Role of CMR in Non-ischemic Cardiomyopathies

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Abstract

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, 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

1 Patient diagnosed with hypertrophic cardiomyopathy (1A–E). 4-chamber view and short axis cine images showing basal septal hypertrophy (1A–B). Intramyocardial LGE basal septal within hypertrophic segments (1C). Corresponding native T1 and T2 Maps (1D–E).

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).
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 no obstructive coronary atherosclerosis (MINOA) [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 persistent 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 diagnoses in NIHD are based on quantitative measures.

In the following sections, we will highlight some aspects of this topic.

**Differentiation of left ventricular hypertrophy**

Left ventricular hypertrophy (LVH) is usually diagnosed by echocardiography or CMR based on detecting a left ventricular wall thickness at end-diastole of at least 13–15 mm [5, 6] and/or an increased left ventricular mass index [7]. Both methods can additionally provide the mass-volume index and the relative wall thickness, which can help to differentiate between concentric and eccentric hypertrophy, and to stratify the risk of cardiovascular events [8, 9]. 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 [10].

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 physiological 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 [11]. Furthermore, CMR can provide quantitative planimetric evaluation of the left ventricular outflow tract. This robust marker can be used to accurately differentiate obstructive from non-obstructive disease and to monitor the effect of septal reduction therapies [10]. It is important to remember that other disorders can hide behind an HCM phenotype.

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 [12] and LGE in a nonspecific intramyocardial pattern [13] (Fig. 1F–J). Follow-up exams with CMR can monitor left ventricular wall thickness in response to anti-remodeling therapy in HHD [14]. Our recent study, currently in review, compared cine acquisitions accelerated by compressed sensing to standard bSSFP acquisitions. We could prove that without compromising diagnostic capability, equivalent function and mass assessment of LV and RV is possible with a time reduction of more than 50%, making frequent CMR exams even more feasible. 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. [15] (Fig. 1K–O).

Another important entity to consider in the workup 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 [16].

LVH can also be caused by storage diseases. This differentiation is one of the strongest applications of CMR as the diagnosis will change the therapy. Different entities will be discussed in the chapter about restrictive cardiomyopathies (RCM).

Figure 1 summarizes different causes of left ventricular hypertrophy and their appearance in CMR.

**Restrictive cardiomyopathies**

A rare but nevertheless important group of NIHD are restrictive cardiomyopathies (RCM) caused by systemic and infiltrative disorders. CMR plays a crucial role in 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 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. 2A–E). The native T1 and ECV values are useful markers for monitoring the progression of the disease [17, 18].

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. 2F–J). Furthermore, CMR can aid in the decision when to start enzyme replacement and monitoring its effects [19].
CMR can provide evidence for cardiac involvement in sarcoidosis by means of cardiac morphology assessment, LGE, or T2-based imaging [10]. Unfortunately, the disease is a great imitator and can appear as HCM-, RCM- or dilated cardiomyopathy (DCM)-phenotypes. Even normal heart chambers on cine imaging can be found. LGE has a negative impact on the prognosis and often presents as a striking hyperintense subepicardial pattern [20] (Fig. 2K–O) [21].

Figure 2 exemplarily shows the wide array of tissue properties that CMR can provide during one scan.

**Dilated cardiomyopathies**

DCM refers to a spectrum of heterogeneous myocardial disorders and is defined by the presence of ventricular dilation and systolic dysfunction in the absence of any condition (hypertension, valvular, congenital, or ischemic heart disease) sufficient to cause global systolic impair-

ment [22]. The role of CMR in the diagnostic and prognostic evaluation as well as in guiding treatment strategies in DCM patients has significantly increased in recent years. A CMR scan as part of the diagnostic workup should deploy a protocol that assesses the heart anatomy, left and right ventricular function, possible edema, myocardial tissue characterization, and scar formation. Cine imaging in long- and short-axis is recommended for right and left cardiac volume, function, and mass assessment due to its high accuracy and reproducibility [23]. A T2-based marker (T2W or T2-mapping) for edema, an essential component of acute or active inflammation, should be included, as well as T1-imaging (preferably T1-mapping and ECV-imaging, if available) for tissue characterization. Therefore, by deploying the updated Lake Louise criteria, CMR offers good specificity and sensitivity in detecting acute myocarditis, a frequent cause of ventricular dilatation [24] (Fig. 3F–J). Furthermore, cardiac involvement in systemic inflammatory diseases, which can cause subclini-
cal myocarditis, can be detected and CMR parameters correlate with disease activity [25]. LGE-imaging is crucial for the diagnostic workup in DCM patients. It can differentiate between ischemic and non-ischemic causes of LV dilatation and systolic dysfunction [26]. In one quarter of patients with DCM, a typical intramural basal anteroseptal LGE is found, also known as “mid-wall sign” (Fig. 3C). LGE imaging in DCM patients can predict sudden cardiac death (SCD) and might identify patients who will benefit from an implantable cardioverter-defibrillator implantation, despite a left ventricular ejection fraction (LV-EF) >35% [27–29]. It should be kept in mind that many infiltrative cardiomyopathies that can present as RCMs can also mimic and present as DCMs. Once again, native T1-mapping and ECV-imaging provides myocardial tissue characterization and combined with specific LGE-patterns shows an excellent diagnostic accuracy in these entities as mentioned above [10] (Fig. 2).

Apart from sarcoidosis, other systemic disorders can also lead to DCM, but might also present with a preserved LVEF. Systemic diseases are characterized by the involvement of multiple organs with an autoimmune background. From a cardiological point of view, these disorders can present with inflammation of the peri- and myocardial tissues as well as early onset arterial disease [25]. The role of CMR is the assessment of potential myocardial involvement by detecting inflammation or fibrosis by the methods mentioned above [24]. Cardiac involvement in systemic lupus erythematosus (SLE) can be detected by CMR applying LGE and parametric sequences, even in subclinical stages [30, 31]. SLE as well as other entities may not only appear as a NIHD, but the coronaries could be affected as well. Especially vasculitic disorders are known to affect all vessels including the coronaries and the small intramyocardial vasculature [32].

Images from a patient with an idiopathic dilated cardiomyopathy and excluded ischemic heart disease (3A–E). 4-chamber view and short axis cine images showing a dilated left ventricle (3A–B). LGE with mid-wall sign (3C). Corresponding native T1 map with increased T1 values in the septal wall and T2 Map with normal values (3D–E).

A case of dilated cardiomyopathy due to myocarditis (3F–J). 4-chamber view and short axis cine images showing a dilated left ventricle (3F–G). Focal subepicardial fibrosis/necrosis basal anterior and anterolateral (3H). Corresponding native T1 and T2 Maps with increased values in segments with positive LGE (3I–J).

A patient with dyspnoe and fatigue after a COVID-19 infection (3K–O). 4-chamber view and short axis cine images (3K–L). Small, focal subepicardial fibrosis basal inferior and septal. Possible of thromboembolic origin (3M). Native T1 Map with increased values anteroseptal and corresponding T2 map with normal T2 values Map (3N–O).
Right ventricular diseases

The assessment and evaluation of the right ventricle is playing an increasing role in cardiovascular imaging. Several CMR studies could show that right ventricular systolic function might have an impact on the prognosis in a wide variety of disorders, including DCM [33], systemic sclerosis [34], sarcoidosis [35], and other forms of NIHD [36]. This evidence underlines the importance of continuing to investigate the role and the disorders of the right ventricle.

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 and left ventricular involvement, the term "arrhythmogenic cardiomyopathy" (AC) has been suggested as a redefinition of this disease [37, 38]. To improve diagnosis and management of the disease, the minor and major Task Force criteria for AC were modified in 2010 by combining multiple aspects such as family history, ECG, arrhythmic, structural and functional, and histopathological findings [39]. Molecular genetics are playing an increasing role in the diagnosis of AC; however, it still remains very challenging.

CMR has become the gold-standard for assessing ventricular volumetric indexed measurements, systolic function, and regional wall motion abnormalities such as akinesia, dyskinesia, aneurysm, and bulging. The characterization of fibrofatty myocardial tissue composition is another method that is gaining clinical importance, but it still needs clinical validation [40]. The presence of intramyocardial fatty infiltration itself was not included due to difficulties in interpretation and low specificity [41]. Cine images are usually performed in four long axes: 4-chamber view (CV), 2CV, 3CV, and RV, as well as in a short-axis stack with whole RV coverage. However, in our experience, transversal cine images are best for evaluating the RV free wall and subtricuspid region [42]. LGE improves the diagnostic accuracy of CMR due to identification of fibrofatty changes (up to 70%) that correspond to the dysfunctional areas of cine imaging (Fig. 4) and to histopathological changes [43]. 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. Interestingly, LV fatty infiltration was shown to be a prevalent finding in ARVC and can also lead to RV wall hypertrophy [44]. For this reason alone, F/W imaging should be a part of AC protocols.

Accurate interpretation of CMR in AC patients (Fig. 4) requires a great deal of expertise. The differential diagnosis should include congenital heart diseases, idiopathic right ventricular outflow tract tachycardia, pulmonary arterial hypertension (Fig. 5), Brugada syndrome, athlete’s heart [45], genetic neuromuscular disorders, and myocarditis.
Summary

NHID may have different etiologies of which only some could be covered in this overview. NHID is 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. The etiology of HF is relevant for therapeutic decision-making. This highlights the impact of CMR, as opposed to other cardiac imaging modalities, because it can differentiate between underlying diseases and, in case of NHID, it may act like a virtual biopsy. The current technology and knowledge allow us to drive 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 in 2016, one could summarize:

Utilizing CMR instead of other imaging techniques provides more definitive, relevant, and actionable answers as 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


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