Utility of Magnetic Resonance Imaging in Cardiomyopathies

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Introduction

Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetics. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability. Pathological myocardial processes and dysfunction that are a direct consequence of other cardiovascular abnormalities such as that which occurs with valvular heart disease, systemic hypertension, congenital heart disease, atherosclerotic coronary artery disease are not included as cardiomyopathies [1].

Cardiomyopathies are divided into 2 major groups based on predominant organ involvement. Primary cardiomyopathies: genetic, mixed (genetic and nongenetic), and acquired, are those solely or predominantly confined to heart muscle. Secondary cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalized systemic disorders [1].

Cardiac magnetic resonance (CMR) has emerged as an important tool for the evaluation of cardiomyopathies, providing highly accurate information on the macroscopic changes of cardiac morphology, function, and tissue composition. The late gadolinium enhancement technique (LGE) allows us to assess the myocardial tissue composition and is a potentially promising tool for diagnosis, management and prognosis in cardiomyopathies. This technique is based on the fact that normal myocardium is composed of tightly packed muscle fibers with a relatively small extracellular space, whereas acute (necrosis with cell rupture) or chronic (fibrotic) myocardial infarction have increased extracellular space. After the injection of gadolinium contrast, there is slow wash out within infarct regions compared with normal myocardium, creating a maximal signal intensity difference about 10 minutes after 0.1 mmol/kg or 0.2 mmol/kg intravenous injection [2]. Although LGE was extensively validated in vivo and in vitro in the acute and chronic myocardial infarction settings, regions of fibrosis or infiltration in nonischemic cardiomyopathies can also appear hyperenhanced. However, the LGE technique is unlikely to detect diffuse necrotic or fibrotic changes as it is designed to optimise contrast between normal and abnormal myocardium and no enhancement will be seen by LGE-CMR in patients with diffuse myocardial damage [3-6].

This review addresses several CMR approaches that are now available to better diagnose, manage and prognosticate cardiomyopathies from a clinical point of view.

Primary cardiomyopathies

Hypertrophic cardiomyopathy
Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous but relatively common autosomal dominant genetic heart disease (1:500 of the general population for the disease phenotype recognised...
by echocardiography) that probably is the most frequently occurring cardiomyopathy. HCM is characterized morphologically and defined by a hypertrophied, nondilated left ventricle (LV) in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening evident (e.g. systemic hypertension, aortic valve stenosis) [1].

Clinical diagnosis is customarily made with 2-dimensional echocardiography by the detection of otherwise unexplained LV wall thickening, usually in the presence of a small LV cavity, after suspicion is raised by the clinical profile or as part of a family screening. The excellent accuracy of CMR in anatomical and functional analysis of the left and right ventricles to quantify ventricular volume and mass has increased the sensitivity and specificity of the diagnosis of HCM. CMR has greater accuracy over echocardiography in diagnosing and differentiating several patterns of hypertrophy. In cases where hypertrophy is more accentuated on the free wall, the echocardiogram did not allow diagnosis and among subjects with confined hypertrophy in anterolateral wall underestimated the wall thickness in relation to CMR [7]. Moreover, in the diagnosis of apical hypertrophic cardiomyopathy, echocardiograms do not properly evaluate the apical segment in up to 40% of HCM subjects [8] (fig. 1). Thus, CMR represents a powerful supplemental imaging test with distinct diagnostic advantages for selected HCM patients.

![Figure 1. Gradient echo with steady state free precession (balanced fast field-echo) cine-MR image obtained at end diastole in cardiac two chamber plane shows thickening of apical segments of the myocardium.](image)

Accuracy of the measurements is fundamental when differentiating HCM from other aetiologies’ of LV hypertrophy, such as hypertrophy seen in the hearts of athletes. In this setting, a new geometric index was applied using the maximal end-diastolic wall thickness to left ventricular end-diastolic volume index ratio. Indices lower than 0.15 mm x m² x ml could differentiate athletes’ hearts from HCM with 99% specificity [9].

Typically, HCM patients display patchy, multifocal hyperenhancement occurring in 50 to 80% of the patients and mostly within hypertrophied regions (fig. 2 and 3). The junctions of the right ventricular free wall with the interventricular septum are frequently affected [10-13].
Although several risk factors have been shown to be associated with increased risk for sudden death and progression to a dilated phase, the predictive accuracy of each of these adverse clinical markers is generally low. The mechanisms underlying sudden death and progression to a dilated phase are incompletely understood, but myocardial disarray and myocardial fibrosis are thought to provide the anatomical substrate for ventricular arrhythmia and left ventricular remodelling. LGE represents regions of increased myocardial fibrosis, and allows a direct assessment of the abnormal myocardial tissue. A previous study showed that greater extent of LGE was associated with two or more markers of risk for sudden death [11]. Our group identified that among these clinical markers, the LGE extent is related to severe hypertrophy (>30mm) and NSVT [13]. Late enhancement may be a potential link between these well known risk factors by which they relate to malignant ventricular arrhythmias. Previous studies showed that LGE extent is associated with lower ejection fraction and with progressive ventricular dilation [10, 11]. We found a relation between the extent of LGE and systolic impairment, since the number of LGE segments correlated positively with the number of segments.
with hypokinesia and inversely with the LV ejection fraction and the capacity to increase subaortic gradient during exercise [13]. Thus, late gadolinium enhancement has a great potential to provide new insights in the assessment of patients with MCH. The extent of LGE reflects a greater expression of this disease. It is associated with a more severe myocardial damage and adverse clinical parameters, suggesting it may be linked to prognosis.

Dilated cardiomyopathy
Dilated forms of cardiomyopathy are characterized by ventricular chamber enlargement and systolic dysfunction with normal LV wall thickness. Dilated cardiomyopathy (DCM) is a common and largely irreversible form of heart muscle disease with an estimated prevalence of 1:2500; it is the third most common cause of heart failure and the most frequent cause of heart transplant. The DCM phenotype with sporadic occurrence may derive from a broad range of causes, including the following: infectious agents, toxins, neuromuscular disorders, autoimmune and systemic disorders, mitochondrial, metabolic, endocrine and nutritional disorders. About 20% to 30% of DCM cases have been reported as familial. The predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance less frequent [11].

In patients with symptoms and signs of heart failure of recent onset, echocardiography often reveals an enlarged, poorly contractile left ventricle and sometimes also signs of right ventricular dysfunction. The challenge is to distinguish between ischemia, infection, inflammation or idiopathic disease. In patients without a typical history of coronary artery disease, an ischemic cause of ventricular dysfunction is still commonly ruled out by routine coronary angiography and CMR could offer an alternative, noninvasive method to initially investigate these patients. Ischemic scar is either subendocardial or transmural. CMR is very sensitive in detecting even small amounts of subendocardial infarction [14]. Thus it is also sensitive in ischemic heart failure as some degree of scar will usually be present in ischamically injured poorly contractile ventricles. Patients with DCM show three distinct LGE pattern: 59% of the patients show no enhancement (fig. 4), 13% have subendocardial or transmural enhancement that is indistinguishable from the ischemic patients (is believed to result from prior undiagnosed myocardial infarction with spontaneous coronary recanalisation or from episodes of coronary embolism), and 28% have longitudinal or patchy midwall enhancement with subendocardial sparing that is not restricted to coronary territories [15]. Hence, with a LGE highly suggestive of DCM, coronary angiography could potentially be avoided.

Interestingly, patients with a clinical diagnosis of dilated cardiomyopathy and midwall LGE have a worse prognosis in terms of unplanned admission to hospital or death than patients with a similar degree of LV dysfunction but with no mid-wall LGE [16]. Inflammation may play a role with such non-endocardial myocardial enhancement in these patients which does not correspond to the perfusion bed of a coronary artery, since the midwall LGE pattern was found to be associated with active or borderline myocarditis by Dallas criteria in patients with a clinical presentation of chronic myocarditis and depressed LV function or repetitive ventricular arrhythmias [17].

Myocarditis
Myocarditis is an acute or chronic inflammatory process affecting the myocardium produced by a wide variety of toxins and drugs or infectious agents, most commonly viral, as well as Whipple disease, giant cell myocarditis, and hypersensitivity reactions to drugs such as antibiotics, etc [1].

The gold standard technique for detecting myocarditis still is histopathologic myocardial samples obtained by endomyocardial biopsy, which is limited by low sensitivity, high variability, and
Invasiveness in a disease that is generally self limited and associated with a good prognosis. However, a minority of these patients, approximately 10% will evolve to dilated cardiomyopathy. Thus, additional noninvasive methods for diagnosis and prognosis evaluation are needed. In this setting, LGE-CMR depicts areas of myocardial fibrosis and necrosis with a high spatial resolution and CMR may also be able to depict tissue edema, when appropriate pulse sequences optimized to reflect differences in the spin-spin relaxation time T2 are used.

In patients with clinically suspected myocarditis, LGE is found in up to 90% of the patients [18]. The regions of LGE are frequently located in the lateral free wall with an epicardial distribution (fig. 5). Another frequently seen pattern is the midwall stria pattern in the basal interventricular septum. Biopsies obtained from the area of LGE show acute or borderline myocarditis in higher percentage than reported in the literature. Therefore, CMR may play a role not only in the diagnosis of myocarditis, but also in helping increase significantly the sensitivity of endomyocardial biopsies. However, as mentioned above, the inability to demonstrate diffuse myocardial changes as encountered in diffuse myocarditis with diffuse edema formation is a disadvantage of the LGE technique, and even localized edema without necrosis might not result in enough increase in extracellular space to cause LGE. Thus, the sensitivity of LGE to detect milder forms of myocarditis may be suboptimal. In a recent study, three different pulse sequences were compared in patients with suspected myocarditis: LGE, T2-weighted imaging (detect myocardial edema), and T1-weighted early myocardial enhancement (detect myocardial hyperemia). In this study the LGE sequence had a lower sensitivity with only 44% but the specificity was high (100%). When any two of the three sequences were positive in the same patient, there was increased sensitivity (76%) and specificity (95%) in the diagnosis of myocarditis [19]. Moreover, CMR may give us prognostic information, since patients with larger size of LGE may have worse prognosis. It has recently found that the pattern of LGE may be related to the clinical course. Patients with a parvovirus B19 infection, most had subepicardial LGE in the lateral wall and recovered within months and patients with herpes virus 6 or especially herpes virus 6 plus parvovirus myocarditis presented septal LGE and progressed toward chronic heart failure [20]. The area of LGE decreases in many patients and enhancement may disappear completely. However, the decrease of enhancement is only moderately correlated to the improvement in ejection fraction [17-20].

Other forms of inflammatory cardiomyopathy

Sarcoïdosis
Sarcoïdosis is a multisystem granulomatous disorder of unknown etiology. Symptomatic cardiac involvement is found in less than 5% of patients, although necropsies studies have documented cardiac involvement in 27%. The usual cardiac manifestations are electrocardiographic repolarisation or conduction abnormalities and even sudden cardiac death due to ventricular fibrillation or complete
heart block. Cine CMR usually demonstrates regional wall motion abnormalities and may also show wall thickening of the involved region. LGE-CMR improved the diagnostic sensitivity over the modified guidelines from the Japanese Ministry of Health and Welfare. The sensitivity, specificity, and positive and negative predictive values were 100%, 78%, 55% and 100%, when the modified criteria was used as the gold standard. Most of the enhanced areas are located in basal and lateral segments with an epicardial pattern similar to that seen in myocarditis. The presence of cardiac involvement by CMR in symptomatic patients indicate poor prognosis. LGE may be used as an accurate guide to obtaining an endomyocardial biopsy, and reveals normalization of the enhancement with corticosteroid treatment which correlates with clinical improvement. Therefore, CMR is an attractive first line noninvasive method to determine cardiac involvement, guide biopsy and follow up of cardiac sarcoidosis [21-23].

**Chagas disease**
Chagas disease is a chronic infectious disease caused by the Trypanosoma cruzi. It is an important cause of heart failure in Latin America. The LGE technique can detect myocardial fibrosis in all three distinct clinical stages of this disease (from asymptomatic with normal LV function to severe LV dysfunction). In agreement with pathologic studies, LV basal, inferolateral, and apical segments were more affected by LGE. The amount of myocardial fibrosis increases with increasing the severity of cardiac dysfunction and is most pronounced in patients with severe ventricular arrhythmias. Thus, LGE-CMR adds important information on disease severity and may became useful for early identification of cardiac involvement in the subclinical phases of this disease when other methods cannot detect any cardiac involvement [24].

**Left ventricular noncompaction**
Noncompaction of the ventricular myocardium is a cardiomyopathy thought to be caused by arrest of normal embryogenesis of the endocardium and myocardium. This abnormality is often associated with other congenital cardiac defects, but is also seen in the absence of other cardiac anomalies. Clinical manifestations are highly variable, ranging from no symptoms to disabling congestive heart failure, arrhymias, and systemic thromboemboli. Although echocardiography has been the diagnostic procedure of choice, the correct diagnosis is often missed or delayed because of lack of knowledge about this uncommon disease and its similarity to other diseases of the myocardium and endocardium. CMR may play a role in cases of poor echocardiographic image quality. Moreover, a recent paper found that a ratio of noncompacted to compacted myocardium in diastole greater than 2.3 had a good accuracy in distinguishing pathologic noncompacted myocardium from other conditions that have increased trabeculations [25,26] (fig. 6).

**Arrhythmogenic right ventricular cardiomyopathy/displasia**
Arrhythmogenic right ventricular cardiomyopathy/displasia (ARVC/D) is a common form of inherited heart muscle disease (estimated 1:5000) with a relatively recent description (20 years ago). ARVC/D involves predominantly the right ventricle with progressive loss of myocytes and fatty or fibrofatty tissue replacement, resulting in RV dysfunction and enlargement. The LV involvement is reported in up to 75% of patients. ARVC/D has a broad clinical spectrum, usually presenting clinically with ventricular tachyarrhythmias with a left bundle branch block pattern. Diagnosis is challenging and requires integration of multiple factors such as personal and family history, electrocardiogram, genetics, electrophysiology study, and information regarding RV function and morphology. The sensitivity of endomyocardial biopsy is low because the disease is segmental, distributed across the
so-called triangle of dysplasia which includes the right ventricular outflow tract, the apex, and the infundibulum, and samples are usually taken from the septum. CMR allows detailed three dimensional evaluation of the RV and is considered one of the most accurate tools to provide anatomic, functional, and tissue characterization data for the diagnosis of ARVD/C [1,3-6]

The criteria for ARVD/C demonstrated by CMR include fatty infiltration of the RV myocardium with high signal intensity on T1-weighted images, fibrofatty replacement leading to focal or diffuse thinning of the RV myocardium, focal aneurysms, and dilatation of the RV and the RV outflow tract. Crucial diagnostic value is usually given to regional contraction abnormalities (from hipokinesia to focal aneurysms formation) and global systolic dysfunction. The identification of fatty infiltration is usually difficult and extreme care has to be taken to avoid confusion with epicardial fat that normally is in close proximity to the thin RV wall. Moreover, the fat replacement is reported to have a very low sensitivity (67%) and it could not be used to rule out ARVD/C. Regional and global RV enlargement and dysfunction are usually easier to identify and small dyskinetic or hipokinetic areas on the RV myocardium can be useful to suspect ARVD/C, in the appropriate clinical context [3-6, 27, 28] (fig. 7). It has recently been demonstrated that noninvasive detection of RV myocardial fibrofatty involvement, using LGE, correlates to histopathology and inducible ventricular tachycardia, suggesting an important role of CMR in the diagnosis and management of ARVD/C [29]

A differential diagnosis should be conducted between ARVD/C and other causes of arrhythmias originating in the RV, such as right ventricular outflow tract tachycardia (RVOT tachycardia) and the Brugada syndrome. Although RVOT tachycardia is considered idiopathic by some authors, myocardial structural and wall motion abnormalities have been visualized in cine-MR imaging. The most common of these abnormalities include fixed focal thinning, regional decreased systolic wall thickening, and areas of abnormal wall motion. The similarities between the abnormalities detected by MR in both RVOT tachycardia and ARVD/C suggest that these conditions are related. MR imaging is a useful tool to demonstrate the normal structure of the heart characteristic of the Brugada syndrome [5].

End-stage pattern of ARVD/C should be differentiated from dilated cardiomyopathy because of the dilatation of the left ventricle. Although, in dilated cardiomyopathy there is biventricular dilatation with left ventricular dominance, differentiation between these two entities may be difficult [5].

Stress induced cardiomyopathy
Left apical ballooning (takotsubo cardiomyopathy) is characterized by acute and reversible LV systolic dysfunction in the absence of atherosclerotic coronary artery disease often triggered by profound physiological stress. CMR contributes to the understanding of this novel entity by demonstrating the absence of irreversible damage (LGE) but edema formation on T2-weighted images and identifying segmental wall motion abnormalities encompassing LV myocardium in multiple coronary arterial vascular territories [30, 31].

Secondary cardiomyopathies
Fabry’s disease

Fabry’s disease is an important differential diagnosis in patients with left ventricular hypertrophy. This disease is characterized by the accumulation of an abnormal glycoprotein in the myocyte due to α-galactosidase deficiency. CMR may detect regional or global myocardial thickening and LGE is seen in > 50% of patients, predominantly in the posterolateral wall but the reason for that is unknown [32].

Amyloidosis

In this disease, the entire myocardium is infiltrated by amyloid protein, resulting in homogeneously increased thickness of the ventricular and atrial wall. An increased thickness of the interatrial septum and right atrial free wall has been described as a typical finding of cardiac amyloidosis, not seen in other restrictive cardiomyopathies. LGE most frequently involves the subendocardium (70%) due to a preference of the fibrillar amyloid for that region and its distribution is often global and the entire LV circumference is involved (fig. 8). This global distribution often makes adjustment of the parameters on the LGE technique difficult. Patients subendocardial T1 is lower than T1 in the subepicardium for the first 8 minutes following the administration of gadolinium-based contrast agent. This difference is no longer apparent at later time intervals. Optical results are achieved when imaging is started after 5 minutes of contrast injection. The expansion of the interstitium by massive amyloid deposit without myocardial death and fibrosis explains the less intense LGE in amyloid heart disease [33].

Siderotic cardiomyopathy

Under the category of siderotic cardiomyopathy, we include a conditions characterized by excessive iron deposition within the myocardium leading to progressive diastolic and systolic dysfunction.

Cardiac failure secondary to transfusional iron overload remain the commonest of death in patients with major thalassemia. Myocardial iron deposition can be quantified using myocardial relaxation time T2-star (T2*). There is a direct relation between reduced myocardial T2* (<20 ms) and LV dysfunction. Considering that cardiac failure can be avoided if intensive chelation therapy is instituted at an early stage of myocardial iron overload, regular determination of myocardial T2* should be able to decrease the incidence of heart failure in thalassemia population [34, 35].

Another cause of siderotic cardiomyopathy is hemochromatosis in which deposition of iron in multiple tissue types, most notably the skin, the liver, pancreas and heart. CMR revealing deposition of iron in the myocardium establishes the diagnosis of hemochromatosis-related cardiomyopathy [3-6].

Conventional T1- and T2-weighted spin-echo MR sequences can be used routinely as noninvasive modalities to assess the presence of iron deposition in the tissues of patients with hemochromatosis or thalassemia [5].

Endomyocardial disease

Endomyocardial disease is a common form of restrictive cardiomyopathy and includes two entities: endomyocardial fibrosis and idiopathic hypereosinophilic syndrome. CMR findings are similar in these two conditions, and include LV and RV apical fillings. Left and right ventricular enlargement, associated with mitral and tricuspid regurgitation can be seen. LGE technique is useful to confirm the diagnosis of these diseases by differentiating apical thrombus from hypotrophy and tumor. Typically, LGE occurs on the endocardial surface of the LV or RV apical myocardium. The core of the apical mass usually is hipoperfused and late hipoenhanced. Often, the endocardial surface of the mass becomes
late-enhanced [3-6, 36]

Conclusions
Cardiomyopathies are a complex group of heart diseases with characteristic morphologic and functional features. Magnetic resonance imaging can be used to assess these heart abnormalities in a noninvasive, objective, and reproducible way. Cardiac MRI has long been used to study cardiac morphology and more recently to assess blood flow, perfusion, contractile function, and tissue characterization. Determining the exact etiology is essential for directing the correct treatment and predicting survival. The traditional techniques of echocardiography, radionuclide imaging and x-ray coronary angiography are limited by the significant overlap of features between the conditions. Even endomyocardial biopsy suffers from limitations such as sampling error and poor sensitivity. LGE has a great potential to differentiate ischemic from non-ischemic etiologies and due to differing LGE patterns among the various non-ischemic cardiomyopathies, it allows discrimination between them. Thus, CMR can provide crucial information for diagnosing, monitoring, and prognosticating many of the cardiomyopathies.

Bibliography


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