Cardiovascular magnetic resonance in rare systemic diseases

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Abstract

The heart may be involved in a number of systemic syndromes. The pericardium, myocardium, heart valves, and coronary arteries may be involved either singly or in various combinations. In most cases the cardiac manifestations are not the dominant feature, but in some it is the primary determinant of symptoms and survival. Both the early identification of cardiac involvement and the etiology underneath is of paramount importance, as some causes require specific treatment and may be correctable. In this respect non-invasive imaging plays a central role especially in the context of rare cardiac disease, where specific imaging features can help to make the appropriate diagnosis on a substantial proportion of them, enabling the physician to choose the best management strategy tailored to the disease.

Imaging cardiac involvement in systemic disease is challenging and requires a multi-modality approach. Echocardiography is the first-line investigation; however, it is limited by poor image quality in some patients and gives very little information about tissue characteristics. Cardiovascular magnetic resonance (CMR) provides additional incremental data in patients with systemic disease. The excellent image quality obtained by CMR allows a detailed examination of cardiac structure and function. However the key advantage, unique to this imaging modality, that has revolutionized the role of CMR in the evaluation of cardiac disease, is the tissue characterization. CMR is excellent for distinguishing different soft tissues based on their magnetic properties described by the relaxations times T1, T2, and T2*. Normal and abnormal myocardium may have different relaxation times, but the addition of a gadolinium contrast agent greatly magnifies these differences. Gadolinium (Gd) is chelated and behaves as a passive, extravascular, extracellular contrast agent. After an intravenous bolus, three time phases are considered. The first pass can be used for perfusion imaging and is often given during vasodilator stress to detect ischemia. Early after contrast, severely hypovascular regions will not enhance (thrombus or microvascular obstruction in acute myocardial infarction). In the late phase (5 min plus post bolus), contrast lingers in areas of infarction or focal fibrosis due to slower contrast kinetics and a greater volume of distribution in extracellular water associated with collagen. Early after the first pass of Gd, a significant fraction of the injected Gd enters the interstitial space. Indeed, several minutes after intravenous administration of Gd, the larger volume of distribution available in necrotic or fibrotic myocardium results in a higher concentration of contrast agent than what is present in viable myocardium. This is typically referred to as late gadolinium enhancement (LGE). This can be assessed either visually or quantitatively based on relative enhancement compared to the background. The extent and pattern of LGE varies according to the underlying disease process and is frequently of prognostic significance and can be diagnostic of the underlying etiology.

In order to improve sensitivity in detection of interstitial diffuse fibrosis, T1 mapping technique have been recently proposed to quantifying T1 values for each voxel in the myocardium. This approach allows generating a parametric map without the need to compare it to a normal reference standard before or after the use of a contrast agent. At the moment the applicability of this method in different settings in still to be standardized.

Currently, a comprehensive CMR protocol including anatomy, function, and LGE imaging is able to identify the cardiac involvement and the underlying etiology in a substantial proportion of patients with systemic disease.

The aim of this review is therefore to delineate the role of CMR in detecting cardiac involvement in patients with rare systemic diseases and delineate the specific imaging features of the different etiologies.

Introduction

The heart may be involved in a number of systemic syndromes. The pericardium, myocardium, heart valves, and coronary arteries may be involved either singly or in various combinations. In most cases the cardiac manifestations are not the dominant feature, but in some it is the primary determinant of symptoms and survival.

Both the early identification of cardiac involvement and the etiology underneath is of paramount importance, as some causes require specific treatment and may be correctable. In this respect non-invasive imaging plays a central role especially in the context of rare cardiac disease, where specific imaging features can help to make the appropriate diagnosis on a substantial proportion of them, enabling the physician to choose the best management strategy tailored to the disease.

Sarcoidosis

Myocardial involvement occurs in 20-60% of patients with sarcoidosis at autopsy. However, only 5% of patients have signs or symptoms of cardiac involvement, making diagnosis of cardiac sarcoidosis an exceptional challenge. Cardiac arrhythmias and progressive congestive HF are the most frequent cause of death in patients with cardiac sarcoidosis. Thus, it is important to identify the presence of cardiac involvement in these patients who may benefit from medical and/or implantable defibrillator therapy. CMR can show some of the features of cardiac sarcoid as septal thinning, left ventricle/right ventricle (LV/RV) dilation, systolic dysfunction or pericardial effusion. However
these structural and functional changes are non specific, as they can be found in different type of cardiac diseases. Several studies have shown the usefulness of LGE-CMR in the detection of characteristic features of cardiac sarcoidosis and evaluation of response to steroid treatment. The LGE in these patients usually shows a non-ischemic pattern with hyper-enhancement of the mid-myocardial wall or the epicardium in an unpredictable distribution (Figure 1 and Table 1). The anteroseptal and inferolateral walls are most frequently involved, although sometimes hyper-enhancement is seen in other territories, including the RV. Follow-up studies showed that the enhanced areas were notably diminished in size and intensity after steroid treatment. The LGE-CMR scan can also be used to guide endomyocardial biopsy in sarcoidosis. Additionally, T2-weighted sequences may monitor disease activity by the identification of edematous areas associated with inflammation and granulomatous lesions.

Recently, myocardial delayed enhancement was correlated to a higher rate of adverse events including cardiac death.

### Amyloidosis

Cardiac involvement in amyloidosis is characterized by fibril deposition within the myocardium causing a concentric wall thickening with severe systo-diastolic dysfunction. Cardiac involvement is common in patients with both amyloid light-chain (AL) and transtiretin amyloidosis. The heart in AL amyloidosis (the most common form and with the worse prognosis) is affected in up to 50% of cases, and congestive heart failure (HF) is the presenting clinical manifestation in about one-half of these patients. Once congestive HF occurs, the median survival is <6 months in untreated patients; therefore, early recognition of the disease and prompt initiation of therapy is critical.

The tissue characterization with cardiac CMR plays a central role in the diagnosis of cardiac amyloidosis. After the administration of the contrast, the presence of amyloid protein in the heart results in accelerated removal of gadolinium from the blood and increased myocardial uptake, such that more gadolinium is present in the myocardium than the blood pool. This change in gadolinium kinetic behaviour is almost unique to amyloidosis. There is a unique pattern of late circumferential enhancement of the subendocardium of the LV and RV.

With subendocardial enhancement of the LV and RV endocardium, there may be a characteristic zebra-stripe appearance sparing the midwall of the interventricular septum. The blood pool appears typically dark, reflecting high myocardial contrast uptake and fast blood pool washout (Figure 1). These characteristic changes may help to detect cardiac amyloidosis also in patients with normal cardiac structure and function by echocardiography.

Recently non contrast techniques using T1 mapping have been shown to have a high diagnostic accuracy for detecting cardiac AL amyloidosis with potential to be more sensitive for detecting early disease than LGE imaging (Figure 2). Additionally a recent study proved the potential of CMR to become the first non invasive technique able to measure the cardiac amyloid burden, raising the possibility that CMR may provide a much needed cardiac surrogate endpoint for the various promising new therapies for amyloidosis currently in preclini-

### Table 1. Myocardial tissue characterization using cardiovascular magnetic resonance.

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ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; LGE, late gadolinium enhancement; LV, left ventricle.
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Review

Systemic sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular pathology, especially of the microvasculature, and tissue fibrosclerosis with involvement of the skin, gastrointestinal tract and organs such as the lungs, heart and kidneys.

During the first five-year period from the onset of the disease, 44% of deaths had a cardiac or renal origin compared to 18% in the successive five-year period, with an overall 40% cardiac mortality.25

Cardiac involvement is present in 50-80% of SSc patients and consists of various pathological changes including hypertrophy, inflammation and myocardial fibrosis, occasionally associated with segmental necrosis of the myocytes and contraction band necrosis due to severe ischemia and reperfusion injury, despite the absence of obstructive coronary lesions.

The usefulness of CMR in SSc has been recently underlined, focusing on LGE abnormalities.26 Late enhancement was characteristically midwall, with a linear pattern, sparing the subendocardium and epicardium (Table 1). These linear striae infrequently appeared interrupted or demonstrated small spiculations. Enhancement involved predominantly the basal and mid-cavity segments of the LV, whereas the apical segments were relatively less involved. In addition to a linear pattern, patchy nodular enhancements at the basal segment of the interventricular septum involving the RV lower or upper insertion points and nodular enhancement in the basal segment of the LV free wall were observed.27 (Figure 1).

Subsequently, Hachulla et al. confirmed that CMR can analyze precisely the different patterns of heart involvement in SSc by differentiating morphological, functional, perfusion and delayed contrast enhancement abnormalities. In this study, patients with limited cutaneous SSc had roughly the same CMR abnormalities as those with diffuse cutaneous SSc, and RV dilatation was not specific for pulmonary arterial hypertension.27

Anderson-Fabry disease

Anderson-Fabry disease (AFD) is an X-linked disorder of lysosomal metabolism caused by the partial or complete deficiency of the enzyme α-galactosidase A, which results in the accumulation of excess cellular glycolipid within the blood vessels and heart.24 This is a cause of LV hypertrophy associated with progressive myocardial fibrosis and death from heart failure. CMR can be used to assess LV function, determine the pattern and extent of LV hypertrophy, and identify areas of fibrosis. The LGE pattern typically spares the subendocardium and shows a striking predilection for the basal inferolateral LV segments (Figure 1). Recently Non-contrast T1 mapping techniques have been shown to have a great potential as a unique and powerful measurement in the imaging assessment of Anderson-Fabry disease with T2 able to completely discriminate between AFD and other diseases with no overlap.29 (Figure 2). Histological data suggest that these areas of LGE correspond to regions of replacement fibrosis.30 Up to 6% of patients who are initially diagnosed with hypertrophic cardiomyopathy actually have evidence of Anderson-Fabry disease.31 The implications of an incorrect diagnosis are considerable because patients with Anderson-Fabry disease respond to enzyme replacement therapy, including an improvement in cardiac function and regression of hypertrophy.25,32 Ideally, the administration of recombinant α-galactosidase A should be started before myocardial fibrosis has developed to achieve long-term improvement in myocardial morphology, function, and exercise capacity.33 Anderson-Fabry disease should always be considered if unexplained LV hypertrophy is seen, particularly in a young patient.

Glycogen storage disease type III

In Glycogen storage disease type III, the functional absence of a glycogen debranching enzyme results in intracellular glycogen accumulation. However, cardiac hypertrophy may also result from interstitial expansion. In a study by Moon et al, gadolinium-diethylenetriaminepenta-acetic acid rest perfusion demonstrated multifocal first pass mid-myocardial defects and late imaging demonstrated hyper-

Figure 1. Tissue characterization in different heart diseases. A) Normal individual [no late gadolinium enhancement (LGE)]; B) sarcoid with patchy LGE and pace-maker lead in the right ventricle; C) global subendocardial LGE in amyloid; D) systemic sclerosis; E) Anderson-Fabry disease with inferolateral LGE; F) Glycogen storage disease type III with extensive multifocal LGE in mid myocardium and other areas; G) apical subendocardial LGE in Churg-Strauss; H) LGE in the inferolateral wall and other areas in Becker muscular dystrophy; I) no LGE in stress-induced (Takotsubo) cardiomyopathy.
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The mid wall of the infero-lateral left ventricle is most commonly affected, with conduction system disease occurring late (Figure 1). Mitral valve involvement is a rare cause of dilated cardiomyopathy.

Eosinophilic diseases

Cardiac hyper-eosinophilia (e.g., malignant, Loeffler’s; Churg-Strauss) can cause endomyocardial fibrosis, valve disease and papillary muscle dysfunction, diastolic dysfunction, intracardiac thrombus formation, and heart failure. These features are highly characteristic and well diagnosed by CMR. T2-weighted sequences may monitor disease activity by the identification of edematous areas associated with inflammation, early gadolinium technique can detect apical thrombus with high diagnostic accuracy and late gadolinium imaging allows the detection of endomyocardial fibrosis (Figure 1). The exclusive involvement of endomyocardium on LGE-CMR in conjunction with normal myocardial function, apical obliteration, and thrombus formation are typical findings in these patients highlighting the diagnostic role of CMR, a comprehensive tool for the early diagnosis of this rare but severe disease.

Conclusions

CMR, using the available range of technique, is establishing itself as the gold standard non invasive test for determining the cardiac involvement in rare systemic diseases, adding prognostic value and guiding therapy. Progress is continuing and rapid with promising new techniques such as diffuse fibrosis assessment. As CMR becomes more widely available, more patients with rare diseases will have access to this important investigation.

References


Figure 2. A pre contrast T1 map (ShMOLLi in this case) of the basal short axis from A) a healthy volunteer; B) patient with Anderson-Fabry disease (AFD); and C) a patient with cardiac amyloid. Normal myocardium is green; blue areas (representing lower T1) are seen in the AFD septum, and red (longer T1) are seen in patients with cardiac amyloid.
Cardiac changes in systemic amyloidosis: visualisation by magnetic resonance imaging. Int J Cardiol 2006;113:E21-3.


