Scientific Literature Review

Role of CMR for the Differential Diagnosis of Non-ischemic Cardiomyopathies

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Introduction

Cardiovascular Magnetic Resonance (CMR) plays a growing role in therapeutic decision-making as it allows to differentiate etiologies and provides prognostic information. Compared with other imaging modalities, CMR has the unique ability to identify myocardial injury, not only in ischemic, but also in non-ischemic heart disease (NIHD). It enables the identification of reversible and irreversible, acute and chronic damage. The detection of inflammation in myocarditis and of myocardial involvement in systemic disorders, and the differentiation of left ventricular hypertrophy (LVH), including storage diseases, were two of the door openers into different clinical guidelines. This was already recognized in 2016, with CMR specifically recommended in more than 50% of the guidelines of the European Society of Cardiology (ESC), and in 50% of AHA/ACC guidelines [1, 2].

The recognition of CMR in guidelines is still growing, leading to an increased understanding of the impact of CMR for patients outside the expert community. Fortunately, in recent years the application of CMR in NIHD has also been integrated into the clinical workup of patients with acute coronary syndrome and non-ST-segment-elevation infarction, as the symptoms might be caused by myocarditis, takotsubo cardiomyopathy, or myocardial infarction with non-obstructive coronary atherosclerosis (MINOCA) [3]. Interestingly, athletes at different levels should be guided based on CMR, as published last year in the ESC Guidelines on sports cardiology [4]. For example, athletes with a history of myocarditis should only return to competitive sports after a persisting myocardial injury has been excluded by CMR.

During the last years, it has become increasingly evident that the quantification of the cardiac function and myocardial structure is crucial for a diagnostic decision. This major step will also challenge the community, as a significant effort is needed to ensure quality assurance and standardization. Most of the diagnosis in NIHD are based on quantitative measures. In the following sections, we will highlight some aspects of this topic.

Images from a patient with hypertensive heart disease (1F–J). 4-chamber view and short axis cine images showing concentric hypertrophy (1F–G). Normal LGE (1H). Corresponding native T1 and T2 Maps (1I–J).

A case with a patient suffering from severe aortic stenosis with a bicuspid aortic valve (1K–O). 4-chamber view and short axis cine images showing concentric hypertrophy (1K–L). Focal (septal) and diffuse fibrosis in a basal slice (1M). Corresponding native T1 and T2 Maps (1N–O).
Differentiation of left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is usually diagnosed by echocardiography or CMR based on detecting a left ventricular wall size at end-diastole of 13–15 or more mm [5, 6] and/or an increased left ventricular mass index [7]. The true challenge lies in breaking down the broad differential diagnosis of LVH, which is either caused by a pathophysiological stimulus like pressure or volume overload, or by pathological causes ranging from genetic to infiltrative disorders [8].

In all cases of unknown LVH, hypertrophic cardiomyopathy (HCM) should be ruled out [5] as it is one of the major contributors to sudden cardiac death (SCD). The strength of CMR in this entity is the detection of areas of fibrosis using late gadolinium enhancement (LGE) (Fig. 1C) as a modifier in the risk stratification and to delineate it from physiologic causes of LVH. Even in cases without LGE, increased native T1 and/or ECV values can detect diffuse fibrosis and aid in the differential diagnosis [9].

One chameleon capable of mimicking HCM is hypertensive heart disease (HHD) due to long-term arterial hypertension. Assessment of LV cine images might show concentric hypertrophy [10] and LGE in a nonspecific intramyocardial pattern [11] (Figure 1F–J). Aortic stenosis, which causes LVH in a similar manner, could lead to diffuse fibrosis of the myocardium. Quantitative markers such as T1 and ECV could help in the future to decide about the timing of therapy and to predict outcomes and prognoses as shown in the central illustration by Everett et al. (Fig. 2) [12] (Fig. 1K–O).

Another important entity to consider in the work up of LVH and HCM is the so-called athlete’s heart, a condition linked to an increased exercise burden. T1, T2, and ECV values are of help as they appear to be in the normal range in most cases with exercise-induced LVH [13].

Figure 1 summarizes different causes of left ventricular hypertrophy and their appearance in CMR, underlining the crucial role of CMR in tissue differentiation and differential diagnosis based on quantitative tissue parameter such as mapping.

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**Restrictive cardiomyopathies**

A rare, yet nevertheless important group of NIHD are restrictive cardiomyopathies (RCM) caused by systemic and infiltrative disorders. CMR plays a crucial role in detecting amyloidosis. LGE shows diffuse myocardial involvement with characteristic hypointense blood and hyperintense myocardium with coexisting pericardial and pleural effusions. This pattern is often diagnosed in amyloid light-chain (AL) amyloidosis, whereas parametric mapping also allows the identification of other subgroups. Typically, significantly elevated T1 and/or ECV values are found throughout the myocardium (Fig. 3A–E) [14]. Furthermore ECV potentially predicts prognosis with lower overall survival in patients with high ECV as demonstrated in the central illustration by Martinez-Naharro et al. (Fig. 4) [15].

On the opposite end of the spectrum is Fabry disease where low native T1 values, caused by lipid accumulation, often raise suspicion. In addition, CMR can often detect a characteristic inferolateral fibrosis by LGE (Fig. 3F–J). Sado et al. could show significantly lower T1 values in comparison to healthy volunteers and other causes of LVH (Fig. 5) [16].

CMR can provide evidence for cardiac involvement in sarcoidosis by means of cardiac morphology assessment, LGE, or T2-based imaging [10]. Presence of LGE has a negative impact on the prognosis and often presents as a striking hyperintense subepicardial pattern [17, 18] (Fig. 3K–O), but additional attention should be paid to the right ventricle as dysfunction and LGE in this location may influence the outcome as shown by Velangi et al. (Fig. 6) [19]. Their central illustration summarizes the prognostic significance of the RV abnormalities. Figure 3 exemplary showcases the wide array of tissue properties CMR can provide during one scan.

**Dilated cardiomyopathies**

The role of CMR in the diagnostic and prognostic evaluation as well as in guiding treatment strategies in dilated cardiomyopathies (DCM) patients has significantly increased in recent years. A CMR scan as part of the diagnostic workup should employ a protocol that assesses heart anatomy, left and right ventricular function, possible edema, myocardial tissue characterization, and scar formation. Deploying the updated Lake Louise Criteria, as shown...
CMR in ATTR

Cardiac magnetic resonance (CMR) with extracellular volume (ECV) was used to characterize cardiac involvement as it related to outcomes in cardiac transthyretin amyloidosis (ATTR). The relationship between late gadolinium enhancement (LGE) patterns and ECV showed a typical correlation of very high ECV values and subendocardial or transmural LGE. Asymmetrical septal left ventricular hypertrophy (LVH) was present in 79% of patients with ATTR, >5 times more frequently than in patients with cardiac light-chain amyloidosis. In patients with ATTR, ECV was independently correlated with mortality.

Non-contrast basal short-axis T1 map from a healthy volunteer (5A) and a patient with Anderson-Fabry disease (AFD; 5B). Blue areas (T1 lowering) are seen in the AFD septum and red (T1 increasing) in the inferolateral wall, correlating with the area of late gadolinium enhancement in the same patient (5C, arrow).

Septal T1 in participants with left ventricular hypertrophy. The line at 940 milliseconds has no patients with Anderson-Fabry disease (AFD) above it and no patients with non-AFD below it. (5D) Septal T1 in healthy volunteers and patients with Anderson Fabry disease (AFD) with and without hypertrophy. Note that 40% of patients with AFD who did not have left ventricular hypertrophy (LVH) were found to have a T1 >2 SD below the healthy volunteer mean.


### RV abnormalities on CMR in patients with sarcoidosis

The prevalence and prognostic significance of right ventricular (RV) abnormalities on cardiac magnetic resonance (CMR) in patients with sarcoidosis. EF = ejection fraction; LGE = late gadolinium enhancement; SCD = sudden cardiac death.

Overview of the Updated Lake Louise Criteria.

ECV = extracellular volume; LGE = late gadolinium enhancement; T2W = T2-weighted.


Images from a patient with an idiopathic dilated cardiomyopathy and excluded ischemic heart disease (8A–E). 4-chamber view and short axis cine images showing a dilated left ventricle (8A–B). LGE with mid-wall sign (8C). Corresponding native T1 map with increased T1 values in the septal wall and T2 Map with normal values (8D–E).

A case of dilated cardiomyopathy due to myocarditis (8F–J). 4-chamber view and short axis cine images showing a dilated left ventricle (8F–G). Focal subepicardial fibrosis/necrosis basal anterior and anterolateral (8H). Corresponding native T1 and T2 Maps with increased values in segments with positive LGE (8I–J).

A patient with dyspnoe and fatigue after a COVID-19 infection (8K–O). 4-chamber view and short axis cine images (8K–L). Small, focal subepicardial fibrosis basal inferior and septal. Possible of thromboembolic origin (8M). Native T1 Map with increased values anteroseptal and corresponding T2 map with normal T2 values Map (8N–O).
Late Gadolinium Enhancement and Outcome in DCM

The study of dilated cardiomyopathy patients shows a nonlinear relationship between late gadolinium enhancement (LGE) extent and all-cause mortality and sudden cardiac death (SCD) events with a large increase in risk with small degrees of LGE. We show the superiority of models based on the location of LGE for the prediction of these end-points. DCM = dilated cardiomyopathy.


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Cardiac mortality risk according to RVEF

The hazard ratios for cardiac mortality are shown according to different levels of right ventricular ejection fraction (RVEF). The yellow dashed line displays the hazard ratio of 1.00 of the reference group with RVEF >55%. Patients with RVEF ≤35% had a significantly higher event risk than did the reference group. Patients with RVEF >35 and ≤45%, as well as those >45% and ≤55%, had similar risk to the group with RVEF >55%. *p < 0.001.


Cine imaging in a 39-year-old patient with AC and ventricular tachycardias and 2x syncope. Long axis (11A–B) and short axis (11D–E) end-diastolic (left) and end-systolic (middle) image. RV dilatation (EDV: 205 ml) and dysfunction (RVEF 38%). Focal RV dyskinetic wall motion (arrows, 11B, 11E). Late gadolinium enhancement long axis (11C) and short axis (11F). Focal enhancement in RV free wall, corresponding to the dysfunctional areas (arrows, 11F).

Right ventricular diseases

The assessment and evaluation of the right ventricle plays an increasing role in cardiovascular imaging. Several studies could show that right ventricular systolic function, as shown by Pueschner et al. covering NIHD, might have an impact on the prognosis in a wide variety of disorders including DCM [22], systemic sclerosis [23], sarcoidosis [19], and other types of NIHD (Fig. 10) [24].

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare inherited heart muscle disease that may be a cause of SCD, particularly in young people. Due to known biventricular involvement the term “arrhythmogenic cardiomyopathy” (AC) has been suggested as redefinition of this disease [25].

LGE improves the diagnostic accuracy of CMR due to identification of fibrofatty changes (up to 70%) that correspond to the dysfunctional areas in cine imaging (Fig. 11) [26]. Additionally, use of LGE is of interest to evaluate concomitant LV involvement. Distinguishing fat from fibrosis by LGE sequences is challenging, but the improvement of fat-water (F/W) techniques has drastically optimized image quality and diagnostic accuracy [27].

Accurate interpretation of CMR in AC patients (Fig. 11) requires a great deal of expertise. The differential diagnosis should include congenital heart diseases, idiopathic right ventricular outflow tract tachycardia, pulmonary arterial hypertension (Fig. 12), Brugada syndrome, athlete’s heart [29], genetic neuromuscular disorders, and myocarditis. Some of the entities to consider are presented in Figure 13 from Corrado et al. [29].
Conclusion

NHID may have different etiologies of which only some could be covered in this overview. NHID are often the cause of heart failure (HF), with reduced or preserved cardiac function. HF affects a high percentage of patients and its impact is increasing in an ageing society, hence the etiology of HF is particularly relevant for therapeutic decision-making in any ever-growing number of patients. This highlights the impact of CMR, as it is able to differentiate between underlying diseases and, in case of NHID, it may act like a virtual biopsy. The current technology and knowledge allow us to make these decisions already today, but the continuous developments on all aspects of the imaging process will enable us to further increase diagnostic accuracy.

Adapting a statement from one of the former SCMR boards, one could summarize:

Utilizing CMR instead of other imaging techniques provides more definitive, relevant, and actionable answers. A CMR exam provides comprehensive information and has superior and often unique diagnostic and prognostic power, without exposing patients to radiation. Therefore, CMR is a key enabler for precision medicine.

References


For the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79.


