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Role of Cardiac Magnetic Resonance in the Diagnosis and Prognosis of Non-Ischemic Cardiomyopathy

Amit R. Patel, MD¹ and Christopher M. Kramer, MD²

¹Department of Medicine and Radiology, University of Chicago, Chicago, IL

²Departments of Medicine and Radiology and the Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, VA

Abstract

Cardiac magnetic resonance (CMR) is a valuable tool for the evaluation of patients with, or at risk for, heart failure and has a growing impact on diagnosis, clinical management, and decision-making. Through its ability to characterize the myocardium using multiple different imaging parameters, it provides insight into the etiology of the underlying heart failure and its prognosis. CMR is widely accepted as the reference standard for quantifying chamber size and ejection fraction. Additionally, tissue characterization techniques such as late gadolinium enhancement (LGE) and other quantitative parameters such as T1-mapping, both native and with measurement of extracellular volume fraction, T2-mapping, and T2-* mapping have been validated against histology in a wide range of clinical scenarios. In particular, the pattern of LGE in the myocardium can help determine the underlying etiology of the heart failure. The presence and extent of LGE determines prognosis in many of the non-ischemic cardiomyopathies. The use of CMR should increase as its utility in characterization and assessment of prognosis in cardiomyopathies is increasingly recognized. Cardiovascular magnetic resonance, cardiomyopathy, heart failure, hypertrophic cardiomyopathy, sarcoidosis, amyloidosis

Keywords

Cardiovascular magnetic resonance; cardiomyopathy; heart failure; hypertrophic cardiomyopathy; sarcoidosis; amyloidosis

Cardiac magnetic resonance (CMR) is a valuable tool for the evaluation of patients with, or at risk for, heart failure and has a growing impact on diagnosis, clinical management, and decision-making (1,2). Through its ability to characterize the myocardium using multiple different imaging parameters, it provides insight into the etiology of the underlying heart

Corresponding Author: Christopher M. Kramer MD, University of Virginia Health System, Depts. of Medicine and Radiology, 1215 Lee St., Box 800170, Charlottesville, VA 22908, ckramer@virginia.edu.

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failure and its prognosis. CMR is considered the reference standard for quantifying chamber size and ejection fraction. Additionally, tissue characterization techniques such as late gadolinium enhancement (LGE) and other quantitative parameters such as T1-mapping with measurement of extracellular volume fraction (ECV), T2-mapping, and T2-* mapping have been validated against histology in a wide range of clinical scenarios. In particular, the pattern of LGE in the myocardium can help determine the underlying etiology of the heart failure. Figure 1 shows examples of LGE in a spectrum of patients with non-ischemic cardiomyopathy. In this review, we will examine the role of CMR in the diagnosis and prognosis of non-ischemic cardiomyopathy.

Determining the etiology of a cardiomyopathy is of clinical importance, as it has implications with regards to the optimal treatment strategy and the prediction of prognosis. Although the recently proposed MOGE(S) [morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E) including genetic defect or underlying disease/substrate, and the functional status (S) of the disease] classification system may play an important role in the understanding of the cardiomyopathies in the future (3), for the purpose of this review, the non-ischemic cardiomyopathies have been divided into just four groups: dilated, genetic, inflammatory, and infiltrative. The genetic cardiomyopathies include disorders such as hypertrophic cardiomyopathy, left ventricular non-compaction, the muscular dystrophies, and arrhythmogenic right ventricular dysplasia. The inflammatory and/or autoimmune cardiomyopathies include cardiac sarcoidosis and conditions associated with connective tissue disorders such as systemic lupus erythematosus, rheumatoid arthritis, etc. The infiltrative cardiomyopathies include cardiac amyloidosis, cardiac siderosis, and Anderson-Fabry's disease.

Dilated Cardiomyopathies

Dilated cardiomyopathy likely represents an end-stage manifestation of multiple non-ischemic disorders that can damage the myocardium. Despite significant treatment advances, a recently published randomized-controlled trial which included over 8,000 heart failure patients with a left ventricular ejection fraction (LVEF) $<40\%$, a significant number of whom had some form of non-ischemic cardiomyopathy, revealed that after a median follow up of just 27 months, the mortality rate was nearly 20% despite use of modern therapies (4). The management plan is often determined by patient symptoms, abnormalities on the electrocardiogram, and LVEF; however, this is an imperfect approach that does not adequately identify those patients who are unlikely to respond to medical therapy or at risk for sudden cardiac death. Recently, there has been growing interest in exploiting the role of myocardial fibrosis, an integral pathophysiologic component of dilated cardiomyopathy, as a biomarker for guiding patient management and determining prognosis. It is increasingly being understood that fibrosis can occur in two forms that can be detected by CMR (5): (A) irreversible replacement fibrosis which corresponds to the presence of LGE and (B) diffuse interstitial fibrosis which better corresponds to findings on T1-mapping. Replacement myocardial fibrosis is often present in the midwall of the interventricular septum and can be identified in approximately 30% of individuals with dilated cardiomyopathy using LGE imaging (6,7) and differentiates it from ischemic cardiomyopathy. The presence of LGE is

associated with abnormalities in contractility and serves as a potential substrate for re-entrant ventricular arrhythmia(8). The presence of LGE identifies a cohort of patients who do not respond as well to optimal medical therapy(9), a finding independent of other standard clinical parameters such as QRS duration and pro N-terminal brain natriuretic peptide levels. The burden of LGE is independently and inversely associated with the change in LVEF that occurs following medical therapy.

Based on a prospective longitudinal study performed in 472 patients with dilated cardiomyopathy(10), patients with mid-wall LGE were significantly more likely to die (27% vs 11%) or have a significant arrhythmic event (30% vs 7%) when compared to those patients without LGE. The findings were independent of LVEF. These findings were subsequently confirmed in a larger, multicenter observational study (11) that showed that the presence and extent of LGE was predictive of all-cause mortality, but also suggested that abnormalities in native myocardial T1 relaxation times may be an even better and independent marker of poor outcomes in these patients. Although not limited to patients with non-ischemic cardiomyopathy, another study revealed that those with an LVEF >30% but who still had LGE involving more than 5% of their left ventricular mass were just as likely to die or receive an implantable cardioverter defibrillator (ICD) shock for ventricular tachycardia as those with an LVEF <30%(12). Conversely, those patients with LVEF <30% who had minimal or no LGE did just as well as those patients with LVEF>30%. The ability of LGE burden to risk stratify patients was independent of LVEF and the presence of inducible ventricular tachycardia during an electrophysiology study. Interestingly, the presence of >5% myocardial LGE burden was associated with an annualized event rate of death or significant arrhythmia of nearly 20%; whereas the absence of LGE was associated with only a 3% annualized event rate. In another study which prospectively enrolled 399 patients with dilated cardiomyopathy who had an LVEF>40%, the presence of a mid-wall pattern of LGE was present in 25% of individuals and was associated with a 9-fold increase in the risk of sudden cardiac death (SCD) or aborted SCD when compared against those without LGE (13). The potential role of LGE-CMR for identifying patients with non-ischemic cardiomyopathy who are at risk of SCD is of particular interest given the findings of recently published randomized controlled trial suggesting that ICD implantation guided by LVEF alone may not be associated with improved survival (14). Similarly, LGE may be helpful for predicting response to biventricular pacemaker resynchronization therapy. In a study of 559 patients with both ischemic and non-ischemic cardiomyopathy(15), LGE-guided biventricular pacemaker implantation was associated with a significant improvement in identifying patients most likely to benefit from biventricular pacing. Those patients who did not have LGE did significantly better following resynchronization therapy relative to those who had LGE and relative to those who underwent implantation without LGE guidance. Regardless of its ability to predict which patients may or may not respond to resynchronization therapy, the presence of LGE in the septal mid-wall was an independent predictor of morbidity and mortality in patients with dilated cardiomyopathy undergoing cardiac resynchronization therapy (16).

Genetic Cardiomyopathies

Hypertrophic Cardiomyopathy (HCM)

HCM is the most common genetic heart disease as it now is identified in up to 1 in 200 to 300 individuals with the advent of more advanced imaging and genetic testing (17). A mutation in a gene coding for any of the cardiac contractile proteins can lead to the phenotype of HCM. Although echocardiography is typically used for screening for HCM, CMR is more sensitive for the identification of more unusual sites of hypertrophy and for apical HCM (18). It is the most accurate way of measuring LV mass which is important as higher LV mass is associated with worse outcome (19). Similarly to echo, CMR can identify systolic anterior motion of the mitral valve, measure the LV outflow gradient using velocity encoded imaging, and assess mitral regurgitation.

In addition and most importantly, CMR offers the ability to identify and quantify myocardial fibrosis. Between half and two-thirds of patients with HCM may have LGE with a characteristic pattern of patchy involvement, particularly at the right ventricular septal insertion sites and in those walls with the greatest hypertrophy. A number of studies have examined the relationship between the presence of LGE and outcome in HCM. One such study of 711 patients followed for a mean of 3.5 years found no relationship between LGE and risk of SCD after adjusting for other risk factors(20). However, a recent meta-analysis of 5 studies including the latter study involving 2993 patients with a median follow-up of 3 years demonstrated that the presence of LGE was associated with a 3.4 fold increase in risk for sudden cardiac death (SCD), 1.8-fold increase in all-cause mortality, 2.9 fold increase in cardiovascular mortality and a trend to increase in heart failure death (21).

Due to the high prevalence of LGE, its presence alone cannot be used as an indication for ICD implantation as the risk of SCD in HCM is <1% per year.

Thus, the extent of LGE may have more discriminatory value than its presence. A 4-center study of 1293 patients followed for 3.3 years showed that LGE 15% of LV mass was associated with a 2-fold increase in SCD event risk (22). The aforementioned meta-analysis showed that after adjusting for baseline characteristics, the extent of LGE was strongly associated with the risk of SCD with a hazard ratio of 1.36 per increase in LGE extent of 10% (21).

Evidence is mounting in regards to the diagnostic and prognostic role of interstitial fibrosis in HCM. One study demonstrated mildly elevated native T1 in HCM, highest in segments that subsequently demonstrate LGE(23). Native T1 is accurate in discriminating HCM from hypertensive heart disease (24). A study of HCM and idiopathic dilated CM showed that native T1 performed better than ECV at discriminating cardiomyopathies from normal (25). ECV is also useful as it is elevated in phenotypically positive HCM as well as genotype positive, phenotype negative individuals(26). Post-contrast T1 time was shown to be associated with nonsustained ventricular tachycardia in a study of 100 HCM patients and thus may be a marker of risk once studied in larger patient groups(27).

In addition to the extent, the location and/or pattern of LGE may be more predictive of adverse outcome than the presence of LGE alone and the role of native T1 and ECV remain to be fully elucidated. The ongoing NIH-funded natural history study “HCMR-Novel Predictors of Prognosis in Hypertrophic Cardiomyopathy” (NCT01915615) using CMR, genetics, and biomarker evaluation of 2750 patients with HCM is likely to offer further insight into identifying risk markers including LGE, native T1, and ECV (28).

Left Ventricular Noncompaction (LVNC)

LV noncompaction cardiomyopathy is characterized by extensive LV trabeculations (Figure 2) and an increased risk of clinical heart failure, thrombosis, and mortality. The accurate diagnosis of LVNC by noninvasive imaging can be quite difficult due to substantial overlap between it and conditions such as dilated cardiomyopathy and even normal LV trabeculation. The role of CMR in the diagnosis of LV noncompaction continues to evolve. Peterson et al proposed CMR criteria of noncompacted to compacted myocardium ratio of 2.3 to 1 (29) and demonstrated a sensitivity of 86% and 99% in a study of 177 patients with and without cardiac disease. However, when using these criteria, up to 43% of individuals who get CMR as part of screening studies such as the Multi-Ethnic Study of Atherosclerosis can meet imaging criteria (30). Similarly, another screening study showed that up to 14.8% of normal individuals met at least 1 diagnostic criterion for LVNC (31). Thus, clinical criteria of symptomatic HF or LV dysfunction on CMR likely need to be included to improve the specificity of diagnosis. Jacquier et al proposed another set of criteria in a study of patients with LVNC compared to those with DCM, HCM, and controls (32). They found that a trabeculated LV mass greater than 20% of the LV mass was 94% sensitive and specific for the diagnosis of LVNC. LGE may be seen in LVNC, but it is infrequent enough that its presence is specific but not sensitive in making the diagnosis (33). However, its presence may be important for prognostic purposes. In a study of 113 patients followed for a mean of 4 years, the presence of LV dilatation, LV dysfunction, and LGE (seen only in 11 patients) were predictive of cardiac events whereas the degree of LV trabeculation was not (34). More CMR studies of this condition are needed to establish its role in this condition as the sensitivity is high, but the specificity remains problematic.

Muscular Dystrophies

Although the muscular dystrophies are often characterized by skeletal muscle degeneration and progressive weakness, a major problem can be the development of a dilated cardiomyopathy which often goes undetected until it is in its advanced stages. Early detection allows for the potential to introduce therapy that could alter the natural history. Despite the fact that cardiomyopathy is an important cause of death in DMD, the majority of patients (~70%) in one cross-sectional study have an LVEF >55%; whereas, 20% of patients had an LVEF between 45–54%, 6% of patients had an LVEF of 35–44%, and only 3% had an LVEF <35%.

Because of the relative insensitivity of LVEF for identifying DMD boys at risk for heart failure, CMR techniques such as myocardial tagging offer the potential to detect abnormalities in systolic function before a reduction in LVEF or LV dilation occurs (35). Circumferential strain may be abnormal even in DMD patients <10 years old, and it

continues to worsen with aging despite the preservation of LV ejection fraction. In those with LV dysfunction, circumferential strain may be abnormal even in the absence of LGE (36). These findings suggest that abnormalities in strain precede both the reduction of LVEF and also the development of myocardial scar.

In addition to abnormalities in circumferential strain, the presence of LGE (Figure 3) may also precede a decrease in LVEF (37). In one study (38), 36% of DMD patients had LGE, and the prevalence increased with age. Only 30% of patients with LVEF >55% had LGE; whereas 84% of those with LVEF <55% had LGE. Importantly, 10% of those individuals with LGE died during an average follow up of 11 months; whereas, only one patient without LGE died. The burden of LGE was also associated with an increased risk of death. The presence of LGE also identifies individuals at risk for progressive LV dysfunction as in those with LGE, the LVEF decreases an average of 2.2% annually (39). Figure 5 is an example of LGE in a patient with DMD.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is an inherited cardiomyopathy that leads to ventricular arrhythmias and often causes SCD in the young. CMR is an important adjunct in making the diagnosis of ARVC, primarily due to its accuracy in assessing right ventricular dilatation and dysfunction (40). Diagnostic findings in this disease include RV dilatation and global or regional dysfunction including focal RV systolic bulging or aneurysm as defined by cine CMR and are carefully defined to meet Task Force Criteria that were redefined in 2010 (40). The finding of fatty infiltration in the RV free wall is not part of the diagnostic criteria as this is a nonspecific finding. The newer criteria are more restrictive than the older 1994 criteria and are more specific but may be less sensitive (41), although this continues to be debated in the literature. In certain cases, LGE of the RV free wall can be seen(42), although this can be difficult to identify definitively due to the thin RV wall in this disorder. LV involvement in ARVC is increasingly recognized(43). Quantitative functional RV imaging with strain measures by CMR feature tracking may objectify regional functional measures and improve upon diagnostic accuracy for ARVC compared to qualitative analysis of cine images (44). The hallmark of the diagnosis, however, remains RV dilatation and dysfunction.

Inflammatory Cardiomyopathies

Sarcoidosis

Sarcoidosis is a multi-organ, inflammatory disorder characterized by non-caseating granulomatous infiltration. Clinical manifestations of cardiac involvement can range from none to SCD or advanced heart failure requiring heart transplantation. Although only 5% of sarcoidosis patients have clinical manifestations of cardiac sarcoidosis (CS), 25% have evidence of cardiac involvement at autopsy (45) and the primary presentation of CS can be SCD. Because CS is a patchy disorder and often involves only small amounts of myocardium without causing obvious abnormalities in LV function, commonly used tests such as the electrocardiogram, ambulatory monitoring, signal averaged electrocardiography, echocardiography, myocardial perfusion imaging, and electrophysiology testing do not

reliably detect it (46). Even endomyocardial biopsy has a poor sensitivity due to myocardial sampling errors related to the patchy pattern of sarcoid infiltration (47).

CMR is becoming the preferred imaging modality for detecting CS and a consensus document published by the Heart Rhythm Society suggested that patients with sarcoidosis undergo CMR if an abnormality on an initial screening test is noted (48). Several groups have shown that CMR can readily identify individuals with CS because of its ability to identify small areas of myocardial involvement using LGE (49,50). Nearly 20% of individuals with extracardiac sarcoidosis have cardiac involvement based on CMR, even when LVEF is preserved (51). The true diagnostic performance of CMR in the detection of CS is unknown because there is no acceptable reference standard. Instead, the use of CMR in the setting of sarcoidosis is currently most often discussed in terms of its ability to risk stratify patients and to impact their treatment plan. The detection of CS using CMR has been shown to better identify patients at risk for cardiac death than the more commonly used diagnostic criteria published by the Japanese Ministry of Health and Welfare (JMHW) (52). The presence of LGE is associated with an increased risk of death or significant ventricular arrhythmia even in patients with preserved LVEF and the risk of adverse outcomes is modulated by the burden of myocardial damage and the presence of RV dysfunction (53). A recent meta-analysis (54) of 11 studies evaluating the role of CMR in patients with sarcoidosis revealed that the presence of LGE had an odds ratio of 7.4 for identifying patients at risk for a composite endpoint that included all-cause mortality and ventricular arrhythmogenic events. Furthermore, the absence of LGE is associated with a low risk of major cardiovascular events even when the LVEF is severely impaired (55). In addition to ventricular arrhythmias, sarcoidosis patients with LGE also have an increased burden of atrial fibrillation and atrial flutter (56).

Although the presence of LGE is a powerful predictor of risk in patients with sarcoidosis, it may not identify patients who have earlier stages of CS prior to the development of myocardial scar or overt inflammation. Abnormalities in myocardial T2-times may precede the development of LGE (57); however, more studies are needed to understand the clinical impact of this finding.

Systemic Lupus Erythematosus (SLE) and Other Connective Tissue Disorders

SLE is associated with a full range of cardiovascular complications including accelerated coronary disease and its associated complications such as myocardial infarction, microvascular disease, myocarditis, vasculitis (58), pericarditis, pulmonary hypertension, conduction disease, and valvular heart disease. Although these complications of SLE are well known, they are often clinically silent and require advanced imaging technologies such as CMR to detect them (59). In one study comparing the utility of echocardiography and CMR in SLE patients, 45% of all SLE patients with a prior history of cardiovascular complication had evidence of LGE on CMR, yet only 33% of those individuals with LGE on CMR were identified by echocardiography (60). The mechanism of accelerated coronary artery disease in SLE patients is not thought to be secondary to traditional risk factors. Varma et al used a novel, post-contrast high-resolution T1-W inversion recovery pulse sequence to evaluate the pattern and burden of coronary wall contrast enhancement in SLE

patients. When compared to patients with coronary artery disease (CAD) those with SLE had a diffuse pattern of coronary wall contrast enhancement; whereas, CAD patients had a patchy pattern of enhancement, despite similar total enhancement burden (61). These findings suggest that SLE is associated with diffuse rather than focal coronary inflammation. In the same study, it was noted that SLE patients had global perfusion defects during hyperemia consistent with microvascular disease, rather than the regional perfusion defects more consistent with obstructive epicardial CAD. In another study that included 20 SLE patients with typical and atypical chest pain without evidence of epicardial coronary disease who underwent adenosine CMR, 44% had visible perfusion defects (62). When compared to controls, patients with SLE also had a significant reduction in myocardial perfusion reserve.

CMR can also detect lupus myocarditis (63). CMR was recently used to evaluate 32 SLE patients with new onset heart failure; 15% had evidence of acute myocarditis, 31% had evidence of transmural myocardial infarction, 28% had diffuse subendocardial scar suggestive of vasculitis, and 15% had LV dysfunction without evidence of inflammation or fibrosis. The burden of CMR abnormalities was correlated to lupus activity and duration. In another study (64), 37% of SLE patients had evidence of LGE that was typically small and most often found in the interventricular septum. Only those patients with a larger burden of LGE had evidence of functional abnormalities such as a decreased E/A ratio on echocardiography or reduced exercise tolerance. The presence of LGE has also been associated with heart block (65).

Interest is growing in quantifying the burden of myocarditis in SLE to guide treatment response (66). Initial approaches utilized T2-W and pre- and post- contrast T1-W images to calculate a T2-ratio as a marker of increased myocardial edema and early global relative contrast enhancement ratio as a marker of increased capillary leak indicative of myocardial inflammation (67). Using such measurements, it was evident that when compared to control subjects or individuals with inactive SLE, patients with active SLE had a higher T2-ratio and early global enhancement ratio. Although promising, these types of measurements are limited by imaging artifacts and absence of an absolute quantitative parameter. Others have advocated for techniques capable of measuring actual T2 and T1 relaxation times to identify lupus myocarditis and to monitor treatment response(68). In one study (69), patients with active SLE had increased myocardial T2 times suggesting the presence of myocardial edema/ inflammation when compared against patients with inactive SLE and control subjects. Furthermore, the T2 relaxation time improved with repeat imaging following clinical improvement. Others have shown similar findings with the use of T1-mapping and ECV techniques (70). Although CMR identifies myocardial involvement in SLE, there are no published studies examining the prognostic value of CMR or whether following treatment response using CMR is associated with improved outcomes in these patients.

CMR plays a similar role in other systemic inflammatory disorders such as rheumatoid arthritis, large and medium vessel vasculitides such as Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, and Kawasaki disease; small vessel vasculitides such as microscopic polyangiitis; and necrotizing vasculitides including Wegener disease and Churg-Strauss syndrome. As a group, these vasculitides can be associated with aneurysm, dissection, and narrowing of arteries and tissue level complications such as myocardial

ischemia and infarction. Like SLE, these disorders can also be associated with the development of myocarditis and, as described above, CMR is well suited to evaluate the full range of potential cardiovascular complications that occur in these patients.

Infiltrative Cardiomyopathies

Cardiac Amyloidosis (CA)

CA is a rare infiltrative disorder in which abnormally folded proteins are deposited within the myocardium. There are two major subtypes that must be distinguished from each other: light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis. AL amyloidosis is a plasma cell dyscrasia that is often treated with chemotherapy or stem cell transplantation; whereas, ATTR amyloidosis is due to the production of an abnormally folded transthyretin (i.e. prealbumin) in the liver and targeted treatments are in development. AL amyloidosis is rare and accounts for only a small percentage of patients with CA. On the other hand, the genetic mutations responsible for ATTR are present in 3–3.5% of American of African decent; however, the penetrance of the mutation is not known and the disease is almost certainly underdiagnosed. The annual mortality of both types of CA is relatively high, especially for AL amyloidosis. Given the development of new treatment strategies, there is a need to diagnose the disease during its earlier stages.

During its advanced stages, CA is often suggested on echocardiography by the presence of severe left ventricular hypertrophy with preserved systolic function, dilated atria, and restrictive physiology. CMR is emerging as a valuable tool for the detection of CA. In addition to the classical abnormalities seen during echocardiography, circumferential subendocardial LGE most pronounced at the base and mid-ventricle is present in 80% of patients with CA, with many of the other 20% of patients having alternative patterns of LGE. Diffuse subendocardial LGE has a specificity of nearly 95% for the diagnosis of CA (71,72). The interpretation of LGE images can often be difficult due to the diffuse nature of LGE and because the nulling time of the LV cavity can often be significantly altered. Typically, on inversion recovery imaging, the LV cavity has a significantly shorter inversion time than the normal myocardium. However, in cardiac amyloidosis, the LV cavity and myocardium often have very similar inversion times and occasionally the inversion time of the myocardium is shorter than that of the LV cavity. These characteristic alterations in inversion time can be readily recognized on inversion time scouts acquired after the administration of gadolinium-based contrast agents and have a very high sensitivity for the diagnosis of CA (73). The difference in inversion time between the LV cavity and the myocardium is also an important prognostic marker, as it provides insight into the burden of CA (74). Similarly, the transmural LGE is another important and independent marker of patient prognosis (75), as the presence of transmural LGE is associated with a greater than 5-fold increase in mortality compared to those CA patients without LGE.

Because it is challenging to quantify the burden of LGE in patients with CA, there is a significant interest the use of quantitative ECV measurements. ECV is significantly elevated in CA patients and is inversely correlated with the QRS voltage and other commonly used biomarkers for CA (76). Similarly, because many patients with amyloidosis have renal disease and gadolinium-based contrast agents cannot be used, there has been significant

interest in the utility of native T1-mapping techniques to diagnose CA (Figure 4). Native T1-times have been shown to be significantly elevated in patients with CA and correlated with other relevant biomarkers (77,78). Both native T1-mapping and ECV have also been shown to predict prognosis in these patients (79).

Cardiac Siderosis

Cardiac siderosis or myocardial iron overload is rare but can occur in conditions such as thalassemia or hemochromatosis. Without treatment, it is associated with significant risk of death and heart failure (80). CMR is particularly well suited to quantitatively detect iron overload by taking advantage of the effect of iron deposits on the T2* relaxation time of surrounding protons in the myocardium (Figure 5). The T2* relaxation time linearly falls with increasing iron load (81). The reduction of T2* relaxation time in the presence of myocardial iron overload is only modestly associated with LVEF and is not associated with abnormalities of diastolic function. Cardiac siderosis patients with severe reductions in T2* relaxation time (<10ms) are at risk for ventricular tachycardia despite having a normal LVEF and diastolic function (82,83). A T2* relaxation time of <20ms has been proposed as a cutoff value for diagnosing cardiac siderosis, whereas, a value of <10ms is associated with poor prognosis and requires initiation of iron chelation therapy (84). T2* relaxation times can be serially monitored in patients who are receiving iron chelation therapy whenever the T2* relaxation time drops below a certain threshold. The therapy is continued until the T2* relaxation times rise above another threshold. Such a strategy has resulted in a significant decrease in cardiac morbidity and mortality in patients with thalassemia who require frequent blood transfusions (80).

Anderson-Fabry Disease (AFD)

Anderson-Fabry Disease is an X-linked lysosomal storage disease characterized by deficiency of α -galactosidase A. Early CMR studies of AFD showed LGE related to the extent of LVH, typically located in the basal inferolateral wall and in the midwall or subepicardium(85). T1 mapping in Anderson-Fabry disease demonstrates characteristically reduced native T1 in patients with phenotypic LVH compared to other hypertrophic diseases (86) (87) which generally have an elevated T1. AFD patients also demonstrate an intermediate reduction in native T1 before the onset of hypertrophy (88). CMR has been used to follow regression of LVH with enzyme replacement therapy in this disorder (89).

Conclusion

Although a discussion of all the available data related to the utility of CMR in non-ischemic cardiomyopathy is beyond the scope of this review, we have selected representative disease states to demonstrate its value. Its ability to characterize the myocardium using techniques such as LGE, T1-mapping, T2-mapping, T2*-imaging, and ECV provides important insights into the underlying etiology of a cardiomyopathy. It additionally can be used to help risk stratify patients, guide patient management plan, and evaluate treatment response. CMR should be routinely used in the workup of patients with non-ischemic cardiomyopathy.

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Abbreviations

CMR	cardiac magnetic resonance
LGE	late gadolinium enhancement
ECV	extracellular volume
LVEF	left ventricular ejection fraction
ICD	implantable cardioverter defibrillator
SCD	sudden cardiac death
HCM	hypertrophic cardiomyopathy
LVNC	left ventricular noncompaction
DMD	Duchenne’s muscular dystrophy
ARVC	arrhythmogenic right ventricular cardiomyopathy
SLE	systemic lupus erythematosus
CA	cardiac amyloidosis

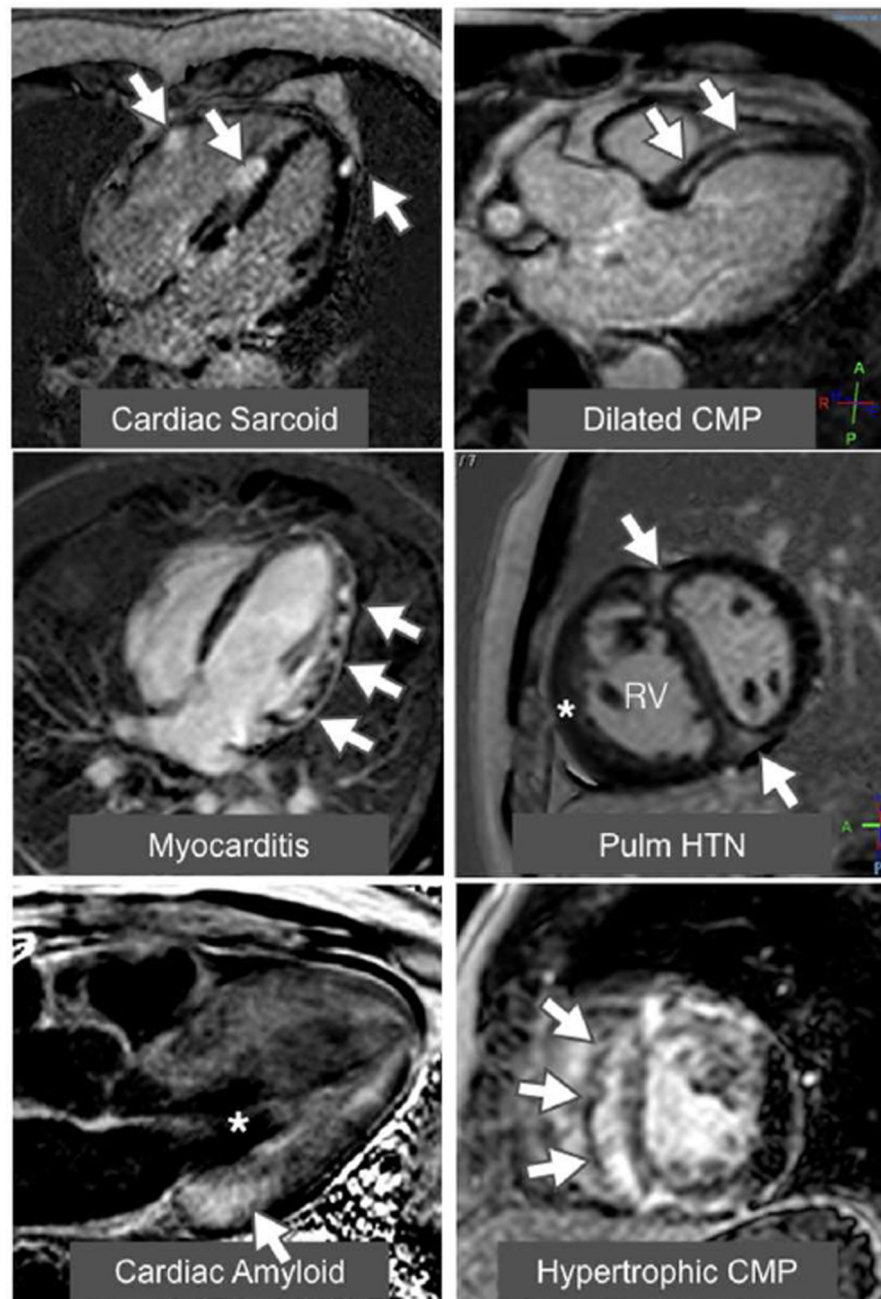


Figure 1. Examples of late gadolinium enhancement (LGE) in a variety of nonischemic cardiomyopathies

The top left image shows a 4-chamber view of a patchy distribution of late mid wall and epicardial LGE in a patient with cardiac sarcoidosis. The top right image shows a 3-chamber view of a mid-wall stripe pattern of LGE in a patient with dilated cardiomyopathy. The middle left image shows a 4-chamber view of patchy epicardial and midwall LGE along the lateral wall in a patient with myocarditis. The middle right image shows a mid-ventricular short axis image in a patient with pulmonary hypertension with right ventricular (RV) dilation and hypertrophy (*) along with LGE in the anterior and inferior right ventricular insertion points (arrows). The bottom left image shows a 3-chamber view of a LGE image in

an amyloid patient. The left ventricular blood pool is nulled (*) and there is subtle circumferential subendocardial LGE throughout the left ventricle (LV). The LGE is most pronounced at the base of LV within hypertrophied myocardium. The bottom right image shows a mid-ventricular short axis image in a patient with HCM with evidence of asymmetric septal hypertrophy with extensive mid-wall LGE within the hypertrophied myocardium.

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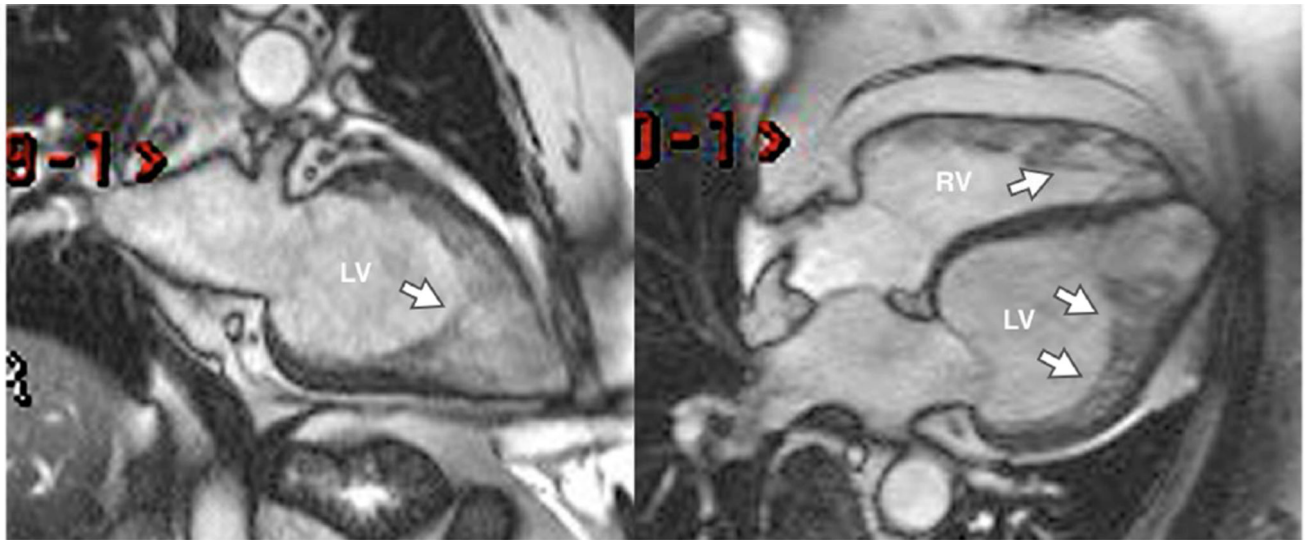


Figure 2. LV Noncompaction

Diastolic still frames from cine images of a two chamber view (left) and four chamber view (right) are shown. The myocardium is thin and the left ventricle (LV) and right ventricle (RV) are heavily trabeculated (arrows).

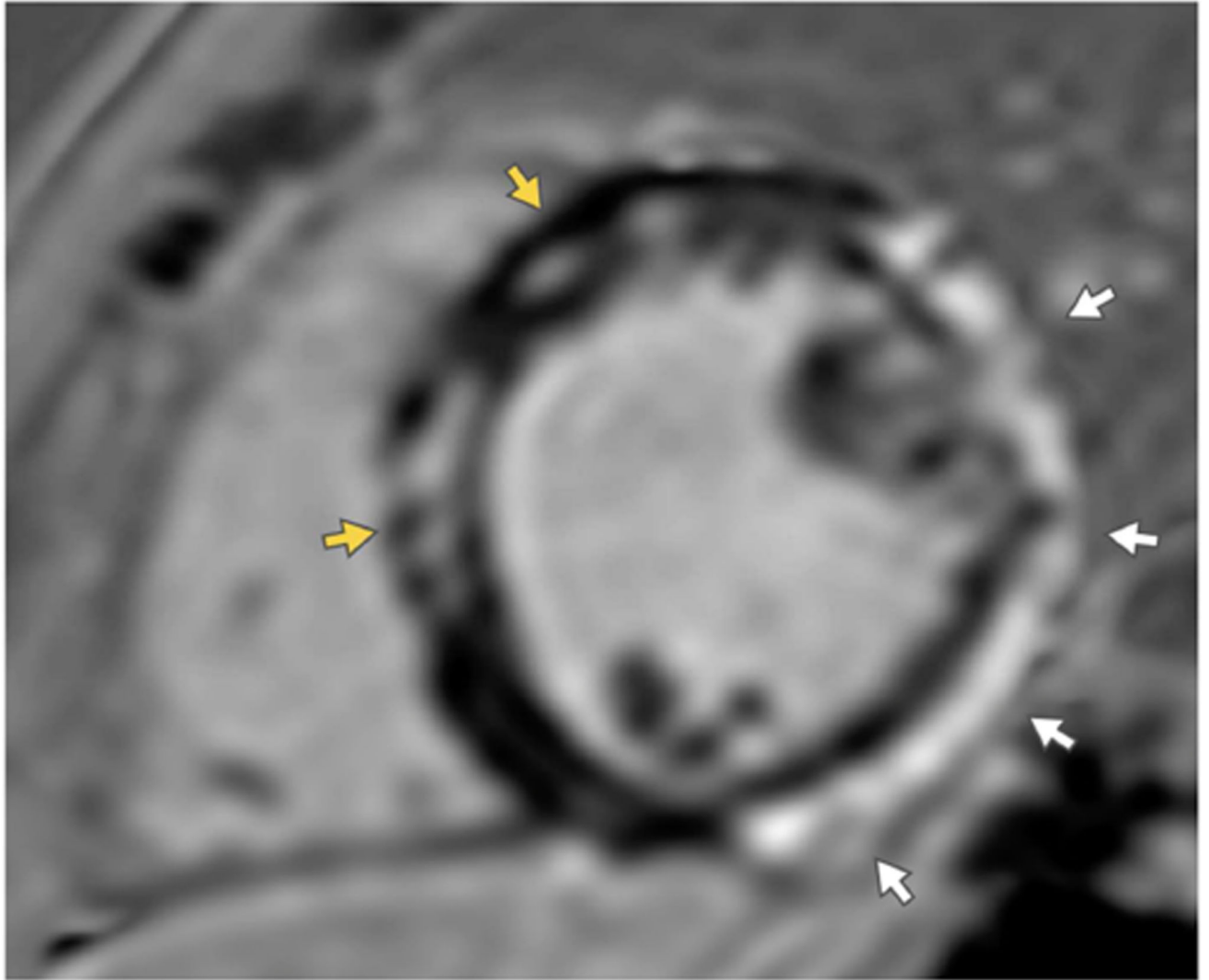
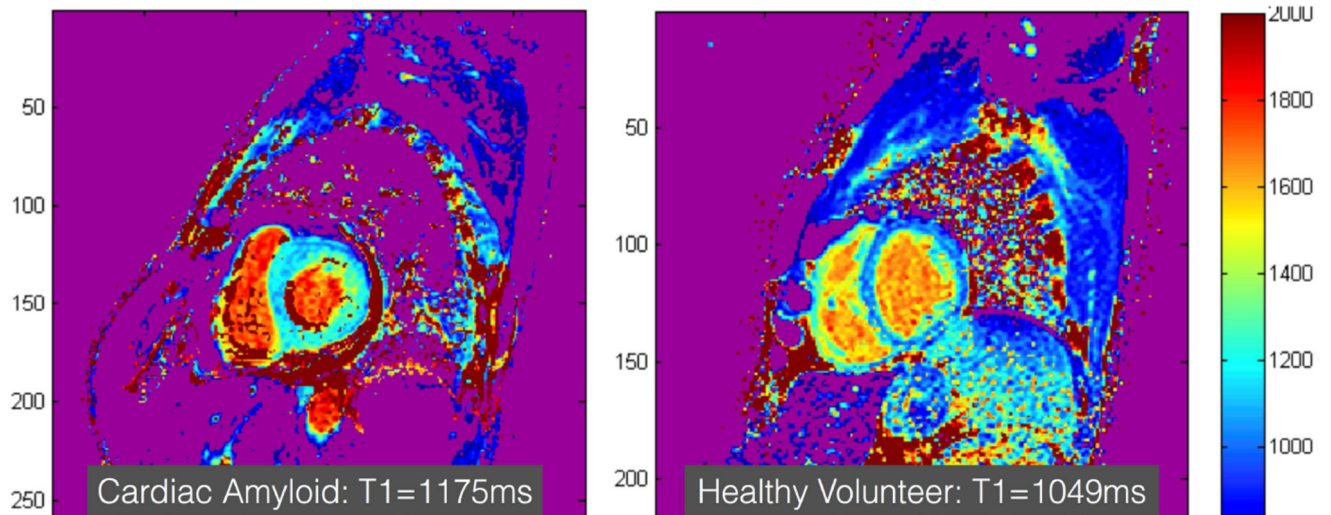


Figure 3. Duchenne's Muscular Dystrophy

A short axis image of the mid ventricle obtained in a patient with Duchenne's Muscular Dystrophy shows epicardial late gadolinium enhancement (LGE) along the lateral wall (white arrows) and mid-wall LGE in the septum.

**Figure 4. Cardiac amyloidosis**

Short axis images of the mid ventricle encoded with a native myocardial T1-color map generated from a series of images acquired at increasing repetition times acquired using MODified Look Locker Image (MOLLI) pulse sequence is shown in a patient with cardiac amyloidosis (left) and a healthy volunteer (right). The T1-time shown in this figure are obtained from a region of interest drawn manually in the inter-ventricular septum. The T1-times can be even higher in patients with more extensive cardiac amyloidosis than the example shown here. Normal native T1 value on the particular scanner used to acquire these images is <1050ms.

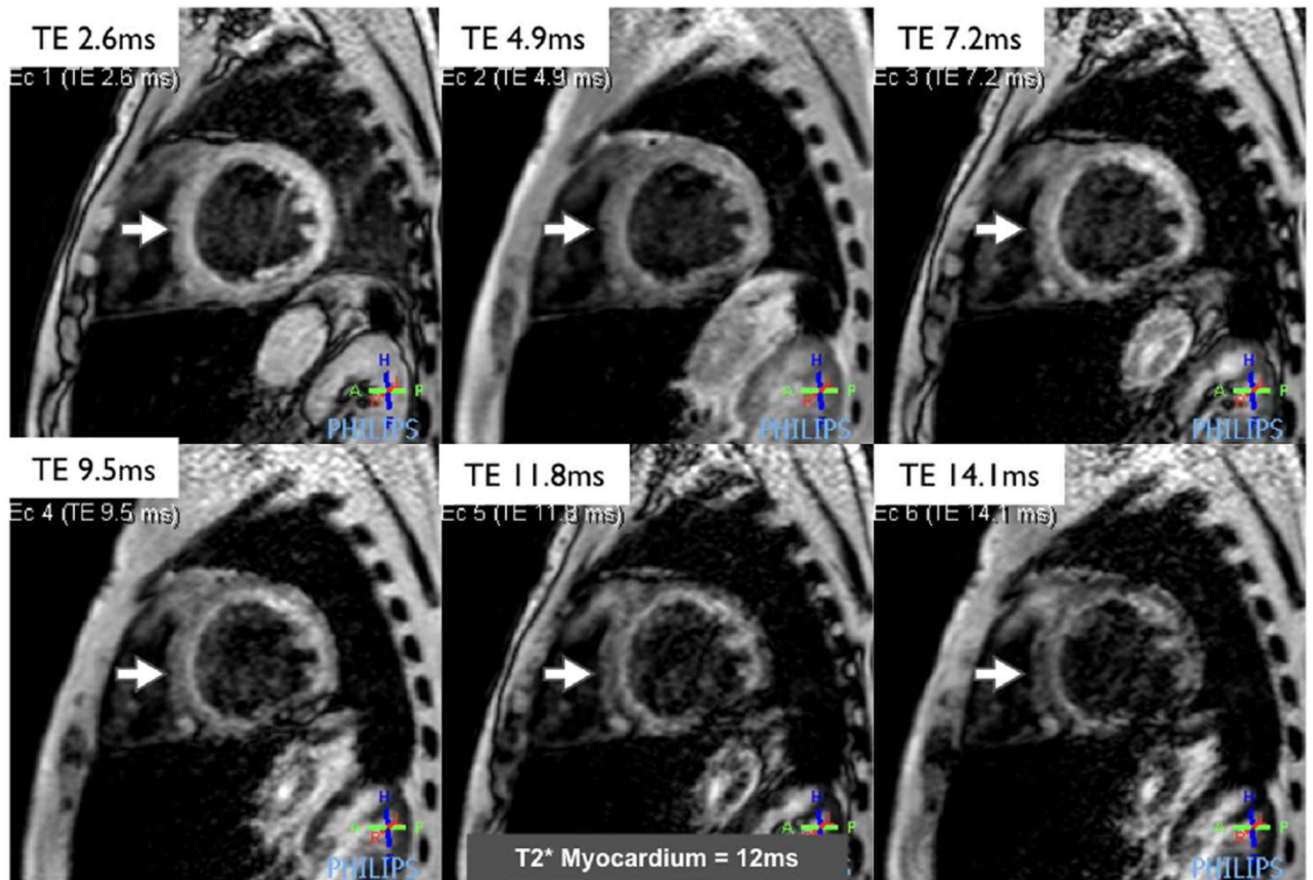
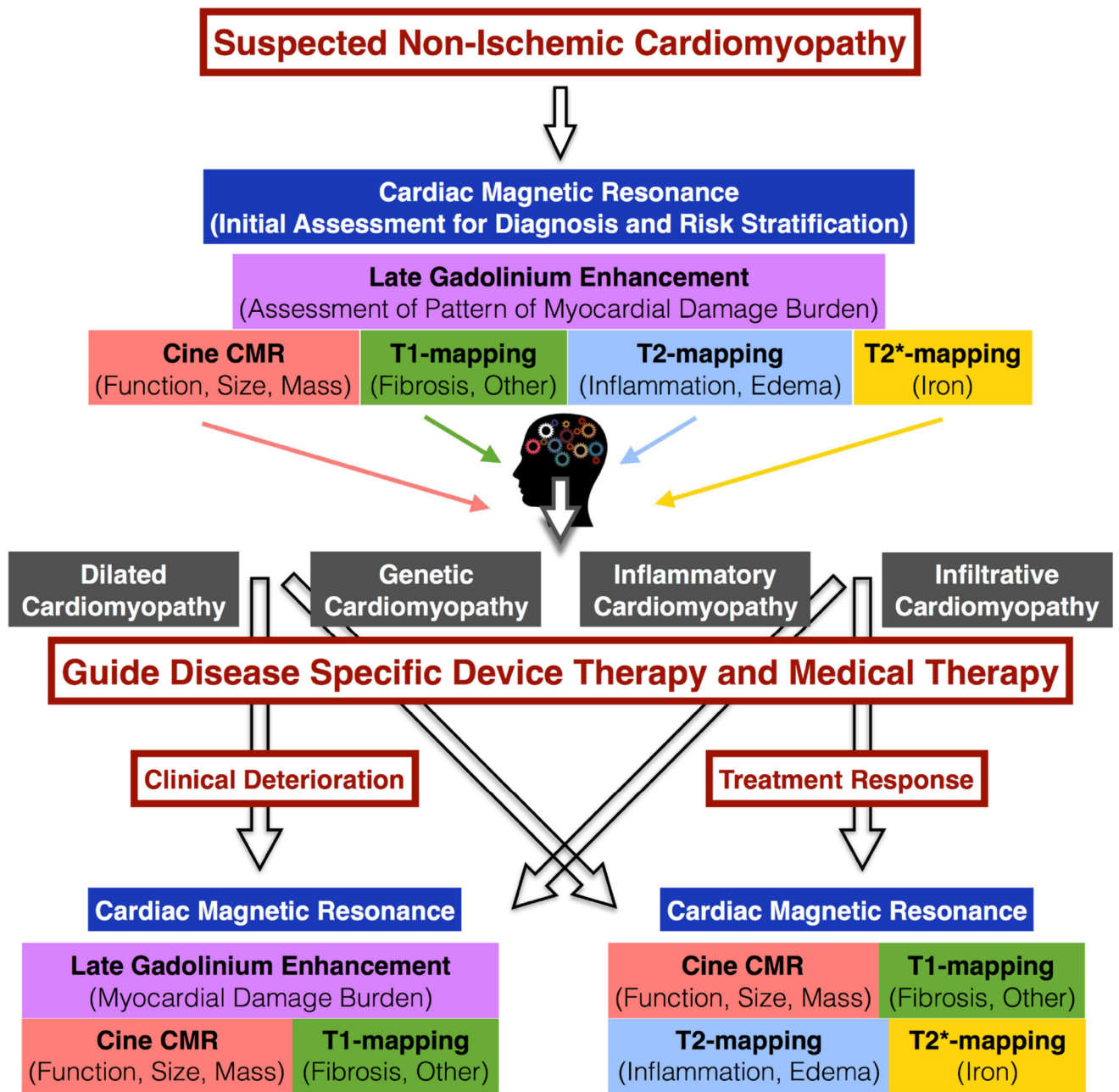


Figure 5. Cardiac siderosis

A series of left ventricular short axis images acquired using a single breath-hold T2* pulse sequence in a patient with sickle cell anemia. A series of images are acquired at increasing echo times (TE). The signal intensity in the myocardium decreases as the TE increases. The rate of decay is used to calculate the T2* relaxation time, which is reduced in this patient and indicates the presence of significant myocardial iron overload.



Central Illustration. Evaluation of Non-ischemic Cardiomyopathy Using Cardiac Magnetic Resonance

This chart demonstrates a potential approach for incorporating the use of cardiac magnetic resonance for the initial evaluation and follow up of patients with cardiomyopathy.