Investigation of Global and Regional Myocardial Mechanics With 3-Dimensional Speckle Tracking Echocardiography and Relations to Hypertrophy and Fibrosis in Hypertrophic Cardiomyopathy

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Background—In hypertrophic cardiomyopathy (HCM), heterogeneous myocardial hypertrophy and fibrosis are responsible for abnormalities of left ventricular (LV) function. We aimed to characterize LV global and regional myocardial mechanics in HCM, according to segmental hypertrophy and fibrosis.

Methods and Results—Fifty-nine patients with HCM underwent standard echocardiography, 3-dimensional speckle tracking echocardiography, and cardiac magnetic resonance with late gadolinium enhancement (LGE); all 3 tests were <24 hours apart. Longitudinal, circumferential, and area strains were investigated according to the extent of LGE (no LGE, LGE<10%, and LGE≥10%), segmental thickness (≥15 versus <15 mm), and segmental LGE (LGE versus non-LGE). Attenuated global longitudinal strain showed association with extent of hypertrophy (indexed LV mass, r=0.32, P=0.01; maximum LV wall thickness, r=0.34, P=0.009; number of segments ≥15 mm, r=0.44, P<0.001), whereas enhanced global circumferential strain was correlated to LV global functional parameters (indexed end-systolic volume, r=0.47, P<0.001; ejection fraction, r=−0.75, P<0.001). Parameters of global myocardial mechanics showed no association with the extent of LGE; in contrast, the extent of LGE was associated with the extent of hypertrophy. All 3 deformation parameters were attenuated both in segments ≥15 mm in thickness and in those with LGE; adjusted analysis demonstrated that segmental presence of LGE was associated with additional attenuation in myocardial deformation.

Conclusions—Both hypertrophy and fibrosis contribute to regional impairment of myocardial shortening in HCM. The extent of hypertrophy is the primary factor altering global myocardial mechanics. Circumferential myocardial shortening seems to be directly involved in preservation of LV systolic performance in HCM. (Circ Cardiovasc Imaging. 2014;7:11-19.)

Key Words: cardiomyopathy, hypertrophic ◼ echocardiography ◼ magnetic resonance imaging

Hypertrophic cardiomyopathy (HCM) is a genetic disease caused by mutations in genes encoding proteins of the cardiac sarcomere, phenotypically characterized by heterogeneous left ventricular (LV) hypertrophy.1–4 Histologically, this condition features cardiomyocyte hypertrophy, fiber disarray, and interstitial fibrosis.5 It has been proposed that contractile force of individual cardiac myocytes is impaired because of these microscopic abnormalities, resulting in intrinsic functional abnormalities, despite apparently normal systolic function by conventional measurements (ie, ejection fraction).6,7

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Studies have investigated the heterogeneity of regional function in these patients, showing a predominant impairment of areas with the most hypertrophy.5,8,9 Moreover, hypertrophy has been shown to have a deleterious effect on LV systolic and diastolic functions.10,11 Factors such as LV mass and regional wall thickness partly affect global and regional myocardial mechanics,12,13 which suggests an association between impaired cardiac performance and extent of hypertrophy. On the other hand, myocardial fibrosis also seems to be associated with worse cardiac performance.14–16 Some studies have underscored that this finding is likely to do with segmental or regional dysfunction associated with the fibrosis;12,17 but other data suggest that fibrosis may not predict all of the LV contractile heterogeneity in HCM.18

Heterogeneous myocardial hypertrophy and fibrosis, both characteristic of HCM, are probably responsible for global and regional abnormalities of LV myocardial mechanics, whose quantitative assessment is challenging by conventional cardiovascular imaging techniques. In this regard, details on global and regional deformation mechanics of LV myocardium have been controversial,8–10,12 and studies on their relationships with hypertrophy and fibrosis are lacking. Therefore, the aim of this study was to characterize LV global mechanics in HCM using 3-dimensional speckle tracking echocardiography (3D-STE),
defining its relationships with standard LV functional parameters, hypertrophy, and fibrosis; in addition, LV regional mechanics were explored with a focus on the effect of both segmental hypertrophy and fibrosis on LV systolic performance.

Methods

The study was conducted at a tertiary care hospital, where patients were referred for extensive assessment on HCM. The study was approved by the institutional review board, and each participant gave written informed consent.

Study Population

Patients were prospectively recruited at the Hypertrophic Cardiomyopathy Center at Tufts Medical Center, Boston, MA. Inclusion criteria were as follows: (1) established diagnosis of HCM based on the demonstration of a hypertrophied nondilated LV (wall thickness ≥15 mm) in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident; (2) performance of echocardiographic and cardiovascular magnetic resonance (CMR) studies ≤24 hours apart. Exclusion criteria were as follows: (1) organic (ie, degenerative or rheumatic) significant (moderate or severe) valvulopathy; (2) end-stage HCM (ejection fraction <50%); (3) myocardial ischemia on a noninvasive test, suggesting coronary artery disease; (4) evidence of obstructive coronary artery disease (lesions, >50% on angiography); (5) prior history of myocardial infarction or myocarditis; and (6) history of invasive septal reduction therapy (ie, septal myectomy or alcohol septal ablation). A control group of age- and sex-matched healthy volunteers (with no known cardiovascular disease, symptoms or complaints compatible with cardiovascular disease, regular use of medication for any cardiovascular condition, or other systemic disease) underwent standard echocardiography and 3D-STE and was used for comparisons of myocardial mechanics. An ECG was run to confirm normal sinus rhythm and rule out previously unrecognized pathology. They were excluded if any of the following were present on standard echocardiography: (1) abnormal size or volume of any cardiac chamber; (2) significant valvulopathy (moderate or severe); and (3) detection of ejection fraction <50%.

Echocardiography

Echocardiography was performed at the Cardiovascular Imaging and Hemodynamic Laboratory at Tufts Medical Center, Boston, MA, using the Scanner Artida 4D System (Toshiba, Tusin, CA). Standard 2D and Doppler echocardiographic studies were performed with the PST-30SBT transducer, according to the recommendations of the American Society of Echocardiography. Subsequently, all study subjects underwent 3D-STE, an advanced echocardiographic technique that has been validated for rendering LV global and regional myocardial mechanics.

Acquisition of 3D data sets and off-line analysis for speckle tracking were performed as previously described. In summary, 3D data sets consisted of LV full pyramidal volumes, were acquired with the Matrix Array PST-25SX transducer from the apical position, and were created by the combination of 6 ECG-gated subvolumes. The off-line speckle tracking analysis was performed using the Wall Motion Tracking software (Toshiba) and blinded to late gadolinium enhancement (LGE) results. The analysis started with axis adjustment to expose the actual endocardial border; subsequently, semiautomated tracing of endocardial and epicardial borders was rendered by manually marking 6 landmarks on the endocardial border. Then the automated tracking of borders throughout the cardiac cycle was started, and the 3D images of the LV walls were automatically divided into a 16-segment model. Finally, the resulting tracings were manually modified only in those areas where the true endocardial and epicardial borders were not correctly tracked. The quality of tracking was visually judged for each LV segment. Decisions about exclusion of echocardiographic studies for results relied on the discretion of the investigator and were based on both general 3D image quality (before attempting analysis) and accuracy to track the LV actual myocardial motion (during the attempt at analysis). If it was not feasible to either automatically or manually track ≥1 segments, the case was excluded; thus, all 16 segments from included cases were considered for results.

Cardiovascular Magnetic Resonance

CMR studies were performed using the Philips Gyroscan ACS-NT 1.5T System (Philips, Best, The Netherlands). Three standard LV cine long-axis (4-, 2-, and 3-chamber views) slices and a stack of contiguous short-axis slices from the atriointerventricular ring to the apex (full LV coverage; slice thickness 8 mm with no overlap and no gap) were acquired using an ECG-gated, breath-hold, steady-state free-precession pulse sequence. LGE sequences were acquired 15 minutes after the intravenous administration of 0.2 mmol/kg of gadodiamine-DTPA (Magnevist; Schering, Berlin, Germany) with a breath-hold 2D-segmented inversion-recovery sequence acquired in the same orientation as the cine images. The inversion time ranged from 240 to 300 ms and was chosen to null normal myocardial signal (inversion time optimized by the Look-Locker scout sequence).

The off-line analysis of CMR images was performed at a core laboratory in the Peter Munk Cardiac Centre at Toronto General Hospital, Toronto, Canada, using commercially available software cmr42 (Circle Cardiovascular Imaging, Calgary, Canada) and blinded to echocardiographic results. All tomographic short-axis LV slices from base to apex were inspected visually for identification, transmurality, and location of LGE according to the same 16-segment model as that rendered by the echocardiographic analysis. In addition, an area of completely nulled myocardium was identified, and mean signal intensity (and SD) of normal myocardium was calculated. A threshold of ≥5 SDs exceeding the mean was used to define areas of LGE. Areas of artifact (ie, blood pool or incomplete nulling of fat and pericardial fluid) were excluded from the analysis by manual adjustment of individual contours. Total volume of LGE (expressed in grams) was calculated by adding the planimetered areas of LGE in all short-axis slices and was expressed as a proportion of total LV myocardium (%LGE).

Reproducibility

Two 3D-STE experienced readers were involved in the present work. For outcome purposes, the speckle tracking analysis of 3D data sets for all patients and controls was performed by only 1 investigator. For reproducibility purposes, all 3D data sets were reanalyzed by the same investigator (28 weeks apart) and by a second blinded investigator. With respect to CMR, 2 experienced readers were involved in the present work. For outcome purposes, the CMR analysis for all patients was performed by only 1 investigator. For reproducibility purposes, visual identification of LGE in all CMR studies was repeated by a second blinded investigator.

Global and Segmental Approach to LV Myocardial Mechanics

This study focused on three 3D-STE–derived variables, namely, peak systolic longitudinal, circumferential, and area strain (LSt, CSt, and ASSt, respectively), to quantify LV systolic myocardial mechanics. These variables were chosen because they stand for the main 3 vectors of myocardial deformation; LSt and CSt represent deformation in the longitudinal and circumferential directions, respectively, and both have shown significant reproducibility; ASSt represents endocardial area change, can be derived from LSt and CSt, and is closely related to radial thickening of myocardium, yielding better reproducibility than radial strain. For each individual, global strain parameters were computed by averaging the peak values corresponding to each of the 16 LV segments. Regional strain parameters were computed by averaging the peak values of specific segments according to segmental thickness on echocardiography (≥15- versus <15-mm segments) and segmental presence of LGE on CMR (LGE segments versus non-LGE segments).

Statistical Analysis

Continuous variables were tested for both normality (by using Kolmogorov–Smirnov test) and skewness and are shown as mean±SD or median (Q1–Q3), as appropriate. Categorical variables...
are expressed as frequencies (percentages). Comparisons about continuous variables between the HCM group and healthy volunteers (control group), ≥15- and <15-mm segments, and LGE segment and non-LGE segments were performed using unpaired Student t test or Mann–Whitney U test, as appropriate. Chi-square test and 1-way ANOVA (for categorical and continuous variables, respectively) were used for comparisons between groups of patients with HCM according to the extent of LGE (non-LGE [n=16], percentage of LGE<10% [n=22], and percentage of LGE≥10% [n=21]; 10% was chosen because it has been reported as the mean amount of LGE seen in patients with HCM who are noted to have LGE, when a threshold of 5 SDs above the mean signal intensity for normal myocardium is used to define areas of LGE)⁵; differences between the corresponding pairs of groups were investigated by the post hoc Tukey HSD test. After normality test and construction of scatter plots for pairs of continuous variables, correlation between them was tested by Pearson and Spearman ρ correlation coefficients, as appropriate. On the global myocardial mechanics aspect, multiple linear regression was conducted to test independent association of hypertrophy with global strain parameters (ie, global LSt). On the regional aspect, myocardial mechanics were analyzed at segmental level to test the actual influence of hypertrophy, the presence of LGE, and their interaction on segmental strain parameters; thus, generalized estimating equation models were used to cluster segments within each patient, and

Table 1. Demographic Data and Baseline Characteristics in HCM and Control Groups, and in HCM Group According to the Extent of LGE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=30)</th>
<th>All HCM (n=59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42±10</td>
<td>46±17</td>
<td>0.2</td>
</tr>
<tr>
<td>Women (%)</td>
<td>12 (40)</td>
<td>21 (36)</td>
<td>0.7</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.9±0.2</td>
<td>2.0±0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68±11</td>
<td>66±9</td>
<td>0.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>120±10</td>
<td>122±18</td>
<td>0.4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73±11</td>
<td>73±11</td>
<td>1.0</td>
</tr>
<tr>
<td>Pattern of hypertrophy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Septal asymmetrical                    | 46 (78)        | ...
| Symmetrical (concentric)               | 6 (10)         | ...
| Predominantly midcavity                | 2 (3)          | ...
| Apical                                 | 4 (7)          | ...
| Lateral asymmetrical                   | 1 (2)          | ...
| NYHA functional class (%)              |                |                |         |
| I/II                                   | 30 (51)/19 (32)| ...
| III/IV                                 | 10 (17)/0 (0)  | ...
| Mitral regurgitation (%)§              |                |                | 0.6     |
| Abence/trace                           | 27 (46)        | ...
| Mild                                   | 21 (35)        | ...
| Moderate                               | 10 (17)        | ...
| Severe                                 | 1 (2)          | ...
| LV outflow obstruction#                |                |                |         |
| At rest (%)                            | 32 (54)        | ...
| Gradient at rest, mm Hg                | 86 (34)        | ...
| At exercise (%)                        | 9 (15)         | ...
| Gradient at exercise, mm Hg            | 77 (38)        | ...
| History of atrial fibrillation (%)     | 6 (10)         | ...
| β-Blockers                             | 35 (59)        | ...
| CC-Blockers                            | 9 (15)         | ...
| Disopyramide                           | 0 (0)          | ...
| Diuretics                              | 5 (9)          | ...

CC-Blockers indicates calcium channel blockers; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; and NYHA, New York heart Association Functional Class.

*Comparison among non-LGE, LGE<10%, and LGE≥10% groups.
†Each pattern versus other patterns.
‡NYHA I–II vs NYHA III–IV.
§Related to systolic anterior motion of mitral leaflet/s.
||Absence or trace/mild vs moderate/severe.
#Gradient ≥30 mm Hg.
thereby accounting for the fact that they were all measured on the same patient. Intra- and interobserver variability for 3D-STE parameters was calculated as the absolute difference of the corresponding pair of repeated myocardial mechanics measurements, expressed as a percentage of their mean; in addition, intraclass correlation coefficients were provided. Kappa statistic was used to describe the level of agreement between 2 CMR readers for visual identification of LGE. Statistical significance was defined as a 2-sided \( P \) value <0.05.

Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY).

**Results**

Of 69 patients with established diagnosis of HCM enrolled in the study protocol, 10 were excluded because of absence of contrast administration for the CMR study (2 cases), significant inaccuracy in tracking LV myocardial motion on off-line speckle tracking analysis (7 cases; feasibility of the echocardiographic technique was 90% [62/69]), and technical inability to perform off-line reading and analysis of the CMR study (1 case). The 3D-STE and CMR analyses of the remaining 59 subjects with HCM were considered for study outcomes. The intra- and interobserver variability obtained for 3D-STE–derived global strain parameters was as follows: LSt, 5±6% and 6±8%; CSt, 6±6% and 8±9%; and ASt, 5±7% and 6±9%; the corresponding intraclass correlation coefficients were 0.94 and 0.92 (for LSt), 0.84 and 0.72 (for CSt), and 0.81 and 0.75 (for ASt).

The level of agreement between the 2 CMR readers for visual identification of LGE was excellent (κ statistic, 0.91).

**Table 2. Echocardiographic Parameters in HCM and Control Groups, and in HCM Group According to the Extent of LGE**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n=30)</th>
<th>HCM (n=59)</th>
<th>P Value</th>
<th>Non-LGE (n=16)</th>
<th>LGE&lt;10% (n=22)</th>
<th>LGE≥10% (n=21)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV internal dimension at end-diastole, mm</td>
<td>46±4</td>
<td>43±6</td>
<td>0.003</td>
<td>42±5</td>
<td>43±6</td>
<td>44±6</td>
<td>0.4</td>
</tr>
<tr>
<td>LV internal dimension at end-systole, mm</td>
<td>28±4</td>
<td>26±7</td>
<td>0.02</td>
<td>25±5</td>
<td>26±7</td>
<td>26±7</td>
<td>0.9</td>
</tr>
<tr>
<td>LV anteroseptal wall thickness, mm</td>
<td>9±1</td>
<td>17±3</td>
<td>&lt;0.001</td>
<td>16±3</td>
<td>17±4</td>
<td>18±4</td>
<td>0.3</td>
</tr>
<tr>
<td>LV interfolateral wall thickness, mm</td>
<td>8±1</td>
<td>11±2</td>
<td>&lt;0.001</td>
<td>10±2</td>
<td>12±3</td>
<td>11±2</td>
<td>0.1</td>
</tr>
<tr>
<td>Maximum LV wall thickness, mm</td>
<td>9 (8–10)</td>
<td>20 (17–22)</td>
<td>&lt;0.001</td>
<td>18 (15–19)‡</td>
<td>20 (17–21)</td>
<td>20 (19–23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of ≥15-mm segments†</td>
<td>…</td>
<td>7±3</td>
<td>…</td>
<td>5±3§</td>
<td>8±4</td>
<td>8±3</td>
<td>0.02</td>
</tr>
<tr>
<td>Anterioposterior left atrium dimension</td>
<td>30±3</td>
<td>40±7</td>
<td>&lt;0.001</td>
<td>38±7</td>
<td>41±5</td>
<td>40±8</td>
<td>0.4</td>
</tr>
<tr>
<td>3D-speckle tracking echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indexed LV end-diastolic volume, mL/m²</td>
<td>68 (64–72)</td>
<td>72 (59–79)</td>
<td>0.3</td>
<td>68 (56–77)</td>
<td>71 (59–80)</td>
<td>73 (61–80)</td>
<td>0.8</td>
</tr>
<tr>
<td>Indexed LV end-systolic volume, mL/m²</td>
<td>29±5</td>
<td>29±9</td>
<td>0.8</td>
<td>28±9</td>
<td>30±8</td>
<td>31±9</td>
<td>0.6</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>58±3</td>
<td>59±5</td>
<td>0.07</td>
<td>61±5</td>
<td>59±6</td>
<td>58±5</td>
<td>0.4</td>
</tr>
<tr>
<td>Indexed LV mass, g/m²</td>
<td>68±11</td>
<td>106±20</td>
<td>&lt;0.001</td>
<td>98±20</td>
<td>109±20</td>
<td>110±19</td>
<td>0.2</td>
</tr>
<tr>
<td>Global longitudinal strain, %</td>
<td>−17±2</td>
<td>−14±3</td>
<td>&lt;0.001</td>
<td>−14±3</td>
<td>−14±3</td>
<td>−13±2</td>
<td>0.6</td>
</tr>
<tr>
<td>Global circumferential strain, %</td>
<td>−29±3</td>
<td>−31±4</td>
<td>0.04</td>
<td>−32±4</td>
<td>−31±3</td>
<td>−30±3</td>
<td>0.1</td>
</tr>
<tr>
<td>Global area strain, %</td>
<td>−42±4</td>
<td>−41±4</td>
<td>0.4</td>
<td>−43±4</td>
<td>−42±4</td>
<td>−40±4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

3D indicates three-dimensional; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; and LV, left ventricular.

*Comparison among non-LGE, LGE<10%, and LGE≥10% groups.

†≥15 mm by standard echocardiogram.

‡vs LGE<10%, \( P =0.05 \), and vs LGE≥10%, \( P =0.001 \) (post hoc Tukey HSD tests).

§vs LGE<10%, \( P =0.04 \), and vs LGE≥10%, \( P =0.03 \) (post hoc Tukey HSD tests).

Results

Of 69 patients with established diagnosis of HCM enrolled in the study protocol, 10 were excluded because of absence of contrast administration for the CMR study (2 cases), significant

**Table 3. Relationship* Between Three-Dimensional Speckle Tracking Echocardiography–Derived Deformation Parameters and Conventional Echocardiographic Measurements in HCM Group**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSt</th>
<th>P Value</th>
<th>CST</th>
<th>P Value</th>
<th>AST</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indexed LV end-diastolic volume</td>
<td>−0.13</td>
<td>0.3</td>
<td>0.22</td>
<td>0.1</td>
<td>0.11</td>
<td>0.4</td>
</tr>
<tr>
<td>Indexed LV end-systolic volume</td>
<td>0.05</td>
<td>0.7</td>
<td>0.47</td>
<td>&lt;0.001</td>
<td>0.39</td>
<td>0.002</td>
</tr>
<tr>
<td>Indexed stroke volume</td>
<td>−0.26</td>
<td>0.05</td>
<td>−0.12</td>
<td>0.4</td>
<td>−0.19</td>
<td>0.2</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>−0.32</td>
<td>0.01</td>
<td>−0.75</td>
<td>&lt;0.001</td>
<td>−0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indexed LV mass</td>
<td>0.32</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td>1.0</td>
<td>0.15</td>
<td>0.3</td>
</tr>
<tr>
<td>Maximum LV wall thickness</td>
<td>0.34</td>
<td>0.009</td>
<td>−0.01</td>
<td>1.0</td>
<td>0.12</td>
<td>0.4</td>
</tr>
<tr>
<td>Number of ≥15 mm segments†</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>0.3</td>
<td>0.30</td>
<td>0.02</td>
</tr>
</tbody>
</table>

AST indicates area strain; CST, circumferential strain; HCM, hypertrophic cardiomyopathy; LST, longitudinal strain; and LV: left ventricular.

*Pearson correlation coefficient, except for indexed LV end-diastolic volume and maximum LV wall thickness, where Spearman \( \rho \) correlation coefficient is shown.

†≥15 mm by standard echocardiogram.
Cardiovascular Magnetic Resonance–Late Gadolinium Enhancement

Demographic data and baseline characteristics of the HCM population and the control group (30 healthy volunteers), as well as the study group stratified by the extent of LGE, are depicted in Table 1. By qualitative evaluation, LGE was detected in 43 patients (73%). In the LGE group, 17 cases (40%) showed ≥1 LV segment with transmural LGE. Regarding LGE location, 63% of LGE subjects had involvement of the inferoseptal wall at the midventricular level, whereas other frequently involved segments were the anteroseptal walls at the basal (49%) and midventricular (42%) levels; involvement of other segments was as follows: inferoseptal at the basal level (28%), inferolateral at the midventricular level (19%), inferior at the apical level (12%), and remaining segments <10% of cases. By quantitative evaluation, the LGE group had a mean %LGE of 12.4±8.7%.

Echocardiography: Standard and 3D-Speckle Tracking Studies

Table 2 shows parameters derived from standard echocardiography and 3D-STE in HCM and control groups and in the HCM group stratified by the extent of LGE. Maximum LV wall thickness and number of ≥15-mm segments were significantly greater in those patients in whom LGE was detected by CMR. Indexed LV mass also showed a clear trend to higher values in those with LGE. None of the myocardial mechanics parameters derived from 3D-STE analysis showed differences between the HCM subsets according to the extent of LGE.

Given the attenuated LSt and enhanced CSt seen in patients with HCM when compared with controls (Table 2), the possible relationships of 3D-STE–derived strain with both conventional echocardiographic parameters related to LV function and extent of LV hypertrophy were tested (Table 3). Circumferential shortening showed significant correlations with standard functional parameters (ie, end-systolic volume and ejection fraction), whereas longitudinal shortening was significantly correlated to the extent of hypertrophy observed (Figure 1). Area strain, as a net result from longitudinal and circumferential deformations, also showed correlations with functional parameters and number of significantly hypertrophied segments. Three multiple linear regression models, each including 1 variable representing extent of hypertrophy (indexed LV mass, LV wall thickness, and number of ≥15-mm segments) and %LGE (all 3 adjusted by age and sex), revealed the independent role that extent of hypertrophy plays in the attenuation of global LSt (standardized regression coefficients and \( P \) values for the 3 tested variables: 0.31, \( P=0.02 \); 0.45, \( P=0.005 \); 0.44, \( P=0.002 \), respectively).

On the basis of the relationship observed between circumferential shortening and conventional LV functional parameters, the presence and extent of LGE and ejection fraction were investigated in a post hoc analysis in a subset of patients with attenuated global CSt (beyond 1 SD of the mean value observed for the entire HCM population [ie, CSt >−27%]). There were 9 patients in this group (CSt range, −23.45%−−26.75%). Eight of them had LGE, with 6 demonstrating %LGE ≥10% (mean±SD, 15±8%). Furthermore, although mean ejection fraction of the entire HCM population was 59±5% (Table 2), ejection fraction in this group was 54±5%, with 6 patients <55%.

Myocardial Mechanics–Myocardial Thickness–LGE

In the regional approach to LV myocardial mechanics, all 3 deformation parameters were attenuated in those segments with hypertrophy and in LGE segments (Table 4). In most patients with LGE—38 of 43 (88%) patients—LGE was...
detected within hypertrophied segments, whereas in 19 (44%) patients LGE was seen within nonhypertrophied segments. There was no difference in strain parameters between hypertrophied segments and LGE segments (Table 4).

To test the effect of fibrosis on regional mechanics independently of significant hypertrophy, an analysis on the LGE group was performed including, on one side, only those segments with thickness ≥15 mm and, on the other side, only those segments <15 mm (Table 5). All 3 deformation parameters showed attenuation in hypertrophied-LGE segments (when compared with hypertrophied non-LGE segments), whereas no differences were observed in the LGE versus non-LGE comparison for segments without hypertrophy. Consistently with these results, the analyses through generalized estimating equation models (Table 6) showed both segmental thickness ≥15 mm and the interaction between the latter and the presence of LGE to be independently associated with attenuation in segmental LSt. In contrast, segmental thickness ≥15 mm and the presence of LGE, but not the interaction between them, independently determined attenuation of CSt and ASt (Table 6). Figure 2 shows an example of regional myocardial mechanics in relation to hypertrophy and LGE.

Discussion
The current work aimed to define LV global and regional myocardial mechanics in HCM, hypothesizing that hypertrophy and fibrosis, both structural and tissue characteristics of this condition, have a significant role in myocardial functional abnormalities. Hypertrophy was measured by standard echocardiography, fibrosis was measured on LGE sequences by CMR, and myocardial mechanics were evaluated by 3D-STE. The results provide several important insights into myocardial function in HCM: (1) global deformation of LV myocardium is attenuated in the longitudinal direction and enhanced in the circumferential direction; (2) increasing extent of LGE is not associated with attenuation of LV global systolic shortening in either the longitudinal or the circumferential directions; however, it is associated with increasing extent of hypertrophy; (3) circumferential shortening correlates the best to LV global functional parameters, whereas longitudinal shortening correlates the best to parameters representing extent of hypertrophy; and (4) although these data suggest a more important role for the extent of hypertrophy rather than fibrosis to myocardial functional performance, segmental analysis demonstrates that both factors have a significant effect on LV myocardial function.

Global Systolic Deformational Mechanics of the LV in HCM
In HCM, even when systolic function as assessed by ejection fraction yields normal values, LV global systolic performance is impaired.3–6 In the present work, longitudinal and circumferential systolic shortening were altered in HCM when compared with healthy controls (Table 2), despite preserved ejection fraction. In this regard, a notable attenuation of global longitudinal shortening was observed in patients with HCM, a finding widely consistent with previous investigations.8,10,12,25–28

Table 4. Myocardial Strain Analysis According to Segmental Thickness in All Patients (n=59) and According to Segmental Presence of LGE in LGE Group (n=43)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Segmental Thickness (n=59)</th>
<th>Segmental LGE (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥15-mm Segments (415)†</td>
<td>&lt;15-mm Segments (529)†</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>−11±4</td>
<td>−15±3</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>−28±5</td>
<td>−33±5</td>
</tr>
<tr>
<td>Area strain</td>
<td>−37±7</td>
<td>−45±6</td>
</tr>
</tbody>
</table>

LGE indicates late gadolinium enhancement.
*LGE segments vs ≥15-mm segments, P≥0.05.
†Number of segments.

Table 5. Myocardial Strain Analysis According to Segmental Presence of LGE in Significantly Hypertrophied and Nonsignificantly Hypertrophied Segments

<table>
<thead>
<tr>
<th>Parameters</th>
<th>≥15-mm Segments (n=37*)</th>
<th>&lt;15-mm Segments (n=19†)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LGE Segments (83)‡</td>
<td>Non-LGE Segments (219)‡</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>−8±3</td>
<td>−12±4</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>−25±6</td>
<td>−29±6</td>
</tr>
<tr>
<td>Area strain</td>
<td>−32±7</td>
<td>−38±7</td>
</tr>
</tbody>
</table>

LGE indicates late gadolinium enhancement.
*Of 43 patients with LGE, 37 featured presence and absence of LGE within different significantly hypertrophied segments (1 patient showed LGE in all significantly hypertrophied segments and 5 showed LGE only in nonsignificantly hypertrophied segments).
†Of 43 patients with LGE, 19 featured presence and absence of LGE within different nonsignificantly hypertrophied segments (the remaining patients showed LGE only in significantly hypertrophied segments).
‡Number of segments.
Impairment of deformation in the longitudinal direction has been linked to the unique distribution of myocytes in a disarray in these patients. Thus, maximal myofiber disarray occurs in the inner region of the myocardium, and, therefore, muscle fibers within the subendocardial region, which are responsible for most of the longitudinal deformation, are likely to be the most impaired functionally.

Global values for circumferential shortening in HCM are inconsistent in previously published literature. In our study, we found increased global circumferential shortening (Table 2). Myocytes in the subepicardium account for circumferential deformation, and in HCM, they are the least affected by disarray. We speculate that these myocytes compensate for the myocardial dysfunction from endocardial myocyte disarray (ie, decreased longitudinal deformation) resulting in increased circumferential deformation, which correlated with conventional LV functional parameters (Table 3). No significant differences were detected in all global deformation parameters according to the extent of LGE (Table 2). This suggests that LGE alone has little role in alteration of LV global systolic mechanics.

Put together, our data demonstrate that hypertrophy and its extent seem to be the major independent factors altering global systolic myocardial mechanics in HCM. Moreover, given the significant attenuation in longitudinal function, and the striking results of the post hoc analyses focused on patients with attenuated CSt, we speculate that analysis of circumferential shortening in HCM might have relevant clinical implications, as a parameter that may contribute to the maintenance of LV systolic performance.

**Regional Systolic Deformational Mechanics of the LV in HCM**

Tables 4 and 5 demonstrate that hypertrophy determined the most marked differences between segments in terms of...
deformation. Interestingly, in segments with hypertrophy, all deformation parameters, including circumferential shortening, were attenuated when compared with segments with thickness <15 mm. This is in agreement with previous studies where all patients had hypertrophy patterns involving septal segments8,10 and that showed diminished circumferential function in the septum.

Regarding the segmental presence of LGE, Table 5 highlights the worst-case scenario for regional dysfunction in patients with HCM (ie, segments with hypertrophy and fibrosis had the most impaired regional function by all deformation parameters). However, our findings suggest that the attenuation in deformation observed for LGE segments might have been driven by the location of fibrosis (their values for LSt, CST, and AST were similar to those for ≥15-mm segments; Table 4), mainly within hypertrophied segments. However, by generalized estimating equation models (Table 6), LGE indeed was shown (along with segmental thickness, ≥15 mm) to be independently associated with segmental dysfunction. Thus, with respect to longitudinal shortening, the presence of fibrosis seems to be associated with incremental dysfunction within significantly diseased areas (ie, where hypertrophy is present).12 In contrast, the net dysfunction resulting from individual fibrotic segments within nonhypertrophied areas probably do not preclude other nonfibrotic segments from deforming to some extent in the longitudinal direction, pulling away from most affected segments (fibrotic ones) and minimizing fibrosis-related dysfunction. In addition, fibrosis would alter circumferential shortening within the less involved segments (ie, where hypertrophy is absent). A possible explanation for this finding is that circumferential deformation, closely related to transmural myocardial involvement, might be impaired by a particular process depending on the region analyzed. Thus, significantly increased wall thickness would lead to maximal circumferential dysfunction within hypertrophied areas, whereas fibrosis distributed through the myocardial thickness would be the factor altering circumferential shortening in nonhypertrophied regions. Area deformation, which showed to be a good correlate of LV functional parameters (Table 3), probably follows the behavior of circumferential shortening, which seems to contribute to the maintenance of systolic function in patients with HCM.

Limitations

Although our comprehensive statistical approach ensures a fair representation of myocardial mechanics in HCM, the study population is small, and the work should be conceived as descriptive, exploratory, and hypothesis generating. Therefore, caution is needed before taking our findings as conclusive data. Although there are likely to be several mechanisms to explain systolic dysfunction in HCM, this study only focused on 2, hypertrophy and fibrosis, that can be detected by noninvasive imaging techniques. The investigation assumes equivalence between LGE and fibrosis; whether LGE in HCM represents only myocardial scarring (ie, replacement fibrosis) or that showed diminished circumferential function in the septum.

LV deformation myocardial mechanics are altered in HCM, with both hypertrophy and fibrosis contributing to regional impairment of myocardial shortening. The extent of hypertrophy is the main factor associated with alteration of myocardial mechanics, superior to even the presence and extent of fibrosis. LV myocardial shortening in the circumferential direction, measured by 3D-STE, seems to be directly involved in the preservation of LV systolic performance in HCM.

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Disclosures

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10. Carasso S, Yang H, Woo A, Vannan MA, Jamorski M, Wigle ED, Rakowski H. Systolic myocardial mechanics in hypertrophic cardiomyopathy: novel work correspond to endocardial deformation, which precludes us from stating that the results of the study entirely define myocardial mechanics in HCM. Finally, discordant results between different ultrasound vendor platforms have been reported,11 which should be taken into consideration when interpreting the strain values in the present work.
This work aimed to define the effect of hypertrophy and fibrosis, both structural and tissue characteristics of hypertrophic cardiomyopathy. Cardiovascular magnetic resonance imaging plays an important role in the diagnosis and management of hypertrophic cardiomyopathy. Three-dimensional speckle tracking echocardiography has emerged as a novel imaging approach to analyze myocardial mechanics. Hypertrophic cardiomyopathy is a major inherited cardiovascular disease, affecting 1 of 500 people in the general population. Clinical implications and warrants further study.

CLINICAL PERSPECTIVE

Hypertrophic cardiomyopathy is a major inherited cardiovascular disease, affecting 1 of 500 people in the general population. Cardiovascular magnetic resonance imaging plays an important role in the diagnosis and management of hypertrophic cardiomyopathy and has been shown to be useful in characterizing the degree and distribution of myocardial fibrosis. Three-dimensional speckle tracking echocardiography has emerged as a novel imaging approach to analyze myocardial mechanics. This work aimed to define the effect of hypertrophy and fibrosis, both structural and tissue characteristics of hypertrophic cardiomyopathy, on left ventricular myocardial mechanics. This study demonstrates that the reduction in global longitudinal shortening is related to the extent of hypertrophy, whereas global circumferential shortening is enhanced, which seems to contribute to the preservation of left ventricular systolic performance. In addition, although it is likely that hypertrophy affects myocardial functional performance more than fibrosis, regional analysis demonstrates that both factors have a significant effect on left ventricular myocardial function. The results of this study should be considered preliminary with uncertain clinical implications and warrants further study.
Investigation of Global and Regional Myocardial Mechanics With 3-Dimensional Speckle Tracking Echocardiography and Relations to Hypertrophy and Fibrosis in Hypertrophic Cardiomyopathy

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