Heterogeneity of Intramural Function in Hypertrophic Cardiomyopathy
Mechanistic Insights From MRI Late Gadolinium Enhancement and High-Resolution Displacement Encoding With Stimulated Echoes Strain Maps

Anthony H. Aletras, PhD; Gauri S. Tilak, MD, PhD, MPH; Li-Yueh Hsu, DSc; Andrew E. Arai, MD

Background—In hypertrophic cardiomyopathy (HCM), myocardial abnormalities are commonly heterogeneous. Two patterns of late gadolinium enhancement (LGE) have been reported: a bright “confluent” and an intermediate intensity abnormality termed “diffuse,” each representing different degrees of myocardial scarring. We used MRI to study the relation between intramural cardiac function and the extent of fibrosis in HCM. The aim of this study was to determine whether excess collagen or myocardial scarring, as determined by LGE MRI, are the primary mechanisms leading to heterogeneous regional contractile function in patients with HCM.

Methods and Results—Intramural left ventricular strain, transmural left ventricular function, and regions of myocardial fibrosis/scarring were imaged in 22 patients with HCM, using displacement encoding with stimulated echoes (DENSE), cine MRI, and LGE. DENSE systolic strain maps were qualitatively and quantitatively compared with LGE images. Intramural systolic strain by DENSE was significantly depressed within areas of confluent and diffuse LGE but also in the core of the most hypertrophic nonenhanced segment (all \( P < 0.001 \) versus nonhypertrophied segments). DENSE demonstrated an unexpected inner rim of largely preserved contractile function and a noncontracting outer wall within hypertrophic segments in 91% of patients.

Conclusions—LGE predicted some but not all of the heterogeneity of intramural contractile abnormalities. This indicates that myocardial scarring or excess interstitial collagen deposition does not fully explain the observed contractile heterogeneity in HCM. Thus, myofibril disarray or other nonfibrotic processes affect systolic function in a large number of patients with HCM. (Circ Cardiovasc Imaging. 2011;4:425-434.)

Key Words: hypertrophic cardiomyopathy ■ MRI ■ DENSE ■ displacement encoding with stimulated echoes ■ myocardial function ■ strain ■ late gadolinium enhancement

Hypertrophic cardiomyopathy (HCM) is a genetic disease characterized by left ventricular (LV) hypertrophy, caused by hyperplasia and hypertrophy of myocytes and hyperplasia of several other cell types. Myofiber disarray and interstitial fibrosis occur commonly. Hypertrophy and fibrosis are associated with LV systolic and diastolic dysfunction, heart failure, arrhythmias, morbidity, and mortality. Myocardial ischemia, infarction, and fibrosis occur in HCM despite widely patent epicardial coronary artery vessels. MRI late gadolinium enhancement (LGE) has revealed 2 types of abnormalities that may be related to infarction or fibrosis. Confluent LGE appears in most respects comparable to the type of bright gadolinium enhancement seen in the myocardial infarctions of patients with ischemic heart disease. Diffuse LGE probably represents less severe myocardial fibrosis or milder degrees of excess collagen deposition. It has also been postulated that the interstitial fibrosis may be a secondary and reversible phenotype.

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Extrapolations from transmural measurements of myocardial strain have led some investigators to postulate that patients with HCM may have preserved endocardial strain, whereas others suggest that there should be reduced endocardial strain. A study by Tseng et al shows that myocardial fiber disarray is related to reduced myocardial strain. However, this study does not address the presence or absence of myocardial fibrosis within the hypokinetic regions. A more recent echocardiographic study by Popovic et al reports that nonfibrotic myocar-
dial segments exhibit increased strain compared with segments with fibrosis. This finding suggests that perhaps some function is preserved in nonfibrotic hypertrophic segments. However, this could also reflect partial volume effects since average midwall strain measurements were studied in a 12-segment model.

High-resolution imaging of intramural strain might provide insight into the relative contribution of myocardial fiber disarray and myocardial fibrosis as distinct mechanisms causing regional LV dysfunction. DENSE18,19 (displacement encoding with stimulated echoes) MRI can quantify short-axis regional systolic function at high spatial resolution. DENSE allows direct measurement of intramural myocardial strain expressed in terms of circumferential shortening (CS) and radial thickening (RT)—a significant advance over transmural measures of regional function such as absolute systolic change in wall thickness (in mm) or percent wall thickening.

The present study aimed to determine whether excess collagen or myocardial scarring, as determined by gadolinium-enhanced MRI, are the primary mechanisms leading to heterogeneous regional contractile function in patients with HCM. We hypothesized that if intramural contractile function in HCM is heterogeneous due to excess collagen deposition or myocardial scarring, then hypokinesis will be localized primarily in areas with LGE. However, if extensive hypokinesis is observed outside the areas of LGE, then excess collagen or myocardial scarring is unlikely to be the only mechanism leading to heterogeneous regional contractile function in patients with HCM. Finally, it is possible that severely hypertrophic myocardium has diffusely abnormal function regardless of regional fibrosis. This possibility is sometimes referred to as “muscle bound.” We also hypothesized that high resolution intramyocardial DENSE strain maps would be able to image these functional abnormalities. Such imaging should be able to resolve these three possibilities.

An unexpected finding of this work was the presence of largely preserved inner wall strain in hypertrophic segments with overall low transmural strain. Although an endocardial ring of preserved contractility in HCM has been postulated to exist,17 no direct visualization has been provided to date. Therefore, additional analysis of this pattern of intramural strain was performed since it was not predicted by geometric models of myocardial hypertrophy.

Methods

Study Population
Twenty-two patients with HCM were studied under research protocol 09-H-N237 approved by the National Heart, Lung, and Blood Institute’s review board. The diagnosis of HCM was established by echocardiography (>15 mm LV wall thickness in the absence of another cause for the increased cardiac mass). Patients with a history of alcohol, septal ablation, or cardiac surgery were excluded. Only patients who underwent both DENSE and LGE imaging were included.LV outflow tract gradients at rest were obtained by cardiac catheterization.

MRI Studies
Subjects were scanned in a 1.5-T MRI scanner, using a cardiac phased array coil. LV systolic function and mass were imaged with cine MRI along contiguous short-axis slices (typically with 1.4×1.4 mm/pixel and 8-mm slice thickness). Intramural CS and RT measurements were made with DENSE with a volumetric preparation. Displacement was mapped for every pixel of the end-systolic image, allowing computation of systolic strain (CS and RT) maps. End-systole was determined from the cine MRI. LGE imaging was performed with an inversion recovery method20 after a dose of 0.2 mmol/kg gadopentetate dimeglumine (typical resolution of 1.4×1.4 mm/pixel, slice thickness of 8 mm), with the inversion time optimized to null normal myocardium.

Data Analysis
LV ejection fraction and total myocardial mass were measured by means of computer-assisted planimetry. The signal intensity was quantified in confluent and diffuse lesions,21 from normal myocardium, and the LV blood pool. In short, confluent lesions were defined as qualitatively having bright signal similar to that found in nonviable myocardium in patients with coronary artery disease. Diffuse lesions were defined as qualitatively having signal brighter than that of nulled myocardium and signal less bright than that of confluent lesions. The “most hypertrophic nonenhancing segment” was defined as the thickest segment (as seen on end-diastolic cine images) without LGE. To mitigate potential through-plane motion misregistration issues between DENSE and LGE, the adjacent slices to the one containing the “most hypertrophic nonenhancing segment” were examined for absence of LGE. Remote myocardium was defined as myocardium diametrically opposite to the hypertrophic segments. After endocardial and epicardial segmentation, DENSE displacement maps were automatically processed to produce CS and radial thickening RT strain maps.22 CS and RT maps were scaled by use of a standardized color scale that displayed quantitative regional function on a pixel-by-pixel basis. Region-of-interest analysis was performed to measure CS and RT within confluent, diffuse, and most hypertrophic nonenhanced areas. Only 1 slice per patient was analyzed to preserve the independence of the samples. Apical slices were excluded from data analysis to avoid partial volume effects.23

Statistical Analysis
Continuous measurements are expressed as mean±SD for descriptive purposes. Standard error of the mean is used in figures where the primary purpose was to depict differences between 2 average values. Comparisons used a paired t test with Bonferroni correction for multiple comparisons (probability values are presented unadjusted and the appropriate level of significance is used within each group of comparisons).

Results

Demographics
Six patients (Table 1) had severe symptoms related to LV outflow obstruction, whereas others had mild or no symptoms. Four were asymptomatic, 7 presented with shortness of breath, 3 with chest pain, and 8 with a combination of shortness of breath and chest pain. The average pulmonary capillary wedge pressure was 12±5 mm Hg, but 6 patients had significantly elevated pulmonary capillary wedge pressure. The maximum wall thickness averaged 25±5 mm. The median value of LV mass was 185 g (range, 76 to 567) and the ejection fraction averaged 66±6%. The median value of LGE was 5.8% of the LV (range, 1.8 to 41.5). Nineteen of the patients had asymmetrical septal hypertrophy, 2 with severe concentric hypertrophy and 1 with hypertrophy localized to the midventricle. Of the 22 individuals evaluated, only 4 had identified mutations after an unbiased screening of the
**Table 1. Demographics and Clinical and Hemodynamic Findings**

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LVOT indicates LV outflow tract; NYHA, New York Heart Association classification; CP, chest pain; SOB, shortness of breath; SAM, systolic anterior motion of the mitral valve; RVOT, right ventricular outflow tract; EP, electrophysiology; NA, not available; AF, atrial fibrillation; LBBB, left bundle-branch block; AVB, atrioventricular block; PAT, paroxysmal atrial tachycardia; VT, ventricular tachycardia; NSVT, nonsustained VT; and TIA, transient ischemic attack.

β-myosin head (exons 1 to 23) (Table 1). Patients 1 and 20 are related and have the R403Q mutation. Patient 5 has the K847E mutation. Patient 15 has a Val95Ala mutation in α-tropomyosin. On the basis of the unbiased screening, it can be concluded that the other patients are very unlikely to have mutations in the β-myosin head.

**DENSE Detects Patterns of Intramural Contractile Function Associated With LGE**

DENSE strain maps and LGE images can directly show that LGE is not a prerequisite for the presence of intramural functional abnormalities. DENSE functional abnormalities that are either more extensive than LGE imaging predicts or that are present in the absence of LGE can directly disprove the primary hypotheses. Figures 1 through 4 summarize the relationship between LGE and intramural cardiac function as depicted by DENSE CS and RT color strain maps. The color scale represents intramural percent circumferential shortening and percent radial thickening respectively. Normal CS and RT are generally mapped white to bright orange. Dark orange and purple hues represent mild and severe strain abnormalities. The transition from blue to green represents zero systolic strain. Green to black represents dyskinetic strain (ie, systolic circumferential stretching or systolic radial thinning). Figures 1 through 4 also show diastolic and systolic frames from cine MRI (first and second images on the top row, respectively) as well as LGE (third image on the top row).

An example that supports the concept that myocardium with confluent LGE does not contract normally in HCM is shown in Figure 1. This patient has a confluent abnormality of LGE in the inferior septum that corresponds to a severe focal abnormality in systolic strain, as represented by the blue and purple patches corresponding to 10% CS and RT. Note that the signal intensity on the LGE is similar to what is typically observed in patients with myocardial infarction caused by coronary artery disease (ie, the myocardial enhanced zone and the LV blood pool present with similar signal intensity) except that the abnormality is not located in the subendocardium.

Diffusely enhancing myocardium also does not contract in HCM (Figure 2). In this example, a diffuse pattern of LGE, which corresponds to a severe intramural strain abnormality on color-coded DENSE, can be seen in the anterior wall and interseptal segments. The myocardial signal intensity in the LGE zone is much lower than in cases with confluent LGE. The DENSE CS and RT maps show normal strain (orange to white) in the septum, inferior, and lateral walls as well as in the inner one-third of the anterior and interseptal segments. Thus, there is a substantial amount of myocardium in all segments with normal strain...
and a zone of very low strain in the outer half of the segment with diffuse gadolinium enhancement. Cine MRI showed normal systolic endocardial excursion and ejection fraction in this patient but could not assess intramural function.

Intramural functional abnormalities can be more extensive than predicted by the extent of LGE. Figure 3 shows a patient with more severe septal hypertrophy but a similarly sized abnormality of confluent LGE to the one seen in Figure 1. Despite severely depressed strain in the two-thirds of the septum near the right ventricle, DENSE maps of intramural strain again showed a nearly circumferential inner ring of largely normal contraction. The amount of myocardium with normal strain (orange-white) is comparable in all segments around this short-axis slice despite large functional abnormalities in the remainder of the septum. Systolic strain in this patient is more heterogeneous than LGE would predict. Cine MRI shows global systolic function (corresponding to an ejection fraction of 64%) that almost obliterates the mid LV cavity.

Intramural functional abnormalities in HCM also exist in the absence of significant LGE. Figure 4 shows an example in which the DENSE maps of intramural strain show 2 large distinct contractile abnormalities (purple to blue/black patches) separated by a zone of nearly normally contracting myocardium in the midseptum. In this patient, there is only a small region of confluent LGE within the inferoseptum. Cine MRI showed hyperdynamic global systolic function in this patient.

**Figure 1.** Patient with confluent LGE in the inferior septum that colocalizes with a severe focal abnormality in radial DENSE (see Results section for details).

**Figure 2.** The diffuse pattern of LGE seen in the anterior septum matches the contractile abnormality seen with DENSE (see Results section for details).
The examples shown in Figures 2 through 4 indicate that reduced contractile function is not necessarily associated with LGE. In most of the patients (17 of 22), the LGE was not localized to the inner third of the heart, consistent with viable myocardium in the regions where strain appeared normal in most of these patients (Table 1).

Heterogeneous Intramural Function Irrespective of Pattern or Presence of Enhancement

Intramural function by DENSE was not only depressed within areas of both confluent and diffuse LGE but also at the core of the most hypertrophic nonenhanced segment (Figure 5). Specifically, CS was significantly reduced within the confluent LGE regions compared with a normal remote nonenhanced nonhypertrophic region (6.1±1.6% versus 20.4±1.8% CS, respectively, P<0.001). Diffuse LGE regions exhibited disproportionally reduced intramural CS compared with a normal remote nonenhanced nonhypertrophic region (7.5±0.9% versus 18.4±2.1% CS, respectively, P<0.001). Interestingly, the most hypertrophic nonenhanced segment also had significantly reduced intramural strain when compared with a normal remote nonenhanced nonhypertrophic region (9.3±1.5% versus 19.1±2.2% CS, respectively, P<0.001). Radial thickening DENSE data showed similar results (confluent enhancement, 7.6±1.3% versus normal, 29.5±1.3%;...
On LGE images, the signal intensity was significantly different for confluent and diffusely enhancing versus normal myocardium (Figure 6, both \( P < 0.001 \)). The signal intensity in the most hypertrophic nonenhancing myocardium was not significantly different from normal myocardium, an important control measurement that indicates the qualitative characterization of amount of gadolinium in these regions was not simply due to the way the images were displayed.

**Preserved Absolute Wall Thickening and Inner Wall Contractile Function**

DENSE intramural contractile function demonstrated a complete circumferential inner rim of largely normal contracting myocardium in 77% of the patients (17 of 22). This group of patients had an average normal ejection fraction (66.8%±4.3). Predominantly transmural hypokinesis in the hypertrophic zone was observed in 2 of 22 patients. These 2 patients had reduced ejection fraction (<55%). The remaining 3 of 22 patients presented with a mixture of both patterns of intramural contractile function within the hypertrophic zones (ejection fraction, 67.7±5.8%). Thus, 91% of patients had a complete or significant amount of myocardium with normal strain in the inner layers of the LV.

Absolute systolic wall thickening by CINE MRI was overall preserved in these patients with HCM (Figure 7A). In particular, absolute systolic wall thickening averaged >6 mm, even with an end-diastolic wall thickness of 20 mm. Even the most hypertrophic segments (end-diastolic thickness >25 mm) exhibited normal absolute systolic wall thickening defined as >3 mm. On average,
5 mm of absolute systolic wall thickening was observed by CINE MRI for both hypertrophic and nonhypertrophic segments, independent of the extent of LGE. These findings of overall preserved absolute systolic wall thickening are concordant with the observed preserved ejection fractions (Table 2). Conversely, a normal ejection fraction or significant regional wall thickening did not preclude large patches of severely depressed intramural systolic function.

On average, percent systolic wall thickening (Figure 7B) was inversely related to end-diastolic wall thickness, suggesting that transmural contractile function in the most hypertrophic myocardial segments is very low.

In nonhypertrophic segments (Figure 8, end-diastolic wall thickness <12 mm), percent wall thickening was inversely related to increasing extent of segment LGE. In hypertrophic segments (Figure 8, end-diastolic wall thickness >12 mm), percent wall thickening was low, irrespective of extent of LGE.

## Discussion

The DENSE systolic strain maps show heterogeneous myocardial function in HCM, which requires a heterogeneous mechanism rather than a diffuse or global process. LGE predicts some but not all of the heterogeneity of intramural contractile abnormalities. Because LGE is a highly sensitive method, myocardial scar and excess collagen deposition cannot explain the spectrum of heterogeneous intramural function encountered in HCM. Myofiber disarray is one mechanism that could impair function without showing abnormalities on late-enhancement images.4 The frequently observed pattern of an inner ring of normal intramural strain provides a mechanism that can explain preserved global LV function despite severe strain abnormalities in the remainder of that segment. That observation could not be predicted by “uniform models” or assumptions about cardiac contraction. There are several factors that lead to heterogeneity of intramural function in patients with HCM, and most of these mechanisms cannot be visualized with transmural or low-resolution methods. Thus, the ability to spatially register high-resolution strain maps with LGE images allows interrogation of the relationships between function and myocardial scar/collagen at an unprecedented level.

Histopathologic studies have identified more than one kind of intramural heterogeneity in HCM that could relate to contractile abnormalities. Sarcomeric disarray is highly heterogeneous26,27 and not even confined within hypertrophic segments.26 Sarcomeric hypertrophy occurs in the endocardium and the midwall.28,29 Diffuse interstitial fibrosis and myocardial scarring are common in HCM.28,30,31 Moreover, a high fraction of young patients with HCM but no coronary artery disease have patchy signs of postmortem acute-subacute ischemia.31

At a clinical level, HCM is characterized by many types of heterogeneous abnormalities. Resting myocardial blood flow is heterogeneous despite metabolic demands similar to that of normal myocardium22 and is related to LGE.10 Multifocal patterns of LGE have also been identified in asymptomatic patients and mildly symptomatic patients with HCM.23 These patterns, which may represent infarction, fibrosis, or excess collagen deposition,33,34 were later correlated with progressive dilation of the ventricle and risk of sudden death.21

### Table 2. Cardiac MR Findings

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Max WTh indicates maximum wall thickening; LVEF, LV ejection fraction; Endo, endocardial; and Trans, transmural.

>5 mm of absolute systolic wall thickening was observed by CINE MRI for both hypertrophic and nonhypertrophic segments, independent of the extent of LGE. These findings of overall preserved absolute systolic wall thickening are concordant with the observed preserved ejection fractions (Table 2). Conversely, a normal ejection fraction or significant regional wall thickening did not preclude large patches of severely depressed intramural systolic function.

Gadolinium delayed enhancement does not fully explain the observed functional abnormalities. For segments with end-diastolic wall thickness (EDWTh) <12 mm, percent wall thickening was inversely proportional to the extent of delayed enhancement. However, for segments with EDWTh ≥12 mm, transmural percent wall thickening was depressed irrespective of the extent of gadolinium delayed enhancement.
Characterization of intramural LV strain, based on simple geometric models, does not apply in HCM because the assumption of a homogeneously contracting medium is not valid. On the basis of such models, there is a largely linear endocardial to epicardial gradient of circumferential strain and HCM. Pioneering myocardial tagging studies may have masked the intramural strain heterogeneity as the result of the coarse spatial resolution (tag spacing of 7 mm). Other MRI tagging studies in patients with HCM have previously reported abnormal contractile function in the LV. Both radial displacement and circumferential shortening are reduced in the septum. Similar results were also obtained for total systolic strain recently with methods that allow full cardiac cycle interrogations, whereas diastolic strain was reduced in all segments.

LGE is not as closely linked to the full range of contractile abnormalities detected in HCM, whereas in coronary artery disease, regional function varies inversely with the transmural extent of gadolinium delayed enhancement. In patients with HCM, the extent of delayed enhancement is inversely related to systolic segmental percent wall thickening. Although the current study also found an inverse relationship between percent wall thickening and the extent of LGE, this only applied to the less severely hypertrophic segments (Figure 8). In the thickest regions of the heart, transmural systolic contraction was independent of the extent of LGE (Figure 8). Although not addressed by this data set, myocardial edema or inflammation may also explain the discrepancy between regional contractile function and LGE.

The DENSE MRI acquisition has many advantages in producing cardiac strain measurements. DENSE has been used to measure postinfarction recovery of function. Myocardial tagging, harmonic phase image processing, and DENSE have yield comparable strain measurements and have been recently shown to rely on the same physics for mapping motion. As implemented in this study, DENSE provided approximately 250 measurements of intramural contractile function per short-axis slice—an order of magnitude more measurements than conventional tagged MRI. Therefore, fitting the strain measurements to a predetermined model of the heart was not necessary—a significant advantage for the irregularly shaped heart in patients with HCM. Because a volumetric preparation is used to sensitize the image to motion, the method intrinsically avoids throughplane motion artifacts.

Regional wall motion assessment by cine MRI and echocardiography can be misleading, depending on whether one chooses to report percent wall thickening (ie, transmural strain) or absolute systolic change in wall thickness (in mm). Percent wall thickening is inversely proportional to end-diastolic wall thickness, yet the average amount of wall thickening in millimeters remains normal or hypercontractile in the same hearts. However, the greatest hazard of interpreting percent wall thickening data is the extrapolation to infer the mechanisms leading to abnormalities in regional contractile function in HCM.

High-resolution images of intramural systolic function can properly address this issue. The fact that LGE and intramural strain show abnormalities with different spatial distributions suggests that the information may be complementary. Larger studies must be performed to determine the prognostic significance of these findings.

Limitations
The current data do not address right ventricular involvement, specifically because it was not possible to delineate the right ventricle–LV border within the septum. Multislice analysis with appropriate statistical methods to correct for data dependence could have provided insight into intra-subject heterogeneity. However, single-slice analysis was favored both for simplicity sake and for preserving the statistical significance level, which degrades by testing multiple hypotheses (eg, through the use of the Bonferroni correction). LGE images were acquired during diastole, whereas DENSE images were acquired during systole. Despite all efforts to properly place the relevant regions of interest, some partial volume averaging may have influenced the results. Further histopathologic studies are needed to shed light on how abnormalities by DENSE may indicate diffuse interstitial fibrosis in visually negative LGE regions.

Conclusions
In conclusion, just as high-resolution LGE images allowed intramural assessments of myocardial infarction and fibrosis, high-resolution DENSE strain maps provide the most detailed view of intramural function obtained to date in patients with HCM. These results show that LGE as a measure of myocardial fibrosis does not fully explain the observed contractile heterogeneity in these patients. An inner rim of preserved strain in the endocardium and midwall, along with otherwise hypokinetic regions, is a contractile pattern unique to HCM that has not been previously visualized with other methods.

Sources of Funding
This work was supported by the Intramural Research Program of the National Heart, Lung and Blood Institute, Z01 HL004607-08 CE.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

MRI can define the anatomic extent of hypertrophy, global ventricular function, and regional wall thickening, with cine MRI providing high-quality information comparable to 2D and 3D echocardiography. Displacement encoding with stimulated echoes (DENSE) is an MRI-specific method for quantifying myocardial strain with physics intrinsically similar to myocardial tagging methods but at higher resolution. DENSE allows quantification of both in-plane directions of motion and, although not implemented in this study, also through plane motion, and minimizes artifacts caused by through-plane motion of tissue. Late gadolinium-enhanced MRI can detect myocardial fibrosis. These methods were used in the current study to examine the intramural relationship between fibrosis and regional contractile function in 22 patients with hypertrophic cardiomyopathy. Intramural systolic strain by DENSE was significantly depressed within areas of confluent and diffuse late gadolinium enhancement but also in the core of the most hypertrophic nonenhanced segment. DENSE demonstrated an unexpected inner rim of largely preserved contractile function and a noncontracting outer wall within hypertrophic segments in 91% of patients. These observations indicate that we should not consider hypertrophic myocardium as a uniform mass. Instead, the myocardium has a heterogeneous nature that is not surprising, considering the heterogeneous abnormalities seen in pathological studies. Late gadolinium enhancement imaging of fibrosis predicted some but not all of the heterogeneity of intramural contractile abnormalities. This indicates that myocardial scarring or excess interstitial collagen deposition does not fully explain the observed contractile heterogeneity in hypertrophic cardiomyopathy. Thus, myofibril disarray or other nonfibrotic processes affect systolic function in a large number of patients with hypertrophic cardiomyopathy.

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Circ Cardiovasc Imaging. 2011;4:425-434; originally published online May 16, 2011; doi: 10.1161/CIRCIMAGING.110.958751
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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