Echocardiographic and cardiac MRI-derived global strains in relation to LGE in hypertrophic cardiomyopathy.

Short title: ***Inter-modality strain analysis in hypertrophic cardiomyopathy***

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All author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Abstract

Objectives: We compared speckle tracking echocardiography (STE) and cardiovascular magnetic resonance feature tracking (FT-CMR) in hypertrophic cardiomyopathy (HCM) patients with a varying extent of fibrosis as defined by late gadolinium enhancement (LGE), to look at the level of agreement between methods and their ability to relate those to myocardial fibrosis.

Background: Strain values by STE or FT-CMR may be related to presence and extent of myocardial fibrosis in HCM patients.

Methods: At two reference tertiary centers, 79 patients (51.9±11.8years, 54.3% male) with HCM and 16, age- and sex-comparable volunteers (controls) underwent STE and CMR with LGE and FT-CMR within 6-months to each-other. Patients were classified in 3 categories: no detectable fibrosis, limited fibrosis and extensive fibrosis based on LGE. Global longitudinal strain (GLS) and global radial strain (GRS) were derived both using FT-CMR and STE.

Results: STE-derived GRS was decreased in all HCM categories compared to controls ($P<0.001$), while FT-CMR GRS was reduced only in HCM patients with fibrosis but not in those without ($P<0.05$). Reduced STE- derived GLS was associated with extensive fibrosis ($P<0.05$) and a value <–15.2% identified those with extensive fibrosis (sensitivity 79%, specificity 92%, Area Under the Curve 0.863, 95% CIs 0.76-0.97, $P<0.001$). Inter-modality agreement was moderate for STE vs. CMR GLS (overall population ICC=0.615, 95% CIs 0.42-0.75, $P<0.001$; HCM patients 0.63, 0.42-0.76, $P<0.001$) and GRS (overall population ICC=0.601, 95% CI 0.397-0.735, $P<0.001$). A low level of agreement for GRS was seen between modalities in HCM patients.

Conclusion: Strain indices measured using both echocardiography and CMR are reduced in patients with HCM compared to controls and correlate well with the burden of focal myocardial fibrosis. Reduced STE-GLS can identify those patients with extensive fibrosis but whether there is added value for risk stratification for sudden cardiac death remains to be determined.

Condensed Abstract

In 79 patients with hypertrophic cardiomyopathy (HCM) from two reference centres, global longitudinal (GLS) and radial (GRS) strain by cardiovascular magnetic resonance feature tracking (FT-CMR) and speckle tracking echocardiography (STE) were reduced as compared to age- and sex-volunteers. Importantly, global strains by both techniques correlated well with the burden of focal myocardial fibrosis while reduced STE- derived GLS< –15.2% identified patients with extensive fibrosis. A moderate inter-modality agreement with respect to GLS was found in patients with HCM but only a low level of concordance was observed for GRS.

List of abbreviations

EF: Ejection Fraction

FT-CMR: Cardiovascular Magnetic Resonance Feature Tracking

GLS: Global Longitudinal Strain

GRS: Global Radial Strain

HCM: Hypertrophic Cardiomyopathy

ICD: Implantable Cardiac Defibrillator

LV: Left Ventricle

LGE: Late Gadolinium Enhancement

TTE: Transthoracic Echocardiography

SCD: Sudden Cardiac Death

STE: Speckle Tracking Echocardiography

1. Introduction

Cardiac imaging plays a crucial role in the diagnosis, risk stratification and follow-up of patients with hypertrophic cardiomyopathy (HCM). Conventionally, diagnosis is made by 2-dimensional (2D) transthoracic echocardiography (TTE). Cardiovascular magnetic resonance (CMR) has emerged as a valuable diagnostic tool in HCM by virtue of its high resolution and potential ability to identify the extent of myocardial fibrosis by late gadolinium enhancement (LGE). According to European Society of Cardiology (ESC) guidelines, CMR with LGE is indicated in patients with suspected HCM and inadequate echocardiographic windows (class I, B) and should be considered in all patients with HCM to assess cardiac anatomy, ventricular function and myocardial fibrosis burden (class IIa, C) [1]. Moreover, CMR could be of value for improving risk stratification for sudden cardiac death (SCD) in HCM patients. To this end, extensive LGE (fibrosis over 15% of LV mass) has been included in the algorithm that identifies HCM patients at increased risk of SCD who could benefit from implantable cardiac defibrillator (ICD) therapy [2, 3].

Global and regional myocardial deformation can be measured using strain derived from speckle tracking echocardiography (STE) and has been shown to be a sensitive and early marker of cardiac dysfunction across a range of cardiac disorders. More recently, similar markers can be measured using CMR with feature tracking CMR (FT-CMR) software enabling measurement from standard cine imaging. Recent evidence suggests that strain indices may be a surrogate marker of underlying myocardial fibrosis in HCM patients [4-7] and may be associated with poor prognosis [8] and higher incidence of ventricular arrhythmias [9].

In hypertrophied myocardium, regional mechanics are differentially influenced by the wall thickness, the location of hypertrophy and the degree of underlying fibrosis [10, 11]. Consequently, alterations in circumferential and longitudinal myocardial shortening show an individualized pattern among patients with HCM and may have prognostic implications [10, 11]. However, there have been no studies systematically comparing STE and FT-CMR mechanics in HCM patients against LGE-defined extent of myocardial fibrosis. Therefore, we sought to:

i. ascertain whether STE and FT-CMR both predict the presence and extent of myocardial fibrosis in HCM patients with varying degrees of fibrosis as defined by LGE; ii. assess concordance between these two methods and; iii. evaluate the clinical value of STE for predicting fibrosis.

2. Methods

The study was conducted in two large tertiary referral centres with specialist inherited cardiovascular disease units where patients were referred for assessment of HCM. The diagnosis of HCM was made based on clinical data including family history, pedigrees and/or genetic testing. Imaging data were collected prospectively between 12/2015 and 12/2017 based on specific echocardiographic and CMR protocols and analysed retrospectively offline. All patients had provided written informed consent conforming to the Declaration of Helsinki (fifth revision, 2000) and contributing centers sharing data had the approval of their institutional review boards. Participants recruited from the Barts Heart Centre were enrolled into the Barts Cardiovascular Registry (Barts BioResource application #8)[12].

Study population

Seventy-nine patients were recruited from Imperial College NHS trust, Hammersmith Hospital and the Barts Heart Centre according to the following inclusion criteria:

(1) Assessment in the Inherited Cardiac Conditions Clinic (Hammersmith Hospital) and the Inherited Cardiovascular Disease Unit (Barts Heart Centre) for confirmation of HCM

(2) Availability of TTE and CMR within 6 months of each other; and

(3) Reasonable image quality.

Patients were divided into groups based on the presence of LGE by American Heart Association segmental classification [2]: no LGE (no focal fibrosis); limited fibrosis (1-4 segments with LGE); and extensive fibrosis (> 5 segments with LGE).

Patients with obstructive HCM (left ventricular outflow tract gradient≥30mmHg at rest) were excluded from this study. Prior history of myocardial infarction or myocarditis, myocardial ischaemia on a non-invasive test suggesting coronary artery disease, left bundle branch block documentation in ECG, organic (degenerative/rheumatic) significant valvulopathy, end-stage HCM with ejection fraction (EF) (<50%), any evidence of any obstructive coronary artery disease

on angiography, history of septal myectomy or alcohol septal reduction and active infection or neoplastic disease were also considered exclusion criteria.

A control group of 16 volunteers matched for age and sex distribution also underwent standard echocardiography and CMR. Offline STE and FT-CMR were carried out for comparison. controls were part of the Genscan UK study (Genetic study of the heart and circulation) [13]. They were excluded if any of the following were present on 2D TTE: a) abnormal size or volume of any cardiac chamber b) significant valvulopathy or c) left ventricular ejection fraction (LVEF of <50%).

Echocardiography

Two-dimensional trans-thoracic echocardiography (2D-TTE) was performed at Hammersmith Hospital, using the Phillips IE 33 cardiac ultrasound systems (Philips Healthcare, Amstelplein 2, 1096 BC Amsterdam, The Netherlands) equipped with a broadband 1-5MHz S5-1 transducer with a frequency range of 2-5MHz. At Barts Heart centre, the GE Vivid E9 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array transducer (1.4-4.6 MHz) was employed. All datasets from both centres were anonymized and exported for analysis offline by a single observer using a vendor-independent analysis software (Tomtec 2D Cardiac Performance, CPA version 4.6, Unterschleissheim, Germany). Details on echocardiography protocol are given in the Supplementary Material.

Cardiovascular magnetic resonance

CMR imaging was performed with a 1.5T Philips Achieva system with a 32-element cardiac phased-array coil (Hammersmith Hospital) or a 1.5T Siemens MAGNETOM Aera (Barts Heart Centre) scanner, with a 32-element cardiac phased array coil. Images were anonymized and exported for off-line analysis using the same Tomtec 2D Cardiac Performance Analysis software. FT-CMR analysis was performed blinded to the LGE imaging and the echocardiographic STE results by a single operator. A detailed description of the method is provided in the Supplementary Material.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) for variables not following the normal distribution. Normality of continuous variables was assessed with the Shapiro-Wilk test and graphically inspected with histograms and Q-Q (quantile-quantile) plots. Variables that deviated from normality were transformed with the natural logarithm in order to decrease skewness when used in linear regression models or parametric tests. Nominal variables are presented as counts and valid percentages.

Differences in baseline characteristics and strain indices among controls and HCM subgroups were evaluated by one-way analysis of variance (ANOVA) using the Tukey's post hoc test for multiple comparisons or the non-parametric Jonckheere–Terpstra test and the Dunn's correction of multiple comparisons; for categorical variables we implemented the chi-squared test. Subsequently, we performed multivariable linear regression analysis of log transformed strain indices on a 4-stratum ordinal variable (control, no fibrosis-, limited- and extensive fibrosis HCM group) after adjusting for the effect of age, sex, LVEF, septal thickness, smoking, systolic blood pressure (SBP), hyperlipidemia and body mass index (BMI). This set of confounders in regression models was pre-specified and no selection technique was used to build the final multivariable models. A ratio of 5 to 10 observations per independent variable was retained in regression analysis. Collinearity was assessed by calculating the Variance Inflation Factor (VIF). Values of VIF >2.5 were considered indicative of multicollinearity. Receiver Operator Characteristic (ROC) curves were constructed by plotting sensitivity to 1-specifity and Area Under the Curve (AUC) was used to evaluate the predictive ability of STE- or FT-CMR GLS for discriminating extensive fibrosis in HCM. Ordinal logistic regression analysis was selected as an alternative method of analysis that does not assume normal distribution of strain parameters. Estimates from ordinal logistic regression analysis are presented as odds ratios.

Agreement in strain calculations between STE and FT-CMR was assessed by intra-class correlation coefficient (ICC) and Bland-Altman analysis with scatter plots showing the difference between the two modalities in the Y axis and the average of both measures in the X axis (Bland Altman plots). Two-way random-effects models were implemented in ICC with calculation of consistency of agreement, along with 95% confidence intervals. Considering ICC adjudication, we followed the

cut offs used in common diagnostic indices, namely: 0.9 – 1.0 excellent; 0.8-0.9 very good; 0.7-0.8 good; 0.6-0.7 moderate and <0.5 poor [14].

We also calculated linear correlations in strain indices by the two modalities (Pearson's r) and graphed fitted values by linear regression analysis. Finally, reproducibility of the analysis techniques for the two imaging modalities (STE and FT-CMR) was assessed in 5 patients with studies analyzed offline one month apart, and the coefficient of variation (COV) was calculated for inter- and intra-observer variability.

Power calculations indicated that 40 subjects in total, allocated in two equal groups (n=20 each) of non-fibrotic and extensive fibrotic HCM, would be needed to provide adequate power (i.e. 85%) to detect a between-groups difference equal to 4% in GLS by the non-parametric Mann-Whitney test (*a priori analysis*). Measures of dispersion for the parameter of interest were retrieved from previous published studies [9]. Power calculation was based on 1,000 simulations with resampling[15]. A value of $P<0.05$ was considered statistically significant. All statistical tests were two-sided. Statistical analysis was performed using STATA 12.1 software (StataCorp, College Station, Texas USA).

3. Results

Baseline characteristics of the study's groups are outlined in Table 1. The control group (mean age 48.9±11.8 years, 43.8% males) was comparable to 79 HCM patients (mean age 51.9±11.8years, 54.3% males) with respect to age and gender. The four groups, namely controls, non-fibrotic HCM, limited and extensive fibrotic HCM patients, did not differ in conventional risk factors for ischemic heart disease ($p>0.05$ for all). As expected, LV wall thickness was significantly increased in HCM patients compared to controls; LVEF in non-fibrotic patients was higher comparing to controls (Table 1). Of interest, conventional markers of HCM severity, including LV wall thickness and LVEF, did not differ between patients with limited and extensive fibrosis. No difference was found with respect to beta blocker treatment across the groups of HCM (Table 1).

Extent of fibrosis and differences in global strains

Overall, STE and FT-CMR-derived GRS and GLS were reduced ($p<0.001$ for all) in all 3 sub-groups. In particular, controls showed higher GRS values compared to all HCM phenotypes (no fibrosis, limited and extensive fibrotic) using both echocardiography and CMR (Table 1). While all patients, had reduced GLS both by STE and FT-CMR (Table 1) (Supplementary Figure 1), only patients with extensive fibrosis had significantly reduced STE GLS (-14.5% and CMR: -16.5%) compared to controls (echo, -20.6% and CMR: -24.1%, respectively) ($P<0.05$ for both) (Table 1) (Supplementary Figure 1).

In Figure 1, there are two typical examples from patients with limited fibrosis (1A) and extensive fibrosis (1B) with corresponding STE, FT CMR and LGE images.

LGE burden as independent predictor of global strain indices in HCM

Using multivariable linear regression analysis, HCM patients were associated with reduced STE GRS compared to controls (mean expected relative reduction: -52.8%, 95% CIs -65.5 to -35.2 for non-fibrotic, -54.4%, 95% CIs -70.6 to -32.5 for limited fibrosis and -59.6%, 95% CIs -74.9% to -34.9% for non-fibrotic, $P<0.001$ for all), independently of age, gender, LVEF, septal thickness, BMI, SBP, smoking and hyperlipidemia (Table 2). In addition, FT-CMR showed significant reduction of GRS between controls and limited fibrosis (mean relative reduction: -35.7%, 95% CI -56.1 to -6.0, $P=0.023$) and extensive fibrosis (mean relative reduction: -37.9%, 95% CI -59.9 to -3.8, $P=0.034$) but not in those with no detectable fibrosis by LGE.

A significant linear relationship of worsening GRS was observed across increasing LGE in both STE GRS (mean expected relative reduction per ascending category of LGE severity=-24.9, 95% -35.7/-12.4, P for linear trend<0.001) and FT-CMR (mean expected relative reduction per ascending category of LGE severity-16.4, 95% CI -27.5/-3.6, P for linear trend=0.014). Using FT CMR, patients with no evidence of LGE did not differ from controls (Table 2) after controlling for covariates. There was no difference between HCM patients with limited and extensive fibrosis by either STE or FT-CMR GRS imaging ($P>0.05$ for all).

STE-GLS was significantly reduced only in patients with extensive fibrosis compared to controls (mean relative reduction: 31.8, 95% CI 0.3 to 53.4, P=0.048) but there was no linear relation of reduced GLS with increasing severity of LGE (P=0.12). Similarly, patients with extensive fibrosis showed worse STE-GLS compared to patients with no fibrosis (mean relative reduction: 26%, 95% CI 3.8 to 42.9, P=0.025). When using FT-CMR, there was no difference in GLS between subgroups of patients with HCM and controls (P=NS for all comparisons) (Table 2).

Using ROC analysis, STE-GLS less than -15.2% identified the presence of extensive fibrosis with 79% sensitivity and 92% specificity (AUC=0.863, 95% CI 0.760-0.967, P<0.001) (Figure 2 left), while a FT-CMR GLS less than -21.8% discriminated extensive fibrosis from controls and less severe LGE burden in HCM patients (AUC=0.884, 95% CI 0.802-0.965, P<0.001, sensitivity 79% and specificity 89%) (Figure 2 right). The two modalities did not differ in their predictive value towards LGE severity in HCM patients (P=0.638).

Level of agreement between echocardiography and CMR derived global strains

Intra-class correlation coefficient indicated moderate correlation between GRS by STE and FT-CMR in the overall population (ICC=0.601, 95% CI 0.397-0.735, P<0.001) (Supplementary Table 1A) and HCM patients with limited fibrosis (Supplementary Table 1B). In contrast, a low level of agreement for GRS was observed in controls, HCM patients overall, as well as the non-fibrotic and extensive fibrotic patients, ranging from 0.012 to 0.367 (Supplementary Table 1A, 1B).

Correlation of STE GLS and FT-CMR was moderate in the overall population (ICC=0.615, 95% CI 0.419-0.745, P<0.001), in HCM patients (ICC= 0.63, 95% CI 0.417-0.764, P<0.001) and HCM patients with fibrosis (P<0.001) (Supplementary Tables 1A, 1B).

Using Bland-Altman analysis, we found a significant (P<0.05) bias for higher FT-CMR derived GRS values compared to STE (Figure 3A). A similar bias (P<0.05) was observed in HCM patients with no or extensive fibrosis (Supplementary Figure 2A). A trend for increasing inter-modality variation in GRS was observed (Figure 3A) but in general a good level of agreement was established in the overall population and subgroups with more than 90% of observations distributed within two standard deviations of the mean difference (Figure 3A, Supplementary Figure 2A).

With respect to GLS, there was a systematic bias (P<0.001) indicating more negative values of FT-CMR derived GLS as compared to STE (Figure 3B). A relevant pattern of higher FT-CMR GLS values in comparison to STE-GLS was evinced in all subgroups (P<0.05 for all) (Supplementary Figure 2B). In contrast, we did not observe a trend for reproducibility of GLS measurements by STE and FT-CMR to vary with their underlying mean value in all populations; more than 90% of observations fell within the range of two standard deviations from the mean difference of modalities. Finally, a moderate but significant linear correlation (P<0.001) was seen between STE and FT-CMR in both GLS and GRS (Figure 3A, 3B).

Reproducibility of STE- and FT-CMR techniques for calculation of strain indices

For echocardiography, the inter-observer variability for GLS and GRS were 4.7%±4.5% and 3.9%±2.8%, respectively. The intra observer variability for GLS and GRS was 2.3%±2.5% and 2.7%±3.0%, respectively. For CMR, the inter-observer variability for GLS and GRS was 4.9%±3.8 and 4.5%±4.2, respectively. The intra-observer variability of GLS and GRS was 3.4%±2.9 and 3.9%±3.8 respectively.

4. Discussion

In this study we demonstrate that the extent of LGE-defined focal myocardial fibrosis in patients with non-obstructive HCM is associated with reduced myocardial contractility both using STE and FT-CMR, and were distinct from normal subjects. While STE GRS was reduced in all HCM subtypes compared to controls, FT-CMR-derived GRS was an independent marker of fibrosis among HCM patients when present but did not discriminate non-fibrotic patients from controls. Conversely, reduced STE- or FT-CMR GLS was best associated with the most extensively fibrotic form of HCM with a cut-off value of < -15.2% with high specificity. Importantly, GLS and GRS by echocardiography and FT-CMR showed a modest level of agreement in the overall population while GLS performed best for both imaging modalities in HCM patients with fibrosis. Finally, we demonstrated than strain is a superior marker to conventional measures of LV function (i.e. LVEF) and structure (LV wall thickness) to discriminate HCM patients accordingly to LGE burden.

To date, few studies have directly evaluated the association of myocardial fibrosis in patients with HCM using strain indices. In a study of 39 patients with HCM stratified according to their fibrotic

status as estimated by LGE, radial strain evaluated by STE was lower in all HCM categories compared to control subjects [16]. Accordingly, among pediatric HCM patients, GRS estimated by FT-CMR was significantly reduced in fibrotic patients compared to those without fibrosis as assessed by LGE [17]. Notably, these results are consistent with our finding that showed reduced STE GRS in all HCM patients compared to normal subjects independent of the fibrotic burden, while FT-CMR GRS was only reduced in fibrotic (both limited and extensive) HCM patients in our cohort.

Lower STE-GLS was independently associated with greater extent of fibrosis as estimated by LGE in two previous studies [5, 18]. STE-GLS was also found significantly impaired in HCM patients compared to individuals without HCM [9]. Of note, this study was cross-sectionally designed and patients were stratified in a binary fashion only according to the presence or not of fibrosis as assessed by LGE not reflecting on the fibrotic burden. Another study showed reduced GLS among HCM patients, irrespective of the level of fibrosis [8]. In the same direction, global myocardial mechanics were not associated with the extent of LGE in 59 patients [10]. Pagourelias et al found that segmental hypertrophy had greater impact on longitudinal deformation than fibrosis in patients with HCM [11]. Conversely, our study showed that only HCM patients with extensive fibrosis are characterized by reduced STE-GLS. In fact, this strain index was able to discriminate HCM patients with extensive fibrosis among all disease phenotypes and control subjects. This could be attributed, at least in part, to different patient cohorts compared to previous studies but also highlighting the difficulties in quantifying LGE semi-quantitatively. It should be noted that GLS was also a significant predictor of LV fibrosis in a recent HCM study that classified the extent of LGE semi-quantitatively [19]. Respectively, mean GLS values were found higher in our cohort with respect to certain previous studies [20] but comparable to others [21-23]; again, enrollment of patients with different phenotypes of HCM and discrepant classification systems of underlying LV fibrosis leading to more patients with extensive LGE might account for this difference.

A unique strength of the present study was the systematic comparison between STE and FT-CMR for both GLS and GRS in the overall HCM population. Both imaging modalities tended to agree on GLS in HCM patients but provided heterogeneous results for GRS. In support of our findings, a study that directly compared FT-CMR and STE GLS, GLS correlations were more reproducible whereas GRS only showed modest reproducibility [24]. Of note, a study in healthy controls and HCM

patients (total n=40) calculated a similar ICC (i.e. 0.57, 95% CI 0.15-0.78) for STE- and FT-CMR GLS to the agreement observed in our total population (i.e. 0.615, 95% CI 0.419-0.745) [25] Moreover, STE-GRS values in our measurements were systematically lower whereas STE-GLS was less negative when compared to FT-CMR. In accordance to our results, patients with a variety of cardiovascular diseases (n=40) alongside healthy subjects (n=10) demonstrated higher GRS values by FT-CMR in comparison to STE [26]. The same study reported overestimation of GLS with STE as compared to FT-CMR; different underlying pathology and cardiac phenotype to our patients may account for this discrepancy [26]. Collectively, observed differences in myocardial deformation analysis between STE and FT-CMR may be partially attributed to discordant endocardial border definition between the two modalities as well as differences in the spatial and temporal resolution [24, 26].

Collectively, our results suggest that GRS can serve as an overall marker for fibrosis in HCM patients in a binary fashion, whereas STE-GLS can distinguish patients with extensive fibrosis who may be considered at high risk for SCD [9]. Interestingly, recent evidence suggests of a plausible association between impaired STE-GLS and SCD, ventricular arrhythmias and appropriate ICD shocks in patients with HCM [27-32]. Impairment in global deformation mechanics in HCM might stem from increased LV wall thickness, fibrosis or combinations of these factors [10, 11, 33]; thus, GLS values can reflect a combined index of myocardial dysfunction with incremental clinical value over hypertrophy or LGE alone in patients with HCM. Although our study was not designed to link the presence of myocardial fibrosis to arrhythmias or SCD, the cut-off of -15.2% using STE-GLS or -21.8% in FT CMR, could identify extensive fibrosis, similar to a cut-off value reported in previous studies [28-31]. Taking into consideration that echocardiography is a widely available and easily accessible modality compared to CMR, STE GLS could serve as a useful and reliable additional criterion for risk stratification in patients with HCM independent of the anatomic phenotype.

Limitations

Firstly, the number of subjects per group was relatively small but similar to previous studies and yielded adequate power according to a priori calculations. In the same context, we did not perform exact matching of controls and HCM patients in terms of age and gender but the groups have comparable distribution for demographic characteristics and traditional risk factors. Secondly, we analyzed only GLS and GRS, but not global circumferential strain. However, most studies have

mainly looked at GLS as it presents consistent association with clinical parameters and outcomes. Thirdly, estimation of regional strain that could associate regional myocardial deformation with segmental fibrosis was not performed as those measurements lack reproducibility. Fourth, echocardiography and CMR were performed within a six-month period of each-other and this could lead to underestimation of agreement between the two methods although fibrotic changes within this time period are unlikely to occur. Fifth, endocardial tracking during STE was visually judged supported by the analysis software and exclusion of echocardiographic studies as not appropriate relied upon the discretion of the investigator. Sixth, we looked at global extent of LGE but not pattern of LGE in HCM patients. There are multiple analysis measures available for quantification of LGE [19, 34], however in real-world clinical practice focal fibrosis is generally reported in broad categories using visual assessment, hence the methods used in this study. Although it is recognized that HCM is associated with increased interstitial fibrosis which can be measured using parametric mapping techniques using CMR (T1 and ECV measurement), these are not included in risk scores for HCM and their relationship with outcome in HCM is not clearly established. Of note, native T1 relaxation time has been associated with circumferential strain in a previous study of 45 patients with HCM [35]. Finally, both the CMR and echocardiographic examinations, were acquired using different manufacturers in the two institutions, however there was no bias between the results and similar numbers of participants recruited in the two institutions.

5. Conclusion

Strain indices measured using both echocardiography and CMR are reduced in patients with non-obstructive HCM compared with controls, and these correlate with the burden of focal fibrosis. STE and FT-CMR showed a good level of agreement in patients with HCM when it comes to GLS. Notably, impaired STE GLS distinguished patients with extensive fibrosis and might be considered as an additional criterion for HCM risk stratification. This may be of particular use in patients unable to undergo CMR, or where CMR is not readily available. Larger studies on subtypes of HCM with better quantitative markers for fibrosis besides LGE as well as assessment of clinical outcomes are warranted to confirm these findings.

Perspectives

Clinical Competencies

The extent of LGE-defined focal myocardial fibrosis in patients with non-obstructive HCM is associated with reduced myocardial contractility both using STE and FT-CMR.

While STE GRS was reduced in all HCM subtypes, FT-CMR-derived GRS was an independent marker of fibrosis when present but did not discriminate non-fibrotic patients from controls.

Conversely, reduced STE- or FT-CMR GLS was best associated with the most extensively fibrotic form of HCM with a cut-off value of < -15.2% with high specificity but both GLS and GRS by echocardiography and FT-CMR showed modest level of agreement in the overall population while GLS performed best for both imaging modalities in HCM patients with fibrosis.

Impaired strain-echocardiography global longitudinal strain distinguishes patients with extensive fibrosis and might be considered as an additional criterion for HCM risk stratification.

Translational Outlook

-Global strain indices in patients with hypertrophic cardiomyopathy may correlate with underlying myocardial fibrosis more accurately than conventional measures of LV function and structure, including LVEF and LV wall thickness

-Global strains can be implemented in the prognostication of HCM and the incidence of ventricular arrhythmias

-Impaired global longitudinal strain might serve as an additional criterion for HCM risk stratification.

- Echocardiography can be used to derived global strains in patients unable to undergo CMR, or where CMR is not readily available.

-Larger studies on subtypes of HCM with better quantitative markers for fibrosis besides LGE as well as assessment of clinical outcomes are warranted to confirm the clinical value of global strain in this population of special interest

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Figure Legends

Figure 1. Cardiac magnetic resonance- and echocardiography-derived measurements of GLS and GRS alongside LGE images in two representative participants with limited (Figure 1A) and extensive fibrosis HCM (Figure 1B).

Abbreviations: GLS: global longitudinal strain; GRS, global radial strain, LGE= Late Gadolinium Enhancement.

Figure 2. A. Receiver Operator Characteristic (ROC) curve analysis for the ability of STE-GLS and B. FT-CMR GLS to identify HCM patients with extensive fibrosis compared to controls and HCM patients with no or limited fibrosis.
Abbreviations: HCM, hypertrophic cardiomyopathy; STE-GLS, global longitudinal strain derived by speckle tracking echocardiography; AUC, area under the curve; CI, confidence intervals

Figure 3. Bland-Altman plots (top) and linear correlations (bottom) for measurements of GRS (3A) and GLS (3B) strains by echocardiography and CMR. The percentages (top right) indicate the percentage of paired measurements that fall within the 2 SDs of the mean difference of all pairs. A positive bias in GRS indicates higher STE derived GRS values as compared to FT-CMR. A positive bias in GLS indicates more negative values of FT-CMR derived GLS as compared to STE. Pearson's correlation coefficient ® alongside corresponding P-value are provided for linear correlations.
Abbreviations: GRS, global radial strain; GLS: global longitudinal strain; CMR, cardiac magnetic resonance imaging, SDs: standard deviations

Table 1. Baseline characteristics and strain indices by echocardiography and CMR in the study's population.

Variable	Controls	Non-fibrotic	Limited fibrosis	Extensive fibrosis	P-Value
N	16	37	19	23	
Age[years], mean (SD)	48.9(11.8)	52.1(13.1)	53.6(10.2)	50.3(11.1)	0.645

Sex[male], n (%)	7(43.75)	17(45.95)	13(68.42)	13(56.52)	0.36
BMI[kg/m2], mean (SD)	25(3.28)	26(6.11)	26.7(4.63)	25.6(3.16)	0.767
SBP[mmHg], mean (SD)	131(13.5)	128(11.8)	127(11.8)	129(10.9)	0.662
DBP[mmHg], mean (SD)	78.8(7.65)	80.5(6.98)	81.4(5.43)	78.2(5.75)	0.347
Hypertension, n (%)	6 (37.5)	9 (24.32)	5 (21.74)	4 (21.05)	0.656
Smoking, n (%)	3(18.75)	11(29.73)	6(31.58)	4(17.39)	0.592
Hyperlipidemia, n (%)	4(25.00)	11(29.7)	4(21.05)	7(30.4)	0.889
DM, n (%)	2(12.5)	2(5.41)	1(5.26)	2(8.7)	0.799
†STE-GRS [%], median (IQR)	40.7(14.8)	*24.1(10.5)	*22.1(3.25)	*21.4(10.5)	<0.001
†STE-GLS [%], median (IQR)	-20.6(5.97)	-19.4(4.6)	-18.5(3.47)	*-14.5(4.6)	<0.001
†CMR-GRS [%], median (IQR)	37.5(14.2)	*30.5(11.7)	*23.8(11.7)	*25.6(2.24)	<0.001
†CMR-GLS [%], median (IQR)	-24.1(3.82)	-28.4(9.9)	-23.1(4.31)	*-16.5(11.2)	<0.001
†Heart rate [bpm], median (IQR)	73(12.5)	78(21)	69(21)	73(13)	0.354
†LVEF[%], median (IQR)	65(6.5)	*73(11)	64(11)	70(9)	0.035
†IVS[mm], median (IQR)	9(1.5)	*15(4)	*20(4)	*20(6)	<0.001
†PW[mm], median (IQR)	8(1)	*13(1)	*14(1)	*14(3)	<0.001
Treatment with beta blockers, n(%)		30(81.1)	17(89.5)	19(82.6)	0.718

P-value is derived from chi-squared test for nominal variables and ANOVA or the Jonckheere–Terpstra test non-parametric test for continuous variables. * indicates significant difference in pairwise comparison to the normal group after Tukey's or Dunn's correction for multiple comparisons. † indicates non-normally distributed variables. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; STE-GRS; global radial strain as derived by speckle tracking echocardiography; STE-GLS, global longitudinal strain as derived by speckle tracking echocardiography; CMR-GRS, global radial strain as measured by CMR; CMR-GLS, global longitudinal strain as measured by CMR; LVEF, left ventricle ejection fraction; IVS, intraventricular septum thickness; PW, posterior wall thickness; ANOVA, analysis of variance; CMR, cardiac magnetic resonance imaging

Table 2. Multivariable linear regression analysis of strain indices on a 4-stratum ordinal variable, control, no fibrosis-, limited- and extensive fibrosis HCM group

	STE-GRS	**CMR-GRS**	**STE-GLS**	**CMR-GLS**

	*Coefficient (95% CIs)	P-value	Coefficient (95% CIs)	P-value	Coefficient (95% CIs)	P-value	Coefficient (95% CIs)	P-value
Controls	(reference category)	-	(reference category)	-	(reference category)	-	(reference category)	-
No fibrosis HCM	-52.8 (-65.5/-35.2)	<0.001	-18.8 (-39.2/8.49)	0.156	-7.70 (-28.3/18.8)	0.528	-16.7 (-37.5/1.00)	0.065
Limited fibrosis HCM	-54.4 (-70.6/-32.5)	<0.001	-35.7 (-56.1/-6.00)	0.023	16.5 (-16.2/40.1)	0.280	16.8 (3.16/33.0)	0.092
Extensive fibrosis HCM	-59.6 (-74.9/-34.9)	<0.001	-37.9 (-59.9/-3.80)	0.034	31.8 (0.3/53.4)	0.048	18.2 (-4.77/36.2)	0.110

Parameters of interest (GRS and GLS) have been transformed with the natural logarithm. All models are adjusted for age, gender, LVEF, BMI, smoking, systolic blood pressure, septal wall thickness and hyperlipidemia. * Coefficients indicate (%) percentages of change in strain indices for categories of HCM phenotypes in comparison to normal subjects. Abbreviations: HCM, hypertrophic cardiomyopathy; STE-GSR, global radial strain as derived by speckle tracking echocardiography; CMR-GRS, global radial strain as measured by magnetic resonance imaging; STE-GLS, global longitudinal strain as derived by speckle tracking echocardiography; CMR-GLS, global longitudinal strain as measured by magnetic resonance imaging; LVEF, left ventricle ejection fraction; BMI, body mass index