Clinical Profile and Significance of Delayed Enhancement in Hypertrophic Cardiomyopathy

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Background—Contrast-enhanced cardiovascular magnetic resonance with delayed enhancement (DE) can provide in vivo assessment of myocardial fibrosis. However, the clinical significance of DE in hypertrophic cardiomyopathy (HCM) remains unresolved.

Methods and Results—Cine and cardiovascular magnetic resonance with DE were performed in 202 HCM patients (mean age, 42±17 years; 71% male), DE was compared with clinical and demographic variables, and patients were followed up for 681±249 days for adverse disease events. DE was identified in 111 (55%) HCM patients, occupying 9%±11% of left ventricular myocardial volume, including >25% DE in 10% of patients. The presence of DE was related to occurrence of heart failure symptoms (P=0.05) and left ventricular systolic dysfunction (P=0.001). DE was present in all patients with ejection fraction ≤50% but also in 53% (102/192) of patients with preserved ejection fraction (P<0.001); %DE was both inversely related to (r=−0.3; P<0.001) and an independent predictor of ejection fraction (r=−0.4; P<0.001). DE (7%±7% of left ventricle) was present in 54 patients who were asymptomatic (and with normal ejection fraction). Over the follow-up period, the annualized adverse cardiovascular event rate in patients with DE exceeded that in patients without DE but did not achieve statistical significance (5.5% versus 3.3%; P=0.5).

Conclusions—In a large HCM cohort, DE was an independent predictor of systolic dysfunction but with only a modest relationship to heart failure symptoms. These data suggest an important role for myocardial fibrosis in the clinical course of HCM patients but are not sufficient at this time to consider DE as an independent risk factor for adverse prognosis.

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Key Words: heart failure ■ MRI ■ fibrosis ■ hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease and the leading cause of sudden cardiac death in the young and is also associated with heart failure, disability, and death at any age.1–8 In HCM, left ventricular (LV) myocardial fibrosis provides a structural substrate, which has been implicated in promoting heart failure as well as risk for arrhythmic sudden death.9–15 Contrast-enhanced cardiovascular magnetic resonance (CMR) with delayed enhancement (DE) imaging can reliably detect myocardial fibrosis in vivo and has been reported to be an important determinant of outcome in ischemic heart disease and nonischemic dilated cardiomyopathy.16–28 However, the clinical significance of DE in HCM remains unresolved.25,26,29 Therefore, we sought to investigate DE in a large HCM cohort by characterizing its prevalence, morphological profile, and relation to clinical and demographic features and prognosis.

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myocardial scars in study patients with DE by virtue of 2 specific clinical or CMR criteria: (1) no study patient experienced an acute coronary event associated with increased cardiac enzymes or Q waves on ECG and (2) in all patients with DE distributed in a single coronary vascular territory, hemodynamically significant coronary artery disease was excluded by arteriography or computed tomography angiogram. In addition, among the 6 patients with transmural or subendocardial DE distributed across multiple coronary artery vascular territories, 4 were <40 years of age with no coronary artery disease risk factors, whereas 2 were >40 years of age and, because of an LV ejection fraction <50% (ie, end stage), underwent coronary arteriography, which demonstrated in both the absence of significant coronary artery disease.

All study patients signed a statement previously approved by the internal review boards of the respective participating institutions, agreeing to the use of their medical information for research purposes. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Definitions
Diagnosis of HCM was based on 2D echocardiographic and CMR documentation of a hypertrophied and nondilated LV in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy at some point in the clinical course of each patient.1,2,6,50 Sudden death was defined as sudden and unexpected collapse in patients who previously had a relatively uneventful clinical course. Progression of heart failure was defined as an advancement of at ≥1 New York Heart Association (NYHA) functional class during the follow-up period. In addition, potentially lethal events in which patients received appropriate implanted cardioverter defibrillator interventions (shocks or antitachycardia pacing triggered by ventricular tachycardia/fibrillation) were regarded as equivalent to sudden death.

CMR
CMR imaging was performed (Gyroscan ACS-NT 1.5T, Philips, Best, the Netherlands, and Sonata 1.5T, Siemens, Erlangen, Germany) using steady-state, free-precession breath-hold cine in 3 long-axis planes and sequential 10 mm short-axis slices (no gap) from the atroventricular ring to apex. DE images were acquired 15 minutes after the intravenous administration of 0.2 mmol/kg of gadolinium-DTPA (Magnevist, Schering; Berlin, Germany) with a breath-hold 2D segmented inversion-recovery sequence acquired in the same views as the cine images. The inversion time ranged from 240 to 300 ms and was chosen to null normal myocardial signal. LV volume, mass, and ejection fraction were measured using standard volumetric techniques and analyzed with commercially available software (MASS version 6.1.6, Medis, Inc, the Netherlands).31 Volume and mass measurements were indexed to body surface area. Maximal LV wall thickness was defined as the greatest dimension at any site within the LV wall. The LV was assessed according to the American Heart Association 17-segment model.32

To ascertain the presence of DE, all tomographic short-axis LV slices from base to apex were inspected visually to identify an area of completely nullled myocardium. The mean signal intensity (and 6 SDs) of normal myocardium was calculated, and a threshold of completely nulled myocardium. The mean signal intensity (and 6 SDs) of normal myocardium was calculated, and a threshold of completely nulled myocardium was determined as a proportion of total LV myocardium (%DE).

DE analysis was performed by 1 experienced reader (C.J.H.; 2 years of CMR experience, including the assessment of >800 CMR studies, of which 600 involved the quantification of DE). These readings were reviewed and confirmed by a second expert reader (E.A.; >7 years of CMR experience). Both these independent observers were blinded to patient identity and clinical profile. Any discrepancies between the 2 readers were adjudicated by a senior observer (W.J.M).

To assess interobserver variability for the presence of DE, a second reader (E.A.) independently reanalyzed all CMR studies. Among the studies in which there was agreement between the 2 readers on the presence of DE, reader E.A. reanalyzed 20 randomly selected studies to determine the interobserver variability for extent of DE. To assess intraobserver variability, reader C.J.H. reanalyzed all 202 CMR studies 4 to 6 months after the initial interpretation, blinded to the previous results.

Statistical Analysis
Continuous data are expressed as mean±SD. Clinical and demographic characteristics of the 2 patient groups (DE and non-DE) were compared with the Wilcoxon rank-sum test for continuous variables and χ² or Fisher exact tests for categorical variables. Clinical features of the study patients were compared with the extent of DE with the Wilcoxon rank-sum test or Kruskal-Wallis equality-of-populations rank test for categorical variables and Spearman’s rank correlation coefficient (ρ) for continuous variables.

The primary clinical end point used in this study was a composite of the following adverse cardiovascular events: sudden death, appropriate implantable cardioverter defibrillator (ICD) discharge, and progressive heart failure symptoms of ≥1 NYHA class. Patient-level characteristics were modeled as linear regressions in unadjusted and adjusted analyses. Per-segment data clustered within a patient were assessed by linear mixed-effects models with a random intercept per patient. Probability values of <0.05 were considered significant. Calculations were performed with Stata SE version 9.2 (StataCorp, College Station, Tex). Kaplan-Meier event rates were calculated to accommodate for differential length of follow-up between patients. The comparison of event rates among patients with and without DE was performed using a log-rank test for equality of survivor functions. Among patients with DE, the relationship between %DE and the likelihood of subsequent cardiovascular events was evaluated using a univariate Cox model.

Results
Patient Characteristics
Baseline clinical and demographic characteristics of the 202 study patients at initial evaluation are summarized in Table 1. Mean age was 42±17 years; 144 (71%) were male. NYHA class was 1.5±0.7 and maximal LV wall thickness was 22±5 mm (range, 14 to 37 mm).

Morphological Features of DE
Prevalence and Extent
DE was present in 111 (55%) of the HCM patients, and %DE was 9%±11% (range, 0.2% to 51%), which was equivalent to 19±21 g (range, 0.4 to 85 g) and included 11 patients (10%) with %DE ≥25% (Table 1).

Location and Distribution
DE was most commonly located in both the ventricular septum and LV free wall (n=35; 32%) but was also confined to the LV free wall (n=29; 26%), the septum (n=27; 24%), the area of right ventricular insertion into the ventricular septum (n=15; 13%), and the LV apex (n=5; 5%).

DE was transmural (occupying ≥75% of LV wall thickness) in 58 patients (52%) in the following segmental distribution: septum (n=10), LV free wall (n=21), septum and LV free wall (n=25), and apex (n=2). In the remaining 53 patients (48%), DE was nontransmural in the following distribution: midmyocardial (n=17), right ventricular insertion areas (n=12), subendocardial (n=9), subepicardial
Relation of DE to Heart Failure Symptoms

A relationship was identified between presence of DE and heart failure symptoms. DE was most common in patients with severe (NYHA class III–IV; 19/25 [76%]) and moderate symptoms (NYHA class II; 31/54 [57%]) and was also present in 61 of 123 (50%) asymptomatic patients ($P=0.05$; Table 1 and Figure 2). %DE was 8.9% ± 9.6% in asymptomatic patients and 9.9% ± 13.4% in those with heart failure symptoms (NYHA classes II–IV) ($P=0.2$; Figure 3).

Patients with areas of transmural DE were no more likely to have heart failure symptoms than were patients with nontransmural DE ($P=0.7$). DE specifically confined to the area of right ventricular insertion into the ventricular septum was unrelated to heart failure symptoms ($P=0.5$). %DE in these areas was relatively small and less than in other patients with DE (3.0% ± 2.2% versus 10.2% ± 12%; $P=0.008$).

Relation of DE to Ejection Fraction

DE was present in all 10 patients with ejection fraction (EF) ≤50% (ie, end-stage phase; each transmural), in 9 of 10 (90%) with EF 51% to 59%, and in 92 of 182 (51%) with EF ≥60%.
Figure 2. Comparison of DE presence in HCM patients with NYHA classes I, II, and III/IV.

\[\text{Patients with DE were no more likely to have LV outflow obstruction at rest than were patients without DE (}\text{P}=0.9).\]

Among patients with obstruction, there was no significant relationship between %DE and magnitude of LV outflow gradient at rest (\(r=0.2; \text{P}=0.23\)).

**LV Outflow Obstruction**

Patients with DE were no more likely to have LV outflow obstruction at rest than were patients without DE (\(P=0.9\)). Among patients with obstruction, there was no significant relationship between %DE and magnitude of LV outflow gradient at rest (\(r=0.2; \text{P}=0.23\)).

**LV Wall Thickness and Mass**

Patients with DE had greater maximal LV wall thickness (23±5 mm) and LV mass index (113±37 g/m²) than patients without DE (20±4 mm and 100±28 g/m²; \(P<0.001\) and \(P=0.02\), respectively). A significant relationship was evident between DE and segmental LV wall thickness (\(P=0.002\)). DE was present in 15 of 112 (13%) LV segments ≤15 mm, 93 of 1216 (8%) LV segments ≤15 mm, 93 of 1216 (8%) LV segments 16 to 20 mm, 131 of 1216 (9%) LV segments 21 to 25 mm, 73 of 608 (12%) LV segments 26 to 30 mm, and 50 of 288 (17%) LV segments ≥30 mm.

**Reproducibility for the Presence and Extent of DE**

For presence of DE, the intraobserver and interobserver agreements were 96% and 93%, respectively. For the intraobserver and interobserver quantifications of DE extent, the mean differences in measurement were 1.4±9 g (11%) and 5.4±18 g (3.4%), respectively (\(\kappa=0.5\) and \(\kappa=0.2\), respectively; both \(P<0.001\)).

**Relation of DE to Clinical Outcome**

Over the follow-up period, adverse cardiovascular events occurred in 11 patients, including 7 patients with DE (2 with sudden death, 2 with appropriate ICD discharge, and 3 with progressive heart failure symptoms) and 4 patients without DE (3 with sudden death and 1 with progressive heart failure).

Annual cardiovascular event rate in HCM patients with DE exceeded that in patients without DE (5.5% versus 3.3%), although this comparison did not achieve statistical significance (\(P=0.5\); hazard ratio, 1.45 [95% CI, 0.43 to 4.97]) (Figure 5). Extent of DE did not differ between patients with and without adverse cardiovascular events (9±11% versus 11±15%; \(P=0.97\)). Patients with transmural or nontransmural DE showed no difference in event rate (7% per year versus 6% per year; \(P=0.89\)).

**Discussion**

Contrast-enhanced CMR imaging provides a novel and noninvasive method for in vivo identification and quantification of myocardial fibrosis.16–18,20,21,35,36 In patients with dilated cardiomyopathy or after myocardial infarction due to coronary artery disease, the presence of DE has been reported to be an independent predictor of ventricular arrhythmias and cardiovascular mortality.22–24,28,36 In HCM, myocardial scars have been commonly reported in necropsy studies9 and by fixed defects on myocardial perfusion imaging15 and it has been suggested that DE represents myocardial fibrosis in this disease,9,11–13,25,29,37–40 as initially recognized by Choudhury et al.11 However, whether DE in HCM are associated with adverse clinical consequences similar to those in coronary artery disease and other nonischemic cardiomyopathies is unresolved. Therefore, we have sought here, in a sizeable
HCM cohort studied with CMR, to characterize the clinical significance of DE and to analyze its relationship to a variety of disease variables.

DE by contrast-enhanced CMR was present in 50% of patients in our HCM study cohort, a prevalence somewhat less than that previously reported by other investigators. In addition, when present, the extent of DE proved to be substantial, occupying on average 10% of overall LV myocardial volume. This extent of DE observed in HCM is similar to that reported after myocardial infarction, raising the consideration of whether myocardial fibrosis or scarring in this genetic cardiomyopathy is a determinant of increased risk for sudden death or disease progression due to heart failure.

In this regard, our data demonstrate a modest relationship between the presence (but not necessarily the extent) of DE and the occurrence of heart failure symptoms. Indeed, >75% of our HCM patients with advanced and disabling symptoms showed areas of DE, often involving extensive areas of LV myocardium. Furthermore, the present data demonstrate an inverse relationship between the presence and extent of DE and LV EF, with DE an independent determinant of systolic dysfunction (ie, end-stage phase, with EF ≤50%). Patients in the end stage showed transmural and extensive DE occupying on average 25% of LV myocardium, greatly exceeding that in our patients with preserved LV function. These findings are consistent with 2 recent case reports in which the explanted hearts of patients in the end stage of HCM were analyzed in detail to show a morphological

![Graph](image)

**Figure 4.** Comparison of %DE in HCM patients with EF ≤50%, 51% to 59%, and >60%.

**Figure 5.** Kaplan-Meier survival estimates for the composite end-point of sudden death, appropriate ICD discharge, and progressive heart failure symptoms in patients with and without DE.
correlation between CMR-DE and extensive areas of myocardial fibrosis.\textsuperscript{10,42} The recognition that CMR has the capability to identify the end-stage phase of HCM by virtue of calculated EF and myocardial fibrosis has important clinical implications, as end-stage patients experience a high rate of unfavorable disease consequences, including progressive heart failure (often requiring heart transplantation) and sudden unexpected death (prompting consideration for prophylactic defibrillator implantation).\textsuperscript{1,2,43} However, whether extensive DE identified by CMR will ultimately prove to be a primary marker and prospectively portend susceptibility for progression to the end stage before development of systolic dysfunction is presently unresolved. Nevertheless, taken together, the present data demonstrating an association between DE and both heart failure and systolic dysfunction suggest that myocardial fibrosis has an important role in symptom production and adverse remodeling among HCM patients.

On the other hand, we also identified a sizeable and novel subgroup of asymptomatic patients with preserved EF in whom, paradoxically, extensive and often transmural myocardial DE was present. Furthermore, many of these patients with substantial amounts of DE have already achieved advanced ages, free of LV remodeling, arrhythmia-related events, or heart failure. That these patients have not experienced adverse consequences from their myocardial fibrosis over many years suggests that DE may result in very different clinical consequences within the broad clinical spectrum of this disease. Our findings also underscore the principle that complex and multifactorial pathophysiologic mechanisms are likely responsible for disease progression in HCM and that myocardial fibrosis may not be the sole or primary determinant of adverse consequences.\textsuperscript{4,44} Nevertheless, given the present data and uncertainty in this area, it would seem judicious for HCM patients with DE to undergo regular clinical surveillance (including serial CMR imaging) for prospective detection of changes in symptoms and LV remodeling.

Moon et al,\textsuperscript{18} using HCM risk factors as surrogates for sudden death events in a retrospective study, suggested that DE may fulfill the aspiration as a predictor for future arrhythmic-related events and prognosis. However, whereas our prospective (short-term) outcome data obtained over an average of almost 2 years showed the adverse cardiovascular event rate to be numerically higher in association with the presence of DE, this difference did not achieve statistical significance. This outcome analysis was clearly underpowered considering the low event rate characteristic of HCM. A substantially longer follow-up period will be required in a particularly large patient population to achieve adequately powered positive or negative data in this respect. Therefore, it is possible that longer longitudinal observation periods (ie, \textasciitilde 5 to 7 years) will allow the presence (or extent) of DE to be fully analyzed and emerge as a possible independent risk factor for sudden death and disease progression.

In addition, it is conceivable that novel CMR-based techniques for identifying specific areas of histologically abnormal myocardium, such as reported in coronary artery disease (using intermediate signal intensity thresholding to define the infarct border zone),\textsuperscript{23} may also emerge as a more reliable predictor in this patient population. Although it is premature at this early juncture to broadly apply DE by contrast-enhanced CMR as a primary risk stratification strategy to HCM, it may nevertheless be reasonable in selected patients (and on a case-by-case basis) to assign weight to DE as an arbitrator in reaching difficult clinical decisions for primary prevention ICDs,\textsuperscript{45} particularly when ambiguity remains regarding risk level after the assessment of conventional risk factors.\textsuperscript{46,47}

To define DE in this analysis, we chose a methodology which used the cutoff point of \textasciitilde 6 SDs above the mean signal intensity of normal myocardium. At present, a general consensus is lacking on this criterion (particularly in nonischemic cardiomyopathy), with previous investigators using a variety of strategies for the identification of DE, including visual assessment (without thresholding)\textsuperscript{34,48} and also 2-SD\textsuperscript{34,48} and 6-SD thresholds.\textsuperscript{18,27,33,34,48} In our experience, the amount of DE quantified with the 6-SD technique most closely approximates that assessed by visual inspection, with the 2-SD cutoff point yielding 22% greater amounts of DE than 6 SDs.\textsuperscript{49} Therefore, our decision to use a 6-SD threshold was based on the view that it provides the highest specificity for detection and quantification of myocardial fibrosis.\textsuperscript{16,33,34} Indeed, considering the extensive amount of DE in the patients reported here using this methodology, it is unlikely that we have significantly underestimated the extent of fibrosis present in our HCM cohort.

In conclusion, in a large hospital-based population of HCM patients, DE was common and often occupied significant proportions of LV myocardium. DE was associated with heart failure symptoms and a strong determinant of LV function (ie, end-stage phase). Paradoxically, significant amounts of DE were also present in many asymptomatic (or mildly symptomatic) HCM patients with preserved LV function. Therefore, DE (ie, myocardial fibrosis) appears to have an important role in the clinical course of many HCM patients but may also be associated with substantially different disease consequences. Nevertheless, at present, DE cannot yet be regarded as an independent risk factor for adverse disease outcome and risk for sudden death in HCM, and prudent restraint is justified before broadly applying the results of contrast-enhanced CMR to clinical decision-making strategies in this disease. These present data also underscore the necessity of long-term follow-up studies to ultimately define the prognostic significance of this newly identified CMR-based component of the cardiomyopathic process in HCM.

\section*{Disclosures}

None.

\section*{References}


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In hypertrophic cardiomyopathy (HCM), a myocardial substrate of fibrosis and scarring has been implicated in promoting heart failure and providing a nidus for the generation of ventricular tachyarrhythmias. Contrast-enhanced cardiovascular magnetic resonance with delayed enhancement (DE) now provides a novel, noninvasive method for detecting myocardial fibrosis in vivo in HCM patients. These data report on the clinical profile and significance of DE (ie, fibrosis) in a large cohort of HCM patients. DE was identified in the majority of HCM patients (55%), occupying on average 10% of total left ventricular mass. The extent of DE was inversely related to ($r = -0.3; P < 0.001$) and an independent predictor of ($r = -0.4; P < 0.001$) LV systolic function; patients showing systolic dysfunction (ejection fraction <50%) demonstrated the greatest amount of DE. The presence of DE was modestly related to the occurrence of heart failure symptoms ($P = 0.05$), with DE in >75% of patients with advanced limiting symptoms. Paradoxically, substantial amounts of DE were also identified in patients with normal systolic function, many of whom had achieved advanced ages, free of adverse disease consequences. Over a short-term follow-up period, patients with DE experienced more adverse disease events than those without DE, although this difference did not achieve statistical significance. These data demonstrate that DE may result in different clinical consequences within the broad HCM clinical spectrum and strongly support the need for further follow-up studies to more definitively define the prognostic significance of DE in this complex disease.
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