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ORIGINAL PAPER

3-Dimensional regional and global strain abnormalities in hypertrophic cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is characterized by myocardial disarray, hypertrophy, and fibrosis. Reduced global longitudinal strain and presence of late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (CMR) have been associated with an adverse prognosis. This study evaluated 3D principal and conventional strain characteristics of non-enhanced myocardium in patients with HCM. 3D principal and conventional strain analysis was conducted in 51 HCM patients and 38 healthy controls. Principal strain was reduced within the non-enhanced myocardium of HCM as compared with controls (maximum principal: 51.5 ± 23.7 vs. 75.1 ± 21.4%, P < 0.0001; minimum principal: − 18.4 ± 4.0 vs. − 20.1 ± 2.9%, P < 0.05). Principal strain within the non-enhanced myocardium was incrementally reduced in HCM patients with extensive global LGE (≥ 15%) (maximum principal: 41.6 ± 17.5 vs. 56.9 ± 25.9%, P < 0.05; minimum principal: − 16.9 ± 3.9 vs. − 19.1 ± 4.0%, P = 0.1), as was longitudinal (− 10.5 ± 2.6 vs. − 12.7 ± 2.6%, P < 0.05) and circumferential strain (− 11.0 ± 2.7 vs. − 14.0 ± 2.9%, P < 0.01). Principal strain within non-enhanced myocardium was significantly correlated with indexed LV mass (P < 0.0001), maximum (P = 0.0008), and mean wall thickness (P < 0.0001), but not LGE (P = 0.0841). In adjusted analysis, all strain measures within non-enhanced myocardium were independently associated with indexed LV mass (maximum principal: P = 0.0003; minimum principal: P = 0.0039; longitudinal: P = 0.0015; circumferential: P = 0.0002; radial: P = 0.0023). 3D principal strain of non-enhanced myocardium was significantly reduced in HCM patients as compared with controls, and was incrementally reduced among patients with more extensive global LGE. Comprehensive strain assessment may be considered in routine CMR assessment of HCM patients.

Keywords Contractile function · Cardiomyopathy · Hypertrophy · Magnetic resonance imaging

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by abnormalities of the cardiac sarcomere that results in varying degrees of myocardial disarray, hypertrophy, and fibrosis [1]. The extent of left ventricular hypertrophy (LVH) may predispose to symptoms and adverse prognosis [2]. Although the left ventricular ejection fraction (LVEF) may be normal or hyperdynamic in HCM, regional function may be impaired, often in the areas of greatest hypertrophy [3].

Myocardial strain evaluation using cardiac magnetic resonance imaging (CMR) tagging has shown greater sensitivity for regional contractile dysfunction than LVEF [4]. Global longitudinal strain has been shown to be reduced in HCM as compared with controls and may be associated with an adverse prognosis [5]. However, CMR tagging requires

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Bobak Heydari takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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additional prospective imaging, time-consuming post processing, and suffers from fading of the tagged contrast due to longitudinal magnetization recovery [4]. In addition, assessment of strain in HCM using conventional directions (longitudinal, circumferential, and radial) may only partially quantify overall myocardial deformation and 2D methods may introduce error from through-plane displacement of 3D structures [6]. Alternatively, principal strain analysis describes deformation in the predominant 3D local directions in which contraction or thickening occurs [7–9, 12, 13]. Recently, CMR feature-tracking (FT-CMR) techniques allow for quantitative analysis of myocardial strain by tracking the endocardial and epicardial borders of the LV from routinely acquired cine imaging [8, 12, 13], including principal strain analysis [12, 13].

Quantitative assessment of replacement fibrosis by late gadolinium enhancement imaging (LGE) has been associated with an increased risk of sudden cardiac death [2, 9]. However, the absence of LGE may not necessarily confer a low enough risk to preclude implantable cardioverter-defibrillator implantation [2], and may underestimate the presence and severity of fibrosis [10]. Characterization of regional strain within non-enhanced myocardium, which may have undergone pathological changes without overt replacement fibrosis or hypertrophy [10], provides further insight into the residual function of the LV, in addition to potentially quantifiable diagnostic and prognostic markers for the evaluation of both patients with suspected or established HCM.

In this study, we sought to evaluate regional 3D principal and conventional (circumferential, radial, and longitudinal) strain characteristics by FT-CMR within the non-enhanced myocardium of patients with HCM as compared to healthy volunteers. We hypothesize that both principal and conventional strain characteristics within myocardium free from LGE are abnormal in patients with HCM as compared to healthy controls, particularly for those with more extensive global LGE. In addition, we hypothesize the existence of discrepancies in this strain reduction across all available measures of strain. In this regard, we seek to assess which particular strain characteristics may highlight this reduction.

Methods

Study subjects

We evaluated 51 consecutive adult patients ($\geq$ 18 years of age) referred for CMR with a diagnosis of HCM by echocardiographic parameters (maximal LV wall thickness $\geq$ 15 mm) and clinical evaluation by a cardiologist. Healthy control subjects were volunteers without any history of cardiac disease, coronary artery disease risk factors (hypertension, hyperlipidemia, or diabetes), or use of regularly prescribed medication. Exclusion criteria included any known contraindication to cardiac MRI, specifically: gadolinium intolerance, severe renal impairment (glomerular filtration rate < 30 ml/min/1.73 m^2) for HCM patients, metallic hazards, or pregnant state. Additional exclusion criteria included those patients with atrial fibrillation and prior septal myectomy or alcohol septal ablation. Prior to CMR, trained study personnel collected detailed clinical data and medical history. The institutional ethics review board approved the study, and informed consent was obtained from all patients.

Cardiac MRI

CMR studies were performed using a 3.0-T scanner (Magnetom Trio, Siemens, Erlangen, Germany) with a 32-element cardiac coil. Cine imaging was performed in both contiguous short axis (8 mm, 2 mm spacing) and long axis views (4-chamber, 2-chamber and 3-chamber) using steady-state free precession (SSFP) imaging (repetition time 3.4 ms; echo time 1.2 ms; matrix 256 × 256). LGE imaging was performed 10–15 min after intravenous gadolinium contrast administration (0.15 mmol/kg; Gadovist; Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ) using an inversion recovery gradient echo sequence with inversion time chosen to maximally null septal myocardium.

All LGE and volumetric analysis was performed by blinded core laboratory personnel using commercially available software (cvi42; Circle Cardiovascular Inc., Calgary, Canada). Sequential short axis cine images underwent semi-automated contour tracing of the endocardial and epicardial contours to obtain indexed LV end-diastolic volume (LVEDVI), end-systolic volume (LVESVI), ejection fraction (EF), and LV mass (LVMI), as previously described [9]. Sequential short axis LGE images were analyzed to obtain total LGE burden as a percentage of total myocardial mass. LGE quantification was performed using semi-automated signal thresholds of > 3 SDs beyond mean nulled myocardium [11].

3D strain analysis

FT-CMR strain analysis was performed by a blinded study investigator using in-house built and validated software [12, 13]. An end-diastolic 3D mesh of the LV was created from the subendocardial and subepicardial contours of long-axis LV views after alignment. Feature tracking was performed for all pixels on each slice throughout the cardiac cycle. The 2D velocity field obtained for each view was used to reconstruct the 3D velocity field, taking into account the orientation of each acquired view in the patient-specific coordinate system, in-plane resolution, and the distance from each node

of the 3D LV mesh. In its turn, each node of the mesh was instructed on its motion throughout the cardiac cycle via the reconstructed 3D velocity field. Using a finite-element approach [14], the deformation of each element was projected in radial, circumferential, longitudinal, and principal local directions, in order to compute radial, circumferential, longitudinal, and principal strain, respectively. Specifically, principal strain was defined as strain in the directions (principal directions) describing the totality of the deformation of each element of the mesh without neglecting the shear deformation [12, 13]. Therefore, in order to obtain the values of maximum and minimum principal strain, the three principal directions are obtained as an orthogonal coordinate system allowing the description of the deformation status without shear. The deformations associated to the three directions are then evaluated. Finally, maximum and minimum principal strain are defined as the most positive and the most negative of the three principal strain amplitudes, respectively. These measures of strain were obtained for subendocardial, subepicardial, and transmural measures in the form of 17-segment AHA polar maps. Myocardial segments ≥ 5% LGE (to ensure AHA segments with a small volume of artifact were not excluded) by volume were excluded to yield strain values for the non-enhanced myocardium of each patient. Subendocardial and subepicardial elements were obtained from the deformation of 4-node mesh elements defined on the subendocardial and subepicardial surfaces, respectively. Conversely, transmural strain was obtained from the deformation of 8-node elements obtained combining the nodal position a 4-node subendocardial and a 4-node epicardial element.

Statistical analysis

Categorical variables were presented as counts with percentages, while continuous variables were expressed as means ± standard deviation or as median values with interquartile range depending on normality of distributions. Categorical variables were compared using the Fisher's exact test, while comparisons for continuous data were performed using 2-sample Student *t* test or Wilcoxon rank-sum test, where appropriate. Multiple comparisons between HCM patients stratified by extent of global LGE (less than or greater than 15%, a threshold associated with increased risk of adverse cardiac events) [2] and healthy control patients were performed using Dunnett's test. Relationships between strain parameters and cardiac MRI characteristics were evaluated with linear regression analysis. Multivariable linear regression analysis was performed to evaluate for an independent association between both principal and conventional strain characteristics of the non-enhanced myocardium and LVH (LVMI) as a marker of global disease severity.

All statistical analysis was performed using commercially available software (SAS version 9.4, SAS Institute, Cary, North Carolina). A two-sided P-value of less than 0.05 was considered statistically significant.

Results

Study subjects

Fifty-one consecutive HCM patients and 38 healthy volunteers were included in this study. Three HCM patients (6%) had non-interpretable LGE imaging and were excluded from analysis. Baseline demographics and CMR characteristics are shown in Table 1 for HCM patients and healthy volunteers. Mean age of the HCM population was 52.8 ± 14.2 years versus 41.0 ± 11.6 years for the healthy volunteers ($P < 0.0001$). HCM patients had a male preponderance (65%) and significantly higher prevalence of diabetes ($P < 0.05$), hypertension ($P < 0.0001$), and hyperlipidemia ($P < 0.001$). Two healthy volunteers (5%) were active smokers of less than 1 pack per day. As compared with controls, HCM patients had a higher LVEF (74.9 ± 9.0% vs. 64.4 ± 5.9%, $P < 0.0001$), LVMI (91.8 ± 28.2 g vs. 55.5 ± 9.5 g, $P < 0.0001$), mean LV wall thickness (10.3 ± 2.3 mm vs. 5.0 ± 0.9 mm, $P < 0.0001$), and RVEF (67.5 ± 9.4% vs. 51.5 ± 4.7%, $P < 0.0001$); while LVESVI (16.0 ± 7.6 ml/m^2 vs. 25.6 ± 7.4 ml/m^2, $P < 0.0001$), and LVEDVI (62.6 ± 14.6 ml/m^2 versus 71.1 ± 12.1 ml/m^2) were significantly lower. The mean maximum wall thickness was 18.9 ± 5.7 mm for the HCM cohort, LGE was present in 41 (80%) of HCM patients with a mean global LGE volume of 15.0 ± 16.0%. Overall, 56% of HCM patients were taking beta-blockers, while 34% were on an angiotensin antagonist.

HCM patients with more extensive global LGE (≥ 15%) were younger in age (48.2 ± 13.4 years vs. 56.2 ± 12.9 years, $P < 0.05$), had a lower mean BMI (25.7 ± 4.6 kg/m^2 vs. 29.2 ± 5.5 kg/m^2, $P < 0.05$), and LVEF (70.5 ± 10.2% vs. 77.6 ± 7.5%, $P < 0.01$); whereas LVESVI (20.3 ± 8.8 vs. 13.3 ± 5.7, $P < 0.01$), LVEDVI (67.8 ± 18.1 vs. 58.6 ± 11.5, $P < 0.05$), and total percent of LGE (32 ± 12% vs. 4 ± 4%, $P < 0.05$) were significantly higher in these patients. There were no differences for medication use by HCM patients with more extensive LGE.

3D strain analysis of non-enhanced myocardium

3D strain results for both mean principal and conventional strain measures of myocardium free from LGE are shown in Table 2. Maximum principal strain in the non-enhanced myocardium was significantly reduced in HCM patients compared with controls (51.5 ± 23.7 vs. 75.1 ± 21.4, $P < 0.0001$). Transmural and epicardial minimum principal

Table 1 Baseline clinical characteristics of healthy control subjects and patients with hypertrophic cardiomyopathy

Parameter	Controls (n = 38)	All HCM (n = 51)	P value	All HCM (n = 51)		P value
				LGE < 15% (n = 30)	LGE < 15% (n = 18)	
Clinical characteristics						
Age (years)	41.0 ± 11.6	52.8 ± 14.2	**< 0.0001**	56.2 ± 12.9	48.2 ± 13.4	**< 0.05**
Female	20 (53%)	18 (35%)	0.13	10 (33%)	8 (44%)	0.54
Body surface area (m^2)	1.9 ± 0.3	2.0 ± 0.3	**< 0.05**	2.1 ± 0.3	1.9 ± 0.2	**< 0.05**
Body mass index (kg/m^2)	24.8 ± 4.1	27.8 ± 5.3	**< 0.01**	29.2 ± 5.5	25.7 ± 4.6	**< 0.05**
DBP (mmHg)	71.2 ± 10.2	76.3 ± 11.5	**< 0.05**	77.7 ± 12.7	72.7 ± 9.3	0.16
SBP (mmHg)	114.7 ± 12.8	128.5 ± 18.8	**< 0.001**	133.1 ± 17.8	119.3 ± 18.4	**< 0.05**
Weight (kg)	73.5 ± 16.5	83.8 ± 18.7	**< 0.01**	88.5 ± 20.2	75.8 ± 14.9	**< 0.05**
Height (m)	171.4 ± 9.1	173.6 ± 10.7	0.31	173.8 ± 10.7	171.6 ± 10.5	0.48
Heart rate (bpm)	65.9 ± 9.5	62.3 ± 13.0	0.16	62.5 ± 10.3	61.39 ± 17.2	0.79
GFR (ml/min)	NA	81.2 ± 19.0	NA	80.3 ± 17.6	81.96 ± 21.8	0.78
QRS (ms)	92.7 ± 10.0	100.0 18.0	0.15	97.2 ± 17.4	98.9 ± 13.7	0.74
Angina, n (%)	0 (0%)	21 (41%)	**< 0.0001**	11 (37%)	9 (50%)	0.38
Hypertension, n (%)	0 (0%)	22 (43%)	**< 0.0001**	15 (50%)	5 (28%)	0.23
Diabetes mellitus	0 (0%)	6 (12%)	**< 0.05**	3 (10%)	2 (11%)	1
Hyperlipidemia	0 (0%)	13 (25%)	**< 0.001**	10 (33%)	1 (6%)	**< 0.05**
Smoking, n (%)	2 (5%)	9 (18%)	0.11	8 (27%)	1 (6%)	0.13
LBBB, n (%)	0 (0%)	1 (2%)	1	1 (3%)	0 (0%)	1
NYHA, n (%)			**0.002**			
I	38 (100%)	35 (69%)				
II	0 (0%)	10 (20%)				
III	0 (0%)	5 (10%)				
IV	0 (0%)	1 (2%)				
Medications						
Aspirin	0 (0%)	13 (27%)	**< 0.001**	8 (30%)	3 (17%)	0.48
Beta-blocker	0 (0%)	27 (56%)	**< 0.0001**	18 (67%)	8 (44%)	0.22
ACE-inhibitor/ARB	0 (0%)	16 (34%)	**< 0.0001**	9 (33%)	5 (29%)	1
Statin	0 (0%)	13 (27%)	**< 0.001**	9 (33%)	2 (11%)	0.16
Oral anticoagulant	0 (0%)	6 (13%)	**< 0.05**	4 (15%)	2 (11%)	1
Calcium channel blockers	0 (0%)	9 (19%)	**< 0.01**	6 (22%)	2 (11%)	0.45
CMR characteristics						
LVEDVI (ml/m^2)	71.1 ± 12.1	62.6 ± 14.6	**< 0.01**	58.6 ± 11.5	67.8 ± 18.1	**< 0.05**
LVESVI (ml/m^2)	25.6 ± 7.4	16.0 ± 7.6	**< 0.0001**	13.3 ± 5.7	20.3 ± 8.8	**< 0.01**
LVEF (%)	64.4 ± 5.9	74.9 ± 9.0	**< 0.0001**	77.6 ± 7.5	70.5 ± 10.2	**< 0.01**
LVMI (g/m^2)	55.5 ± 9.5	91.8 ± 28.2	**< 0.0001**	92.7 ± 30.6	92.0 ± 26.7	0.94
RVEDVI (ml/m^2)	76.5 ± 12.1	59.3 ± 20.1	**< 0.01**	57.4 ± 19.7	61.6 ± 22.3	0.49
RVESVI (ml/m^2)	37.2 ± 7.0	19.5 ± 10.0	**< 0.0001**	18.7 ± 9.2	21.7 ± 11.7	0.34
RVEF (%)	51.5 ± 4.7	67.5 ± 9.4	**< 0.0001**	67.6 ± 8.3	65.8 ± 11.0	0.52
LGE positive, n (%)	0 (0%)	41 (80%)	**< 0.0001**	23 (77%)	18 (100%)	**< 0.05**
LGE (%)	0.0 ± 0.0	15.0 ± 16.0	**< 0.0001**	4.0 ± 4.0	32.0 ± 12.0	**< 0.0001**
LV mean wall thickness (mm)	5.0 ± 0.9	10.3 ± 2.3	**< 0.0001**	10.3 ± 2.5	10.5 ± 2.1	0.74
LV maximal wall thickness (mm)	7.1 ± 1.3	18.9 ± 5.7	**< 0.0001**	19.0 ± 5.4	19.5 ± 6.6	0.79

Bold highlights P-values lower than 0.05

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *DBP* diastolic blood pressure, *GFR* globular filtration hypertrophic cardiomyopathy, *LBBB* left bundle branch block, *LGE* late gadolinium enhancement, *NYHA* new york heart asclassification, *LVEDVI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVESVI* left ventricular volume index, *LVMI* left ventricular mass index, *NA* not applicable, *QRS* QRS duration, *RVEDVI* right ventricular end-diastolic, *RVEF* right ventricular ejection fraction, *RVESVI* right ventricular end-systolic volume index, *SBP* systolic blood pressure

Table 2 Principal and conventional strain characteristics of non-enhanced myocardium

Parameter	Controls (n = 38)	All HCM (n = 51)	P value	All HCM		P value
				LGE < 15% (n = 30)	LGE ≥ 15% (n = 18)	
Principal directions						
Maximum	75.1 ± 21.4	51.5 ± 23.7	**< 0.0001**	56.9 ± 25.9	41.6 ± 17.5	**< 0.05**
Minimum						
Transmural	− 20.1 ± 2.9	− 18.4 ± 4.0	**< 0.05**	− 19.1 ± 4.0	− 16.9 ± 3.9	0.1
Endocardial	− 22.9 ± 3.1	− 23.2 ± 5.1	0.78	− 24.5 ± 5.2	− 20.5 ± 4.3	**< 0.05**
Epicardial	− 16.9 ± 2.7	− 14.1 ± 3.6	**< 0.001**	− 14.2 ± 3.7	− 13.6 ± 3.9	0.62
Conventional directions						
Circumferential						
Transmural	− 15.1 ± 2.1	− 13.0 ± 3.1	**< 0.001**	− 14.0 ± 2.9	− 11.0 ± 2.7	**< 0.01**
Endocardial	− 19.4 ± 2.5	− 18.9 ± 4.6	0.51	− 20.4 ± 4.4	− 15.8 ± 3.8	**< 0.01**
Epicardial	− 10.0 ± 1.8	− 8.2 ± 2.3	**< 0.0001**	− 8.8 ± 2.4	− 7.1 ± 2.0	**< 0.05**
Longitudinal						
Transmural	− 12.6 ± 2.4	− 12.0 ± 2.7	0.32	− 12.7 ± 2.6	− 10.5 ± 2.6	**< 0.05**
Endocardial	− 15.3 ± 2.8	− 15.7 ± 4.4	0.6	− 17.0 ± 4.2	− 13.0 ± 4.0	**< 0.01**
Epicardial	− 10.0 ± 1.9	− 9.2 ± 2.3	0.11	− 9.4 ± 2.6	− 8.8 ± 1.7	0.41
Radial	56.7 ± 16.9	32.1 ± 19.6	**< 0.0001**	35.7 ± 22.5	26.0 ± 12.7	0.13

Bold highlights P-values lower than 0.05

HCM hypertrophic cardiomyopathy, *LGE* late gadolinium enhancement

strain was also reduced in HCM patients as compared with controls, while there was no significant difference for endocardial minimum principal strain. For the conventional strain measures, circumferential transmural (− 13.0 ± 3.1 vs. − 15.1 ± 2.1, P < 0.001), circumferential epicardial (− 8.2 ± 2.3 vs. − 10.0 ± 1.8, P < 0.0001), and radial strain (32.1 ± 19.6 vs. 56.7 ± 16.9, P < 0.0001) were all significantly reduced in HCM patients as compared with controls. There were no significant differences for any measures of longitudinal strain (transmural, epicardial, or endocardial) between the non-enhanced myocardium of HCM patients and healthy volunteers.

For HCM patients with more extensive global LGE (≥ 15%), maximum principal strain (41.6 ± 17.5 vs. 56.9 ± 25.9, P < 0.05), and both circumferential transmural (− 11.0 ± 2.7 vs. − 14.0 ± 2.9, P < 0.01), and circumferential epicardial (− 7.1 ± 2.0 vs. − 8.8 ± 2.4, P < 0.05) remained significantly reduced. Radial strain was not significantly different (26.0 ± 12.7 vs. 35.7 ± 22.5, P = 0.13) between the HCM groups. Although not significantly different between HCM patients and healthy volunteers, certain measures of strain were significantly reduced in HCM patients with more extensive global LGE (endocardial minimum principal strain, circumferential strain, and both transmural and endocardial longitudinal strain). Multiple group comparisons are shown in Fig. 1 between HCM patients stratified by proportion of global LGE (≥ 15%) for maximum and minimum transmural principal strain, as well as conventional transmural strain measures.

Global 3D strain analysis

Global 3D strain results, inclusive of all myocardial segments irrespective of LGE, are shown in Table 3 for both HCM patients and healthy volunteers. HCM patients had significantly reduced maximum principal strain (45.1 ± 17.7 vs. 75.1 ± 21.4, P < 0.0001), transmural minimum principal (− 18.0 ± 3.6 vs. − 20.1 ± 2.9, P < 0.01), and epicardial minimum principal strain (− 16.9 ± 2.7 vs. − 13.4 ± 3.2, P < 0.0001) compared with healthy controls. Multiple conventional strain measures, including transmural circumferential, epicardial circumferential, radial, and transmural longitudinal and epicardial longitudinal were significantly reduced in HCM patients as compared with controls. Evaluation of global 3D strain in patients with more extensive global LGE (≥ 15%) revealed reduced transmural (− 10.3 ± 2.8 vs. − 12.0 ± 2.5, P < 0.05) and endocardial longitudinal strain (− 13.5 ± 3.5 vs. − 16.0 ± 3.1, P < 0.05) measures. No other comparison of strain measures reached statistical significance.

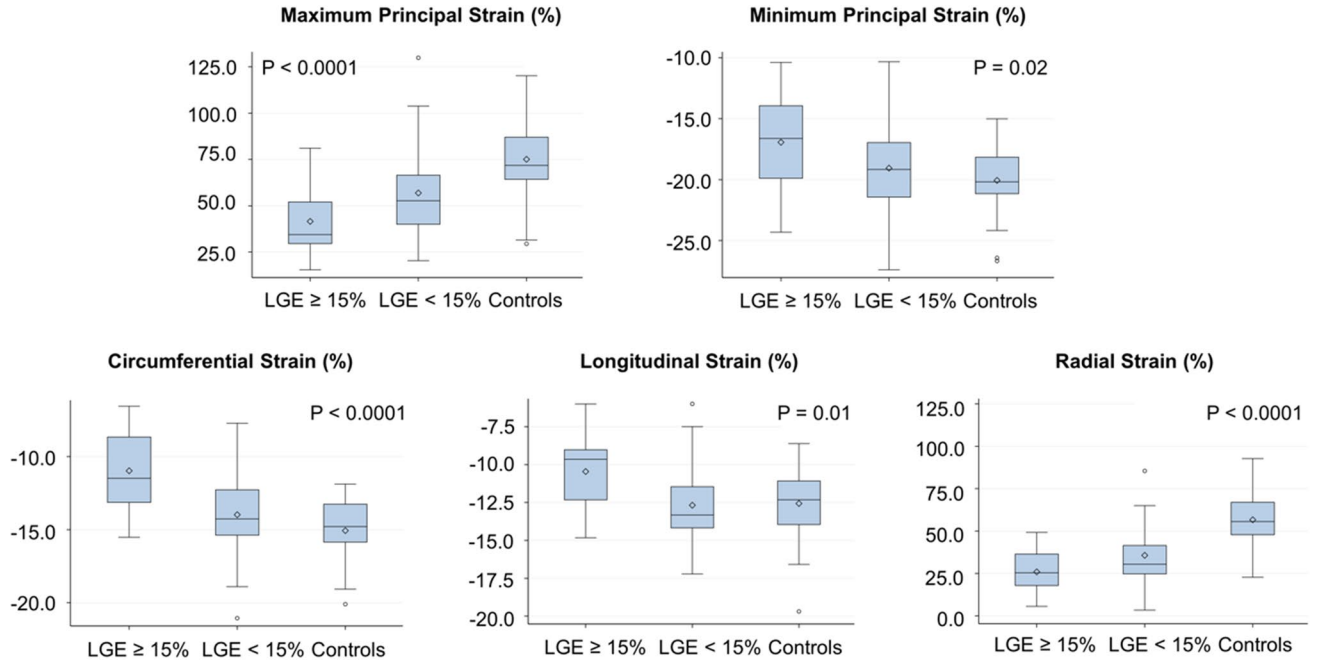

Fig. 1 Comparisons of principal and conventional non-enhanced myocardial strain characteristics for controls and HCM patients stratified by proportion of LGE (≥ 15%). Group comparisons between HCM patients stratified by proportion of LGE (≥ 15%) for maximum and minimum transmural principal strain, as well as conventional transmural strain measures. *P < 0.05 for comparisons to the healthy control group

Table 3 Principal and conventional global strain characteristics

Parameter	Controls (n = 38)	All HCM (n = 51)	P value	All HCM		P value
				LGE < 15% (n = 30)	LGE ≥ 15% (n = 18)	
Principal directions						
Maximum	75.1 ± 21.4	45.1 ± 17.7	**< 0.0001**	48.7 ± 18.4	38.8 ± 16.6	0.07
Minimum						
Transmural	− 20.1 ± 2.9	− 18.0 ± 3.6	**< 0.01**	− 18.5 ± 3.4	− 16.9 ± 3.9	0.13
Endocardial	− 22.9 ± 3.1	− 23.0 ± 4.4	0.98	− 23.7 ± 4.3	− 21.5 ± 4.6	0.1
Epicardial	− 16.9 ± 2.7	− 13.4 ± 3.2	**< 0.0001**	− 13.7 ± 3.1	− 12.5 ± 3.2	0.22
Conventional directions						
Circumferential						
Transmural	− 15.1 ± 2.1	− 12.8 ± 2.7	**< 0.0001**	− 13.3 ± 2.5	− 11.9 ± 3.0	0.08
Endocardial	− 19.4 ± 2.5	− 18.9 ± 3.8	0.47	− 19.7 ± 3.7	− 17.5 ± 3.9	0.05
Epicardial	− 10.9 ± 1.8	− 8.0 ± 2.1	**< 0.0001**	− 8.4 ± 2.1	− 7.4 ± 2.0	0.11
Longitudinal						
Transmural	− 12.6 ± 2.4	− 11.5 ± 2.6	**< 0.05**	− 12.0 ± 2.5	− 10.3 ± 2.8	**< 0.05**
Endocardial	− 15.3 ± 2.8	− 15.1 ± 3.3	0.84	− 16.0 ± 3.1	− 13.5 ± 3.5	**< 0.05**
Epicardial	− 10.0 ± 1.9	− 8.6 ± 2.3	**< 0.01**	− 9.0 ± 2.3	− 7.8 ± 2.3	0.08
Radial	56.7 ± 16.9	28.7 ± 13.7	**< 0.0001**	31.0 ± 14.9	25.2 ± 12.1	0.17

Bold highlights P-values lower than 0.05

HCM hypertrophic cardiomyopathy, *LGE* late gadolinium enhancement

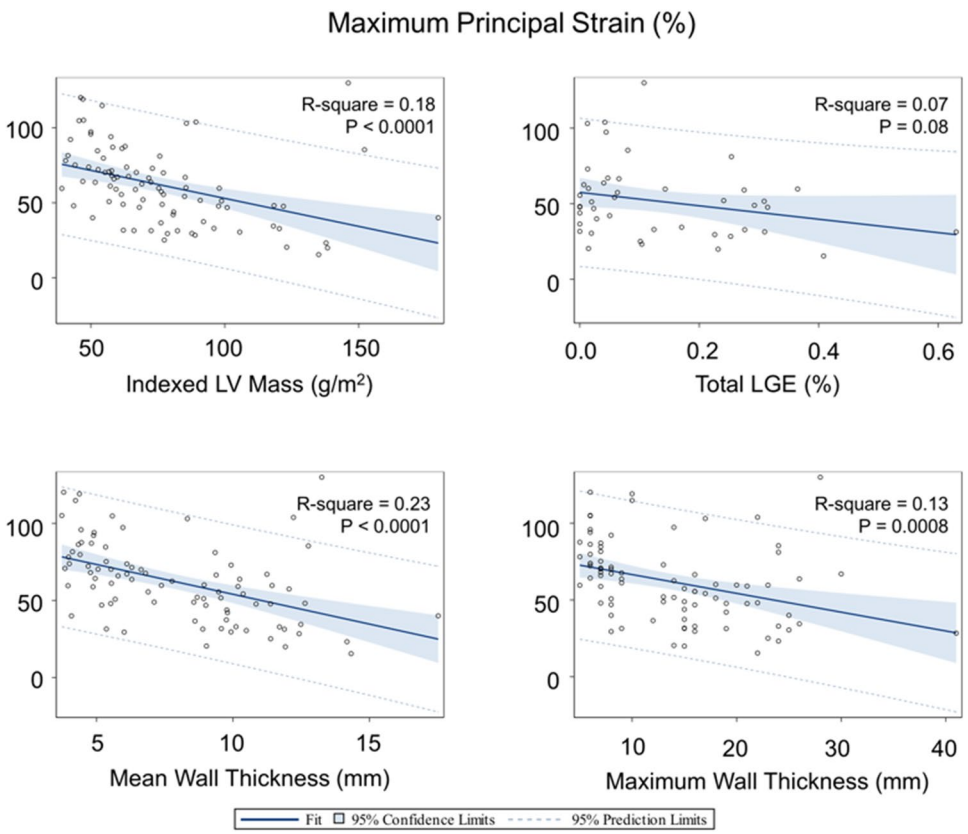

Fig. 2 Maximum principal strain of non-enhanced myocardium versus LV characteristics. Linear regression analysis for maximum principal strain of the non-enhanced myocardium and LV characteristics

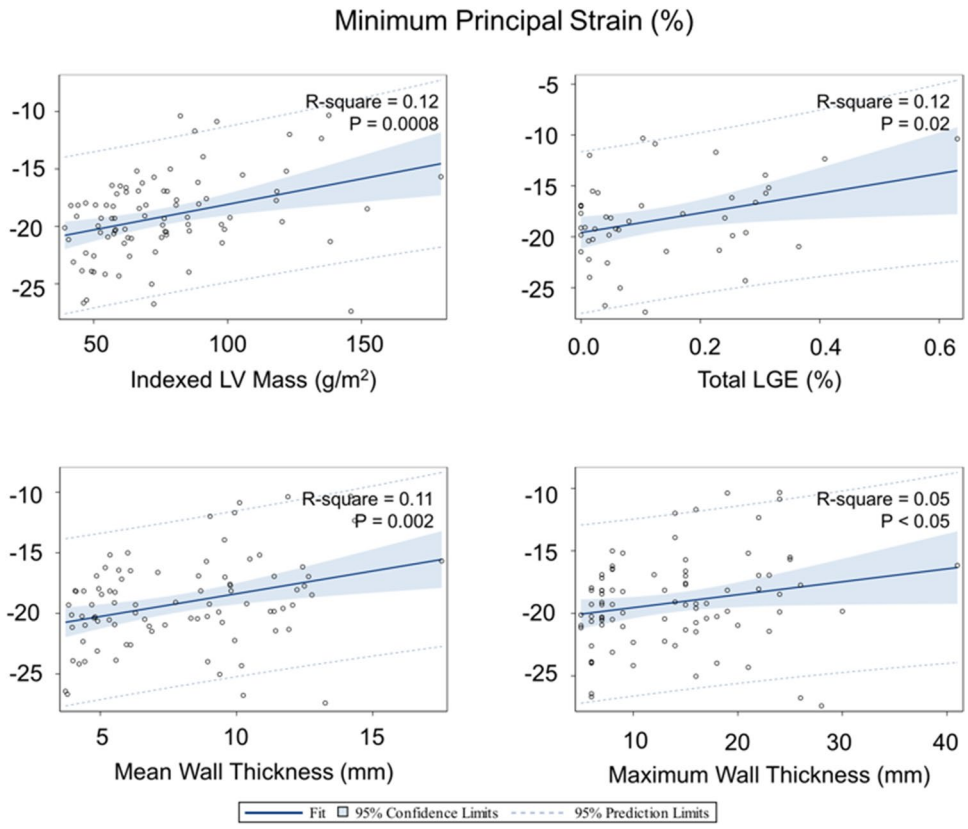

Fig. 3 Minimum principal strain of non-enhanced myocardium versus LV characteristics. Linear regression analysis for minimum principal strain of non-enhanced myocardium and LV characteristics

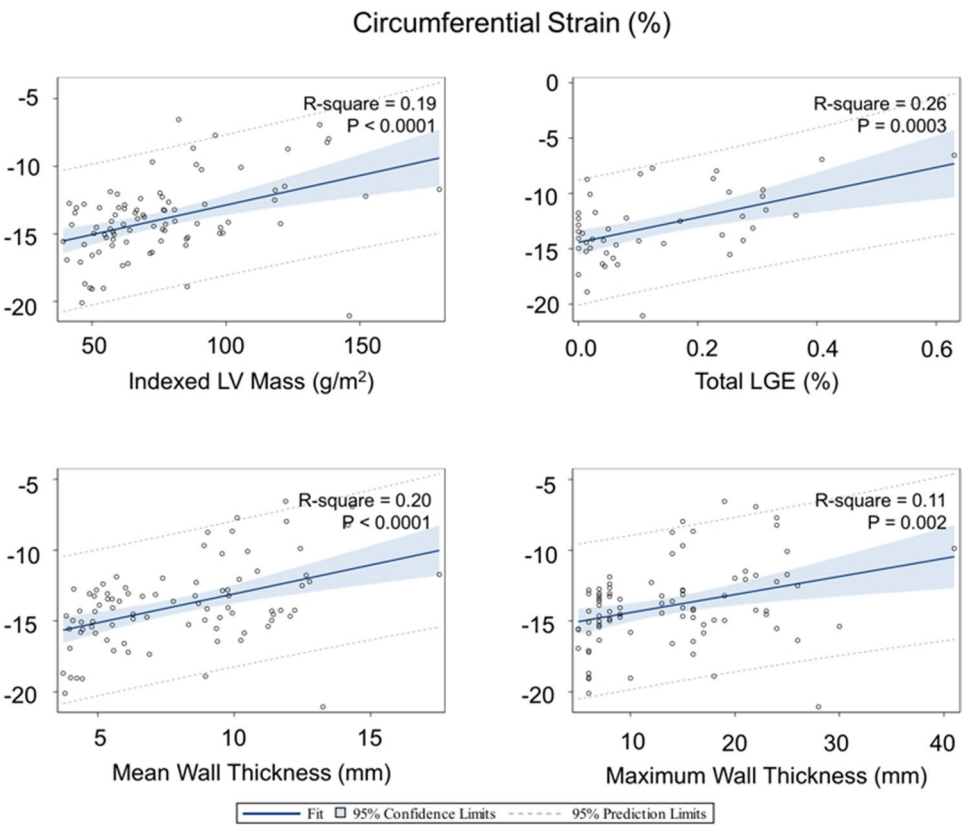

Fig. 4 Circumferential strain of non-enhanced myocardium versus LV characteristics. Linear regression analysis for circumferential strain of non-enhanced myocardium and LV characteristics

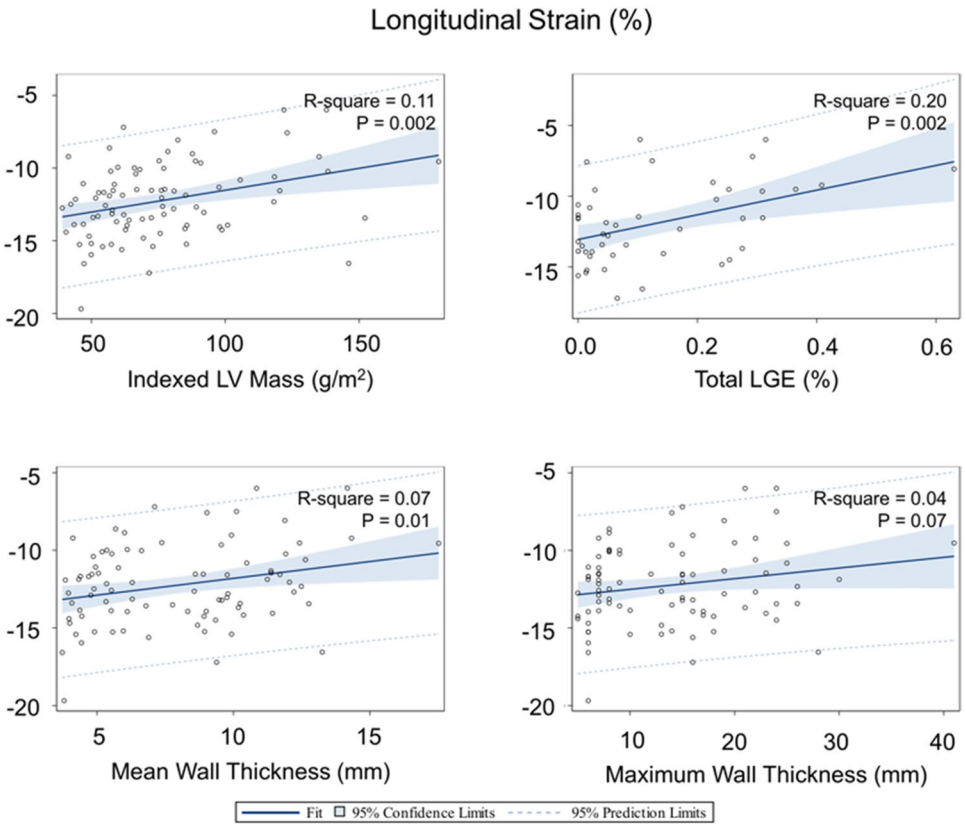

Fig. 5 Longitudinal strain of non-enhanced myocardium versus LV characteristics. Linear regression analysis for longitudinal strain of non-enhanced myocardium and LV characteristics

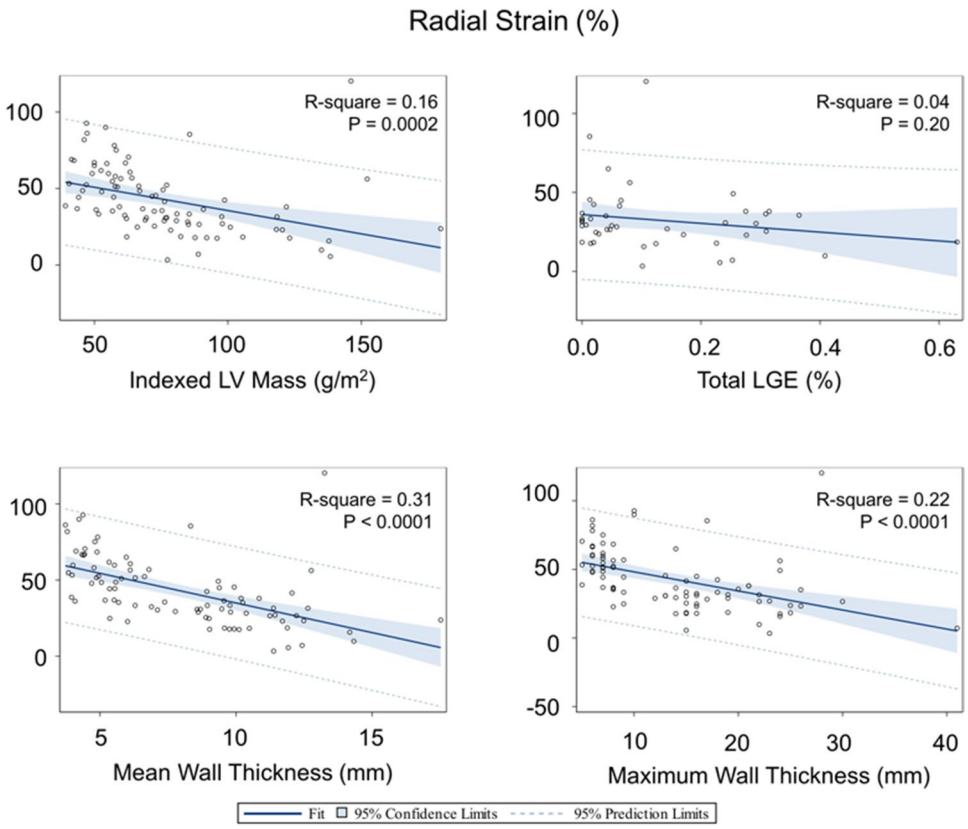

Fig. 6 Radial strain of non-enhanced myocardium versus LV characteristics. Linear regression analysis for radial strain of non-enhanced myocardium and LV characteristics

Association of non-enhanced myocardial 3D strain with LV measures

Linear regression analysis for maximum and minimum principal strain of the non-enhanced myocardium and LV characteristics are shown in Figs. 2 and 3, respectively. Maximum principal strain was strongly correlated with LVMI ($R^2 = 0.18$, $P < 0.0001$), maximal wall thickness ($R^2 = 0.13$, $P = 0.0008$), and mean wall thickness ($R^2 = 0.23$, $P < 0.0001$). No correlation was found with global LGE. Similarly, minimum principal strain was also correlated with LVMI ($R^2 = 0.12$, $P = 0.0008$), maximal ($R^2 = 0.05$, $P < 0.05$), and mean ($R^2 = 0.11$, $P = 0.002$) wall thickness, in addition to global LGE ($R^2 = 0.12$, $P = 0.02$). Correlations for conventional 3D strain measures of the non-enhanced myocardium with LV characteristics are shown in Figs. 4, 5 and 6. Transmural circumferential strain was correlated with LVMI, maximal and mean wall thickness, and global LGE ($P < 0.01$ for all). Transmural longitudinal and radial strain measures were both correlated with LVMI and mean wall thickness ($P < 0.01$ for all). Radial strain was not significantly correlated with global LGE and transmural longitudinal strain was not correlated with maximal wall thickness.

Multivariable regression analysis was performed with increasing levels of covariate adjustment (Table 4) for prediction of LVMI. Age, hypertension status, and body mass index (BMI) were added to the unadjusted model (Model 1) as fixed covariates (Model 2). Additional adjustment with global LGE as a measure of HCM disease severity was included in Model 3. After adjustment by fixed covariates, all measures of principal strain, with the exception of endocardial minimum principal strain, were significantly correlated with LVMI ($P < 0.01$ for all). Conventional 3D strain measures of non-enhanced myocardium also demonstrated significant correlation with LVMI ($P < 0.01$ for all), with the exception of endocardial derived strain values (longitudinal and circumferential). After adjustment for global LGE (Model 3), epicardial minimum principal ($R^2 = 0.29$, $P = 0.0007$), epicardial circumferential ($R^2 = 0.35$, $P = 0.0001$), transmural longitudinal ($R^2 = 0.20$, $P = 0.009$), and epicardial longitudinal ($R^2 = 0.28$, $P = 0.0009$) strain measures remained significantly correlated with LVMI. There was also a marginally significant correlation between LVMI and both transmural minimum principal ($R^2 = 0.12$, $P = 0.08$) and transmural circumferential ($R^2 = 0.13$, $P = 0.05$) strain measures (Model 3).

Table 4 Multivariable regression analysis of strain characteristics for prediction of LVMI

Parameter	Model 1			Model 2			Model 3		
	R^2	β, 95% CI	P	R^2	β, 95% CI	P	R^2	β, 95% CI	P
Principal directions									
Maximum	0.18	− 0.37, − 0.55 to − 0.20	**< 0.0001**	0.29	− 0.42, − 0.64 to − 0.20	**0.0003**	0.07	− 0.22, − 0.63 to 0.18	0.26
Minimum									
Transmural	0.12	0.04, 0.02 to 0.07	**0.0008**	0.24	2.32, 0.76 to 3.87	**0.004**	0.12	2.13, − 0.27 to 4.53	0.08
Endocardial	0.003	0.008, − 0.02 to 0.04	0.61	0.17	0.60, − 0.75 to 1.96	0.38	0.05	0.34, − 1.64 to 2.32	0.73
Epicardial	0.33	0.07, 0.05 to 0.09	**< 0.0001**	0.38	4.09, 2.58 to 5.60	**< 0.0001**	0.29	4.21, 1.91 to 6.52	**0.0007**
Conventional directions									
Longitudinal									
Transmural	0.11	0.03, 0.01 to 0.05	**0.002**	0.26	3.52, 1.38 to 5.66	**0.002**	0.20	4.66, 1.25 to 8.07	**0.009**
Endocardial	0.006	0.010, − 0.02 to 0.04	0.49	0.17	0.93, − 0.65 to 2.51	0.25	0.06	0.97, − 1.39 to 3.33	0.41
Epicardial	0.20	0.03, 0.019 to 0.05	**< 0.0001**	0.31	5.26, 2.74 to 7.79	**< 0.0001**	0.28	6.39, 2.81 to 9.96	**0.0009**
Circumferential									
Transmural	0.19	0.04, 0.02 to 0.06	**< 0.0001**	0.29	3.75, 1.84 to 5.66	**0.0002**	0.13	3.25, − 0.005 to 6.51	0.05
Endocardial	0.01	0.01, − 0.01 to 0.04	0.34	0.17	0.87, − 0.66 to 2.40	0.26	0.04	0.24, − 2.12 to 2.60	0.84
Epicardial	0.42	0.06, 0.04 to 0.07	**< 0.0001**	0.46	6.74, 4.75 to 8.72	**< 0.0001**	0.35	7.63, 4.06 to 11.20	**0.0001**
Radial	0.16	− 0.30, − 0.46 to − 0.15	**0.0002**	0.25	− 0.42, − 0.69 to − 0.16	**0.002**	0.04	− 0.03, − 0.52 to 0.46	0.91

Bold highlights P-values lower than 0.05

CI confidence interval, R^2 R-square, *P* P value

Model 1, unadjusted model; Model 2, adjusted for age, hypertension status, and body mass index; Model 3, adjusted for age, hypertension status, body mass index, and late gadolinium enhancement

Discussion

This study reports the first comprehensive evaluation of both 3D principal and conventional strain characteristics in HCM patients by routinely acquired cine imaging using CMR and their variation as compared with healthy volunteers. In comparison with controls, both mean principal and conventional myocardial strain characteristics were all significantly reduced within the non-enhanced myocardium of HCM patients, with the exception of longitudinal strain. Mean principal, circumferential, and longitudinal strain measures were also incrementally reduced within the non-enhanced myocardium of HCM patients with more extensive global LGE (≥ 15%). Additionally, in adjusted multivariable regression analysis, all mean principal and conventional strain characteristics of the non-enhanced myocardium were significantly associated with LVMI. These findings suggest that 3D strain analysis may provide further discrimination of residual contractile function and disease severity beyond global LGE, as well as the potential to evaluate earlier stages of pathology with high technical feasibility.

The presence and extent of global LGE, which is a non-invasive measure of dense replacement fibrosis [5], has been associated with an adverse prognosis in HCM [2]. However, the myocyte hypertrophy that defines HCM is a diffuse process that may occur concomitantly with increased interstitial fibrosis and altered myocardial energetics independently of LVH [15]. Expansion of the extracellular volume fraction measured by CMR [10] and upregulation of myocardial type I collagen synthesis [1] have been shown in the absence of LGE in HCM patients, as well as in sarcomere mutation carriers without established LVH, and is associated with diastolic dysfunction [16]. In combination with LVH, which can alter both regional and global cardiac performance [17], the extent of abnormal strain within the non-enhanced myocardium may enhance our understanding of HCM disease progression and subsequent risk of adverse cardiovascular outcomes. Although LGE is generally irreversible, earlier degrees of diffuse fibrosis and hypertrophy within the non-enhanced myocardium may be dynamic and modifiable by novel therapies [18]. We observed that 3D principal and conventional strain characteristics were more abnormal for those HCM patients with a greater extent of global LGE, suggesting that quantifying the pathological variations in strain along all its directional measures may be of interest in characterizing disease progression or higher risk phenotypes. Furthermore, 3D strain analysis does not require the administration of gadolinium contrast that is contraindicated in patients with significant renal impairment, providing a

potentially independent marker of functional impairment and disease severity for these patients.

Numerous 2D and 3D studies assessing strain characteristics with MRI tagging and speckle tracking echocardiography (STE) in patients with HCM have reported reduced global longitudinal strain, with divergent results for circumferential strain [7, 17, 19]. In particular, recent studies with 3D STE have shown conflicting results for global circumferential strain [19]. In contrast to prior studies, we evaluated principal strain, which provides an integrated evaluation of the magnitude and direction of myocardial deformation, that may provide a more reproducible and facile assessment of cardiac strain within HCM patients. Additionally, our study demonstrates the capability to evaluate both regional and global transmural, endocardial, and epicardial strain in all directions for characterization of myocardial contraction. When comparing statistically significant differences for global mean peak systolic strain characteristics, maximum principal strain had much greater differences in magnitude (75.1 ± 21.4 vs. 45.1 ± 17.7, $P < 0.0001$) than conventional strain parameters. Furthermore, in this study both epicardial and transmural parameters of global circumferential, longitudinal, and radial strain were reduced for HCM, consistent with prior strain studies using CMR tagging [3, 7]. Interestingly, there were no differences for either principal or conventional global strain characteristics measured on the endocardial surface. Longitudinal strain of the non-enhanced myocardium was not significantly different between controls and HCM patients, but was statistically different amongst HCM patients with more extensive LGE. This would suggest longitudinal strain may be a less sensitive marker of myocyte disarray and interstitial fibrosis than principal or circumferential strain, exhibiting differences only in more advanced stages of disease. These findings suggest that a multi-layer (subepicardial, subendocardial and transmural) and multi-directional approach to strain analysis for HCM may be preferable. Additionally, this study found more significant differences in subepicardial strain between controls and HCM than in its subendocardial counterpart. We hypothesize this may be due to the variance in extent that the subendocardial portion of our ventricular mesh demonstrates according to the level of hypertrophy of the patients. While not proven, these results are in accordance to other deformation analysis in HCM by Zhao et al. [20], who also reported higher diagnostic value for subepicardial strain measures in differentiating HCM patients from healthy controls.

This study has a number of important limitations, chiefly the small sample size, and single-center, cross-sectional design. Furthermore, histological data evaluating the degree of myocyte disarray and diffuse interstitial fibrosis within the non-enhanced myocardium was not available, which would have provided an enhanced understanding of the association between these structural changes and reductions in myocardial strain. Torsion or twist were not available from the developed software strain platform at the time when the study was conducted. Shear measures were not provided, as shear consists of six components, each in their turn dependent on a combination of two chosen axes and their order. However, the mutable nature of shear is the reason why more concise measures of strain are provided, such as principal strain. While T1-mapping has gained interest as an independent marker of diffuse interstitial fibrosis, the imaging protocol used in this study cohort did not include this particular CMR imaging technique. Furthermore, the present study does not discuss the association between left atrial size and strain markers, thus warranting its investigation in future studies. Finally, there are multiple definitions of peak systolic strain, including the maximum peak systolic strain locally achieved versus the peak systolic strain at the instant of lowest intra-cavitary volume. We chose to use the former definition for all study analysis. Despite these study limitations, we found highly consistent associations between the regional strain characteristics of non-enhanced myocardium and surrogate markers of disease severity in HCM, including LVMI and maximal wall thickness. Due to the existing challenges of risk profiling in HCM, these findings should be prospectively evaluated for associations with adverse cardiac outcomes, such as sudden cardiac death.

In conclusion, we found that both 3D principal and conventional strain characteristics of myocardium free from LGE were abnormal in HCM patients as compared to healthy controls, and that these differences were more significant for particular measures of strain. Additionally, HCM patients with more extensive global LGE, a risk factor for adverse cardiac events, demonstrated further incremental reductions in principal, circumferential, and longitudinal peak systolic strain. These imaging markers of myocardial contractile dysfunction were evaluated from routinely acquired cine CMR imaging without the need for contrast administration and with high technical feasibility. Accordingly, comprehensive measurement of regional and global 3D principal strain may represent an important tool in the evaluation of disease pathophysiology and progression in HCM.

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Compliance with ethical standards

Conflict of interest Dr. Andrew G. Howarth receives consulting fees from Amgen. Dr. Nowell M. Fine receives consulting fees from Novartis and Pfizer. Dr. James A. White receives support from Circle Cardiovascular Inc., and is a shareholder of Cohesic Inc. All other authors declare no conflict of interest. This research was funded in part by the Calgary Health Trust.

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