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ROLE OF CARDIAC MRI IN THE ASSESSMENT OF NONISCHEMIC CARDIOMYOPATHIES

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Abstract

In this review, we will highlight the role of late gadolinium enhancement, along with other strengths available by cardiac MRI, in determining the underlying etiology of various nonischemic cardiomyopathies. Furthermore, we will also emphasize how late gadolinium enhancement may serve as a novel risk stratification tool to further impact patient care.

Introduction

Nonischemic cardiomyopathies are generally defined as diseases of the myocardium associated with mechanical dysfunction and either inappropriate dilation or hypertrophy in the absence of an underlying etiology.[1] They are generally divided into those that are predominantly confined to the myocardium (primary) or those that involve the myocardium as part of a systemic disorder (secondary). Patients may be asymptomatic but frequently present with advanced stages of disease associated with heart failure and arrhythmic events. Management and prognosis frequently depends on the etiology of the cardiomyopathy involved. The first-line imaging test for assessing cardiomyopathies is echocardiography. It is readily available, rapidly performed, and provides accurate hemodynamic assessment in addition to identifying possible etiologies noninvasively. Recently, cardiac magnetic resonance imaging (CMR) has proven to be a powerful and effective adjunct to echocardiography in the evaluation of cardiomyopathies.

In a single 45- to 60-minute CMR study, a thorough assessment of a patient's cardiomyopathy can be performed. With its high spatial and temporal resolution, detailed three-dimensional (3D) images of cardiac and thoracic anatomy can be obtained free of limitations from body habitus or standard imaging planes. The gold standard for quantification, accurate and reproducible assessment of biventricular cardiac volumes and function can have profound implications regarding medical management. Concomitant valvular heart disease can be quantified with phase contrast techniques, and ischemia testing can be performed with first-pass perfusion during vasodilator stress. Finally, a feature most unique to CMR is the opportunity for accurate tissue characterization. Noncontrast T1- and T2-weighted sequences reliably assess edema and fat infiltration, and T2* sequences identify myocardial overload. The administration of gadolinium contrast, on the other hand, helps in the assessment of thrombus, and late gadolinium enhancement (LGE) techniques accurately image areas of myocardial fibrosis or infiltration.

In this review, we will highlight CMR imaging characteristics of the more common nonischemic cardiomyopathies and how the extent and pattern of LGE can not only help identify the underlying pathological process but, importantly, also may now provide novel insight into predicting prognosis (Table 1).

Dilated Cardiomyopathies

Dilated cardiomyopathy (DCM) is defined as systolic dysfunction, either the left ventricle alone or biventricular, with concomitant dilation. Although the etiology is not known in many cases, it is broadly defined as either ischemic or nonischemic (e.g., genetic, myocarditis, cardiac toxins). CMR aids in the evaluation of cardiomyopathies by readily providing accurate and reproducible measurements of biventricular volumes and ejection fractions without geometric assumptions, evaluating valvular heart disease and detecting thrombus. The addition of LGE can detect patterns of fibrosis that can help differentiate between ischemic versus nonischemic etiologies. With coronary artery disease (CAD), LGE is noted to spread from the subendocardium to epicardium and also follow a typical coronary artery distribution (Figure 1A). In a study comparing DCM patients with and without significant coronary disease by angiography, all CAD patients demonstrated subendocardial scarring.[2] In contrast, in those with non-ischemic disease, there is absent LGE (59%) or there is endocardial sparing with replacement fibrosis LGE patterns noted to be mid-wall (28%), epicardial, or diffusely in a noncoronary artery distribution (Figure 1B). Effectively detecting the presence of significant CAD is important as it identifies both a potentially reversible cause for the patient's cardiomyopathy and also a higher-risk patient cohort.[3]

Mid-wall LGE determined by CMR in nonischemic DCM has been shown to have prognostic value. In a prospective longitudinal study of 472 patients with nonischemic DCM, the presence and extent of mid-wall fibrosis was associated with significantly worse all-cause mortality (absolute risk difference, 16.2% [95% CI, 8.2%-24.2%]; P <.001) during a median follow-up of 5.3 years independent of age, New York Heart Association (NYHA) functional class, and left ventricular ejection fraction (LVEF).[4] In addition, mid-wall fibrosis was also independently associated with the prespecified secondary endpoint of sudden cardiac death (SCD) or aborted SCD. This study further demonstrated how the addition of fibrosis to LVEF significantly improved risk reclassification for all-cause mortality and the SCD composite, suggesting a new paradigm with which to guide implantable cardioverter-defibrillator (ICD) implantation. Other smaller studies with broad composite endpoints have also similarly shown that the presence and extent of mid-wall fibrosis predicts worse outcomes.[5-7]

Table Summarizing CMR Features of Various Nonischemic Cardiomyopathies

Type	Cine Characteristics	Late Gadolinium Enhancement (LGE) Patterns	LGE and Prognosis
Dilated Cardiomyopathy	Systolic dysfunction (left ventricle alone or biventricular) with concomitant dilation, valvular lesions, thrombus	• Ischemic heart disease: subendocardial scarring • Nonischemic heart diease: absent LGE or patterns of fibrosis noted to be midwall, epicardial, or diffuse in a noncoronary distribution	Midwall LGE associated with all-cause mortality, sudden cardiac death (SCD), or aborted SCD
Hypertrophic Cardiomyopathy	Abnormal LV hypertrophy (asymmetrical septal, apical, localized, or concentric), systolic anterior motion of the anterior mitral leaflet with dynamic outflow tract obstruction, mitral regurgitation, apical aneurysms, myocardial clefts, and papillary muscle abnormalities	Patchy, midmyocardial LGE generally occurring in areas of hypertrophy and at the junction of the interventricular septum and the right ventricular free wall	All-cause mortality, cardiac mortality, unplanned heart failure admissions, deterioration to New York Heart Association functional class III or IV, or heart failure-related death, ventricular arrhythmias, and SCD
Infiltrative Diseases: **Amyloidosis**	Homogenously thickened myocardium, interatrial septum and valve leaflets, and the presence of pleural and pericardial effusions	Widespread subendocardial hyperenhancement often including the interatrial septum and right ventricle	Worsening long-term survival, greater abnormalities in NYHA functional class, ECG voltage, left ventricular mass index, right ventricular wall thickness, troponin-T, and B-type natriuretic peptide levels.
Sarcoidosis	Localized areas of wall thinning and regional wall motion abnormalities with high signal intensity on T2 weighted images	Patchy, midwall, subepicardial, or even subendocardial with a predilection to involve the basal and midseptal segments. LGE of the RV free wall may also be a frequent finding	Higher rates for death, defibrillator shock, pacemaker, diastolic dysfunction, decreased right ventricular ejection fraction, and evidence of nonsustained ventricular tachycardias
Iron Overload	Findings of dilated cardiomyopathy with reduced myocardial T2* values	Uncommon	Unknown
ARVD (Arrythmogenic Right Ventricular Dysplasia)	Focal thinning, segmental aneurysms, both regional and global RV dilation, and depressed function	RV and/or LV LGE indicates intramyocardial fibro-fatty replacement	Induction of ventricular tachycardia during electrophysiologic testing
Left Ventricular Noncompaction (LVNC)	Extensive trabeculations and intratrabecular recesses, absence of well-formed papillary muscles	Various patterns?	Related to worse EF?

Table 1. Cardiac magnetic resonance features of nonischemic cardiomyopathies.

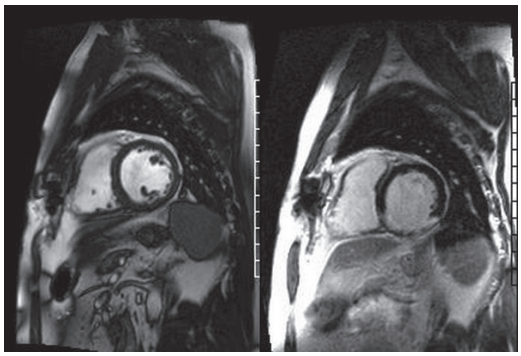

Figure 1A. Ischemic cardiomyopathy. Note large, near transmural infarct extending from the subendocardium involving the midinferoseptum and inferior wall, and posteromedial papillary muscle. Total scar burden was 18% of the left ventricle (LV). LV ejection fraction was mildly reduced (44%) with akinesis of the infarcted segments.

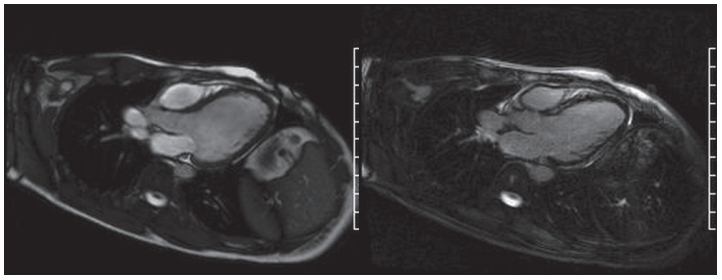

Figure 1B. Nonischemic cardiomyopathy with scar. Left ventricle (LV) is moderately dilated with mild globally depressed LV systolic function and normal right ventricular (RV) systolic function (LV ejection fraction 50%; RV ejection fraction 53%). Patchy midwall myocardial scarring is evident in the anteroseptum with late gadolinium enhancement.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most frequent genetic cardiac disease. Affected individuals demonstrate myocyte hypertrophy, disarray, and fibrosis presenting clinically as sudden death, heart failure, or significant morbidity at any age. With excellent spatial resolution and border definition, CMR provides complete visualization of the LV chamber, allowing precise localization of the distribution of hypertrophy and measurement of wall thickness and cardiac mass (Figure 2). Distribution and extent of LV hypertrophy is diverse (asymmetrical septal, apical, localized, or concentric hypertrophy) with most cases, however, demonstrating hypertrophy by CMR of the basal anterior LV free wall and the contiguous anterior ventricular septum.[8] Furthermore, although HCM may be focal (1-2 LV segments), the vast majority of cases have three or more LV segments involved with at least 15 mm wall thickness.[8] CMR is also superior to echocardiography in the detection of apical and focal basal anteroseptal variants and in recognizing noncontiguous areas of hypetrophy.[9] CMR cine imaging provides assessment of additional morphological information including systolic anterior motion of the anterior mitral leaflet with dynamic outflow tract obstruction, mitral regurgitation, apical aneurysms, myocardial clefts, and papillary muscle abnormalities. In addition, stress perfusion imaging can identify areas of microvascular dysfunction or mismatch between LV mass and coronary flow.

In addition to the detection of hypertrophy, late gadolinium enhancement (LGE) plays a further important role in diagnosing and risk stratifying HCM patients. Myocardial fibrosis is present in up to 80% of patients with HCM, with a characteristic pattern

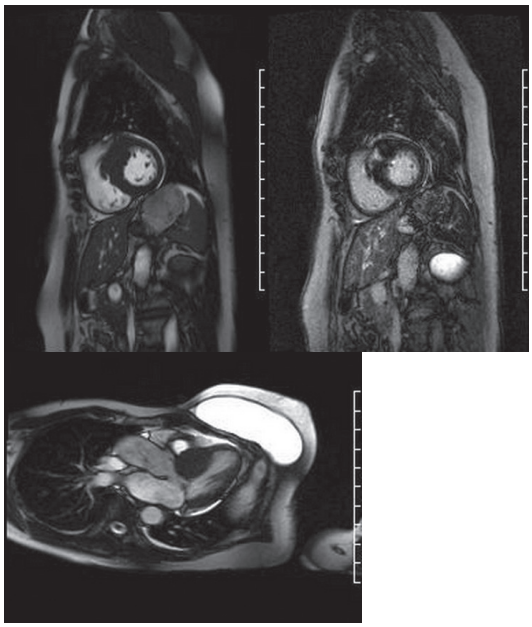

Figure 2. Obstructive hypertrophic cardiomyopathy. Severe asymmetric left ventricular hypertrophy (septum 2.6 cm, lateral wall 0.7 cm) with patchy, non-coronary artery disease scarring at the hypertrophied areas and right ventricular insertion sites. Cine steady-state free precession imaging demonstrated systolic anterior motion and dynamic left ventricular outflow tract obstruction with posteriorly directed mitral insufficiency.

of LGE (patchy, mid-myocardial) generally occurring in areas of hypertrophy and at the junction of the interventricular septum and the right ventricular free wall.[10] In addition, the extent of scarring has been shown to correlate positively with regional hypertrophy and inversely with regional contraction. The presence and extent of LGE has further been shown to have prognostic value in risk stratifying HCM patients. In 243 consecutive patients with HCM, the presence of scar was an independent predictor of death, with an odds ratio of 5.47 for all-cause mortality and of 8.01 for cardiac mortality.[11] Similarly, the risk of unplanned heart failure admissions, deterioration to NYHA functional class III or IV, or heart failure-related death has been shown to be greater in those with fibrosis (HR: 2.5, P = .021).[12] Although currently not considered an independent risk factor for SCD, LGE extent appears related to ventricular arrhythmias and SCD. In another 424 HCM patients, LGE-positive patients were more likely to have episodes of nonsustained ventricular tachycardia, more episodes of nonsustained ventricular tachycardia per patient, and a higher frequency of ventricular extrasystoles per 24 hours, with all cases of SCD and appropriate ICD discharges occurring in LGE-positive patients.[13] Recently, a meta-analysis of four studies evaluating 1,063 HCM patients over an average follow-up of 3.1 years demonstrated significant relationships between LGE and cardiovascular mortality, heart failure death, and all-cause mortality and a trend toward significance for LGE and SCD/aborted SCD.[14]

Infiltrative Cardiomyopathies

The presence of infiltrative cardiomyopathies (amyloidosis, hemochromatosis, sarcoidosis) portends a significantly poorer survival compared to patients with idiopathic cardiomyopathies.[15] Although echocardiography is very useful in their evaluation, it lacks the ability for reliable myocardial tissue characterization. With several infiltrative cardiomyopathies having characteristic features by CMR, this technique can play a significant role in the

correct noninvasive diagnosis of different infiltrative disorders, thus guiding treatment, assessing its outcome, and predicting prognosis.

Cardiac amyloidosis results from diffuse deposition of amyloid fibrils in the interstitial space. This deposition can virtually affect any part of heart, and cardiac involvement in itself portends poor prognosis. CMR features of cardiac amyloidosis also seen by echo include a homogenously thickened myocardium, interatrial septum and valve leaflets, and the presence of pleural and pericardial effusions. However, on scar imaging, a distinctive pattern of LGE is frequently seen with widespread hyperenhancement of the subendocardium or a global transmural pattern often including the interatrial septum and right ventricle (Figure 3A).[16] This scar pattern has been shown to have a high diagnostic accuracy for detecting cardiac amyloid when compared to endomyocardial biopsy and has also been shown to be the single best noninvasive imaging parameter for cardiac amyloid.[17,18] Other less common patterns include mid-wall and subepicardial LGE. Fast washout kinetics of gadolinium into the expanded extracellular space results in suboptimal myocardial nulling on T1 inversion time scout images, which may also help with diagnosis (Figure 3B). Furthermore, LGE has also been shown to have prognostic value in cardiac amyloidosis. Global LGE pattern is associated with greater abnormalities in NYHA functional class, ECG voltage, left ventricular mass index, right ventricular wall thickness, troponin-T, and B-type natriuretic peptide levels.[19] The presence of LGE has also been shown to be associated with worsening long-term survival.[20-22]

Sarcoidosis involves the myocardium in 20% to 30% of cases. Manifestations of cardiac sarcoidosis include conduction abnormalities, arrhythmias, heart failure, or sudden death. With current treatment options, early diagnosis is beneficial as morbidities can be avoided. CMR cine findings may include localized areas of wall thinning and regional wall motion abnormalities secondary to underlying inflammation. These areas of myocardial inflammation may be seen on T2 weighted images as high-signal intensity. LGE is further beneficial as it identifies areas of myocardial damage and may help guide the site for endomyocardial biopsy. A variety of nonspecific LGE patterns, including patchy, midwall, subepicardial, or even subendocardial, have been described in cardiac sarcoid with a predilection to involve the basal and mid-septal segments.[23] LGE of the RV free wall may also be a frequent finding. In patients with sarcoidosis, the application of LGE has shown to be more than twice as sensitive in detecting cardiac involvement than current consensus criteria (modified Japanese Ministry of Health), and the occurrence of LGE portends a nine-fold higher rate for adverse events (death, defibrillator shock, or pacemaker).[24] The presence of LGE is also associated with more diastolic dysfunction, decreased right ventricular ejection fraction, and evidence of nonsustained ventricular tachycardias.[25] Recently, it was shown that patients with LVEF of 35% or lower had more transmural and subepicardial lesions and significantly more transmural lesions compared to patients with LVEF >35%, and that the number of affected segments of LGE positively correlated with the duration of sarcoidosis.[26]

A major cause of death in patients dependent on blood transfusions is iron overload cardiomyopathy. CMR has made possible accurate detection of both liver and myocardial siderosis using the T2* imaging technique (Figure 4).[27] The presence of iron deposition in myocardium results in local magnetic field

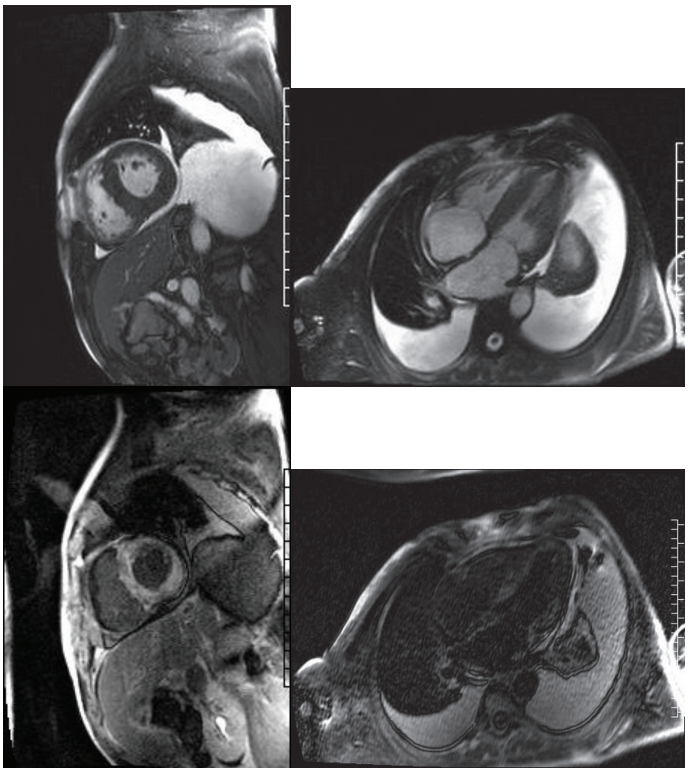

Figure 3A. Cardiac amyloidosis. Cine steady-state free precession images demonstrated biatrial enlargement, moderate concentric LVH, small pleural effusion, large bilateral pleural effusions and moderate global left ventricle (LV) and right ventricle (RV) systolic dysfunction (LV ejection fraction 33%, RV ejection fraction 27%). Late gadolinium enhancement images demonstrated diffuse subendocardial involvement of the LV and left atrium with sparing of the RV.

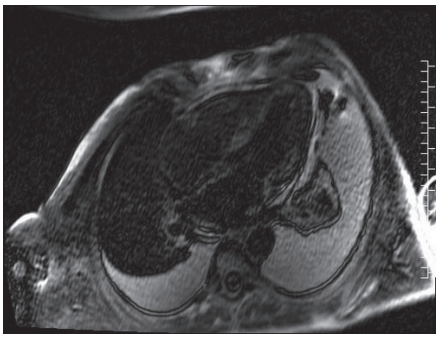

Figure 3B. Cardiac amyloidosis. T1 scout images demonstrate nulling of the blood pool (dark) before the myocardium (bright). This is a characteristic finding, with the myocardium having shorter T1 values than blood due to extensive extracellular space expansion and rapid myocardial gadolinium uptake.

inhomogeneities, which in turn results in reduced T2* values. T2* relaxation times <10 ms defines severe cardiac iron overload and has been shown to accurately identify patients at highest risk for developing heart failure and arrthymias.[28] In fact, cardiac T2* magnetic resonance is superior to serum ferritin and liver iron for risk stratification. Astoundingly, using cardiac T2* to identify the earlier need for intensified iron chelation treatment in high-risk patients has been shown to reduce the high burden of cardiac mortality in myocardial siderosis. Since the introduction of T2* CMR in the United Kingdom in 1999 to identify myocardial

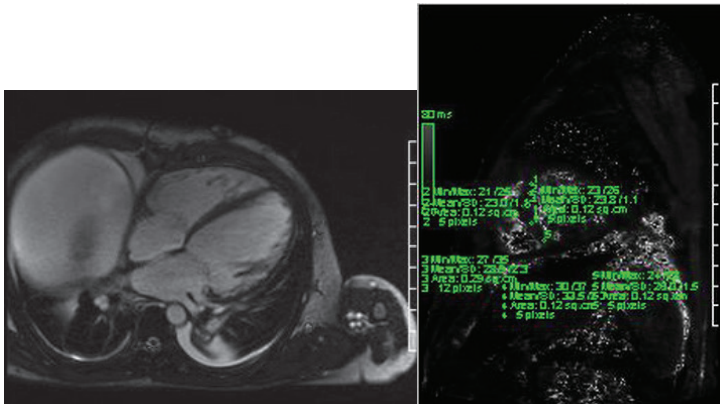

Figure 4. Iron overload cardiomyopathy under treatment. Severe left ventricular (LV) enlargement with moderate global biventricular dysfunction (LV ejection fraction 32%, right ventricular ejection fraction 36%) with definite iron overload in the liver (T2* 4 msec) and borderline iron overload in the myocardium (T2* 18 msec). Late gadolinium enhancement was not performed due to contraindication for gadolinium (renal failure).

siderosis, the appropriate intensification of iron chelation treatment alongside other clinical care improvements has reduced the annualized death rate from iron overload by 71% in the UK's thalassemia major patients.[29] Finally, the presence of macroscopic fibrosis, as evidenced by LGE, is uncommon in thalassemia major patients with a broad spectrum of myocardial iron loading.[30]

Other Cardiomyopathies

Arrhythmogenic right ventricular dysplasia (ARVD) is a genetic disorder of cardiac desmosomes characterized pathologically by fibro-fatty replacement of the RV myocardium. Diffuse disease may later result in LV involvement. Clinical findings include ventricular arrhythmias, sudden cardiac death, and heart failure. Currently, the diagnosis is based on a combination of major and minor diagnostic criteria proposed by the 1994 International Task Force of Cardiomyopathies that include global and regional RV dysfunction and structural alterations, fibro-fatty replacement of the myocardium, ECG changes, and family history.[31] By providing high-resolution 3D multi-planar images, CMR is the best modality for complete RV evaluation and can accurately detect focal thinning, segmental aneurysms, both regional and global RV dilation, and depressed function. Tissue characterization with CMR can further assess for intramyocardial fatty infiltration and fibrosis. Though not a Task Force criterion for the diagnosis of arrhythmogenic right ventricular dysplasia, intramyocardial fat can be suspected with high signal intensity on T1 weighted imaging that is nulled on T2 weighted imaging with fat suppression.[32] LGE, on the other hand, can assess for myocardial fibro-fatty changes in both the right and left ventricles. The presence of LGE has shown a high degree of correlation with endomyocardial biopsy in ARVD patients and predicts induction of ventricular tachycardia during electrophysiologic testing.[33]

Left ventricular noncompaction (LVNC) is characterized by extensive trabeculations and intratrabecular recesses, occurring more frequently in apical and lateral segments, which give the LV a "spongy" appearance. Clinical manifestations potentially include cardiac failure, thromboembolism, and malignant arrhythmias. Superior CMR image quality with steady-state free precession cine frames allows the trabeculations to be easily identified (Figure 5). The ratio of 2.3 between the thickness

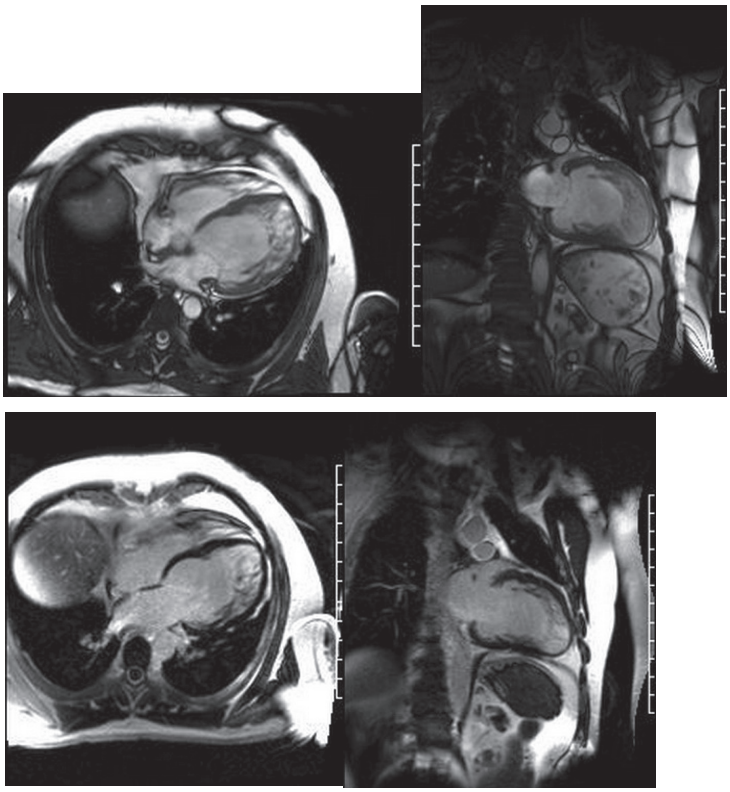

Figure 5. Noncompaction cardiomyopathy. Severely enlarged left ventricle (LV) with LV ejection fraction of 29%. Prominent LV apical trabeculations are seen with a ratio of noncompacted to compacted myocardium of 2.5:1. Late gadolinium enhancement demonstrated contrast uptake within the trabeculations.

of the noncompacted and compacted myocardial layers in diastole distinguishes pathological LVNC from the degrees of noncompaction observed in healthy, dilated, and hypertrophied hearts.[34] Others have used CMR to quantitate volumetric parameters (LV noncompacted myocardial mass percentage >25%; LV noncompacted myocardial mass index >15 g/m^2) to more accurately identify LVNC.[35] Absence of well-formed papillary muscles is also a helpful clue for diagnosis. Different patterns of LV LGE distribution can be appreciated, and the presence and extent of LV LGE is shown to be independently related to LVEF.[36] However, the presence of LGE has not reproduced in all the studies, and the role of the absence or presence of LGE in LVNC must be further investigated.

Conclusion

CMR is a particularly helpful and complementary test to echocardiography in the assessment of nonischemic cardiomyopathies. CMR assets include its excellent unhampered visualization of cardiac structures, quantitative LV and RV analysis, and simultaneous flow assessment. Uniquely, it affords the opportunity for noninvasive tissue characterization that readily distinguishes edema, fat, thrombus, and fibrosis. A body of literature is now accumulating delineating the role of LGE in clarifying a diagnosis and in providing further risk stratification independent of other diagnostic variables to further impact patient management.

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