Cardiac Magnetic Resonance Feature-Tracking Identifies Preclinical Abnormalities in Hypertrophic Cardiomyopathy Sarcomere Gene Mutation Carriers

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BACKGROUND: Assessing myocardial strain by cardiac magnetic resonance feature tracking (FT) has been found to be useful in patients with overt hypertrophic cardiomyopathy (HCM). Little is known, however, of its role in sarcomere gene mutation carriers without overt left ventricular hypertrophy (subclinical HCM).

METHODS: Thirty-eight subclinical HCM subjects and 42 healthy volunteers were enrolled in this multicenter case-control study. They underwent a comprehensive cardiac magnetic resonance study. Two-dimensional global radial, circumferential, and longitudinal strain of the left ventricle (LV) were evaluated by FT analysis.

RESULTS: The subclinical HCM sample was 41 (22–51) years old and 32% were men. FT analysis revealed a reduction in global radial strain (29±7.2 versus 47.9±7.4; $P<0.0001$), global circumferential strain (−17.3±2.6 -versus -20.8±7.4; $P<0.0001$) and global longitudinal strain (−16.9±2.4 versus −20.5±2.6; $P<0.0001$) in subclinical HCM compared with control subjects. The significant differences persisted when considering the 23 individuals free of all the structural and functional ECG and cardiac magnetic resonance abnormalities previously described. Receiver operating characteristic curve analyses showed that the differential diagnostic performances of FT in discriminating subclinical HCM from normal subjects were good to excellent (global radial strain with optimal cut-off value of 40.43%: AUC, 0.946 [95% CI, 0.93–1.00]; sensitivity 90.48%, specificity 94.44%; global circumferential strain with cut-off, −18.54%: AUC, 0.849 [95% CI, 0.76–0.94]; sensitivity, 88.10%; specificity, 72.22%; global longitudinal strain with cut-off, −19.06%: AUC, 0.843 [95% CI, 0.76–0.93]; sensitivity, 78.57%; specificity, 78.95%). Similar values were found for discriminating those subclinical HCM subjects without other phenotypic abnormalities from healthy volunteers (global radial strain with optimal cut-off 40.43%: AUC, 0.966 [95% CI, 0.92–1.00]; sensitivity, 90.48%; specificity, 95.45%; global circumferential strain with cut-off, −18.44%: AUC, 0.866 [95% CI, 0.76–0.96]; sensitivity, 92.86%; specificity, 77.27%; global longitudinal strain with cut-off, −17.32%: AUC, 0.838 [95% CI, 0.73–0.94]; sensitivity, 90.48%; specificity, 65.22%).

CONCLUSIONS: Cardiac magnetic resonance FT-derived parameters are consistently lower in subclinical patients with HCM, and they could emerge as a good tool for discovering the disease during a preclinical phase.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiac magnetic resonance ■ early phenotypes ■ feature tracking ■ hypertrophic cardiomyopathy ■ sarcomere gene mutation carriers ■ strain imaging

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CLINICAL PERSPECTIVE

Pathogenic gene mutations in hypertrophic cardiomyopathy (HCM) induce subtle cardiac structural changes before the development of left ventricular hypertrophy and, usually, before overt clinical manifestations. The clinical management (ie, the identification and diagnosis of early phenotypic abnormalities, surveillance/follow-up, preventive strategies, and potential early treatments) of mutation carriers without overt hypertrophic phenotype remains a challenge. More advanced imaging techniques may help identify early phenotypic abnormalities in HCM gene mutation carriers. Since assessing myocardial strain by cardiac magnetic resonance feature tracking (FT) has been found to be useful in patients with overt HCM, we hypothesized that FT is also abnormal in subclinical HCM. In this multicenter study, we explored the role of FT in subclinical HCM. The results provide important information for clinicians. First, with the use of cardiac magnetic resonance-FT subtle myocardial dysfunction is detectable in subclinical HCM. Second, strain is reduced in subclinical HCM regardless of the presence of other instrumental abnormalities. Third, the identification of strain abnormalities may promote stricter clinical surveillance of subclinical HCM. Finally, cardiac magnetic resonance FT analysis might become part of a multiparametric score useful for early diagnosis and for planning personalized follow-up strategies in subclinical HCM mutation carriers.

Nonstandard Abbreviations and Acronyms

CMR	cardiovascular magnetic resonance
FT	feature tracking
GCS	global peak systolic circumferential strain
GLS	global peak systolic longitudinal strain
GRS	global peak systolic radial strain
HCM	hypertrophic cardiomyopathy
LGE	late-gadolinium enhancement
LV	left ventricle
LVH	left ventricular hypertrophy
MYBPC3	myosin-binding protein C
PICP	procollagen type I C-terminal propeptide

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease affecting one in 500 of the general population. It is defined as the presence of increased left ventricular (LV) wall thickness (ie, ≥15 mm in ≥1 myocardial segments in probands or ≥13 mm in first-degree relatives, as measured using any cardiac imaging technique).[1] The proportion of HCM affected by mutations in sarcomere protein genes is ≈40%, with variable age-related clinical expressions.[2,3] HCM is probably the most frequent cause of sudden death in young people (including professional athletes).[1–3] Hence, the importance of early identification of phenotypic abnormalities in individuals who carry a causative mutation without left ventricular hypertrophy (LVH) and clinical manifestations. Cardiovascular magnetic resonance (CMR) has proved to be useful in identifying subtle morphological and functional abnormalities in sarcomere gene mutation carriers without LVH and overt clinical phenotype (subclinical HCM). These abnormalities include smaller LV volumes, myocardial crypts, increased trabeculation, and poorly formed papillary muscles, abnormal septal convexity into the LV, increased extracellular volume and anterior mitral valve leaflet elongation.[4–10] Furthermore, the quantitative measurement of myocardial strain with CMR feature-tracking (FT) techniques has been shown to be useful for prognostic stratification in patients with overt HCM.[11] Myocardial disarray, ischemia, and fibrosis, typical features of the disease, may represent the anatomic substrate underlying the impairment of myocardial deformation (strain). However, the role of CMR-FT analysis in subclinical HCM has never been adequately investigated so far. We hypothesized that (1) CMR-FT may reveal subtle functional myocardial impairment in subclinical HCM subjects; (2) CMR-FT is able to accurately distinguish subclinical HCM subjects from controls; and (3) that the aforementioned hypotheses could be confirmed also in patients with subclinical HCM but without other preclinical ECG and/or CMR abnormalities.

METHODS

The data that support the findings of this study are available from the corresponding author (G.D. Sanna) or the senior author (M. Merlo) upon reasonable request.

Study Population

This is a retrospective case-control study. Genotyped relatives of HCM probands, identified as mutation carriers without evidence of LVH (subclinical HCM) who underwent CMR, were screened for eligibility at 5 Italian university hospitals.

Inclusion criteria were (1) a family history of HCM (HCM in a first-degree relative); (2) the presence of pathogenic/likely pathogenic mutations for HCM; (3) maximal LV wall thickness <13 mm on CMR (short axis stack). Exclusion criteria were (1) contraindications to CMR (eg, pregnancy, non-CMR conditional metal foreign bodies, and severe claustrophobia); (2) known cardiovascular diseases (eg, ischemic, valvular, and hypertensive heart diseases); (3) active cancer or previous treatments (eg, chemotherapy).

For this study, subjects with subclinical HCM and without other early ECG and CMR abnormalities were considered. The following ECG abnormalities were taken into account: abnormal Q waves, T-wave inversion, and LVH. CMR abnormalities included the presence of more than two myocardial crypts, an aortic root angle ≤100°, and the presence of late-gadolinium enhancement (LGE).[4,12,13]

The study population was compared with a control group that included healthy subjects with no family history of inherited heart disease or sudden cardiac death and carrying normal ECG, echocardiogram and CMR. Controls were similar to subclinical HCM subjects for both sex and age at the time of CMR. All subclinical HCM subjects provided detailed medical history and underwent 12-lead ECG, transthoracic echocardiogram, and CMR. Furthermore, they underwent genetic testing to identify DNA sequence variants in genes with definite, strong, or moderate evidence of pathogenicity of HCM, in line with the European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society Expert Consensus Statement on the state of genetic testing for cardiac diseases.[14]

All the healthy volunteers provided detailed medical history and underwent a comprehensive CMR scan.

Trieste acted as coordinator center. The study was conducted in accordance with the Declaration of Helsinki and received institutional review board approval (CERU N.O. 43/2009, 211/2014/Em). Informed consent was obtained under the institutional review board policies of the hospital administration.

Electrocardiography and Echocardiography

Standard 12-lead electrocardiography was performed in accordance with the recommendations of the American Heart Association, and tracings were analyzed based on the existing literature.[15–17] LVH was evaluated using the Romhilt-Estes score, Sokolow-Lyon index, and Cornell voltage criteria. Pathological Q waves were defined as any Q wave with >40 ms width or a depth more than one-third of the adjacent R wave in ≥2 leads. Electrocardiographic tracings were analyzed by an experienced cardiologist (Francesco Negri) blinded to both clinical and CMR data.

Transthoracic echocardiography included standard 2-dimensional, color Doppler imaging, using commercially available ultrasound systems. Image analysis and measurements were performed according to international recommendations.[18,19] In particular, LV end-diastolic and end-systolic diameters and volumes, left atrial end-systolic diameter and volume, end-diastolic thicknesses of the interventricular septum, posterior wall, and maximum wall thickness were measured. Relative wall thickness was calculated as 2×posterior wall end-diastolic thickness/left ventricular end-diastolic diameter to avoid overestimation due to the presence of septal bulge. Left ventricular mass was calculated from M-mode or 2-dimensional images using the Devereux formula: 0.8×(1.04×[(interventricular septum+left ventricular end-diastolic diameter+posterior wall thickness (end-diastolic))^3 —(left ventricular end-diastolic diameter)^3])+0.6 g. All measurements were indexed to body surface area.[18] Echocardiographic images were centrally analyzed by an experienced cardiologist (Francesco Negri) blinded to both clinical and CMR data.

Cardiovascular Magnetic Resonance

CMR was performed using 1.5T magnets from various manufacturers (Aera, Siemens Medical Solutions, Erlangen, Germany; Achieva, Philips, Amsterdam, the Netherlands; Signa, General Electric Medical Systems, Waukesha, WI) with a cardiac phased-array receiver surface coil, ECG-gating, and breath-hold technique.

We included Steady State Free Precession cine images in 2-, 3-, and 4-chamber views, and a stack of contiguous short-axis slices from the atrioventricular plane to the apex were acquired using a Steady State Free Precession pulse sequence (temporal resolution ≤50 ms; mean acquisition pixel size≃1.6×1.6 mm; slice thickness=5–8 mm; no inter-slice gap; repetition time/echo time≃3.0/1.5 ms, flip angle 45–60°).

All CMR studies were analyzed offline by 1 expert blinded operator (A. De Luca), using a commercially available software package (CVi42, Circle Cardiovascular Imaging, Inc, Calgary, Canada). Ventricular volumes, mass, and function were assessed from serial short-axis cine loops using the standard volumetric technique, as previously described (see also Supplemental Materials).[20] Several additional parameters were evaluated, as follows: (1) maximal LV end-diastolic wall thickness on short axis images; (2) convexity of the interventricular septum into the LV from the apical 4-chamber view;[7] (3) LV-aortic root angle defined as the angle between a line drawn along the border of the interventricular septum, and a line drawn through the long axis of the aortic root;[12] (4) the presence of myocardial crypts defined as V-shaped invaginations penetrating >50% of the thickness of adjoining compact myocardium in diastole in the basal to mid-inferior LV wall and ;[4,5] (5) anterior mitral valve leaflet length (Figure 1).[5,10]

The presence of myocardial fibrosis was visually evaluated through the presence of LGE, defined as areas with increased signal intensity following contrast medium administration on

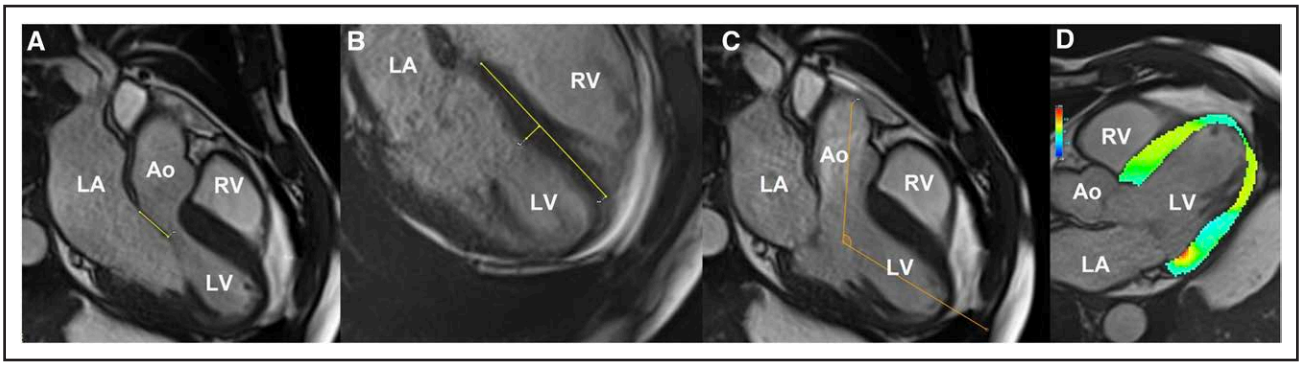

Figure 1. Cardiovascular magnetic resonance imaging.
Assessment of morphological and functional abnormalities in hypertrophic cardiomyopathy (HCM) mutation carriers. **A**, Anterior mitral valve length. **B**, Septal convexity into the left ventricle. **C**, Assessment of aorto-septal angulation. **D**, Feature tracking (global longitudinal strain). Ao indicates aorta; LV, left ventricle; LA, left atrium; and RV, right ventricle.

2 orthogonal planes. The extent of LV LGE was quantified by measuring regions with signal intensity > 6 SDs above nulled remote myocardium and expressed as percentage of total LV mass.[21]

Feature-Tracking Analysis

The assessment of LV myocardial mechanics was performed using dedicated CMR tissue tracking software (Tissue Tracking module, CVI42, Circle Cardiovascular Imaging, Calgary, Canada, version 5.3.4) by an imaging expert (M. Merlo) blinded to clinical and all other CMR data. Global peak systolic longitudinal strain (GLS) was derived from the long-axis cine images analysis, whereas global peak systolic circumferential (GCS) and radial (GRS) strain were derived from the short-axis cine images analysis, as previously described (Figure 1).[11]

Statistical Analysis

Statistical analyses were performed using Stata13 software (StataCorp, College Station, TX). All variables were tested for normality using the Shapiro-Wilk test. Results were expressed as mean±SD or median and interquartile range for continuous variables, or as number of cases and percentage for categorical variables. The Student's *t* test and Mann-Whitney *U* test or the χ^2 test and Fisher exact test were used to compare the differences between groups. $P<0.05$ values were considered statistically significant. Receiver operating characteristic curves were generated, the values of the area under the curve (AUC) calculated, and the best cut-off values of GLS, GRS, and GCS useful to distinguish G^+ from controls estimated according to the Youden index.

RESULTS

Study Population

The clinical characteristics of the study sample are summarized in Table S1. Thirty-eight subclinical HCM relatives (mean age at diagnosis 35±15 years, median age at CMR, 41 [22–51] years, males 32%) were enrolled. In the subclinical HCM subjects, a family history of sudden death was present in 13 (37%), aborted sudden death occurred in one patient during the follow-up and endomyocardial biopsy showed interstitial fibrosis and myocardial fiber disarray (Figure S1). The distribution of genetic variants is shown in Figure S2, and the main patient characteristics are described in detail in Table S2.

All subclinical HCM subjects were in sinus rhythm, and ECG criteria for LVH were present in a minority of cases (4%, Sokolow-Lyon; 4%, Romhilt-Estes score; 15% Cornell voltage criteria). T wave inversions were more common (21%), whereas abnormal Q waves were less frequently found (13%).

Mean echocardiographic LV wall thickness was 10±2 mm, relative wall thickness was 0.40, whereas median LV mass indexed by body surface area was 73 (65–85) g/m^2. None of the patients exhibited left ventricular outflow tract obstruction. Mean LV ejection fraction was 64±6%, and median E/e′ ratio was 7. CMR features are summarized in Table 1. In subclinical HCM,

Table 1. CMR Features of Subclinical HCM (ie, G^+/LVH^-) Versus Healthy Controls

	Subclinical HCM, n=38	Controls, n=42	*P* value
Male sex, n (%)	12 (32)	21 (50)	0.095
Age at CMR date, y	41 (22–51)	31.5 (28–42)	0.3046
BSA, m^2	1.72 (1.58–1.87)	1.71 (1.62–1.97)	0.583
Max wall thickness, mm	9.9±1.8	6.5±1.1	<0.0001
Site max wall thickness			
Basal anteroseptal	4 (31)		
Midanteroseptal	5 (38)		
Basal and midanteroseptal	3 (23)		
Midanteroseptal and apical septal	1 (8)		
PWd, mm	7 (6–7)	4.2 (3.7–4.8)	<0.0001
Relative wall thickness, mm	0.27 (0.24–0.30)	0.17 (0.15–0.19)	<0.0001
Left ventricular mass, g	83 (74–92)	91 (76–114)	0.07
Left ventricular mass index, g/m^2	51 (44–52)	51 (46–59)	0.08
Septal convexity into LV	1.97±3.49	−0.49±3.3	0.002
LV-aortic root angle	133±10	137±8	0.002
Myocardial crypts, n (%)	12 (32)	0 (0)	<0.001
Number of myocardial crypts, n			
1	4 (11)		
2	5 (13)		
>2	3 (8)		
Anterior mitral valve leaflet length, mm	21±3	20±2	0.004
LVEDV, mL	118 (99–146)	135 (117–149)	0.04
LVEDVi, mL/m^2	71±14	78±14	0.048
LVESV, mL	38 (29–48)	49 (38–57)	0.015
LVESVi, mL/m^2	23 (17–26)	27 (22–33)	0.009
Left ventricular ejection fraction, %	66±6	64±7	0.16
Stroke volume, mL	80 (68–99)	84 (75–97)	0.20
Stroke volume index, mL/m^2	47±8	49±9	0.17
2D global radial strain, %	29±7.2	47.9±7.4	<0.0001
2D global circumferential strain, %	−17.3±2.6	−20.8±2.2	<0.0001
2D global longitudinal strain, %	−16.9±2.4	−20.5±2.6	<0.0001
LGE, n (%)	3 (8)	0 (0)	0.103
LGE location			
IVS	1		
IVS and anterior wall	2		
Left atrial area, cm^2	21±5	N.A.	
Right ventricular hypertrophy, n (%)	1 (3)	0 (0)	0.455
Right ventricular ejection fraction, %	63±6	57±8	0.0001
Right ventricular LGE, n (%)	0 (0)	0 (0)	---
Right ventricular 2D global longitudinal strain, (%)	−24.32±5.39	−23.67±3.82	0.56

2D indicates 2 dimensional; BSA, body surface area; CMR, cardiovascular magnetic resonance; HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LGE, late gadolinium enhancement; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume indexed; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume indexed; LVH, left ventricular hypertrophy; and PWd, posterior wall diameter.

mean maximum LV wall thickness was 10±2 mm. When considering subtle cardiac structural changes, we found myocardial crypts in 12 patients (32%). (one crypt in four patients [11%)], two crypts in five patients [13%], and > 2 crypts in three patients [8%]). None of the subclinical HCM patients included in the present study had abnormal aorto-septal angulation (mean LV-aortic root angle of 133±10°).

LGE was found in 3 (8%) subclinical patients with HCM. Those with LGE were all MYBPC3 (myosin-binding protein C) mutation carriers. The extension of LGE, compared with the whole mass, was 0.6% to 2.9%. One of these patients had a completely normal ECG, 1 showed T-wave inversion, and the other LVH according to Cornell voltage criteria.

Comparison With Healthy Controls: The Role of CMR-FT Analysis

The study sample was compared with 42 healthy controls similar for both sex (*P*=0.095) and age at the moment of CMR (*P*=0.3046; median age at CMR 31 [28–42] years, 50% males, median body surface area, 1.71 m^2).

Patients with subclinical HCM showed a trend toward concentric remodeling (ie, smaller LV cavity size and higher values of both absolute and relative wall thickness). Moreover, subclinical patients with HCM showed other CMR features consistent with early phenotypic abnormalities (see Table 1 for details).

Significant differences were found in the CMR-FT analysis. In fact, subclinical HCM subjects showed altered GCS values (−17.3±2.7% in G^+/LVH^- versus −20.8±2.2% in controls; *P*<0.0001), GRS (29±7.3% versus 47.9±7.4%; *P*<0.0001) and GLS (−16.49 [−18.9/−14.7]% versus −20.49 [−22.36/−19.1]%; *P*<0.0001). Comparing the average strain values between the 23 subjects without any subtle ECG or CMR phenotypic abnormalities with the 15 subjects showing subtle ECG or CMR abnormalities (Table S2), no differences were found (Table 2). Furthermore, a significant difference in terms of myocardial strain with controls persisted when comparing subclinical HCM free of all the other structural and functional cardiac abnormalities previously described with healthy controls (GRS 27.7±7.8% in subclinical HCM versus 47.9±7.4% in controls; *P*<0.001; GCS, −16.7±2.8% versus −20.8±2.2%; *P*<0.001; and GLS, −17.0±2.4% versus −20.5±2.6%; *P*<0.001; Table 3).

We also conducted an exploratory analysis based on the fact that LV ejection fraction tends to be significantly higher in subclinical HCM, to compare the strain values between patients with (n=9) or without (n=29) LV ejection fraction of ≥70%. We did not find significant differences in terms of myocardial deformation (Table S3).

Table 2. Differences in Terms of Myocardial Strain (CMR-FT) Between Patients with Subclinical HCM With Abnormal ECG or CMR Findings and Those With Normal ECG and CMR

	ECG and CMR abnormalities−(n=23)*	ECG and CMR abnormalities+(n=15)	*P* value
GRS, %	27.7±7.8	31.2±5.8	0.16
GCS, %	−16.7±2.8	−18.1±2.1	0.14
GLS, %	−17±2.4	−16.8±2.6	0.79

CMR indicates cardiovascular magnetic resonance; FT, feature tracking; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LGE, late-gadolinium enhancement; LVH, left ventricular hypertrophy; and TWI, T-wave inversion.

*ECG abnormalities: abnormal Q waves; TWI, LVH – Cornell and Sokolow-Lyon and Romhilt-Estes criteria.

CMR abnormalities: >2 myocardial crypts, aortic root angle ≤100°, LGE.

GLS showed good diagnostic accuracy (AUC, 0.8437) in discriminating subclinical HCM subjects from controls, with the best cut-off value from controls of −19.06% (sensitivity, 78.57% and specificity, 78.95%, correctly classified, 78.75%) (Figure 2A). Thirty (>78%) subjects of 38 subclinical HCM relatives had GLS <−19.06%.

AUCs and best cut-off values were 0.8492% and 18.54% for GCS, and 0.9649% and 40.43% for GRS, respectively (Figure 2A). Similar values were found for the discrimination of subclinical HCM subjects without other phenotypic abnormalities (Figure 2B).

DISCUSSION

The penetrance of HCM genetic mutations is typically incomplete, with variable clinical expression. This means that many individuals who carry a causative mutation without overt clinical and instrumental features of the disease (mainly LVH) may be falsely reassured when they still go on to manifest HCM over time. Therefore, the early identification of abnormalities may help in the management of subclinical HCM, identifying those subjects at a higher risk of developing overt HCM and having early malignant arrhythmias. Our findings suggest that (1) myocardial deformation (strain) assessed by CMR-FT is significantly reduced subclinical HCM without phenotypic expression of the disease compared with healthy subjects; (2) CMR is able to reveal several

Table 3. Differences in Terms of Myocardial Strain (CMR-FT) Between Patients with Subclinical HCM With Normal ECG or CMR Findings and Control Group

	ECG and CMR abnormalities−(n=23)*	Control group (n=42)	*P* value
GRS, %	27.7±7.8	47.9±7.4	<0.0001
GCS, %	−16.7±2.8	−20.8±2.2	<0.0001
GLS, %	−17±2.4	−20.5±2.6	<0.0001

CMR indicates cardiovascular magnetic resonance; FT, feature tracking; GCS, global circumferential strain; GLS, global longitudinal strain; and GRS, global radial strain.

*ECG abnormalities: abnormal Q waves, TWI, LVH – Cornell and/or Sokolow-Lyon and/or Romhilt-Estes criteria.

CMR abnormalities: > 2 myocardial crypts, aortic root angle £ 100°, LGE.

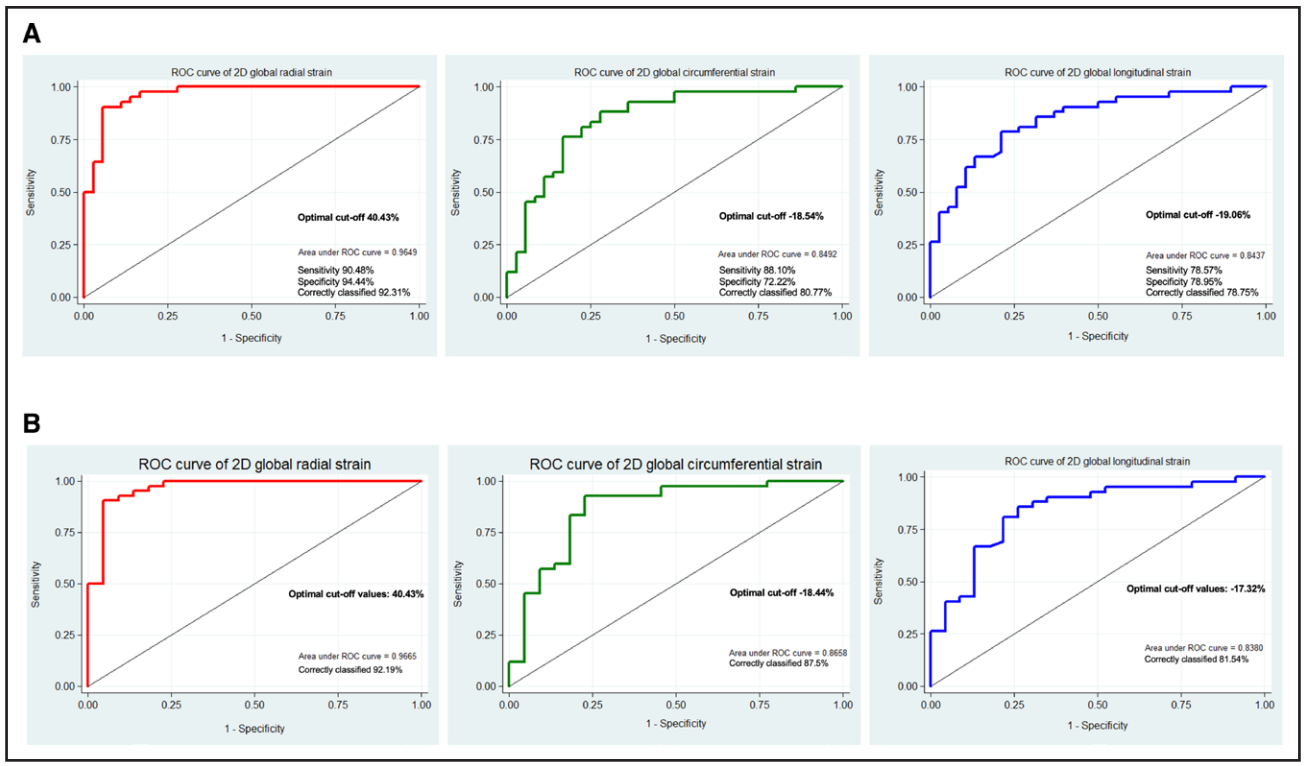

Figure 2. Receiver operating characteristic (ROC) curves and the optimal cut-off values of strain parameters to discriminate between subclinical hypertrophic cardiomyopathy (HCM; ie, genotype-positive/left ventricular hypertrophy negative [G+/LVH−]) and controls.

A, ROC curves of strain values for discriminating all subclinical HCM from healthy controls. **B**, ROC curves for discriminating subclinical HCM without other cardiac structural and functional abnormalities previously described from controls. 2D indicates 2-dimensional.

preclinical abnormalities in subclinical HCM individuals and the CMR-FT analysis may provide early additional and complementary diagnostic information, irrespective of the presence of subtle morphological abnormalities. Indeed, CMR strain values (GRS, GCS, and GLS) were consistently and similarly altered also in patients free of all the cardiac structural and functional abnormalities previously described. We also tested, although in a very preliminary way, the hypothesis that higher LV ejection fraction in subclinical HCM might reflect higher sarcomere hyper activation, as this is an important potential therapeutic target in the near future.

The role of CMR-FT in subclinical HCM without phenotype has not been extensively investigated so far. In a prospective multicenter observational study involving 99 participants (34 HCM mutation carriers, 42 with overt disease, and 23 controls) undergoing CMR-FT analysis limited to GCS, Vigneault et al[22] found that GCS was abnormal in overt HCM and subclinical HCM compared with controls. However, no data on GLS were provided. This is relevant, since previous data suggested that GLS analysis may be useful in HCM as a surrogate marker to identify patients at high arrhythmic risk, and data deriving from echocardiography suggest that GLS is the strain parameter used most in clinical practice with more robust scientific evidence.[11,23–25] Moreover, apart from that of Vigneault et al, previous studies investigated the role of CMR strain only in patients with overt HCM phenotype.[11,23,24,26] Our study includes a comprehensive analysis of CMR strain (including GCS, GRS, and GLS) on the LV in subclinical HCM. Our results suggest that myocardial deformation is globally reduced in subclinical HCM subjects (even in those without other instrumental phenotypic abnormalities) compared with healthy subjects, and CMR-FT analysis might be used as the first tool when looking for cardiac abnormalities, addressing the follow-up strategies in these individuals. This is particularly important; in fact, echocardiography (although appealing due to its known advantages including wide availability and low costs) does not provide significant clues in this scenario. Abnormalities of diastolic function assessed by Doppler tissue imaging (ie, lower mean early diastolic myocardial velocities) precede the development of LVH in individuals with HCM caused by β-myosin heavy chain mutations.[27] However, although the idea of using a simple, low-cost parameter to detect early abnormalities is intriguing, lower mean early diastolic myocardial velocity alone is not sufficiently sensitive as a sole diagnostic criterion.[25,27]

Furthermore, echocardiographic strain failed to provide definite, solid results in subclinical HCM. In a cohort of 146 subjects (including 68 G^+/LVH^-) Ho et al did not find any significant differences in terms of global

and regional longitudinal strain and strain rate values between subclinical HCM and healthy controls.[28] More recently, Baudry et al[29] found that regional longitudinal strain, but not global strain was significantly reduced at the early stage of HCM before LVH.

There are several potential underlying pathophysiological mechanisms able to explain our results. First, HCM mutations may affect the stability of a super-relaxed state of cardiac myosin with very slow ATP hydrolysis and thereby change the number of myosin heads accessible to actin.[30] This is accompanied by increased calcium sensitivity, which is recognized as a pathophysiological feature of the disease. Second, myocardial perfusion defects have been demonstrated in subclinical HCM.[31] In a recent echocardiographic and CMR study using the blood oxygen level-dependent technique, MYBCPC3 mutation carriers (with overt or subclinical HCM) showed myocardial deoxygenation during stress, even in the presence of normal LV diastolic function, LV GLS, and wall thickness. Interestingly, a blunted blood oxygen level-dependent response to stress was also seen in G^+/LVH^- subjects when compared with gene-negative siblings.[32] Third, levels of serum PICP (procollagen type I C-terminal propeptide) are significantly higher in HCM mutation carriers without LVH and LGE compared with controls. This may promote myocardial type I collagen synthesis, thus, creating a profibrotic myocardial milieu.[33] These features were in agreement with CMR findings, since precontrast and postcontrast T1 measurements showed a significant increase in myocardial extracellular volume in subclinical HCM subjects, supporting the thesis that sarcomere gene mutations cause a profibrotic state early in HCM pathogenesis.[9] In any case, CMR parameters (including the more recent and complex diffusion tensor imaging) suggest the presence of altered microstructure in subclinical HCM.[34] In this scenario, we might postulate that CMR-FT reduction reflects the hallmarks of the disease: myocardial disarray, fibrosis and reduced perfusion.

Clinical Implications and Future Perspectives

Our results on CMR strain, including GLS, GCS, and GRS with optimal cut-off values to distinguish subclinical HCM from healthy controls, may have significant clinical implications. The identification of early phenotypic abnormalities in HCM relatives otherwise considered phenotypically negative may promote stricter clinical surveillance. Despite the need of confirmation in future analyses, CMR-FT analysis might become part of a multiparametric score (including clinical, genetic, and instrumental data) useful for the early diagnosis and planning of personalized follow-up strategies in subclinical HCM. Moreover, although specific and confirmatory studies are needed, CMR-FT might potentially help clinicians to identify subjects at risk of developing the disease in families with negative genetic testing. Further larger confirmatory studies are needed to validate cut-off values, to demonstrate the potential additional informative value of GCS and GRS over GLS in isolation, and the ability of CMR strain to predict how many subclinical HCM subjects with abnormal strain will develop an overt HCM phenotype in the future. Finally, the role of CMR-FT in assessing HCM patients with or without hypertension and in gene-negative siblings represents two scenarios of future research.

Study Limitations

The results of the present study should be interpreted in the light of some limitations, the relatively small sample probably being the main one. However, almost all the principal studies focusing on the imaging features of subclinical HCM have included a similar number of subjects. It is important to underline that this is the largest sample of subclinical HCM that has been comprehensively investigated with CMR-FT so far. Although we have conducted an extensive assessment of instrumental phenotypic abnormalities according to preexisting literature, some features were not systematically evaluated (eg, thickness of septomarginal trabecula, papillary muscle mass, and complexity); this may have limited our ability to completely exclude phenotypic abnormalities in subclinical HCM. Furthermore, T1 mapping and extracellular volume were not systematically analyzed in our cohort. We did not perform a sensitivity analysis computing segment-specific strain/mass, as it was beyond the scope of this article; this parameter should nevertheless be explored in future research. The suboptimal sex-matching (with a higher, although not statistically significant, number of females among subjects with subclinical HCM), the absence of both ECG and echocardiographic data, and genetic analysis in controls might be other potential methodological limitations. Also, the lack of follow-up data (both clinical and instrumental) does not allow us to provide definite answers on CMR strain evolution over time, its prognostic role and potential use in guiding patient management and surveillance. Finally, the multicentric nature of the study (clinical and instrumental data collected by different operators with different instruments) might have constituted a potential source of bias. All ECG tracings, echocardiographic images, and CMR scans were, however, subsequently centrally reviewed by experienced and blinded operators.

Conclusions

Individuals with subclinical HCM show a significant reduction in myocardial strain assessed by CMR-FT compared with controls, independently from the presence of other instrumental phenotypic abnormalities. This finding could reflect the alterations of myocardial architecture in HCM, even in the preclinical phase of the disease. CMR strain should be a promising, simple tool

to discover early features of the disease and monitor its progression over time.

ARTICLE INFORMATION

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None.

Supplemental Material

Supplemental Methods
Tables S1–S3
Figures S1–S2

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