

Cardiac Magnetic Resonance Imaging

Toward Clinical Risk Assessment in Hypertrophic Cardiomyopathy With Gadolinium Cardiovascular Magnetic Resonance

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- OBJECTIVES** We sought to assess whether hyperenhancement by gadolinium cardiovascular magnetic resonance (CMR) occurs in hypertrophic cardiomyopathy (HCM) and correlates with the risk of heart failure and sudden death.
- BACKGROUND** The myocardial interstitium is abnormal in HCM at post-mortem. Focally increased interstitial myocardial space appears as hyperenhancement with gadolinium CMR.
- METHODS** In a blinded, prospective study, HCM patients were selected for the presence (n = 23) or absence (n = 30) of an increased clinical risk of sudden death and/or progressive adverse left ventricular (LV) remodeling. Gadolinium-enhanced CMR was performed.
- RESULTS** Myocardial hyperenhancement was found in 42 patients (79%), affecting 10.9% (range 0% to 48%) of the LV mass. There was a greater extent of hyperenhancement in patients with progressive disease (28.5% vs. 8.7%, $p < 0.001$) and in patients with two or more risk factors for sudden death (15.7% vs. 8.6%, $p = 0.02$). Improved discrimination was seen in patients >40 years old (29.6% vs. 6.7%, $p < 0.001$) for progressive disease and for patients <40 years old for risk factors for sudden death (15.7% vs. 2.1%, $p = 0.002$). Patients with diffuse rather than confluent enhancement had two or more risk factors for sudden death (87% vs. 33%, $p = 0.01$).
- CONCLUSIONS** Gadolinium CMR reveals myocardial hyperenhancement in HCM. The extent of hyperenhancement is associated with progressive ventricular dilation and markers of sudden death. (J Am Coll Cardiol 2003;41:1561-7) © 2003 by the American College of Cardiology Foundation

An important minority of patients with hypertrophic cardiomyopathy (HCM) are at high risk of sudden death and/or progressive left ventricular (LV) impairment (1,2). Predicting these outcomes is a major management challenge, and new methods are needed. The abnormal myocardial substrate is probably the key determinant of clinical events (3-6), consisting of interstitial

would be demonstrated in vivo by hyperenhancement on gadolinium CMR in HCM and that hyperenhancement would be associated with markers of risk of sudden death and the presence of progressive disease.

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fibrosis, myocardial disarray, small-vessel disease, and macroscopic scarring. Fibrosis caused by myocardial infarction can be detected by cardiovascular magnetic resonance (CMR) using the extra-cellular fluid tracer gadolinium-diethylenetriaminepentaacetic acid (DTPA), or gadolinium CMR (7-9). We hypothesized that abnormal myocardium

METHODS

Patients. This was a blinded, prospective study of 53 patients selected from a dedicated HCM clinic at St. George's Hospital, London, which consists of 1,074 patients. The selected patients fulfilled conventional criteria for HCM with left ventricular hypertrophy (LVH) ≥ 15 mm at some time point in their disease (10). The only exclusion criterion was the presence of an implantable device. We aimed to recruit approximately equal numbers of patients with two or more risk factors or progressive disease, as those without these factors. Four patients had undergone gradient reduction therapy (two surgical myectomies and two transcatheter alcohol ablations). All patients gave written, informed consent, and the institutional Ethical Review Committee approved the study.

Sudden death risk stratification. Five clinical risk factors for sudden death were used to stratify patients: a family history of HCM and sudden premature cardiac death;

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Abbreviations and Acronyms

CMR = cardiovascular magnetic resonance
 DTPA = diethylenetriaminepentaacetic acid
 FISP = fast imaging with steady-state precession
 HCM = hypertrophic cardiomyopathy
 LV = left ventricle/ventricular
 LVH = left ventricular hypertrophy

unexplained syncope at any time during follow-up; non-sustained ventricular tachycardia; an abnormal blood pressure response during upright exercise testing in subjects ≤ 40 years old; and echocardiographic presence of severe LVH ≥ 30 mm.

Diagnosis of progressive disease. Progressive disease was defined as a decrease in maximal LV wall thickness ≥ 5 mm and an increase in LV end-systolic dimension ≥ 5 mm during five or more years of follow-up on a serial in-house echocardiogram. This definition selects a poor prognostic group, including patients with “pseudonormalization” of initial supra-systolic function and LVH on the way to a dilated phase.

The CMR technique. CMR was performed on a 1.5-T Sonata scanner (Siemens, Erlangen, Germany). Fast imaging with steady-state precession (FISP) sequential short-axis cine loops (7-mm slice thickness, 3-mm gap) were acquired. A peripheral bolus injection of gadolinium-DTPA (0.1 mmol/kg) was then given, and contrast-enhanced images were acquired using a segmented inversion-recovery sequence (11), with the following modifications: imaging was started at 5 min; segmentation was from 17 to 23 lines; inversion pulse every 2 to 3 heart beats depending on the RR interval and heart rate variability; a 90° presaturation pulse was placed over the cerebrospinal fluid to eliminate ghosting; and two-chamber, four-chamber, and all short-axis views were acquired twice with different phase-encoding direction and meticulous attention to the inversion time. The typical voxel size was $1.7 \times 1.4 \times 8$ mm.

Image analysis. Ventricular function was analyzed from the serial short-axis true FISP cine loops using manual segmentation (CMRtools Imperial College, London). End-diastolic volume, end-systolic volume, ejection fraction, and myocardial volume of the LV were calculated. For the gadolinium-enhanced images, hyperenhancement was only considered to be present if it was also present in the same slice after swapping phase encoding, thus excluding artifact. Analysis was performed by manually defining the areas of hyperenhancement on all short-axis slices from the base to apex. Summing the areas yielded the total volume of hyperenhancement, which was expressed as a percentage of total myocardium.

Statistical analysis. Non-parametric Wilcoxon rank comparisons were made to compare the extent of hyperenhance-

Table 1. Demographics and Baseline Characteristics

Characteristics	
Age (yrs)	47 \pm 16 (range 15–73)
Male gender	37 (70%)
Years since diagnosis	12 \pm 10
Years of local echocardiographic follow-up	7 \pm 5
NYHA functional class	
I	30 (57%)
II	21 (40%)
III	2 (3%)
FH of HCM and ≥ 2 sudden deaths	11 (21%)
Unexplained syncope	14 (26%)
NSVT on Holter monitor	11 (21%)
Documented sustained VT/VF	3 (6%)
Abnormal exercise BP response	12 (23%)
Maximum LV wall thickness ≥ 30 mm	8 (15%)
Echocardiographic LV outflow gradient (mean 43 mm Hg [range 30–100])	
<30 mm Hg	44 (83%)
≥ 30 mm Hg	9 (17%)

Data are presented as the mean value \pm SD or number (%) of subjects.

BP = blood pressure; FH = family history; HCM = hypertrophic cardiomyopathy; LV = left ventricle/ventricular; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

ment between patients with ≤ 1 and ≥ 2 risk factors for sudden death, and between patients with and without the presence of progressive disease. Linear regression analysis was performed to compare the extent of hyperenhancement with patient age, LV function, and mass.

RESULTS

Patient baseline characteristics. The baseline characteristics of the patients are given in Table 1. There were 0, 1, 2, 3, 4, and 5 risk factors in 19, 16, 13, 3, 2, and 0 patients, respectively. Of 34 patients with >5 years of follow-up, nine had progressive disease (of these, four patients also had ≥ 2 risk factor for sudden death). There was no age difference between patients with and without progressive disease (49 vs. 51 years, $p = 0.8$), but patients with ≥ 2 risk factors for sudden death were younger than patients with ≤ 1 risk factors for sudden death (35 vs. 53 years, $p < 0.001$).

Extent of hyperenhancement. Myocardial hyperenhancement was present in 42 patients (79%). The mean percentage of myocardium involved was $10.9 \pm 11\%$ (range 0% to 48%). Abnormal myocardium was not visible without contrast (Fig. 1). Regions of hyperenhancement had a mean image intensity of 27; remote myocardium, 5.7; and background noise, 4.24. The percentage elevation in signal from hyperenhanced regions was 430% (range 120% to 1,000%); the mean difference in image intensity between hyperenhanced and remote regions was 16 standard deviations of remote region intensity. There was no relationship between percentage hyperenhancement and patient age ($r = 0.1$, $p = 0.47$). The percentage hyperenhancement correlated weakly with LV mass index ($r = 0.24$, $p = 0.04$), end-diastolic

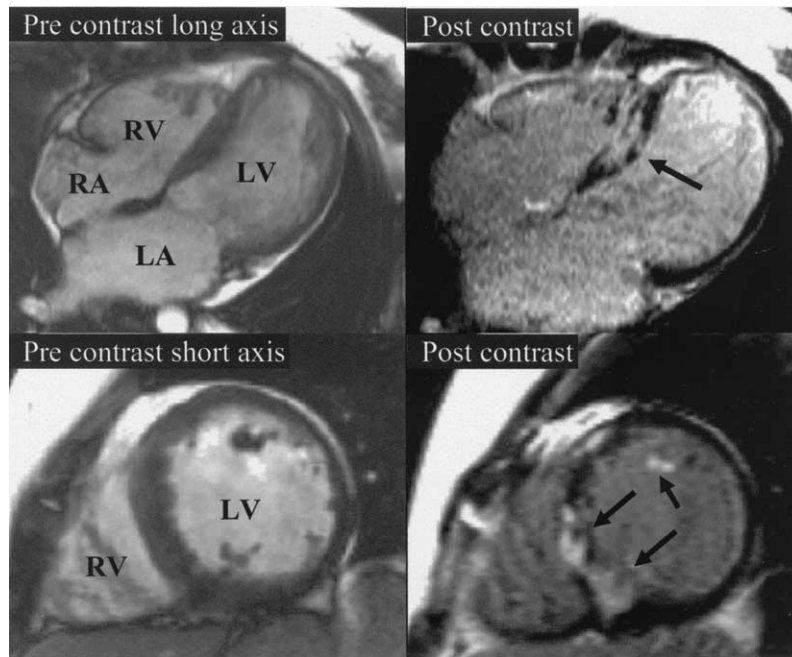


Figure 1. Pre- and post-contrast images demonstrating hyperenhancement. The pre-contrast images are the diastolic frames of fast imaging with steady-state precession cine loops. In the post-contrast images, normal myocardium appears dark. There is a large area of septal hyperenhancement, with additional papillary muscle hyperenhancement and subendocardial hyperenhancement of the lateral wall. The patient is a 33-year-old female with two risk factors for sudden death. Eight years previously, echocardiography demonstrated marked asymmetric septal hypertrophy, but the ventricle is now thinning and dilating and left bundle branch block has developed. The total extent of hyperenhancement was 25% of the left ventricular (LV) mass. LA = left atrium; RA = right atrial; RV = right ventricle.

volume ($r = 0.42$, $p = 0.002$), and end-systolic volume ($r = 0.64$, $p < 0.001$) and inversely with ejection fraction ($r = 0.64$, $p < 0.001$).

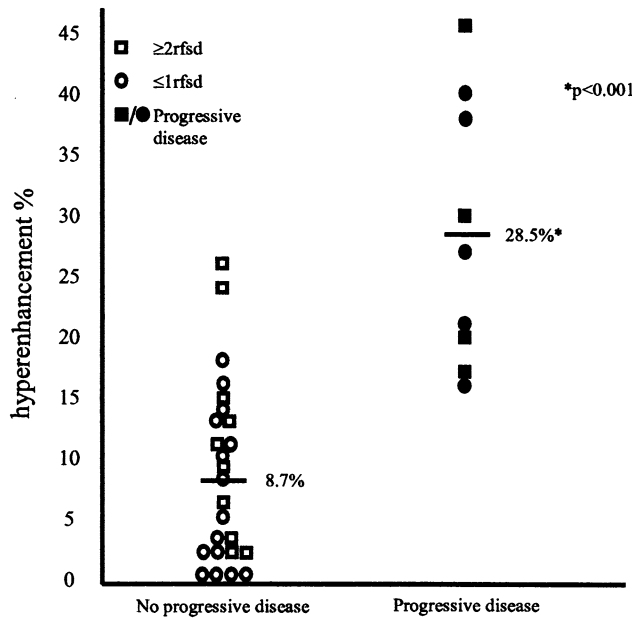
There was more hyperenhancement in patients with progressive disease than in those without (28.5% vs. 8.7%, $p < 0.001$) (Fig. 2A). This remained significant when patients with ≥ 2 risk factors for sudden death were excluded (28.4% vs. 6.9%, $p = 0.04$) (Fig. 2B). This finding appeared more marked in patients >40 years old (29.6% vs. 6.7%, $p < 0.001$) (Fig. 2C), and remained significant when patients with ≥ 2 risk factors for sudden death were excluded (28.4% vs. 6.9%, $p = 0.04$) (Fig. 2D). There was greater hyperenhancement in patients with ≥ 2 risk factors for sudden death (15.7% vs. 8.6%, $p = 0.02$) (Fig. 3A). This remained significant when patients with progressive disease were excluded (12.0% vs. 5.3%, $p = 0.02$) (Fig. 3B). This finding appeared more marked in patients <40 years old (15.7% vs. 2.1%, $p = 0.002$) (Fig. 3C), which remained significant when patients with progressive disease were excluded (14.1% vs. 2.1%, $p = 0.003$) (Fig. 3D).

Patterns of hyperenhancement. Specific patterns of hyperenhancement were evident. There were two broad patterns: diffuse hyperenhancement and confluent hyperenhancement. Patients with diffuse ($n = 8$) rather than confluent ($n = 21$) enhancement had ≥ 2 risk factors for sudden death (87% vs. 33%, $p = 0.01$). Further classification could be made, but the number of patients is too small to draw strong conclusions. The distributions are shown in Figure 4 and Table 2.

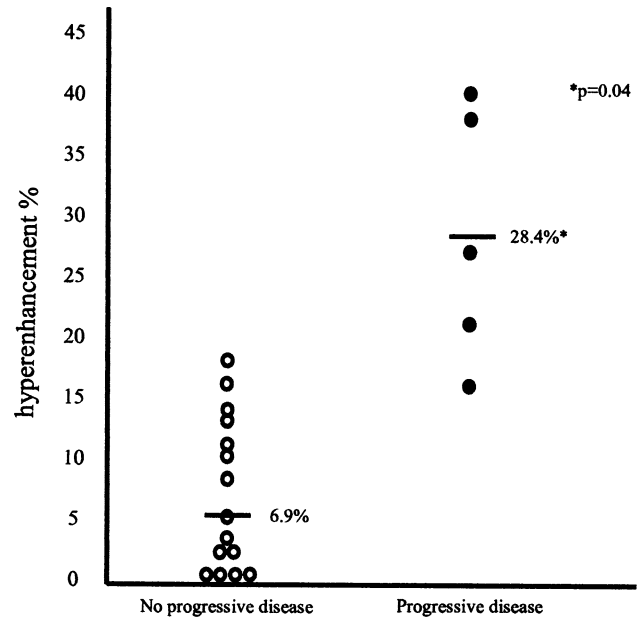
DISCUSSION

Identifying patients at high and low risk is an important but problematic aspect of the clinical management of HCM, particularly with the availability of an effective but not hazard-free treatment option—the implantable cardioverter-defibrillator (12). Likewise, there are few markers for the risk of heart failure before LV dysfunction is evident (13,14). Neither the genotype nor the extent of hypertrophy fully predicts the clinical risk (15–17). Ideally, assessment would involve a global assessment of the underlying histology, the substrate for myocardial pump failure, and arrhythmia. The histology consists of myocardial disarray (18) and small-vessel disease or replacement fibrosis (19–21).

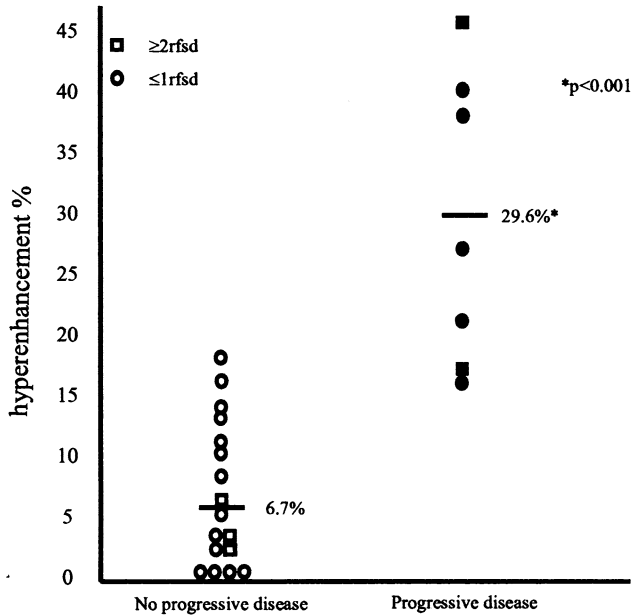
Gadolinium-enhanced CMR has been validated for the detection of irreversible injury in myocardial infarction (22). Hyperenhancement is considered to occur in areas of expanded extracellular space. Gadolinium bound to DTPA diffuses into the interstitial space between cells but not across cell membranes. In fibrosis and extracellular expansion, there is a greater extracellular space for gadolinium-DTPA accumulation, and the distribution kinetics are slower than normal myocardium (8,9). These two effects result in a delayed and persistently higher relative concentration of gadolinium in areas in the heart where extracellular tissue is abnormal. We therefore hypothesized that this technique might prove useful in the clinical assessment of the myocardial substrate in HCM. In



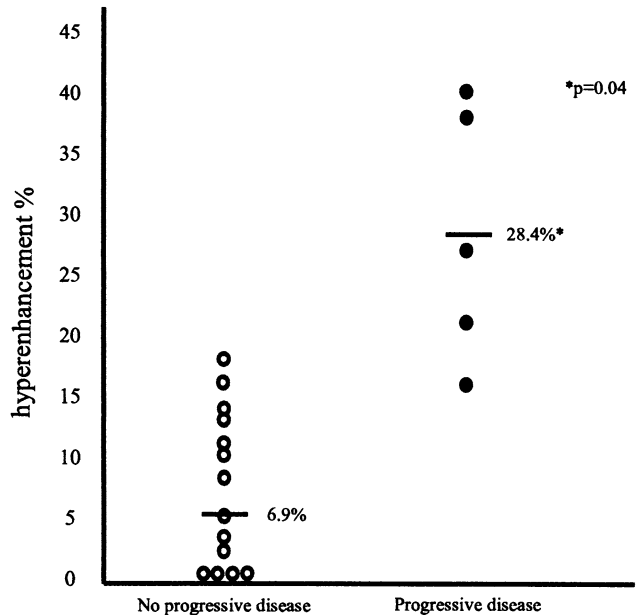
A All patients with 5 year follow-up (n=34)



B Patients with 5 year follow-up, high risk of sudden death excluded (n=20)



C Patients with 5 year follow-up and >40years old (n=24)



D Patients with 5 year follow-up, >40years old, high risk of sudden death patients excluded (n=19)

Figure 2. Extent of hyperenhancement and presence of progressive disease. Hyperenhancement was associated with the presence of progressive disease (A), even when patients at high risk of sudden death were excluded (B), and appeared more marked in patients >40 years old, regardless of the risk of sudden death (C, D). rfsd = risk factors for sudden death.

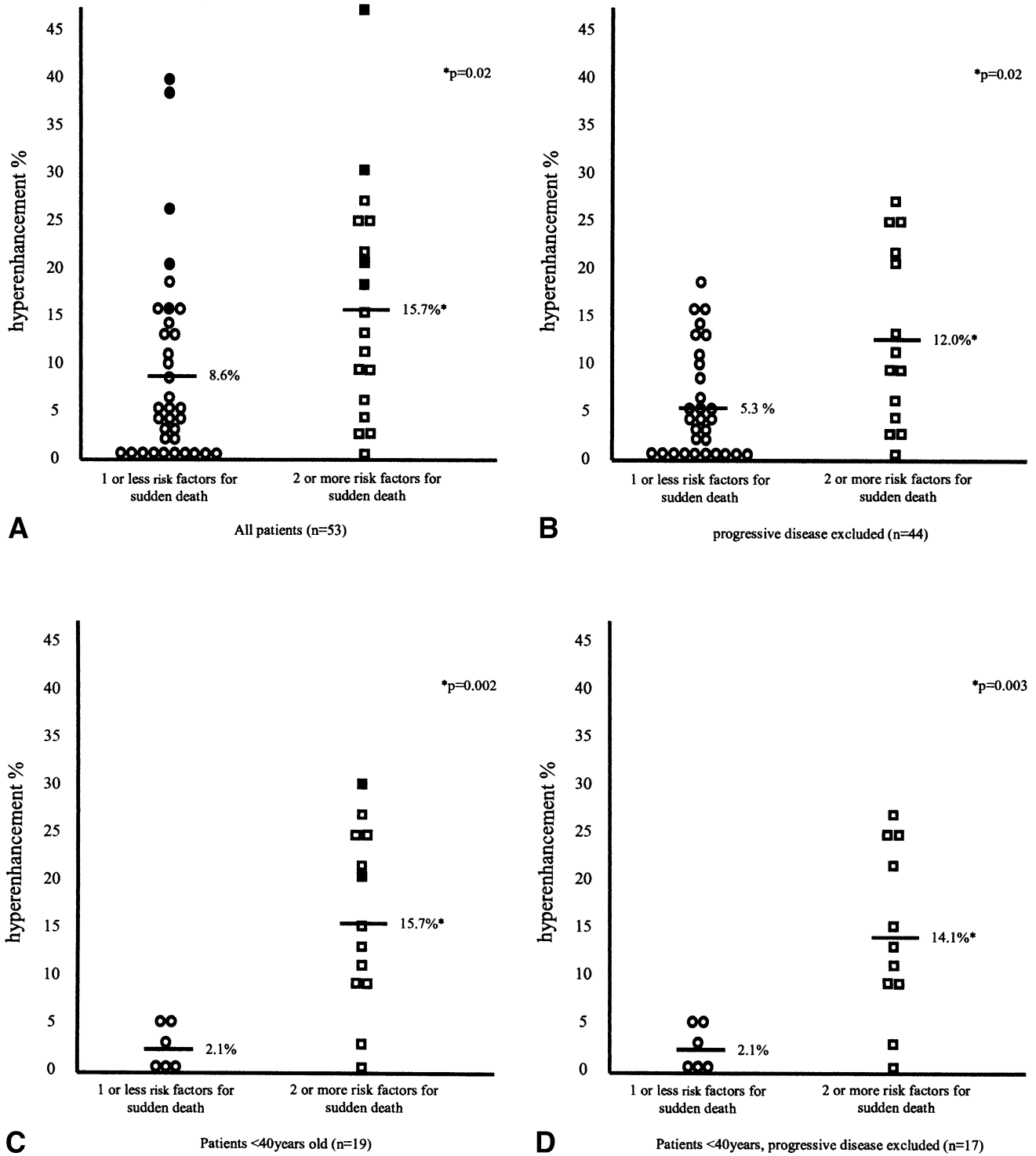


Figure 3. Extent of hyperenhancement and clinical risk factors for sudden death. Hyperenhancement was associated with an increased clinical risk of sudden death (A), even when patients with progressive disease were excluded (B), and appeared more marked in patients <40 years old, regardless of the presence of progressive disease (C, D).

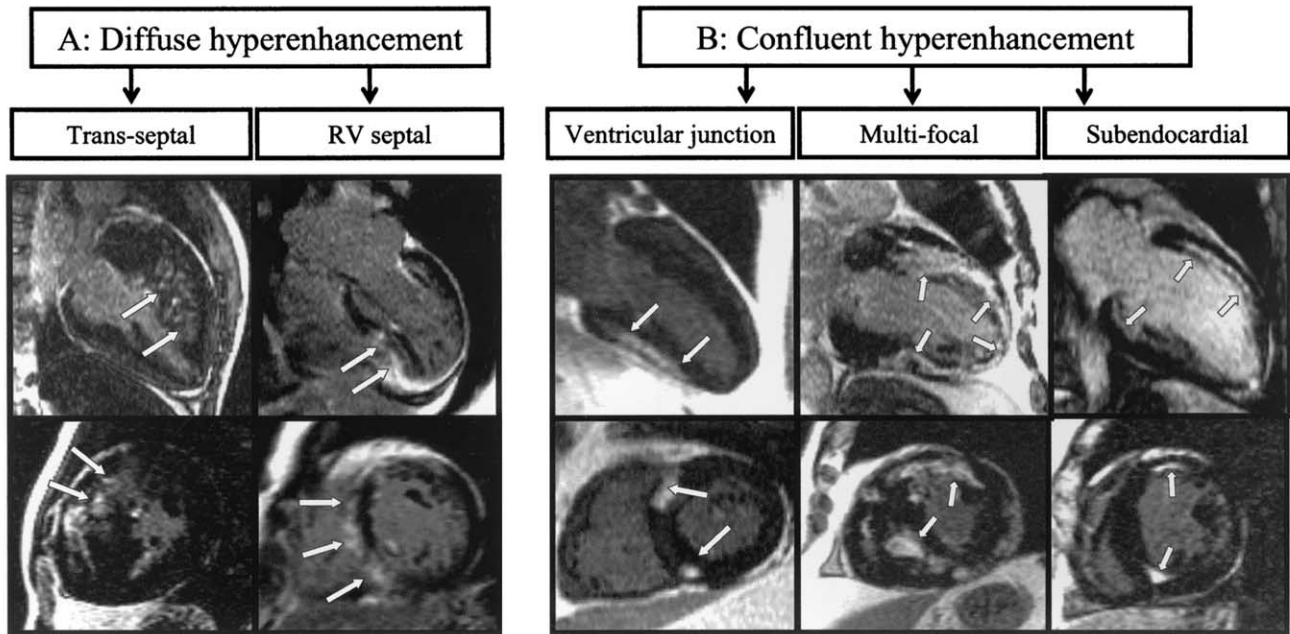


Figure 4. (A and B) Patterns of hyperenhancement in hypertrophic cardiomyopathy by cardiovascular magnetic resonance. The patterns of hyperenhancement are grouped into diffuse or confluent types (**upper rows:** long-axis, vertical, or horizontal; **lower rows:** short-axis views). These were further subclassified as shown. The different patterns may have clinical or prognostic significance, and this qualitative classification may complement the overall quantification of hyperenhancement. RV = right ventricular.

myocardial infarction, fibrosis always includes the subendocardium because of the nature of the ischemic wave front that starts there. In HCM, gadolinium enhancement could occur in myocardial replacement fibrosis, but this may well show different characteristics. First, fibrosis in HCM can occur throughout the myocardial wall, even with subendocardial sparing. In addition, areas of focal myocardial disarray and fine interstitial fibrosis may be seen. Therefore, the distribution and pattern of gadolinium uptake will be

Table 2. Associations Between Pattern of Hyperenhancement and Clinical Phenotype

Type of Hyperenhancement	n (%)	Clinical Phenotype
Trans-septal	4 (7%)	Young, gross asymmetric LVH; extensive diffuse hyperenhancement; high risk of sudden death
RV septal	4 (7%)	Extensive RV surface of septal hyperenhancement; strong family history of sudden death
Ventricular junction	12 (23%)	Moderate symmetrical LVH; limited hyperenhancement at RV insertion points; lower risk of sudden death
Multi-focal	9 (17%)	Large focal areas of hyperenhancement; LBBB if basal septum; associated with progressive disease
Subendocardial	2 (4%)	Like infarcts, but not IHD, in these patients
Other	11 (21%)	Other patterns or trivial hyperenhancement
None	11 (21%)	Typically young and at low risk

IHD = ischemic heart disease; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; RV = right ventricular.

different between these two conditions, as we have confirmed in this study.

Histologic correlations between hyperenhancement and pathology are not yet available. We believe that hyperenhancement is the result of a number of pathologic processes that result in different forms of fibrosis (replacement scar or myocyte dropout) or in relation to myocardial disarray and consequent local interstitial expansion. The different patterns of hyperenhancement seen are likely to be linked to the different pathologic processes occurring in different patients, and the different stages that such processes had reached at the time of scanning.

Study limitations. In this preliminary study, the HCM patients were highly selected, which could introduce a referral bias. Some patients had both progressive disease and two or more risk factors for sudden death, but this reflects the HCM population. Although this complicated the interpretation of the findings, exclusion of these patients did not alter the results. Future work is required to identify histologic correlations and prospective prediction of events based on hyperenhancement findings.

Conclusions. Areas of hyperenhancement are seen in HCM by CMR. The extent of hyperenhancement is linked with progressive disease and markers of clinical risk for sudden death.

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REFERENCES

1. Cannan CR, Reeder GS, Bailey KR, et al. Natural history of hypertrophic cardiomyopathy: a population-based study, 1976 through 1990. *Circulation* 1995;92:2488-95.
2. Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis: clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 1968;37:759-88.
3. Varnava AM, Elliott PM, Mahon N, et al. Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. *Am J Cardiol* 2001;88:275-9.
4. Varnava AM, Elliott PM, Sharma S, et al. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart* 2000;84:476-82.
5. Maron BJ, Epstein SE, Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am J Cardiol* 1979;43:1086-102.
6. Spirito P, Seidman CE, McKenna WJ, et al. The management of hypertrophic cardiomyopathy. *N Engl J Med* 1997;336:775-85.
7. Wu E, Judd RM, Vargas JD, et al. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet* 2001;357:21-8.
8. Kim RJ, Chen EL, Lima JAC, et al. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. *Circulation* 1996;94:3318-26.
9. Flacke SJ, Fischer SE, Lorenz CH. Measurement of the gadopentetate dimeglumine partition coefficient in human myocardium in vivo: normal distribution and elevation in acute and chronic infarction. *Radiology* 2001;218:703-10.
10. Report of the 1995 World Health Organisation. International Society and Federation of Cardiomyopathy Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;93:841-2.
11. Simonetti OP, Kim RJ, Fieno DS, et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology* 2001;218:215-23.
12. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;36:2212-8.
13. Ikeda H, Maki S, Yoshida N, et al. Predictors of death from congestive heart failure in hypertrophic cardiomyopathy. *Am J Cardiol* 1999;83:1280-3.
14. Spirito P, Maron BJ, Bonow RO, et al. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in hypertrophic cardiomyopathy. *Am J Cardiol* 1987;59:123-9.
15. Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2001;33:655-70.
16. Elliott PM, Gimeno Blanes JR, Mahon NG, et al. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;357:420-4.
17. Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:1778-85.
18. Davies MJ. The current status of myocardial disarray in hypertrophic cardiomyopathy. *Br Heart J* 1984;51:361-3.
19. St. John Sutton MG, Lie JT, Anderson KR, et al. Histopathological specificity of hypertrophic obstructive cardiomyopathy: myocardial fibre disarray and myocardial fibrosis. *Br Heart J* 1984;44:433-43.
20. Maron BJ, Wolfson JK, Epstein SE, et al. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;8:545-57.
21. Varnava AM, Elliott PM, Baboonian C, et al. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. *Circulation* 2001;104:1380-4.
22. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;16:1445-53.