

Special Article - Cardiac Magnetic Resonance Imaging

The Prognostic Significance of Late-Gadolinium Enhancement Identified by Cardiac MRI in Association with Renal Function

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Abstract

Objectives: Cardiac MRI with late-gadolinium enhancement (LGE) provides a noninvasive assessment of myocardial fibrosis. LGE is associated with an increased risk of adverse cardiovascular events. Renal impairment is associated with the development of myocardial fibrosis and cardiac remodeling. However, the prognostic significance of LGE in association with renal function has not been assessed.

Methods: Using the Mayo Clinic Cardiac MRI Database, we collected data from patients who underwent gadolinium contrast cardiac MRI beginning in January 2006 to June 2008 and had a baseline serum creatinine measurement within 30 days of the scan. Patients with a history of congenital heart disease, hypertrophic cardiomyopathy, hemochromatosis, cardiac sarcoidosis, cardiac amyloidosis, myocarditis and arrhythmogenic right ventricular cardiomyopathy were excluded from the study. Each patient's estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula. MRI data for 966 patients were included in the study.

Results: The mean age of the cohort was 55.5 ± 16.7 years with 41% females. The presence of LGE in the total cohort was associated with a lower eGFR (73.2 ± 22.6 mL/min/1.73 m²) as compared to patients without LGE (78.4 ± 22.8 mL/min/1.73 m², $p < 0.001$), even after adjustment for gender, LVEF and LVEDMi ($p = 0.006$). There were statistically significant associations between the presence of LGE and reduced LVEF ($46.8 \pm 14.3\%$, $p < 0.001$), increased LVEDMi (56.6 ± 19.4 g/m², $p = 0.015$) and elevated plasma B-type natriuretic peptide (BNP) (524.5 ± 655.3 pg/mL, $p < 0.001$) as compared to those subjects without LGE, even after adjustment for age, gender, hypertension, CAD and MI. The presence of LGE was independently associated with increased mortality (HR 1.78, 95% CI (1.21, 2.63); $p = 0.003$), even after adjustment for age, gender and MI (HR 1.61, 95% CI (1.03, 2.51); $p = 0.0356$). Overall mortality was greatest in patients with LGE and eGFR less than 70 mL/min/1.73 m² (HR 1.38, 95% CI (1.17, 1.63); $p < 0.001$).

Conclusion: This retrospective analysis demonstrates that the presence of late-gadolinium enhancement on cardiac MRI is more commonly associated with renal impairment and markers of adverse ventricular remodeling. In addition, subjects with LGE have an increased risk of mortality and the combination of LGE and renal impairment significantly elevates the overall risk of mortality compared to subjects with neither.

Keywords: Cardiac MRI; Myocardial fibrosis; Late gadolinium enhancement; Renal insufficiency; Prognosis

Abbreviations

LGE: Late Gadolinium Enhancement; LVEF: Left Ventricular Ejection Fraction; LVEDMi: Left Ventricular End Diastolic Mass Index; eGFR: Estimated Glomerular Filtration Rate; CAD: Coronary Artery Disease; MI: Myocardial Infarction; CHF: Congestive Heart Failure; PVD: Peripheral Vascular Disease; BNP: B-Type Natriuretic Peptide

Introduction

Late-gadolinium enhancement (LGE) by cardiac MRI has been

shown to provide an accurate non-invasive method of detecting myocardial fibrosis and has been validated against histopathologic examination [1-3]. Over the last several years, many studies have characterized the clinical significance of LGE in various forms of cardiovascular disease. The presence of LGE has an increased association with clinical parameters of structural remodeling, such as diastolic dysfunction, left ventricular hypertrophy (LVH) and increased left ventricular end-diastolic volume [4, 5]. The presence of LGE in the setting of various cardiomyopathies has been shown to have an increased association with adverse clinical outcomes, such

as heart failure hospitalizations and arrhythmic events [6-9]. Several important studies have also shown that the LGE in non-ischemic cardiomyopathy is associated with an increased risk of mortality beyond left ventricular ejection fraction [8-12]. These findings have led to the increased use of cardiac MRI as a clinical tool for risk stratification.

The relationship between myocardial fibrosis and renal dysfunction has been suggested by endomyocardial biopsy studies in patients with chronic kidney disease [13]. Renal impairment is felt to contribute to the development of myocardial fibrosis through a combination of hemodynamic, neurohormonal and cytokine-mediated processes [13-21]. Small cardiac MRI studies of patients with chronic kidney disease have sought to characterize the patterns of LGE in this population [22, 23]. However, the prognostic association between the presence of LGE and renal function has not been well established. Hence, the objectives of the current study are to determine the association between LGE and renal function and the additive prognostic value of the combination of LGE and renal function.

Materials and Methods

The study protocol was approved by the Mayo Clinic Investigational Review Board and Ethical Committee in January 2011. Using the Mayo Clinic cardiac MRI database, we collected data from patients who underwent gadolinium contrast cardiac MRI from January 2006 to June 2008 and had a baseline serum creatinine measurement within thirty days of the study. These subjects were followed for a mean of 2.28 years and total duration of 6.8 years. The MRI data collected included left ventricular ejection fraction (LVEF), left ventricular end-diastolic mass index (LVEDMi) and the presence of late-gadolinium enhancement. All exams were performed on GE 1.5 Tesla Twin Speed EXCITE or HD systems. After localizing scouts, functional assessment of the ventricles were performed by pre-contrast cine images obtained using ECG-gated steady state free precession imaging. An initial 4 chamber view was obtained from the scout views, then followed by short axis slices (8mm slice thickness, 1mm gap) covering the entire ventricle from base to apex. Scan parameters include TR 3.5ms, TE 1.6ms, bandwidth 125 kHz, flip angle 45, temporal resolution 40ms, matrix 192x160-192. Three short axis slices at the base, mid ventricle, and apex were acquired using a grid tagging ECG-gated gradient echo sequence, with parameters including TR/TE 6.8/3.7 ms, flip angle 30, bandwidth 32 kHz, 8 mm slice thickness, matrix 224x128, tag spacing 7 mm. Contrast enhanced myocardial late enhancement images were obtained approximately 10 minutes after injection of intravenous gadolinium-DTPA (0.2mmol/kg) in the same location used for the short axis cine images using a segmented inversion recovery prepared fast gradient echocardiographic sequence for detection of infarction. Typical scan parameters include TR 6.5ms, TE 3.1ms, inversion time (adjusted for optimal myocardial nulling) 175-225ms, matrix 256x192. Analysis of MRI images: Short axis cine images were used to calculate left ventricular ejection fraction, end diastolic, end systolic volumes, and left ventricular mass based on endocardial contours traced using computer-assisted planimetry at end-diastole and end-systole (Mass Analysis, GE Medical Systems).

Each subject's estimated glomerular filtration rate (eGFR)

Table 1: Overall Demographic Information.

Variable	Overall (N=966)	Enhancement DGE (+) (N=322)	No Enhancement DGE (-) (N=644)	P value DGE (+) vs. DGE (-)
Age, years (SD)	55.5 (16.7)	62.4 (14.1)	52.1 (16.8)	<.001
Gender, n (%)				
Female	397 (41%)	100 (31%)	297 (46%)	<.001
Male	569 (59%)	222 (69%)	347 (54%)	
Baseline Comorbidities				
Hypertension, n (%)	456 (47%)	204 (63%)	252 (39%)	<.001
CAD, n (%)	273 (28%)	174 (54%)	99 (15%)	<.001
MI, n (%)	227 (23%)	177 (55%)	50 (8%)	<.001
Diabetes, n (%)	158 (16%)	77 (24%)	81 (13%)	<.001
CHF, n (%)	267 (28%)	111 (34%)	156 (24%)	<.001
Hyperlipidemia, n (%)	387 (40%)	182 (57%)	205 (32%)	<.001
PVD, n (%)	44 (5%)	25 (8%)	19 (3%)	<.001

Values are mean \pm SD or n (%). DGE: Delayed Gadolinium Enhancement; CAD: Coronary Artery Disease; MI: Myocardial Infarction; CHF: Congestive Heart Failure; PVD: Peripheral Vascular Disease.

was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Baseline comorbidities were collected using prior documented ICD-9 diagnoses. The characterization of late-gadolinium enhancement as secondary to infarction or non-infarction was based on the pattern of fibrosis in association with coronary artery distribution as identified by the interpreting cardiac MRI specialist at the time of the study.

Patients with a history of congenital heart disease, hypertrophic cardiomyopathy, hemochromatosis, cardiac sarcoidosis, cardiac amyloidosis, myocarditis and arrhythmogenic right ventricular cardiomyopathy were excluded from the study to prevent a confounding degree of myocardial fibrosis.

Statistical Analysis

Categorical variables were summarized as percentages and continuous variables as mean \pm standard deviation. Univariate and multivariate associations of late-gadolinium enhancement and eGFR were performed with Cox's proportional hazard modeling. A p-value less than 0.05 was considered significant in this study.

Results and Discussion

MRI data from a total of 966 patients were included in the study. The mean age of the cohort was 55.5 \pm 16.7 years with 41% females. Table 1 outlines the baseline comorbidities of the total cohort. In addition, baseline demographics and comorbidities with respect to the presence or absence of late-gadolinium enhancement on cardiac MRI were also compared. There were statistically significant associations between increased age, male gender, baseline hypertension, coronary artery disease (CAD), myocardial infarction (MI), diabetes, congestive heart failure (CHF), hyperlipidemia and peripheral vascular disease (PVD) in patients with LGE compared to those without (Table 1).

The presence of LGE in the total cohort was associated with a lower eGFR (73.2 \pm 22.6 mL/min/1.73 m²) as compared to patients without LGE (78.4 \pm 22.8 mL/min/1.73 m², p <0.001), even after adjustment for gender, LVEF and LVEDMi (p =0.006) (Figure 1). Furthermore, there were statistically significant associations between

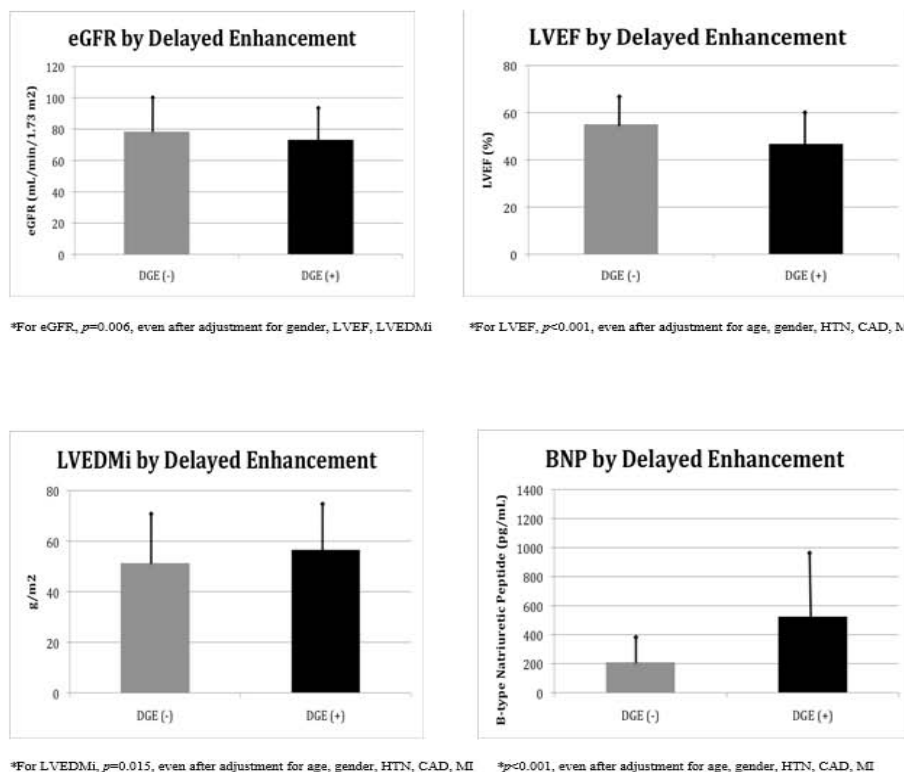


Figure 1: MRI Data by Delayed-Gadolinium Enhancement.

Top left: Comparison of estimated glomerular filtration rate (eGFR) by the presence (DGE+) or absence (DGE-) of delayed gadolinium enhancement. Top right: Comparison of left ventricular ejection fraction (LVEF) by the presence (DGE+) or absence (DGE-) of delayed gadolinium enhancement. Bottom left: Comparison of left ventricular end-diastolic mass index (LVEDMi) by the presence (DGE+) or absence (DGE-) of delayed gadolinium enhancement. Bottom right: Comparison of B-type natriuretic peptide (BNP) levels by the presence (DGE+) or absence (DGE-) of delayed gadolinium enhancement.

the presence of LGE and reduced LVEF ($46.8 \pm 14.3\%$, $p<0.001$), increased LVEDMi ($56.6 \pm 19.4 \text{ g/m}^2$, $p=0.015$) and elevated plasma B-type natriuretic peptide (BNP) ($524.5 \pm 655.3 \text{ pg/mL}$, $p<0.001$) as compared to those subjects without LGE, even after adjustment for age, gender, hypertension, CAD and MI (Figure 1).

The pattern of late enhancement in association with coronary distribution was also assessed in our study. Of the subjects with LGE, 282 (87.6%) were due to infarction, based on the pattern of enhancement in association with coronary distribution, and 40 (12.4%) were due to non-infarction. When comparing infarction with non-infarction enhancement, there were statistically significant associations with CAD, MI and hyperlipidemia in the infarction group, but none with regard to age, gender, other co-morbidities, eGFR, LVEF, LVEDMi or BNP (Table 2).

When stratifying patients by eGFR greater than or less than $70 \text{ mL/min/1.73 m}^2$, a history of increased age, male gender, hypertension, CAD, MI, diabetes, CHF and hyperlipidemia was statistically more likely in patients with lower eGFR (Table 3). Patients with an eGFR less than $70 \text{ mL/min/1.73 m}^2$ also had reduced LVEF ($49.9 \pm 15.5\%$, $p<0.001$), increased presence of LGE ($n=156$, $p<0.001$) and increased BNP ($447.4 \pm 639.7 \text{ pg/mL}$, $p<0.001$) when compared with patients with an eGFR greater than $70 \text{ mL/min/1.73 m}^2$, even after adjustment for age, gender, hypertension, CAD, MI and diabetes (Table 3).

By univariate and multivariate analyses of the overall cohort,

Table 2: Demographic and MRI Data by Presence of Infarction.

Variable	Infarction (N=282)	Non-Infarction (N=40)	P-value
Age, years (SD)	63.1 (13.4)	57.4 (17.5)	0.07
Gender, n (%)			
Female	85 (30%)	15 (38%)	0.35
Male	197 (70%)	25 (63%)	
Baseline Comorbidities			
Hypertension, n (%)	184 (65%)	20 (50%)	0.06
CAD, n (%)	164 (58%)	10 (25%)	<.001
MI, n (%)	175 (62%)	2 (5%)	<.001
Diabetes, n (%)	68 (24%)	9 (23%)	0.82
CHF, n (%)	97 (34%)	14 (35%)	0.94
Hyperlipidemia, n (%)	171 (61%)	11 (28%)	<.001
PVD, n (%)	24 (9%)	1 (3%)	0.18
MRI Data			
LVEF, % (SD)	46.9 (14.0)	46.0 (16.6)	0.73
LVEDMi, g/m ² (SD)	55.8 (16.6)	62.7 (32.7)	0.63
BNP, pg/mL (SD)	550.8 (667.6)	396.2 (526.0)	0.29
eGFR, mL/min/1.73 m ² (SD)	73.3 (22.3)	72.1 (25.3)	0.55

Values are mean \pm SD or n (%). DGE: Delayed Gadolinium Enhancement; CAD: Coronary Artery Disease; MI: Myocardial Infarction; CHF: Congestive Heart Failure; PVD: Peripheral Vascular Disease; LVEF: Left Ventricular Ejection Fraction; LVEDMi: Left Ventricular End Diastolic Mass Index; BNP: B-type Natriuretic Peptide; eGFR: Estimated Glomerular Filtration Rate.

Table 3: Demographic and MRI Data by eGFR Category.

Variable	eGFR<70 (N=372)	eGFR>70 (N=594)	P-value
Age, years (SD)	63.3 (13.1)	50.7 (16.9)	<.001
Gender, n (%)			
Female	183 (49%)	214 (36%)	<.001
Male	189 (51%)	380 (64%)	
Baseline Comorbidities			
Hypertension, n (%)	219 (59%)	237 (40%)	<.001
CAD, n (%)	132 (35%)	141 (24%)	<.001
MI, n (%)	101 (27%)	126 (21%)	0.034
Diabetes, n (%)	78 (21%)	80 (13%)	0.002
CHF, n (%)	142 (38%)	125 (21%)	<.001
Hyperlipidemia, n (%)	179 (48%)	208 (35%)	<.001
PVD, n (%)	22 (6%)	22 (4%)	0.11
MRI Data			
LVEF, % (SD)	49.9 (15.5)	53.9 (13.1)	<.001*
LVEDMi, g/m ² (SD)	54.1 (10.8)	52.3 (18.5)	0.18
DGE, n (%)	156 (42%)	166 (28%)	<.001*
BNP, pg/mL (SD)	447.4 (639.7)	193.7 (345.1)	<.001*

Values are mean ± SD or n (%). eGFR: Estimated Glomerular Filtration Rate; CAD: Coronary Artery Disease; MI: Myocardial Infarction; CHF: Congestive Heart Failure; PVD: Peripheral Vascular Disease; LVEF: Left Ventricular Ejection Fraction; LVEDMi: Left Ventricular End Diastolic Mass Index; DGE: Delayed Gadolinium Enhancement; BNP: B-type Natriuretic Peptide. (*) adjusted for age, gender, hypertension, CAD, diabetes and MI.

the presence of LGE was noted to be independently associated with increased mortality (HR 1.78, 95% CI (1.21, 2.63); $p=0.003$), even after adjustment for age, gender and MI (HR 1.61, 95% CI (1.03, 2.51); $p=0.0356$) (Figure 2). When stratifying survival rates based on combined eGFR and LGE status, overall mortality was greatest in patients with LGE and eGFR less than 70 mL/min/1.73 m² (HR 1.38, 95% CI (1.17, 1.63); $p<0.001$) (Figure 3). Of note, in patients with eGFR greater than or equal to 70 mL/min/1.73 m², the presence of LGE was not associated with an increased risk of mortality compared to patients without LGE (HR 1.43, 95% CI (0.77, 2.65); $p=0.26$). In contrast, in patients with eGFR less than 70 mL/min/1.73 m², the presence of enhancement was associated with an increased risk of mortality compared to patients without LGE (HR 1.80, 95% CI (1.07, 3.04); $p=0.026$).

In the current study, we determined that the presence of late-gadolinium enhancement on cardiac MRI is more commonly associated with renal impairment and markers of adverse ventricular remodeling, including elevated BNP, reduced LVEF and increased LVEDMi. In addition, subjects with impairment of renal function were more likely to have LGE along with increased BNP and reduced LVEF. Lastly, our results confirm that subjects with LGE have an increased risk of mortality and the combination of LGE and renal dysfunction significantly elevates the overall mortality risk compared to subjects with neither.

The results of this study correlate with prior studies which established the role of LGE as a predictor of adverse outcomes. However, we extend this risk association to demonstrate that the combined presence of LGE and renal dysfunction corresponds to an increased risk of death above LGE alone. In fact, LGE was not

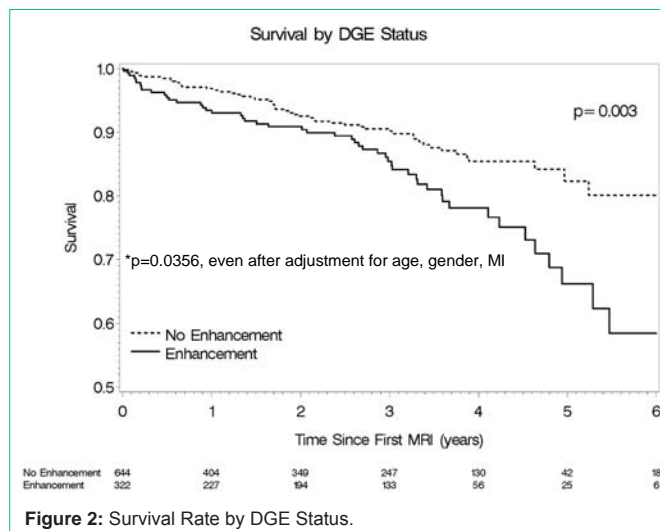


Figure 2: Survival Rate by DGE Status.

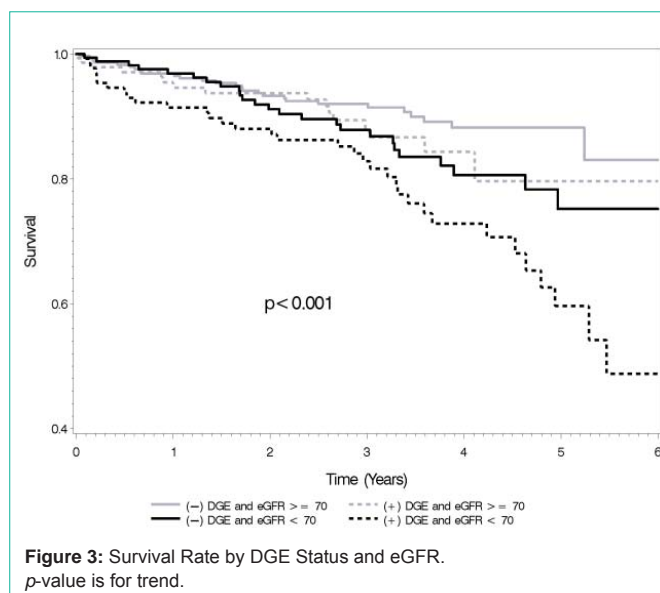


Figure 3: Survival Rate by DGE Status and eGFR. p -value is for trend.

predictive of an increased risk of mortality in subjects with eGFR >70 mL/min/1.73 m².

The association between renal impairment and adverse cardiac remodeling and increased mortality seen in this study is also consistent with previous studies which show evidence of a cardiovascular disease process in the early stages of chronic kidney disease. In a cross-sectional echocardiographic study of over 3,000 patients, Park *et al.* reported a 32% prevalence of LVH in patients with eGFR >60 mL/min/1.73 m² [24]. Compared with healthy controls, Edwards *et al.* showed that patients with stage II CKD (eGFR 60-89 mL/min/1.73 m²) had reduced aortic distensibility and increased arterial and ventricular systolic and diastolic stiffness [25]. A meta-analysis of general population cohorts analyzing over 100,000 participants showed an increased risk of mortality associated with eGFR <75 mL/min/1.73 m² [26].

Prior to our current study, the previous largest analysis of LGE in association with renal function was performed Schietinger *et al.* in 2008. They sought to characterize the presence of LGE by

cardiac MRI in hemodialysis patients at high risk for cardiovascular events. Twenty-four patients were included in the study and 79% had evidence of LGE. Patients were followed for an average of one year with five deaths in the LGE group and two deaths in the non-LGE group [23]. With over 900 patients included in our cohort, the current study makes a significant contribution towards advancing our understanding of relationship between LGE and renal function.

Important limitations of this study include its retrospective nature with an inability to account for all confounding variables. In addition, the inclusion of baseline comorbidities relies on appropriate ICD-9 documentation with an inability to completely exclude asymptomatic or undocumented disease and co-morbidities.

Conclusion

This retrospective analysis demonstrates that the presence of late-gadolinium enhancement on cardiac MRI is more commonly associated with renal impairment and markers of adverse ventricular remodeling. In addition, subjects with LGE have an increased risk of mortality and the combination of LGE and renal impairment significantly elevates the overall risk of mortality compared to subjects with neither.

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