypertensive heart disease.[13]

In this study, endocardial strain at apical level was preserved comparable to that of controls, resulting in the apical End/Epi ratio was significantly higher at any level (Table 3 and Figure 3). End/Epi ratio was correlated with LV maximum wall thickness (Figure 4) and the value of 1.31 was the strong factor associated with abnormal wall thickness of HCM (Figure 5). Moreover, the results of our multivariable analysis (Table 4) suggest that End/Epi ratio may have the potential to be a feasible marker to detect HCM regardless of age, gender, or body mass index. The hypertrophied myocardium may remodel differently in response to various etiologies, resulting in different epicardial and endocardial strain. LSS gradient differs depending on the type of LV hypertrophic diseases such as aortic stenosis,[16] HCM,[12] and Fabry disease.[17] Therefore, End/Epi ratio can distinguish the etiologies of hypertrophied myocardium.

### 4.1 | Limitations

This study presents several limitations. First, the number of patients enrolled was small and located in a single center; therefore, our results should be confirmed in a large population. Second, LSS is unable to evaluate all 3 layers in markedly thickened LV segments. However, our study did not contain cases with markedly thickened LV wall. Third, since this study was conducted only on GE equipment, other equipment data are not sufficient. However, in our previous study, it has been reported that there are no differences between GE and Philips equipment in the longitudinal strain.[18] Fourth, since this study did not obtain CT, CMR, or pathological data, our LSS data were not validated by the other types of imaging.

## 5 | CONCLUSION

In HCM patients with preserved LVEF, LSS can elucidate the pathophysiology of impaired LV wall motion in HCM and accurately detect HCM.

### CONFLICT OF INTEREST

None.

### AUTHOR CONTRIBUTIONS

Toshimitsu Tsugu: Concept/design, Data collection, Statistics, Drafting article, Data analysis/interpretation. Raluca Dulgheru: Critical revision of article. Yuji Nagatomo: Drafting article, Critical revision of article. Patrizio Lancellotti: Concept/design, Drafting article, Critical revision of article, Approval of article.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### REFERENCES

1. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733-2779.
2. Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:1778-1785.
3. Greenbaum RA, Ho SY, Gibson DG, et al. Left ventricular fibre architecture in man. *Br Heart J*. 1981;45:248-263.
4. Ishizu T, Seo Y, Kameda Y, et al. Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease. *Hypertension*. 2014;63:500-506.
5. Stohr EJ, Shave RE, Baggish AL, et al. Left ventricular twist mechanics in the context of normal physiology and cardiovascular disease: a review of studies using speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol*. 2016;311:H633-H644.
6. Lancellotti P, Badano LP, Lang RM, et al. Normal Reference Ranges for Echocardiography: rationale, study design, and methodology (NORRE Study). *Eur Heart J Cardiovasc Imaging*. 2013;14:303-308.
7. Tsugu T, Postolache A, Dulgheru R, et al. Echocardiographic reference ranges for normal left ventricular layer-specific strain: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging*. 2020;21:896-905.

8. Manganaro R, Marchetta S, Dulgheru R, et al. Echocardiographic reference ranges for normal non-invasive myocardial work indices: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging*. 2019;20:582-590.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233-270.
10. Maron BJ, Gottdiener JS, Epstein SE. Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. A wide angle, two dimensional echocardiographic study of 125 patients. *Am J Cardiol*. 1981;48:418-428.
11. Okada K, Yamada S, Iwano H, et al. Myocardial shortening in 3 orthogonal directions and its transmural variation in patients with nonobstructive hypertrophic cardiomyopathy. *Circ J*. 2015;79:2471-2479.
12. Ozawa K, Funabashi N, Takaoka H, et al. Characteristic myocardial strain identified in hypertrophic cardiomyopathy subjects with preserved left ventricular ejection fraction using a novel multi-layer transthoracic echocardiography technique. *Int J Cardiol*. 2015;184:237-243.
13. Sun JP, Xu TY, Ni XD, et al. Echocardiographic strain in hypertrophic cardiomyopathy and hypertensive left ventricular hypertrophy. *Echocardiography*. 2019;36:257-265.
14. Yajima R, Kataoka A, Takahashi A, et al. Distinguishing focal fibrotic lesions and non-fibrotic lesions in hypertrophic cardiomyopathy by assessment of regional myocardial strain using two-dimensional speckle tracking echocardiography: comparison with multislice CT. *Int J Cardiol*. 2012;158:423-432.
15. Kuribayashi T, Roberts WC. Myocardial disarray at junction of ventricular septum and left and right ventricular free walls in hypertrophic cardiomyopathy. *Am J Cardiol*. 1992;70:1333-1340.
16. Ozawa K, Funabashi N, Kobayashi Y. Left ventricular myocardial strain gradient using a novel multi-layer transthoracic echocardiography technique positively correlates with severity of aortic stenosis. *Int J Cardiol*. 2016;221:218-226.
17. Esposito R, Santoro C, Sorrentino R, et al. Layer-specific longitudinal strain in Anderson-Fabry disease at diagnosis: a speckle tracking echocardiography analysis. *Echocardiography*. 2019;36:1273-1281.
18. Sugimoto T, Dulgheru R, Bernard A, et al. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging*. 2017;18:833-840.

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