Regional Heterogeneity of Function in Hypertrophic Cardiomyopathy

Christopher M. Kramer, MD; Nathaniel Reichek, MD; Victor A. Ferrari, MD; Teresa Theobald, RDCS; Janice Dawson, RN; Leon Axel, PhD, MD

Background In patients with hypertrophic cardiomyopathy (HCM), left ventricular ejection performance may be normal while segmental myocardial function is distinctly abnormal. The advent of magnetic resonance tissue tagging has allowed the noninvasive evaluation of intramyocardial segmental shortening in vivo in a topographic and temporal manner.

Methods and Results Ten patients with HCM documented by echocardiography and 10 healthy volunteers were studied with magnetic resonance tissue tagging by spatial modulation of magnetization. Percent circumferential myocardial shortening (%S) was compared at endocardium, midwall, and epicardial levels at four regions around the left ventricular short axis and from four short axis slices from apex to base at four or five time intervals during systole. In 8 patients and 8 control subjects, longitudinal shortening was evaluated within the septum and the lateral free wall at three levels from apex to base. Circumferential %S was less in HCM patients than in control subjects in the septal (13±5% versus 24±6%, P=.0002), inferior (13±5% versus 21±4%, P=.001), and anterior (17±5% versus 21±3%, P<.03) regions but not in the lateral region. Circumferential end-systolic %S was reduced in patients with HCM compared with control subjects at all levels from apex to base. The normal transmural gradient in circumferential end-systolic shortening was preserved with greatest %S at the endocardium. Most of the total cumulative circumferential shortening occurred earlier in systole in patients compared with control subjects, especially within the septum. Longitudinal end-systolic %S was depressed throughout the septum in patients compared with control subjects, most markedly at the base, but was normal in the lateral free wall.

Conclusions Circumferential myocardial segment shortening is depressed in HCM in the septum, inferior, and anterior regions and at all levels from apex to base, and much of the total cumulative shortening occurs early in systole. Longitudinal shortening is reduced in the basal septum in HCM. The heterogeneity of regional function in these patients may reflect the regional variation in the myocardial disarray and fibrosis that is characteristic of this disorder.

Key Words • cardiomyopathy • magnetic resonance imaging

To accurately assess segmental intramyocardial function, previous studies have required invasive implantation of sonomicrometry crystals or metallic markers to localize myocardial segments.1-3 Such methods are not well suited for research in human disease. With the advent of magnetic resonance tissue tagging by spatial modulation of magnetization (SPAMM), the potential for noninvasive evaluation of intramyocardial myocardial shortening has been realized.4,5 This technique is capable of characterizing the regional and temporal heterogeneity of myocardial function in human subjects.

Using magnetic resonance tissue tagging by SPAMM, we compared intramyocardial circumferential and longitudinal segment shortening in healthy volunteers and in patients with hypertrophic cardiomyopathy (HCM). We hypothesized that the regions most affected by the hypertrophic process, the septum and the base, would manifest reduced function relative to healthy subjects, whereas function in other regions in HCM would be similar to that in healthy subjects.

Patient Population

We studied 10 patients with HCM documented by echocardiography (age range, 16 to 71 years; mean age, 44 years) (Table 1). There were 8 males and 2 females. By two-dimensional guided M-mode echocardiography, the mean septal and posterior wall thicknesses were 2.1±0.4 cm and 1.4±0.3 cm, respectively (Table 1). The mean fractional shortening was 45±8%. Three patients had Doppler echocardiographic evidence of dynamic left ventricular (LV) outflow obstruction with peak gradients of 62, 35, and 16 mm Hg. None had a history of hypertension or echocardiographic evidence of global LV dysfunction or significant valvular disease.

We also studied 10 healthy volunteers (age range, 20 to 36 years; mean age, 27 years). None had clinical or echocardiographic evidence of cardiac disease. The mean septal and posterior wall thicknesses were both 0.8±0.1 cm, and the mean fractional shortening was 35±2%.

This study was approved by the Committee on Studies Involving Human Beings of the University of Pennsylvania. All patients and healthy subjects gave informed consent.

Methods

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TABLE 1. Clinical and Echocardiographic Data for Patients With Hypertrophic Cardiomyopathy

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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
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<th>Posterior</th>
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<th>FS</th>
<th>PSG</th>
<th>LA</th>
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</table>

Mean     | 44   | 2.1   | 1.4   | 3.7   | 45 | 11 | ... | 3.9|           |

Septal indicates septal wall thickness; posterior, posterior wall thickness; EDD, left ventricular end-diastolic dimension; FS, fractional shortening of the left ventricle; PSG, peak systolic pressure gradient across left ventricular outflow tract; LA, left atrial dimension; and long axis, long-axis set of images available for analysis.

were echo time (TE) of 20 milliseconds, repetition time (TR) equal to the RR interval, 40-cm field of view, 5-mm-thick slices with 5-mm skips, and 128×256-pixel matrix interpolated to 256×256 for display. To identify end systole, a multiphase, single-slice, axial cine series at the level of the mitral valve was acquired with TE of 13 milliseconds, TR of 25 milliseconds, 20° flip angle, and flow compensation. A set of single-phase compound oblique short-axis images using the SPAMM pulse sequence was then obtained perpendicular to the ventricular long axis to evaluate centering on the long axis and stripe persistence.

The SPAMM grid of black stripes with initial center-to-center separations of 7 mm is generated by a preimaging sequence of nonselective radiofrequency pulses separated by magnetic field gradient pulses. The SPAMM stripes result from the intersection of the resulting sets of parallel planes of reduced signal in three-dimensional space with the imaging plane. Thus, initial stripe spacing is the same throughout the cardiac volume. Imaging parameters were TE of 27 milliseconds, TR equal to the RR interval, 5-mm-thick slices, 5-mm skips, 32-cm field of view, and a 128×256 acquisition matrix yielding a final interpolated pixel size of 0.88 mm. To enhance myocardial signal and stripe persistence, flow compensation, a SPAMM flip angle of 130°, and a number of signals averaged of 2 were used.

Multislice, multiphase, short-axis, SPAMM spin-echo images were obtained from end diastole, defined at 13 milliseconds after the R-wave peak, to end systole. Four short-axis slices (Fig 1) spanning the entire LV were imaged at four or five time instances with an intersequence delay adjusted to ensure that the last image coincided with end systole as defined by the cine series. A long-axis, multiphase image series was then acquired perpendicular to the imaged short-axis planes and perpendicular to the midseptum and lateral left ventricular wall (Fig 2). Four or five long-axis slices were imaged at four or five time instances between and including end diastole and end systole. Total imaging time was approximately 90 minutes.

Data Analysis

Quantitative analysis was performed on a SUN workstation using an operator-driven interstripe distance–measuring software tool developed in the VOLUMETRIC IMAGE DISPLAY AND ANALYSIS software package (VIDA, University of Pennsylvania) (Fig 3). A SPAMM short- and long-axis images were magnified on the screen for ease of analysis. To measure intramyocardial shortening, pairs of SPAMM stripes oriented perpendicular to the endocardium were selected, and an operator-defined line was drawn through the myocardium normal to the selected stripe pair. VIDA digitally displays the pixel signal values on a line normal to the SPAMM stripes, allowing the reproducible identification of the SPAMM stripe centers marked by trough signal values. Using trough-to-trough separations, we performed measurement of interstripe separations in pixels or segment lengths on end-diastolic (Ldes), early systolic (Les), midventricular (Lmv), late systolic (Lls), and end-systolic (Les) frames from short-axis slices. Cumulative percent shortening (S%), from end diastole to end systole, was calculated as %S = 100(Ldes - Lls)/Ldes. Calculation of S% from end diastole to early, mid, and late systole in the circumferential plane was performed by substituting the appropriate value for segment length for Lmv in the above equation. In two patients, only four systolic time instances were imaged, including end diastole and end systole, and the two intermediate points were termed early systole and late systole, respectively. Therefore, only eight data points were available for calculation of mid systolic S%. Measurement of S% in the longitudinal direction was performed only at end systole.

Percent intramyocardial circumferential shortening was measured at endocardial, midwall, and epicardial sites in the anterior, lateral, septal, and inferior regions in the LV short axis in four slices from apex to base in each study. Longitudinal shortening was measured at endocardial and epicardial sites within the lateral free wall and at LV endocardial and right ventricular (RV) endocardial sites within the septum. Three interstripe distance measurements from within each third of the LV long axis (apical, mid, and basal) were averaged to assess longitudinal shortening.

Statistical Analysis

Comparisons of circumferential S% and longitudinal S% between patient and control groups were made using Student’s t test for unpaired comparisons. Full data sets of longitudinal S% were available in eight patients and eight control subjects. Comparisons of circumferential S% at endocardial, midwall, and epicardial sites and among anterior, lateral, septal, and inferior regions within each group of subjects were made using repeated-measures ANOVA with Scheffé subtesting. Similarly, comparisons of averaged S% across the wall in anterior, lateral, septal, and inferior regions in each of the four slices were compared using repeated-measures ANOVA. To evaluate circumferential S% over time, averaged values for each region separately and then for the average of all four regions were compared over four time intervals from end diastole to early, mid, late, and end systole by repeated-measures ANOVA with Scheffé subtesting. For longitudinal S%, com-
Fig 1. A, End-systolic left ventricular short-axis image tagged with spatial modulation of magnetization from a healthy volunteer. Interstripe distances at end systole are fairly uniform around the left ventricular short axis. B, End-systolic left ventricular short-axis image tagged with spatial modulation of magnetization from a patient with hypertrophic cardiomyopathy. End-systolic segment shortening appears reduced compared with the healthy subjects image in all walls except for the lateral free wall.
Fig 2. A: End-systolic left ventricular long-axis image tagged with spatial modulation of magnetization from a healthy volunteer. B, End-systolic left ventricular long-axis image tagged with spatial modulation of magnetization from a patient with hypertrophic cardiomyopathy. End-systolic segment shortening appears normal in the lateral wall but is reduced in the septum.
Intramyocardial Circumferential Shortening

Intramyocardial end-systolic segment shortening within the septum, inferior, and anterior regions of patients with HCM was lower than in control subjects when values from endocardial, midwall, and epicardial sites in all four slices from apex to base were averaged (Fig 4). However, lateral circumferential end-systolic \%S was not different from that of control subjects. Intramyocardial end-systolic circumferential shortening was lower than that for healthy subjects at each level along the LV long axis when values from all transmural levels in each region were averaged (Fig 5).

Within the group of patients, circumferential end-systolic shortening was less in the septum (13±5\%) and inferior wall (13±5\%) than in the lateral wall (19±5\%) (Fig 5). Circumferential end-systolic \%S in the anterior region was intermediate at 17±5\% and not significantly

$$\text{FIG 3. Picture of a SUN workstation monitor loaded with the VOLUMETRIC IMAGE DISPLAY AND ANALYSIS software (VIDA). An end-systolic image from a patient with hypertrophic cardiomyopathy is seen with an operator-drawn line across four spatial modulation of magnetization tags in the septum. Lower left, Graph depicting the signal intensity of the image crossed by the operator-drawn line. The signal nadirs representing the tissue tags in the septum are easily seen. Within the graphic interface, the operator can measure the distance between the two middle nadirs as shown, representing the end-systolic interstripe distance of the middle two tags, or L_{es}. This measurement is displayed at the upper left and is used, along with the measurement of end-diastolic interstripe distance, L_{ed}, to measure segment shortening through systole using the formula } \%S = 100\left(\frac{L_{ed} - L_{es}}{L_{ed}}\right).$$

Fig 4. Graph depicting percent circumferential shortening of the four regions around the left ventricular short axis when values for endocardial, midwall, and epicardial percent shortening from all four short-axis slices were averaged in control subjects and in patients with hypertrophic cardiomyopathy. Statistically significant differences between control subjects and patients were evaluated with unpaired Student’s t test. *P<.03 for patients vs control subjects. No statistically significant difference between regions was seen in healthy subjects by repeated-measures ANOVA. In patients, significant differences between regions were noted (ANOVA P<.005). With Scheffe subtesting, 1P<.05 vs lateral region.
shown in Figure 6. In healthy subjects, a stepwise increase in shortening throughout systole was seen, whereas in patients with HCM, more than half of cumulative end-systolic shortening occurred in early systole, and no shortening occurred in the last phase of systole. Similarly, in the lateral wall in HCM, much of shortening occurred early in systole as it progressed from 7±3% at early systole to 15±5% at mid systole to 18±5% at late systole to 19±5% at end systole (ANOVA, \( P<.0001 \)). In the lateral wall of healthy subjects, the time course of shortening was a stepwise progression, similar to that found in the healthy subjects septum.

**Intramyocardial Longitudinal Shortening**

The analysis of longitudinal shortening, all at end systole, within the septum in healthy subjects and patients is demonstrated in Fig 7. Basal longitudinal shortening was significantly lower in patients than in control subjects (0±5% versus 12±6%, \( P<.001 \)). Systolic lengthening of some basal segments in the longitudinal direction in some patients accounted for the finding of 0% mean shortening. No significant differences between the two groups were seen at more apical levels, although a trend toward lower %S in HCM patients was present. Within the group of healthy subjects, there was no gradient in longitudinal %S from apex to base. Within the group of patients, longitudinal %S was significantly lower at the base than in the more apical regions (9±12% and 9±10% in the mid ventricle and apex, respectively). In contrast, within the lateral free wall, there were no differences in longitudinal %S between or within groups of patients and control subjects (Table 6).

**Discussion**

In the present study, patients with HCM demonstrated reduced intramyocardial circumferential end-systolic shortening in the septum as well as in the inferior and anterior regions compared with healthy subjects. End-systolic shortening was reduced compared with healthy subjects at all levels from apex to base. In HCM patients, septal and inferior wall circumferential end-systolic shortening values were the most depressed. The transmural gradient in circumferential end-systolic shortening that was seen in healthy volunteers was also seen in patients with HCM. Most of the total cumulative circumferential shortening occurred earlier in systole in patients with HCM compared with control subjects, especially within the septum. Intramyocardial longitudinal end-systolic shortening was depressed in the basal septum compared with healthy controls and with more apical regions in HCM patients. Lateral longitudinal

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**Table 2. Mean Values of Endocardial, Midwall, and Epicardial Percent Circumferential Shortening in Control Subjects**

<table>
<thead>
<tr>
<th>Region</th>
<th>Apex</th>
<th>Subapex</th>
<th>Subbase</th>
<th>Base</th>
<th>ANOVA P</th>
</tr>
</thead>
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<td>Septal</td>
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<td>21±6</td>
<td>23±4</td>
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<tr>
<td>Inferior</td>
<td>22±5</td>
<td>22±6</td>
<td>20±4</td>
<td>20±6</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral</td>
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<td>23±4</td>
<td>21±8</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior</td>
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<td>21±2</td>
<td>25±6</td>
<td>19±5</td>
<td>NS</td>
</tr>
<tr>
<td>ANOVA P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>
end-systolic %S in HCM patients was similar to that in healthy subjects.

Previous investigators have used echocardiography or left ventriculography and invasive hemodynamics to evaluate myocardial function in concentric hypertrophy due to hypertension and in HCM. Hattori et al17 measured circumferential and meridional shortening of the left ventricular midwall in HCM patients. They defined shortening as changes in midwall circumference and perimeter on parasternal short-axis and apical two-chamber echocardiographic views, respectively, from end diastole to end systole. Their findings of reduced circumferential and meridional shortening in patients compared with control subjects and reduced meridional compared with circumferential shortening in both groups correlate well with our findings. However, this more global method of measuring shortening does not account for the expected regional heterogeneity of function within myocardium associated with well-documented variations in fiber direction and orientation, local geometry, and histopathology.

Pouleur et al18 found end-systolic stress in patients with HCM with supranormal ejection fraction to be lower than in healthy subjects. They demonstrated reduced slopes of force-length, force-velocity, and late systolic stress-volume curves. These investigators suggested that contractility is depressed in HCM patients despite an increased ejection fraction. Bectoci et al19 evaluated regional wall motion in 22 patients with HCM using ventriculographic techniques and found asynergy in regional contraction in 82% of patients with HCM. They detected increased wall motion in the anterobasal, anterior, anteroapical, and inferoapical regions in the right anterior oblique view and in the lateral and posteroapical regions of the left anterior oblique projection. However, their analysis was limited by the nature of the technique to changes in regional areas circumscribed by endocardium, essentially a measure of endocardial translation and not intramyocardial function.

To evaluate segmental function in the setting of concentric hypertrophy, Shimizu et al10 used cineangiography and an ellipsoid model of the LV as an indirect means to assess midwall fiber length transients, assuming nonuniform transmural thickening. They found reduced midwall shortening and mean systolic circumferential stress in patients with LV hypertrophy and an increased LV mass index. To track three-dimensional intramyocardial motion in vivo, in one study9 investigators implanted radiopaque markers at the time of surgery in patients with LV hypertrophy secondary to aortic stenosis. These investigators demonstrated reduced circumferential and longitudinal shortening.

Magnetic resonance imaging was initially recognized as a powerful method to measure wall thickness in patients with HCM.11,12 More recently, magnetic resonance tissue tagging has been used to examine segmental function in hypertrophied hearts. Using techniques similar to ours, Palmon et al13 evaluated intramyocardial shortening in hypertensive patients with mild concentric LV hypertrophy with normal pump function. They found reduced end-systolic circumferential shortening at all transmural levels in hypertensives compared with healthy subjects. Mean shortening was more reduced in patients with HCM in our study than in patients with hypertensive LV hypertrophy in Palmon et al's study (21±7% versus 29±6% in the endocardium, 15±5% versus 20±6% in the midwall, and 11±4% versus 13±5% in the epicardium). Like patients with HCM, patients with hypertensive LV hypertrophy demonstrated a preserved transmural gradient and no apex-to-base gradient in shortening. Circumferential end-systolic %S was least in the inferior wall and septum and maximal in the lateral wall, as it was in patients with HCM. Longitudinal %S was likewise uniformly depressed in hypertensives, more at the base than at the apex. These similarities between patients with hypertensive LV hypertrophy and those with HCM suggest that

### TABLE 3. Mean Values of Endocardial, Midwall, and Epicardial Percent Circumferential Shortening In Patients With Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Region</th>
<th>Apex</th>
<th>Subapex</th>
<th>Subbase</th>
<th>Base</th>
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*P<.05 vs control subjects. †P<.05 vs lateral region.

### TABLE 4. Average Values of Circumferential Shortening From All Slices From Apex to Base In Control Subjects

<table>
<thead>
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<th>Midwall</th>
<th>Epicardial</th>
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</table>

*P<.05 vs endocardial. †P<.05 vs midwall.

### TABLE 5. Average Values of Circumferential Shortening From All Slices From Apex to Base In Patients With Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Region</th>
<th>Endocardial</th>
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<th>ANOVA P</th>
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<td>Anterior</td>
<td>23±7</td>
<td>16±5*</td>
<td>12±4*</td>
<td>&lt;.0001</td>
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</tbody>
</table>

*P<.05 vs endocardial. †P<.05 vs midwall.
features common to both disorders, such as myocyte hypertrophy per se, may be important factors. In addition, increased wall thickness itself may present a mechanical disadvantage in the septum and inferior walls, especially at the base.

A recent study used magnetic resonance tissue tagging to evaluate myocardial motion relative to a chamber centroid in two dimensions in patients with HCM. These investigators demonstrated clockwise rotation in healthy subjects and patients at the base. They found less counterclockwise rotation at the apex in patients with HCM than in control subjects, especially in the posterior region. Radial displacement of intramyocardial points was significantly reduced in the septum and inferior walls in HCM patients. These findings correlate well with our findings of reduced intramyocardial circumferential shortening in those regions. Their techniques, however, did not distinguish intrinsic intramural segmental function from cardiac rigid body motion.

Myofibrillar disarray may account for much of the heterogeneity of segment shortening in HCM. Maron et al. found no correlation between wall thickness and the disorganization of myocardial fibers when tissue sections from the septum, anterolateral, and posterior free walls were examined. The anterolateral and posterior regions demonstrated normal or only mildly increased wall thickness, but approximately 80% of sections from these regions exhibited some degree of disorganization.

Other investigators have shown a predominance of myocardial fibrosis in regions where myofibrillar disarray is maximal, notably at the junction of the septum and LV and RV free walls, where 77% of segments demonstrate fascicular disarray and destruction of the normal circular architecture. They found deep tissue clefts in the junctional area that may interfere with circumferential segment shortening in these regions. They also demonstrated that the lateral free wall was free of myocardial disarray and fibrosis, at least in its midwall layer. We found that the relatively spared lateral free wall manifests preserved circumferential shortening at the base and normal longitudinal shortening throughout. In a preliminary study using magnetic resonance tissue tagging with SPAMM, White et al. demonstrated an inverse correlation between regional mean midwall velocity of circumferential fiber shortening and fiber disarray and fibrosis with r values of -.67 and -.52, respectively. Others have found a similar negative correlation with percent regional systolic wall thickening.

Another potential mechanism for the increased regional variation of segment shortening in HCM is the...
heterogeneity of regional wall stress in these hearts. Heng et al. postulated that the wall stress in the ventricular septum is theoretically higher due to its greater radius of curvature, suggesting a geometric determinant of altered intramyocardial strains in this region. This hypothesis, however, would not fully explain the reduction in circumferential shortening in the inferior and anterior regions in HCM. Pouleur et al. previously postulated a reduction in afterload to account for increased ejection fraction despite depressed myocardial contractility, but this again would not explain regional variation in myocardial function.

Limitations of our study include that our study population was small and nonrandomized because HCM is a heterogeneous disease entity. Another potential limitation of our methods is the effect of through-plane cardiac motion on the tagged images. However, measurements of intramyocardial segment shortening are not compromised by through-plane motion. Initial stripe separations in the short-axis plane are uniform throughout the myocardium because myocardial tags are orthogonal to this plane. The change in interstripe distance at end-systole, for example, therefore is a measurement of true shortening in the end-systolic segment of myocardium. Good correlation has also been found with results obtained with implanted sonomicrometry crystals for circumferential shortening and wall thickening. In addition, good intraobserver and interobserver reproducibilities (r = 0.92 for both) have been obtained with these methods.

In conclusion, circumferential and longitudinal myocardial shortening is depressed in patients with HCM. Septal and inferior circumferential end-systolic shortening and basal septal longitudinal end-systolic shortening are most depressed compared with healthy subjects. Most of the total cumulative shortening in the circumferential direction occurs early in systole. The normal transmural gradient in function is preserved. The regional and temporal heterogeneity of myocardial segment shortening in HCM may reflect the characteristic myocardial disarray and fibrosis that is regional in its manifestation.

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