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Role of Cardiac Magnetic Resonance Imaging in the Detection of Cardiac Amyloidosis

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OBJECTIVES Our aim was to evaluate the role and mechanism of late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) in identifying cardiac amyloidosis (CA) and to investigate associations between LGE and clinical, morphologic, functional, and biochemical features.

BACKGROUND CA can be challenging to diagnose by echocardiography. Recent studies have demonstrated an emerging role for LGE-CMR.

METHODS LGE-CMR was performed in 120 patients with amyloidosis. Cardiac histology was available in 35 patients. The remaining 85 patients were divided into those with and without echocardiographic evidence of CA.

RESULTS Of the 35 patients with histologically verified CA, abnormal LGE was present in 34 (97%) patients and increased echocardiographic left ventricular wall thickness in 32 (91%) patients. Global transmural or subendocardial LGE (83%) was most common and was associated with greater interstitial amyloid deposition ($p = 0.03$). Suboptimal myocardial nulling (8%) and patchy focal LGE (6%) were also observed. LGE distribution matched the deposition pattern of interstitial amyloid. Among patients without cardiac histology, LGE was present in 86% of those with evidence of CA by echocardiography and in 47% of those without evidence of CA by echocardiography. In patients without echocardiographic evidence of CA, the presence of LGE was associated with worse clinical, electrocardiographic (ECG), and cardiac biomarker profiles. In all patients, LGE presence and pattern was associated with New York Heart Association functional class, ECG voltage, left ventricular mass index, right ventricular wall thickness, troponin-T, and B-type natriuretic peptide levels.

CONCLUSIONS LGE is common in CA and detects interstitial expansion from amyloid deposition. Global transmural or subendocardial LGE is most common, but suboptimal myocardial nulling and focal patchy LGE are also observed. LGE-CMR may detect early cardiac abnormalities in patients with amyloidosis with normal left ventricular thickness. The presence and pattern of LGE is strongly associated with clinical, morphologic, functional, and biochemical markers of prognosis. (J Am Coll Cardiol Img 2010;3:155–64) © 2010 by the American College of Cardiology Foundation

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Cardiac amyloidosis (CA) is a manifestation of a diverse group of diseases characterized by the extracellular deposition of insoluble fibrillary amyloid proteins (1,2). The most common form is systemic amyloidosis derived from immunoglobulin light chains (AL amyloidosis). Cardiac involvement is an important determinant of treatment options and prognosis (3–5). Senile cardiac amyloidosis (SCA) is derived from the deposition of wild-type transthyretin. Familial amyloidosis is derived from the deposition of a mutant transthyretin protein, and cardiac involvement is variable.

See page 165

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide
CA = cardiac amyloidosis
CMR = cardiac magnetic resonance
EF = ejection fraction
FOV = field of view
Gd = gadolinium
LGE = late gadolinium enhancement
LV = left ventricle/ventricular
LVMI = left ventricular mass index
NYHA = New York Heart Association
PF = patchy focal
RV = right ventricle/ventricular
SCA = senile cardiac amyloidosis
SN = suboptimal nulling
TE = echo time
TI = inversion time
TR = repetition time

CA is characterized by interstitial amyloid infiltration leading to thickened cardiac walls and diastolic dysfunction eventually resulting in restrictive cardiomyopathy (6,7). A definitive diagnosis is made by endomyocardial biopsy, but this is invasive and undesirable to perform routinely (8). Echocardiography is the noninvasive test of choice, but a diagnosis can be challenging in the absence of systemic disease or when other causes for left ventricular (LV) hypertrophy exist (9–12). Recently, gadolinium (Gd)-enhanced cardiac magnetic resonance (CMR) has been reported to demonstrate late gadolinium enhancement (LGE) in CA (13–15). These pilot data described findings in relatively small numbers of selected patients with echocardiographic evidence of CA. Pathologic correlation for the mechanism of LGE, thought to be interstitial expansion from amyloid deposition, is restricted to 1 patient. The role of CMR in identifying early cardiac involvement in patients with normal LV thickness by echocardiography has not been defined. The association of LGE with clinical, morphologic, functional, and biochemical markers is also unknown.

We investigated the role of LGE-CMR in identifying CA in a large population of amyloidosis patients with and without echocardiographic evidence of cardiac disease with pathologic correlation when available and association of LGE with clinical, morphologic, functional, and biochemical features.

METHODS

Study population. Patients with documented amyloidosis referred for CMR at our institution between January 2006 and December 2007 were screened for inclusion. CMR was performed at the discretion of the attending physician. Inclusion criteria were histologically proven amyloidosis and, in the case of AL amyloidosis, confirmatory evidence of monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow. Exclusion criteria were prior myocardial infarction or myocarditis, prior peripheral blood stem cell transplantation, or prior heart transplantation. Data were entered into a centralized database prospectively and analyzed retrospectively. Of 151 screened patients, 120 patients were included. Reasons for exclusion were: localized organ amyloidosis without monoclonal protein in 11, contraindication to Gd administration in 10, stem cell transplantation in 6, prior myocardial infarction in 3, and prior cardiac transplant in 1 patient.

Cardiac involvement was defined as the mean value of LV thickness (average of ventricular septum and inferolateral walls) >12 mm (16). Patients were divided into 3 groups: those with positive cardiac histology for CA (n = 35); those without cardiac histology but with echocardiographic evidence of CA (n = 49); and those without cardiac histology or echocardiographic evidence of CA (n = 36). The study was approved by the institutional review board at our institution.

Endomyocardial biopsy or cardiac autopsy. Cardiac histology was available in 35 patients. Endomyocardial biopsy was performed in 33 patients and consisted of 3 to 5 specimens from the right ventricle (RV). LV tissue was available in 5 patients (4 autopsy, 1 explanted heart), and histologic sections were obtained from anterior, septal, inferior, and lateral segments at the mid-LV level. Histologic sections were examined by standard hematoxylin and eosin, sulfated alcian blue, and Congo red stains. The location (interstitial or vascular) of amyloid deposits was determined. The extent of interstitial amyloid involvement was graded semiquantitatively as trace (<5%), mild (5% to 25%), moderate (25% to 50%), or severe (>50%), which is a minor modification of a previously described method (8). Vascular involvement was classified as mild (<33%), moderate (33% to 67%), or severe (>67% or obstructive) corresponding to vascular circumference. Immunohistochemical stains using antibodies directed against serum amyloid P component, transthyretin, kappa and lambda light chains, beta$_2$-microglobulin, and serum amyloid A were performed. For transthyretin amyloid, DNA sequencing was performed.

Echocardiograms and laboratory tests. Echocardiograms were performed in all patients. Mean LV thickness >12 mm (average of end-diastolic septal and inferolateral walls in the parasternal long-axis

view) represented evidence of CA in patients, all of whom had a tissue diagnosis of amyloidosis (16). Standard 12-lead electrocardiograms (ECGs) were obtained and analyzed for standard characteristics and maximal precordial and limb lead voltages. Cardiac troponin-T and B-type natriuretic peptide (BNP) measured within 2 weeks of CMR were documented.

CMR protocol. ECG-gated CMR was performed with a 1.5-T system (Twin speed EXCITE, GE Healthcare, Waukesha, Wisconsin in 113 patients; and Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany in 7 patients). After initial scout images, multiple long-axis and short-axis cine steady state free precession images were obtained from the atrioventricular ring to the apex. The sequence parameters for the GE scanner were: echo time (TE) 1.7 ms, repetition time (TR) 3.4 ms, flip angle 45°, matrix 256 × 192, field of view (FOV) 320 to 440 mm with phase FOV 0.75 to 1.0, and 8 mm slice thickness with 1 mm interslice gap. The Siemens scanner sequence parameters were: TE 1.6, TR 3.2, flip angle 60°, matrix 192 × 192, FOV 320 to 440 mm, phase FOV 0.75 to 1.0, and 8 mm slice thickness with 1 mm interslice gap. LGE images covering the LV in multiple short-axis and long-axis views were obtained between 7 to 12 min after an intravenous bolus of 0.2 mmol/kg gadodiamide (Omniscan; GE Healthcare, Princeton, New Jersey) with segmented inversion recovery fast gradient echo sequences (TE 1.6 ms, TR 3.7 ms, flip angle 20°, matrix 256 × 160, FOV 320 mm). In CA, it is often difficult to determine the optimal inversion time (TI) to null myocardium. Selection of optimal TI for LGE images was accomplished using a multi-TI cine fast gradient echo sequence, which generates 40 images in a single slice location with increasing TIs. Multiple sets of images were obtained to optimize LGE images.

CMR analysis. Ventricular volumes, mass, regional thickness, and ejection fraction (EF) were measured by tracing epicardial and endocardial borders manually with commercial software (MASS Analysis 6+; Medis, Leiden, the Netherlands). Papillary muscles were excluded from LV mass. Mean of septal and inferolateral LV wall thickness >12 mm represented increased LV thickness based on established echocardiographic criteria (16). LGE images were reviewed by consensus by 2 readers (I.S.S. and P.A.A.) blinded to clinical history and the remainder of the CMR. To assess interobserver variability, an additional investigator (D.F.) independently interpreted LGE images using a test set of 20 patients.

Statistical analysis. Data analysis was performed using commercial software (JMP version 6, SAS, Inc., Cary, North Carolina; and STATA version 10, MP version, Statacorp Ltd., College Station, Texas). Data are presented as mean ± SD for continuous values and as counts/percentages for categorical values. A 2-tailed Student *t* test or 1-way analysis of variance where appropriate, was used to compare continuous variables. The chi-square or Fisher exact test was used for categorical variables. BNP and troponin-T were log-transformed to accomplish the assumption of normal distribution. Comparisons of trend were performed using Cochrane-Armitage and chi-square for trend tests as appropriate. A probability value of <0.05 was considered statistically significant. Bonferroni correction was used for multiple comparisons (corrected $\alpha = \alpha/\kappa$ where κ is the number of comparisons). A weighted kappa statistic was computed to assess interobserver variability and was defined as follows: very good = 0.81 to 1, good = 0.61 to 0.80, moderate = 0.41 to 0.60, fair = 0.21 to 0.40, and poor ≤0.20.

RESULTS

All patients. AL amyloid was present in 100, SCA in 9, and familial amyloid in 11 patients. Clinical, morphologic, and functional findings are summarized in Table 1.

Cardiac histology group. Cardiac histology was available in 35 patients, all of whom had confirmation of CA. AL amyloid was present in 22 (63%), familial amyloid in 5 (14%), and senile amyloid in 8 (23%) patients. Increased echocardiographic LV wall thickness was present in 32 (91%) patients. See Table 1 for details.

Compared with those without cardiac histology, the histology subgroup had a higher proportion of senile/familial amyloid (37% vs. 8%, $p < 0.0001$), greater LV (16.6 ± 2.7 vs. 13.5 ± 3.1 mm, $p < 0.0001$) and RV (7.2 ± 1.4 vs. 5.8 ± 2 mm, $p < 0.0001$) thickness, greater left ventricular mass index (LVMI) (100 ± 24 vs. 71 ± 28 g/m^2, $p < 0.0001$), greater troponin-T elevation (84% vs. 52%, $p = 0.001$) and BNP levels (829 ± 791 vs. 449 ± 576, $p = 0.005$) and worse New York Heart Association (NYHA) functional class (class III to IV in 46% vs. 20%, $p = 0.004$).

LGE was present in 34 (97%) patients. Global LGE was present in 29 (83%) patients: global transmural pattern (homogenous or heterogeneous) seen in 21 (60%) and global subendocardial pattern in 8 (23%) patients. Patchy focal (PF) LGE was present in 2 (6%) patients. This was in the basal inferolateral LV segment in 1 patient, and in the basal septal and inferior LV segment in the other. In 3 (8%) patients, there was

Table 1. Clinical and CMR Features in All Patients and in Cardiac Histology Group

	All Patients (n = 120)	AL (n = 100)	Familial (n = 11)	Senile (n = 9)	p Value	Cardiac Histology (n = 35)	AL (n = 22)	Familial (n = 5)	Senile (n = 8)	p Value
Age (yrs)	60 ± 11	58 ± 10	61 ± 15	72 ± 5	0.0006*†	61 ± 11	56 ± 9	62 ± 11	72 ± 6	0.0007*
Sex (M:F)	86:34:00	67:33:00	10:10	9:00	0.036	28:7:00	15:07	8:00	5:00	0.12
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.3	2.2 ± 0.2	0.10	2 ± 0.2	1.9 ± 0.2	2 ± 0.2	2.1 ± 0.1	0.047*
NYHA functional class III to IV	33 (28%)	26 (26%)	1 (9%)	6 (67%)	0.012	16 (46%)	10 (45%)	0 (0%)	6 (75%)	0.04
Echo LV wall >12 mm (%)	81 (68%)	63 (63%)	9 (82%)	9 (100%)	0.03	32 (91%)	20 (91%)	4 (80%)	8 (100%)	0.48
CMR parameters										
LV thickness (mm)	14.4 ± 3	13.9 ± 3	15.9 ± 3.2	18.7 ± 1	<0.0001*	16.6 ± 2.7	15.8 ± 2.5	16.9 ± 2.9	18.6 ± 2	0.04*
RV thickness (mm)	6.2 ± 1.9	6 ± 1.9	6.9 ± 1.8	7.4 ± 1.1	0.046	7.2 ± 1.4	7.2 ± 1.5	7.2 ± 1.9	7.1 ± 0.6	0.98
LVMI (g/m^2)	80 ± 30	75 ± 28	93 ± 31	112 ± 27	0.0004*	100 ± 24	95 ± 20	101 ± 32	112 ± 29	0.26
LVEF (%)	57 ± 11	57 ± 11	58 ± 9	56 ± 7	0.92	53 ± 9	51 ± 8	57 ± 14	58 ± 6	0.09
LVEDV (ml)	128 ± 33	126 ± 32	134 ± 30	151 ± 39	0.07	141 ± 29	136 ± 26	140 ± 15	153 ± 41	0.37
LVESV (ml)	56 ± 22	55 ± 23	56 ± 18	65 ± 16	0.42	65 ± 16	67 ± 15	60 ± 20	64 ± 17	0.65
Pericardial effusion (%)	52	56	27	33	0.113	54	68	40	25	0.11
Pleural effusion (%)	41	45	9	33	0.06	46	59	20	25	0.15
LGE pattern					0.073					0.795
Global	59 (49%)	43 (43%)	7 (64%)	9 (100%)		29 (83%)	17 (77%)	4 (80%)	8 (100%)	
Suboptimal nulling	19 (16%)	18 (18%)	1 (9%)	0		3 (8%)	2 (9%)	1 (20%)	0	
Focal patchy	17 (14%)	15 (15%)	2 (18%)	0		2 (6%)	2 (9%)	0	0	
None	25 (21%)	24 (24%)	1 (9%)	0		1 (3%)	1 (5%)	0	0	
ECG limb lead voltage (mm)	6.9 ± 3.3	6.7 ± 3.4	8.8 ± 2.9	6.2 ± 2.6	0.11	6.2 ± 3	5.6 ± 2.7	9.4 ± 3.6	5.8 ± 2.3	0.028‡
Elevated troponin-T (%)	59	59	63	83	0.602	84	82	100	80	0.81
BNP (pg/ml)	555 ± 662	595 ± 707	229 ± 155	515 ± 307	0.33	829 ± 791	1,053 ± 900	319 ± 172	519 ± 331	0.10

p Value <0.0167 (Bonferroni correction) for *AL versus senile, †senile versus familial, ‡AL versus familial.
AL = systemic amyloidosis of light chains; BNP = B-type natriuretic peptide; CMR = cardiac magnetic resonance; ECG = electrocardiogram; LGE = late gadolinium enhancement; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass index; NYHA = New York Heart Association; RV = right ventricle.

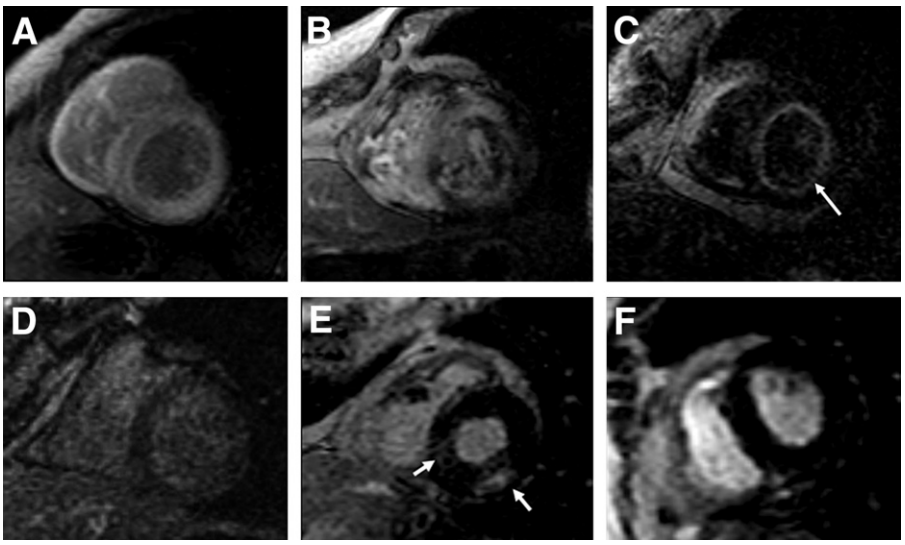

Figure 1. Midventricular Short-Axis LGE-CMR Images in 6 Patients With Systemic Amyloidosis

(A) Global transmural late gadolinium enhancement (LGE) in a homogenous pattern in the left ventricle and right ventricle. The blood pool has a characteristic dark appearance commonly seen in cardiac amyloidosis. **(B)** Global transmural LGE in a heterogeneous pattern in the left ventricle and right ventricle. **(C)** Global subendocardial LGE **(arrow)** with dark blood pool. **(D)** Suboptimal myocardial nulling without discrete hyperenhancement. Normally the LGE sequence forces normal myocardium to be nulled at an appropriately selected inversion time. The blood pool is darker than usual, and the image has poor signal-to-noise ratio with a grainy appearance, as has been described in cardiac amyloidosis. **(E)** Patchy focal LGE **(arrows)** in the basal inferolateral segment, and to a lesser extent in the inferoseptal segment. **(F)** Normally nulled myocardium. CMR = cardiac magnetic resonance.

suboptimal nulling (SN) where adequately nulled "black" images of the myocardium could not be obtained despite the use of a TI scout (Cine-IR) and multiple TIs but who differed from patients with diffuse LGE in that they did not have "bright white" hyper-enhanced myocardium. One patient (3%) who had normal LV thickness by echocardiography did not demonstrate LGE. Of the 3 patients with normal echocardiographic LV thickness, 2 had LGE (global LGE and SN LGE). Representative LGE patterns are shown in Figure 1.

Global transmural or subendocardial LGE was associated with greater interstitial amyloid deposition on RV histologic specimens ($p = 0.03$) (Table 2, top). The one patient without LGE had mild interstitial amyloid. Global LGE was also associated with higher

Table 2. Cardiac Histology Group*

	Nonglobal LGE	Global LGE	p Value
Interstitial amyloid			
None-mild (n = 5)	3 (60%)	2 (40%)	0.03
Moderate-severe (n = 28)	3 (11%)	25 (89%)	0.03
Vascular amyloid			
None-mild (n = 16)	4 (25%)	12 (75%)	0.40
Moderate-severe (n = 17)	2 (12%)	15 (88%)	0.40

		Interstitial Amyloid				
	LGE Pattern	LV-Anterior	LV-Septum	LV-Inferior	LV-Lateral	RV
Case 1†	Global transmural	Severe	Severe	Severe	Severe	Severe
Case 2‡	Focal patchy	Mild	Moderate	Mild	Trace	Trace
Case 3	Global transmural	Moderate	Moderate	Severe	Moderate	Moderate
Case 4	Global transmural	Moderate	Moderate	Moderate	Moderate	Moderate
Case 5	Global transmural	Moderate	Moderate	Moderate	Moderate	Moderate

*(Top) Correlation of late gadolinium enhancement (LGE) pattern with amount of interstitial and vascular amyloid on right ventricular (RV) endomyocardial biopsy; (bottom) correlation of LGE with amount and location of interstitial amyloid deposition in the left ventricle (LV); †shown in Figure 2A; ‡shown in Figure 2B.

LVMI than SN LGE and PF LGE (105 ± 21 vs. 79 ± 23 vs. 58 ± 3 gm/m^2, p = 0.01). No correlation existed between LGE and vascular amyloid deposits (p = 0.40) or between the histologic type of amyloidosis and pattern of LGE (p = 0.73).

LV tissue was available in 5 patients (Table 2, bottom). Four had global transmural LGE and moderate-severe global amyloid deposition corresponding to the distribution of LGE (Fig. 2A). There was no transmyocardial difference in amyloid deposition. One patient had PF LGE and PF amyloid deposits corresponding to the distribution of LGE (Fig. 2B).

Noncardiac histology group. Of the 85 patients without cardiac histology, echocardiographic evidence of CA was present in 49 patients of whom 42 (86%) had LGE on CMR. LGE pattern was global in 26 (53%)—global transmural in 18 (37%) and global subendocardial in 8 (16%), SN in 10 (20%), PF in 6 (12%), and absent in 7 (14%). Patients with LGE had greater LV and RV wall thickness, lower LVEF, and a trend toward greater symptoms (NHYA functional class III to IV 38% vs. 0%) and higher BNP levels compared with patients without LGE. Findings are summarized in Table 3.

The remaining 36 patients did not have echocardiographic evidence of cardiac involvement. Of these, 17 (47%) had LGE on CMR. LGE pattern was global subendocardial in 3 (8%), SN in 6 (17%), PF in 8 (22%), and absent in 19 (53%). The presence of LGE was associated with higher LVMI, greater LV and RV wall thickness, greater incidence of low voltage on ECG and lower absolute limb lead voltages, and higher BNP and troponin-T levels. Findings are summarized in Table 3.

Association between LGE patterns and clinical, biochemical, and morphologic findings. NYHA functional class, low voltage ECG, limb lead voltage and pseudoinfarct pattern on ECG, LVMI, LV and RV thickness, troponin-T and BNP levels were highest in the setting of global LGE and trended downwards in SN LGE, PF LGE, and no LGE in that order. LVEF was lower in patients with global LGE. Results are shown in Table 4. Interobserver agreement for the presence and pattern (absent, PF, SN, or diffuse LGE) of LGE (kappa 0.90, 95% confidence interval: 0.77 to 1.0) was very good.

DISCUSSION

CMR-LGE is very common in CA and represents interstitial expansion from amyloid deposition. The most frequent prototypical pattern is global transmural or subendocardial LGE, which is associated with the greatest interstitial amyloid deposition and the worst clinical, morphologic, functional, and biomarker profile. Suboptimal myocardial nulling and PF LGE are associated with lesser degrees of amyloid deposition. LGE was present in a substantial proportion of patients with normal LV thickness by echocardiography, suggesting that tissue characterization by LGE may identify cardiac involvement before morphologic abnormalities.

There was a high prevalence (97%) of LGE in patients with cardiac histology available as a gold standard. Global LGE (transmural or subendocardial) was associated with increased interstitial amyloid deposition compared with other LGE patterns (Table 2), and detailed multisite histologic analysis in 5 patients showed the distribution of LGE matched the distribution of interstitial amyloid deposition (Figs. 2A and 2B). These findings provide confirmatory and conclusive evidence of the mechanism of LGE in CA as initially described by Maceira et al. (13), which is interstitial expansion from amyloid infiltration. Since amyloid can deposit in intramural arteries, infarction-related fibrosis has been postulated as a possible mechanism (14,17). This is unlikely since interstitial fibrosis was minimal or absent, and no correlation existed between LGE and vascular amyloid deposits. Notably, patients with cardiac histology in this study had more advanced cardiac disease compared with those without histology, and the prevalence of LGE may be lower in a population with less advanced CA. The absence of LGE in 1 patient with mild interstitial amyloid indicates a threshold level of amyloid is required for LGE.

If the presence and pattern of LGE is reflective of interstitial amyloid burden, does this translate into an adverse clinical, morphologic, functional, and biomarker profile? Global LGE was associated with the greatest abnormalities in morphologic parameters such as LVMI, LV, and RV thickness followed by those with SN LGE, PF LGE, and no LGE (Table 4). A similar relationship was observed for clinical findings such as NYHA functional class, ECG findings such as limb lead voltage and pseudoinfarct pattern, and biomarkers such as troponin-T and BNP levels. LVEF was also lower in patients with global LGE. This suggests that global LGE represents advanced CA compared with SN LGE and PF LGE, which reflect earlier stages of infiltration. This also provides indirect evidence that LGE may have prognostic implications since it is strongly associated with NYHA functional class, LV thickness, LVEF, troponin-T and BNP levels, which have proven prognostic value (1,4,18–20).

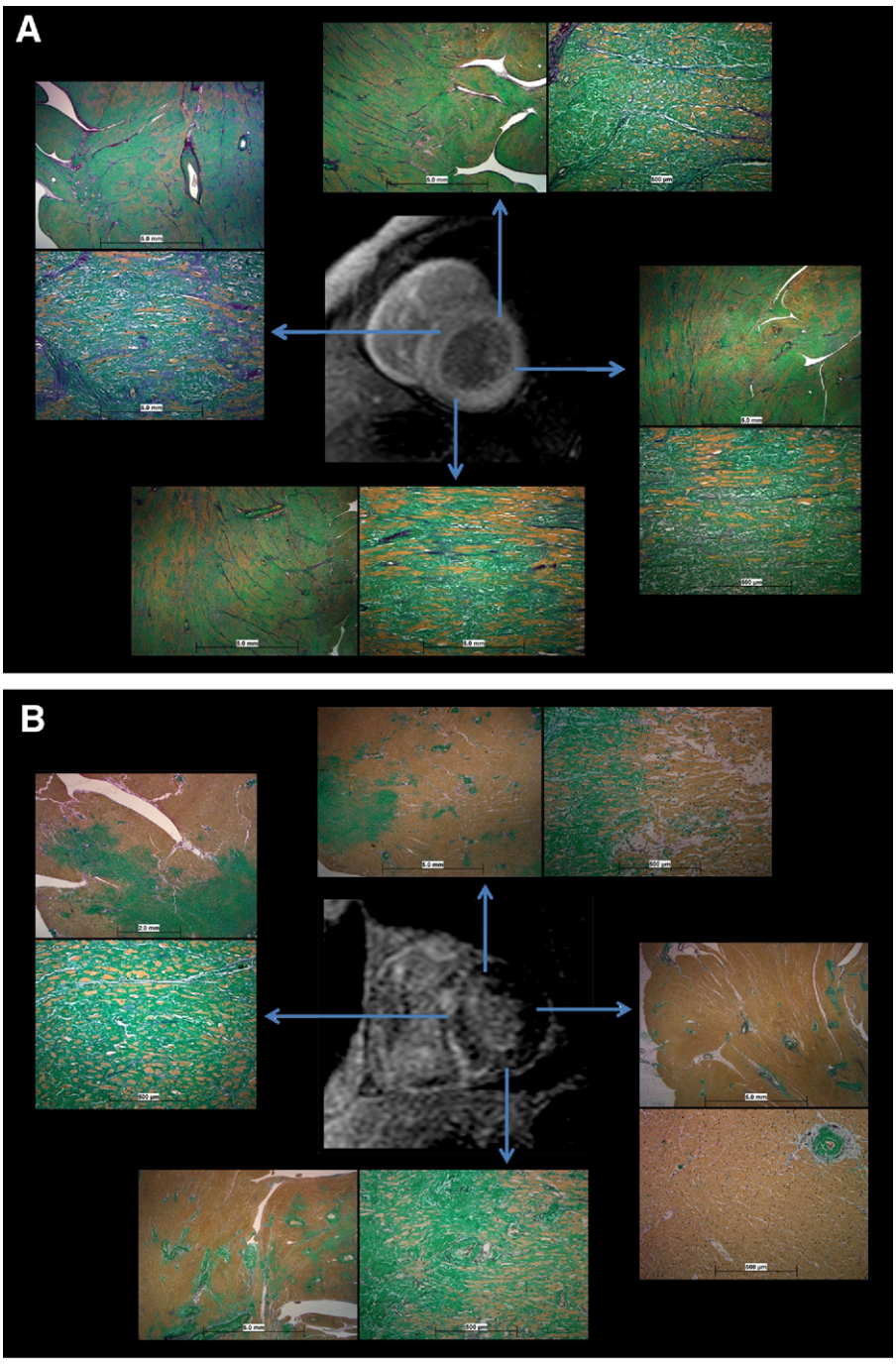

Figure 2. CMR-Histopathologic Correlation

(A) Midventricular short-axis CMR image demonstrates global transmural LGE. Corresponding low- and high-power sections from midventricular myocardium stained with sulfated alcian blue are shown. Amyloid stains as **green** and collagen as **pink**. There is globally diffuse severe interstitial amyloid (>50%) and minimal interstitial fibrosis. **(B)** Midventricular short-axis CMR image demonstrates focal patchy LGE in the ventricular septum (right ventricular side) and to a lesser extent in the anterior and inferior segments. Corresponding low- and high-power sections from midventricular myocardium stained with sulfated alcian blue are shown. The septum has moderate interstitial amyloid (25% to 50%), most prominently near the right ventricular endocardium. The anterior and inferior segments show mild interstitial amyloid (5% to 25%). The lateral wall has trace interstitial amyloid (<5%). Amyloid deposition matches the distribution of LGE. Severe obstructive vascular amyloid is present in all sections. Abbreviations as in Figure 1.

Table 3. Noncardiac Histology Group: LGE in Patients With (Echo +) and Without (Echo −) Echocardiographic Criteria for Cardiac Amyloidosis

					Echo (+) (n = 49)			Echo (−) (n = 36)		
	Histo (+) (n = 35)	Echo (+) (n = 49)	Echo (−) (n = 36)	p Value	LGE (+) (n = 42)	LGE (−) (n = 7)	p Value	LGE (+) (n = 19)	LGE (−) (n = 17)	p Value
Clinical features										
NYHA functional class III to IV	16 (46%)	16 (33%)	1 (3%)	<0.0001*†	16 (38%)	0 (0%)	0.08	1 (5%)	0 (0%)	1
CMR parameters										
LVMI (g/m^2)	100 ± 24	86 ± 27	51 ± 15	<0.0001*†‡	88 ± 26	71 ± 24	0.11	57 ± 16	45 ± 10	0.012
Increased LV thickness	34 (97%)	46 (94%)	8 (22%)	<0.0001*†	41 (98%)	5 (71%)	0.049	7 (37%)	1 (13%)	0.044
LV thickness (mm)	16.6 ± 2.7	15.4 ± 2.3	10.9 ± 1.7	<0.0001*†	15.8 ± 2.2	13.2 ± 1.4	0.0016	11.8 ± 1.5	9.9 ± 1.3	0.0002
RV thickness (mm)	7.2 ± 1.4	6.7 ± 2	4.6 ± 1.2	<0.0001*†	7 ± 1.9	4.9 ± 1.3	0.004	4.9 ± 1.2	4.2 ± 1	0.06
LVEF (%)	53 ± 9	57 ± 11	62 ± 10	0.0021*	55 ± 11	64 ± 5	0.0036	61 ± 12	63 ± 7	0.45
Pericardial effusion	19 (54%)	33 (67%)	10 (28%)	0.0014†	28 (67%)	5 (71%)	1	7 (37%)	3 (18%)	0.27
Pleural effusion	16 (46%)	26 (53%)	7 (19%)	0.0061†	24 (57%)	2 (29%)	0.23	6 (32%)	1 (6%)	0.09
ECG features										
ECG, low voltage	18 (51%)	24 (49%)	10 (28%)	0.08	23 (55%)	1 (14%)	0.10	10 (53%)	0 (0%)	0.004
ECG, limb voltage	6.2 ± 3	6.7 ± 3.9	7.6 ± 2.8	0.18	6.6 ± 4	7.7 ± 3.4	0.44	5.8 ± 1.8	9.7 ± 2.2	<0.0001
Cardiac biomarkers										
Troponin-T elevation	27 (84%)	37 (76%)	7 (19%)	<0.0001*†	32 (76%)	5 (71%)	1	6 (32%)	1 (6%)	0.09
Troponin-T (ng/ml)	0.08 ± 0.09	0.05 ± 0.06	0.01 ± 0.03	<0.0001*†	0.06 ± 0.06	0.03 ± 0.03	0.53	0.02 ± 0.04	0.001 ± 0.005	0.04
BNP (pg/ml)	829 ± 791	647 ± 672	181 ± 217	<0.0001*†	704 ± 701	303 ± 306	0.09	267 ± 263	84 ± 82	0.0046

p Value <0.0167 (Bonferroni correction) for *cardiac histology (+) group versus echo (−) group, †echo (+) versus echo (−) group, ‡cardiac histology (+) group versus echo (+) group. Histo = cardiac histology; other abbreviations as in Table 1.

Does LGE-CMR allow for early detection of CA before increased LV wall thickness is evident on echocardiography? Early detection is important, especially in patients with AL amyloid, where cardiac involvement adversely impacts treatment options and prognosis (3). These patients usually have an extracardiac tissue diagnosis, and cardiac involvement is assessed noninvasively, largely on the basis of increased LV thickness on echocardiography. Important limitations are the inability to know "pre-amyloid" thickness and confounding effects of other causes of LV hypertrophy. Direct tissue characterization using the LGE technique is attractive from a diagnostic viewpoint. Among patients with histologically proved CA, LGE-CMR detected more patients than echocardiography (97% vs. 91%, 2 patients with normal LV

Table 4. Association of LGE With Clinical, Morphologic, Functional, ECG, and Biochemical Features

	LGE (−) (n = 25)	FP (n = 17)	SN (n = 19)	Global (n = 59)	p Value	p Value for Trend Test
Clinical features						
NYHA functional class III to IV*†	0	0	4 (21%)	29 (49%)	<0.0001	<0.0001
CMR parameters						
LVMI (g/m^2)*†‡	54 ± 20	60 ± 15	72 ± 21	98 ± 26	<0.0001	<0.0001
Increased LV thickness (%)*†§	28	53	79	97	<0.0001	<0.0001
Average LV thickness (mm)*†‡§	10.9 ± 2	12.6 ± 2.4	13.8 ± 1.8	16.6 ± 2.4	<0.0001	<0.0001
RV thickness (mm)*†‡§	4.5 ± 1.2	5.1 ± 1.2	6.1 ± 1.8	7.3 ± 1.7	<0.0001	<0.0001
LVEF (%)*†‡	63 ± 6	62 ± 8	60 ± 10	52 ± 11	<0.0001	<0.0001
ECG						
Low voltage (%)*§	4	29	42	64	<0.0001	<0.0001
Limb lead voltage (mm)*†§	9 ± 2.7	8.2 ± 4.6	6.5 ± 3.3	5.6 ± 2.6	<0.0001	<0.0001
Pseudoinfarct pattern (%)*†	12	18	42	59	<0.0001	<0.0001
Cardiac biomarkers						
Elevated troponin-T (%)*†	28	29	58	86	<0.0001	<0.0001
Troponin-T (ng/ml)*†	0.01 ± 0.02	0.01 ± 0.03	0.06 ± 0.10	0.07 ± 0.07	<0.0001	<0.0001
BNP (pg/ml)*‡§	159 ± 202	172 ± 134	616 ± 896	823 ± 668	<0.0001	<0.0001

p Value <0.0083 (Bonferroni correction) for *global versus LGE (−), †global versus FP, ‡global versus SN, §SN versus LGE (−). SN versus FP and FP versus LGE (−) were not significant. FP = focal patchy enhancement; SN = suboptimal nulling; other abbreviations as in Table 1.

thickness had LGE). Furthermore, among patients with normal LV thickness without cardiac biopsy, almost one-half (47%) had LGE and these patients had worse clinical, ECG, and biomarker profiles compared with those without LGE, indicating cardiac abnormalities despite normal LV thickness. LGE pattern was more likely to be PF or SN LGE in these patients, consistent with our observation that these patterns reflect an early stage of amyloid infiltration. Evaluation of the myocardial substrate with LGE-CMR may thus detect CA earlier than would otherwise be possible by morphologic assessment, with implications for screening of subclinical early cardiac involvement. However, 14% of patients with increased LV thickness did not have LGE. This may reflect mild diffuse infiltration below the threshold for detection by LGE, or hypertrophy due to causes other than amyloid infiltration.

How specific are these patterns of LGE for CA and might LGE obviate the need for cardiac biopsy? Global LGE, subendocardial or transmural, coupled with a dark blood pool can be considered an "amyloid LGE pattern" due to its unique appearance. However, the presence of PF LGE and SN LGE in some patients with CA raises an important question regarding the specificity of these patterns for CA (15). Focal LGE may be present in other cardiac conditions as a result of fibrosis or inflammation and cannot be considered a specific finding for CA in the absence of other supporting data (21). Histologic evaluation of the LV in 1 patient with focal LGE proved amyloid deposition could indeed be localized. Prior experience with cardiac biopsy has also shown that amyloid deposition can be uneven, with multiple biopsy specimens required for diagnosis in 20% of cases (8). Suboptimal myocardial nulling can result from technical issues or incorrect TI selection (22). In an unselected population, given the rarity of CA, it may not be possible to diagnose CA on the basis of these findings, although an inability to optimally null myocardium in a technically adequate study should raise concern, especially if the blood pool appears unusually dark. The real clinical significance of PF LGE or SN LGE may be in patients with confirmed AL amyloidosis when evidence of early cardiac involvement is being sought. In patients with SCA, confirmation of diagnosis often requires a cardiac biopsy because extracardiac involvement is often not present. All SCA patients in this study had global transmural or subendocardial LGE, likely a reflection of severe interstitial amyloid deposition since these patients had the most marked increase in LVMI. In patients with a clinical work-up that suggests SCA (e.g., suspicious echocardiographic findings but negative serum/urine electrophoresis and fat biopsy), CMR demonstration of global transmural or subendocardial LGE may obviate the need for cardiac biopsy.

Finally, how do our findings relate and add to those of previous investigators? Maceira et al. (13) and Vogelsberg et al. (15) described a distinct "amyloid LGE pattern" of global subendocardial LGE. In contrast, Perugini et al. (14) described a more variable pattern of LGE, which could be globally transmural or subendocardial as well as PF. We observed global transmural and subendocardial LGE most commonly but also PF LGE. There are several possible explanations. First, our study population was larger, which allowed us to detect less common LGE patterns. Second, prior studies enrolled patients with echocardiographic evidence of CA, and in the case of Vogelsberg et al. (15) also required restrictive filling physiology, which limited study populations to those with relatively advanced CA. We included patients with less advanced CA (32% had normal echocardiographic LV thickness), and many of these patients tended to have PF LGE. Finally, technical factors may contribute to differences compared with those seen in the studies of Maceira et al. (13) and Vogelsberg et al. (15) and render direct comparison difficult. Our CMR protocol consisted of an intravenous bolus of 0.2 mmol/kg gadodiamide with a standard delay time of approximately 10 min in contrast to the lower dose of Gd (0.1 mmol/kg) and shorter delay time used by Maceira et al. (13) and Vogelsberg et al. (15). We elected not to use a short delay time since short delays are unlikely to be used when patients in whom a diagnosis of amyloidosis is not known a priori undergo CMR as may happen in "real-world" clinical scenarios, and use of a standard protocol in our opinion yields valuable information. The global subendocardial LGE pattern (rather than transmural) may be more apparent with short delays when transmyocardial differences in T1 are maximal, as demonstrated by Maceira et al. (13). Perugini et al. (14), whose protocol was a similar protocol to ours, also failed to find global subendocardial LGE as the predominant LGE pattern. When LV tissue was available for correlation, we did not encounter a significant subendocardial predominance in amyloid deposition.

Study limitations. Our aim was to study the potential of LGE-CMR to define the myocardial substrate and to identify CA in a wide spectrum of patients with amyloidosis and examine the relationship between LGE and clinical and imaging features. Given the rarity of CA, a meaningful assessment of predictive accuracy would require a prohibitively large control population (23). Hence, we did not include a control group to study sensitivity and specificity. A detailed comparison with echocardiography, including correla-

tion with diastolic function and strain analysis, was outside the scope of this study, and further work is needed for this. Third, cardiac histology was only present in a subset of patients, and the decision to perform a cardiac biopsy was made on clinical grounds, which may introduce bias. Fourth, although LGE was often observed in the RV, especially when the RV was thick, this was difficult to reliably assess in all patients (14,24). Finally, an important limitation exists in patients with significant renal dysfunction in whom the risk of nephrogenic systemic fibrosis precludes the use of Gd.

CONCLUSIONS

LGE is very common in CA and results from interstitial expansion from amyloid deposition. Global transmural or subendocardial LGE is most common, but suboptimal myocardial nulling and PF LGE can also be observed. Abnormal LGE precedes a morphologic increase in LV thickness in a significant proportion of patients and LGE-CMR may allow for early detection of cardiac infiltration. The presence and pattern of LGE is strongly associated with other clinical and imaging markers of prognosis in CA. Further studies are needed to examine the sensitivity and specificity of this technique, to compare CMR with echocardiography including abnormalities in diastolic function and myocardial strain for detection of early cardiac involvement, and to directly evaluate the prognostic value of LGE.

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