The Added Value of Cardiac Magnetic Resonance in Muscular Dystrophies

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Abstract

Muscular dystrophies (MD) represent a heterogeneous group of rare genetic diseases that often lead to significant weakness due to progressive muscle degeneration. In many forms of MD, cardiac manifestations including heart failure, atrial and ventricular arrhythmias and conduction abnormalities can occur and may be a predominant feature of the disease. Cardiac magnetic resonance (CMR) can assess cardiac anatomy, global and regional ventricular function, volumes and mass as well as presence of myocardial inflammation, infiltration or fibrosis. The role for cardiac MRI has been well-established in a wide range of muscular dystrophies related cardiomyopathies. CMR is a more sensitive technique than echocardiography for early diagnosis of cardiac involvement. It has also great potential to improve the prediction of long-term outcome, particularly the development of heart failure and arrhythmic events; however it still has to be validated by longitudinal studies including large populations. This review will outline the utility of CMR in patients with muscular dystrophies for assessment of myocardial involvement, risk stratification, and in guiding therapeutic management.

Keywords: Muscular dystrophies, cardiac magnetic resonance, myocardial involvement, cardiomyopathy, sudden death

INTRODUCTION

Muscular dystrophies (MD) represent a heterogeneous group of rare genetic diseases that often lead to significant weakness due to progressive muscle degeneration. In many forms of MD, cardiac manifestations including heart failure, atrial and ventricular arrhythmias and conduction abnormalities can occur and may be a predominant feature of the disease [1]. Patients with MD may have subclinical involvement for years prior to symptom onset and even otherwise asymptomatic genetic carriers of muscular dystrophies may develop cardiac manifestations [2]. Many patients with cardiac involvement are at higher risk for advanced heart failure and/or sudden cardiac death [3, 4]. It is important to identify early on markers of cardiac involvement to initiate cardio-protective therapies, to limit progression and to attenuate symptoms of heart failure [5, 6].

While echocardiography is widely used to assess cardiac structure and function given portability, low cost and availability, it has limitations in terms of satisfactory acoustic window, image quality and inter-observer variability [7, 8].

Cardiac magnetic resonance (CMR) is the non-invasive gold standard method for the assessment of ventricular volumes, mass and global systolic function due to its high reproducibility and low variability [9]. In addition, CMR gives information regarding tissue characterization, and has been used for over two decades in different populations with muscular dystrophies to assess for global and regional function, presence of fibrosis or fatty infiltration [10, 11]. CMR can also uncover early cardiac involvement when standard cardiac assessment appears unrevealing [12, 13]. This review will outline the utility of CMR in patients with muscular dystrophies for assessment of myocardial involvement, risk stratification and in guiding therapeutic management.

COMPLETE CARDIAC MAGNETIC RESONANCE EVALUATION

CMR provides anatomic and functional information, as well as tissue characterization in one scan. It has high spatial and temporal resolution and no ionizing radiation is used (Table 1). Basic sequences of black blood imaging with fast spin echo pulses can provide rapid anatomic information [14]. Cardiac function and ejection fraction measurement is assessed by bright blood cine imaging, mostly by steady-state free precession (SSFP) technique, which has higher contrast-to-noise and signal-to-noise ratio than gradient-echo (GRE) [14]. Post processing feature-tracking analysis from cine SSFP images can also provide myocardial deformation assessment with strain measurement [15].

| Table 1 |
|---------|
| Cardiac MRI advantages and disadvantages |
| 1. High spatial and temporal resolution |
| 2. No ionizing radiation |
| 3. Basic sequences of black blood imaging |
| 4. Fast spin echo pulses |
| 5. Cine imaging |
| 6. Steady-state free precession (SSFP) technique |
| 7. Feature-tracking analysis |

Myocardial edema and inflammation can be assessed visually and semi-quantitatively by standard T2 weighted sequences and quantitatively with parametric T2 mapping.

With gadolinium contrast administration, the presence and extent of myocardial fibrosis can be assessed [16]. Gadolinium-based contrast agents distribute in the extracellular space and when there is cardiomyocyte damage and cell loss, gadolinium distribution will be of greater volume than in
normal myocardium. Gadolinium is used usually with T1-weighted sequences and it decreases the tissue proton relaxation time, providing a hyperintense signal in the areas with fibrosis [17], that remains detectable for around 20–30 minutes after contrast has already washed out of normal myocardial segments.

The presence of late gadolinium enhancement (LGE) in most chronic conditions indicates myocardial fibrosis and the pattern of LGE can differentiate between an ischemic versus non-ischemic myocardial damage. Moreover, in non-ischemic cardiomyopathies, LGE pattern can help identify the type of cardiomyopathy [18].

Parametric T1 mapping techniques provide quantification of native and post-contrast T1 values as well as estimation of extracellular volume fraction (ECV). ECV measures the interstitial expansion that occurs due to diffuse myocardial processes - e.g. fibrosis or amyloid deposition, with gadolinium relative to the plasma. While changes in these values are not disease specific, they can serve as biomarkers in the context of specific scenarios, as they reflect alterations in myocardial tissue composition (Fig. 1). They can be abnormal in areas even before LGE is detected [19, 20].

A complete CMR scan with contrast takes usually around 40 min to be acquired. General contraindications for CMR are intracranial aneurysm clips and iron particles in the eye [21]. Claustrophobia is also a limitation for the scan as well the inability of breath holding, which can be an issue for some of these patients. CMR can present unique challenges given rapid and complex motion of the heart in addition to respiratory motion. However, this is usually compensated by electrocardiogram (ECG) gated images as well as breath-hold and motion correction techniques. Additionally, there exist sequences with real time free breathing or motion correction to facilitate acquisitions.

Tolerance of supine position should be systematically assessed beforehand, as it may be poorly tolerated in some patients with muscular dystrophy. In patients with restrictive respiratory insufficiency and particularly in those who are ventilated, MRI feasibility should be discussed with pneumologist and primary care physician and an alternative imaging modality might be considered. During the procedure, pulse oxygen saturation monitoring is recommended in patients with restrictive respiratory insufficiency and excessive oxygen administration should be avoided.

Regarding devices such as pacemaker and defibrillator, currently there are magnetic resonance imaging (MRI) conditional devices and patients can be safely scanned at 1.5T field strength, if followed specific recommendations from the device company [22, 23].

**CMR IN MUSCULAR DYSTROPHY**

In patients with cardiomyopathy related to muscular dystrophies, CMR can identify left and right ventricular dilatation, hypertrophy, presence of fatty infiltration, diffuse or focal fibrosis, and ventricular dysfunction [24–26].

Some patients with muscular dystrophies (i.e. myotonic dystrophy) can present mainly with arrhythmias and no structural abnormalities seen on echocardiogram. These patients can still have fibrosis identified on CMR, which can be a substrate for arrhythmias as well as provide prognostic information [10, 27, 28]. These patients can also have subclinical signs of ventricular dysfunction even with preserved left ventricular ejection fraction (LVEF) [26]. Strain analysis can help identify early regional dysfunction [29] (Fig. 2).

**DYSTROPHINOPATHIES: DUCHENNE AND BECKER, ISOLATED CARDIOMYOPATHY**

**DMD gene**

More than 2000 mutations in the *DMD gene* have been identified in patients with either Duchenne or Becker muscular dystrophy. With 79 exons and 2.6 million base pairs of the genomic sequence, *DMD*-gene is the largest in the human genome, which is approximately 1.5% of the entire X chromosome [30]. Dystrophin is a sarcomemmal protein of skeletal and cardiac muscle cells, responsible for connecting the cytoskeleton with the extracellular matrix maintaining muscle integrity [31]. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked
recessive disorders primarily affecting males with affected female carriers presenting with milder weakness or isolated cardiomyopathy [32]. Dystrophinopathies are caused by mutations in the dystrophin gene causing nearly absence in DMD and reduced or abnormal in BMD [33]. The mechanism thought to be responsible for cardiac involvement in both DMD and BMD is dysfunctional sarcomella, stretch-activated channels and fragile membrane. That results in an increase influx of intracellular calcium, leading to impairment of myocard contraction, mitochondrial deregulation, inflammation and eventually myocyte death [34]. The death of myocytes activates an inflammatory cascade that ultimately leads to fibrosis and scar. Increased fibrous deposition reduces normal heart contraction and function. Myocardial fibrosis can also lead to conduction defects and arrhythmias [34].

Cardiomyopathy is the primary cause of death in a high proportion of patients with BMD and DMD. The frequency of cardiac involvement can reach 60% to 75% in BMD [33, 35, 36] and almost every DMD patient will have some form of cardiac involvement after 18 years of age [1, 37]. Thus, prophylactic use of ACE-inhibitors (ACEi) is recommended by the age 10 years in DMD regardless to their cardiac function. Nevertheless, there are still unanswered questions regarding the optimal timing of initiation of cardio-protective therapies, e.g. ACEi, particularly in BMD patients. Cardiac MRI has the potential to help identify patients with early cardiac abnormalities in order to start on more aggressive therapeutic measures; however such approach has not been validated yet [36].

Randomized controlled trials have assessed ACEi in patients with DMD and showed slower progression of disease and lower mortality rate when treatment started early, while LVEF still normal [5, 24, 38–40]. A prospective study using this time CMR assessment of LGE and LVEF in patients with DMD or BMD under steroids treatment showed preserved LVEF and lack of LGE when treatment was associated with perindopril [41]. Another study compared lisinopril versus losartan (an angiotensin receptor blocker – ARB) in patients with DMD and recent diagnosis of heart involvement. It showed that there was no difference in terms of efficacy to improve or preserve LVEF [39].

A multicenter randomized placebo-controlled trial is ongoing to establish evidence of prophylactic use of ACEi and beta-blocker (BB) in DMD patients with normal LVEF [42].

A multicenter controlled trial added a mineralocorticoid receptor antagonist (MRA) in the treatment of DMD patients, treated with ACEi or ARB, with early cardiomyopathy (positive LGE) but preserved LVEF, compared with placebo. CMR demonstrated that patients treated with Eplerenone had slower rate of decline in LV circumferential strain and LVEF by CMR [43, 44]. Beta-blocker administration has also been studied in this population, usually added to ACEi or ARB and could help reduce arrhythmias and cardiac events [40, 42, 45].

The cardiac assessment with CMR has great implication on the diagnosis of subclinical and/or overt cardiomyopathy and can help identify patients that could benefit from therapy. Florian et al. (2014) studied the correlation between the cardiac phenotype of DMD and BMD patients based on CMR and genotype. Patients with deletions of exons 50/51 showed absence of late gadolinium enhancement (LGE) more frequently than patients with dystrophin duplications. The presence of LGE in this population is a sensitive early detection tool, as it usually precedes LV systolic dysfunction and the extent of fibrosis is related to the degree of dysfunction. These patients present a characteristic, myocarditis-like pattern of non-ischemic LGE starting in the subepicardium/mid-wall of the lateral/infarolateral wall and usually extending over years towards transmurality and to other myocardial segments (i.e. septum) (Table 2). Transmural LGE has also been observed in these patients and this correlates with lower LV ejection fraction (LVEF) and worse prognosis [36, 46]. In addition, in a retrospective study including DMD patients, more extensive LGE in the lateral wall and/or mid-wall LGE in septum were associated with a higher burden of ventricular arrhythmias and death [47]. The use of parametric mapping can also provide quantitative biomarkers related to fibrosis and inflammation, can depict subtle diffuse fibrosis in areas with normal appearing myocardial on LGE images and could potentially stratify disease severity [46, 48–50].

| Table 2 |
| --- |
| Most common muscular dystrophy genes associated with cardiomyopathy |

Importantly, patients with cardiac involvement on CMR may have normal transthoracic echocardiograms. In a group of patients with DMD, 7 out of 10 of them presented LGE while only 2 had abnormal LVEF on echocardiogram [51]. Similarly, in another study, 73% of BMD patients displayed LGE and only 53% an impaired LVEF on echocardiography [52]. A more recent CMR study showed a correlation between LGE and progression of LV dysfunction in a large DMD cohort. LGE was present in 30% of patients with normal LVEF (>55%) reaching 84% in patients with LVEF <55% [53].

Isolated cardiomyopathy can occur in female carriers of the dystrophin gene mutations [54, 55]. A systematic review showed prevalence of dilated cardiomyopathy without muscle weakness in 7% to 16.7% of female carriers for DMD and up to 13% of BMD carriers. Most commonly these patients had deletions (54%), mostly located between exons 44 and 55. Some patients had duplications (16%), point mutations (17%), translocations (3%) or
other mutations (7%). Eight large CMR studies assessed LGE and LVEF in female carriers. LV dysfunction was present in 14 to 40% of DMD carriers and 6% of BMD carriers. LGE was present in 35–65% of DMD carriers and 19–20% of BMD carriers. The pattern demonstrated is the same as male relatives and mostly in the inferolateral/lateral wall [32].

MYOTONIC DYSTROPHIES

DMPK gene

Myotonic Dystrophy type 1 (DM1) is caused by expansion of a CTG triplet repeat in the 3’ non-coding region of DMPK, the gene encoding the DM protein kinase in chromosome 19q13.3 [56]. Myotonic dystrophy type 1 (DM1) is one of the most common lethal monogenic disorders in populations of European descent and DM1 prevalence estimates in Europe ranged from 1 in 8,300 to 1 in 10,700 [57, 58]. The highest known prevalence has been reported in the French Canadian population (1 in 475) because of a founder effect [59–61].

Clinical severity of DM1 roughly correlates with the trinucleotide expansion of CTG-repeats with higher number of repeats associated with worsening severity of clinical manifestations [62]. DM1 is a multisystemic disease (myotonia, cataracts, diabetes, hypersonemolence, etc.). Cardiac involvement in DM1 primarily includes conduction abnormalities, such as first-degree and advanced atrioventricular blocks, right/left bundle branch blocks, and nonspecific intraventricular conduction delay [33]. Updated guidelines have recognized an earlier indication for permanent pacing in patients with DM1 when second or third degree AV block (class of recommendation (COR) I) or infrahisian conduction defects on electrophysiologic study with HV interval >70ms, or first degree with PR interval >240ms or QRS >120ms or fascicular block (COR IIb) [6]. Atrial arrhythmias such as atrial fibrillation and atrial flutter and LV dysfunction are also common [63].

Patients with DM1 and cardiac involvement are at higher risk for sudden cardiac death and therefore determination of cardiac involvement is essential [64]. Cardiac MRI can demonstrate myocardial fibrosis even in the absence of conduction abnormalities on ECG [25]. A study with 80 DM1 patients showed that 16% of patients had abnormal CMR, out of those 39% with normal ECG. Of those 61% with normal ECG, 61% had abnormal CMR. Functional or structural abnormalities on cardiac MRI included LV systolic dysfunction (25%), LV dilatation (9%), LV hypertrophy (8%), RV (right ventricle) systolic dysfunction (5%) and RV dilatation (1%). Myocardial fibrosis was found in 13% of all patients, mostly as mid-myocardial LGE in the septum and basal inferolateral wall. Most patients with LGE had abnormal ECG [65]. The predictive value of CMR for arrhythmias and advanced LV dysfunction remains unknown due to lack of studies with long-term follow-up. An additional cohort analysis of 57 DM1 patients showed abnormal CMR in 44%, with non-ischemic LGE detected in 32%, with the same, above mentioned distribution. The presence of LGE was the only independent predictor for occurrence of atrial tachyarrhythmias and the authors suggest a more intensified monitoring for arrhythmias in these patients [28].

A recent research including DM1 patients highlights the high burden of subclinical cardiac involvement in asymptomatic patients without rest- or Holter ECG abnormalities. DM patients had significantly lower LVEF and strain values compared to controls, and LGE could be depicted in 29% of them [66]. The prognostic utility of these findings needs to be evaluated in future, follow-up studies.

CMR also can detect diffuse fibrosis with parametric mapping. Post-contrast myocardial T1 values were found to be lower than healthy controls, suggesting the presence of diffuse fibrosis even when focal fibrosis with LGE was not found - and was associated with PR and QRS interval progression during long-term follow-up [67].

ZNF9 gene

DM type 2 (DM2) is caused by a (CCTG)n expansion mutation in the first intron of zinc-finger protein 9 (ZNF9) in chromosome 3q21 [68, 69]. Patients with DM2 usually have more subtle presentation of symptoms and less cardiac involvement than DM1. However, DM2 can be also associated with atrioventricular and intraventricular conduction defects, arrhythmias, cardiomyopathy, and sudden cardiac death (SCD) [70].

CMR can demonstrate subclinical involvement of the myocardium in patients with DM2 and preserved LVEF [26]. Just as histopathological abnormalities in DM2 include fibrosis and fatty infiltration in the skeletal muscle, so too the autopsy data have shown the presence of fibrosis and fatty infiltration in the heart [71]. The pattern of LGE described is subepicardial in the basal inferolateral wall and increased native T1 values and extracellular volume were also demonstrated in the inferolateral segments [26].

As in DM1, a great number of patients can have cardiac abnormalities by CMR without ECG alterations [66]. Furthermore, specific CMR techniques can also detect fat infiltration beyond presence of fibrosis, which is an additional marker of cardiac disease [26].

LMNA gene

Genetic mutations in LMNA have been linked to dilated cardiomyopathy (DCM) with variable myopathy, limb girdle muscular dystrophy (LGMD), autosomal variant of Emery-Dreifuss muscular dystrophy (EDMD), LMNA-related congenital muscular dystrophy (L-CMD) and familial partial lipodystrophy (FPLD) [72]. Lamin A/C gene mutation (LMNA) is identified in up to 10% of familial DCM [73]. Male gender, LVEF ≤50% at first
clinical contact and non-missense *LMNA* mutations have been identified as independent predictors of life threatening ventricular tachy-arrhythmias [3, 74]. These patients are at higher risk for SCD and this might be their initial clinical presentation. Most patients with *LMNA* mutations have a malignant long-term disease course and will experience atrial and/or ventricular arrhythmias, conduction blocks, embolic events or heart failure [75]. Moreover, a high percentage of patients will require the implantation of an antiarrhythmic device [75]. Cardiac manifestations can be isolated or associated with neuromuscular diseases [76].

CMR can detect focal and diffuse myocardial fibrosis in patients with pathogenic *LMNA* mutations prior to clinical symptoms or LV dysfunction. This, in turn, can predict functional and electrical abnormalities, as further shown. A mid-myocardial LGE pattern in the basal interventricular septum is a common and early CMR finding in patients with *LMNA* mutations, with similar distribution to fibrosis identified on autopsy from affected relatives [77, 78]. Positive LGE was correlated with diastolic dysfunction and these patients had significant left atrial enlargement when compared to controls [79]. In addition, Fontana et al. showed that *LMNA* carriers have increased ECV values compared to healthy controls, even in absence of LGE [73]. Septal myocardial fibrosis was associated with conduction abnormalities in asymptomatic or mildly symptomatic *LMNA*-mutation carriers [78]. Additionally, it has been correlated with reduced regional septal function by strain analysis, and to prolonged PR interval on ECG, which has been previously correlated with ventricular arrhythmias [80, 81].

**TTN gene – cardiac phenotype**

*TTN* has the longest coding sequence in the human gene (>100kb) with 364 exons and encodes the largest protein (titin) [82]. Patients with *TTN* mutations have various phenotypes (Table 2). Truncating titin variants (*TTNtv*) are the most prevalent genetic cause of dilated cardiomyopathy DCM [83]. *TTN* mutations can also cause core myopathies associated with primary cardiac disease. CMR identifies DCM with LV or biventricular dysfunction and diffuse LGE, as well as other forms of cardiac disease such as left ventricular non-compaction (LVNC) [84]. Patients with DCM associated with *TTN* mutations are more susceptible to ventricular arrhythmias and the presence of interstitial fibrosis [83].

**MITOCHONDRIAL MYOPATHIES**

Mitochondrial diseases are complex and heterogeneous disorders due to either nuclear DNA or mitochondrial DNA pathogenic gene mutations, leading to a decrease in oxidative phosphorylation and cellular energy (ATP) production. Increasing knowledge about molecular, biochemical, and genetic abnormalities related to mitochondrial dysfunction has expanded the cardiac imaging phenotypes of mitochondrial disorders. These disorders usually present with multi-organ involvement and have a slow progressive course. Cardiac involvement is mostly described as conduction disorders and arrhythmias but can also affect ventricular function and can present as dilated or hypertrophic cardiomyopathy [85]. Gadolinium-contrast enhanced CMR demonstrates presence of fibrosis by LGE as well as perfusion defects [86]. CMR-based phenotype patterns were also identified in different mitochondrial myopathy syndromes [87].

**CONCLUSION**

The role for cardiac MRI has been well-established in a wide range of muscular dystrophies related cardiomyopathies. CMR can provide a complete assessment of function, anatomy, perfusion and tissue characterization. CMR is a more sensitive technique than echocardiography for early diagnosis of cardiac involvement. It has also great potential to improve the prediction of long-term outcome, particularly the development of heart failure and arrhythmic events; however it still has to be validated by longitudinal studies including larger populations.

The pattern and extension of myocardial fibrosis as identified by LGE and with more sensitive techniques such as parametric mapping can assist with the diagnosis and provide prognostic information. During the same image acquisition, both global and regional function can be accurately assessed.

CMR is bound to play a future increasing role in clinical trials for patient selection with regard to their cardiac status and assessment of the efficacy of treatments on the heart.

Although CMR has class I indication for assessment in various cardiac diseases (i.e., ischemic cardiomyopathy, non-ischemic cardiomyopathy, valvular disease, congenital disease, pericardial disease, hypertrophic cardiomyopathy, heart failure, arrhythmogenic right ventricular cardiomyopathy, etc.) [88, 89], there are no current specific guidelines for the indications of cardiac MRI in the muscular dystrophy population. However, every patient with muscular dystrophy that is at risk for cardiac involvement should benefit from at least one diagnostic CMR scan to identify the extent of cardiac involvement and further follow up with an individualized frequency, according to baseline findings and further cardiac status (usually, in 1- to 3-year intervals). Although the gadolinium-based contrast is relatively safe from nephrotoxicity perspective, being contraindicated only in patients with renal failure, specially when GFR is below 30 mL/min/1.73 m² given the risk of nephrogenic systemic fibrosis [90], follow up CMR can also be done without contrast if there is no need to reassess scar. Diffuse fibrosis, as previously mention, can also be assessed contrast-free with native T1 mapping. CMR can be also combined with whole body MRI for diagnostic assessment of the muscular disease and natural history studies for clinical trials.

Particularly in dystrophinopathies, further randomized clinical trials using CMR as a tool for assessment of (early) cardiac involvement and response to therapies are needed. This could more clearly establish the optimal timing for initiation of early cardio-protective therapies with the purpose of
CONFLICTS OF INTEREST

None of the authors has any conflict of interest to declare.

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