Hypertrophic cardiomyopathy (HCM) is a disease characterized by asymmetric left ventricular (LV) hypertrophy caused by >400 mutations in genes encoding 10 sarcomeric proteins. Phenotypically, the vast majority of patients express hypertrophy that is greatest in the interventricular septum (septal HCM). About 7% of patients with HCM demonstrate mainly apical hypertrophy (apical HCM). These two patterns of hypertrophy differ in their clinical presentation, hemodynamic characteristics, and prognoses.

The evaluation of two-dimensional (2D) myocardial mechanics has become a very sensitive echocardiographic tool to evaluate myocardial function. Regional cardiac displacement and velocity (longitudinal, circumferential, and rotation), strain, and strain rate are readily measured by 2D tissue tracking. We recently demonstrated that patients with septal HCM have decreased longitudinal strain but increased circumferential strain, with preservation of their strain vector magnitudes. LV twist was shown to be abnormal in septal HCM as mid LV rotation became clockwise rather than the normal counterclockwise direction. We have also demonstrated that patients with apical HCM have a good long-term prognosis, with a low incidence of sudden death, but have significant morbidity, which includes apical myocardial infarction and atrial fibrillation. The purpose of this study was to determine the relationship between myocardial mechanics and the pattern of hypertrophy in HCM.

METHODS

Study Population

We retrospectively studied 94 adult patients (aged > 16 years) with HCM who were evaluated clinically and by echocardiography.
between January 2002 and December 2005 at the Toronto General Hospital. The diagnosis of HCM was established by the echocardiographic detection of septal or apical hypertrophy. Patients with septal HCM had asymmetric septal hypertrophy, with septal wall thickness ≥ 13 mm and septal wall/posterior wall thickness ratios ≥ 1.3 in the absence of a known cause for LV hypertrophy such as systemic hypertension or aortic stenosis. Patients with apical HCM had asymmetric apical hypertrophy, with apical wall thickness ≥ 15 mm and ratios of maximal apical to posterior wall thickness ≥ 1.5. All patients had normal LV systolic function by echocardiography (defined as LV ejection fraction ≥ 60%). Patient inclusion also required a Digital Imaging and Communications in Medicine echocardiographic file, with a minimum 2D frame rate of 40 frames/sec and good demarcation of the LV endocardial border.

We excluded 22 patients with HCM with associated systemic hypertension, epicardial coronary artery disease, bundle branch blocks, paced rhythms, previous interventions for the management of LV outflow tract (LVOT) obstruction, or concomitant valvular disease, leaving 72 patients for analysis (27 with apical HCM and 45 with septal HCM). The control group consisted of 25 healthy, age-matched subjects with normal clinical and echocardiographic examinations and no family histories of HCM. The study was approved by the Research Ethics Board of the Toronto General Hospital, University Health Network.

Clinical Data

Hospital records were reviewed to obtain demographic data, symptoms, New York Heart Association functional class, family history, and medications at the time of index echocardiography. Patients with HCM were followed for 34 ± 28 months (range, 6–99 months) for cardiovascular events, including atrial fibrillation, hospitalization for congestive heart failure, stroke, cardiac arrest, pacemaker or defibrillator implantation, cardiovascular procedures (septal ethanol ablation, surgical myectomy, and other cardiac surgical procedures), and death.

Doppler Echocardiographic Studies

Echocardiographic studies were interpreted by a cardiologist blinded to patients’ clinical findings. Two-dimensional, Doppler, and Doppler tissue imaging parameters were measured according to the guidelines of the American Society of Echocardiography.

Quantitation of LV Hypertrophy

Quantitative assessment of LV regional wall thickness was made from parasternal short-axis images. A total of 15 segments were analyzed, from five walls at three levels (basal, mid, and apical): the anterior interventricular septum (basal, mid, and apical), the posterior interventricular septum (basal and mid), the anterior wall (basal, mid, and apical), the lateral wall (basal, mid, and apical), the posterior wall (basal, mid, and apical), and the true apex (defined as the thickness of the apex at the junction of the apical septal and apical lateral wall segments). Maximum and average wall thickness was assessed.

Strain, Strain Rate, and Rotation Evaluation

Resting circumferential strain, strain rate, radial and rotation velocities, and angles were measured at three parasternal short-axis planes (basal, mid, and apical) in the septal and lateral walls. Longitudinal septal and lateral wall strain and strain rates were measured from the apical four-chamber view, at the basal, mid, and apical levels. Measurements were performed using Velocity Vector Imaging (VVI) version 1.0 (Siemens Medical Systems, Mountain View, CA) from archived 2D echocardiographic studies as previously described. The VVI version used did not provide positive radial strain (thickening) analysis.

Postprocessing Calculations

Circumferential regional LV mechanics were analyzed at the three (basal, mid, and apical) short-axis views for the septal, anterior, lateral, and inferior walls. In the apical four-chamber view, regional LV longitudinal mechanics were analyzed for six segments (basal, mid, and apical for the septal and lateral walls). Averaged myocardial rotation angles were used to calculate LV twist. To standardize the temporal evaluation of twist regardless of heart rate, all times were normalized and presented as percentages of the cycle length. Twist was defined as the maximal instantaneous basal-to-apical angle difference.

Reproducibility

Five normal subjects and five patients with HCM from the study cohort were randomly selected, and their echocardiographic studies were analyzed by another investigator and by the same investigator 1 month later. The linear correlation and standard deviation of percentage difference between intraobserver and interobserver measurements were calculated for the LV mechanic variables.

Statistical Analysis

Summary statistics are expressed as mean ± SD. One-way analysis of variance was used with least square difference post hoc multiple comparisons to compare LV regional mechanics among the normal, apical HCM, and septal HCM groups and among differing degrees of LV hypertrophy. Categorical data were compared using χ² or Fisher’s exact tests as appropriate. The correlations between strain parameters and wall thickness were determined by Pearson’s correlation coefficients. A two-tailed P value < .05 was considered statistically significant. SPSS version 11.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis.

RESULTS

Distribution of LV Hypertrophy

LV wall thickness at 15 measurement sites were taken from patients with septal and apical HCM and are summarized in Figure 1. The pattern of increased thickness differed significantly between the two HCM groups, as expected. In patients with septal HCM, all septal segments were abnormal, with the posterior and lateral walls relatively spared at the basal and mid levels and the septum primarily involved at the basal and mid levels. In patients with apical HCM, average values for all apical wall segments were all increased.
Clinical Characteristics
The mean ages were similar in the three groups studied (47.9 ± 12.4, 54.2 ± 16.4, and 49.5 ± 17.4 years for 25 normal controls, 27 patients with apical HCM, and 45 patients with septal HCM, respectively). Table 1 compares the clinical characteristics of patients with apical HCM and those with septal HCM at the time of index echocardiography and during follow-up. Patients with septal HCM had higher New York Heart Association functional classes and were more symptomatic, primarily with a higher incidence of dyspnea and presyncope. Patients with septal HCM also differed from those with apical HCM in terms of a significantly higher prevalence of LVOT obstruction, significant mitral regurgitation, and procedures to alleviate LVOT obstruction. Arrhythmic complications and related device implantation procedures did not significantly differ between the groups, but there was a trend toward higher rates in the patients with septal HCM.

Conventional 2D and Doppler Echocardiography
LV systolic dimensions were normal in patients with apical HCM and smaller than normal in those with septal HCM (Table 2). Diastolic parameters differed among the analyzed groups. Patients with apical HCM had lower early diastolic mitral inflow and annular velocities, longer isovolumic relaxation times, and increased left atrial volumes indexed to body surface area compared with normal controls. Patients with septal HCM had normal mitral early diastolic flow velocities, low mitral annular velocities, and prolonged isovolumic relaxation times compared with normal controls. Mitral early diastolic deceleration times were longer, and indexed left atrial volumes and calculated E/E' ratios were higher, compared with normal controls and patients with apical HCM. Thus, diastolic dysfunction was evident in both patterns of HCM.

Regional Myocardial Mechanics
Longitudinal Strain. Long-axis shortening (longitudinal strain; Figure 2A) was uniform in the three levels examined in the normal control group (~21 ± 4%). In the two groups of patients with HCM, longitudinal strain varied with the pattern of regional hypertrophy. Compared with normal controls, patients with apical HCM had decreased longitudinal strain in the hypertrophied mid and apical segments, while nonthickened basal segments demonstrated normal longitudinal strain. In patients with septal HCM, longitudinal strain was lower than in normal controls in all segments except the apical lateral segment. In these patients, the extent of the decrease in longitudinal strain followed the extent of segmental hypertrophy (Figures 2 and 3). Thus, regional changes reflected the pattern of hypertrophy in both patient groups, with reductions of longitudinal strain of the mid segments common to both groups.

Longitudinal Strain Rate. Because the rate of long-axis shortening (strain rate S) paralleled the changes in strain, it did not introduce new information and is not discussed. Long-axis early diastolic stretching rate (longitudinal strain rate E) was reduced in patients with apical HCM at the mid and apical lateral segments compared with normal controls, whereas in patients with septal HCM, it was reduced at the basal and mid levels. Interestingly, there were no differences between apical HCM and septal HCM in strain rate E. The late diastolic longitudinal strain rate (strain rate A) was highly variable and did not differ between normal controls and the two HCM groups.

Circumferential Strain. Apical-to-basal circumferential strain gradients were present in normal controls and in both HCM groups. Circumferential strain showed similar regional variability in HCM as longitudinal strain, but in the opposite direction. Instead of being lower in thickened segments (less negative), it was found to be higher (more negative). Compared with normal controls, patients with septal...
HCM had increased circumferential strain at the basal and mid septal segments and the mid anterior segment. Compared with patients with apical HCM, those with septal HCM had increased circumferential strain at the basal and mid septum and mid anterior segment (Figure 2).

**Circumferential Strain Rate.** Systolic circumferential strain rate demonstrated changes similar to circumferential strain. Circumferential diastolic strain rate E and A did not differ among the three groups (P > .05).

**Correlations Between LV Regional Thickness and Mechanics.** There were 393 pairs of wall thickness and longitudinal strain and early diastolic strain rate (L-SR-E), 25 pairs from the normal group (basal septal segments) and 368 pairs from two HCM groups (septal and lateral walls at three levels), available for correlation assessment (Figure 4). Longitudinal strain and diastolic strain rate varied according to the degree of hypertrophy: in segments with wall thicknesses ≤ 15 mm, the average strain was −18.2 ± 5.5%; and L-SR-E was 0.94 ± 0.43 s⁻¹; in segments with thicknesses of 16 to 20 mm, strain was −15.5 ± 5.1%; and L-SR-E was 0.76 ± 0.40 s⁻¹; and in segments with thicknesses > 20 mm, strain was −13.8 ± 5.3% and L-SR-E was 0.72 ± 0.32 s⁻¹. There were significant differences in strain among the three groups when classified by degree of wall thickness (P < .00001), representing a stepwise decrease in longitudinal strain with increased LV wall thickness. There was also a difference in L-SR-E between wall thickness ≤ 15 mm and the other two groups (P = .0002). However, no difference was found between thickness of 16 to 20 mm and thickness > 20 mm. Regional thickness was found to correlate with the longitudinal strain and strain rate E (r = 0.50 and r = 0.57, respectively, P < .0001; Figures 4A and 4B).

**Rotation.** Rotation in the normal subjects was clockwise (as imaged from the apex) at the basal level and anticlockwise at the mid and apical levels. The rotation velocities and directions of patients with HCM were similar to those of normal subjects at the basal and apical levels, yielding normal LV maximal twist (maximal instantaneous basal-to-apical angle difference). However, regardless of the pattern of hypertrophy in patients with HCM, rotational velocities at the mid segment followed the basal direction (clockwise), opposite to the normal anticlockwise direction of the normal group (Figure 5). Twist and twist time (time to peak basal-to-apical angle difference, standardized to cycle length) was similar in the three groups (45 ± 14% of cycle length). The rotational velocity of the mid segment in patients with apical HCM still followed that of the basal direction, but the absolute value was significantly decreased compared with that at the base (Figure 5).

**DISCUSSION.** Few studies have addressed regional myocardial mechanics in patients with septal and apical HCM. Most either included only patients...
Patterns of LV Hypertrophy
The two HCM groups in our study differed in their degrees of myocardial hypertrophy in 11 of 15 LV segments, as expected by their classification into the two different subtypes of HCM. As previously reported, patients with septal HCM were more symptomatic (New York Heart Association status, chest pain, presyncope) than patients with apical HCM, probably representing the consequences of LVOT obstruction. They also had more procedures, most of which were to alleviate LVOT obstruction.

Systolic LV Circumferential and Longitudinal Deformation in HCM
As we have previously reported, in patients with septal HCM, changes in myocardial mechanics showed disparity in longitudinal and circumferential strain. Although longitudinal strain decreased, it increased circumferentially. This finding is emphasized by software programs such as VVI, which predominantly describe endocardial strain. The same disparity was demonstrated in both HCM subtypes and in all segments analyzed. Segments without marked hypertrophy still demonstrated some abnormality, implying a global

Figure 2 Segmental longitudinal and circumferential strain distribution. (A) Longitudinal strain, demonstrating decreased strain in both HCM patterns compared with normal controls. (B) Circumferential strain demonstrating increased strain that is more specific for apical versus septal HCM. $^*P < .05$ versus normal controls; $^{†}P < .05$, apical HCM versus septal HCM.

with septal HCM or grouped various patterns of HCM together. The new technique of VVI allows determination of local and global mechanics, including shortening and stretching (strain), rate of shortening (strain rate), short-axis rotation and twist, and timing of events. Our study defined differences in regional mechanics in two different patterns of HCM (septal and apical) and demonstrated that they were related to regional wall thickness.
myocardial mechanical change, expected from mutations affecting all myocytes, even in the region with relatively normal thickness. 28–30 This disparity in strain probably maintains near-normal LV systolic function by more circumferential orientation of strain.9 Whether this is a true compensatory mechanism or fundamental to fiber reorientation or disarray or the result of subendocardial fibrosis in HCM is unknown.

Relationship Between LV Regional Mechanics and Hypertrophy in HCM

Although the change in strain was global, its extent followed the HCM hypertrophy pattern and severity of regional hypertrophy. Correlating wall thickness and strain yielded only modest correlation coefficients when both were treated as continuous variables. Correlations for specific segments were more significant, and treating wall thickness as a noncontinuous variable yielded a highly significant inverse relationship between the degree of thickness and longitudinal strain. Although wall thickness may be the most important factor in abnormal mechanics, the degree of fiber disarray and regional fibrosis may also play an important role, thus confounding the direct relationship between the degree of thickness and longitudinal strain. The site of adjacent hypertrophy may also play a role, as there was less thickening of the mid segments in apical HCM, yet they still demonstrated decreased longitudinal strain. Longitudinal early diastolic strain rate decreased in HCM following the same regional wall thickness pattern, but no differences were noted between moderately and severely thickened wall dimensions. The overall correlation of wall thickness with early diastolic strain rate was weaker than with strain. This is reasonable, as shortening (strain) is largely a local phenomenon, whereas relaxation may be more sensitive to interregional influences, causing strain rate abnormalities even in normal thickness segments.

Diastolic Dysfunction in Both Types of HCM

Both types of HCM demonstrated LV diastolic dysfunction by conventional Doppler echocardiography (decreased lateral E’ velocity, increased isovolumic relaxation time and indexed left atrial volume); however, deceleration time was prolonged and the E/E’ ratio was higher in septal HCM, suggesting more pronounced diastolic dysfunction in septal HCM than in apical HCM. Diastolic mechanics confirmed this distinction. L-SR-E was decreased in both HCM types compared with controls, while early diastolic circumferential strain rate did not differ from normal. Moreover, more segments showed decreased L-SR-E in septal HCM compared with apical HCM. Thus, the presence of more abnormally relaxing segments had an additive effect that resulted in more abnormal diastolic parameters.

LV Basal, Mid, and Apical Rotational Orientations in the Three Groups

Normal LV cross-sectional rotation was found to be clockwise at the base and counterclockwise at the apex (viewed from the apex) when
measured by magnetic resonance imaging (MRI) tagging. The mid section was clearly shown to rotate counterclockwise as the apex but peaked at a lower degree (+13.2 ± 4.0° vs +3.4 ± 1.0°, respectively). We have previously shown that in septal HCM, while the base and apex rotated in their normal respective directions, the mid cross-section rotated clockwise, as the base. This phenomenon nullified twist (cross-sectional rotation angle difference) for most of the left ventricle, displacing the equator (zero-rotation zone) apically (Figure 3). These changes may affect both systolic ejection and diastolic suction in septal HCM. Interestingly enough, this pattern of rotation was found to be similar in apical HCM as well, although mid rotation was lower. This finding is surprising, as the base was apparently less affected (thickening, normal strain) in these patients, and an “apical” counterclockwise rotation could have been expected at the mid level. The reasons for this change in rotation direction are not clear but could be related to LV hypertrophy, fibrosis, disarray, and change in fiber directions. Although in apical HCM, mid peak rotation direction was similar to septal HCM, its extent was lower, implying that rotation was mostly directed by global changes and to a lesser extent by regional hypertrophy.

Comparison With Previous Studies

Previous studies addressing LV mechanics using MRI tagging have shown inconsistent results, both in normal controls and in patients with HCM (Table 4). Most studies used 1.5-T machines, with only five to eight systolic frames. This may present a significant shortcoming of the method in identification of peak systolic strains. It has been shown that only end-systolic strain differed significantly in HCM compared with normal controls. This probably means that strain development patterns differ between groups, which makes low frame rate on obstacle to identification of peak strains, especially in MRI of patients with HCM. Moreover, these studies mostly analyzed small numbers of symptomatic patients, who probably represent only a subgroup of the HCM population. Even in the analysis of normal strain, MRI studies were inconsistent regarding the presence of an apical-to-basal strain gradient for either longitudinal or circumferential strain.

Circumferential strain changes were less consistent and were found to be normal, mildly reduced, or increased. This could reflect the extent of patients with worse functional classes with lower apical circumferential strain in the study cohort. Moreover, VVI probably measures subendocardial strain, whereas strain measured by other modalities is averaged for the full thickness of the myocardium and affected by the presence of an endocardial-epicardial strain gradient. It would appear that subendocardial strain is more affected in HCM, and thus software that allows for the selective assessment of endocardial strain may be more sensitive in detecting abnormalities. In patients with apical HCM and apical infarcts or aneurysms, low apical circumferential strain can be demonstrated, with areas of systolic stretching rather than contraction (Figure 5).
Our finding that in apical HCM, circumferential strain was not enhanced as in septal HCM may imply that these segments were actually dysfunctional. We did not find areas of paradoxical systolic lengthening, as has been described, and this may reflect the nature of our study population.

Our peak rotation measurements were generally lower than in most previously published studies. We believe that this difference may have been due to a stronger smoothing algorithm used in the VVI version we used. In any case, it should similarly affect both the control and the study groups.

**Study Limitations**

This study was undertaken in a tertiary referral center, and therefore, some selection bias may have been introduced, so our patients may not represent the general HCM population. Strain analysis was done retrospectively. Although conventional echocardiographic parameters were measured at the time of acquisition, 2D HCM pattern was generally recognizable at the time of strain analysis.

Circumferential mechanics measurements may differ according to technique.37–40 We used VVI measurements of mechanics whose circumferential measurements of strain and strain rate likely reflect mainly endocardial function, whereas other techniques average measurements over the full thickness of the myocardium. Endocardial function, however, may be more appropriate for the assessment of pathologies that are more subendocardial. The finding of low interobserver variability does not by itself guarantee accuracy.

**CONCLUSIONS**

Our results show that apical HCM and septal HCM have common mechanical abnormalities. Longitudinal strain is lower, circumferential strain is higher, and twist is apically displaced. The extent of these abnormalities and their regional expressions vary according to the degree of hypertrophy in a segment as well as its pattern. However, some abnormalities are present, even in segments with relatively normal wall thickness, likely because of underlying disarray or fibrosis in segments without marked thickening. These findings validate the concept that abnormalities in function are related to the site and degree of hypertrophy.

**REFERENCES**


