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Heart Failure (W Tang, Section Editor)

Advances in MRI Applications to Diagnose and Manage Cardiomyopathies

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Abstract

Purpose of review The prevalence of heart failure continues to rise, and imaging characterization of the cardiomyopathic process is important for identifying myocardial disease, initiating appropriate treatment, and improving outcomes. We aimed to summarize recent advances in cardiac magnetic resonance imaging (CMR) applications for the diagnosis, characterization, and implications on management of various cardiomyopathies.
Recent findings Parametric mapping by CMR has emerged as an important advancement in quantification of myocardial fibrosis, increased extracellular space, and myocardial edema. In addition, improved assessment of myocardial function with myocardial strain assessment may provide early identification of patients at risk and determining responsiveness to therapeutic interventions. Novel MRI techniques and the advent of artificial intelligence may help to uncover important mechanistic insights into the cardiomyopathic process.
Summary Innovative CMR techniques continue to evolve, and it will be of interest to determine how these advances can be incorporated into clinical practice to improve diagnosis, treatment, and management of patients with cardiomyopathies.

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Introduction

The prevalence of heart failure continues to rise, and over 1 million hospitalizations each year are due to heart failure (HF). By 2030, the prevalence of HF is estimated to increase 25% from 2013 [1]. Heart failure is associated with 50% mortality at 5 years. Therefore, cardiac imaging has emerged as a critical tool for the diagnosis and assessment of response to various treatment strategies. Early identification of the underlying etiology of HF of utmost importance, as early initiation of disease-specific treatment, may result in improved outcomes.

While echocardiography is an essential imaging modality and is ideal for initial screening, cardiac magnetic resonance imaging (CMR) has emerged as a powerful imaging tool, providing three-dimensional assessment of contractile function and myocardial tissue characterization which is essential for differential diagnosis and clinical management of the various cardiomyopathies. CMR is the gold standard for quantification of left ventricular volumes and function, with superior reproducibility [2–4]. Contrast-enhanced CMR also provides assessment of viability, infarct quantification/characterization, ischemia, and accurate identification of ventricular thrombus [5, 6].

The purpose of this review is to present the latest advances in CMR techniques to diagnose and manage the various types of cardiomyopathies.

Advanced techniques in CMR

A standard comprehensive CMR test includes T1- and T2-weighted sequences, cine functional analysis, perfusion imaging, and late gadolinium enhancement (LGE) to assess fibrosis. Advances in MRI techniques that have emerged include T1 mapping and ECV quantification, T2 mapping, myocardial strain, MRI spectroscopy, MR elastography, MR fingerprinting, and diffusion tensor imaging [7].

Quantitative T1 mapping and ECV quantification

Common pathophysiologic features of many of the various cardiomyopathies include interstitial fibrosis, replacement fibrosis, deposition of extracellular proteins, and myocardial edema. While late gadolinium enhancement (LGE) has been shown to be an extremely robust and powerful tool for identifying replacement fibrosis, the technique assumes that reference non-enhanced myocardium is healthy. However, because the myocardium is diffusely diseased in many of the cardiomyopathic processes, LGE assessment is limited in accurately providing more precise quantitative tissue characterization. Several techniques for T1 mapping have emerged, and numerous studies have demonstrated the utility of T1 mapping and extracellular quantification in patients with heart failure with preserved ejection fraction (HFpEF), hypertensive heart disease, myocarditis, valvular heart disease, hypertrophic cardiomyopathy, amyloidosis, and Fabry's disease [8–15].

T2 and T2* mapping

T2 mapping can be utilized to detect and quantify the extent of myocardial edema in patients with acute myocardial infarction, myocarditis, stress cardiomyopathy, and sarcoidosis. T2 mapping has also been used as a powerful non-invasive method for transplant monitoring and cardiac allograft rejection [16]. T2 relaxation time is lengthened in myocardial edema due to increased

interstitial free water. In addition, T2* relaxation time can be used to assess for iron deposition in tissues. A normal mean T2* above 40 ms has been considered normal (healthy volunteers). The presence of increased tissue iron yields faster T2* relaxation and can be visualized as darkening of myocardial tissue due to iron load [17]. T2* has also been used to monitor treatment response of iron chelation therapy, with improvement in T2* and LVEF after therapy [18].

MR fingerprinting

MR fingerprinting (MRF) is a novel technique that uses measured MR signal evolutions which are matched to a dictionary of signal evolutions to yield quantitative information about the underlying myocardium. Instead of conducting repeated serial acquisition of data, MRF uses a highly-accelerated, pseudo-randomized acquisition that causes signals from various tissues to formulate a unique 'fingerprint' that is matched to predicted signal evolutions typically generated with a Bloch simulator [19]. With the use of this pattern matching approach, MRF can achieve high scan efficiency while improving robustness to noise or motion. The method enables simultaneous mapping of T1, T2, and proton density and has been extended to fat fraction mapping [20••], simultaneous multi-slice [21], and simultaneous acquisition of cine tissue maps via cine-MRF which can be used for ejection fraction quantification [22]. This technique holds great promise for providing a more powerful method for providing comprehensive assessment of myocardial tissue characterization and structure.

Myocardial strain

Myocardial strain can be assessed by CMR by myocardial tagging, strain-encoded imaging (SENC), phase velocity mapping, and deformation encoding with stimulated echoes (DENSE), and feature tracking with cine SSFP imaging. Global longitudinal strain by speckle-tracking echocardiography has been shown to provide early detection of decreased myocardial contractility in valvular heart disease and in cardio-oncology patients. Therefore, quantification of myocardial deformation and contractility by CMR techniques may also prove to provide important mechanistic insights into cardiomyopathic processes.

Quantitative myocardial perfusion imaging

Quantitative myocardial perfusion imaging can aid in the evaluation of microvascular dysfunction. In myocardial perfusion imaging, gadolinium contrast material is injected, and a series of images, typically T1-weighted, are acquired before and during the uptake phase as well as during the wash-out phase [23]. Whereas visual assessment of uptake has been reported for the evaluation of ischemia for some time [24], and quantitative perfusion has been explored in recent years for coronary disease [25], quantitative perfusion also has great potential to evaluate microvascular dysfunction in cardiomyopathies by quantifying myocardial blood flow at rest and/or stress. For example, patients with dilated cardiomyopathy exhibited elevated resting state myocardial blood flow and reduced myocardial perfusion reserve compared to controls, suggesting a reduced vasodilatory capacity [7]. Patients with hypertrophic cardiomyopathy similarly exhibited a stunted myocardial perfusion reserve that was associated with late gadolinium enhancement [26]. Perfusion imaging can also quantify tissue permeability and myocardial blood volume [27], both of which may

change in the presence of cardiomyopathies. Thus, perfusion imaging will likely grow as a methodology to characterize the myocardial microvascular which can aid in disease diagnosis and management.

MRI spectroscopy and MR elastography

MRI spectroscopy is an advanced technique for measurement of adenosine triphosphate (ATP) and phosphocreatine (PCr), and PCr/ATP ratio has been established as biomarker for most major cardiac disease states such as dilated cardiomyopathy [28]. Another emerging imaging approach in CMR is shear wave elastography. Using 3D high-frequency cardiac MR elastography technique, myocardial stiffness can be measured and quantified in diseases such as cardiac amyloidosis [29].

Diffusion tensor imaging

Diffusion tensor imaging is a technique that is sensitive to anisotropic diffusion of water in tissue and allows for nondestructive examination of myocardial tissue structure. This technique can be used to assess for directionality of myocardial fibers and laminar sheets without histology of tissue. Studies have been able to show the orientation of myocardial fibers in various diseases without tissue sampling; for example, HCM patients demonstrated myocardial fibers primarily oriented in an abnormal fashion both in systole and diastole [30, 31].

While MRI spectroscopy, elastography, and diffusion tensor imaging provide fascinating insights into the pathophysiology and mechanism of myocardial disease, they require specialized imaging protocols which are not widely available and are currently limited to research applications.

CMR in cardiomyopathies

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a leading cause of heart failure and is characterized as impairment in systolic LV function, with ventricular chamber enlargement but normal ventricular wall thickness. There are various causes of DCM including idiopathic, familial, viral, and inflammatory diseases [32]; however, the etiology of the initiating myocardial insult or remodeling is often unclear. Despite the use of modern heart failure therapies, a large study of 8000 patients demonstrated a high mortality rate of close to 20% at 27 months [33]. Given the potential for elucidating the complex mechanistic interplay between myocardial tissue characterization, remodeling, and function, CMR is the ideal imaging modality to guide the development of novel treatment strategies and development of pharmacologic therapies to impact clinical outcomes.

Myocardial fibrosis has been shown to play an integral role in the pathophysiology of DCM. The two predominant types of fibrosis seen in DCM are permanent replacement fibrosis and diffuse interstitial fibrosis [34]. CMR-LGE has been shown to correlate with isolated, irreversible replacement fibrosis, whereas T1 mapping correlates with diffuse myocardial fibrosis, and has been validated with histology [35]. Identifying the presence of both categories of myocardial fibrosis provides important prognostic risk stratification. The presence of LGE within first 2 weeks of diagnosis of DCM is independently associated with increased rehospitalizations for heart failure and absence of LGE

predicts favorable long-term survival [36, 37]. Moreover, Raman et al. demonstrated that presence of mid-wall LGE discovered at the initial presentation was independently associated with subsequent MACE [36] and the presence of midwall fibrosis is an independent prognosticator beyond LVEF [38].

Among patients with DCM, LGE has been shown as a strong and independent predictor of ventricular arrhythmias and sudden cardiac death in a meta-analysis studying 2948 patients [39••]. This association between LGE and malignant arrythmias even in patients with LVEF is greater than 35% [39]. LGE may play a role in risk-stratifying patients to determine patients that would benefit from implantable cardioverter defibrillator (ICD) implantation, despite normal LVEF. Furthermore, LGE may be helpful in not only determining those that benefit from ICD placement, but also predicting response to biventricular pacemaker resynchronization therapy. Leyva et al. demonstrated that LGE-guided left ventricular lead implantation was associated with improved clinical outcomes after resynchronization therapy [40]. In addition, left ventricular septal midwall fibrosis has been shown to be an independent predictor of morbidity and mortality in patients with DCM undergoing resynchronization therapy [41].

T1 mapping has emerged as a powerful technique to provide further important risk stratification in patients with DCM [42]. In fact, increased native T1 time/ECV fraction emerged as stronger prognostic predictors of all-cause mortality and heart failure endpoints compared to LGE in a prospective multicenter longitudinal study of 637 patients with DCM [43].

New CMR techniques such as CMR spectroscopy have also been recently studied and used as non-invasive tool for assessing myocardial metabolism and predict mortality in DCM patients [44]. Cardiac magnetic resonance fingerprinting may provide superior comprehensive parametric quantification of T1, T2, and ECV. This novel parametric technique has potential for improved standardization and reproducibility of measurements, which will be essential for directing therapies and assessing response to treatment.

Myocarditis

Given the ability to provide comprehensive myocardial tissue characterization, CMR has emerged as the primary imaging modality for the evaluation of patients with suspected myocarditis. Traditionally, the hallmark features of myocarditis, assessed by CMR, were outlined in the original Lake Louise Criteria and included edema (regional or global myocardial signaling intensity increased in T2-weighted images), hyperemia (calculated global myocardial early gadolinium enhancement ratio between myocardial and skeletal muscle T1-weighted images), and necrosis (LGE in non-ischemic pattern). The presence of two out of the three criteria was associated with accurate diagnosis of acute myocarditis in almost 80% of cases [45] (Fig. 1). However, given the advent of parametric mapping, the Lake Louise criteria were recently updated. This updated criteria categorized abnormal CMR findings into T2-based criteria (global or regional increase on T2 relaxation time measured by T2 mapping, or increased signal on T2-weighted imaging) and T1-based criteria (increased native T1 time, increased ECV, or presence of LGE). Fulfilling at least of the criteria for both of the T1/T2 parameters is likely to increase the specificity of the diagnosis of acute myocarditis. While the expert panel decided that having only two of the criteria could still be consistent with the diagnosis of acute myocarditis in the

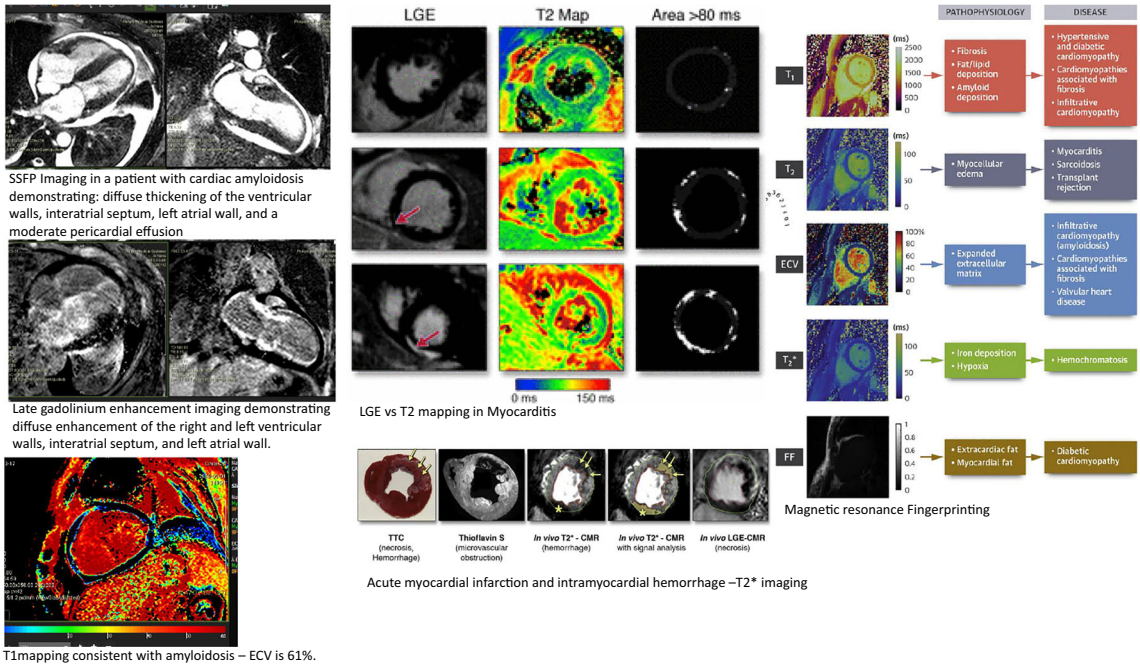

Fig. 1. Tissue characterization with Cardiac MRI.

correct clinical context, the presence of only one criteria could result in decreased specificity [46••] (Table 1).

Recently, a large study of 670 patients with suspected myocarditis demonstrated the ability of LGE to predict adverse outcomes. This study also demonstrated that not only the presence, but also the location and pattern of LGE was also important to determine adverse outcomes, with septal and mid wall LGE demonstrating independent association with adverse outcomes [62]. It is also important to note that only 44% of patients with suspected myocarditis demonstrated LGE. Therefore, T1 and T2 mapping techniques are likely more sensitive in identifying patients with increased extracellular space due to inflammation, which has not resulted in cell necrosis. Native T1 and ECV have shown to identify this pattern of myocardial injury in patients with normal appearing, LGE negative myocardium. While T2 mapping should theoretically be the ideal technique to identify and quantify myocardial inflammation, this technique has not been shown to be as robust as T1 mapping, and normal T2 values may be seen even in diseased areas [57, 63]. Given the importance of both T1 and T2 criteria for the diagnosis of myocarditis, cardiac magnetic resonance fingerprinting may emerge as a powerful technique for quantifying the degree of myocardial inflammation, necrosis, and may provide more robust prediction of ensuing adverse ventricular remodeling and risk for malignant ventricular arrhythmias.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is present in one in 500 of the general population and is the most frequent cause of sudden cardiac death in young people [47]. HCM can lead to heart failure and is often identified by unexplained left ventricular hypertrophy (wall thickness > 15 mm) on echocardiogram or CMR. Although ACC/AHA guideline recommends EKG and echocardiogram as

Table 1. Various types of cardiomyopathies

Type of cardiomyopathy	T1 mapping	T2 mapping	T2 STIR	Cine imaging	LGE
	Increased native T1 time/ECV correlates with interstitial fibrosis and/or increased extracellular volume	Quantifies the degree increased water content which correlates with severity of myocardial edema.	Identifies areas of increased water content.	Precise assessment of ventricular volumes and ventricular mass	Identifies areas of replacement fibrosis
Dilated CM Key References: # [36, 37, 39••, 42, 43]	**Diagnostic utility:** Can be used to detect more subtle interstitial fibrosis or inflammation that would otherwise be missed by delayed enhancement **Therapeutic utility:** Potential for tracking response to treatment. Increased values are also associated with increased risk had may help to guide therapeutic strategies for more advanced heart failure therapies. **Limitations:** Limited standardization of technique and threshold values	**Diagnostic utility:** presence of myocardial edema raises concern for the presence of myocarditis or sarcoidosis **Therapeutic utility:** can be used to track response to treatment or resolution of the acute injury **Limitations:** Limited standardization of technique and threshold values. Imaging technique is sensitive to artifacts	**Diagnostic utility:** similar to T2 mapping **Therapeutic utility:** To be determined **Limitations:** inability for quantification, and artifact prone	**Diagnostic utility:** Gold standard method of quantifying ventricular dysfunction **Therapeutic utility:** use to guide response to treatment and decision-making regarding implantation of CRT/ICD	**Diagnostic utility:** patterns of fibrosis can identify the underlying etiology of fibrosis **Therapeutic utility:** Predicts ventricular arrhythmias and mortality. Could help to guide decision making regarding implantation of devices or pursuit of more aggressive advanced heart failure therapies **Limitations:** Assumes normal remote myocardium. Limited standarization of thresholding techniques for quantification of LGE
Hypertrophic CM Key References: # [47–50]	**Diagnostic utility:** Identifies myocardial scarring as well as interstitial fibrosis and ECV fraction can be used to differentiate HCM from myocardial hypertrophy of athletes or hypertensive heart disease **Therapeutic utility:** To be determined	**Diagnostic utility:** Variable, shows myocardial edema which can occur within LGE areas. **Therapeutic utility:** To be determined	**Diagnostic utility:** Hyperintensity correlated with greater LV mass, lower LVEF, and increased risk of arrhythmic burden. **Therapeutic utility:** Can determine those that have worse HCM and in need of aggressive therapies.	**Diagnostic utility:** Assess morphology of HCM, measure cardiac function and define between various HCM phenotypes. **Therapeutic utility:** Assessment of ventricular morphology, and mechanism of LVOT obstruction	**Diagnostic utility:** LGE pattern can help differentiate differential diagnosis for the etiology of left ventricular hypertrophy/increased wall thickness. LGE assessment provides risk stratification for VT and sudden cardiac death. **Therapeutic utility:** > 15% of LV mass LGE might require ICD placement or myectomy.
Amyloidosis Key references: # [51, 52••, 53]	**Diagnostic utility:** Significantly elevated Native T1 time and ECV fraction are diagnostic for amyloidosis. Improved sensitivity and can provide early detection of cardiac amyloid. **Therapeutic utility:** Can be used to assess treatment response.	**Diagnostic utility:** Native T2 mapping can differentiate between light chain and transthyretin amyloid, with increased T2 in light chain comparatively. **Therapeutic utility:** To be determined	–	**Diagnostic utility:** Quantification of LV size, function, and degree of wall thickening of the cardiac chambers **Therapeutic utility:** Assess progression or stabilization of ventricular wall thickening with disease progression or response to treatment	**Diagnostic utility:**. LGE pattern can help differentiate differential diagnosis for the etiology of left ventricular hypertrophy/increased wall thickness. LGE assessment provides risk stratification **Therapeutic utility:** Prognostic risk stratification can help guide treatment decisions **Limitation:** LGE imaging quality is often significant adversely affected in patients with advance amyloidosis due to abnormal gadolinium kinetics. GLE is insensitive to early amyloid deposition

Table 1. (Continued)

Type of cardiomyopathy	T1 mapping	T2 mapping	T2 STIR	Cine imaging	LGE
Sarcoidosis Key references: # [54, 55]	**Diagnostic utility:** Native T1 and ECV assessment can quantify the extent of myocardial involvement. **Therapeutic utility:** T1 mapping along with T2 mapping show response to anti-inflammatory treatment and can therefore be used to assess response to therapy.	**Diagnostic utility:** Can be utilized in detection of myocardial inflammation and early cardiac involvement in systemic sarcoidosis. **Therapeutic utility:** Can be used to track response to treatment with anti-inflammatory agents.	–	–	**Diagnostic:** LGE pattern can help identify enhancement pattern that is characteristic of sarcoidosis. Presence of LGE is independent predictor of sudden cardiac death. **Therapeutic utility:** Not well studied in assessing treatment response, however can identify those at risk for worse prognosis and who may benefit from device therapy and/or advance heart failure management strategies.
Siderosis Key references: # [19, 56]	**Diagnostic utility:** T1 mapping has been shown to detect iron even in those with normal T2* time **Therapeutic utility:** Unclear at this time but could be used to track response to treatment.	–	**Diagnostic utility:** T2* relaxation time decreases in presence of iron overload. T2* < 10 ms is associated with ventricular tachycardia despite normal EF. **Therapeutic utility:** Highly reduced T2* time is associated with worse outcomes, indicating need for aggressive intervention	–	–
Myocarditis Key references: # [57, 58]	**Diagnostic utility:** T1 mapping and ECV can be used to identify myocardial inflammation/myocyte cell necrosis/fibrosis. **Therapeutic utility:** Can be used assess extent of inflammation, which may guide therapeutic/management decisions	**Diagnostic utility:** Can identify and quantify the degree of myocardial inflammation **Therapeutic utility:** Can be used assess extent of inflammation, which may guide therapeutic/management decisions **Limitations:** More prone to artifacts and myocardial edema is unstable in myocarditis which could result in normal T2 values.	**Diagnostic utility:** Higher global STIR ratio is seen. This ratio is reduced in follow up after therapy. **Therapeutic utility:** Can be used assess extent of inflammation, which may guide therapeutic/ management decisions	**Diagnostic utility:** Assessment of impact on ventricular function and adverse remodeling	**Diagnostic utility:** Extent, pattern, and location of LGE is important of diagnosis and risk stratification **Therapeutic utility:** Extent of enhancement may guide therapeutic/management decisions **Limitations:** LGE is less sensitive to more subtle or diffuse areas of myocardial inflammation.
Ischemic Cardiomyopathy Key references: # [59] LVNC Key references: # [60, 61]	**Diagnostic utility:** Detects acute myocardial infarction in both STEMI and NSTEMI patients,. Can be used to define the peri-infarct zone/area-at-risk. Can be used to determine extent of diffuse interstitial fibrosis in the remote myocardium. **Therapeutic utility:** T1 mapping can help determine between acute and chronic MI, and help determine urgency of reperfusion therapy.	--**Diagnostic utility:** Identify area of microvascular obstruction and T2* imaging can help to discern intramyocardial hemorrhage **Therapeutic utility:** Further infarct characterization which may be important for determining risk for subsequent adverse events and management strategies.	**Diagnostic utility:** Identify area of microvascular obstruction and intramyocardial hemorrhage **Therapeutic utility:** patients with intramyocardial hemorrhage are at higher risk for adverse remolding and should be followed more closely. -	**Diagnostic utility:** Assessment of impact on ventricular function and adverse remodeling, and presence of ischemic mitral regurgitation **Therapeutic utility:** Can guide decision to refer patients for device therapy (ICD/CRT) based on degree of left ventricular dysfunction	**Diagnostic utility:** Infarct characterization can provide important risk stratification that can guide management decisions regarding revascularization, mitral valve intervention, ICD/CRT implantation **Limitations:** Assumes normal remote myocardium. Limited standardization of thresholding techniques for quantification of LGE

initial evaluation modalities, CMR provides superior assessment of left ventricular morphology, distribution of left ventricular hypertrophy (LVH), papillary muscle morphology, and mitral valve geometry, which are essential to determine the mechanism of left ventricular outflow tract obstruction (LVOT) [64].

Myocardial fibrosis is one of the hallmark features of HCM, and the presence and extent of LGE have been shown to be independently associated with greater burden and longer episodes of nonsustained ventricular tachycardia [65]. A meta-analysis of approximately 3000 HCM patients demonstrated that the presence of LGE was associated with 3.4-fold increase in risk of sudden cardiac death, 2.9-fold increase in cardiac mortality, and 1.8-fold increase in all-cause mortality [48]. LGE > 15% LV mass has been defined as the threshold of fibrosis that is associated with increased risk, and a recent study also demonstrated that patients with > 15% LGE was significantly associated with a higher rate of myectomy, increased risk of SCD, and appropriate ICD discharge even in low-risk patients with HCM [66]. Therefore, LGE > 15% LV should raise consideration for primary prevention therapies for sudden cardiac death with ICD placement [47]. Identification of myocardial edema may also be of importance in HCM, as patients with myocardial hyperintensity on T2-STIR had greater LV mass index, lower EF, and greater extent of LGE with increased arrhythmic burden [49]. Myocardial strain analysis might play a role in early identification of HCM, given that the difference in strain between endocardium and epicardium may be abnormal even in patients with early HCM with normal ventricular wall thickness [67]. In addition, studies in CMR spectroscopy have shown reduced PCr/ATP ratio in patients with asymptomatic HCM and are present despite degree of LV hypertrophy. This indicates the utility of CMR spectroscopy to assess metabolic derangement in myocardial tissue early into the disease, even prior to the development of overt hypertrophy [68]. Therefore, MR spectroscopy provides further differentiation in genotype-positive patients, or patients with family history of HCM, but with phenotypically normal left ventricular morphology.

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is defined as nondilated left or right ventricular diastolic dysfunction and most often caused by infiltrative disorders such as cardiac amyloidosis or cardiac sarcoidosis, storage diseases such as hemochromatosis, noninfiltrative disease such as idiopathic or scleroderma, and endomyocardial diseases such as heart failure due to chemo/radiation therapy, carcinoid, etc. Restrictive physiology results from increased myocardial stiffness leading to impaired ventricular filling, usually in the setting of normal biventricular chamber size [51].

Cardiac amyloidosis

Extracellular deposition of misfolded proteins is the hallmark of cardiac amyloidosis (CA), which leads to cardiomyocyte separation, cellular toxicity, and tissue stiffness [51]. Differentiating between CA and other diseases that result in increased ventricular wall thickness is often difficult to discern by echocardiography alone. Given the superior ability to provide tissue characterization, CMR can play a critical role in diagnosis. Amyloidosis typically results in a characteristic LGE pattern, and transmural LGE is associated with 5-fold increase in mortality in CA patients compared to those without LGE [52••]. However,

LGE may not be present in a significant proportion of patients in the early phase of their disease, and therefore, CA may not be appropriately identified by LGE assessment alone [52••, 69]. Because prognosis may be positively impacted by early identification and early treatment of the disease, it is important that patients are diagnosed earlier in their disease course. Myocardial T1 mapping has emerged as an important technique with increased sensitivity for identifying CA and determining the severity of amyloid deposition. Recently, native T1 and ECV values were shown to be elevated even in patients whom LGE imaging suggested no cardiac involvement, demonstrating that T1 mapping may provide early detection of CA. Furthermore, the authors of this study demonstrated that the degree of ECV elevation is also associated with worse survival and is also important for risk stratification [53, 69].

Recently, the pattern of amyloid deposition was demonstrated, with greater LGE, native T1, and increased ECV seen at the base than at apex [54]. Similarly, relative apical sparing of longitudinal strain, assessed by CMR feature tracking, has been shown to be specific to cardiac amyloidosis and may be helpful for discerning the presence of amyloidosis from other cardiomyopathies with similar phenotypic appearances [70].

Native T1 and ECV have also been shown to correlate with treatment response in CA. In patients treated with tafamidis, native T1 and ECV showed no significant worsening after 12 months of treatment suggesting that tafamidis may have suppressed disease progression [71]. Myocardial T2 measurement has also been used to differentiate between light-chain versus transthyretin cardiac amyloidosis, however did not impact the overall survival of patients [72]. Advanced CMR techniques, specifically CMR elastography, have also been recently utilized to quantitatively measure myocardial stiffness in patients with cardiac amyloidosis. This technique can help distinguish patients with cardiac amyloid compared to healthy subjects [29]. Given the robust data demonstrating the applicability of T1/ECV mapping in cardiac amyloidosis, cardiac magnetic resonance fingerprinting also may prove to provide important utility in the identification and quantification of amyloid deposition, the degree of myocardial inflammation, and the ensuing impact on adverse ventricular remodeling. Furthermore, cardiac magnetic resonance fingerprinting has the promise of providing the ability to predict and track treatment response.

Cardiac sarcoidosis

Sarcoidosis is inflammatory disorder due to T lymphocytes, mononuclear phagocytes, and noncaseating granulomas. CMR in sarcoidosis patients shows areas of LGE in subepicardial or transmural distribution [51]. Studies have shown that presence of myocardial scar indicated by LGE was the most powerful independent predictor of sudden cardiac death, ICD discharge, and ventricular tachycardia in patients with cardiac sarcoidosis (CS) [19]. Furthermore, the absence of LGE in patients with sarcoidosis and severely decreased LVEF (EF < 35%) was associated with low risk of major cardiovascular events even if the LV was severely enlarged [19]. Recently, conventional cardiac testing was compared with CMR evaluation in 321 patients with biopsy-proven cardiac sarcoidosis, and CMR was found to be the most sensitive and specific test in diagnosing CS, with an area under the curve of 0.984 [73]. However, it is often difficult to detect concurrent inflammation within areas of LGE, and hybrid CMR/PET imaging

has emerged as a novel approach that holds promise for providing more robust evaluation of active sarcoidosis in a single scan [74].

Corticosteroids and immunosuppressive drugs have been primarily used in treatment of CS and CMR can be utilized to gauge clinical response to therapy. T1 and T2 mapping indexes have been shown to identify active cardiac sarcoidosis and were able to track response to anti-inflammatory treatment in CS, which correlated with reduction in C-reactive protein level [55]. Cardiac magnetic resonance fingerprinting has the potential to emerge as a powerful technique for identifying the degree of myocardial inflammation, myocardial fibrosis/necrosis, and the ensuing impact on adverse ventricular remodeling and risk for malignant ventricular arrhythmias in cardiac sarcoidosis.

Cardiac siderosis

Cardiac siderosis is caused by iron accumulation in the cardiac muscle [51] and can include various diseases such as hemochromatosis or thalassemia. CMR has emerged as an extremely useful imaging modality for evaluating patients with hemochromatosis and thalassemia. Myocardial iron overload can be quantitatively measured with T2* imaging. T2* relaxation time decreases in the presence of myocardial iron overload, and T2* relaxation time < 10 ms has been shown to be associated with ventricular tachycardia despite normal LVEF or diastolic function [75]. T1 mapping has been shown to play a complementary role in concordance with T2* in patients with cardiac iron overload. In those with T2* range 20–30 ms, T1 mapping was able to detect iron in cardiac tissue; however, the clinical significance of low T1 with normal T2* has yet to be studied [56].

Ischemic cardiomyopathy

CMR has emerged as the most comprehensive imaging modality for the assessment of ventricular remodeling, scar quantification and characterization, viability assessment, and assessment of ischemic mitral regurgitation. Quantification of myocardial fibrosis assessed by CMR is a powerful independent and incremental predictor of all-cause mortality in patients with advanced ischemic cardiomyopathy. Furthermore, assessment of left ventricular size and myocardial scarring may help to predict which patients will benefit from revascularization and device therapy [76–78].

Adverse ventricular remodeling can affect mitral valve geometry and papillary muscle architecture, resulting in the development of ischemic mitral regurgitation. Because ischemic mitral regurgitation is associated with poor prognosis with limited treatment options for improving outcomes, more sophisticated criteria and imaging parameters are likely needed to stratify survival benefit from procedures such a percutaneous mitral valve repair/replacement. CMR is likely to emerge as an essential imaging tool for establishing selection criteria, as it is best suited to characterize the complex interplay between left ventricular remodeling, infarct characterization, mitral valve/papillary muscle geometry, mitral regurgitation severity, right ventricular remodeling, and the risk for progressive ischemic mitral regurgitation over time [79–82]. Furthermore, assessment of the extent of myocardial scarring has been shown to help predict which patients derive the most benefit from procedural mitral interventions. [74]

Assessing infarct heterogeneity and quantifying the peri-infarct zone with LGE analysis has also been shown to be associated with increased malignant ventricular arrhythmias [83]. Furthermore, CMR-guided VT ablation has been shown to be associated with improved procedural safety and outcomes [5].

T1, T2 mapping, and T2* imaging can be utilized to define acute myocardial infarction, the presence of intramyocardial hemorrhage, and determine the area at risk [84–86]. Diffusion tensor imaging can be used to assess infarcted regions, which display substantial myofiber disarray, and diffusion coefficient is lower in infarcted region and increases a function of time after infarction [87].

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare genetic disease with myocardial fibro-fatty replacement of predominantly right ventricle and can lead to biventricular heart failure and sudden cardiac death [88]. Patients with ARVC are prone to malignant ventricular arrhythmias and often require ICD placement as primary prevention. CMR is an important adjunct in diagnosing ARVC, because of its superior accuracy in measuring RV dilation and dysfunction [89]. However, ARVC cannot be diagnosed with imaging findings alone, and more comprehensive diagnostic system is often needed for this complex disease. The diagnosis of ARVC is based on a scoring system that uses combination of defects in RV morphology, depolarization/repolarization EKG abnormalities, tissue pathology, family history, presence of ventricular arrythmias, and genetic testing [90]. However, there is no single gold standard test in diagnosing ARVC. The CMR imaging criteria for ARVC were simplified in 2010 and involve assessment of right ventricular size, function, and the presence of regional akinesia, dyskinesia, or dyssynchronous RV contraction [89]. While tissue characterization is not included in task force criteria of the diagnosis of ARVC, the presence of LGE and fatty infiltration has been shown to be important for the prediction of risk and adverse cardiac events [91]. Circumferential strain analysis can be measured with tissue tracking software on cine CMR. In a recent study with 21 ARVC patients, global strain was significantly lower in segments with dense scar compared to those without dense scar on endocardial and epicardial voltage mapping. Successful VT ablation sites were found to have lower mean strain compared to rest of the RV and increase in strain correlated with decreased odds of localized VT culprit site. In this study, abnormal regional myocardial strain more accurately identified arrhythmogenic substrate than LGE alone. In addition, strain was lower in segments with LGE compared with those without LGE [92]. LGE in ARVC patients can demonstrate fibrofatty ventricular scar. However, LGE was shown to only modestly correlate with endocardial electroanatomic mapping, likely due to thin RV wall [93].

LV noncompaction

LV noncompaction cardiomyopathy (LVNC) occurs in patients who have poorly formed left ventricle with presence of trabeculations. It is a poorly understood disease and can lead to heart failure and arrythmias. A recent meta-analysis demonstrated the improved diagnostic utility of CMR when compared to echocardiography [94]. However, the clinical significance of identifying LVNC in accordance with the current criteria remains unclear, as there is likely significant overlap between pathologic disease and adaptive left ventricular

remodeling. For example, a few studies have shown that when evaluating these patients with CMR, LV dilation and LGE were both predictors of cardiac events, while the degree of LV trabeculations seems to have no role in prognosis [60, 61].

Fabry's disease

Fabry's disease is a rare X-linked lysosomal storage disorder where sphingolipid accumulates in organs due to mutations in α-galactosidase, with cardiac involvement, causing LVH, fibrosis, or cardiomyopathy, as the leading cause of death in this population [95]. CMR can be used to assess left ventricular mass and LGE has been shown to histologically correlate with replacement fibrosis in this disease, with thinning of basal inferolateral wall and collagen deposition in areas of LGE [96]. Enzyme replacement therapy (ERT) is the only specific treatment for Fabry's disease in those with multiple organ involvement. CMR can also be used to prognosticate and assess treatment response in these patients. LGE distribution pattern has been shown to evolve with disease progression, with initial involvement limited to midwall and epicardial regions of the lateral basal region that transforms into transmural LGE. In patients with high LGE burden, development of myocardial fibrosis cannot be reversed by ERT [97]. Extent of LGE has also been shown to be an independent predictor of ventricular arrhythmias and identification of these patients is important for primary prevention interventions and earlier treatment initiation [98].

Studies have also shown that native T1 is lower in Fabry's disease compared to other LVH etiologies [99]([100]. Pica et al. showed that in subjects with Fabry's disease without LVH, reduced myocardial T1 has a 50% prevalence and is associated with cardiac dysfunction compared with patients with echocardiographic findings consistent with Fabry's disease. These findings suggest that low T1 times can be used to detect early cardiac disease [101]. In severe disease, however, septal T1 values can pseudo-normalize likely due to the development of concomitant myocardial fibrosis [102]. However, because the MR signal of a mixed lipid and fibrotic tissue may differ from a homogeneous normal tissue, the limitation of concomitant fibrosis and lipid deposition may be addressed by recently proposed multi-component decomposition techniques in MRF [20••, 103].

CMR has thus emerged as an important non-invasive tool in detecting fibrosis in Fabry's disease and can be used for prognostication as well as to predict treatment response in this patient population.

Artificial intelligence in CMR

There is tremendous interest in harnessing the possibilities of artificial intelligence to improve CMR image reconstruction, analysis, and diagnostic accuracy. With automated transform by manifold approximation (AUTOMAP), the image reconstruction process can be made more immune to noise and artifacts [104]. Neural networks also may improve the speed and robustness of MR fingerprinting [105] and have potential to improve other mapping techniques. CMR image analysis may be expedited by the development of rapid and robust CMR image segmentation algorithms, e.g., in a deep-learning-based left ventricle segmentation algorithm [106]. Biomarker extraction may be improved;

recently, Oktay et al. described a new image analysis framework that utilizes autoencoder and T-L networks to train neural network (NN) models and demonstrated that learnt codes of 3D shapes can be used as biomarkers for classification of various cardiac pathologies [107]. Last, a vast array of spatial and spatio-temporal textural features may be used as inputs to classification algorithms for disease diagnosis and risk stratification, for example in automated detection of nonviable myocardium using a support vector machine [108]. Because CMR provides the most comprehensive phenotypic assessment, the application of artificial intelligence holds great promise for discovering novel imaging patterns that may greatly impact therapeutic management strategies and outcomes.

CMR limitations and contraindications

It is important to note the major limitations and contraindications of CMR. While non-conditional pacemakers and ICDs were previously considered to be contra-indicated, a large observation study demonstrated the safety of performing CMR on non-conditional pacemakers and defibrillators [109]. Though CMR can now be safely conducted in patients with these devices, and though CMR conditional pacemakers and defibrillators are now widely available, it is important to note that the image quality might be compromised due to the artifact generated by these devices. Cardiac and aortic stents, prosthetic heart valves, IVC filters are CMR safe. Limitations to CMR include ability of patients to hold their breath, claustrophobia, and the risk of developing nephrogenic systemic fibrosis with contrast agents [110]. The presence of any ferrous based metallic foreign body is an absolute contraindication to MRI.

Conclusion

CMR has emerged as an extremely valuable imaging modality in diagnosis, assessment, prognostication, and treatment monitoring of various cardiomyopathies. In this review, we have discussed the use of CMR imaging techniques such as LGE and T1/T2 parametric mapping and how myocardial tissue characterization can impact diagnosis and management of cardiomyopathies. With continued advancement in imaging techniques, CMR continues to provide deeper insights into myopathic pathophysiology, which will likely continue to impact disease management and prognosis.

Compliance with Ethical Standards

Conflict of Interest
Ramya Vajapey, Brendan Eck, and Deborah H. Kwon each declare no potential conflicts of interest.
Wilson Tang is a section editor for *Current Treatment Options in Cardiovascular Medicine*.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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