Value Of Cardiac Magnetic Resonance In Assessment Of Non Ischemic Dilated Cardiomyopathy

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Abstract

Imaging is crucial for establishing the diagnosis of DCM, as well as for risk stratification, patient management, and treatment monitoring. DCM can have very diverse clinical outcomes, ranging from LV reserve remodeling and recovery of systolic function to acute heart failure, arrhythmias, or SCD. Thus, the therapeutic management of DCM patients necessitates a constant update on the underlying cardiac structural and functional status. Cardiac Magnetic Resonance (CMR) has emerged as a fundamental tool for diagnosis, risk stratification, and management of DCM patients. CMR not only represents the gold standard for an accurate and reproducible assessment of ventricular volumes and function, but it is also the only technique that provides noninvasive tissue characterization. Using imaging techniques such as LGE and qualitative/quantitative parameters including T1 mapping, T2 mapping, and T2* mapping, tissue characterization is useful in the differential diagnosis of secondary causes of DCM and in the assessment of the probability of LVRR with a potential role in guiding individualized treatment strategies

Keywords: COVID-19- mortality.

Introduction

Imaging is crucial for establishing the diagnosis of DCM, as well as for risk stratification, patient management, and treatment monitoring. DCM can have very diverse clinical outcomes, ranging from LV reserve remodeling and recovery of systolic function to acute heart failure, arrhythmias, or SCD. Thus, the therapeutic management of DCM patients necessitates a constant update on the underlying cardiac structural and functional status [1].

Among the available imaging modalities, transthoracic echocardiography (TTE). Cardiovascular magnetic resonance (CMR), nuclear imaging single-photon emission computed tomography (SPECT) and positron emission tomography (PET) and cardiac computed tomography (CCT) are the forefront techniques for implementing DCM diagnosis and patients' workup (Table 1). However, there are practical limitations to the use of each imaging modality (cost, availability, and radiation exposure) which dictate a judicious choice of the optimal imaging technique [1].

Table 1: Different imaging modalities for the evaluation of dilated cardiomyopathy. Quoted from Masci and Maestrini [2].

	Echo	CMR	SPECT	PET	CT
Chamber dimensions	++	+++	++	++	++
Systolic function	++	+++	++	++	++
Diastolic function	+++	+	+	-	-
Morphologic assessment	++	+++	-	-	-
Dyssynchrony	++	+	+	-	-
Ischemia	++	+++	++	+++	-
Metabolism	-	+	-	+++	-
Tissue characterization	-	+++	-	+	+
Coronary arteries	-	++	-	-	+++
Valve disease	+++	++	-	-	+
Pulmonary hypertension	++	-	-	-	-
Limitations	Acoustic window limitation Operator dependency	Availability Metallic implants Use of contrast	Radiation exposure Attenuation artifacts	Radiation exposure Availability Cost	Radiation exposure Low quality in arrhythmias

Echo, echocardiography; CMR, cardiac magnetic resonance; CT, computed tomography; PET, positron emission tomography; SPECT, single photon emission computed tomography. The crosses represent how helpful each test is in assessing the index parameter.

Transthoracic echocardiography (TTE) still has a central role in diagnosis and in follow-up of patients with CMP [3].

TTE is a widespread low-cost technique that provides morphological and functional information [16]

It allows the estimation of LV volumes and LVEF and the exclusion of associated cardiac abnormalities, such as congenital and valvular heart disease. In addition, echocardiography is an important tool for prognostic stratification allowing the identification of many aspects of cardiac remodeling, such as functional mitral regurgitation [4].

The use of 3D echo reduces some of the limitations of the standard two-dimensional technique, and with dedicated applications, it is possible to evaluate deformations of the ventricular wall. Furthermore, echocardiography provides for the evaluation of the diastolic function as well as an accurate assessment of the valve system. However, all these possibilities are sometimes limited by a suboptimal acoustic window and inter-observer variability. Finally, echocardiography as a method to characterize myocardial tissue is limited [16]

Cardiac Magnetic Resonance

CMR has emerged as a fundamental tool for diagnosis, risk stratification, and management of DCM patients. CMR not only represents the gold standard for an accurate and reproducible assessment of ventricular volumes and function, but it is also the only technique that provides noninvasive tissue characterization. Using imaging techniques such as LGE and qualitative/quantitative parameters including T1 mapping, T2 mapping, and T2* mapping, tissue characterization is useful in the differential diagnosis of secondary causes of DCM and in the assessment of the probability of LVRR with a potential role in guiding individualized treatment strategies [8].

The clinical picture of DCM is defined by left or biventricular dilatation and systolic dysfunction in the absence of coronary artery disease, hypertension, valvular disease or congenital heart disease [9]. The diagnostic criteria are LV end-diastolic volumes or diameters >2 s.d. from normal according to normograms (z-scores >2 s.d.) corrected for age and body surface area and ejection fraction <50% [15].

LV reverse remodeling (LVRR), defined as an improvement in LV ejection fraction (LVEF) and a reduction in LV enlargement, is one of the main determinants of prognosis in DCM, and it is the key therapeutic goal. Cardiac adverse remodeling characteristics in DCM include LV dilation and wall thinning, LV dyssynchrony manifested by left bundle branch block, functional mitral regurgitation, myocardial fibrosis, remodeling of other cardiac chambers, and RV dysfunction [16]

An accurate and reproducible cardiac evaluation always includes chamber size quantification, myocardial wall thicknesses, ventricular function and mass measurement with traditional cine sequences, steady-state free precession (SSFP), in short and long axis (2, 3, and 4 chamber) view. DCM is characterized by LV dilation, thin-walled, quite trabeculated, impaired contractility with diffuse hypo-akinesia, and reduced LVEF. At present, LVEF is considered one of the most important prognostic factors in DCM, and current guidelines recommend ICD in symptomatic heart failure with LVEF less than 35%. In addition, velocity-encoded CMR is a useful alternative to echocardiography for evaluating functional mitral regurgitation, another aspect of adverse myocardial remodeling.

The use of tissue characterization CMR sequences is fundamental in this pathology [16]

The lack of radiation exposure and the safety of non-linear gadolinium-based contrast agents render CMR suitable and safe for serial scans in adults and in pediatric subjects [1].

The limitations of CMR include lack of availability, inability to image patients with specific contraindications, and cost [9, 10].

There are also concerns regarding the risk of nephrogenic systemic fibrosis as a result of the use of gadolinium in patients with severely impaired renal function. while CMR contrast use should be avoided in patients with end-stage renal disease, chelated gadolinium-based contrast agents used in CMR imaging are not nephrotoxic. Yet in patients with severe kidney failure, gadolinium-containing contrast agents pose the risk for nephrogenic systemic fibrosis (NSF) [11].

In patients with severe kidney failure, gadolinium-containing contrast agents pose the risk for nephrogenic systemic fibrosis (NSF), formally called nephrogenic fibrosing dermopathy. Nephrogenic systemic fibrosis results in bilateral, fibrotic, indurated papules, plaques, and subcutaneous nodules commonly involving the extremities, and the fibrosis may be sufficiently severe to cause flexion contractures, joint immobility, pain, paresthesias, and severe pruritus. Systemic involvement resulting in muscle induration, joint contracture or affection of other organs (including lung, esophagus, and kidney) [11, 12].

Although the symptoms are disabling and not treatable, NSF is very rare, occurring exclusively in patients with kidney failure, with most cases involving patients who require dialysis or patients who have advanced renal failure with a glomerular filtration rate < 30 mL/min, acute kidney injury, or those hospitalized for a proinflammatory event. The prevention of NSF involves avoiding gadolinium-containing contrast in these higher-risk patients. If the benefits of administering gadolinium outweigh the risks and adequate diagnostic information cannot be obtained with a noncontrast study, decreasing the gadolinium dose to the lowest dose deemed necessary (ie, a single dose [0.1 mmol/kg] rather than a double dose [0.2 mmol/kg]) may reduce the risk. Although NSF is presumed to occur with any gadolinium-containing contrast agent, most reported cases of NSF have occurred using gadodiamide, a gadolinium-containing contrast agent with a chelating agent that binds gadolinium less tightly, and the risk may be decreased by using a gadolinium formulation with a tighter-binding chelating agent (eg, gadoteridol) [11, 12].

The current approach to prevent the onset of NSF is based on minimizing the impact of predisposing risk factors and performing hemodialysis sessions right after GBCA exposure in patients with a history of ESRD on renal replacement therapy. Hemodialysis or peritoneal dialysis should take place the same day and within 2 or 3 h after contrast administration. Maintaining adequate hydration and minimizing the concomitant exposure to nephrotoxic agents (NSAIDs, diuretics, and certain antibiotics) are also recommended, as well as not exceeding the recommended dose of administration [12].

Nonetheless, a recent meta-analysis concluded that the risk of nephrogenic systemic fibrosis from the use of cyclic gadolinium-based contrast agents in patients with chronic kidney disease stages 4 and 5 is likely less than 0.07%. Therefore, contrast-enhanced CMR scans are likely to outweigh the risk of nephrogenic systemic fibrosis in these patients [13].

Assessment of remodeling:

The extent of LV dilation and contractile impairment in DCM is a major determinant of adverse outcomes, and reversal of these abnormalities, LV reverse remodeling, is a key therapeutic goal. In addition to LV wall thinning and dilation, adverse remodeling characteristics in DCM include functional mitral

regurgitation (FMR), myocardial fibrosis, dyssynchronous ventricular contraction, and enlargement of other chambers. Increasingly, detailed characterization of these parameters may also hold value in predicting prognosis and guiding treatment [18]

CMR imaging techniques for quantifying LV volume and ejection fraction

An ejection fraction (EF) <30% confers the most adverse prognosis. LVEF is clearly a marker of disease severity but is neither a specific nor sensitive marker for SCD [14].

ICD therapy is a mainstay in the prevention of sudden cardiac death (SCD) and reduction of overall mortality in DCM patients with reduced left ventricular ejection fraction. The primary criterion for selection of candidates for primary prevention ICD is LVEF <35% [15].

At present, CMR can be considered the gold standerd for the quantification of ventricular volumes, functional parameters, and evaluation of chamber size, to measure wall thickness and ventricular mass in patients with DCM [16, 17].

Measurement of left ventricular volumes, ejection fraction, and mass by CMR are highly accurate and have been shown to be more reproducible (coefficient of variation for left ventricular ejection fraction [LVEF] in normal subjects is 2.4%) than left ventricular volumes and mass by echocardiography (coefficient of variation for LVEF in normal subjects up to 8.6%) or radionuclide ventriculography [18].

Cardiac magnetic resonance imaging provides the reference standard assessment of LV systolic function, owing to its excellent temporal resolution, spatial resolution, and tissue contrast abilities, differentiating the endocardial border of the myocardium from the blood pool, enabling precise quantification of cardiac chamber volumes. Cine movie images to assess LV systolic function are most often performed with steady-state free precession imaging by displaying the same myocardial slice at different points within the cardiac cycle [12].

Cardiac magnetic resonance (CMR) imaging with a cardiac short-axis stack acquisition (CMR_{SAX}) is the gold standard for LVEF estimation because of its volumetric approach for nonsymmetric ventricles with wall motion abnormalities [19].

The systolic and diastolic cavities can be traced in multiple contiguous short-axis images of the LV cavity starting at the mitral valve level and moving toward the LV apex [11].

creating a 3-dimensional volumetric structure for analysis. Measurements made with this 3-dimensional (3D) data set do not require geometric assumptions and are therefore less prone to error than 2D methods such as 2D echocardiography in ventricles deformed by cardiomyopathies [20].

(Figure 1) [21].

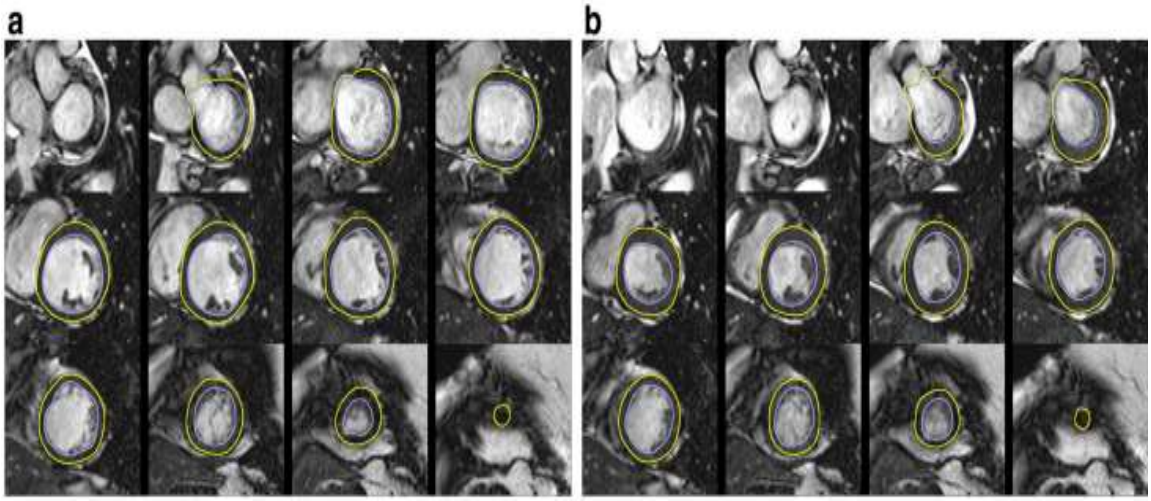


Figure 1 : Left ventricular (LV) chamber quantification. For LV chamber quantification, the endocardial (blue) and epicardial (yellow) contours are delineated in diastole (left) and systole (right) in a stack of short axis slices that cover the whole left ventricle. a and b illustrate the approach with inclusion of the papillary muscles as part of the LV volume. Quoted from Schulz-Menger, J. et al. [21].

There are several different methods available for measuring left ventricular volume and ejection fraction with CMR. The two most common include the Simpson's rule technique and area-length technique. With the Simpson's rule technique, LV volumes are determined by summing the endocardial area within multiple short axial slices spanning the base to the apex of the heart and multiplying each area determination by slice thickness. This technique is advantageous, because one can calculate LV volumes without using formulae that require assumptions about LV shape. For this reason, the Simpson's rule technique is useful in patients who have cardiomyopathy or regional wall motion abnormalities.

The area length techniques are based on formulae that assume the left ventricle exhibits the shape of a prolate ellipse. Because patients who have distorted LV geometry caused by dilated cardiac chambers or resting regional wall motion abnormalities do not exhibit left ventricles in the shape of a prolate ellipse, LV volume determinations may be less precise than those generated with the Simpson's rule method. With both methods, LV ejection fraction is calculated by subtracting end–diastolic volume from end–systolic volume and dividing by end–diastolic volume [22].

There is significantly more heterogeneous end-diastolic LV wall thickness in patients with DCM compared to a reference normal population; furthermore, the physiological gradient in systolic wall thickening between LV basal and apical segments disappears with DCM DCM [16].

Previous studies showed that RV mass is preserved in DCM patients as compared to normal subjects, whereas LV mass is significantly greater with evidence of larger trabeculae as compared to normal subjects. In advanced cases, LV dysfunction may be associated with diffuse myocardial wall thinning (diastolic wall thickness < 5.5 mm) DCM [16]. Figure 2 [15].

Remodeling of other cardiac chambers.

Left atrial (LA) dilation is frequently observed in DCM as a consequence of diastolic dysfunction, FMR, atrial fibrillation, and LV cavity enlargement. LA volume is the preferred measure of LA size and predicts adverse outcomes in DCM [18]

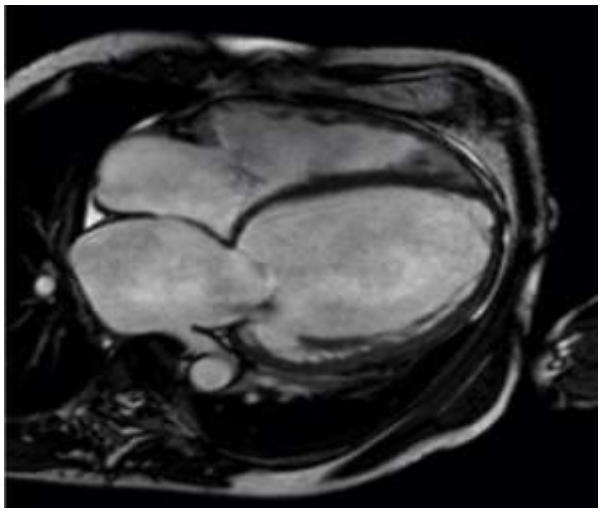
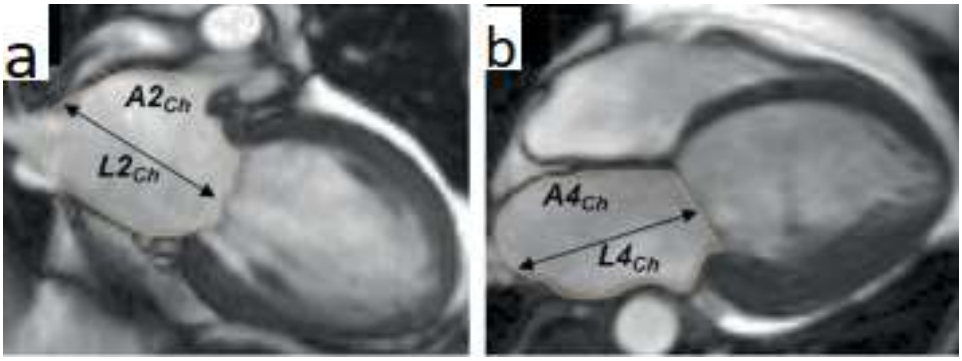
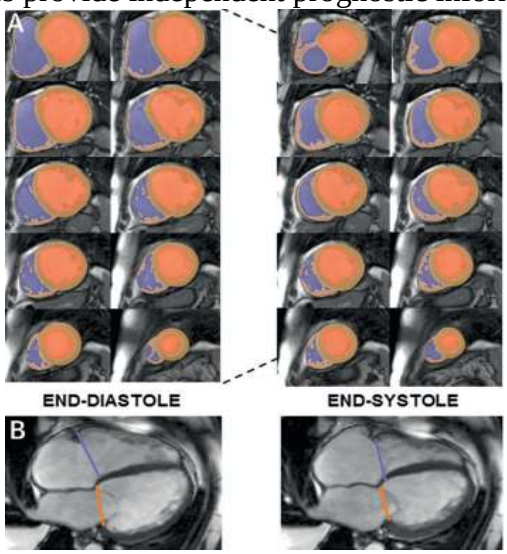


Figure 2: Four-chamber SSFP imaging showing the typical appearance of dilated cardiomyopathy-related ventricular thinning and dilatation. Quoted from Lahoti [15].



Figures 3: Measurement of left atrial volume by the biplane area-length method, Quoted from Japp et al. [18]

Adverse right ventricular (RV) remodeling, resulting from secondary pulmonary hypertension or primary myocardial disease, is also common in DCM patients. TTE enables accurate assessment of tricuspid regurgitation and pulmonary artery systolic pressure, but has a limited estimation of RV size and function. CMR offers greater accuracy and reproducibility for measurement of RV volumes and ejection fraction (Figures 4), and these indexes provide independent prognostic information in DCM [18]



Figures 4: Measurement of biventricular volumes and ejection fraction (a and b). Quoted from Japp et al. [18]

Functional mitral regurgitation (FMR).

Increasing LV size and sphericity causes tethering of the mitral leaflets, which, together with annular dilation, leads to defective leaflet coaptation and "functional" regurgitation. FMR perpetuates LV remodeling and is associated with increased morbidity and mortality, independently of LVEF. [18]

The increasing severity of mitral regurgitation, especially in moderate/severe patients remains an independent predictor of heart failure and sudden cardiac death [23].

Reduction of FMR severity in DCM patients receiving optimal medical therapy and/or cardiac resynchronization therapy (CRT) is associated with improved transplant-free survival. Surgical annuloplasty can also reduce FMR and is accompanied by improvements in LV remodeling and symptoms. With the emergence of percutaneous transcatheter mitral valve therapies, such as the edge-to-edge MitraClip repair system, the importance of FMR assessment in DCM is likely to increase [18]

The quantification of regurgitant volume is crucial to the management of mitral valve disease. The guidelines for the management of valvular heart disease place significant emphasis on differentiating severe from non-severe mitral regurgitation (MR) when deciding which patients are appropriate candidates for mitral valve surgery [24].

The 3D echocardiographic color Doppler techniques permit direct and accurate assessment of effective regurgitant orifice area, circumventing the geometric assumptions inherent to 2D assessment. At present, such measurements are time-consuming and technically demanding. [18]

CMR has proven to be a reliable imaging modality in the qualitative assessment of MR as compared to traditional echocardiography. CMR overcomes most of the current limitations of TTE including inter-observer variability, overestimation of MR and inability to predict the impact of intervention of postsurgical outcomes [17].

MRI has become the "gold standard" for evaluating cardiac chamber function and size, It is then a natural extension to apply all of the considerations of an ideal chamber volumetric capability toward a valvular volumetric challenge [17].

Mitral regurgitation in DCM patients is associated with morphological and functional abnormalities of left heart and mitral valve annulus. The indexed LVESD, LAESD, and minimum MAA (mitral annulus area) values can assist in predicting the severity of mitral regurgitation with a high sensitivity and specificity [23].

A comprehensive CMR study is able to quantitate both atrial and ventricular remodeling, which is important in understanding both the severity and the mechanism of mitral regurgitation. Quantitative parameters include regurgitant volume, regurgitant fraction, and regurgitant orifice area. CMR offers several important advantages in the assessment of MR. This includes identifying the mechanism of MR, quantifying MR severity, and determining its consequences on cardiac remodeling [17].

There are many clinically applicable methods to assess the severity of mitral regurgitation via CMR. Most commonly, **indirect quantitative methods** are used to quantify mitral regurgitant volume utilizing 3D ventricular stroke volumes along with phase-contrast velocity encoded mapping (to quantify forward flow) [25].

***Left and Right Ventricular Stroke Volumes**

Standard volumetric assessment of LV and RV function is done using SSFP imaging, which gives accurate measurements LV and RV systolic and diastolic dimensions and volumes, stroke volume, and ejection fraction; these can be interpreted both as absolute and indexed and standardized based on body surface area [17].

LVSV and right ventricular stroke volume (RVSV) are quantified using segmentation of the ventricles from the base to the apex of the heart in both end-diastole and end-systole [25].

The current ACC/AHA guidelines highlight left ventricular ejection fraction and end-systolic dimension as important parameters in determining which patients are appropriate for mitral valve surgery, and the ASE recommends quantifying the left atrial and ventricular size when assessing mitral regurgitant severity [26].

The intra- and inter-reader variability for calculating LV size and function is low for CMR, making it an excellent tool for long-term patient follow-up [27].

***Forward Flow: Aortic and Pulmonary Artery Flow**

Phase contrast imaging applications of gradient pulses induce phase shifts in moving protons that are directly proportional to their velocity along the direction of the gradient. Phase contrast is capable of measuring velocities, and thus flows, in the "through plane" orientation. The imaging plane is acquired perpendicular to the desired vessel. This technique allows measurement of blood flow in vessels and is particularly suited to measuring flow in the ascending aorta and the main pulmonary artery (PA) [25].

Table 2: Recommended grading of MR by CMR assessment. [28].

Type of MR	**Grading of Severity**			
	Mild	**Moderate**	**Severe**	**Very severe**
Primary	**MR_{RF}** < 20%	**MR_{RF}** = 20-39%	**MR_{RF}** 40-50%; **MR_{vol}**> 55-60 mL	**MR_{RF}** > 50%
Secondary	**MR_{vol}** < 30 mL	**MR_{vol}** = 30-60 mL	**MR_{vol}** ≥ 60mL	

MR = mitral regurgitation; MRRF = mitral regurgitation fraction; MRvol = mitral regurgitation volume.

Other less semi-quantitative method for assessment of mitral regurge include the use of signal void, regurgitant jet size, and regurgitant orifice area measures using phase velocity encoded mapping [17].

Myocardial fibrosis:

Here comes the unique ability of MRI to add information regarding tissue composition and in vivo tissue characterization. The ability to detect subtle myocardial fibrosis is a major rationale for using MRI for myocardial disease [4, 29].

While endomyocardial biopsy is considered the gold standard for detecting and classifying myocardial tissue abnormalities, its invasiveness, poor diagnostic utility, and lack of well-established management pathways limit its widespread use in clinical practice [30].

Late gadolinium enhancement [LGE] has become a reference standard for detection of focal myocardial scar/fibrosis using cardiac magnetic resonance (MR) with delayed imaging after administration of a gadolinium-based contrast agent [31].

CMR with administration of gadolinium-based contrast agent allows non-invasive evaluation of localised cardiac replacement fibrosis, seen when a collagen matrix is laid down in response to myocyte damage, necrosis and/or apoptosis, leading to a distinct myocardial scar [14].

Gadolinium shortens the T1 relaxation time of the scarred tissue which consequently appears bright when the inversion recovery sequence is set to null normal myocardium [32].

For late-enhancement images, optimal contrast differentiation between viable and nonviable myocardium is individually evaluated for each patient by determining the exact time the signal of the normal myocardium is nulled or black. The inversion time will vary considerably from patient to patient and must be determined on an individual basis [29].

Normal inversion times vary but generally are between 200 and 350 msec, depending on the manufacturer of the MR unit, the cardiac output, the time of image acquisition after contrast agent injection, and the dose of contrast agent administered [33].

The appropriate inversion pulse used aims to optimally suppress normal myocardial tissue, thus highlighting the enhancing region of the heart. Myocardial scar is readily identified as focal regions of delayed enhancement. The reason for delayed enhancement is that the washout rate of gadolinium is reduced in areas of myocardial fibrosis or collagen deposition. Increased gadolinium concentration causes T1 shortening or enhancement on delayed gadolinium enhancement MRI [29].

The presence of myocardial replacement fibrosis seen on late gadolinium enhancement (LGE)-CMR has been shown to correlate with histological areas of plexiform fibrosis [34].

While attempting to diagnose the etiology of cardiomyopathy, it is important to exclude CAD as the etiology, given the differences in management. CMR technique of late gadolinium enhancement (LGE) becomes valuable in establishing the proper diagnosis. Gadolinium chelates are extracellular contrast agents that cannot cross myocyte cell membranes. Normal myocardium is densely packed with viable myocytes that do not permit entrance of gadolinium into the cell; thus, there is little gadolinium enhancement of normal myocardium. However, in the setting of an acute myocardial infarction, myocardial cell membrane rupture will allow gadolinium to freely diffuse into the cell resulting in gadolinium hyperenhancement. The necrosis begins in the subendocardium and grows toward the epicardial area near the occluded artery. In chronic myocardial infarction, myocytes get replaced with collagenous scar tissue in the subendocardial region leading to increased gadolinium concentration and hyperenhancement in the subendocardium [35].

Thus, ischemic cardiomyopathy tends to cause LGE in the subendocardium or transmurally and follows a vascular distribution, which lies in stark contrast to nonischemic cardiomyopathy, which generally does not correspond to any particular coronary artery distribution and is often located in the midwall or epicardial regions. Therefore, the pattern of LGE can be used to differentiate between cardiomyopathies of ischemic and nonischemic etiologies [36].

Replacement fibrosis, focal “reparative” scarring that follows myocyte injury or necrosis, occurs in approximately one-third of patients with advanced DCM, typically in the midwall. [18]

It provides a substrate for ventricular re-entrant arrhythmia [37] and is independently associated with an increased risk of mortality and HF morbidity in DCM [38]

Moreover, its presence and extent in DCM hearts substantially determines the likelihood of LV reverse remodeling in response to pharmacological therapy [39] and CRT [40].

However, multiple presentations of LGE have been identified in DCM patients, and examining the prognostic value of different extents, locations, or patterns could allow for optimization of the risk stratification value of this technique [41].

- Septum (16.2%).
- Both the septum and the free wall of the left ventricle (13.3%).
- Left ventricle free wall alone (4.8%).

The most common patterns of LGE were:

- Linear mid-wall (21.1%).
- Multiple patterns (7.8%).
- Sub-epicardial (2.9%).
- Focal (2.5%).

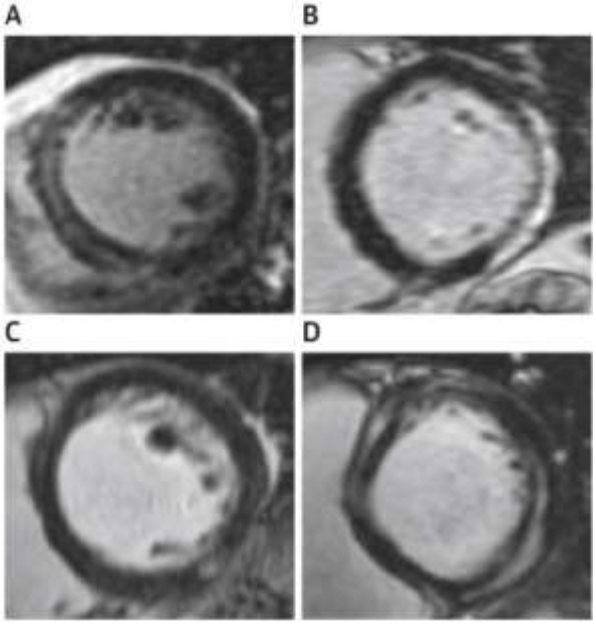


Figure 5: Late Gadolinium Enhancement in Dilated Cardiomyopathy. Late gadolinium enhancement images showing (A) linear mid-wall enhancement in the septum, (B) sub-epicardial enhancement in the lateral wall, (C) focal enhancement of the inferior wall, and (D) mid-wall enhancement of the septum, lateral and inferior wall. Quoted from Halliday et al. [41].

A systematic review and meta-analysis of a homogeneous population of selected DCM patients, we found that the presence of LGE embodied important prognostic information. Patients in whom LGE was present had a 3.40 (2.04 to 5.67) higher odds for cardiovascular mortality, an odd of 4.52 (3.41 to 5.99) for ventricular tachyarrhythmic events, and only 0.15 (0.06 to 0.36) higher odds for LV reverse remodeling [42].

Another systematic review and meta-analysis demonstrated that the presence of LGE by CMR provides excellent risk stratification for patients with NICM.

NICM patients without LGE have low (<2%) annualized Event Rates (AERs) for all-cause mortality, heart failure hospitalization (HFH), or sudden cardiac death (SCD), whereas patients with LGE have significantly higher AERs for the same individual outcomes, so this meta-analysis supported the role of LGE-CMR in identifying patients with NICM at risk for SCD, HFH, and overall mortality [43].

Examining the prognostic value of different extents, locations, or patterns of LGE in DCM could allow for optimization of the risk stratification value of this technique. Halliday et al. examined these different factors in 874 nonischemic DCM patients against a primary outcome of all-cause mortality, and a secondary outcome of a composite of SCD and aborted SCD [41].

As per previous literature, LGE was present in 34.3% of the patient cohort, and this LGE cohort represented the more severely affected patients within the cohort, with lower LVEF and worse NYHA class [41].

Overall, as with previous studies in the literature, the presence of LGE was associated with increases in both the primary and secondary outcome [44].

Overall analysis showed that in all measured outcomes, location of LGE was more predictive than either extent or pattern of LGE. Septal LGE was the most predictive factor for the primary outcome, whereas for the secondary outcome, concomitant LGE in both the septum and free wall was more important, although LGE only in the septum did have some predictive value [15].

In addition to risk prediction, the presence of LGE may also be used to optimize the timing of ICD implantation (e.g., it seems reasonable to postpone ICD implantation in patients who present with DCM in whom no LGE is present, and re-evaluate LVEF after 3 months of optimal medical therapy, because chance of LV reverse remodeling is substantial and risk of arrhythmias low). Conversely, in patients who first present with DCM with extensive LGE, protection by implantable or wearable ICD might be considered before discharge given the low chance of recovery and increased risk of major ventricular arrhythmic events. However, this is in contrast with current guidelines, according to which all patients with LVEF ≤35% should receive ≥3 months optimal medical therapy before prophylactic ICD therapy should be considered [42].

Besides reduced cardiac function, DCM is characterized by the development of conduction abnormalities, mainly left bundle branch block, thus leading to ventricular dyssynchrony. The inferolateral segment of LV-free wall generally presents the highest delay time and has been identified as the target region for lead placement and electric stimulation. The likelihood of response to CRT depends on proper lead position and vital cardiac muscle to be depolarized. Since LGE detects myocardial fibrosis in DCM, LGE positivity may be helpful for predicting response to CRT, improving our ability to identify patients eligible for this therapy [4].

T1 mapping and ECV

Issues surrounding the use of LGE include limitations in assessing other types of changes in heart muscle, such as diffuse myocardial fibrosis. Diffuse fibrosis is difficult to image via the LGE method, as there are fewer clearly defined boundaries between diffusely fibrotic areas and healthy myocardium than there are between focal scars and surrounding tissue. Thus, we need new techniques to image this type of scarring [15].

Techniques, such as extracellular volume fraction (ECV) characterization via T1 mapping, have shown to be effective in imaging histologically validated diffuse fibrosis in NIDCM patients [15, 45].

Myocardial T1 mapping is a noninvasive modality to assess extracellular volume fraction (ECV) for estimating diffuse myocardial fibrosis, by measuring myocardial and blood T1 relaxation time before and after contrast enhancement [46, 47].

CMR with T1 mapping and extracellular volume (ECV) calculation allows one to demonstrate diffuse fibrosis in a non-invasive manner and unlike LGE does not rely on local differences in image contrast (Figure 6) [[14].

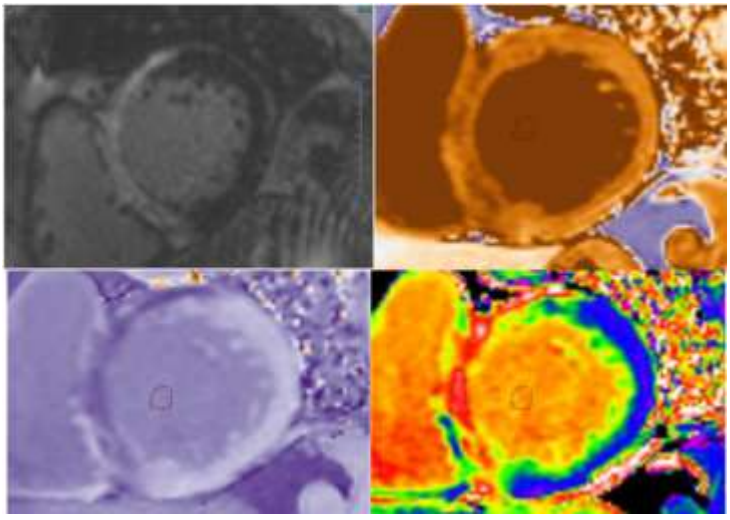


Figure 6: Mid-wall fibrosis (MWF) in a clockwise direction from upper left corner on late gadolinium enhancement (LGE) imaging, native T1, postcontrast T1 and extracellular volume (ECV) maps. Quoted from Brown et al. [14].

In a T1 map, the T1 value is encoded in each pixel and corresponds to the T1 relaxation time constant of the corresponding myocardial voxel. T1 maps can be created both before (native T1) and after gadolinium contrast and generally in DCM, native T1 values increase and after contrast T1 values get shorter [32,48].

By comparing signal intensity changes (as a function of contrast concentration changes) in the extracellular compartment with those in the blood pool and integrating the available blood volume distribution (1 haematocrit (HCT)) one can calculate the partition coefficient lambda which in turn allows estimation of the myocardial extracellular volume space using the formula $ECV=(1-HCT\times lambda)$. Calculated ECV is comparable with histological collagen volume fraction in DCM and increased ECV and native T1 is seen in those with DCM compared with controls [49].

Puntmann et al [50] found that in those with cardiomyopathy native T1 was longer, post contrast T1 was shorter and ECV was significantly higher. Following ROC analysis native T1 was found to be the best independent discriminator between healthy and diseased myocardium with a specificity of 97% and sensitivity of 100%.

Currently, T1 mapping is predominantly used in research settings and it is recommended that each center establishes their own reference ranges given the potential between scanner and vendor variation related in part to field strength, sequence and acquisition parameters [51].

ECV has generally less variability than native T1 values as the acquisition of precontrast and postcontrast T1 cancels out factors affecting the precision of native T1 when acquired in isolation, specifically the total volume (fraction) of possible contrast distribution, degree of patient hydration and degree of renal impairment. Normal values have been published by multiple groups for T1 and ECV at both 1.5T and 3T field strength and have found to be consistent with surprisingly little interobserver differences and good test-retest variability [52, 53].

Although most published T1 mapping studies gave the highest priority to the assessment of ECV and post-contrast T1 value [50, 54-58].

Recent studies reported that non-contrast-enhanced T 1 mapping can be used for assessment of myocardial fibrosis associated with DCM by using the appropriate threshold [59] and that native myocardial T1 values provide the best discrimination of normal and diffusely diseased myocardium, in DCM [50].

CMR-derived ECV simply quantifies the interstitial uptake of gadolinium contrast media relative to the plasma. Therefore, CMR-derived ECV strongly correlated with histological extracellular space component but only modestly correlated with histological collagen volume fraction in DCM. In addition, the positive y-intercept in the relationship between histological collagen volume fraction and CMR-derived ECV indicates that CMR-derived ECV is a surrogate for all of the multiple components of the myocardial interstitium, which include not only collagen but also non collagenous extracellular matrix proteins, fibroblasts, vessels, and incompressible fluid. The extent of non collagen extra-cellular space can directly influence the accuracy of CMR-derived ECV estimation of myocardial fibrosis and lead to overestimation in cases with large amount of non collagen extracellular space in the myocardium. In contrast, native T1 value represented interstitial fibrosis rather than extracellular spaces, leading to comparable ability for predicting histological collagen volume fraction as ECV assessment in the present study [60].

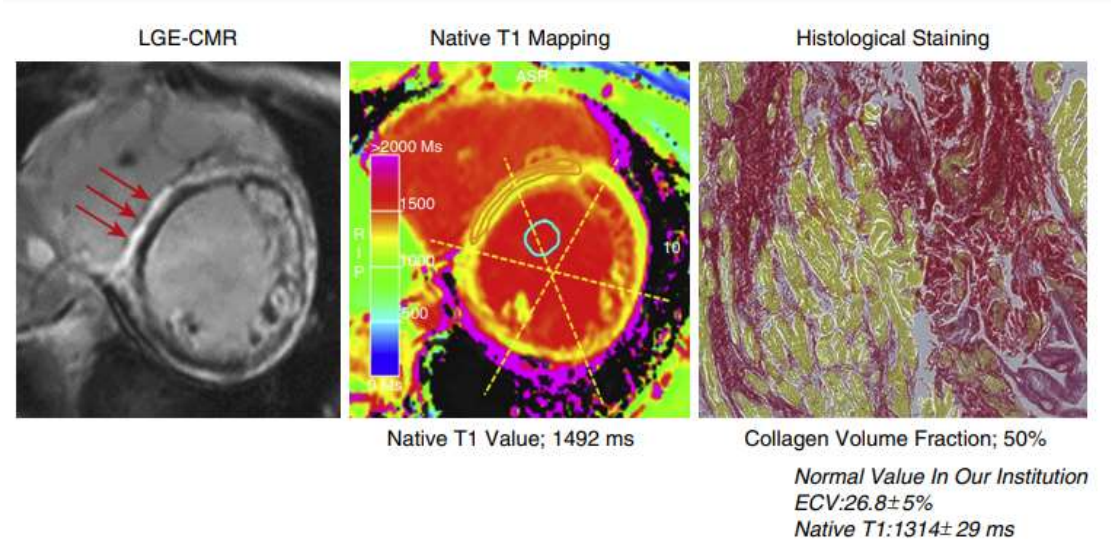


Figure 7: Nonischemic late gadolinium enhancement (LGE) was detected in the ventricular septum by visual assessment of the mid–left ventricular short-axis LGE image. An elevated native T1 value of 1,492 ms was observed on the native T1 map corresponding to the LGE image. The histological sample demonstrated extensive myocardial fibrosis with a collagen volume fraction of 50%. Quoted from Nakamori et al. [60].

Patients with HF often have associated (chronic kidney disease [CKD]), and gadolinium-based contrast agents cannot be used for patients with HF and end-stage CKD because of the risk of nephrogenic systemic fibrosis. Therefore, for patients with renal dysfunction, non-contrast-based magnetic resonance imaging of myocardial fibrosis is clinically needed. Diffuse myocardial fibrosis in DCM may be reliably assessed by native T1 mapping without the administration of gadolinium contrast agent [59, 60].

Native T1 imaging can also be used in early diagnosis of DCM. LV dilatation is typically the earliest noted hallmark on cardiac imaging of DCM. However, it can also develop as a normal physiological adaptive response to chronically sustained physical exertion, in a condition known as 'athlete's heart' [15].

A study by Mordi et al. showed the value of T1 mapping in this regard. T1 mapping was the only independent discriminator between athletes and DCM patients [61].

A study of 89 patients with non-ischaemic cardiomyopathy found that an ECV>32% was a prognostic predictor of mortality beyond echo parameters and that ECV was raised compared with controls even in those without LGE. [62].

In those with DCM, native T1 was significantly associated with all-cause mortality independent of both LVEF ≤35%and LGE presence [63].

Summary of the various roles of cardiac MRI in dilated cardiomyopathy:

Table 3: Summary of the various roles of cardiac MRI in dilated cardiomyopathy. Quoted from Lahoti et al. [15].

CMR sequence	Relevant findings in DCM
Ejection fraction measurement	• A mean difference in EF measurement between TTE and CMR of 4% • LVEF as measured by CMR being more predictive of mortality • The choice of imaging technique for EF could result in the reclassification of a significant number of patients for life-saving ICD implantation
Late gadolinium enhancement	• LGE occurs in approximately 30% of patients • Different patterns and locations of LGE are associated with both different risks of adverse events and different etiological subsets of DCM • Not a purely binary measurement as variances in intensity of LGE can be predictive of variances in outcome
Extracellular volume fraction	• More accurate than LGE in imaging diffuse fibrosis, with increased predictive value for major adverse events, such as death or hospitalization • Increased percentage of ECV correlated with increased risk of adverse events • Similar to LGE, the location of ECV had a predictive role • Can be combined with LVEF to increase predictive value
T1 sequences	• T1 mapping shown to be most predictive factor in differentiating cause of initial LV dilatation, i.e., athlete's heart or the initial stages of DCM in comparison to T2 mapping or ECV measurements • Can be used in other organ systems, such as the liver, to track development of DCM to heart failure

CMR: Cardiac MRI; DCM; Dilated cardiomyopathy; ECV: Extracellular volume fraction; EF: Ejection fraction; ICD: Implanted cardioverter defibrillator; LGE: Late gadolinium enhancement; LV: Left ventricle; LVEF: Left ventricular ejection fraction; TTE; Transthoracic echocardiography.

Declarations

Consent for publication: I attest that all authors have agreed to submit the work.

Availability of data and material: Available

Competing interests: None

Funding: No fund

Conflicts of interest: no conflicts of interest.

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