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Delayed Hyper-Enhancement Magnetic Resonance Imaging Provides Incremental Diagnostic and Prognostic Utility in Suspected Cardiac Amyloidosis

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OBJECTIVES We sought to assess the diagnostic accuracy and incremental prognostic value of delayed hyper-enhancement cardiac magnetic resonance (DHE-CMR) compared with electrocardiographic and transthoracic echocardiographic (TTE) parameters in such patients.

BACKGROUND Utility of DHE-CMR in the diagnosis of patients with suspected cardiac amyloidosis (CA) has recently been demonstrated, but its incremental prognostic utility is unclear.

METHODS Forty-seven consecutive patients (mean age 63 years, 70% men, 55% New York Heart Association functional class >II) with suspected CA who underwent electrocardiography (ECG), TTE, DHE-CMR, and biopsy (38 endomyocardial, 9 extracardiac) were studied. Low voltage on ECG was defined as S-wave in lead V_1 + R-wave in lead V_5 or V_6 <15 mm. TTE parameters, including deceleration time, E/E′ ratio, and diastolic grade were recorded. CMR was considered positive with diffuse DHE of the subendocardium extending to adjacent myocardium. All-cause mortality was ascertained.

RESULTS In the study population, 59% had low voltage on ECG, 30% had abnormal deceleration time ≤150 ms, 38% had E/E′ ratio >15, and 47% had advanced (pseudonormal or restrictive) diastology. The diagnostic accuracy of DHE-CMR in patients undergoing endomyocardial biopsy was as follows: sensitivity 88%, specificity 90%, positive predictive value 88%, and negative predictive value 90%. On multivariable logistic regression testing of the diagnostic ability of various noninvasive imaging parameters, only DHE-CMR was significant (Wald chi-square statistic 9.6, $p < 0.01$). At 1-year post-biopsy, there were 9 (19%) deaths. On Cox proportional hazards analysis, only positive DHE-CMR was a predictor of 1-year mortality (Wald chi-square statistic 4.91, $p = 0.03$).

CONCLUSIONS A characteristic DHE-CMR pattern is more accurate for diagnosis and is a stronger predictor of 1-year mortality in patients with suspected CA as compared with other noninvasive parameters. (J Am Coll Cardiol Img 2009;2:1369–77) © 2009 by the American College of Cardiology Foundation

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One of the most robust predictors of mortality in systemic amyloidosis is cardiac involvement (1). Cardiac amyloidosis (CA) has a poor, albeit variable, prognosis (2,3); and early recognition could potentially alter prognosis by prompting initiation of aggressive medical treatment and evaluation for transplant candidacy. However, current techniques do not provide sufficient diagnostic information to supplant endomyocardial biopsy (EMB) as the gold standard, due in large part to relative lack of sensitivity and inconsistent diagnostic ability of standard electrocardiographic (ECG) and echocardiographic (transthoracic echocardiography [TTE]) parameters (4–6).

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ABBREVIATIONS AND ACRONYMS

CA = cardiac amyloidosis

CMR = cardiac magnetic resonance

DHE-CMR = delayed hyper-enhancement cardiac magnetic resonance

ECG = electrocardiogram

EMB = endomyocardial biopsy

LV = left ventricle

LVEF = left ventricular ejection fraction

MPI = myocardial performance index

NYHA = New York Heart Association

SSDI = Social Security Death Index

TTE = transthoracic echocardiography

Although multiple attempts using noninvasive imaging parameters, including TTE and ECG, have been made with regard to prognostication, the data are variable. In patients with systemic amyloidosis and suspected cardiac involvement, previous studies have demonstrated that increased myocardial echogenicity (7), mitral deceleration time <150 ms (8), right ventricular dilation (9), left ventricular ejection fraction (LVEF) <45% (10), left ventricular wall thickness >15 mm (1), and myocardial performance index (MPI) (11) are associated with worse outcomes. However, prognostic importance of MPI was refuted in a follow-up study (7). Low ECG voltage has also been reported to be predictive of decreased survival (10), as have elevated biomarkers such as B-type natriuretic peptide and troponin (12).

With the recent emergence of delayed hyper-enhancement cardiac magnetic resonance (DHE-CMR), it is possible to precisely detect areas of myocardial fibrosis/scarring in-vivo with a high degree of precision. Furthermore, preliminary work has demonstrated that CMR is very sensitive in diagnosis of amyloid deposition within the heart (3,13). However, its diagnostic accuracy has not been compared with other traditional noninvasive parameters, nor has its prognostic utility been previously described. The aims of this study were: 1) to compare the diagnostic accuracy of DHE-CMR with traditional noninvasive imaging parameters in patients with suspected CA that underwent EMB; and 2) to assess the prognostic value of DHE-CMR in patients with suspected CA who underwent tissue biopsy, including either EMB or extracardiac biopsy.

METHODS

Patient population. This was an observational study of 84 consecutive patients with suspected restrictive or infiltrative cardiomyopathy or patients with known systemic amyloidosis and suspected to have cardiac involvement referred for biopsy between January 2005 and August 2008. Of these, 37 were excluded because they did not have DHE-CMR as part of their initial evaluation. Also, patients with standard contraindications to CMR (pacemakers, defibrillators, aneurysmal clips) were not imaged. Beginning in June 2007, following the Food and Drug Administration's advisory regarding the use of gadolinium in patients with advanced renal failure, we did not perform DHE-CMR examination in such patients. Hence, the final study population consisted of 47 patients undergoing multimodality imaging evaluation.

Each patient underwent a comprehensive assessment, typically within a 24- to 48-h period, including clinical evaluation, ECG, Doppler TTE, DHE-CMR, and biopsy (38 EMB and 9 extracardiac) (Figs. 1 to 3). New York Heart Association (NYHA) functional class was ascertained at the time of their clinical evaluation with a cardiologist. Presence or absence of coronary artery disease was ascertained on coronary angiography (if performed) within 1 month of CMR. Significant disease was defined as ≥70% stenosis in at least 1 epicardial coronary vessel. The electronic medical record was reviewed for clinical and histopathologic data. Glomerular filtration rate (GFR) was calculated in each individual using the Modified Diet in Renal Diseases formula: GFR (ml/min/1.73 m^2) = 186 × (serum creatinine) 1.154 × (age)$^{-0.203}$ × (0.742, if female) × (1.210, if African American) (14). All-cause mortality was determined using Social Security Death Index (SSDI) inquiry. This retrospective study was approved by the institutional review board with waiver of informed consent.

ECG. Standard 12-lead ECG measurements were made. Based on previously described criteria by Carroll et al. (6), low voltage was defined as the sum of the S-wave in lead V_1 + R-wave in lead V_5 or V_6 <15 mm. We also classified patients based on other voltage criteria that have been described by Rahman et al. (4) (<5 mm in the limb leads and <10 mm in the precordial leads).

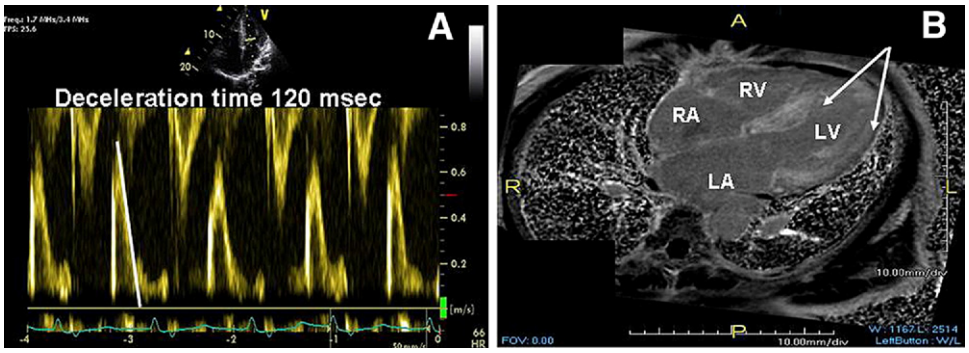

Figure 1. Positive Echocardiography and CMR in a Patient With CA

A 64-year-old man who underwent Doppler echocardiography and cardiac magnetic resonance (CMR), followed by endomyocardial biopsy (EMB) that demonstrated cardiac amyloidosis (CA) is shown. Electrocardiogram revealed low voltage. Further staining revealed this to be transthyretin-type. Patient was alive at 1 year. **(A)** Transmitral Doppler pattern showing a deceleration time of 120 ms. **(B)** 4-chamber delayed hyper-enhancement (DHE)-CMR image demonstrating the characteristic diffuse, delayed hyper-enhancement pattern throughout the left ventricle (LV) **(arrow)**. A = anterior; L = left; LA = left atrium; P = posterior; R = right; RA = right atrium; RV = right ventricle.

Echocardiography. Clinical TTE was performed using commercially available HDI 5000 (Philips Medical Systems, N.A., Bothell, Washington) and Acuson Sequoia (Siemens Medical Solutions USA Inc., Malvern, Pennsylvania) machines. Increased myocardial "speckling" was a subjective visual assessment noted only if reported by the original interpreters. End-diastolic interventricular septal and posterior wall thickness was measured in a standard fashion (15). Left atrial size and left ventricular (LV) end-diastolic and -systolic volume were also measured, using Simpson's biplane method. LVEF was measured using Simpson's biplane method (15). The mitral inflow velocity pattern was recorded from the apical 4-chamber view with pulsed-wave Doppler sample volume positioned at the tips of mitral leaflets during diastole. Deceleration time, measured as the distance from peak of the E-wave in the mitral inflow view to the baseline and peak velocities of E and A waves were measured (in patients in sinus rhythm). Tissue Doppler imaging, including mitral annulus septal E′ velocity, was measured. Grades of diastology were assigned by an experienced echocardiographer (M.Y.D.) without knowledge of DHE-CMR results based upon multiple standard criteria, including mitral inflow Doppler pattern, pulmonary venous inflow Doppler pattern, tissue Doppler data, left atrial size, and LVEF. All diastolic data were acquired over 10 consecutive beats using sweep

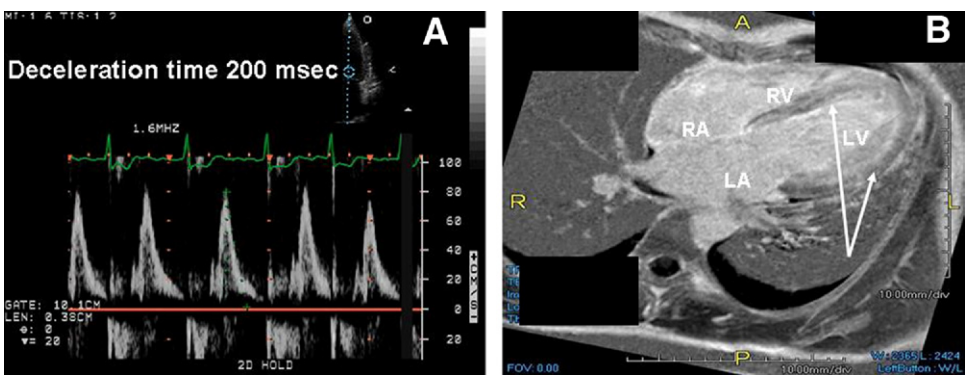

Figure 2. Negative Echocardiography and Positive CMR in a Patient With CA

A 56-year-old man who underwent Doppler echocardiography and CMR, followed by EMB that demonstrated CA is shown. Electrocardiogram did not reveal low voltage. Further staining revealed this to be amyloid light-type. The patient was dead within 1 year. **(A)** Transmitral Doppler pattern showing a deceleration time of 200 ms. **(B)** DHE-CMR image in a 4-chamber orientation demonstrating the characteristic diffuse, delayed hyper-enhancement pattern throughout the LV **(arrow)**. Abbreviations as in Figure 1.

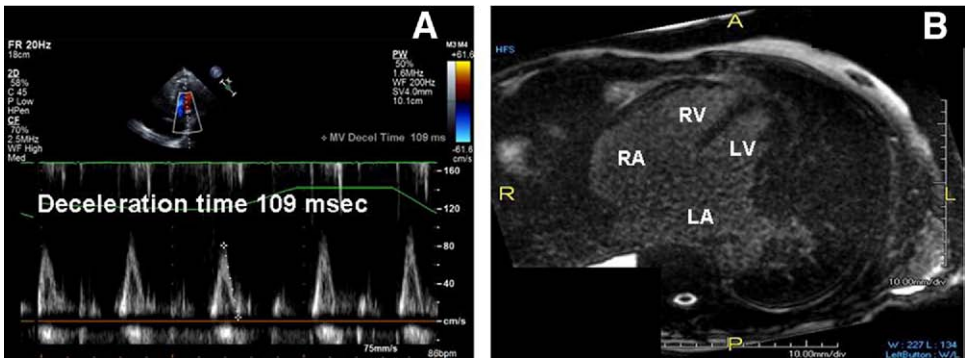

Figure 3. Positive Echocardiography and Negative CMR in a Patient Without CA

A 78-year-old man who underwent Doppler echocardiography and CMR, followed by EMB, which demonstrated myocyte hypertrophy and fibrosis, is shown. There was no evidence of amyloidosis. Electrocardiogram revealed low voltage. Patient was alive at 1 year. **(A)** Transmitral Doppler pattern showing a deceleration time of 109 ms. **(B)** DHE-CMR image in a 4-chamber orientation without the characteristic diffuse, delayed hyper-enhancement pattern. Abbreviations as in Figure 1.

speeds of 50 and 100 cm/s in a standard fashion. MPI was calculated using a previously described technique (11,16). All Doppler measurements were made over 3 cardiac cycles and averaged. In patients with atrial fibrillation, the data were averaged over 5 cardiac cycles. The Doppler measurements were made by an independent observer (B.A.A.) without knowledge of patient outcomes.

CMR. The CMR examinations were performed on 1.5-T MR Scanners (Siemens Medical Solutions, Erlangen, Germany), either Sonata (40 mT/m maximum gradient strength, 200-T/m/s maximum slew rate) or Avanto (45 mT/m maximum gradient strength, 200-T/m/s maximum slew rate), using ECG gating. Following scout imaging, balanced steady-state free precession images were acquired: echo time = 1.6 ms, repetition time = 3.3 ms, flip angle = 70°, and slice thickness = 6 mm (long-axis images), or 8 to 10 mm (contiguous short-axis images encompassing the entire LV, from apex to base). For patients able to suspend respiration, breath-hold duration was 10 to 15 s; otherwise, images were acquired using 3 signal averages. Subsequently, DHE-CMR images were obtained in the same long- and short-axis orientations as the above-described cine images approximately 10 to 20 min after injection of 0.2 mmol/kg of gadolinium dimenglumine (Magnevist, Berlex Imaging, Wayne, New Jersey) using a phase-sensitive inversion recovery spoiled gradient echo sequence (17): echo time = 4 ms, repetition time = 8 ms, inversion time = 260 ms, flip angle = 30°, bandwidth = 140 Hz/pixel, and 23 k-space lines acquired every other RR-interval.

LVEF was calculated using clinically available software (Argus, Siemens Medical Solutions). Characteristic appearance for amyloidosis was defined as presence of DHE in a circumferential pattern involving the entire subendocardium, extending in various degrees into the surrounding myocardium (Figs. 1 and 2B). For this study, other patterns, including focal areas of DHE at right ventricular insertion points and patchy DHE in hypertrophied LV (both suggestive of hypertrophic cardiomyopathy) or subepicardial DHE (suggestive of myocarditis) were deemed negative for CA. Although the referring physicians were aware of DHE-CMR results at the time of decision making, the findings were confirmed in a blinded manner by the corresponding author.

Endomyocardial biopsy. Right ventricular biopsy (3 to 5 samples of myocardium) was performed under fluoroscopic guidance, after obtaining informed consent, via the right internal jugular vein. Biopsies were immediately fixed in buffered formaldehyde solution (4%) and embedded in paraffin within 1 day after fixation. These sections were analyzed with standard hematoxylin–eosin and Congo red staining for visualization of amyloid deposition. Electron microscopy was performed in those with negative Congo red staining. Presence of amyloid light chain (AL)-type was ascertained either by staining of the myocardium for antibodies to light chains or by a positive bone marrow biopsy ± positive urine/serum protein immunoelectrophoresis. Similarly, determination of those with positive biopsies for amyloidosis who had familial type amyloidosis was determined either with staining of

Table 1. Baseline Data of the Study Population

	Total Population (N = 47)	Biopsy-Negative (n = 22)	Biopsy-Positive (n = 25)	p Value
Age (yrs)	62 [51 to 75]	58 [49 to 69]	66 [57 to 79]	0.04
Male sex	33 (70%)	15 (68%)	18 (70%)	0.8
New York Heart Association functional class >II	26 (55%)	12 (55%)	14 (56%)	0.9
Brain natriuretic peptide level (pg/ml)	563 [162 to 572]	517 [99 to 608]	607 [232 to 555]	0.4
Diuretic use	31 (66%)	11 (50%)	20 (80%)	0.03
Beta-blocker use	27 (57%)	13 (59%)	14 (56%)	0.8
Glomerular filtration rate (ml/min/1.73 m^2)	75 [47 to 90]	71 [48 to 95]	75 [46 to 89]	0.5
Low voltage on electrocardiogram (Carroll's criteria)	27 (59%)	12 (55%)	15 (60%)	0.6
Low voltage on electrocardiogram (Rahman's criteria)	4 (9%)	1 (5%)	3 (13%)	0.3
Atrial fibrillation	8 (17%)	4 (18%)	4 (16%)	0.8
Speckled appearance	4 (9%)	0	4 (16%)	0.04
Left ventricular ejection fraction (%)	55 [47 to 60]	48 [45 to 55]	52 [46 to 60]	0.6
Interventricular septal thickness (cm)	1.5 [1.1 to 1.9]	1.3 [1.1 to 1.6]	1.7 [1.4 to 2]	0.004
Posterior wall thickness (cm)	1.4 [1.1 to 1.6]	1.2 [0.9 to 1.4]	1.6 [1.2 to 1.9]	0.001
Left ventricular mass (g)	271 [195 to 351]	232 [171 to 312]	306 [210 to 363]	0.03
Dilated left atrium (>20 cm^2)	30 (64%)	15 (68%)	15 (60%)	0.7
Deceleration time (ms)	172 [137 to 209]	168 [120 to 205]	176 [147 to 212]	0.6
Deceleration time ≤150 ms	14 (30%)	6 (27%)	8 (32%)	0.5
E/E′ ratio >15	18 (38%)	8 (36%)	10 (40%)	0.7
Pseudonormal or restrictive diastology	22 (47%)	9 (41%)	13 (50%)	0.5
Myocardial performance index	0.51 [0.29 to 0.71]	0.46 [0.22 to 0.74]	0.54 [0.40 to 0.70]	0.2
Characteristic DHE on CMR	22 (47%)	3 (14%)	19 (76%)	<0.0001

Values are n [95% confidence interval] or n (%).
CMR = cardiac magnetic resonance; DHE = delayed hyper-enhancement.

the myocardium for antibodies to transthyretin or by positive genetic testing for mutant transthyretin or apolipoprotein A1. Further histopathologic assessment to evaluate for hypertrophic cardiomyopathy, Fabry's disease, and inflammatory myocarditis was performed as deemed necessary by the pathologist. In the 9 patients that did not undergo EMB, 3 had kidney biopsies, 2 had fat pad biopsies, 1 rectal, 1 liver, 1 muscle, and 1 stomach biopsy.

Statistical analysis. Discrete variables are presented as counts and percentages. Continuous data are expressed as median and interquartile range. Continuous nonparametric variables were compared using the Mann-Whitney test. Categorical variables were analyzed using chi-square test or Fisher exact test. Logistic regression analysis was performed to test the association between dependent and multiple independent variables. For multivariable analysis, only those variables with a p value <0.05 on univariable analysis were entered into the model. Survival analysis was performed using Cox proportional hazards analysis. The potential predictors tested on univariable analysis

Table 2. Diagnostic Accuracy of Various Noninvasive Imaging Criteria in Patients With Suspected CA That Underwent EMB (n = 38)

	Low Voltage by Carroll's ECG Criteria	Abnormal DT (≤150 ms) on Doppler Echocardiography	Combined ECG-Echocardiography Criteria	Presence of DHE-CMR
True positive	13	6	15	15
True negative	10	13	6	19
False positive	11	8	15	2
False negative	4	11	2	2
Sensitivity	76%	35%	88%	88%
Specificity	48%	62%	29%	90%
Positive predictive value	54%	43%	50%	88%
Negative predictive value	71%	54%	75%	90%

CA = cardiac amyloidosis; DT = deceleration time; ECG = electrocardiogram; EMB = endomyocardial biopsy; other abbreviations as in Table 1.

Table 3. Characteristics of Patients With False Negative and False Positive DHE-CMR Results

False negative: DHE-CMR negative, EMB positive	
Patient #1, 77-year-old man	History of coronary artery bypass grafting, chronic renal failure. Patient alive at 1 year. Transmural DHE in apex, distal anteroseptal, and distal inferior walls, interpreted as an ischemic scar.
Patient #2, 75-year-old man	History of coronary artery bypass grafting, aortic valve replacement, and left ventricular outflow tract obstruction. Patient alive at 1 year. DHE of the basal anteroseptal, basal inferior, basal lateral, basal inferolateral, and basal inferoseptal in a patient with an asymmetrically thickened septum, interpreted as hypertrophic cardiomyopathy.
False positive: DHE-CMR positive, EMB negative	
Patient #1, 48-year-old man	History of chronic kidney disease, hypertensive heart disease. EMB negative. Patient alive at 1 year. Diffuse subendocardial pattern of DHE.
Patient #2, 68-year-old man	History of coronary artery disease and myocardial infarction. EMB negative. Patient alive at 1 year. Diffuse subendocardial pattern of DHE.

Abbreviations as in Tables 1 and 2.

(clinical, ECG, and TTE) have been demonstrated to be associated with outcomes in previous studies. In addition, presence of characteristic DHE on CMR as a potential predictor of survival was also tested. Univariable chi-square statistics are reported for each variable. To be potentially considered for multivariable analysis, a p value threshold of <0.05 was specified. Cumulative mortality rates of patients stratified into different subgroups (with or without DHE on CMR) as a function over time were also obtained by the Kaplan-Meier method. Data assembly and basic statistical comparisons were performed with JMP Software version 6.0.2 (SAS Institute Inc., Cary, North Carolina). Advanced statistical analysis was performed using Statistica version 6.1 (Statsoft, Tulsa, Oklahoma). A p value <0.05 was considered significant.

Table 4. Logistic Regression Analysis Testing the Diagnostic Ability of Various Noninvasive Imaging Parameters in Patients With Suspected CA Who Underwent EMB

	Univariable		Multivariable	
Noninvasive Imaging Parameters	Wald Chi-Square Statistic	p Value	Wald Chi-Square Statistic	p Value
Carroll's criteria on ECG	2.23	0.1		
Rahman's criteria on ECG	0.60	0.4		
Dilated left atrium (>20 cm^2)	0.98	0.3		
Interventricular septal thickness	8.6	0.003	1.7	0.19
Left ventricular ejection fraction	0.04	0.8		
Speckled appearance on surface echocardiography	0.0	0.9		
Pseudonormal or restrictive physiology on Doppler echocardiography	2.1	0.2		
E/A ratio	1.9	0.2		
E/E′ ratio ≥15	1.06	0.3		
Abnormal deceleration time (≤150 ms)	0.002	0.9		
Myocardial performance index	1.7	0.2		
Positive DHE-CMR	16	<0.001	9.6	0.002

Abbreviations as in Table 2.

RESULTS

The baseline clinical characteristics are shown in Table 1. The vast majority of the patients were symptomatic at baseline, with 27% in NYHA functional class II, 47% in NYHA functional class III, and 8% in NYHA functional class IV. Five patients (3 in the EMB group) in the population that underwent DHE-CMR had a GFR <30 ml/min/1.73 m^2; and all were performed prior to 2007. In the study group, 27 patients had a prior coronary angiogram; of which 6 had significant coronary artery disease (4 had prior revascularization).

Of the 47 patients, 25 (53%) patients had biopsy-proven amyloidosis. Of these 25 biopsies, 17 were EMB and 8 were extracardiac biopsies. Of the 21 patients with a negative biopsy in this cohort, 4 had glycogen-storage disease, 7 had hypertrophic cardiomyopathy, 9 had nonspecific fibrosis (likely related to advanced hypertensive heart disease) and 1 had myocarditis on histopathologic examination. One patient had a negative fat pad biopsy.

The baseline characteristics of the current study population also were similar to the patients with suspected CA in whom EMB (but not CMR) was performed (n = 37, excluded from final analyses, but shown in the Online Appendix).

Diagnostic accuracy of various noninvasive imaging parameters. The baseline imaging characteristics are demonstrated in Table 1. Biopsy-positive patients had increased septal thickness and cardiac mass compared with biopsy-negative patients. Characteristic DHE-CMR pattern was seen more frequently in biopsy-positive patients compared with biopsy-negative patients. In the entire study population, 22 patients had "typical amyloid pattern" DHE, 12 had no DHE, and 13 had some degree (mostly patchy) DHE. Within the biopsy-positive population (n = 25), 19 patients had the characteristic diffuse pattern, 2 had patchy DHE, and 4 had no DHE on CMR.

Subsequently, we ascertained the diagnostic accuracy of Carroll's ECG criteria, abnormal deceleration time (≤150 ms) and DHE-CMR in the subset of patients that underwent EMB (n = 38). Patients with extracardiac biopsies (n = 8) were excluded from accuracy analysis. The results are demonstrated in Table 2. Similarly, the accuracy of DHE-CMR in the subgroup of patients undergoing EMB with GFR >30 ml/min/1.73 m^2 (n = 35) was as follows: sensitivity 88%, specificity 95%, positive predictive value 93%, and negative predictive value 90%. Table 3 shows the characteristics of patients with a false positive or false negative DHE-CMR, as compared with EMB. Univariable and multivariable logistic regression analysis testing the diagnostic utility of various noninvasive imaging parameters, in patients with suspected CA that underwent EMB, is shown in Table 4. The presence of a characteristic pattern of DHE on CMR was the strongest noninvasive predictor of EMB-positive results (Table 4).

Survival analysis. Survival analysis was performed on the entire study population of 47 patients. At 1 year following biopsy, there were 9 (19%) deaths in the biopsy-positive patients (7 in the DHE-CMR–positive and 2 in the DHE-CMR–negative groups, respectively, p = 0.03). Table 5 shows the predictors of 1-year mortality. Presence of DHE on CMR was the strongest predictor of 1-year mortality. None of the other predictors achieved significance and so were not entered into the multivariable model. Figure 4 shows the Kaplan-Meier survival curve demonstrating significantly worse survival in patients who have the characteristic pattern of DHE on CMR.

Of the 25 patients with biopsy-proven amyloidosis, 15 had primary, AL-type amyloidosis (4 survivors and 11 nonsurvivors), and 9 (8 survivors and 1 nonsurvivor) had transthyretin-type amyloidosis. One patient had positive Congo red staining, but no special stains were performed, as was the routine practice at our institution prior to 2006 unless specifically requested by the clinician, and work-up with serum testing, bone marrow biopsy, and immunoelectrophoresis did not reveal the specific amyloid type. One patient underwent heart transplantation, whereas the remainder underwent standard treatment, including chemotherapy.

DISCUSSION

We examined the potential of DHE-CMR for providing both diagnostic and prognostic information in patients with suspected CA. Presence of DHE on CMR was more accurate in predicting presence of EMB-positive CA as compared with ECG and TTE variables. Additionally, characteristic DHE on CMR in patients with suspected CA

Table 5. Cox Proportional Hazard Analysis of Various Predictors of 1-Year Mortality in the Entire Study Population With Suspected CA Who Underwent DHE-CMR (N = 47)

Variable	Wald Chi-Square Statistic	p Value
Age	2.9	0.09
Gender	0.15	0.7
Beta-blocker use	2.61	0.11
Diuretic use	0.005	0.9
Brain natriuretic peptide level	0.05	0.8
New York Heart Association functional class	3.3	0.07
Glomerular filtration rate	1.96	0.15
Low voltage on electrocardiogram (Carroll's criteria)	0.67	0.4
Low voltage on electrocardiogram (Rahman's criteria)	0.82	0.4
Left atrial size >20 cm^2	0.76	0.4
Left ventricular ejection fraction	2.21	0.2
Interventricular septal thickness	1.7	0.2
Cardiac mass	0.88	0.4
E/E′ >15 on Doppler echocardiography	0.83	0.3
Deceleration time on Doppler echocardiography ≤150 ms	2.5	0.1
Myocardial performance index	1.10	0.3
Pseudonormal or restrictive diastology	0.004	0.9
DHE-CMR	4.91	0.03

Abbreviations as in Table 1.

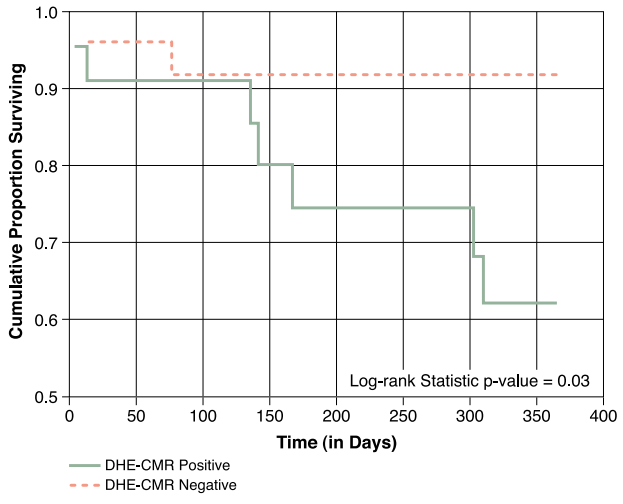

Figure 4. Kaplan-Meier Survival Analysis Based on Presence of Delayed-Hyper-Enhancement

Cumulative mortality rates of the entire study population (N = 47), stratified into different subgroups, with or without DHE-CMR, were obtained by the Kaplan-Meier method. It demonstrates that patients with characteristic DHE on CMR had significantly worse 1-year survival compared with those without. Abbreviations as in Figure 1.

better predicted 1-year mortality as compared with ECG and TTE parameters. Because all but 1 patient (who underwent cardiac transplantation) had standard medical therapy, difference in treatment did not affect prognosis.

Although the presence of a characteristic DHE pattern on CMR is highly accurate in the diagnosis of CA, there are some potential pitfalls, as follows: patchy subendocardial DHE early in the disease process can lead to a "false negative" DHE-CMR interpretation, or EMB may miss a patchy area (due to sampling error), resulting in the DHE-CMR interpretation being deemed "false positive." Additional problems can arise when there are other comorbid conditions, such as ischemic heart disease, that may affect DHE patterns on CMR. Indeed, for the current study, we deliberately kept the criteria for "positive" DHE-CMR very stringent and classified patchy DHE-CMR patterns as "negative" for the diagnosis of CA.

The diagnostic accuracy in this study compares favorably with previous reports, including a recent study by Vogelsberg et al. (13). However, that study did not compare the accuracy of DHE-CMR with other standard noninvasive measurements. Maceira et al. (18) examined the accuracy of DHE-CMR complemented by evaluation of subendocardial T1 mapping. They found this parameter to be significantly different in those with CA compared with hypertensive controls and that it correlated with increased wall thickness and LV mass (18). A follow-up study from their group found that abnormal T1 mapping was predictive of mortality (19). They did not find an association between the presence of DHE on CMR and mortality. This may have been due to difference in patient profile, as the diagnosis of CA in their cohort was made almost exclusively with extracardiac biopsy, as well as to the binary interpretation of DHE-CMR in our investigation. The difference in timing of DHE acquisitions also might have potentially played a role. An ideal study would test the prognostic ability of both DHE-CMR and T1 kinetics in a larger amyloid cohort undergoing EMB.

A variety of TTE parameters have been associated with prognosis in CA in previous reports (1,7–11). In those investigations that looked at a population with systemic amyloidosis using extracardiac biopsy, the ECG and TTE variables that were associated with adverse prognosis may have acted as surrogate markers for cardiac involvement, which is known to impart poor prognosis in systemic amyloidosis. Additionally, ours is intentionally a highly selected cohort of patients who underwent both DHE-CMR and biopsy as part of their diagnostic evaluation, and there may be a referral bias. Of note, decision making regarding sending patients for EMB was not based upon presence or absence of DHE on CMR.

Because of its accuracy in detecting even very small areas of fibrosis/amyloid deposition, DHE-CMR holds the promise to facilitate early diagnosis of CA. However, the current study was not designed to answer that question. A larger cohort of EMB-positive patients with quantitative DHE-CMR assessment will be needed to reliably identify patterns consistent with early cardiac amyloidosis. The potential next step is to establish clinical care pathways where DHE-CMR can be appropriately incorporated in evaluation and management of amyloidosis. Due to the small and exploratory nature of this analysis, it would not be appropriate to recommend that DHE-CMR supplant other noninvasive modalities such as ECG and echocardiography, nor is it a replacement at this point for a definitive tissue diagnosis. Instead, it should be seen as a valuable complementary technique that can provide incremental diagnostic and prognostic information.

The obvious next step would include determination of whether degree of DHE-CMR is associated with outcomes. Also, in those patients in whom results are somewhat equivocal (i.e., "patchy" subendocardial DHE), the CMR results may be used to guide EMB in order to maximize the diagnostic yield. Indeed, DHE-CMR has been utilized in some small studies as a guide to EMB in order to increase the diagnostic yield (12,20). Finally, it remains to be seen whether CMR could play a role in further discriminating between different types of amyloid (i.e., AL vs. transthyretin type).

Limitations and future outlook. The observational, single-center nature of the study limits the generalizability of the findings and raises the possibility of a selection bias. The absolute number of patients examined is not large. This leads to lack of stable results, at least from a statistical standpoint. In order to conclusively ascertain comparative and additive prognostic utility of different variables (clinical, echocardiographic, and CMR), we would require a much larger sample size with a much longer follow-up, perhaps in a multicenter format. Also, we only performed percutaneous right (as opposed to left) ventricular biopsy, as is the standard in most U.S. hospitals. This could have resulted in potential sampling errors. Although specific cardiovascular events, including cardiovascular mortality, were not recorded during follow-up and may be considered a limitation, it has been demon-

strated previously that all-cause mortality is more objective and unbiased than "cardiac mortality" (21,22).

The current data are certainly hypothesis generating, and follow-up with a larger population is needed to conclusively establish the incremental prognostic value of DHE-CMR. With the emerging knowledge of nephrogenic systemic fibrosis, patient selection is further restricted, particularly in patients with tenuous renal function (e.g., amyloid patients with renal involvement) (23). The patients in this cohort who underwent CMR with a GFR <30 ml/min/1.73 m^2 were evaluated prior to 2007 and the more recent concerns over possibility of nephrogenic systemic fibrosis. To the best of our knowledge, none have developed nephrogenic systemic fibrosis.

CONCLUSIONS

In our evaluation of noninvasive parameters for both diagnosis and risk stratification in patients with biopsy-positive CA, we found that a characteristic DHE-CMR pattern was both highly accurate for diagnosis and significantly associated with 1-year mortality. Further investigation testing whether quantitative assessment of the disease burden as assessed by DHE-CMR adds incremental prognostic value is warranted.

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Key Words: amyloidosis ■ cardiac magnetic resonance ■ echocardiography ■ biopsy ■ mortality.

▶APPENDIX

For a supplementary table, please see the online version of this article.