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TOPIC HIGHLIGHT

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Distribution of late gadolinium enhancement in various types of cardiomyopathies: Significance in differential diagnosis, clinical features and prognosis

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Abstract

The recent development of cardiac magnetic resonance (CMR) techniques has allowed detailed analyses of cardiac function and tissue characterization with high spatial resolution. We review characteristic CMR features in ischemic and non-ischemic cardiomyopathies (ICM and NICM), especially in terms of the location and distribution of late gadolinium enhancement (LGE). CMR in ICM shows segmental wall motion abnormalities or wall thinning in a particular coronary arterial territory, and the subendocardial or transmural LGE. LGE in NICM generally does not correspond to any particular coronary artery distribution and is located mostly in the mid-wall to subepicardial layer. The analysis of LGE distribution is valuable to differentiate NICM with diffusely impaired systolic function, including dilated cardiomyopathy, end-stage hypertrophic cardiomyopathy (HCM), cardiac sarcoidosis, and myocarditis, and those with diffuse left ventricular (LV) hypertrophy including HCM, cardiac amyloidosis and Anderson-Fabry disease. A transient low signal intensity LGE in regions of severe LV dysfunction is a particular feature of stress cardiomyopathy. In arrhythmogenic right ventricular cardiomyopathy/dysplasia, an enhancement of right ventricular (RV) wall with functional and morphological changes of RV becomes apparent. Finally, the analyses of LGE distribution have potentials to predict cardiac outcomes and response to treatments.

Key words: Cardiomyopathy; Cardiac magnetic resonance; Late gadolinium enhancement; Cardiac function; Clinical features; Prognosis

Core tip: We review characteristic cardiac magnetic resonance (CMR) features in ischemic and non-ischemic cardiomyopathies (NICM), especially in terms of location and distribution of late gadolinium enhancement (LGE). LGE in NICM does not correspond to any particular coronary artery distribution and is located mostly in the mid-wall to subepicardial layer. The analysis of LGE distribution is valuable to differentiate NICM with diffusely impaired systolic function; dilated cardiomyopathy, end-stage hypertrophic cardiomyopathy (HCM), cardiac sarcoidosis, and myocarditis, and those with diffuse LV hypertrophy; HCM, cardiac amyloidosis and Anderson-Fabry disease. The analyses of LGE distribution have potentials to predict cardiac outcomes and response to treatments.

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INTRODUCTION

The management of patients with left ventricular (LV) dysfunction starts from the identification of underlying myocardial disorders. The primary diagnostic issue is the differentiation between ischemic and non-ischemic cardiomyopathies (ICM and NICM). NICM include several disorders, such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), cardiac sarcoidosis, stress cardiomyopathy, and others[1,2], but often show similar clinical presentations which lead to progressive heart failure, a high risk of fatal arrhythmias, and a high mortality rate[3].

NICM have been traditionally diagnosed non-invasively with chest roentgenography, standard 12-lead electrocardiography (ECG), transthoracic and/or transesophageal echocardiography and nuclear imaging, and invasively with coronary angiography, left ventriculography, and endomyocardial biopsy.

Imaging with cardiac magnetic resonance (CMR) is non-invasive, uses no ionizing radiation, and has high spatial resolution. Recent advantage of CMR has enabled us to assess cardiac morphology, function and tissue characteristics both in ICM and NICM[4,5]. Thus, CMR is capable of identifying cardiac abnormalities not readily recognized by conventional imaging modalities[6-8].

We have been studying the late gadolinium enhancement (LGE) in various NICM and attempting to verify the values for differential diagnosis, clinical features, and prognosis[9-13]. This review article focuses on various types of NICM, and discusses initially about CMR techniques and differential diagnosis from ICM, and then about the usefulness of CMR, especially the clinical significance of location and distribution of LGE.

RECENT DEVELOPMENT OF CMR

CMR imaging comprises several techniques of magnetic resonance imaging (MRI) sequences. Cine-CMR, which is based on the steady state free precession sequence, provides accurate information about cardiac morphology and function. First-pass contrast enhanced perfusion-CMR with and without vasodilators can provide assessment of myocardial perfusion reserve[14].

LGE-CMR relies on the delivery of intravenous gadolinium chelate to the myocardium, which is a biologically inert tracer that freely distributes in extracellular space but does not cross the intact cell membrane. Due to a combination of increased extracellular volume and slower washout kinetics, there is a relative accumulation of gadolinium in areas of necrosis, fibrosis, infiltration, and inflammation in the late washout phase. Since gadolinium shortens T1 relaxation time, it produces brighter signal intensity, and this technique is sensitive and reproducible in the detection of myocardial scarring both in ICM and NICM[15,16]. However, since LGE is ascribed to relative accumulation of gadolinium in areas of damaged myocardium, LGE-CMR techniques may miss a diffuse type of fibrosis[16,17]. Recently, T1 mapping with a Look-Locker sequence after injection of gadolinium has become a promising tool to quantify interstitial myocardial fibrosis[18].

There are also special sequences that are used less often to clarify the cause of NICM. These include fat suppression black blood for detection of fatty infiltration, T2-weighted imaging for myocardial edema, and T2-star (T2*) for the assessment of myocardial iron[19-21].

Thus, the combination of multiple CMR sequences helps clinicians differentially diagnose NICM. The characteristic features in each CMR sequence will be discussed below under each specific NICM.

DIFFERENTIAL DIAGNOSIS OF ICM AND NICM

The diagnosis of patients with NICM originates with the differentiation of ICM. In general, coronary angiography is routinely performed for the differentiation, and when patients have no obstructive coronary arteries or coronary risk factors, the diagnosis of NICM is usually made. However, it has to be kept in mind that no obstructive coronary artery on angiography is inadequate to exclude ICM[16]. The spontaneous recanalization after coronary occlusion caused by a rupture of minimally stenotic but unstable plaque, embolization or spasm may mask the occurrence of coronary events. Conversely, it is also a common situation that patients with DCM have coronary arterial disease during their natural courses. An autopsy study in some patients diagnosed with DCM has described subendocardial and transmural fibrosis indistinguishable from myocardial infarction[22].

CMR technique is now recognized as a useful tool to determine whether the LV dysfunction is caused by ischemic coronary events. Cine-CMR with excellent spatial and temporal resolution can detect segmental wall motion abnormalities or wall thinning in a particular coronary arterial territory. LGE-CMR can also define the subendocardial or transmural LGE as fibrosis caused by coronary events because the ischemic wave front starts from subendocardium.

On the other hand, LGE in NICM generally does not correspond to any particular coronary artery distribution and is often located in the mid-wall[23]. A previous study detected striated or patchy pattern of LGE in a certain part of patients diagnosed with DCM[16].

The differential diagnosis of ICM and NICM is also crucial for management of patients with cardiac dysfunction. Treatment with β-adrenoceptor blockers and renin-angiotensin-aldosterone inhibitors are recommended for both ICM and NICM. Patients with ICM have worse outcome but may benefit from revascularization and/or aneurysmectomy and from secondary prevention with aspirin and statins. Furthermore, LV remodeling after

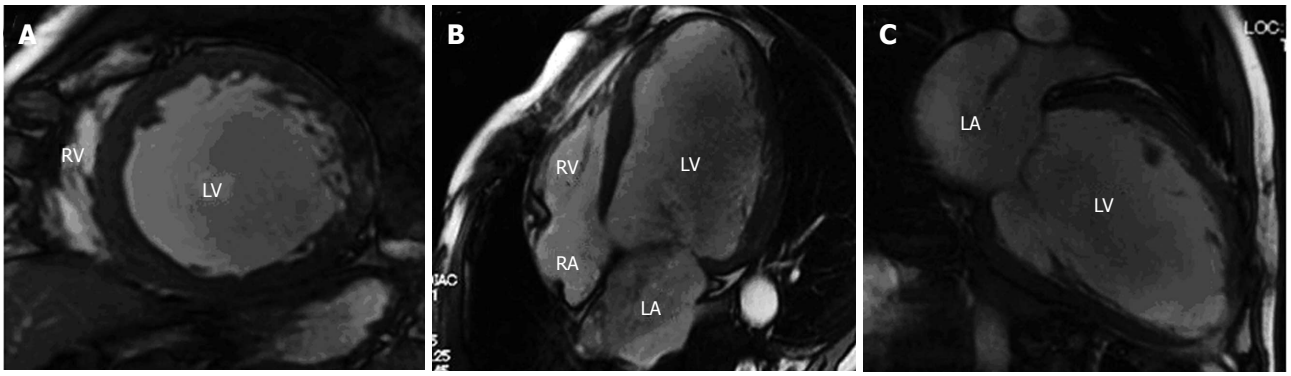

Figure 1 Representative cine-cardiac magnetic resonance images in a 62-year-old male patient with dilated cardiomyopathy. The images show mid-ventricular short axis (A), horizontal axis (4-chambers) (B) and vertical long axis views (C). The images reveal dilatation of left ventricular (LV) cavity and diffuse wall thinning (relatively homogenous). The LV end-diastolic volume, LV end-systolic volume, LV ejection fraction (EF) and LV mass are 329.1 mL, 252.5 mL, and 23.3%, 153.2 g, respectively. LV and RV: Left and right ventricles; LA and RA: Left and right atria; LV: Left ventricular.

myocardial infarction often occurs with non-extensive infarction but the absence of suitable preventive therapy. Conversely, in patients with NICM, the early diagnosis may recommend genetic studies to indentify inherited abnormalities and help to start early aggressive study with intensified medical and device therapies[2,16].

DCM

General

DCM is the most common isoform of NICM, and is characterized by dilatation of LV chamber and systolic dysfunction, which leads to progressive heart failure, high risk for fatal arrhythmias and high mortality rate[3].

Although over the half of cases are idiopathic, DCM is not a single tree of disease spectrum but may include several undetermined etiologies, such as chronic myocarditis, tachycardia-induced cardiomyopathy, undiagnosed sarcoidosis, and end-stage HCM[16,24].

CMR features

In cine-CMR, all cardiac chambers are enlarged and a decrease in LV ejection fraction (EF) is evident. The LV wall thickness is normal or decreased, but relatively homogenous. Figure 1 shows representative cine-CMR images of different views in a patient with DCM.

In LGE-CMR, DCM has been shown to demonstrate mostly a lack of LGE or the presence of mid-wall enhancement, and a fewer part of cases shows patchy or diffuse striated LGE. The distribution of LGE is unrelated to a particular coronary arterial territory, and corresponds to focal fibrosis at autopsy[1,9,25]. Our recent study showed various patterns of LGE as described in Figure 2[13]. However, the prevalence of LGE varies among reports between 12% and 67%, which may be caused by different etiologies, disease states and duration, or by a limitation of LGE-CMR technique. The mechanisms of myocardial fibrosis in DCM are complex and include inflammation, genetic predisposition, micro-vascular ischemia, and neurohumoral changes[9]. LGE-CMR technique may miss a diffuse type of fibrosis, and hence a certain part of DCM patients may have no LGE[16,17]. Different thresholds used to detect LGE may also affect the variation in the prevalence of LGE. A recent development of T1 mapping technique is expected to estimate such a diffuse type of fibrosis[17,18].

Clinical implications

Several previous studies showed the lack of relationship between the presence of LGE or LGE volume, and LV volume and function[9,12,26]. We and other investigators found that LGE volume did not correlate with LV end-diastolic volume, global left ventricular ejection fraction (LVEF) or segmental LV contraction, but the washout rate of 99m-technecium-sestamibi (^{99m}Tc-MIBI) did[12,27]. Since the increase in washout rate of ^{99m}Tc-MIBI reflects mitochondrial dysfunction in cardiomyocytes[28], the increased LV volume and impairment of LV function in DCM may be ascribed to the dysfunction of individual myocytes rather than segmental fibrosis. However, recent studies have shown the resistance of patients with mid-wall LGE to reverse remodeling by β-adrenergic blockers and/or cardiac re-synchronization therapy[9,29]. We also showed that reverse remodeling occurred after treatment in patients with no LGE and with LGE localized in inter-ventricular septum, but did not in patients with extensively distributed LGE[13]. Since LV segments with a lower amount of LGE are expected to have more viable but functionally disturbed cardiomyocytes and reversible matrix fibrosis, they are more likely to benefit from therapies[12,27].

The mid-wall LGE in DCM correlates with intraventricular conduction disturbance, and is independently predictive of sudden cardiac death (SCD) or ventricular tachycardias (VTs)[13,30,31]. Thus, LGE-CMR can help to identify the arrhythmogenic substrate and plan an appropriate mapping and ablation strategy.

In DCM, a series of factors is associated with adverse prognosis, such as age, gender, LVEF, QRS duration and cardiac biomarkers[13]. Although the larger LGE volume is associated with poor prognosis in patients with ICM[15,32], the prognostic implication of LGE in DCM remains controversial. However, the severity of irrevers-

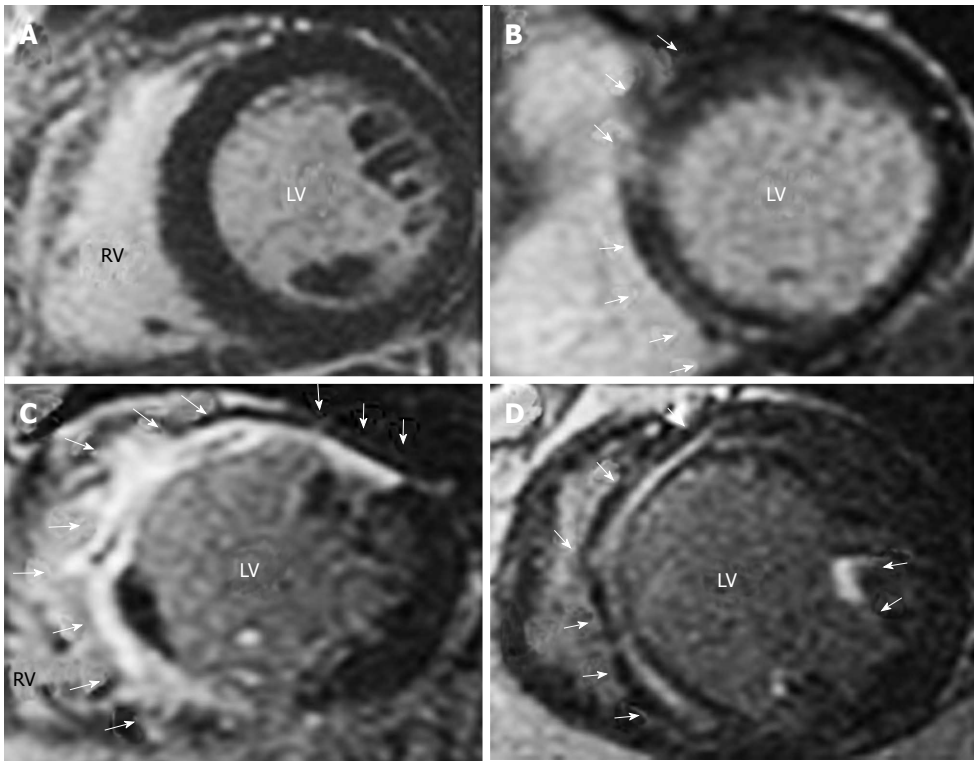

Figure 2 Representative short axis late gadolinium enhancement-cardiac magnetic resonance images in patients with dilated cardiomyopathy. A: No LGE; B: localized LGE. Mid-wall LGE distributed only into anterior and inferior septum; C: Extensive LGE. LGE distributed at anterior and inferior septum, anterior, anterolateral and inferior LV segments; D: Extensive LGE. Mid wall LGE distributed at anterior and inferior septum, and at anterior papillary muscle. Arrows indicate LGE in LV wall segments. All the images are taken from Machii *et al*[13] with permission. LGE: Late gadolinium enhancement; LV: Left ventricular.

ible fibrosis is related to the impairment of cardiac function, the propensity to ventricular arrhythmias and the resistance to reverse remodeling, and recent studies have shown that LGE volume is well concordant with high probabilities of cardiac mortality and morbidity[30,33,34]. We also exhibited the lowest event-free survival rate in patients with extensively distributed LGE[13]. Therefore, the analysis of LGE volume or distribution, not only the presence of LGE, may be valuable to predict prognosis and identify high-risk patients in DCM.

HCM

General

HCM is a relatively common genetic disorder of the cardiac sarcomere, characterized by an idiopathic LV hypertrophy. Typically, this disorder demonstrates asymmetric septal hypertrophy, but can also present atypical patterns of hypertrophy involving the mid-ventricle and apex. Hence, HCM has a wide variety of morphological, functional, and clinical features.

CMR features

Because of various phenotypic expressions of HCM and other mimicking diseases which show LV hypertrophy, cardiac imaging has a central role in establishing the final diagnosis. Although transthoracic echocardiography has been the standard tool for the diagnosis of HCM, it has limitations for precise visualization of whole ventricles and quantification of hypertrophy. CMR is capable of identifying regions of LV hypertrophy not readily recognized by echocardiography[6-8], especially for apical hypertrophy and apical aneurysm[11,35,36].

The myocardial LGE is a common feature of HCM, and can be focal or spread diffusely into any areas of LV[11,37,38]. A previous study showed that more than 55% of HCM patients have some LGE, most commonly at the anterior and posterior RV insertion points. Gene-positive patients are more likely to have LGE and may even precede hypertrophy[39,40]. LGE in HCM usually represents areas of increased interstitial fibrosis but may also indicate myocardial disarray, necrosis, and scarring[41]. Figure 3 shows representative cine-CMR and LGE-CMR images in various types of HCM.

In other MRI sequences, a previous study showed focal T2 abnormalities in the areas of LGE with severe LV hypertrophy[42]. In addition, stress CMR can demonstrate reduced vasodilator response in subendocardium particularly in the area of severe hypertrophy[14].

Clinical implications

In contrast to DCM, the presence of LGE and LGE volume have been well associated with New York Heart Association (NYHA) functional classes, LV systolic and diastolic function, and left atrial volume[9,11,43]. Since 15% to 20% of HCM patients have progressive heart failure[44], determining the prognostic implications of LGE in HCM patients is crucial in order to identify high-risk

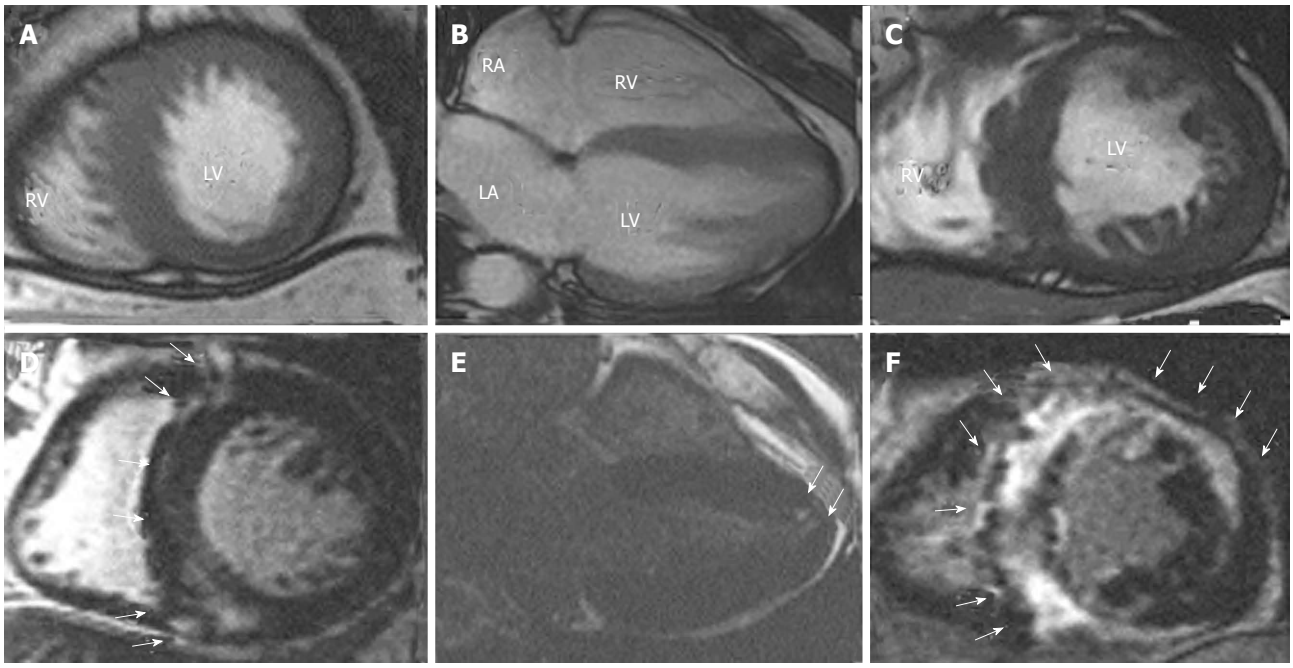

Figure 3 Representative cine-cardiac magnetic resonance (A-C) and late gadolinium enhancement-cardiac magnetic resonance (D-F) images in patients with various phenotypes of hypertrophic cardiomyopathy. A, D: ASH (short axis views); B, E: APH (horizontal views); C, F: End-stage HCM (short axis views). LGE was mainly localized in the ventricular septum and right ventricular insertion points in ASH and in the apex in APH (arrows). Note the inhomogeneous LV wall thickness and diffusely spread LGE in end-stage HCM. All the images are taken from Satoh *et al*[11]. ASH: Asymmetrical septal hypertrophy; APH: Apical hypertrophy; LGE: Late gadolinium enhancement; LV: Left ventricular; HCM: Hypertrophic cardiomyopathy.

patients who are most likely to benefit from early aggressive therapies.

Since myocardial fibrosis may provide an arrhythmogenic underlying substrate, previous studies examined the correlation between LGE and ECG abnormalities or ventricular arrhythmias in HCM. The disturbance of conduction system, exhibited as prolonged QRS duration and/or QRS axis deviation was correlated with LGE volume and LGE distribution into inter-ventricular septum[11,45]. Although the contribution of LGE to abnormal Q waves still remains controversial, the segmental and transmural extent rather than the mere presence of LGE may be the underlying mechanism of abnormal Q waves[11,45,46]. The apical hypertrophy (APH) is a common type of HCM especially in Japan[47]. The giant negative T waves are one of the characteristics of APH, and the depth of negative T waves was related to the asymmetric distal hypertrophy[11]. We and others also reported the progression of apical myocardial damage expressed as LGE reduced the QRS voltage, the depth of negative T waves, and caused fragmentation of QRS waves[48]. Recent studies have also shown that HCM patients with LGE are more likely to have episodes of non-sustained VTs, higher frequency of ventricular extrasystoles as well as VT inducibility in the electrophysiological study[9,13,49].

Risk stratification in HCM is difficult because of the heterogeneity in the clinical and phenotypic expression and the low event rate[44,49]. However, HCM is one of the most common disorders causing SCD. There are five clinically accepted high-risk factors for SCD, including a family history of sudden death, extreme LV hypertrophy (> 30 mm), unexplained syncope, a documentation of non-sustained VTs, and an abnormal blood pressure response during upright exercise[50]. A recent review has shown a close relationship between LGE and cardiovascular mortality, heart failure death, and all-cause mortality in HCM[51]. Additionally, stress perfusion CMR could be used to further stratify the risk for SCD, since inducible myocardial ischemia is another risk in HCM, which was proven by a study on single-photon emission computed tomography (SPECT)[52].

End-stage (dilated phase) HCM

End-stage HCM, which is characterized by LV systolic dysfunction and enlargement of LV cavity, is recognized as a part of HCM disease spectrum[53]. Since the clinical condition in end-stage HCM resembles that in DCM, the differential diagnosis of them becomes difficult, if the hypertrophy was undiagnosed or underestimated during the natural course of the disease. Patients with end-stage HCM frequently exhibit severe heart failure and lethal ventricular arrhythmias, thus resulting in higher mortality rates than the overall HCM or DCM population[13,53]. Therefore, the early and correct recognition of those patients is necessary to start aggressive medical and device therapies.

Cine-CMR exhibits that LV wall thickness in end-stage HCM is normal or relatively larger and is inhomogeneous among LV segments compared with that in DCM (Figure 3)[13]. LGE-CMR also shows that LGE in end-stage HCM distributes more diffusely into all the LV segments, whereas that in DCM is localized mainly in the

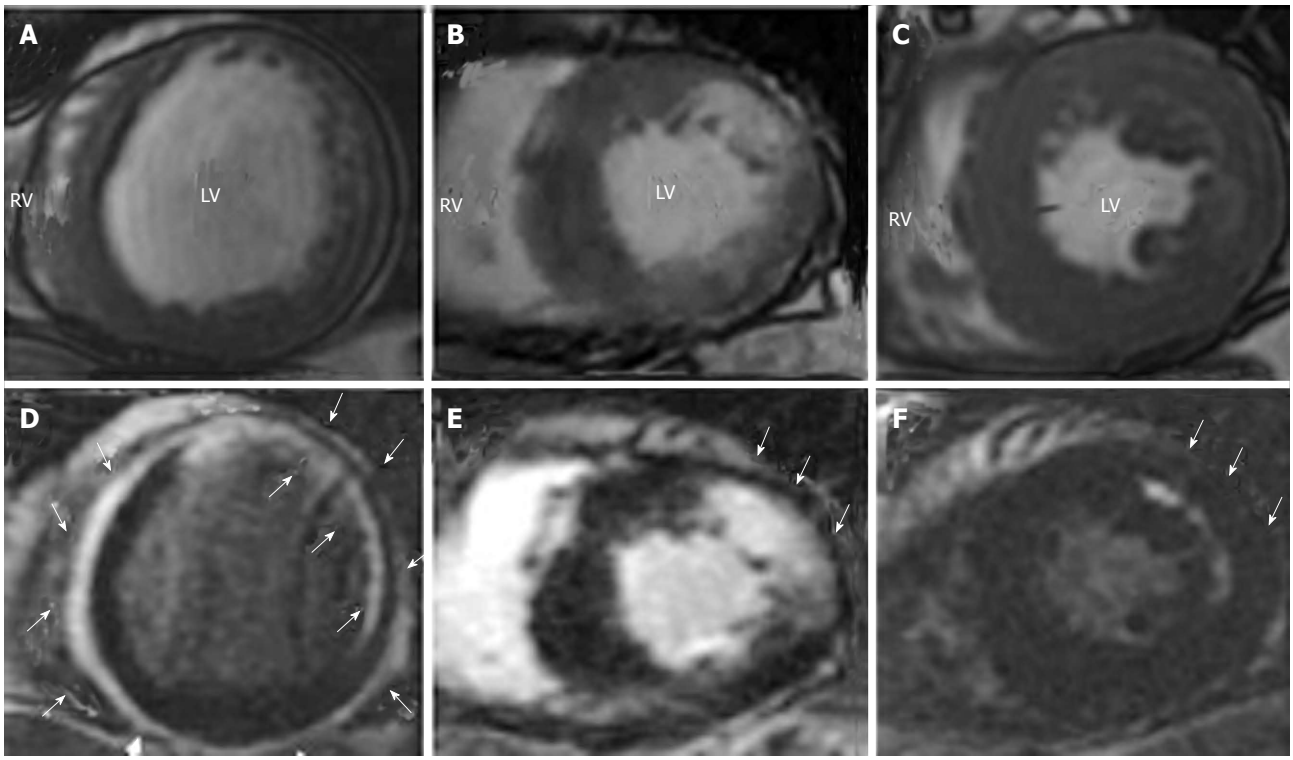

Figure 4 Representative cine-cardiac magnetic resonance (A-C) and late gadolinium enhancement-cardiac magnetic resonance (D-F) images in patients with cardiac sarcoidosis. A, D: A patient with LV dilatation, reduced LVEF (22%) and circumferential subepicardial and subendocardial LGE with spared mid-myocardium; B, E: A patient with reduced LVEF (38%) and nodular LGE in antero-lateral wall; C, F: A patient with preserved LVEF (58%) with mid-wall striated LGE in antero-lateral wall. White arrows indicate LGE areas. A part of the images is taken from Matoh *et al*[10] with permission. LGE: Late gadolinium enhancement; LV: Left ventricular; LVEF: Left ventricular ejection fraction

inter-ventricular septum[6,9,11,38]. Detailed analyses of both cine-CMR and LGE-CMR can help differentiation of end-stage HCM from DCM and other secondary cardiomyopathies that exhibit LV dysfunction with hypertrophy (*e.g.*, cardiac amyloidosis and Anderson-Fabry disease).

CARDIAC SARCOIDOSIS

General

Sarcoidosis is a multi-system disorder of unknown etiology. Clinical cardiac involvement is found in only 5% to 7% of patients with sarcoidosis, whereas postmortem studies have identified myocardial lesions in 20% to 60%[54]. Autopsy studies showed that cardiac sarcoid lesions were mainly non-transmural and located in the basal LV and subepicardial myocardium[55-57].

The diagnosis of cardiac sarcoidosis has been made with endomyocardial biopsy, and the guideline of Japanese Ministry of health and welfare (JMH) is also based on histological diagnosis[58]. However, biopsy results are sometimes false negative because of discrete distribution of sarcoid lesions. Hence, patients with systemic sarcoidosis and those with impaired LV function who are suspected cardiac involvement of sarcoidosis are not always positive according to the guideline. Therefore, some patients have been misdiagnosed with normal or DCM, and do not benefit from immunosuppressive therapies. Since patients with cardiac sarcoidosis have a poor prognosis, and a treatment with corticosteroid can improve long-term prognosis, an earlier diagnosis of cardiac involvement of sarcoidosis with non-invasive imaging modalities is crucial.

CMR features

In cardiac sarcoidosis, cine-CMR can image segmental wall motion abnormalities, wall thinning, and aneurysm formation. LGE-CMR identifies LGE in the LV wall[10,55-58]. The mechanism of LGE in cardiac sarcoidosis is considered to be heterogeneous, and may contain not only fibrotic scar but also an increased interstitial space due to the formation of non-caseating epithelioid cell granuloma[59]. LGE in cardiac sarcoidosis may reflect irreversible myocardial damage, since we and others could not demonstrate a reduction in LGE volume during various follow-up periods[10,58].

Previous studies compared findings between LGE-CMR and SPECT or ^{18}F-fluorodeoxyglucose-positron emission computed tomography (FDG-PET) in the diagnosis and assessment of cardiac sarcoidosis. A previous paper noted that the transmural extent of LGE was well associated with defect scores in ^{201}Tl-SPECT[56]. We found that LGE distributed mostly into the basal and mid inter-ventricular septum, but also spread into all the LV segments. Additionally, we and other investigators found that nodular, circumferential, and subepicardial and subendocardial types of LGE distribution exhibited high specificity for differential diagnosis from DCM (97%-100%, Figure 4)[57,58]. Although the new JMH guideline includes

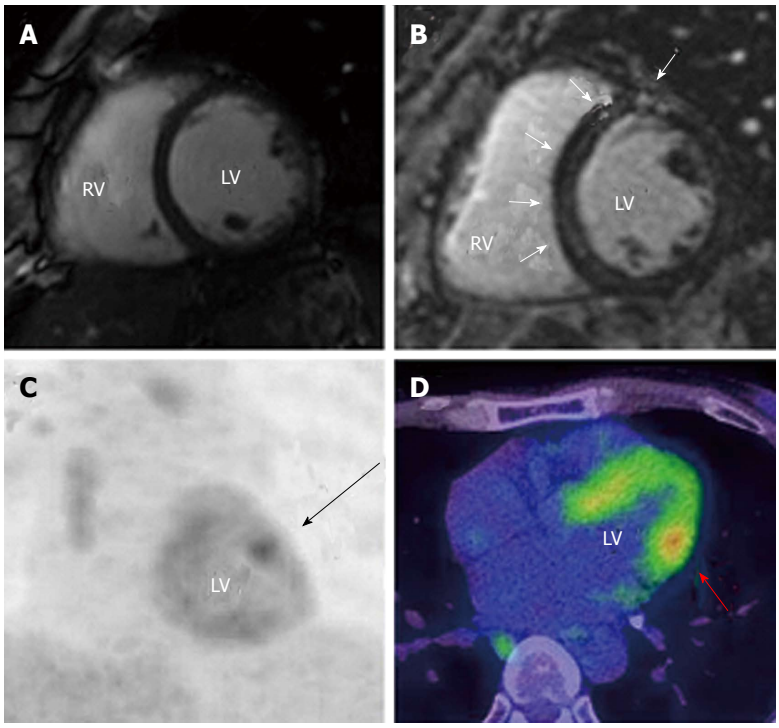

Figure 5 Representative short axis cine- cardiac magnetic resonance (A), late gadolinium enhancement-cardiac magnetic resonance (B), ^{18}F-fluorodeoxyglucose-positron emission computed tomography (C), and positron emission computed tomography (D) images in a 57-year-old male patient with systemic sarcoidosis. The diagnosis of sarcoidosis was made with liver biopsy. Cine-CMR images shows normal LV size and contraction (LVEDV: 119 mL, LVEF: 73%), but LGE-CMR reveals patchy and striated LGE in anterior wall and inter-ventricular septum (white arrows). The patient was negative for cardiac involvement of sarcoidosis according to the guideline of Japanese Ministry of Health and Welfare. However, FDG-PET and PET-CT images demonstrate hot spot in postero-lateral wall of LV, indicative of active inflammatory change (black and red arrows). FDG-PET: ^{18}F-fluorodeoxyglucose-positron emission computed tomography; LGE: Late gadolinium enhancement; LV: Left ventricular; LGE-CMR: Late gadolinium enhancement-cardiac magnetic resonance.

the presence of LGE as a minor criterion for cardiac sarcoidosis[60], the characteristic patterns of LGE distribution may help more precise diagnosis.

T2-weighted CMR sometimes shows punctuated or patchy signals in the acute lesions of cardiac sarcoidosis with myocardial edema[61].

Clinical implications

In sarcoidosis, patients with LGE in myocardium show heart failure symptoms, and a higher prevalence of ECG abnormalities and VTs[58]. The correlations between LGE volume, and LV volume and function are also described. Hence, the cardiac outcome in patients with LGE is significantly lower than that without LGE[57,58].

While LGE and defects in ^{201}Tl-SPECT represent irreversible fibro-granulomatous replacement, the hot spots in ^{67}Ga-SPECT or FDG-PET indicate active inflammatory change, which can also be used for assessing the effect of corticosteroid therapy[62,63]. Since FDG-PET can provide better sensitivity compared with SPECT, the combination of CMR and FDG-PET may improve overall sensitivity for diagnosis and help therapeutic strategies (Figure 5)[63,64].

STRESS (TAKOTSUBO) CARDIOMYOPATHY

General

Stress cardiomyopathy (SC), initially reported in Japan as Takotsubo cardiomyopathy, is characterized by an acute, severe but reversible LV dysfunction without significant coronary artery disease[65,66]. The majority of patients have a clinical presentation similar to that of acute coronary syndrome (ACS)[66]. The precise incidence of SC is unknown, but recent studies have revealed a prevalence of approximately 2% of patients presenting ACS in the United States and Europe[66,67]. There is a high predominance in elderly women, and several instances are possibly triggered by physical or emotional stress[68,69]. Despite severe presentation in acute phase, complications are rare and the prognosis of patients with SC is generally considered favorable[67,70].

Although the mechanism of SC has not yet been fully clarified, considerable evidence suggests that enhanced sympathetic activity might play a pathogenic role in the transient myocardial dysfunction observed in SC[71]. At the tissue level, myocardial edema as a sign of acute but reversible injury and diffuse inflammation in the absence of significant necrosis/fibrosis are characteristics of SC. However, other histological analyses of the heart in SC showed sparse foci of myocardial necrosis with contraction bands in the akinetic area[71,72].

CMR features

CMR at acute phase (approximately 5 d after onset) is mostly suited for the evaluation of patients with SC. Since CMR imaging can provide markers for reversible and irreversible injury, it may be particularly important to diagnose SC from ACS and myocarditis[66,70,73].

A previous study suggested diagnostic criteria with CMR: (1) severe LV dysfunction in a non-coronary regional distribution pattern; (2) myocardial edema co-located with the regional wall motion abnormality; (3) absence of high-signal areas in LGE images; and (4) increased early myocardial gadolinium uptake[66]. The LV dysfunction in cine-CMR is typically apical ballooning shape with akinesis of apical and mid-ventricular LV segments (so-called Takotsubo-like). However, fewer patients presented a mid-ventricular variant with apical sparing or with isolated basal ballooning[66,69]. Mean LVEF was 39%

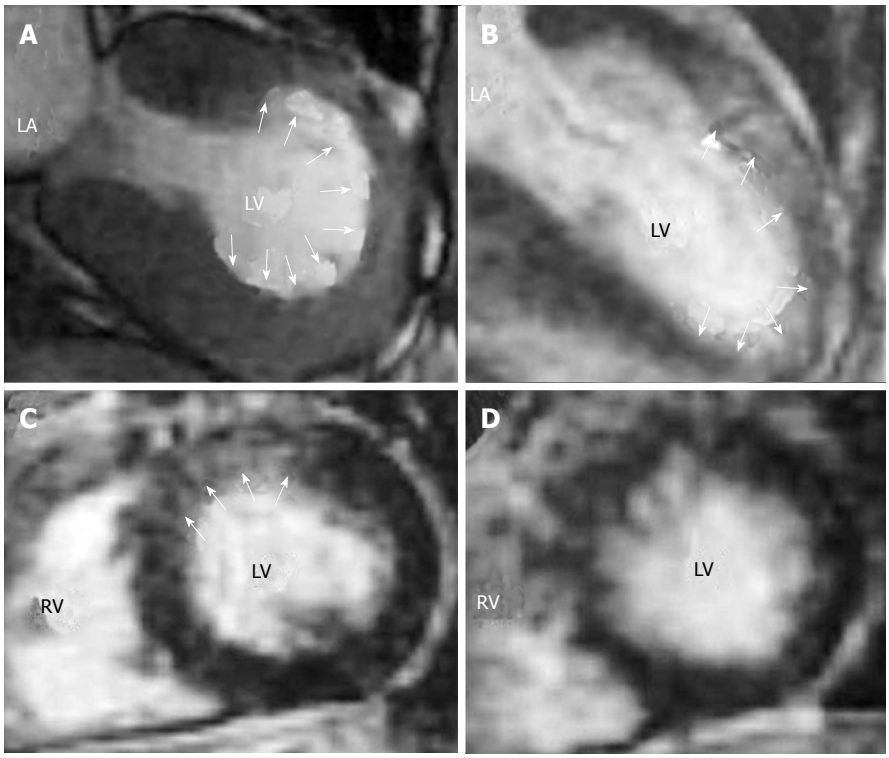

Figure 6 Representative cine-cardiac magnetic resonance (A) and late gadolinium enhancement-cardiac magnetic resonance (B-D) images in a case of stress (Takotsubo) cardiomyopathy. The images show vertical long axis (A, B) and mid-ventricular short axis (C, D) views. The cine-CMR image during systole (A) shows mid-anterior dyskinesis (white arrows). LGE-CMR images on the sub-acute phase (B, C) show that the area of LGE was well matched with the area of wall motion abnormality (white arrows). On the follow-up phase, LV systolic function recovered, and the LGE-CMR image (D) could not detect significant LGE in the LGE area observed on the sub-acute phase. All the images are taken from Naruse *et al*[69] with permission. LGE: Late gadolinium enhancement; LV: Left ventricular; LGE-CMR: Late gadolinium enhancement-cardiac magnetic resonance.

in the acute setting and 65% in the recovery phase. Cine-CMR also clarified right ventricular (RV) dysfunction in 38.5% of patients, and apical thrombus in 5.1%[73]. T2-weighted images can also show myocardial edema co-located with the regional wall motion abnormality[66]. The absence of LGE has been described in many case studies and is a common diagnostic criterion[66,70]. However, a recent meta-analysis has demonstrated LGE in a certain part of cases with SC[73]. A previous study showed evidence for the immune-histological basis of the LGE phenomenon in patients with SC[74].

We found LGE in 8 of 20 patients with SC[69]. The signal intensity was lower than that usually documented in cases of myocardial infarction or myocarditis (Figure 6). Another study also showed that focal and patchy LGE was detected in a certain part of patients when using a threshold of 3 standard deviation (SD) instead of 5 SD above the mean of remote myocardium to define significant enhancement[66]. Possible speculations are that severe stress-induced stunning of the apical segments leads to a patchy pattern of myocardial contraction-band necrosis possibly accompanied by a certain amount of transient focal/patchy edema or deposition of extracellular matrix resulting in LGE with low signal intensity. We also detected LGE at the recovery phase in fewer patients.

Clinical implications

Although the LV dysfunction in SC is mostly reversible, an involvement of RV is associated with longer hospitalization, heart failure, and older age. Cine-CMR can clarify the exact incidence of bi-ventricular ballooning[66,75]. We also showed that patients with LGE experienced cardiogenic shock more frequently and had a longer duration to ECG normalization and recovery of wall motion than did those without LGE[69]. Contrary, another study exhibited that the presence of less rigorously defined LGE during the acute phase had no persisting effect on global LV function, and there was no evidence of LGE at CMR follow-up[66]. Thus, the clinical implications of such type of LGE remain still elusive. In both studies, however, the absence of significant LGE was consistent with the complete normalization of LV function in patients with SC.

OTHER CARDIOMYOPATHIES

Arrhythmogenic right ventricular cardiomyopathy/dysplasia

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a disease of heart muscle characterized by structural and functional abnormalities of RV wall due to replacement of the myocardium by fatty and fibrous tissue. This disorder is relatively uncommon but life-threatening cardiomyopathy with progressive RV failure, ventricular arrhythmias and SCD. Although RV is the predominantly diseased chamber, LV can also be the affected chamber in some cases[76].

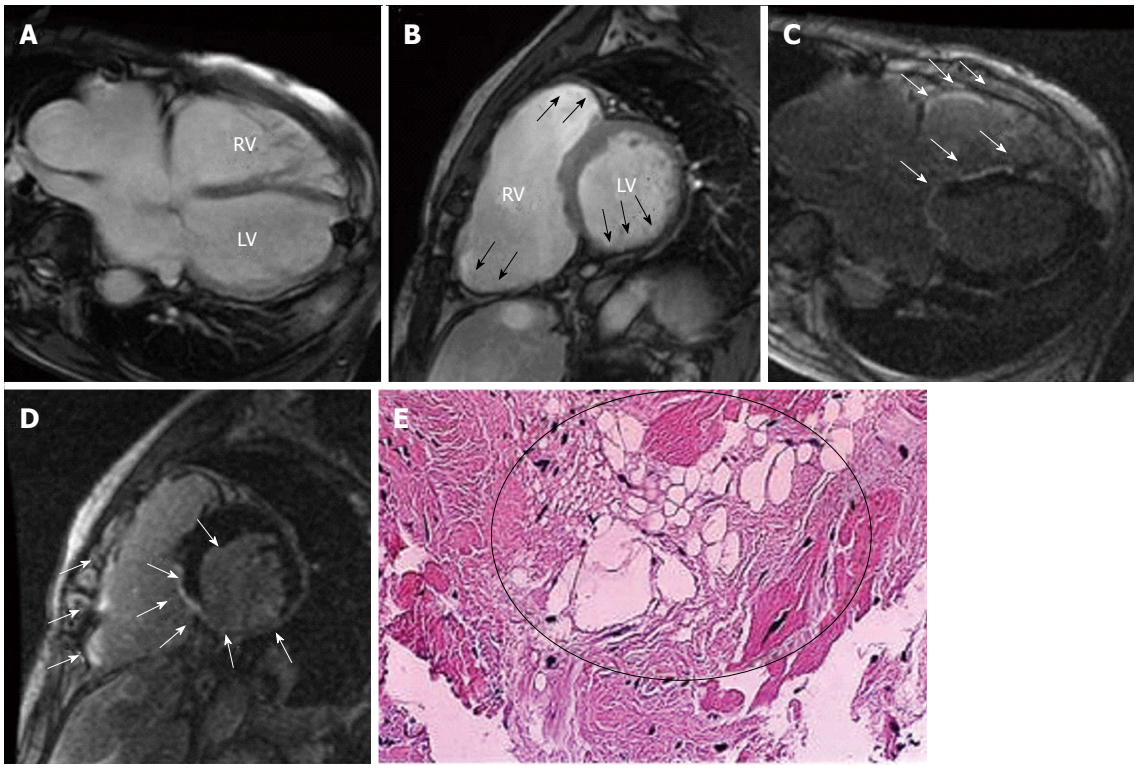

Figure 7 Representative cine- cardiac magnetic resonance (A, B) and late gadolinium enhancement-cardiac magnetic resonance (C, D) images in a 55- year-old male patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia. The images show horizontal axis (4-chambers) (A, C) and mid-ventricular short axis (B, D) views. Cine-CMR images reveal dilatation of both RV and LV chamber. Focal dilatation of RV and wall thinning in inferior LV wall are also apparent (black arrows). LGE-CMR images show diffuse LGE in RV wall and in inferior LV wall (white arrows). A sub-endocardial biopsy demonstrates fatty infiltration in RV myocardium (Circle, H-E stain, 100×). LGE: Late gadolinium enhancement; LV: Left ventricular; LGE-CMR: Late gadolinium enhancement-cardiac magnetic resonance; RV: Right ventricular.

The diagnosis of ARVC/D is challenging due to heterogeneous clinical presentation and non-specific ECG findings[77,78]. The diagnosis is currently made on the presence of major and minor Task Force criteria that include structural, functional, histological, electrocardiographic, arrhythmic, and genetic factors[79]. Endomyocardial biopsy is considerably unreliable for the diagnosis of ARVC/D, because the patchy distribution of the fibro-fatty change may cause sampling error.

CMR can visualize RV wall better than echocardiography. Functional abnormalities in cine-CMR include regional wall motion defects, focal aneurysms, global RV dilation and dysfunction[1,21]. In addition, the diagnosis could be supported by the presence of fatty infiltration of RV free wall that can be suppressed in fat suppression sequences[2,21]. LGE imaging has been shown to provide additional evidence of fibrosis which often co-exists in the fat-infiltrated RV myocardium (Figure 7).

Despite the limitations of thin RV wall and small volume of affected myocardium, CMR frequently identifies individuals with early disease, in whom Task Force criteria are relatively insensitive[21]. The presence of LGE can also predict inducible VTs on electrophysiological studies[80].

Cardiac amyloidosis

Cardiac involvement has been described in most forms of amyloidosis, but is most common and clinically significant in type AL amyloidosis (primary amyloidosis)[81]. Cardiac amyloidosis is a common cause of restrictive cardiomyopathy, and reduced ventricular wall compliance leads to impairment of diastolic filling and diastolic heart failure even when systolic function was preserved. At a histological level, amyloidosis is evident by extra-cellular deposition of insoluble fibrillar proteinaceous material (amyloid fibrils) in various cardiac tissues including valve leaflets and coronary vessels.

On cine-CMR, diffuse myocardial hypertrophy including both ventricles and atria is seen with thickened valve leaflets and pericardial effusion. The accumulation of amyloid fibrils in the myocardial interstitium also results in unique LGE appearances. In the early disease stage, a characteristic subendocardial enhancement of LV and RV, sparing the mid-wall of the inter-ventricular septum has been reported. However, as the accumulation of amyloid fibrils expands interstitial space, the volume of distribution of gadolinium increases. Therefore, there is usually a homogeneous pattern of enhancement, such that the signal from the myocardium cannot be adequately suppressed and differentiated from the adjacent blood pool. Actually, previous studies showed an atypically dark appearance of the blood pool, which reflects the similar myocardial and blood T1 values attributable to high myocardial uptake and fast blood pool washout (Figure 8)[1,2,82].

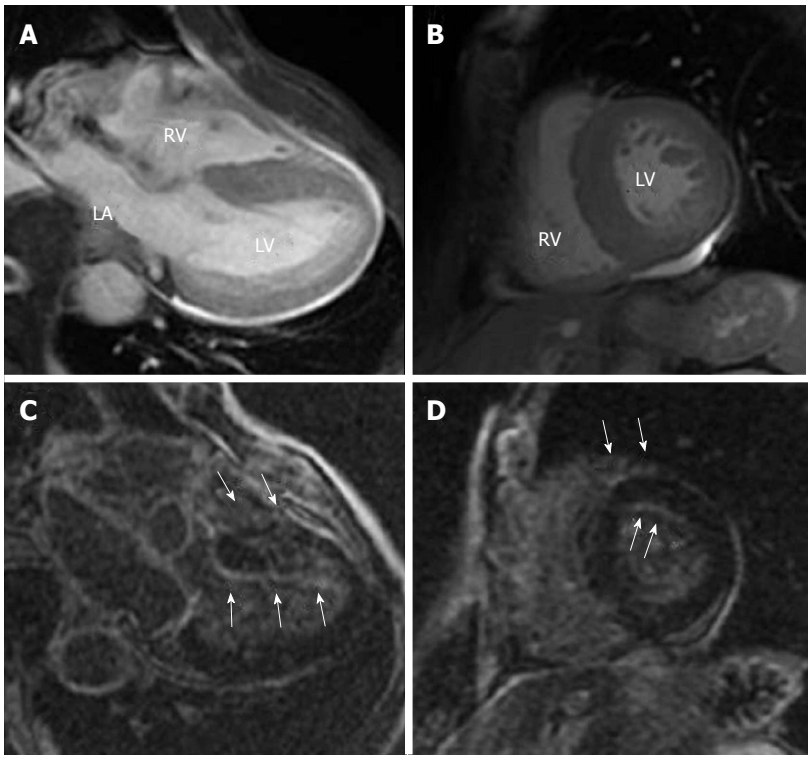

Figure 8 Representative cine-cardiac magnetic resonance (A, B) and Late gadolinium enhancement-cardiac magnetic resonance (C, D) images in a 76-year-old male patient with AL amyloidosis (IgAλ type multiple myeloma, Bence-Jones protein positive). The images show horizontal axis (4-chmbers) (A, C) and mid-ventricular short axis (B, D) views. Cine-CMR images reveal diffuse hypertrophy in LV and RV wall. LGE-CMR images show a characteristic subendocardial enhancement of the LV and RV with an atypically dark appearance of the blood pool (white arrows). LGE: Late gadolinium enhancement; LV: Left ventricular; LGE-CMR: Late gadolinium enhancement-cardiac magnetic resonance; RV: Right ventricular.

A recent study has also demonstrated a potential of remarkable prolongation of non-contrast (native) T1 in AL amyloidosis[83].

A positive CMR finding, that is biventricular hypertrophy, characteristic LGE distribution, and pericardial effusion, is associated with poor outcomes (heart failure and death) in patients with AL amyloidosis[82,84].

Myocarditis

Myocarditis is most commonly caused by a viral infection resulting in myocardial inflammation and immune-mediated damage in cardiomyocytes. Acute myocarditis causes chest pain, ST-T changes and elevated cardiac enzymes, which are sometimes difficult to be differentiated from ACS, and is occasionally complicated by fulminant heart failure and SCD[85]. Chronic myocarditis is one of the common causes of NICM, and sometimes misdiagnosed as DCM[1].

The most characteristic features in CMR are the presence of myocardial edema, diffuse wall motion abnormalities, subepicardial patchy myocardial LGE, and the concomitant involvement of the pericardium[86,87]. Edema imaging using T2 black blood sequences plays an important role in the evaluation of patients with suspected myocarditis[20,61]. Edema should be verified by a quantitative signal intensity analysis, best by calculating the ratio between myocardium and skeletal muscle. Early gadolinium enhancement and prolonged native T1 are also indicative of myocardial edema[20,88]. On LGE-CMR, the subepicardial layer especially in postero-lateral wall has LGE, and in severe cases, LGE may be more diffuse and circumferential[89].

Anderson-fabry disease

Anderson-fabry disease (AFD) is an X-linked lysosomal storage disorder caused by the partial or complete deficiency of α-galactosidase A. The enzymatic deficit results in progressive intracellular accumulation of excess cellular glycosphingolipid substrate in multiple organs[90]. Cardiac involvement in AFD is frequent, and the myocardial accumulation of glycosphingolipids acts as a trigger leading to myocardial cell hypertrophy and interstitial fibrosis. Hence, most patients present LV hypertrophy, and often exhibit conduction defects, supra-ventricular and ventricular arrhythmias, and heart failure symptoms associated with progressive LV dysfunction[91,92]. The presence and extent of cardiac damage increase progressively with age. Enzyme replacement therapy with recombinant α-galactosidase A clears microvascular deposits of glycosphingolipids, and several recent studies have shown a reduction in LV hypertrophy and improvement in systolic function after treatment[93,94].

Therefore, differentiating AFD from other causes of LV hypertrophy is critical but is usually difficult on common imaging modalities including echocardiography. A binary endocardial appearance, initially expected as a highly sensitive and specific finding in AFD, was later ascertained to be insufficient for a screening tool[95,96].

Instead, CMR has become a promising tool to diagnose cardiac involvement of AFD. Cine-CMR can exhibit a symmetrical and non-obstructive LV hypertrophy, and LGE-CMR can demonstrate a particular LGE distribution to the infero-lateral wall of mid to basal LV and to mid-myocardial layer (Figure 9)[92,97]. Furthermore, a recent non-contrast T1 mapping technique has potential to detect early cardiac involvement of AFD by showing T1 shortening[98]. Thus, AFD should always be considered if unexplained LV hypertrophy is seen, particularly in a young patient with family history.

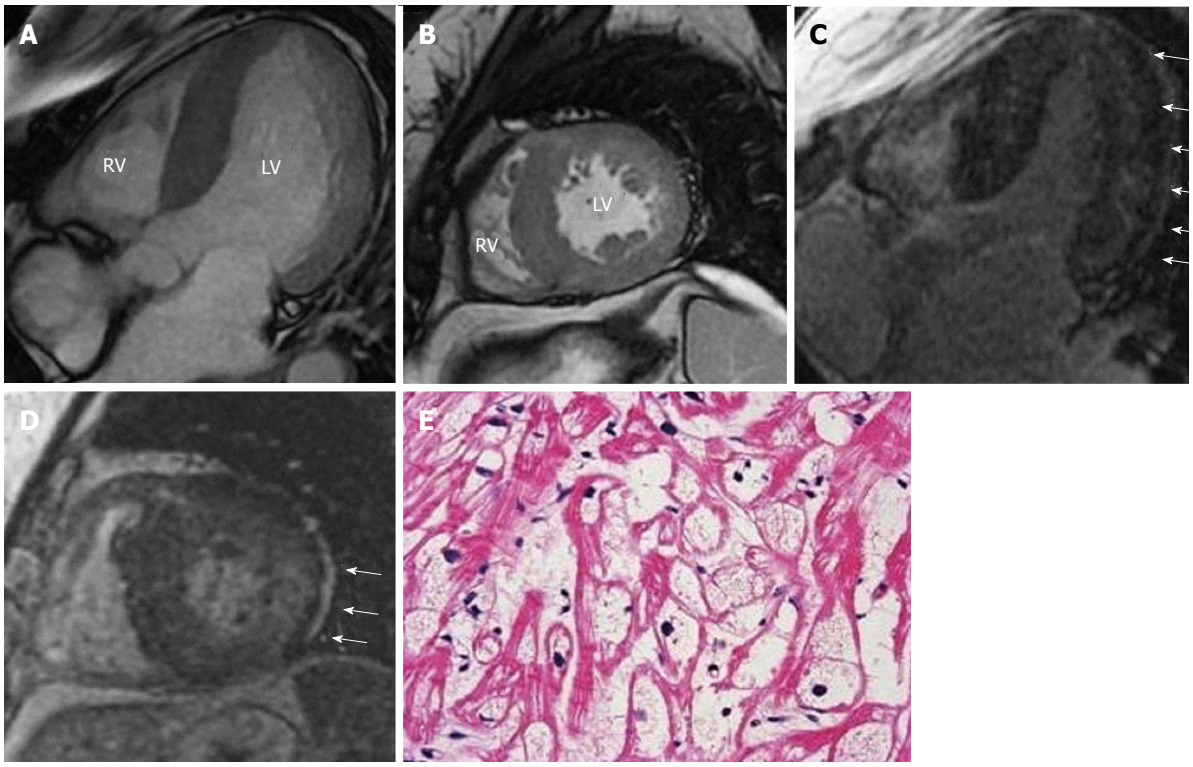

Figure 9 Representative cine- cardiac magnetic resonance (A, B) and late gadolinium enhancement-cardiac magnetic resonance (C, D) images in a 46-year-old female patient with Anderson-fabry disease. The images show horizontal axis (4-chambers) (A, C) and mid-ventricular short axis (B, D) views. Cine-CMR images reveal diffuse hypertrophy of LV wall. LGE-CMR images show a particular LGE distribution pattern to the infero-lateral mid to basal segments and to mid-myocardial layer (white arrows). E: A sub-endocardial biopsy from RV wall demonstrates interstitial fibrosis and cardiomyocyte hypertrophy with cytoplasmic vacuolization (H-E stain, 40×). LGE: Late gadolinium enhancement; LV: Left ventricular; LGE-CMR: Late gadolinium enhancement-cardiac magnetic resonance; RV: Right ventricular.

Endomyocardial fibrosis

Endomyocardial fibrosis (EMF) is the most frequent restrictive cardiomyopathy especially affecting poor children and young adults in the tropical zone. The characteristic features are fibrotic tissue deposition in the endocardium of the inflow tract and apex of one or both ventricles. The pathogenesis of EMF is poorly understood, but early hypereosinophilia may play a role[99].

Cine-CMR can clearly demonstrate distorted ventricles with normal or reduced volume and enlarged atria. LGE-CMR can also show areas of LGE in the endocardium where the histopathological examination revealed extensive fibrous thickening, proliferation of small vessels and scarce inflammatory infiltrate. The LGE pattern may have a "V sign" at the ventricular apex, characterized by a 3-layer appearance of myocardium, thickened fibrotic endocardium, and overlying thrombus[100]. The relationships between increased LGE burden and worse NYHA functional classes, and increased probability of surgery and mortality rate are reported [100].

Since the reports of EMF have been increasing in areas where the disease had not been previously recognized, the role of CMR may increase for the early diagnosis of EMF[101].

Systemic sclerosis

Systemic sclerosis (SSc) is characterized by vascular changes and fibrosis of the skin and internal organs. Among many autoimmune disorders, SSc has been considered to have a high prevalence of cardiac involvement. The prevalence is clinically 1.4% to 5.4% for systolic or 18% to 30% for diastolic dysfunction[102,103]. While in autopsy, myocardial fibrosis was identified in 50% to 80%[104]. Cardiac involvement in SSc is assumed to be derived from impairment of the microcirculation and primary myocardial fibrosis, and from ischemic damage due to coronary atherosclerosis[105,106]. Patients with cardiac involvement have a poor prognosis because of congestive heart failure and fatal arrhythmias associated with conduction disturbance[107]. Unfortunately, most patients with cardiac involvement are asymptomatic and difficult to be detected in subclinical stage.

Recently, the values of CMR are suggested for the early detection of cardiac involvement in SSc. Actually, previous reports revealed LGE in 21% to 66% of patients with SSc[108-110]. LGE distributed mainly into the basal to mid inter-ventricular septum and RV insertion points, and spread into all the myocardial layers, reflecting various mechanisms for myocardial fibrosis.

We showed the correlations between LGE and enlargement of LV/RV volume, impaired LV/RV function and pulmonary arterial hypertension. The ability of LGE-CMR to detect cardiac fibrosis in the subclinical stage may help identification of high risk patients and early initiation of therapeutic interventions, although the relevance in long term prognosis remains to be elucidated.

Table 1 Distribution and patterns of late gadolinium enhancement and other cardiac magnetic resonance findings in various types of cardiomyopathies

Cardiomyopathies		LGE distribution		LGE patterns	Other CMR features
		Intra-cardiac	Intra-myocardium		
Ischemic		LV regions corresponding to coronary distribution	Subendocardium to transmural	Striated, transmural	LV wall motion abnormality, wall thinning, aneurysm
Non-ischemic	Dilated cardiomyopathy	Inter-ventricular septum	Mid-wall	Striated	Diffuse LV wall thinning, shortened post-contrast T1
	Hypertrophic cardiomyopathy	Regions with hypertrophy	Any	Patchy, striated	Asymmetrical or symmetrical LV hypertrophy
	End-stage HCM	Diffuse	Any	Patchy, striated, transmural	LV dilatation with Inhomogenous LV wall thickening
	Cardiac sarcoidosis	Any	Any	Patchy, striated, transmural	LV aneurysm, myocardial edema in T2 black blood sequences
	Stress cardiomyopathy	Regions with ballooning	Any	Patchy, transient	Myocardial ballooning, RV motion abnormality
	Arrhythmogenic right ventricular cardio-myopathy/ dysplasia	RV (sometimes with LV)	Any	Striated	Focal or global RV dilatation, fatty infiltration in fat suppression sequence
	Cardiac amyloidosis	Any	Subendocardial, transmural	Diffuse	Diffuse hypertrophy, thickened valve leaflets, prolonged native T1
	Myocarditis	Any	Subepicardial	Diffuse	Myocardial edema in T2 black blood sequences, early GE, prolonged native T1
	Anderson-Fabry disease	Postero-lateral LV	Mid-wall	Striated	Concentric/eccentric but non-obstructive LV hypertrophy, shortened native T1
	Endomyocardial fibrosis	Inflow tract to apex	Subendocardial	Diffuse	Distorted ventricles with normal or reduced volume and enlarged atria
	Cardiac involvement in SSc	Any	Any	Any	
	LV non-compaction	NA	NA	NA	High non-compacted/compacted myocardial ratio
	Iron-overload cardio- myopathy (cardiac hemochromatosis)	NA	NA	NA	Shortened T2-star

LV: Left ventricular; LGE: Late gadolinium enhancement; CMR: Cardiac magnetic resonance; RV: Right ventricular; NA: No available information; ICM: Ischemic; NICM: Non-ischemic; DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy.

Table 1 summarizes the typical distribution and patterns of LGE, and other characteristic CMR features in ICM and NICM. In addition to above mentioned NICM, cine-CMR can show clearer images in terms of the presence of apical trabeculations, deep inter-trabecular recesses and high non-compacted/compacted myocardial ratio in patients with LV non-compaction[111]. In addition, a T2* technique allows to estimate iron deposition in myocardium, and to correlate it with cardiac function and the effect of chelation in iron overload cardiomyopathy (cardiac hemochromatosis)[19].

LIMITATION OF CMR

Despite the benefits with much evidence, CMR is not necessarily available in all institutes and patients, and has a problem of cost. Claustrophobia is a frequent reason to cancel MRI. Patients with decompensated heart failure cannot be tolerant to long data acquisition time of MRI. MRI is still contraindicated in patients who have had device implantation (*e.g.*, permanent pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy with and without defibrillation). Furthermore, gadolinium contrast agents cannot be administered to patients with chronic renal failure because of the risk of nephrogenic systemic fibrosis. The determination of threshold and quantification of LGE are also limitations in NICM.

CONCLUSION

Currently, CMR has become one of the most important methods to diagnose and follow-up patients with ICM and NICM. This review showed that the analysis of LGE distribution in myocardium is particularly valuable for differential diagnosis and risk stratification. However, the differential diagnosis of cardiomyopathies should be made generally on the basis of combination of various CMR sequences and with other imaging modalities and endomyocardial biopsy.

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