Clinical Profile and Significance of Delayed Enhancement in Hypertrophic Cardiomyopathy

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ABSTRACT

Background. Contrast-enhanced cardiovascular magnetic resonance (CMR) 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 CMR-DE were performed in 202 HCM patients (42±17 years; 71% male) and DE was compared to 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 LV myocardial volume, including >25% DE in 10% of patients. Presence of DE was related to occurrence of heart failure symptoms (p=0.05) and LV systolic dysfunction (p=0.001). DE was present in all patients with ejection fraction (EF) ≤ 50%, but also in 53% (102/192) of patients with preserved EF (p<0.001); %DE was both inversely related to (r= -0.3; p<0.001) and an independent predictor of EF (r= -0.4; p<0.001). Delayed enhancement (7±7% of LV) was present in 54 patients who were asymptomatic (and with normal EF). 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 % vs. 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.
Key Words: MRI, hypertrophic cardiomyopathy, fibrosis

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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 \textit{in vivo}, and has been reported to be an important determinant of outcome in ischemic heart disease and non-ischemic 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, and morphologic profile, as well as its relation to clinical and demographic features and prognosis.

METHODS

Selection of patients

We prospectively evaluated 202 HCM patients presenting to centers at Tufts-New England Medical Center (Boston, MA) and Minneapolis Heart Institute Foundation (Minneapolis, MN) between April 2002 to November 2006. The initial clinical evaluation was defined as the time of the CMR examination at each institution. The duration of follow-up from CMR to the most recent evaluation (October 1, 2007) or death, was 681±249 days; no patient was lost to follow-up. LV outflow tract obstruction was defined as a peak instantaneous outflow gradient $\geq$30 mmHg, assessed by continuous-wave
Doppler echocardiography under resting conditions (8). No study patient underwent an alcohol septal ablation or surgical septal myectomy procedure.

We excluded significant atherosclerotic coronary artery disease (CAD) (>50% stenosis in one major artery) as a cause of pre-existent myocardial scars in study patients with DE by virtue of two specific clinical and/or CMR criteria: 1) No study patient experienced an acute coronary event associated with increased cardiac enzymes or Q waves on ECG; 2) in all patients with DE distributed in a single coronary vascular territory, hemodynamically significant CAD was excluded by arteriography or CT 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 CAD risk factors, while 2 patients were >40 years and because of an LV ejection fraction <50% (ie., end stage) underwent coronary arteriography, which demonstrated in both the absence of significant CAD.

All study patients signed a statement previously approved by the Internal Review Board (IRB) 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 two-dimensional echocardiographic and CMR documentation of a hypertrophied and nondilated LV in the absence of another cardiac or systemic disease capable of producing similar magnitude of hypertrophy, at some point in the clinical course of each patient (1,2,6,30). Sudden death was defined as sudden and
unexpected collapse in patients who had previously had a relatively uneventful clinical course. Progression of heart failure was defined as an advancement of at least one NYHA functional class during the follow-up period. In addition, potentially lethal events in which patients received appropriate implanted defibrillator interventions (shocks or anti-tachycardia pacing triggered by ventricular tachycardia/fibrillation) were regarded as equivalent to sudden death.

**Cardiovascular magnetic resonance (CMR)**

CMR imaging was performed (Philips Gyroscan ACS-NT 1.5T, Best, Netherlands and Siemens Sonata 1.5T, Erlangen, Germany) using steady-state, free precession breath-hold cines in 3 long-axis planes and sequential 10 mm short-axis slices (no gap) from the atrioventricular 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 two-dimensional segmented inversion-recovery sequence acquired in the same views as the cine images. The inversion time (TI) ranged from 240-300 ms and was chosen to null normal myocardial signal.

LV volumes, mass and ejection fraction (EF) were measured using standard volumetric techniques, and analyzed with commercially available software (MASS®, version 6.1.6 Medis, Inc., Netherlands)(31). Volume and mass measurements were indexed to body surface area (BSA). 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 null ed myocardium.
Mean signal intensity (and standard deviation) of normal myocardium was calculated and a threshold $\geq 6$ SD exceeding the mean was used to define areas of DE (18,27,33,34). Areas of artifact (ie., blood pool, incomplete nulling of fat and pericardial fluid) were excluded from the analysis by manually adjusting the individual contours. Total volume of DE (expressed in grams [g]) was calculated by summing the planimetered areas of DE in all short-axis slices and was expressed as a proportion of total LV myocardium (% DE).

DE analysis was performed by one experienced reader, C.J.H. (with 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.; with over 7 years of CMR experience). Both these independent observers were blinded to patient identity and clinical profile. Any discrepancies between the two 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 re-analyzed all CMR studies. Among the studies in which there was agreement between the two readers on the presence of DE, reader E.A. re-analyzed 20 randomly selected studies in order to determine the interobserver variability for extent of DE. To assess intraobserver variability, reader C.J.H. re-analyzed 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 $\pm$ standard deviation (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 chi-square or Fisher exact
tests for categorical variables. Clinical features of the study patients were compared to 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 ($\rho$) for continuous variables.

The primary clinical end-point used in this study was a composite of adverse cardiovascular events: sudden death, appropriate ICD discharge and progressive heart failure symptoms of $\geq 1$ 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. P-values of $p<0.05$ were considered significant. Calculations were performed with Stata SE version 9.2 (College Station, TX). 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 amount of 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 $42\pm17$ years; 144 (71%) were male. NYHA class was $1.5\pm0.7$ and maximal LV wall thickness was $22\pm5$ mm (range 14 to 37 mm).
Morphologic features of DE

Prevalence and extent. DE was present in 111 (55%) of the HCM patients. Percent DE volume of LV myocardium was 9±11% (range 0.2 to 51%), equivalent to 19±21 g (0.4 to 85 g), and including 11 patients (10%) with % DE ≥25% (Table 1).

Location and distribution. DE was most commonly located in both ventricular septum and LV free wall (n = 35; 32%), but was also confined to the LV free wall (n = 29; 26%), septum (n=27; 24%), the area of right ventricular insertion into ventricular septum (n=15; 13%), and 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: mid-myocardial (n=17), right ventricular insertion areas (n=12), subendocardial (n=9), subepicardial (n=8), or ≥2 of these non-transmural distributions (n=7) (Figure 1).

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 (class III/IV; 19/25 [76%]) and moderate symptoms (class II; 31/54[57%]), and was also present in 61 of 123 asymptomatic patients (50%)(p=0.05; Table 1)(Figure 2). %DE was 8.9±9.6% in asymptomatic patients and 9.9±13.4% in those with heart failure symptoms (classes II-IV)(p=0.2; Figure 3).

Patients with areas of transmural DE were no more likely to have heart failure symptoms than patients with non-transmural DE (p=0.7). DE specifically confined to the area of RV insertion into ventricular septum was unrelated to heart failure symptoms.
Relation of DE to ejection fraction

DE was present in all 10 patients with EF ≤50% (i.e., end-stage phase; each transmural), in 9 of 10 (90%) with EF 51-59%, and in 92 of 182 (51%) with EF ≥60% (p=0.001)(Table 2). Also, % DE was more extensive in patients with EF ≤50% compared to those with 51-59% or ≥60% (27% vs. 12% vs. 7%, respectively; p=0.004)(Figure 4) and an inverse relationship was present between EF and %DE (r = -0.3; p<0.001).

Multivariable Cox regression analysis (including LV outflow obstruction, maximal wall thickness, mass index, end-diastolic dimension, age, gender, left atrial size and NYHA functional class) showed %DE as an independent predictor of EF (r= -0.4; 95% CI –0.6 to –0.2; p<0.001).

Of the 182 patients with EF ≥60%, 54 (30%) were both asymptomatic (NYHA class I) and had DE occupying 7±7 % (range 1 to 34%) of LV myocardium (Table 2), including 26 with transmural DE. Twenty-three other patients (12%) with EF ≥60% experienced only mild symptoms (class II) had DE occupying 9±12% of LV (range 0.2 to 51%), including 9 with transmural DE.

Relation of DE to other demographic and clinical variables

Age and Gender. Patients with DE were 43±17 years of age (range 1-79), including 23 (21%) ≤30 years and 21 (19%) ≥60 years. Patients with and without DE did not differ significantly with respect to age (p=0.3); also, %DE was unassociated with age
(r= 0.05; p = 0.8). Presence of DE did not differ with respect to gender (female 57% vs. male 54%; p = 0.7)

*LV outflow obstruction.* Patients with DE were no more likely to have LV outflow obstruction at rest than 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; 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 0.02, respectively). A significant relationship was evident between DE and segmental LV wall thickness (p=0.002). DE was present in: 15/112 (13%) LV segments ≤15 mm; 93/1216 (8%) 16-20 mm; 131/1216 (9%) 21-25mm; 73/608 (12%) 26-30 mm; and 50/288 (17%) with ≥30 mm.

*Reproducibility for the Presence and Extent of DE.* For the presence of DE the intraobserver and interobserver agreement was 96% and 93%, respectively. For the intraobserver and interobserver quantification of DE extent the mean differences in measurement were 1.4±9 g or 11% and 5.4±18 g or 3.4%, respectively (κ=0.5; κ=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 one with progressive heart failure).
Annual cardiovascular event rate in HCM patients with DE exceeded that in patients without DE (5.5% vs. 3.3%), although this comparison did not achieve statistical significance (p=0.5; hazard ratio 1.45 [95% CI, 0.43-4.97]) (Figure 5). Extent of DE did not differ between patients with and without adverse cardiovascular events (9±11% vs. 11±15%; p=0.97). Patients with transmural or non-transmural DE showed no difference in event rate (7%/year vs. 6%/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 following 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 studies (9) and by fixed defects on myocardial perfusion imaging (15) and it has been suggested that DE represents myocardial fibrosis in this disease (9,11-13,25,29,37-42), as initially recognized by Choudhury et al. (11). However, whether DE in HCM is associated with adverse clinical consequences similar to those in coronary artery disease and other non-ischemic 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 about 50% of patients in our HCM study cohort, a prevalence somewhat less than that previously reported by other
investigators (11,38). In addition, when present, the extent of DE proved to be substantial, occupying on average about 10% of overall LV myocardial volume. This extent of DE observed in HCM is similar to that reported following myocardial infarction (19,23), 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, over 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 ejection fraction, with DE an independent determinant of systolic dysfunction (ie., end-stage phase, with ejection fraction ≤50%)(43). Indeed, patients in the end-stage showed transmural and extensive DE occupying on average about 25% of LV myocardium, greatly exceeding that in our patients with preserved LV function. These findings are consistent with two recent case reports in which the explanted hearts of patients in the end-stage of HCM were analyzed in detail to show a morphologic correlation between CMR-delayed enhancement and extensive areas of myocardial fibrosis (39,42). 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)(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 prior to 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 suggests 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 (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.(38), 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 events and prognosis. However, while 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., about 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”)(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 (45), particularly when ambiguity remains regarding risk level after the assessment of conventional risk factors (46,47).

To define DE in this analysis, we chose a methodology which employed the cut-off of $\geq 6$ standard deviations above the mean signal intensity of normal myocardium. At present, a general consensus is lacking on this criterion (particularly in non-ischemic cardiomyopathy) with previous investigators using a variety of strategies for the
identification of DE, including visual assessment (without thresholding)\(^\text{(34,48)}\) and also 2 SD \(^\text{(34,48)}\) and 6 SD thresholds \(^\text{(18,27,33,34,48)}\). 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 cut-off yielding 22% greater amounts of DE than 6 SD \(^\text{(49)}\). 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 \(^\text{(16,33,34)}\).

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 dysfunction (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 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.
LEGENDS

Figure 1. Left ventricular short-axis delayed-enhanced CMR images from 6 HCM patients showing diverse patterns of DE. A.) extensive transmural area in anterior ventricular septum (VS) extending into contiguous anterior free wall (arrow). Small focal area of DE is also present in the region of right ventricular insertion into posterior septum (double arrow); B.) multifocal mid-myocardial distribution within septum (arrows); C.) predominate transmural DE in inferolateral LV free wall (arrows); D.) DE on right ventricular side of septum (arrows) and subepicardial area in contiguous anterior free wall (double arrow); E.) subendocardial distribution within septum and anterior wall (arrows); F.) focal area (arrow) of DE at right ventricular (RV) insertion with posterior septum (VS). RV=right ventricle; VS=ventricular septum

Figure 2. Comparison of DE presence in HCM patients with NYHA classes I, II and III/IV.

Figure 3. Mid-ventricular short-axis delayed enhanced image from two HCM patients, both with extensive DE, but with significantly different clinical courses. A.) NYHA functional class III with EF = 40% and 30% DE in LV; B.) NYHA functional class I with EF = 65% and 46% DE in LV. VS=ventricular septum; RV=right ventricle
**Figure 4.** Comparison of % DE in HCM patients with EF ≤50%, 51-59% 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.
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Table 1. Demographic and Clinical Characteristics of 202 HCM Patients with CMR

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>DE (+)</th>
<th>DE (-)</th>
<th>p-value*</th>
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<tr>
<td>No. (%) patients</td>
<td>202 (100)</td>
<td>111 (55)</td>
<td>91 (45)</td>
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<tr>
<td>Age, y</td>
<td>42±17</td>
<td>43±17</td>
<td>40±18</td>
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<td>Male, n (%)</td>
<td>144 (71)</td>
<td>78 (70)</td>
<td>66 (73)</td>
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<tr>
<td>Body surface area (g/m²)</td>
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<td>1.96±0.3</td>
<td>1.99±0.3</td>
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<td>NYHA class, n (%)</td>
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<td></td>
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<tr>
<td>I</td>
<td>123 (61)</td>
<td>61 (55)</td>
<td>62 (68)</td>
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<tr>
<td>II</td>
<td>54 (27)</td>
<td>31 (28)</td>
<td>23 (26)</td>
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<tr>
<td>III/IV</td>
<td>25 (12)</td>
<td>19 (17)</td>
<td>6 (7)</td>
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<td>Mean</td>
<td>1.5±0.7</td>
<td>1.6±0.8</td>
<td>1.4±0.6</td>
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<td>Ejection fraction, n (%)</td>
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<td>≥60%</td>
<td>182 (90)</td>
<td>92 (83)</td>
<td>90 (99)</td>
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<td>51-59%</td>
<td>10 (5)</td>
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<tr>
<td>≤50%</td>
<td>10 (5)</td>
<td>10 (9)</td>
<td>0 (0)</td>
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<td>Basal LVOT gradient ≥30 mmHg, n (%)</td>
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<td>26 (23)</td>
<td>22 (24)</td>
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<td>Max LV thickness, mm</td>
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<td>23±5</td>
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<td>219±85</td>
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<td>LV mass index, g/m²</td>
<td>107±34</td>
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<td>LA dimension (mm)</td>
<td>67±11</td>
<td>69±10</td>
<td>65±11</td>
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<td>LVED dimension (mm)</td>
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<td>53±7</td>
<td>51±6</td>
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<td>19±21 (0.4 to 85)</td>
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<td>% LV with DE, (range)</td>
<td>N/A</td>
<td>9±11 (0.2 to 51)</td>
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Abbreviations:
DE, delayed enhancement; LV, left ventricle; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; Max=maximum; N/A, not applicable

Symbol:
*Based on comparison between DE (+) and DE (-) patients
Table 2. Clinical and Demographic Findings According to Ejection Fraction in HCM Patients with Delayed Enhancement

<table>
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<tr>
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<th>Total</th>
<th>≥60 %</th>
<th>51-59%</th>
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<th>p-value</th>
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<td>Patients, n</td>
<td>111</td>
<td>92</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>43±17</td>
<td>43±17</td>
<td>46±17</td>
<td>43±22</td>
<td>0.9</td>
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<tr>
<td>Male, n (%)</td>
<td>78 (70)</td>
<td>66 (72)</td>
<td>5 (56)</td>
<td>7 (70)</td>
<td>0.6</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>53±7</td>
<td>52±6</td>
<td>53±9</td>
<td>58±9</td>
<td>0.14</td>
</tr>
<tr>
<td>Max LV thickness, mm</td>
<td>23±5</td>
<td>24±5</td>
<td>20±3</td>
<td>20±5</td>
<td>0.008</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>219±85</td>
<td>226±89</td>
<td>171±31</td>
<td>203±70</td>
<td>0.08</td>
</tr>
<tr>
<td>LV mass index, g/m</td>
<td>113±37</td>
<td>116±37</td>
<td>91±21</td>
<td>110±43</td>
<td>0.08</td>
</tr>
<tr>
<td>DE, g</td>
<td>19±21</td>
<td>16±18</td>
<td>19±23</td>
<td>47±28</td>
<td>0.005</td>
</tr>
<tr>
<td>% DE</td>
<td>9±11</td>
<td>7±8</td>
<td>12±17</td>
<td>27±17</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>I</td>
<td>61 (55)</td>
<td>54 (59)</td>
<td>4 (44)</td>
<td>3 (30)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31 (30)</td>
<td>23 (25)</td>
<td>3 (33)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>19 (17)</td>
<td>15 (16)</td>
<td>2 (22)</td>
<td>2 (20)</td>
<td></td>
</tr>
<tr>
<td>DE pattern, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Transmural</td>
<td>58 (53)</td>
<td>44 (49)</td>
<td>4 (44)</td>
<td>10 (100)</td>
<td>0.006</td>
</tr>
<tr>
<td>Non-transmural</td>
<td>53 (48)</td>
<td>48 (51)</td>
<td>5 (56)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Only Subepicardial</td>
<td>8 (7)</td>
<td>8 (9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Only Midmyocardial</td>
<td>17 (15)</td>
<td>16 (17)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Only Subendocardial</td>
<td>9 (8)</td>
<td>9 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>≥2 Non-transmural</td>
<td>7 (6)</td>
<td>7 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.029</td>
</tr>
<tr>
<td>distributions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only at RV Insertion into LV</td>
<td>12 (11)</td>
<td>8 (9)</td>
<td>4 (44)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations:
DE, delayed enhancement; LV, left ventricle; NYHA, New York Heart Association; Max=maximum; RV, right ventricle
Figure 2

% of Patients with DE

p=0.05

NYHA Class at Study Entry

I

II

III/IV
**Figure 3**

A. 

B. 

LV VS RV

LV VS RV
Figure 4

Ejection Fraction (%) vs. % Myocardium with DE

- ≤50
- 51-59
- ≥60

P = 0.004
Figure 5

Event-free rate vs. follow-up duration (years) for DE (-) and DE (+) groups. The p-value is 0.5.
Clinical Profile and Significance of Delayed Enhancement in Hypertrophic Cardiomyopathy
Martin Maron, Evan Appelbaum, Caitlin Harrigan, Jacki Buros, C. Michael Gibson, Connie Hanna, John R. Lesser, James E. Udelson, Warren J. Manning and Barry J. Maron

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