Spectrum and Clinical Significance of Systolic Function and Myocardial Fibrosis Assessed by Cardiovascular Magnetic Resonance in Hypertrophic Cardiomyopathy

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In hypertrophic cardiomyopathy (HCM), the clinical significance attributable to the broad range of left ventricular (LV) systolic function, assessed as the ejection fraction (EF), is incompletely resolved. We evaluated the EF using cardiovascular magnetic resonance (CMR) imaging in a large cohort of patients with HCM with respect to the clinical status and evidence of left ventricular remodeling with late gadolinium enhancement (LGE). CMR imaging was performed in 310 consecutive patients, aged 42 ± 17 years. The EF in patients with HCM was 71 ± 10% (range 28% to 89%), exceeding that of 606 healthy controls without cardiovascular disease (66 ± 5%, p <0.001). LGE reflecting LV remodeling showed an independent, inverse relation to the EF (B-0.69, 95% confidence interval −0.86 to −0.52; p <0.001) and was greatest in patients with an EF <50%, in whom it constituted a median value of 29% of the LV volume (interquartile range 16% to 40%). However, the substantial subgroup with low-normal EF values of 50% to 65% (n = 45; 15% of the whole cohort), who were mostly asymptomatic or mildly symptomatic (37 or 82% with New York Heart Association functional class I to II), showed substantial LGE (median 5% of LV volume, interquartile range 2% to 10%). This overlapped with the subgroup with systolic dysfunction and significantly exceeded that of patients with an EF of 66% to 75% and >75% (median 2% of the LV volume, interquartile range 1.5% to 4%; p <0.01). In conclusion, in a large cohort of patients with HCM, a subset of patients with low-normal EF values (50% to 65%) was identified by contrast-enhanced CMR imaging as having substantial degrees of LGE, suggesting a transition phase, potentially heralding advanced LV remodeling and systolic dysfunction, with implications for clinical surveillance and management. © 2010 Published by Elsevier Inc. (Am J Cardiol 2010;106:261–267)

Hypertrophic cardiomyopathy (HCM) is widely regarded as a disease predominantly associated with hyperdynamic left ventricular (LV) systolic function, although the disease of a few patients is known to evolve into overt systolic dysfunction and the so-called end-stage phase.[1–7] To date, the potential clinical significance attributable to the wide range in measured ejection fractions (EFs) is incompletely resolved, in part because of the inherent limitations of 2-dimensional echocardiography in the accurate quantification of the LV volume in this disease.[8,9] Cardiovascular magnetic resonance (CMR) imaging, with contrast enhancement, because of its high-resolution volumetric reconstruction of the LV chamber, affords a highly accurate and reproducible quantitative assessment of LV size and systolic function. It also provides in vivo contrast visualization of late gadolinium enhancement (LGE), generally considered indicative of myocardial fibrosis.[3,10–16] Therefore, in the present study, we evaluated LV systolic function by CMR imaging in a large cohort of patients with HCM, to characterize the early stages of disease progression preceding systolic dysfunction.

Methods

The study population included 310 patients with HCM consecutively referred for CMR imaging from 2001 to 2008 at centers in Minneapolis and Boston (Table 1). CMR imaging was routinely offered to all patients with HCM evaluated at our institutions during the study period for the purpose of defining the extent and distribution of LV hypertrophy, LV volumes, LV mass, and LGE. Those with specific contraindications, such as implanted cardioverter-defibrillators or pacemakers, metallic fragments, known claustrophobia, renal insufficiency, and pregnant or lactating women were excluded. The diagnosis of HCM was determined from CMR imaging and 2-dimensional echocar-

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Table 1
Clinical, demographic and echocardiographic findings stratified by left ventricular (LV) ejection fraction (EF) in 310 patients with hypertrophic cardiomyopathy (HCM)

Clinical/Demographic Data	Overall	Ejection Fraction				p Value
		<50%*	50–65%	66–75%	>75%	
Patients	310	15	45	144	106	
Men	218 (70%)	9 (60%)	33 (73%)	110 (76%)	66 (62%)	0.08
Age at study entry (years)	42 ± 17	43 ± 17	40 ± 17	41 ± 18	46 ± 17	0.12
Age at diagnosis (years)	37 ± 17	30 ± 17	35 ± 15	36 ± 18	41 ± 16	0.04
New York Heart Association functional class at study entry	1.3 ± 0.6	1.5 ± 05	1.4 ± 0.6	1.2 ± 0.5	1.4 ± 0.6	0.08
I	221 (71%)	4 (27%)	29 (64%)	117 (81%)	71 (67%)	
II	43 (14%)	8 (53%)	8 (18%)	8 (6%)	19 (18%)	
III	46 (15%)	3 (20%)	8 (18%)	19 (13%)	16 (15%)	
Angina pectoris	109 (35%)	3 (20%)	17 (38%)	51 (35%)	38 (36%)	0.64
Syncope	68 (22%)	4 (27%)	10 (22%)	30 (21%)	24 (23%)	0.95
Atrial fibrillation	39 (13%)	6 (40%)†	5 (11%)	19 (13%)	9 (8%)	0.019
Medical treatment	220 (71%)	13 (87%)	24 (53%)	92 (64%)	91 (86%)‡§	<0.01
β Blockers	179 (58%)	12 (80%)	19 (42%)	76 (53%)	72 (68%)‡	0.004
Verapamil	65 (21%)	2 (13%)	8 (18%)	26 (18%)	29 (27%)	0.24
Amiodarone	6 (2%)	2 (13%)¶	0	3 (2%)	1 (1%)	0.008
Disopyramide	7 (2%)	0	0	6 (4%)	1 (1%)	0.20
Diuretics	38 (12%)	5 (33%)§	3 (7%)	11 (8%)	19 (18%)	0.004
Angiotensin-converting enzyme inhibitors	39 (13%)	6 (40%)†	5 (11%)	14 (10%)	14 (13%)	0.01
Systemic hypertension	72 (23%)	3 (20%)	10 (22%)	30 (21%)	29 (27%)	0.66
Implantable cardioverter-defibrillator	59 (19%)	7 (47%)§¶	11 (24%)	23 (16%)	18 (17%)	0.03
Echocardiography						
Left atrium (mm)	42 ± 8	45 ± 10	44 ± 7	41 ± 8	42 ± 7	0.22
Maximum left ventricular wall thickness (mm)	21 ± 6	21 ± 7	21 ± 7	21 ± 6	21 ± 5	0.91
Left ventricular end-diastolic diameter (mm)	44 ± 7	48 ± 11¶	47 ± 6¶	44 ± 6	43 ± 7	0.002
Left ventricular outflow tract obstruction at rest (≥30 mm Hg)	61 (20%)	0	7 (16%)¶	24 (17%)	30 (28%)	0.03
Moderate-to-severe mitral regurgitation	26 (8%)	1 (7%)	3 (7%)	9 (6%)	13 (12%)	0.36

* EF range 28–48%.
† $p < 0.05$ versus all other groups; ‡ $p < 0.05$ versus 50–65%; §$p < 0.05$ versus 66–75%; ¶$p < 0.001$ versus >75%.

diographic evidence of a hypertrophied left ventricle (maximum wall thickness ≥15 mm) with a normal or small cavity size (defined by an end-diastolic volume index <75 ml/m^2),[17] in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident, at some point during the patient's clinical course.[1,2] None of our patients had significant coronary artery disease (defined as >50% stenosis in one major artery), as ascertained by specific clinical and/or CMR evidence. First, no patient had experienced an acute coronary event associated with increased cardiac enzymes or Q waves on the electrocardiogram. Second, when LGE was present in a subendocardial or transmural distribution within a single coronary artery vascular territory, hemodynamically significant coronary artery disease was excluded by arteriography or computed tomography angiography.[12] Patients with previous cardiac surgery or percutaneous alcohol septal ablation were excluded from the study. The respective internal review board or research ethics committees of each participating institution approved the study protocol, and all subjects provided written inform consent. Selected data from subsets in this patient cohort have been reported as a part of other analyses.[10,12]

A reference population of 606 healthy adult participants in the Framingham Heart Study Offspring Cohort (239 men and 367 women) without evidence of clinical cardiovascular disease underwent CMR imaging, using a scanning protocol similar to that reported in the present study for patients with HCM.[18] The mean age was 61 ± 8 years for both men and women. The body surface area was 2.0 ± 0.2 m^2 for men and 1.7 ± 0.2 m^2 for women.

Comprehensive 2-dimensional and Doppler echocardiographic studies were performed for each patient using commercially available instruments.[17] LV hypertrophy was assessed by 2-dimensional echocardiography, and the site and extent of the maximum wall thickness were identified.[19] The peak instantaneous LV outflow gradient, resulting from mitral valve systolic anterior motion and mitral–septal contact, was estimated with continuous wave Doppler under basal conditions.[20] The left atrial dimension was measured at end-systole in the anteroposterior linear diameter from the parasternal long-axis view.[19]

CMR imaging was performed (Philips Gyroscan ACS-NT 1.5 T, Best, The Netherlands; and Siemens Sonata 1.5 T, Erlangen, Germany) using steady-state, free precession breath-hold cines in 3 long-axis planes and contiguous 10-mm (no gap) or 8-mm (2-mm gap) short-axis slices from the atrioventricular ring to the apex.

All measurements on the CMR studies in the patients with HCM and controls were performed by a centralized core laboratory (PERFUSE Angiographic Core Laboratory and Data Coordinating Center, Harvard Medical School,

Table 2
Cardiovascular magnetic resonance (CMR) findings stratified by left ventricular (LV) ejection fraction (EF) in 310 patients with hypertrophic cardiomyopathy (HCM)

Variable	Overall	LV EF (%)				p Value
		<50%	50–65%	66–75%	>75%	
Patients	310	15	45	144	106	
Age at study entry (y)	42 ± 17	43 ± 17	40 ± 17	41 ± 18	46 ± 17	0.12
Body surface area (m^2)	1.9 ± 0.3	1.9 ± 0.3	2.0 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	0.74
Body mass index (kg/m^2)	29 ± 7	29 ± 4	31 ± 9	28 ± 6	30 ± 7	0.10
Left ventricular end-diastolic volume (ml)	161 ± 45	197 ± 61*†	167 ± 48	162 ± 46	153 ± 36	0.003
Left ventricular end-diastolic volume index (ml/m^2)	83 ± 18	104 ± 29‡	84 ± 19	83 ± 17	79 ± 16	<0.001
Left ventricular end-systolic volume (ml)	47 ± 24	114 ± 35‡	65 ± 19*†	47 ± 14†	31 ± 9	<0.001
Left ventricular end-systolic volume index (ml/m^2)	24 ± 12	60 ± 19‡	32 ± 8*†	24 ± 6†	16 ± 4	<0.001
Left ventricular mass (g)	203 ± 85	264 ± 142*†	214 ± 99	195 ± 78	200 ± 75	0.02
Left ventricular mass index (g/m^2)	103 ± 38	137 ± 64‡	107 ± 46	99 ± 34	102 ± 33	0.002
Left ventricular mass/volume ratio	1.3 ± 0.5	1.4 ± 0.6	1.3 ± 0.6	1.2 ± 0.4	1.3 ± 0.5	0.24
Left ventricular ejection fraction (%)	71 ± 10	42 ± 7	61 ± 4	71 ± 3	80 ± 3	NA

* $p < 0.05$ versus 66–75%; † $p < 0.001$ versus >75%; ‡$p < 0.05$ versus all other groups.

Boston, Massachusetts), previously used in other studies.[12] The LV volumes, ejection fraction, mass, and wall thickness were analyzed using a commercial workstation (MASS, version 6.1.6, Medis, Best, The Netherlands). The endocardial and epicardial borders of the left ventricle were manually measured using planimetry by an experienced observer (CJH) on successive short-axis cine images at end-diastole, with only the endocardial border measured using planimetry on the end-systolic frame. The LV volume and mass were derived by summation of disks, with the mass calculated by multiplying the myocardial muscle volume by 1.05 g/cm^3. The LV EF was calculated by dividing the LV stroke volume by the end-diastolic volume. The maximum LV wall thicknesses were taken as the greatest dimension determined automatically by the MASS software at any site within the LV wall. The anatomic parameters were normalized to the body surface area.

LGE images were acquired 10 to 15 minutes after intravenous administration of 0.2 mmol/kg gadolinium-diethylene triamine pentaacetic acid (Magnevist, Schering) with a breath-held segmented inversion-recovery sequence, acquired in the same orientations as the cine images. An inversion time scout was used initially to find the optimal inversion time to null the normal myocardium (typically 240 to 300 ms).

To ascertain the presence of LGE, all tomographic short-axis LV slices from base to apex were inspected visually to identify an area of completely nulled myocardium. The mean signal intensity (and SD) of the normal myocardium was calculated, and a threshold ≥6 SD exceeding the mean was used to define areas of LGE.[3,12] The choice of 6 SD was determined from our experience that semiautomated LGE-CMR gray-scale thresholding using ≥6 SD greater than the mean of visually normal, remote myocardium was the most reliable method for assessing the extent of LGE in the LV myocardium of patients with HCM.[21]

The total LGE volume (expressed in grams) was calculated by summing the planimetered areas of LGE present on each short-axis slice and multiplying it by the slice thickness (10 mm). It was expressed as a proportion of the total LV myocardial volume (percentage of LGE).

The unpaired Student t test or one-way analysis of variance followed by Bonferroni's post hoc test were used for the comparison of normally distributed data. The Kruskal-Wallis H test was used to compare the extent of LGE (which was not normally distributed) across different EF subgroups. The chi-square test or Fisher's exact test was used to compare noncontinuous variables, expressed as proportions. Multivariate linear regression analysis was performed to assess the relation of the EF to several clinical variables and LGE. p Values are 2-sided and considered significant at <0.05. The calculations were performed using the Statistical Package for Social Sciences, version 12.0, software (SPSS, Chicago, Illinois).

Results

The EF in the 310 patients with HCM was significantly greater than in the reference healthy control population (71 ± 10% vs 66 ± 5%; $p < 0.001$). The EF was <50% (overt systolic dysfunction) in 15 (5%), 50% to 65% in 45 (15%), 66% to 75% in 144 (46%), and >75% in 106 (34%). Patients with an EF <50% and an EF of 50% to 65% had similar transverse LV end-diastolic and left atrial dimensions, exceeding those of patients with an EF of 66% to 75% or >75% (Table 1).

In the overall study group, no significant relation was evident between the EF and age, gender, body surface area, LV volumes, or maximum LV thickness or LV mass (Tables 1 and 2). Also, no significant relation was evident between patients with HCM who had or had not received treatment with β blockers (72 ± 11% vs 70 ± 8%, respectively; $p = 0.18$), verapamil (73 ± 10% vs 71 ± 9%; $p = 0.09$), or disopyramide (73 ± 3% vs 71 ± 10%; $p = 0.48$). Patients with an EF <50% were more likely to have atrial fibrillation and to incur heart failure symptoms (New York Heart Association class II or III) than were the other 3 EF subgroups (Table 1).

LGE was present in 157 (51%) of the 310 patients (Figures 1 and 2) and was located in the ventricular septum ($n = 56$) or LV free wall ($n = 40$), or both ($n = 61$). Delayed enhancement was most commonly located in both the ventricular septum and LV free wall ($n = 53$; 34%) but

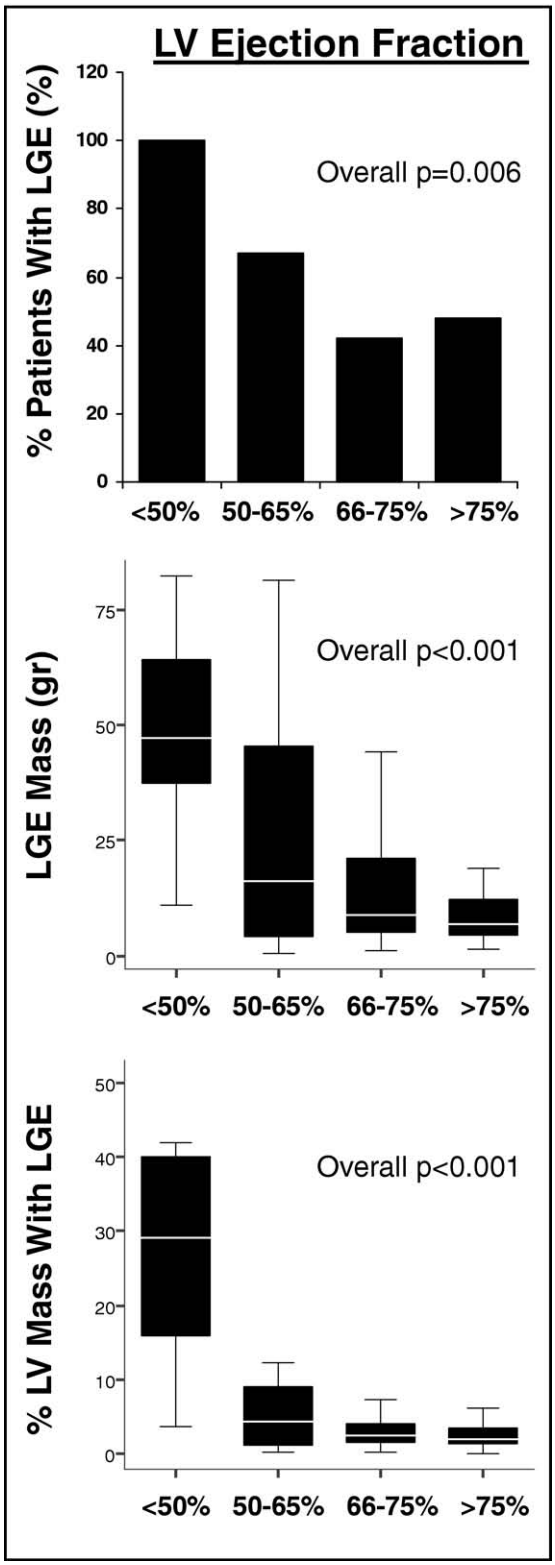

Figure 1. Relation of LV EF to frequency and extent of contrast CMR late gadolinium enhancement (LGE) in 310 patients with HCM. *(Top)* Prevalence of LGE in 4 EF subgroups. *(Center)* Box plot representing extent of LGE expressed as absolute mass in grams. *Black boxes* represent interquartile range; *horizontal white lines* represent median for each subgroup. *(Bottom)* Box plot representing LGE expressed as percentage of overall LV myocardial mass.

was also confined to the LV free wall (n = 31; 20%), septum (n = 38; 24%), right ventricular insertion areas (n = 27; 17%), and LV apex (n = 8; 5%). Delayed enhancement was transmural (occupying ≥75% of the wall thickness in any LV site) in 89 patients (57%) and nontransmural in 68 (43%; mid-myocardial in 46 [68%], subepicardial in 10 [14%], and subendocardial in 12 [18%]).

The LGE mass had a median value of 10 g (interquartile range 5 to 25), representing 2.4% of the overall LV wall (interquartile range 1.5% to 5.6%). Although LGE showed similar morphologic patterns and locations across the range of EFs, the percentage of LV volume occupied by LGE was inversely related to the EF ($R^2 = 0.29$, $p < 0.001$; Figure 1). In a multivariate linear regression model that included age, LV outflow gradient, left atrial size, and LV mass, the percentage of LV myocardium occupied by LGE was the only independent predictor of systolic dysfunction, showing a strong, inverse relation to the EF (B −0.69, 95% CI −0.86 to −0.52; $p < 0.001$).

In each of the 15 patients with overt systolic dysfunction (EF <50%, range 28% to 49%), the LGE was diffusely distributed and constituted a median value of 29% of the LV volume (interquartile range 16% to 40%; Figures 1 and 2). In patients with intermediate, low-normal EF values of 50% to 65%, LGE was also common (30 of 45 patients; 67%) and substantial (median 5% of LV volume, interquartile range 2% to 10%), ranging from limited (<2% of LV; n = 11 patients) to substantial (>15% of LV volume; n = 8 patients; Figure 1). The LGE values in the latter 8 patients (representing 17% of the group with an EF of 50% to 65%) overlapped with those observed in the subgroup with an EF of <50% (Figure 2). In contrast, among the patients with intact systolic function and an EF >65%, LGE was present in <1/2 (110 of 250, 44%; $p < 0.01$ vs patients with EF of 50% to 65%), and was limited in magnitude (median 2% of LV volume, interquartile range 1.5% to 4%), with no significant difference between the 66% to 75% and >75% EF subgroups (Figure 1).

Discussion

Remodeling of the LV chamber in HCM has been shown to occur in several clinical circumstances, including progression of LV hypertrophy during adolescence[22] and evolution to the end-stage with overt systolic dysfunction.[3–7] In the present cross-sectional analysis, we used CMR in a large consecutive HCM cohort to examine the relation of EF to a variety of clinical variables potentially relevant to LV remodeling and systolic performance.

In our HCM cohort, the EF values encompassed a broad range, from hyperdynamic to impaired, but on average significantly exceeded that in healthy controls, consistent with the view that HCM is a disease often expressed by a hypercontractile left ventricle.[1,2] However, we found little or no relation between CMR-measured EF and several standard clinical and demographic parameters such as age, gender, LV cavity dimension, and LV wall thickness or LV mass. In contrast, our contrast-enhanced CMR studies demonstrated that LV remodeling expressed by LGE, generally regarded as an in vivo representation of myocardial replacement fibrosis,[3,11,16] is relevant to systolic function in HCM,

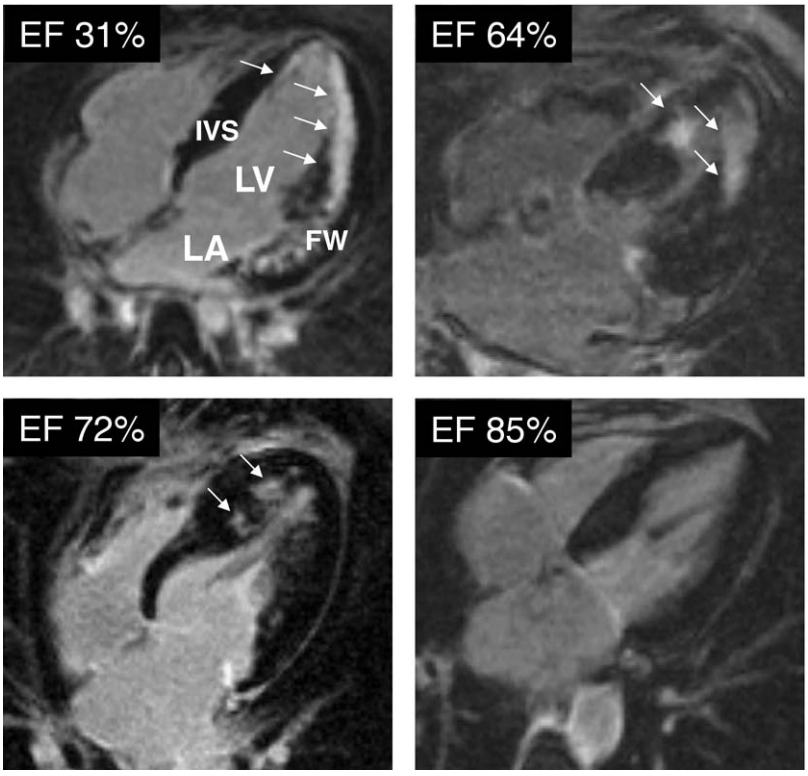

Figure 2. Relation of myocardial fibrosis to systolic function in representative patients with HCM from 4 EF categories. LGE in 4-chamber vertical long-axis images. *(Top Left)* Image of 20-year-old woman with end-stage progression and EF 31% showing extensive transmural myocardial fibrosis (LGE occupying 43% of LV wall; *arrows*). *(Top right)* Image of 61-year-old woman with low-normal EF (64%) showing considerable transmural fibrosis (LGE occupying 24% of LV; *arrows*). *(Bottom Left)* Image of 35-year-old man with preserved systolic function (EF 72%) showing limited and nontransmural fibrosis (LGE occupying 8% of LV wall; *arrows*). *(Bottom Right)* Image of 45-year-old patient with supernormal systolic function (EF 85%) showing absence of LGE. Atherosclerotic coronary artery disease was excluded in all patients by coronary arteriography. FW = free wall; LA = left atrium; LV = left ventricle; IVS = inter ventricular septum.

in that patients with the lowest EF demonstrated the most extensive and diffusely distributed LGE, and those with supernormal LV systolic function had minimum LGE. Despite these quantitative differences, the patterns and location of LGE were substantially similar across the spectrum of LV EF values, supporting the principle of a continuum in the generation of myocardial fibrosis by HCM hearts.

In this respect, we were able to confirm and expand our previous observation that the LV EF is inversely related to the LGE in HCM,[12] by addressing the issue in a multivariate model. LGE proved to be the only independent predictor of impaired systolic function in our 310 patients with HCM, of several other potentially relevant clinical variables ranging from the presence of obstruction to clinical status. Such a strong relation between LGE and EF raises important considerations regarding the pathophysiology of LV remodeling and systolic dysfunction in HCM. Myocardial fibrosis expressed as LGE can be considered in part to represent the long-term consequence of microvascular ischemia, leading to myocyte death and replacement fibrosis as a repair process, and ultimately to progressive systolic impairment in some patients.[3,7,23–25] Furthermore, HCM causing sarcomere mutations are know to cause metabolically inefficient contractions, potentially provoking myocyte energy depletion in the long term.[26,27] Such a mechanism has been invoked to explain the genesis of hypertrophy in HCM, but it might also represent a pathway, leading to progressive systolic dysfunction, by triggering apoptosis and collagen deposition.[28] In addition, LGE is associated with an increased prevalence of ventricular tachyarrhythmias and sudden death in patients with HCM.[29,30] Such an observation is consistent with the considerable rate of arrhythmia-related mortality observed in patients entering the end-stage phase, by virtue of profound LV remodeling and myocardial scarring.[3]

The substantial size of the present study cohort permitted several EF subsets of sufficient size to be analyzed and compared. Given this advantage, we were able to discern that the extent of myocardial fibrosis was considerable in the relatively small, but potentially important, subgroup of patients with low-normal EF values of 50% to 65%. In this subgroup, LGE occupied almost 10% of the LV myocardium (ie, was significantly greater than that seen in patients with hyperdynamic LV function) and substantially overlapped with patients exhibiting overt systolic dysfunction (EF $<$50%). This novel and most important finding suggests that we have identified a subset of patients with HCM with low-normal EF (50% to 65%) and evidence of myocardial fibrosis, in whom LV remodeling could potentially represent a transition phase in evolution to the end-stage phase.[3–7] This concept was also supported by the observation that the subset of patients with an EF of 50% to 65% had greater similarities to the subgroup with an EF of $<$50% than to those with intact systolic function (EF $>$65%) with respect to the relevant clinical variables such as LV chamber size and prevalence of outflow obstruction.[1,3,25]

Ultimately, we would expect only a few patients in this low-normal EF subgroup to develop overt systolic dysfunction, given that the prevalence of end-stage disease does not exceed 5% in most cross-sectional HCM cohort studies,[3–5] and our 50% to 65% EF subset was 3 times larger, at 15%. Nevertheless, this subset with intermediate degrees of LV remodeling and systolic function is likely to represent the reservoir of patients from which those with end-stage disease will evolve. Therefore, this subgroup with an EF of 50% to 65% and substantial LGE deserves particularly close clinical follow-up and imaging surveillance (with contrast CMR imaging) as a prudent measure for assessing on-going LV remodeling associated with decreasing systolic function.[3,12]

Consequently, the findings of the present study have potential implications for the natural history and long-term management strategies of patients with HCM. Disease progression may occur in HCM over extended periods,[6,7] and the anticipation of developing systolic dysfunction is important to permit timely intervention with specific pharmacologic strategies, including modulators of the renin-angiotensin system and β blockers.[2] Furthermore, patients with marked disease progression and LV remodeling (i.e., those entering the end-stage phase) eventually become candidates for primary prevention of sudden death with implantable defibrillators[2,3] and timely evaluation for future heart transplantation.[4] At present, however, the clinical implications of our findings are limited by the cross-sectional nature of the study design and the degree of overlap evident in the extent and distribution of LGE across the EF spectrum. Greater availability of CMR data in dedicated longitudinal studies of patients with HCM will lead to more precise identification of such predictors of disease progression in HCM.

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