

Delayed-enhancement cardiac MRI in the evaluation of cardiomyopathies

Cardiomyopathies are a diverse group of disorders with etiologies ranging from ischemic to infiltrative. Clinical differentiation may be complex, but diagnosis is essential as complications include congestive heart failure and sudden death. Recent developments in cardiac MRI, particularly the implementation of delayed-enhancement imaging has introduced a novel approach to noninvasive tissue characterization that can more accurately differentiate the spectrum of cardiomyopathies. This article summarizes the comprehensive diagnostic abilities of cardiac MRI in defining cardiac anatomy and physiology and, more importantly, identifying pathologic tissues and differentiating those with substrates amenable to therapy. The value of delayed-enhancement imaging in prognostics will also be presented.

KEYWORDS: cardiomyopathy ■ infiltrative disorders ■ ischemic heart disease ■ MRI ■ noninvasive imaging

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Cardiomyopathy is an important entity in the cardiovascular disease spectrum, with etiologies including coronary artery disease, valvular heart disease, intrinsic and infiltrative myocardial diseases and hypertension. Cardiomyopathy, particularly when leading to congestive heart failure, contributes to considerable mortality, morbidity and substantial economic burden throughout the world. An early diagnosis of a specific cardiomyopathy's underlying etiology may be important, as some etiologies necessitate specific treatment and may be readily treatable.

Noninvasive imaging is playing an evolving role in establishing specific diagnoses, identifying etiologies, providing prognostic information and even assessing potential therapeutic effect. Cardiovascular magnetic resonance (CMR) is a particularly promising modality for the imaging of cardiomyopathy, given the spectrum of information obtained in a single examination. CMR has the ability to provide accurate and highly reproducible quantification of biventricular systolic function and mass without geometric assumption, assessment of regional wall motion or myocardial perfusion. This article, however, will focus on CMR's ability to characterize tissue, including myocardial viability and the presence of interstitial fibrosis via the delayed-enhancement (DE) technique.

DE technique

The classically described segmented k-space, inversion-recovery gradient-echo sequence following administration of gadolinium-based contrast media (the DE MRI technique [DE-MRI])

is predicated on the concept that infarcted myocardium accumulates a greater amount of gadolinium than surrounding noninfarcted tissue and becomes 'hyperenhanced' or bright in appearance. Two mechanisms are believed to explain the increased accumulation of gadolinium in regions of infarction: a differential wash-in and wash-out rate of gadolinium and a different volume of distribution between viable and nonviable tissue. Normal myocardium is believed to have a relatively rapid wash-in and wash-out rate, whereas a slower, more delayed, wash-in and wash-out rate is observed in the infarcted, nonviable tissue as a result of impaired coronary and microvascular blood supply. Altered volumes of distribution also play a role. Gadolinium chelates, used clinically (with the exception of the recently approved gadofosveset trisodium [1]), are extracellular, interstitial agents that rapidly distribute from the intravascular space and equilibrate with the interstitial space; these agents are typically excluded from the intracellular space. In normal myocytes, gadolinium is precluded from the intracellular space by intact sarcolemmal membranes and, thus, only approximately 15–20% of a given volume of myocardium is available for gadolinium accumulation. In acute myocardial injury, the sarcolemmal membrane integrity is disrupted and the intracellular space effectively becomes additional interstitial space. The interstitial space increases to approximately 75% of a given volume, thereby permitting increased accumulation of gadolinium. In the setting of chronic myocardial infarction, the intracellular

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space is relatively small as a result of the fibrosis and collagen replacement, and the available interstitial space similarly expands the volume of distribution [2].

An increased amount of gadolinium chelate per unit volume shortens T_1 , hence, increases signal intensity on a T_1 -weighted image. The image acquisition is typically performed 10–20 min after intravenous administration of gadolinium chelate (usually 0.10–0.20 mmol/kg) to allow physiologic wash-out of contrast in normal myocardium. In order to maximize the contrast between normal myocardium and infarcted myocardium, the inversion time is optimized to null the signal from normal myocardium (FIGURE 1) [3]. The standard segmented k-space, inversion-recovery gradient-echo sequence technique requires optimized timing of scan acquisition relative to the volume of contrast administered, along with an appropriate selection of inversion time to null normal remote myocardium [4]. The same is true for variations on the technique, such as single-shot techniques that acquire each image in a single heartbeat (albeit at lower spatial and temporal resolution) [5] and inversion-recovery

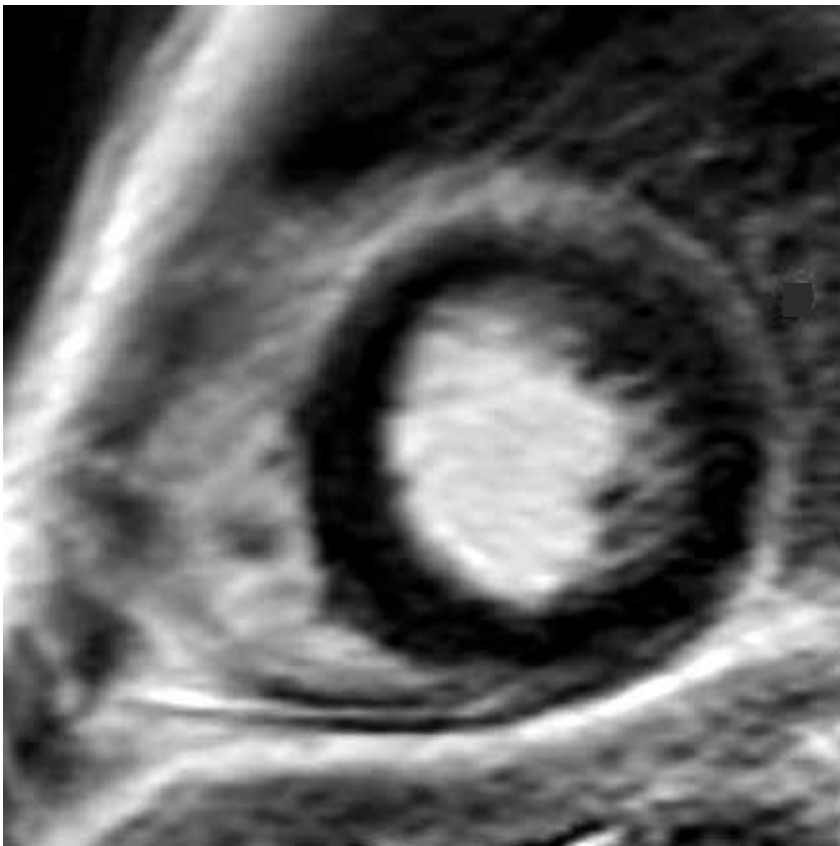


Figure 1. Delayed-enhancement MRI findings in a patient with normal myocardium. Normal myocardium is full thickness and homogeneously 'nulled' (i.e., black) after optimization of the inversion time.

steady-state free-precession approaches. A recently introduced modification of the technique, called phase-sensitive inversion recovery, corrects for variations in the inversion-recovery time and allows greater flexibility in imaging [6,7]. While there are differences between and among the various DE-MRI techniques, when applied correctly they provide similar information regarding the extent and degree of fibrosis present. There are also multiple advantages of the DE-MRI technique: in particular, it is straightforward to implement and does not require physiologic or pharmacologic stress.

Accuracy of DE-MRI

■ Comparison to histopathology

The close correlation between DE-MRI and histopathology-determined infarct size has been demonstrated in multiple studies. Results consistently demonstrate the near-identical quantification of infarct size in both acute and chronic myocardial infarct settings [8–10].

■ Comparison to other noninvasive modalities

Precise differentiation between viable and non-viable myocardium has a direct impact on clinical decision-making in the setting of cardiac dysfunction. Several noninvasive modalities have been proposed for the evaluation of myocardial viability, including DE-MRI, SPECT, PET, dobutamine stress echocardiography and CT.

SPECT defines infarcted myocardium based on regional discrepancies in radiotracer uptake as a result of impaired mitochondrial function (sestamibi SPECT) or impaired cellular membrane integrity (thallium SPECT). DE-MRI was superior to SPECT in multiple head-to-head studies [11,12]. These studies have demonstrated that DE-MRI and SPECT detect transmural infarct (>50% transmural) at similar rates, while DE-MRI detects subendocardial infarcts (<50% transmural) missed by SPECT. The explanation for this discrepancy appears to reflect the superior spatial resolution of DE-MRI compared with SPECT.

In PET, infarcted myocardium is identified by impaired metabolic function, manifested as matched defects of reduced myocardial blood flow (^{13}N -ammonia) and metabolism (^{18}F -fluodeoxyglucose). Previous studies have demonstrated that DE-MRI detects subendocardial infarcts not seen by PET, similar to the findings compared with SPECT; specifically, PET missed 36–55% of subendocardial infarcts identified by DE-MRI [13,14].

Low-dose dobutamine stress echocardiography determines myocardial viability based on inotropic response of hypocontractile segments. One study compared DE-MRI with dobutamine stress echocardiography and revealed that few segments with transmural or nearly transmural infarct by DE-MRI had contractile reserve by dobutamine stress echocardiography, while half of the segments found to be fully viable by DE-MRI demonstrated absence of contractile reserve [15]. The possible mechanisms explaining these discrepancies are tethering of viable segments to infarcted segments, myocyte adaptation that impairs dobutamine response and absent coronary flow reserve in the chronically hypoperfused region of viable but dysfunctional myocardium.

CT assesses myocardial viability based on relative tissue contrast concentrations on delayed postcontrast imaging similar to DE-MRI. However, DE-MRI provides approximately a three- to five-fold higher difference in image intensity between viable and infarcted myocardium [16,17]. To date, there are only limited data in humans comparing DE-MRI versus postcontrast CT (using a 16-detector CT scanner). These data reveal close agreement in overall infarct size, but disagreement in degree of infarct transmural [17]. A later study in a pig model used a 64-detector CT scanner for delayed postcontrast CT images and DE-MRI with histopathology as the gold standard. This study revealed close correlation with histopathology for the detection of ischemic irreversible myocardial damage for both delayed postcontrast CT and DE-MRI [16]. While CT has potential to determine myocardial viability with delayed postcontrast images, its clinical

applicability remains limited as a result of the not insignificant radiation dose and need for potentially nephrotoxic contrast agent.

Pattern of DE

■ Ischemic cardiomyopathy

Ischemic cardiomyopathy is characterized by a scar that typically involves the subendocardial layer, and in more severe ischemic damage can have a more complete gradient of transmural-ity, becoming a full-thickness scar (TABLE 1). This pattern is secondary to the wavefront phenomenon of ischemic cell death [18] and characteristically occurs in the distribution corresponding to coronary artery territories (FIGURE 2).

Delayed-enhancement MRI is a robust, non-invasive technique for the assessment of viable myocardium owing to its excellent spatial resolution. The traditional myocardial viability techniques of SPECT and PET have been demonstrated to be comparable to DE-MRI for the evaluation of a transmural scar, although, as noted previously, inferior to DE-MRI in the setting of a subendocardial scar [11,13]. The ability to differentiate between subendocardial and transmural scars has an important clinical impact as the degree of transmural-ity has a direct correlation with the extent of irreversible damage and an inverse relationship with recovery of contractile function after revascularization [19,20]. The predictive value of DE-MRI remains even after adjustment for traditional well-known prognosticators of all-cause mortality or cardiac transplantation [21]. Furthermore, the extent of infarct is a better predictor of inducible ventricular tachycardia than the classically used left ventricular ejection fraction [22].

Table 1. Delayed-enhancement patterns in cardiomyopathies.

Cardiomyopathy	Cardiac MRI delayed-enhancement pattern
Ischemic	Subendocardial to transmural in coronary artery territories
Nonischemic dilated	Mid-myocardial, thin linear hyperenhancement, typically in the septum
Hypertrophic	Patchy, 'sand-like' hyperenhancement in mid-myocardium, most prominent in hypertrophied segments, and particularly involving the septum at the right ventricular free wall insertion sites
Amyloidosis	Diffuse, subendocardial to epicardial; may be patchy
Sarcoidosis	Focal hyperenhancement usually mid-myocardial to epicardial, commonly involving the base of the heart
Anderson–Fabry disease	Mid-myocardial hyperenhancement, often 'hazy' and involving the basal inferolateral wall
Endomyocardial fibrosis	Subendocardial 'rind' of hyperenhancement often involving the apical half of the ventricle, and may have adherent thrombus
Arrhythmogenic right ventricular dysplasia	Right ventricular free wall, and may involve the left ventricular myocardium
	No classic pattern of delayed-enhancement defined

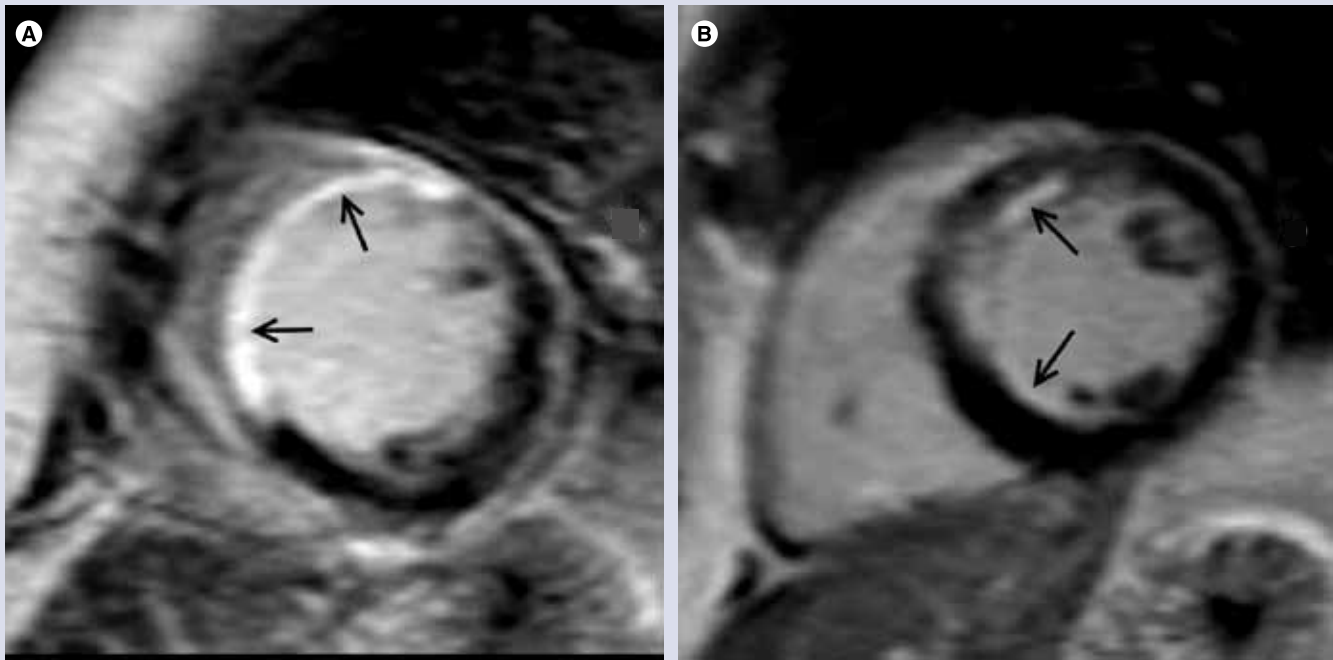


Figure 2. Delayed-enhancement MRI of patients with ischemic cardiomyopathy. Infarcted myocardium can be detected in coronary artery territories spanning the range from transmural or full-thickness hyperenhancement (arrows) (A) to partial thickness subendocardial hyperenhancement (arrows) (B).

In addition to the benefits derived from localization and quantification of chronically damaged nonviable myocardium, DE-MRI can identify acutely irreversibly damaged myocardium and directly identify areas of no-reflow with microvascular obstruction. Microvascular obstruction is seen on DE-MRI as a central black area within a region of hyperenhancement. The core of the infarcted tissue remains dark as neither blood nor gadolinium chelate is able to penetrate the area of microvascular obstruction owing to extensive myocyte necrosis and localized edema compressing supplying feeding vessels [23]. Recognition of microvascular obstruction is becoming increasingly important as a potent predictor of adverse ventricular remodeling and cardiovascular outcomes [24,25].

■ Nonischemic cardiomyopathy

Although various classification schemes of cardiomyopathy have been proposed, including classifications based on genetic interrogation, this article will follow the categories advocated by the WHO owing to its broad-based acceptance and practical application to clinical practice.

■ Dilated cardiomyopathy

Discrimination between ischemic and non-ischemic etiology of cardiomyopathy is critical as there are significant disparities in therapeutic options and prognosis. The gold standard for

this differentiation remains invasive coronary angiography, with the demonstration of significant epicardial coronary stenosis indicating ischemic etiology. Nevertheless, the presence of normal coronary arteries may be insufficient to exclude ischemic etiology as some cases, although felt to be a small minority, may be caused by spontaneous recanalization of a previously occluded vessel, embolization with subsequent lysis or vasospasm. The evolving role of DE-MRI to distinguish between these separate categories is based on a high sensitivity of 81–100% to detect hyperenhancement in an ischemic pattern along a coronary artery territory in concert with impaired left ventricular function [26,27].

By contrast, hyperenhancement is only present in 10–26% of patients with nonischemic, dilated cardiomyopathy, and the majority have absence of hyperenhancement [26–28]. Furthermore, the pattern of hyperenhancement is distinctly different: mid-wall longitudinal striae are seen, typically in the basal septum, and are not related to coronary territories (FIGURE 3). This characteristic finding has been correlated to focal fibrosis from autopsy study [29].

Similar to data from ischemic cardiomyopathy, the presence of hyperenhancement in dilated cardiomyopathy also serves as an independent predictor of all-cause mortality, hospitalization and inducible ventricular

arrhythmia, even after adjustment for left ventricular ejection fraction [30–32]. The existence of hyperenhancement contributes to an eight-fold higher composite end point of heart failure hospitalization, implantable defibrillator shocks and cardiac mortality. In at least one study, DE-MRI has been successfully used to identify the arrhythmogenic substrate and, thereby, guide electrophysical mapping and ablation [33].

■ Hypertrophic cardiomyopathy

Cardiac MRI has a spectrum of tools available for the assessment of hypertrophic cardiomyopathy (HCM), including the pattern and magnitude of myocardial hypertrophy, which may be particularly valuable in regions that are difficult to visualize by transthoracic echocardiography (e.g., the apex and inferolateral walls), accurate determination of left ventricular mass and the identification of papillary muscle abnormalities. In addition, DE-MRI has proved particularly adept at identifying the presence of myocardial interstitial fibrosis. The characteristic pattern of hyperenhancement is patchy, mid-wall, and commonly involves the interventricular septum at the anterior and inferior insertion points of the right ventricular free wall and, in more severe forms, can extend into the more apical portions of the ventricular myocardium (FIGURES 4 & 5) [34,35]. The relationship between the presence of hyperenhancement and increased fibrosis and collagen components has been demonstrated histologically [36]. The existence and magnitude of hyperenhancement generally correlates with the degree of wall thickness, nonetheless, it may be found in areas with normal wall thickness [37]. The ability of DE-MRI to identify interstitial fibrosis even in regions of normal wall thickness is particularly advantageous as the degree of fibrosis is related to the risk of ventricular arrhythmias in HCM [38].

■ Restrictive cardiomyopathy

Amyloidosis

Cardiac involvement is common in patients with systemic amyloidosis. Furthermore, cardiac mortality is the most common cause of death with a median survival time of less than 6 months [39]. The hyperenhancement pattern demonstrated by DE-MRI is global diffuse or patchy, but may have a ‘zebra-stripe’ pattern of subendocardial hyperenhancement of the left and right ventricles, with sparing of the mid-wall of the interventricular septum (FIGURE 6) [39,40]. Using endomyocardial biopsy as a gold standard,

typical DE-MRI hyperenhancement patterns have a strong correlation with cardiac involvement (80% sensitivity and 94% specificity of typical DE-MRI findings), and are distinctly different from those seen in other restrictive cardiomyopathies and HCM [41]. On the basis of histopathologic correlation, the hyperenhancement probably represents interstitial expansion from amyloid protein deposition.

Another unique feature of DE-MRI in cardiac amyloidosis is an atypically dark appearance of the blood pool, apparently reflecting fast blood pool depletion from high myocardial uptake [39].

From a prognostic perspective, Ruberg *et al.* noted that the presence of hyperenhancement on DE-MRI correlates with the level of B-type natriuretic peptide in patients with light-chain amyloidosis, but did not report a relationship with survival [42]. By contrast, Austin *et al.* studied 47 patients with biopsy-proven amyloidosis and found that only DE-MRI was associated with worsening heart failure and worsened survival [43].



Figure 3. The characteristic delayed-enhancement MRI pattern of dilated, nonischemic cardiomyopathy reveals mid-wall longitudinal striae (arrows), unrelated to coronary artery territories.

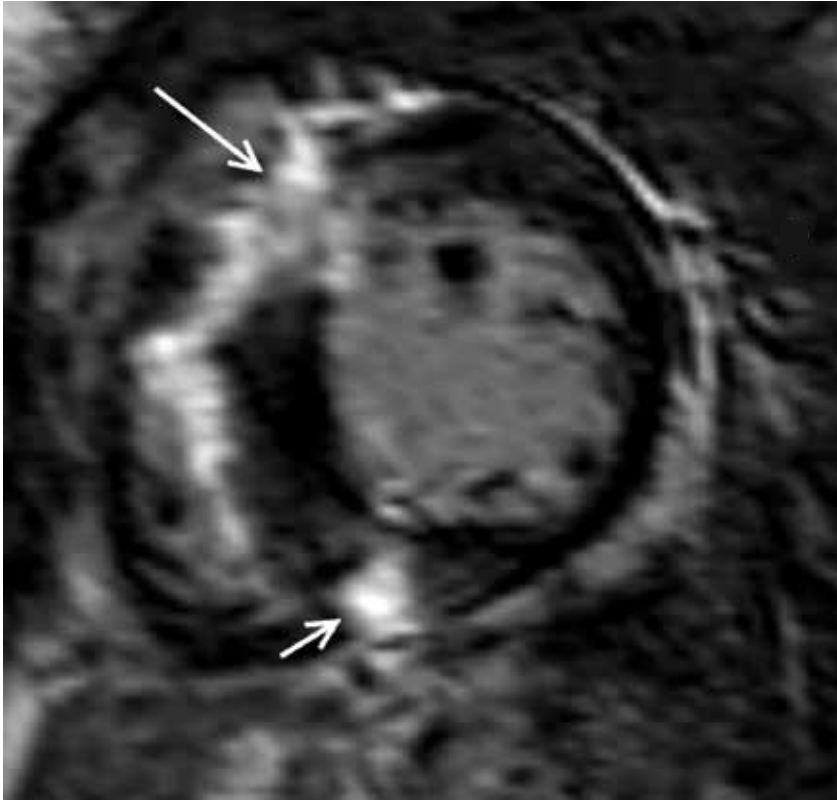


Figure 4. Delayed-enhancement MRI findings in a patient with hypertrophic cardiomyopathy. The typical patchy and sometimes dense hyperenhancement at the anterior (long arrow) and inferior (short arrow) interventricular septum at the insertion points of right ventricular free wall is shown.

Sarcoidosis

Cardiac involvement in sarcoidosis remains challenging as a substantial proportion of patients have no clinical manifestations, thereby creating difficulties in early diagnosis. Nonetheless, it is important to attempt early and precise diagnosis as affected patients can develop progressive heart failure and sudden cardiac death from arrhythmias, which can be prevented by optimized therapy [44].

Endomyocardial biopsy is considered the gold standard in diagnosis, but naturally imposes a not insignificant risk and may be insensitive owing to the patchy nature of infiltration. Echocardiography may be ineffective in the absence of left ventricular wall-motion abnormalities, which may only present later in the disease state, whereas CMR offers the benefit of tissue characterization by DE-MRI revealing granulomatous infiltrates in the myocardium. The noncaseating granulomas create an increase in extracellular space and, therefore, result in focal hyperenhancement. Interestingly, the hyperenhancement may be seen in patients without left ventricular dilation or focal wall-motion abnormality,

suggesting that DE-MRI may be beneficial in the diagnosis in the early, asymptomatic stage of disease.

The characteristic DE-MRI pattern is usually focal areas of mid-wall or subepicardial hyperenhancement, frequently in the anteroseptal and inferolateral walls (FIGURE 7). Two recent studies have demonstrated that approximately a quarter of patients with biopsy-proven sarcoidosis, but no known cardiac involvement or symptoms have cardiac infiltrates on DE-MRI [45,46]. One of these studies used the Japanese Ministry of Health guideline as a gold standard with DE-MRI demonstrating 100% sensitivity and 78% specificity [45].

To date, there is little prognostic data available, aside from a single study by Patel *et al.*, where myocardial damage detected by DE-CMR appeared to be associated with future adverse events, including cardiac death; however, the number of events was small, thus limiting extrapolation [47]. The extent and intensity of hyperenhancement may be used to evaluate response to steroid treatment as shown in one recent follow-up study [48].

■ Anderson–Fabry disease

Anderson–Fabry disease is amenable to therapy using enzyme replacement, which can regress myocardial hypertrophy and improve cardiac function [49]. Thus, early diagnosis is particularly important in an effort to limit deleterious complications and improve outcomes.

The typical DE-MRI features involve subepicardial hyperenhancement with a predilection to the basal inferolateral region [50]. Histopathologic data demonstrate a close correlation between DE-MRI hyperenhancement and replacement fibrosis [51].

Anderson–Fabry disease is similar to other entities with increased myocardial thickness, such as HCM and cardiac amyloidoses, but can be differentiated by the unique patterns of hyperenhancement by DE-MRI.

■ Endomyocardial fibrosis

In endomyocardial fibrosis, left ventricular wall thickening occurs as a result of fibrous replacement and thrombus formation. In some situations, it may be difficult to differentiate endomyocardial fibrosis from forms of myocardial hypertrophy, such as the apical variety of HCM. However, DE-MRI can reveal a ‘rind’ of endocardial fibrosis (a thickened rim of hyperenhancement along the endocardial border) frequently accompanied by adjacent thrombus

at the apex (FIGURE 8). DE-MRI is also adept at identifying intracavitary thrombus, which can then be treated with anticoagulation therapy.

■ Arrhythmogenic right ventricular dysplasia

The diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) is still challenging, despite a multidisciplinary workup approach based on the Task Force criteria [52]. The disease process is

morphologically and functionally characterized by right ventricular dilation and dysfunction, focal aneurysms and fibro-fatty replacement of the myocardium, sometimes with concomitant involvement of the left ventricle.

While endomyocardial biopsy remains the gold standard and Task Force criteria requirement for identification of myocardial fibro-fatty replacement, CMR's ability to characterize tissue, both fatty tissue using spin-echo image sequences

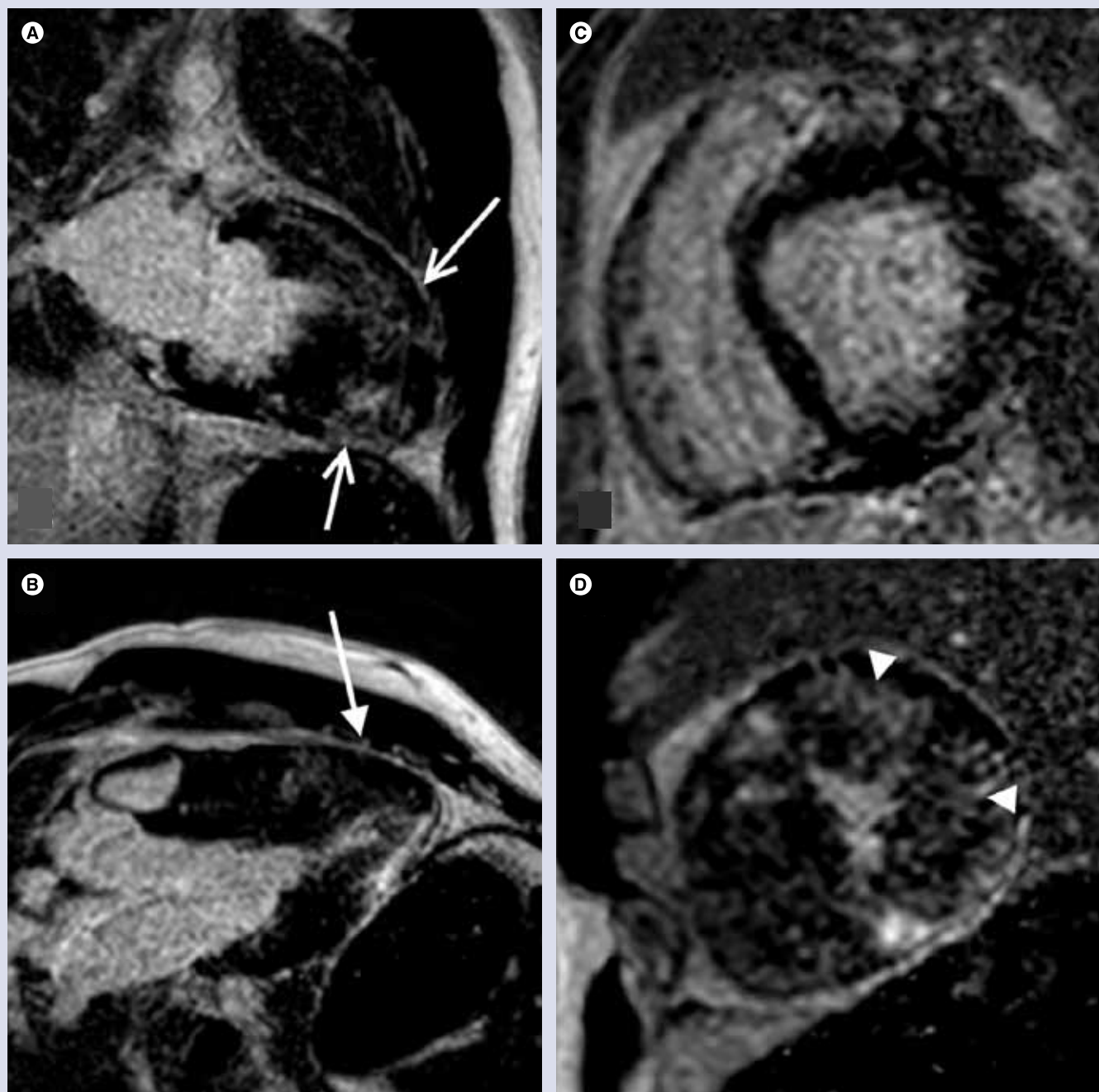


Figure 5. Apical form of hypertrophic cardiomyopathy. (A) Vertical long axis view, (B) left ventricular outflow tract view and (C & D) short axis images at the base and near the apex, respectively. The patchy, 'sand-like' hyperenhancement (arrows in (A & B) and arrowheads in (D)) is found primarily at the hypertrophic apex. Note that the thickness of the myocardium at the base (C) is normal.

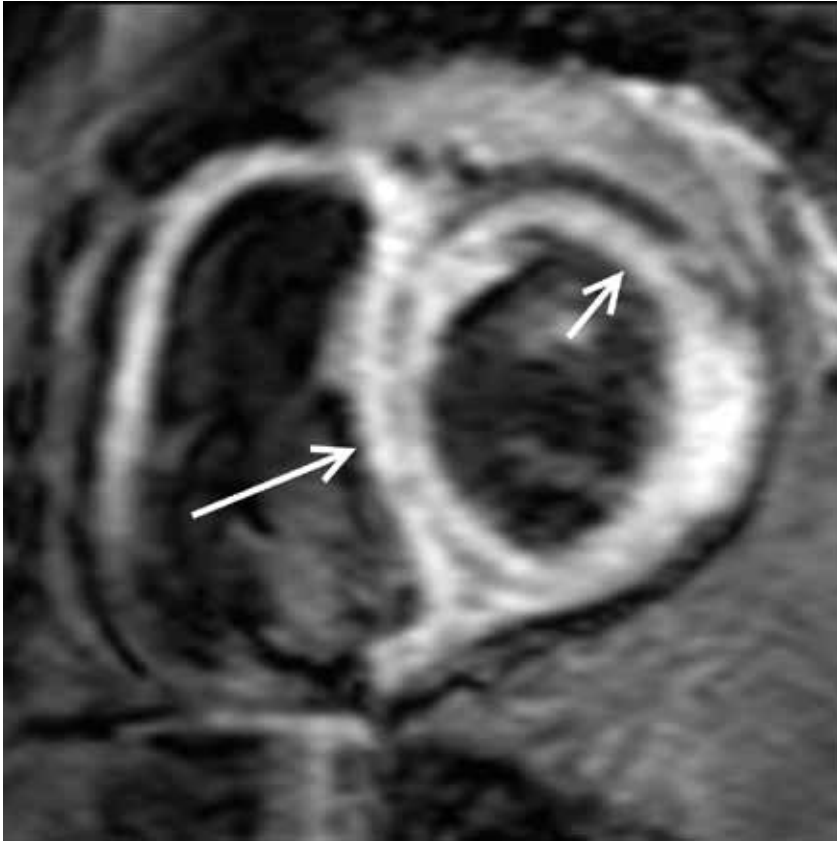


Figure 6. Delayed-enhancement MRI in patients with cardiac amyloidosis. Cardiac amyloidosis is characterized by global subendocardial hyperenhancement (short arrow), and may be seen as the unique ‘zebra-stripe’ subendocardial hyperenhancement involving both the left and right ventricles (long arrow).

and fibrous tissue with DE-MRI, presents an emerging and unique opportunity for noninvasive diagnosis of ARVD. The use of DE-MRI may be particularly advantageous as the identification of fibrous tissue is proposed to be more diagnostic than the presence of fat alone, and fibrous tissue replacement has been documented to be more arrhythmogenic than fatty tissue replacement [53]. In a recent study, fibrous replacement identified by DE-MRI was common in the right ventricle

of patients with ARVD, while fatty infiltration was rare (FIGURE 9) [54]. Furthermore, the presence of hyperenhancement by DE-MRI and right ventricular dysfunction has been linked to inducible ventricular tachycardia in a recent study [55]. Unfortunately, there is no classic pattern of DE yet established or included in Task Force criteria.

To date, data suggest that regional wall-motion abnormalities remain the principal imaging criterion for the diagnosis of ARVD [56]. It is important to reiterate that the accuracy and inter-observer variability of CMR in this difficult diagnosis are insufficient for CMR to be the sole investigation in the diagnostic workup, but CMR remains a critical final component in this evaluation [57].

■ **Left ventricular noncompaction**

Left ventricular noncompaction is an unusual congenital cardiomyopathy secondary to developmental arrest of compaction of the fetal loose, myocardial fiber meshwork and, in the isolated form more typically seen in adults, is characterized by severe left ventricular dysfunction, arrhythmias and thromboembolic events. Imaging diagnoses have been predicated on an exaggerated ratio of noncompact hyper-trabeculated to compact myocardium, yet the diagnostic criteria remain insufficiently well established [58]. Based on cine functional imaging, a ratio of the noncompacted to compacted layer of myocardium of greater than 2.3, or when the percentage of the mass of left ventricle trabeculations compared with global left ventricle mass is greater than 20%, has been used in two recent studies with reasonable accuracy [59,60]. DE-MRI is also useful in demonstrating the fibrosis that occurs subendocardially and in the deep trabecular recesses of the noncompacted layer [61]. In addition, an initial correlation has been established between the degree of DE and impairment of left ventricular function [59]. The condition is uncommon enough that no prognostic data relative to DE-MRI is available to date.

■ **Takotsubo cardiomyopathy**

This recently defined cardiomyopathy is characterized by transient regional wall-motion abnormalities without significant coronary artery obstruction, typically occurs in middle-aged to elderly females and is often associated with emotional or other stress. The presentation is similar to that of acute myocardial infarction with electrocardiographic and enzymatic abnormalities present. However, the wall-motion abnormalities usually involve the entire apical half of

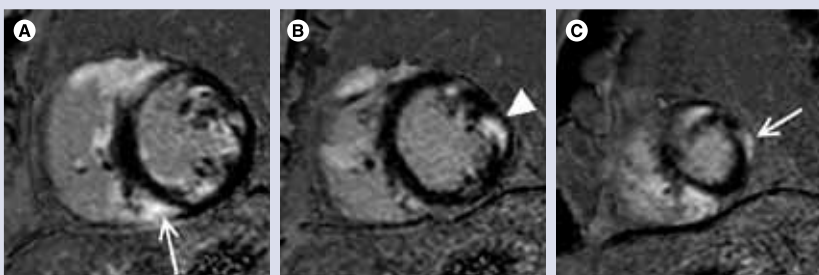


Figure 7. Cardiac sarcoidosis is manifested by focal delayed-hyperenhancement in noncoronary artery territories. (A–C) The three short-axis delayed-enhancement MRI images, from base to apex, demonstrate focal areas of mid-myocardial (arrowhead in (B)) and epicardial (arrows in (A & C)) hyperenhancement involving the left ventricle, as well as the right ventricle.

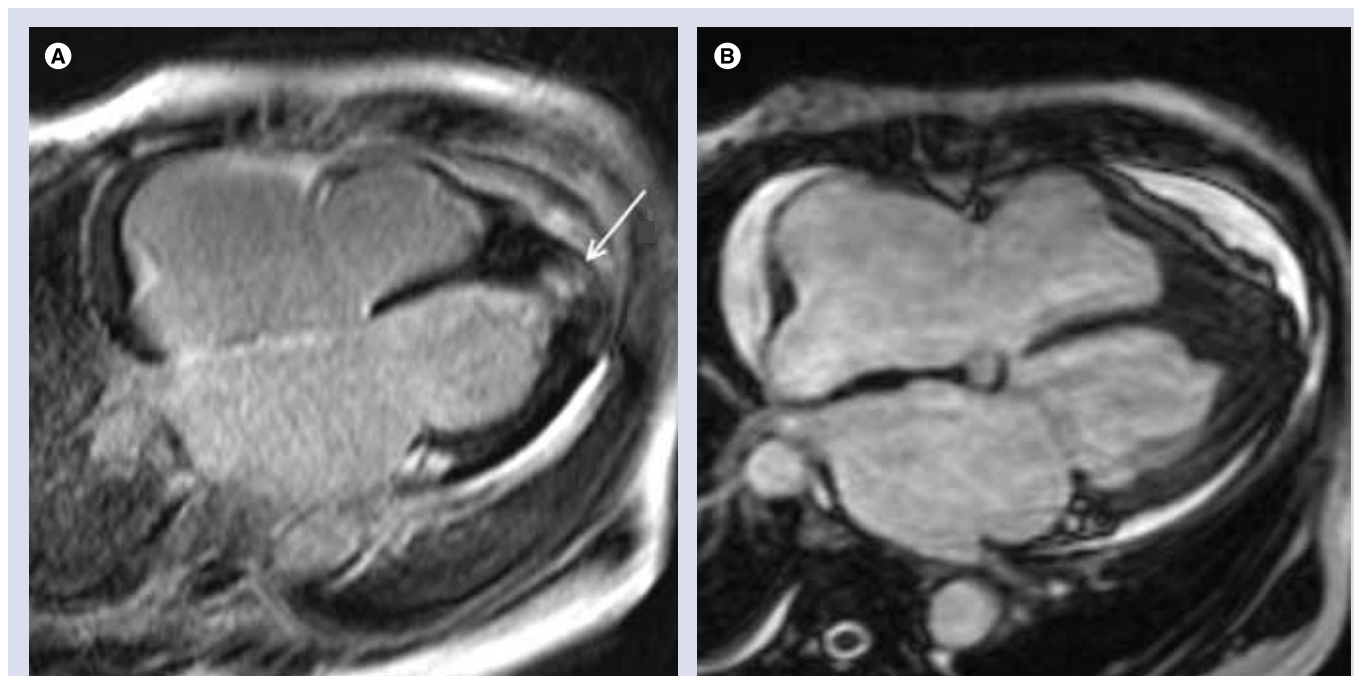


Figure 8. Delayed-enhancement MRI in a patient with endomyocardial fibrosis. The delayed-enhancement MRI demonstrates endocardial fibrosis (A) as indicated by hyperenhancement at the apex of the left ventricle (arrow) and is distinct from apical hypertrophic cardiomyopathy (B) as there is no abnormal myocardial thickening.

the left ventricle in what is considered a non-coronary artery distribution. CMR has revealed the regional dysfunction patterns and, perhaps more importantly, DE-MRI has demonstrated the lack of DE indicating that there is no detectable, irreversible myocardial damage within the limits of spatial resolution of the technique [62–64]. Similar to left ventricular noncompaction there are no prognostic data relative to DE-MRI presently available.

Clinical implications

Cardiac MRI can be considered as a pivotal non-invasive modality for the evaluation of cardiomyopathy, encompassing diagnostic, therapeutic and prognostic perspectives. The roles of CMR

have been established in the 2006 ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR Appropriateness criteria for cardiac CT and cardiac MRI (TABLE 2) [65].

Diagnostic perspective

The ability of DE-MRI to differentiate between ischemic and nonischemic etiologies of cardiomyopathy can further reduce the small, but not insignificant risk of invasive coronary angiography in a substantial portion of patients with systolic dysfunction but normal coronary arteries. Furthermore, DE-MRI can differentiate some specific etiologies of nonischemic cardiomyopathy, thereby, potentially avoiding the risk of endomyocardial biopsy.

Table 2. Appropriateness criteria for cardiac MRI in the setting of cardiomyopathy.

Indication	Median score
Evaluation of left ventricular function after myocardial infarction or heart failure in patients with a technically limited image from echocardiography	A (8)
Quantification of left ventricular function if discordant information is clinically significant from prior tests	A (8)
Evaluation of specific cardiomyopathies (infiltrative [amyloidosis and sarcoidosis], hypertrophic cardiomyopathy or caused by cardiotoxic therapy) with the use of delayed-enhancement MRI	A (8)
Evaluation of arrhythmogenic right ventricular dysplasia	A (9)
Evaluation of myocarditis or myocardial infarction with normal coronary arteries	A (8)
Determination of the presence and extent of myocardial necrosis including no-reflow regions in postacute myocardial infarction	A (7)
Determination of viability prior to revascularization	A (9)

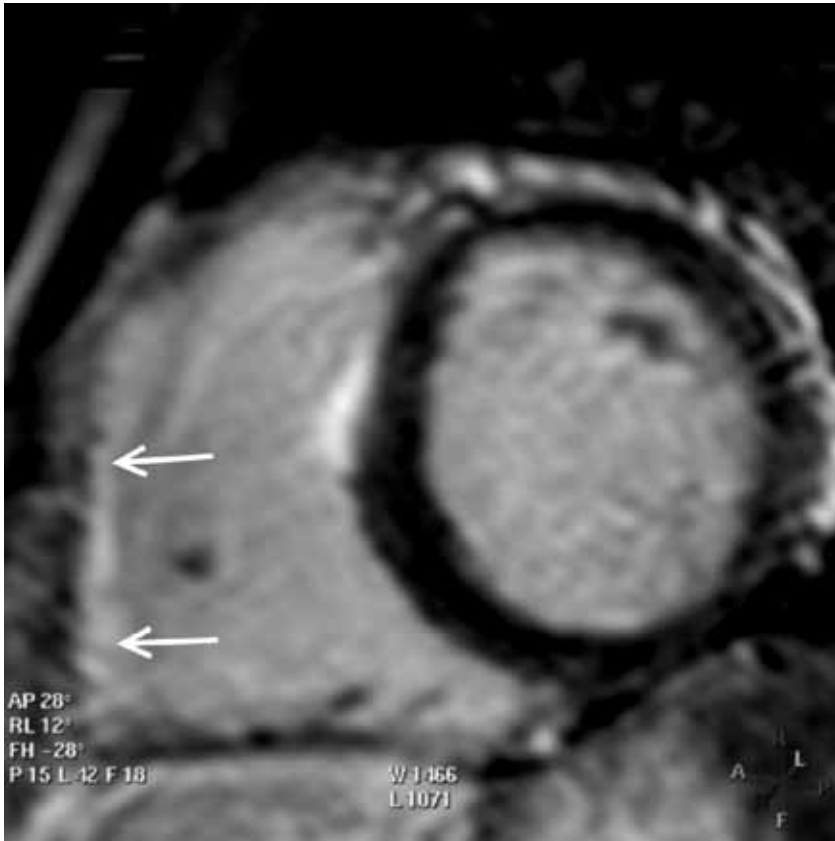


Figure 9. Delayed-enhancement MRI of arrhythmogenic right ventricular dysplasia. It is characterized by fibro-fatty replacement of the right ventricular myocardium. Delayed-enhancement MRI demonstrates hyperenhancement of the right ventricular free wall (arrows) reflecting the presence of fibrous replacement of myocardium.

Therapeutic perspective

In patients with ischemic cardiomyopathy, the discrimination between viable and nonviable myocardium is crucial for therapeutic decisions centered on the benefit or lack of revascularization. The diminished likelihood of functional recovery in the setting of transmurally or near-transmurally infarcted myocardium will help preclude those patients from the higher risk of surgery in left ventricular dysfunction without likelihood of significant benefit. In non-ischemic cardiomyopathies, less data are available; however, the spatial extent and amount of delayed-hyperenhancement was used to evaluate response to steroid treatment in one recent follow-up study in patients with sarcoidosis [48]. More data are certain to follow on other etiologic entities.

Prognostic perspective

Cardiac MRI has demonstrated a potent prognostic role in the majority of cardiomyopathies investigated, where the presence and extent of hyperenhancement correlates closely with

increased hospitalization rates, arrhythmias, higher mortality and worse overall outcomes. The predictive value of DE-MRI remains even after adjustment for traditional well-known prognosticators of all-cause mortality or hospitalization in both ischemic and dilated cardiomyopathy [66]. Furthermore, the extent of infarct is a better predictor of inducible ventricular arrhythmia in ischemic, dilated and HCM, although it has not yet been established as one of the criteria for internal cardioverter-defibrillator placement [22,31,32,38,67].

Among the uncommon cardiomyopathies, such as amyloidosis or sarcoidosis, the prognostic significance has been investigated in a few small studies [47,68,69].

Future perspective

■ Volumetric scanning

Delayed-enhancement MRI has relied primarily on qualitative assessment of the degree of hyperenhancement within the myocardium for both ischemic or nonischemic cardiomyopathies. The majority of imaging is performed using 2D techniques that require manual or semi-quantitative summing of the areas of DE on acquired slices throughout the ventricle. Despite solid diagnostic and prognostic data using these approaches, multiple investigators have documented the potential errors as a result of slice misregistration, gaps between slices and other mathematical assumptions.

Advances in CMR hardware and software, including improved imaging at 3 T field strength are leading to true, 3D volumetric imaging of the left ventricle. In addition, high-field-strength imaging (i.e., 3.0 T) has the benefit of an increased signal-to-noise ratio and contrast sensitivity, as compared with 1.5 T scanners [70]. Such data sets will eliminate the intrinsic, small but real errors of current approaches and provide more comprehensive information regarding the ventricle. As a further benefit, imaging may be simpler (by eliminating or reducing complex planning approaches) as well as faster, thereby facilitating throughput, increasing efficiency and enhancing the patient experience with cardiac MRI.

■ Quantification

There are currently varied approaches to determining the absolute amount of fibrosis – manifested by delayed-hyperenhancement – within the myocardium. Fortunately, owing to the intrinsic robustness of DE-MRI data, the values obtained by different approaches to semi-quantification or quantification are similar; however,

there remains a lack of standardization. Regions of hyperenhancement are commonly defined by determining the standard deviation of the signal within normal remote myocardium and setting threshold values above the mean signal level of normal remote myocardium. Investigators have used thresholds ranging from two standard deviations up to six standard deviations above normal remote myocardium. For ischemic cardiomyopathy this approach has worked well with only minor differences in quantitative values despite a range of thresholds.

This is considerably more complicated and perhaps more important in the nonischemic and infiltrative cardiomyopathies where interstitial fibrosis and smaller areas of replacement fibrosis occur. The hyperenhancement is more diffuse and small areas of hyperenhancement are interspersed between islands of normal myocardial cells. As a result, instead of bright hyperenhancement voxels, the myocardium may be gray because of averaging between normal dark myocardium and bright fibrosis, all of which are below the limits of spatial resolution for individual differentiation. To correctly quantitate the interstitial fibrosis present a combination of even further improvements in spatial resolution (which are already beyond alternative noninvasive imaging techniques) are required, as well as novel approaches using phase-sensitive reconstruction techniques, gradations of inversion times and other, yet to be developed, tools.

■ Novel contrast agents

The majority of gadolinium-chelate contrast agents currently used for DE-MRI are considered interstitial, nonintravascular agents. These agents have been responsible for the important development of tissue characterization capable by CMR, and will likely remain the primary workhorse in CMR DE imaging of cardiomyopathies. Nonetheless, newer contrast agents are imminent, including those that are intravascular [71], or borne via nanoparticles [72] or specific ligands [73]. Theoretically, an intravascular gadolinium-chelate contrast agent could have similar abilities for enhancing areas of irreversible myocardial damage compared with the current interstitial agents. While the distribution into the interstitial space is less, the greater degree of relaxivity or 'brightness' from the contrast agent could compensate. A potential concern is that the intravascular contrast agents may in actuality have a lower degree of relative myocardial enhancement compared with the interstitial agents, although only limited investigation has been performed to

date. Other agents with a greater ability for metabolic characterization, and amenable to MRI are in development, but not yet available for clinical testing [74].

■ Integrated prognostication

In the coming genomic medical revolution, there will be increasing trends toward detecting disease in the earliest, presymptomatic stages. CMR already includes functional, morphologic, hemodynamic and tissue characterization among its abilities, and each of these components will only continue to increase in the speed with which it can be acquired, as well as the sophistication of its discriminatory abilities. Providing a more comprehensive integration of these components, along with genomic information and risk profiles should result in greater precision for individual patient prognosis. The role of CMR in the evaluation of early pathophysiologic changes in patients at risk of cardiomyopathy will remain challenging, but the promise of precision diagnoses, leading to earlier intervention, may limit congestive heart failure and cardiac death to substantially smaller fractions of cardiomyopathy patients.

Conclusion

The cardiomyopathies constitute a group of particularly challenging diagnoses with a diverse set of investigational and therapeutic strategies. Comprehensive care not only requires knowledge of cardiac anatomy and physiology, but also characterization of pathologic tissues and an understanding of modifiable substrates (i.e., those amenable to therapy). CMR represents a single, comprehensive modality with the ability to address most, and in many cases, all of these aspects. Specifically, DE-MRI can provide valuable data regarding tissue characterization and continues to provide data for further defining prognosis. Continued application of CMR and, in particular, DE-MRI in the cardiomyopathies promises further improvements in diagnosis and therapeutic outcomes.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Clinical importance of cardiomyopathy

- Cardiomyopathy contributes to considerable mortality, morbidity and substantial economic burden throughout the world, and is increasing as populations age and coronary artery disease escalates.

Imaging of cardiomyopathy with cardiac MRI

- Noninvasive imaging is playing an increasing role in characterizing and categorizing cardiomyopathies.
- Cardiac MRI has become a central noninvasive imaging tool to provide accurate and reproducible biventricular systolic function and mass, regional wall-motion information, myocardial perfusion and tissue characterization, including myocardial viability and the presence of interstitial fibrosis via the delayed-enhancement MRI (DE-MRI) technique.
- DE-MRI is a simple T₁-weighted imaging sequence using an inversion-recovery pulse for nulling and performed following the administration of gadolinium chelate.
 - Both scar tissue and interstitial fibrosis accumulate gadolinium to a greater degree than normal myocardium.
 - Hyperenhancement on DE-MRI corresponds closely to histopathology of irreversibly damaged tissue in ischemic damage and to interstitial fibrosis in nonischemic disease.
 - DE-MRI is superior to nuclear techniques in identifying nontransmural scar tissue as a result of higher spatial resolution.
- Ischemic and nonischemic cardiomyopathies have distinct patterns of hyperenhancement that can be used for discreet categorization.
- The degree and amount of myocardial hyperenhancement has an inverse association with prognosis in the majority of cardiomyopathies.

Future perspective

- Advances in cardiac MRI hardware and software will lead to true, 3D volumetric imaging of the left ventricle, providing more comprehensive information, facilitating throughput and increasing efficiency, both necessities for the increasing population of patients with cardiomyopathy.
- Quantification of hyperenhancement will improve further as a result of enhanced spatial resolution from higher field strength magnets and evolving algorithms for assessing 'gray' zones of myocardium; this will be particularly important in the nonischemic and infiltrative cardiomyopathies where interstitial fibrosis occurs.
- Cardiac MRI will provide a more comprehensive integration of functional, morphologic, hemodynamic and tissue characterization data, and combine it with genomic information and risk profiles for greater diagnostic precision.

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