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Cardiac Magnetic Resonance Imaging as a Prognostic Tool in Patients with Nonischemic Cardiomyopathy

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Abstract

Technical advancements have enabled cardiac magnetic resonance (CMR) imaging to provide a noninvasive assessment of cardiomyopathy. Cardiac magnetic resonance imaging acts as the reference standard for quantifying left and right ventricular function. It also assesses the etiology of cardiomyopathy by demonstrating the presence and size of myocardial scar and by detecting myocardial inflammation and interstitial infiltration. Cardiomyopathy can result in early mortality and arrhythmic risk, and CMR imaging aids in risk stratification among this group of patients. Left ventricular ejection fraction predicts which patients will benefit most from implantable cardioverter-defibrillators (ICDs), but this is not a perfect marker of arrhythmic risk. The etiology of cardiomyopathy, as assessed with CMR imaging, adds further prognostic information with infiltrative cardiomyopathies, resulting in higher mortality than idiopathic cardiomyopathies. Among patients with nonischemic cardiomyopathy (NICM), the degree of fibrosis as determined by the CMR imaging sequence of late gadolinium enhancement (LGE) imaging offers further prognostic information. Late gadolinium enhancement imaging in patients with NICM portends an approximately 3- to 8-fold greater risk of death or hospitalization than NICM without LGE imaging. Further research is needed to determine if the presence of LGE will be helpful in predicting which patients may benefit from ICD implantation.

Keywords

CMR imaging; cardiomyopathy; nonischemic cardiomyopathy; prognosis; late gadolinium enhancement

Introduction

Technical advancements have now enabled cardiac magnetic resonance (CMR) imaging to provide a noninvasive assessment of the etiology of cardiomyopathy.¹ Besides being considered by many as the reference standard for assessment of left and right ventricular

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(LV and RV) systolic function, CMR imaging allows tissue characterization for detecting the presence and size of myocardial scar, myocardial inflammation, and infiltration of the interstitium by materials such as amyloid and sarcoid granulomas. Tissue characterization can aid in the differentiation between ischemic and nonischemic cardiomyopathy (NICM),² as well as among the different etiologies of NICM. Cardiomyopathies can result in early mortality and arrhythmic risk; therefore, in order to ensure optimal management of this complicated and heterogeneous group of patients, an ideal imaging modality should not only provide information regarding the etiology of the cardiomyopathy but also assist in patient prognostication.

Benefits and Limitations of CMR Imaging

While other imaging modalities can assess LV structure and function, CMR imaging is currently the only modality that can be used for tissue characterization. Compared with echocardiography, CMR imaging has the advantage of excellent endocardial definition when assessing ejection fraction. Compared with radiograph-based cardiac imaging modalities, CMR imaging does not use ionizing radiation. In addition, while CMR contrast use should be avoided in patients with end-stage renal disease, chelated gadolinium-based contrast agents used in CMR imaging are not nephrotoxic.

In patients with severe kidney failure, gadolinium-containing contrast agents pose the risk for nephrogenic systemic fibrosis (NSF), formally called nephrogenic fibrosing dermopathy. Nephrogenic systemic fibrosis results in bilateral, fibrotic, indurated papules, plaques, and subcutaneous nodules commonly involving the extremities, and the fibrosis may be sufficiently severe to cause flexion contractures, joint immobility, pain, paresthesias, and severe pruritus. Systemic involvement resulting in muscle induration, joint contracture or fibrosis of the lung, myocardium, pericardium, or pleura have also been reported.³

Although the symptoms are disabling and not treatable, NSF is very rare, occurring exclusively in patients with kidney failure, with most cases involving patients who require dialysis or patients who have advanced renal failure with a glomerular filtration rate < 30 mL/min,⁴ acute kidney injury,⁵ or those hospitalized for a proinflammatory event.⁵ The prevention of NSF involves avoiding gadolinium-containing contrast in these higher-risk patients. If the benefits of administering gadolinium outweigh the risks and adequate diagnostic information cannot be obtained with a noncontrast study, decreasing the gadolinium dose to the lowest dose deemed necessary (ie, a single dose [0.1 mmol/kg] rather than a double dose [0.2 mmol/kg]) may reduce the risk.⁶ Although NSF is presumed to occur with any gadolinium-containing contrast agent, most reported cases of NSF have occurred using gadodiamide,^{5,6} a gadolinium-containing contrast agent with a chelating agent that binds gadolinium less tightly, and the risk may be decreased by using a gadolinium formulation with a tighter-binding chelating agent (eg, gadoteridol). In addition, the risk for NSF in renal patients without another imaging option appeared to be further reduced by performing dialysis within 12 to 24 hours after gadolinium exposure.

CMR Imaging Techniques for Quantifying LV Ejection Fraction

Cardiac magnetic resonance imaging provides the reference standard assessment of LV systolic function, owing to its excellent temporal resolution, spatial resolution, and tissue contrast abilities, differentiating the endocardial border of the myocardium from the blood pool.⁷ Cine movie images to assess LV systolic function are most often performed with steady-state free precession imaging by displaying the same myocardial slice at different points within the cardiac cycle. The systolic and diastolic cavities can be traced in multiple contiguous short-axis images of the LV cavity (typically at 1-cm intervals) starting at the

mitral valve level and moving toward the LV apex. An accurate assessment of LV ejection fraction can be made using Simpson's rule (Figure 1).

CMR Imaging for Determining the Etiology of Cardiomyopathy

Cardiac magnetic resonance imaging can differentiate the etiology and severity of the cardiomyopathy by its unique ability to characterize tissue types. By using special pulse sequences, myocardium can be clearly differentiated from fat and fluid. Regions of myocardial inflammation can be identified due to the high fluid content in these regions, which can be seen in active myocarditis as well as in some infiltrative cardiomyopathies that involve active inflammation, such as sarcoid. Gadolinium can be administered to the patient during the study and further information regarding myocardial perfusion can be assessed. Sequences obtained around 10 minutes after gadolinium injection can demonstrate late gadolinium enhancement (LGE), which indicates areas of gadolinium accumulation, suggesting myocardial fibrosis, inflammation, scar, or expansion of the myocardial interstitium, which develops as a result of infiltrative cardiomyopathies. In this technique, normal myocardium is set to appear black (Figure 2A) with regions of gadolinium accumulation appearing white.

Ischemic cardiomyopathy is most often characterized by the presence of subendocardial LGE, indicative of scar consistent with myocardial infarction (MI). The subendocardial location of the scar results from the fact that the major coronary arteries course epicardially and, when coronary stenosis develops, the endocardium is relatively deprived of myocardial blood flow. The other clue that a scar represents infarct is that it is located within an epicardial coronary artery territory (Figure 2B).⁸

Among nonischemic causes, different etiologies of infiltrative cardiomyopathies can be recognized based on their patterns on LGE imaging or other tissue-characterizing pulse sequence techniques. Cardiac amyloidosis frequently demonstrates diffuse, global, subendocardial LGE (Figure 2C) and occasionally atrial enhancement. In many patients with heavy systemic amyloid burden, the speed of contrast wash-out from the blood pool increases substantially compared with normal patients. Late gadolinium enhancement images should be acquired earlier, starting 5 minutes after gadolinium administration in patients with a suspicion of cardiac amyloid.⁹ Cardiac sarcoid can demonstrate patchy LGE in myocardium of the LV or RV (Figure 2D). Common locations for LGE in sarcoid are the anteroseptal and inferolateral walls.¹⁰ Patel et al¹¹ compared LGE imaging with standard clinical evaluation based on the Japanese Ministry of Health guidelines for cardiac involvement in patients with sarcoidosis, showing that LGE imaging is more than twice as sensitive as the current consensus criteria.

Hypertrophic cardiomyopathy (HCM) demonstrates increased LV wall thickness, but wide variation in phenotypic expression exists. Asymmetric hypertrophy of the basal interventricular septum is common, but other variants, including symmetric LV hypertrophy, apical LV hypertrophy, or focal LV hypertrophy of any LV wall, can occur. Late gadolinium enhancement represents foci of diffuse scarring but the pattern of LGE in HCM also demonstrates a wide variation. Late gadolinium enhancement is commonly seen as patchy, midwall hyperenhancement that involves the insertion point of the right and left ventricle and the regions of greatest hypertrophy; however, LGE can also be detected in regions of normal wall thickness.¹⁰

Patients with dilated cardiomyopathy have been recognized to have a typical midwall, linear LGE pattern, commonly in the ventricular septum (Figure 2E).¹² Active myocarditis demonstrates epicardial LGE (Figure 2F). Patients with thalassemia or any medical conditions that require frequent blood transfusions can experience myocardial iron overload.

Reduction of the LV ejection fraction occurs with myocardial iron overload, but identifies patients at a relatively late stage. Direct assessment of myocardial iron with CMR imaging has been used because iron deposits alter the appearance of myocardium in specific CMR sequences, including T1, T2, and T2*. Of these, the measurement of T2* has become the most widely used in the heart because it is shown to be the most sensitive to iron deposition.¹³ An iron-overload cardiomyopathy has a black appearance that can be quantified using commercial software with T2* imaging.¹ Using these tissue-characterization properties, the etiology of cardiomyopathy can be derived in many cases and may obviate the need for invasive myocardial biopsy.

Assessment of Prognosis in Cardiomyopathy

Left ventricular ejection fraction offers important prognostic information and currently remains the most robust marker in determining which patients benefit most from implantable cardioverter-defibrillators (ICDs) in both ischemic cardiomyopathy¹⁴ and NICM.¹⁵ However, LV ejection fraction provides only limited assessment of a patient's need for ICD therapy. It is well known that the most common cause of mortality among patients with “mild dysfunction” is cardiac arrhythmia¹⁶ and the majority of patients with prophylactic ICDs never develop ventricular arrhythmias.¹⁷

The specific etiology of the cardiomyopathy has been shown to add further prognostic information. Ischemic cardiomyopathy tends to carry a worse prognosis than nonischemic causes.¹⁸ Even among the nonischemic causes, risk for cardiac events varies widely depending on the etiology of the cardiomyopathy. Within the nonischemic causes, with the exception of cardiomyopathy due to HIV, infiltrative cardiomyopathies have the worst prognosis, portending a 4.4-fold greater risk of death relative to idiopathic cardiomyopathy after adjustment for cardiac function. Patients with amyloid and iron-overload cardiomyopathy have the worst prognosis among the infiltrative cardiomyopathies, with an associated 7.4-fold and 8.9-fold greater risk of mortality relative to idiopathic cardiomyopathy, respectively.¹⁹ In patients with sarcoidosis, sudden death is a leading cause of mortality, which may represent unrecognized cardiac involvement.¹¹ Identifying these patients remains imperative because some of the conditions can be improved by medical therapy. In addition, it may provide further risk stratification information for patients who could potentially benefit from ICD placement.

LGE Imaging Predicting Prognosis in Ischemic Cardiomyopathy

The role of LGE imaging as a prognostic tool in patients with coronary artery disease (CAD) has been explored in a number of studies. In 2006, our group showed that among 195 patients with a clinical suspicion of CAD but without a history of MI, the presence of LGE by CMR imaging was associated with an increased risk for major adverse cardiac events and cardiac death (hazard ratio [HR], 8.29 and 10.9, respectively; both $P < 0.0001$).²⁰ This association was maintained after adjusting for clinical, angiographic, and functional variables. In another study, Kwong et al²¹ evaluated the prognostic value of the presence of LGE in patients with diabetes without any clinical evidence of MI, showing again that the presence of scar is associated with major adverse cardiac events and mortality hazards (HR, 3.71 and 3.61, respectively; $P < 0.001$ and $P = 0.007$, respectively), which are incremental to clinical, electrocardiogram, and LV function combined.

For patients with a known prior MI, Yan et al²² quantified the extent of the peri-infarct zone by contrast-enhanced CMR and demonstrated that patients with larger areas of peri-infarct tissue were at higher risk for death compared with those with a below-median area (28% vs

13%; log-rank $P < 0.01$). This study suggested that CMR imaging might be a unique and valuable noninvasive predictor of post-MI mortality.

LGE Imaging Predicting Prognosis in NICM

Our current ability to improve mortality rates in patients with NICM is hampered by lack of a more precise risk-stratifying method. It has been shown that while prophylactic ICDs in patients with NICM and a LV ejection fraction $< 36\%$ result in a significant reduction in death from arrhythmia, there is no statistically significant reduction in total mortality.²³ This suggests that better risk stratification methods are required for patients with NICM. The extent of myocardial fibrosis characterized by LGE has been shown to provide prognostic information in NICM with this pattern of myocardial scar being implicated as a substrate to patients' propensity to develop ventricular arrhythmias.²⁴ Emerging evidence suggests that assessing LGE may be a viable contender in this regard, although more prospective studies are required to establish this future role of CMR imaging.

Among patients with NICM, there is also growing evidence of the prognostic value of CMR imaging. Assomull et al¹² investigated 101 consecutive patients with ischemic cardiomyopathy presenting with congestive heart failure symptoms of > 12 months' duration and a LV ejection fraction $< 57\%$. Patients were excluded if they had significant CAD, ongoing symptoms of myocarditis, valvular heart disease, an infiltrative cardiomyopathy, and hypertrophic cardiomyopathy. Patients underwent CMR imaging to assess for the presence or absence of midwall LGE, suggesting fibrosis from a nonischemic origin. If midwall LGE was present, the volume of fibrosis was quantified. Patients were followed-up for a mean of 658 days. Midwall LGE was present in 35% of patients and was associated with a 3.4-fold greater risk of all-cause death and hospitalization ($P = 0.01$). Midwall LGE remained a significant predictor of this outcome when adjusted for LV volumes and ejection fraction. Sudden cardiac death or ventricular tachycardia was also predicted by the presence of midwall LGE (HR, 5.2; $P = 0.03$). A larger volume of midwall LGE further predicts adverse outcomes. The receiver-operating curves demonstrate that LGE occupying $> 4.8\%$ of the myocardium predicts all-cause death and hospitalization.

Wu et al²⁵ also assessed how the presence and extent of LGE by CMR imaging predicts outcomes in patients with NICM who were referred for ICD placement. These patients represented a group with a more severely reduced LV ejection fraction than that in the study by Assomull et al.¹² Patients were also excluded if they had an infiltrative cardiomyopathy. In 65 patients with NICM and LV ejection fraction $< 35\%$, LGE was present in 42% of patients. Over the 17-month median follow-up, 44% of patients with LGE developed the composite endpoint of hospitalization for heart failure, appropriate ICD firing, and cardiac death, compared with 8% in patients without LGE. The presence of LGE predicted an 8-fold higher risk for adverse outcomes when adjusted for LV volumes and functional class ($P < 0.001$ for Kaplan-Meier survival curves).

Most recently, Cheong et al²⁶ studied 857 patients referred for CMR imaging in their institution between 2001 and 2004, regardless of patients' LV function or CAD status. Patients were excluded if they had myocarditis or infiltrative cardiomyopathy. The primary composite endpoint was all-cause mortality or cardiac transplantation. Two hundred fifty-two patients (29%) reached 1 of the endpoints. In the entire population, the authors observed that the presence of LGE appears to predict a 1.3-fold increase in the risk for the primary composite endpoint (HR, 1.26; 95% confidence interval [CI], 1.02–1.55; $P = 0.033$). Similarly, in subsets of patients with or without CAD, scar index also independently predicted mortality or transplantation (HR, 1.33; 95% CI, 1.05–1.68; $P = 0.018$; and HR, 5.65; 95% CI, 1.74–18.3; $P = 0.004$, respectively). Cox regression analysis demonstrated

that LGE resulted in a worse outcome in patients with and without a preserved ejection fraction (LV ejection fraction < 50%), but patients with the combination of decreased ejection fraction and LGE had the worst prognosis.

Other CMR Imaging Features Predicting Prognosis in NICM

Late gadolinium enhancement is a frequent finding in HCM with the incidence reported as 41% in an asymptomatic to mildly symptomatic population,²⁷ to 63% in an unselected population of HCM patients referred for CMR imaging.²⁸ Late gadolinium enhancement often reflects regions with decreased myocardial contractility²⁹ and portends a 7-fold increased risk for nonsustained ventricular tachycardia.²⁷ Recently, LGE has been shown to be a prognostic marker among patients with HCM. O'Hanlon et al²⁸ demonstrated that LGE was associated with a relatively modest 3.4-fold greater risk for the combined primary endpoint of cardiovascular death, unplanned cardiovascular admission, sustained ventricular tachycardia/ventricular fibrillation, or appropriate ICD discharge, with the incremental increase in the extent of fibrosis further increasing the risk. However, in multivariate analysis, nonsustained ventricular tachycardia remained an independent predictor of arrhythmic endpoints, whereas LGE did not. Rubinshtein et al³⁰ also demonstrated that LGE predicted sudden cardiac death or appropriate ICD discharge in patients with HCM, with patients with LGE demonstrating a small but statistically greater event rate of 0.94%/year relative to patients without LGE, who had a 0% event rate. Late gadolinium enhancement remained an independent risk factor after controlling for other variables. However, due to the high incidence of LGE within the HCM population, the relatively small risk that it entails, and the fact that the ICD complication and inappropriate shock rate in HCM is significant,³¹ a more specific risk stratification tool would be required to determine if there are features of the LGE that may place a patient at higher risk for sudden death.

Late gadolinium enhancement reflects regions of gross focal scarring, but the process of diffuse myocardial fibrosis is accelerated in HCM and this cannot be detected by LGE imaging. The partition coefficient of gadolinium (the contrast agent that decreases T1 time) can be performed with T1 mapping. With this technique, decreases in the T1 time of the myocardium reflect increased interstitial space (fibrosis) and increased gadolinium concentration diffusely throughout the myocardium. The relative distribution of gadolinium between the blood pool and myocardium can assess the amount of diffuse fibrosis within the myocardium. The relative distribution of gadolinium in the myocardium has been shown to correlate with the presence of fibrosis on surgical biopsies in patients with HCM.³² In the future, this may prove to be a predictor of prognosis in HCM or even a reversible process that can be treated prior to the later formation of focal, dense myocardial scar.

The prognostic value of CMR imaging in patients with cardiac amyloidosis has also been studied. Maceira et al³³ prospectively followed a group of 29 patients with proven cardiac amyloidosis over a mean period of 1.7 years. All patients underwent CMR imaging with T1 mapping as described above, and LGE imaging was also performed. The presence of myocardial LGE by itself was not a significant predictor of mortality. However, death was predicted by gadolinium kinetics, with blood gadolinium clearance occurring faster in patients who died. Also, the 2-minute post-gadolinium intramyocardial T1 difference between subepicardium and subendocardium predicted mortality with 85% accuracy at a threshold value of 23 ms (the lower the difference, the worse the prognosis).

Patients with thalassemia tend to develop a dilated cardiomyopathy due to chronic blood transfusion, and, consequently, myocardial iron overload. Kirk et al¹³ assessed the value of cardiac T2* by CMR imaging for predicting cardiac events from 652 thalassemia major patients compared with the established predictors of outcome, including liver iron and serum

ferritin. They showed that patients with cardiac T2* values < 10 ms (compared with > 10 ms) presented a relative risk for heart failure of 160 (95% CI, 39–653). The area under the receiver-operating characteristic (ROC) curve for predicting heart failure was significantly greater for cardiac T2* (0.948) than for liver T2* (0.589; $P < 0.001$) or serum ferritin (0.629; $P < 0.001$). The area under the ROC curve for predicting arrhythmia was significantly greater for cardiac T2* (0.747) than for liver T2* (0.514; $P < 0.001$) or serum ferritin (0.518; $P < 0.001$). These results show that CMR imaging is a valuable method for determining the prognosis in this group of patients, identifying the ones at higher risk for heart failure and arrhythmia.

Summary

Cardiac magnetic resonance imaging is a powerful diagnostic tool in patients with cardiomyopathy, and aids in determining the LV and RV function as well as the etiology of cardiomyopathy. Recently, the presence and amount of LGE, representing fibrosis, has been found to add further prognostic information to the risk assessment of patients with ischemic cardiomyopathy and NICM. Cardiac magnetic resonance imaging characteristics also provide further prognostic information in cardiomyopathy due to iron overload and cardiac amyloidosis. Further research should focus on whether ICD placement helps to reduce risk of death in patients deemed to be at higher risk based on the presence of LGE.

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Figure 1. Steady-state free precession image of the short axis of the left ventricle at papillary muscle level demonstrating the left ventricular diastolic volume (A) and left ventricular systolic volume (B) to quantify the left ventricular ejection fraction by Simpson's rule.

Figure 2A.

Tissue characterization using cardiac magnetic resonance imaging. A late gadolinium enhancement image of the short-axis view of the left ventricle demonstrating normal myocardium (black) with no areas of hyperenhancement (white) to suggest scar, fibrosis, or expansion of the myocardial interstitium, such as in an infiltrative cardiomyopathy.

Figure 2B.

Tissue characterization using cardiac magnetic resonance imaging. A late gadolinium enhancement image of the left ventricle demonstrating an ischemic cardiomyopathy with subendocardial late gadolinium enhancement in the anterior, anteroseptal, and inferoseptal walls (arrow), consistent with an infarction of the left anterior descending coronary artery territory.

Figure 2C.

Tissue characterization using cardiac magnetic resonance imaging. A late gadolinium enhancement image of the short-axis view of the left ventricle demonstrating cardiac amyloid with increased left ventricular mass and global subendocardial late gadolinium enhancement (arrow). Note that the blood pool is relatively dark due to rapid removal of gadolinium from blood into amyloid-infiltrated organs.

Figure 2D.

Tissue characterization using cardiac magnetic resonance imaging. A late gadolinium enhancement image of the left ventricle demonstrating bright epicardial enhancement in the anterior, septal, and right ventricular walls, indicating active cardiac sarcoid granulomatous infiltration (arrow).

Figure 2E. Tissue characterization using cardiac magnetic resonance imaging. Late gadolinium enhancement image of the left ventricle demonstrating a dilated cardiomyopathy with midwall late gadolinium enhancement (arrows).

Figure 2F. Tissue characterization using cardiac magnetic resonance imaging. Late gadolinium enhancement image of the left ventricle demonstrating subepicardial hyperenhancement (arrow), consistent with active myocarditis.