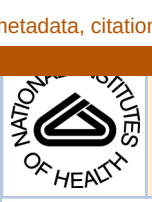

Published in final edited form as:

Circ Cardiovasc Imaging. 2011 January ; 4(1): 67–76. doi:10.1161/CIRCIMAGING.110.960740.

Cardiac Involvement in Patients with Muscular Dystrophies: Magnetic Resonance Imaging Phenotype and Genotypic Considerations

David Verhaert, MD, **Kathryn Richards, MD**, **Jill A. Rafael-Fortney, PhD**, and **Subha V. Raman, MD**

Keywords

muscles; cardiomyopathy; magentic resonance imaging; genetics

Muscular dystrophy (MD) connotes a heterogeneous group of inherited disorders characterized by progressive wasting and weakness of the skeletal muscles. In several forms of MD, cardiac dysfunction occurs and cardiac disease may even be the predominant manifestation of the underlying genetic myopathy. Cardiologists may be unfamiliar with these diseases due to low incidence; also, significant advances in respiratory care have only recently unmasked cardiomyopathy as a significant cause of death in MD[1].

Early detection of MD-associated cardiomyopathy is important, since institution of cardioprotective medical therapies may slow adverse cardiac remodeling and attenuate heart failure symptoms in these patients[2–6]. Although electrocardiography (ECG) and echocardiography are typically advocated for screening[7, 8], cardiovascular magnetic resonance (CMR) has shown promise in revealing early cardiac involvement when standard cardiac evaluation is unremarkable[9, 10].

This review will focus on four groups of skeletal muscle disease most commonly associated with cardiac complications (Table): 1) dystrophin-associated diseases such as Duchenne and Becker muscular dystrophy, 2) Emery-Dreifuss muscular dystrophy, 3)limb-girdle muscular dystrophy and 4) myotonic dystrophy.

I. Dystrophin-Associated Muscular Dystrophies

I.1 Molecular and Genetic Features

Duchenne and Becker muscular dystrophy (DMD and BMD, respectively) are X-linked disorders affecting the synthesis of dystrophin, a large sarcolemmal protein that is absent in DMD[11] and reduced in amount or abnormal in size in BMD patients[12]. Dystrophin provides the connection between a large multimeric complex of glycoproteins in the muscle cell membrane (termed the dystrophin-glycoprotein complex, DGC) and intracellular actin filaments (Fig. 1), thereby transmitting forces generated by sarcomere contraction to the extracellular matrix[13, 14]. Correlations between dystrophin mutations and onset of cardiomyopathy have been noted[15]; some mutations result in only cardiomyopathy without

Correspondence to: Subha V. Raman, MD, Davis Heart and Lung Research Institute, Ohio State University, 473 W. 12th Ave, Suite 200, Columbus, OH 43210, Raman.1@osu.edu, Phone 614 293-8963, Fax 614 293-5614.

Disclosures

Dr. Raman receives research support from Siemens.

skeletal myopathy[16]. Other proteins not shown in Fig. 1 that are particularly involved in both inside-out and outside-in transmission between the myocyte and the extracellular matrix include vinculin and talin; ongoing investigations are further defining their role in cardiomyopathies, particularly those associated with muscular dystrophies.

Dystrophin has an important role in stabilizing the cell membrane of both skeletal and cardiac myocytes[17, 18], and its absence produces sarcolemmal fragility and muscle cell degeneration. Dystrophin deficiency may also lead to conformational changes in stretch-activated calcium channels, resulting in pathologic leakage of calcium in the muscle cytosol[19]. Intracellular calcium accumulation then leads to protease activation, increased reactive oxygen species production and cell death[20, 21]. Finally, impaired vasoregulation occurs via marked reduction in membrane-associated neuronal nitric oxide synthase (nNOS, Fig. 1) in both cardiac and skeletal muscle[22]. Without dystrophin, nNOS mislocalizes to the cytosol; this greater distance between nNOS and the sarcolemma may impair NO diffusion through the myocyte membrane to the microvasculature. As a consequence, insufficient NO release follows muscle contraction resulting in muscle ischemia[23]. Unopposed vasoconstriction may, therefore, explain the necrosis observed in skeletal and cardiac muscle of dystrophinopathy patients. Microvasculature abnormalities have also been shown to result primarily from absence of dystrophin or sarcoglycan components of the DGC in cardiomyocytes[24, 25].

X inactivation, the random process by which one of the two X chromosomes in female cells becomes transcriptionally inactive, may result in cardiomyocytes with an active X-chromosome with the abnormal dystrophin gene. The X-chromosome containing the normal dystrophin gene may become inactivated in cardiac muscle to a greater degree than in skeletal muscle, causing female carriers to develop dystrophinopathic cardiomyopathy. The exact prevalence and severity of such in the carrier population is uncertain[26–29].

I.2 Cardiac Disease and Imaging Phenotype

Almost all DMD patients who survive to the third decade of life display cardiomyopathy[30]. Recognition may be delayed by relative physical inactivity obscuring symptomatology. This most common and severe form of childhood muscular dystrophies is associated with increased R/S ratio in the right precordial ECG leads, deep Q waves in the lateral leads, conduction abnormalities and arrhythmias (mainly supraventricular but also ventricular).

BMD patients, whose skeletal myopathy occurs later and progresses more slowly, experience worse cardiomyopathy than DMD patients: up to 70% have LV dysfunction by echocardiography. Perhaps because of less skeletal muscle weakness, these patients can perform more strenuous exercise with dystrophin-deficient myocardial muscle fibers and have earlier manifestations of myocardial disease[31].

Most CMR data in muscular dystrophies currently exists for patients with DMD and BMD. The pathology of cardiomyopathy in patients with dystrophinopathy classically produces subepicardial fibrosis of the inferolateral wall[32], remarkably similar to the pattern observed in some patients with viral myocarditis (Figs. 2–3, Movie Files 1–2). Myocardial damage in DMD/BMD has been postulated to result from mechanical stress imposed on a metabolically and structurally abnormal myocardium, although it remains unclear how a genetic abnormality presumably affecting the heart in a diffuse manner may result in a segmental distribution. Whether the inferolateral wall is more vulnerable due to regional molecular changes caused by the mutation or if this regional susceptibility results from exposure to higher mechanical stress remains to be elucidated[10]. Of note, enterovirus infection has been shown to produce myocardial damage via cleavage of dystrophin[33]; this

mechanism may help explain the similarity in LGE pattern between myocarditis and dystrophin-associated cardiomyopathy.

The rationale to perform CMR in BMD/DMD patients in addition to the current standard of care (monitoring by echocardiography and ECG) is based on 2 sets of observations. First, studies have shown that early initiation of standard heart failure therapy can delay the onset and progression of left ventricular systolic dysfunction and potentially even lead to reverse remodeling in patients with X-linked dystrophinopathy[2–6]. Second, it has been shown that myocardial fibrosis detected by late gadolinium-enhancement imaging may be observed even when findings by echocardiography are still normal[9, 10] (Fig. 2). CMR can therefore serve as a more sensitive means to detect early cardiac involvement and help to decide when cardioprotective treatment should be instituted. In addition to late gadolinium-enhancement, CMR also provides accurate and reproducible quantification of LV volumes, making this modality well suited for monitoring response to both standard therapy and novel treatment strategies.

Cardiac screening has been recommended for female DMD/BMD mutation carriers, particularly beginning after the teenage years as they are known to be at risk for developing cardiomyopathy[28]. Interestingly, CMR has revealed a similar pattern of myocardial fibrosis in mutation carriers as that seen in DMD patients (Fig. 4)[34]. Since myocardial damage in carriers has been observed even in absence of clinically-apparent muscular weakness, cardiac screening should be considered in female relatives of DMD/BMD patients.

II. Emery-Dreifuss Muscular Dystrophies

II.1 Clinical and Genetic Features

The nuclear envelope is composed of a double lipid bilayer that separates the contents of the nucleus from the cytoplasm. Within the inner nuclear membrane are a variety of integral proteins. Emery-Dreifuss muscular dystrophy (EDMD) is a form of muscular dystrophy caused by mutations in these nuclear membrane proteins. One of these proteins, emerin, (Fig. 1) is almost completely absent in the X-linked form of EDMD due to a mutation in the EMD gene[35]. The exact function of emerin is not clear; it binds to a variety of other nuclear factors involved in gene regulation, mRNA splicing, ordering of chromatin structure and nuclear assembly[36]. EDMD can also occur as an autosomal dominant (AD) or recessive (AR) disorder resulting from mutations in the LMNA gene that encodes lamins A and C[37]. Lamins A and C are nuclear intermediate-filament proteins which closely interact with emerin and other nuclear membrane proteins, thereby forming aproteinaceous meshwork (the nuclear lamina) that underlies the inner nuclear membrane (Fig. 1). This meshwork has an important role inmaintaining the architecture and mechanical strengthof the nucleus; it also serves as a scaffold for various other nuclear factors involved in DNA replication, chromatin organization and transcription[38–41]. Deficiency in either emerin or lamin A/C typically results in the triad of contractures, muscle weakening and cardiac conduction defects by mechanisms that remain elusive.

Cardiac involvement in EDMD patients is common and usually becomes evident in the third decade as muscle weakness progresses[8], though cardiac manifestations have also been reported in young adults without muscle weakness. Since cardiac dysfunction portends a high risk of sudden death[42], careful follow-up of these patients is mandatory. In EDMD, normal myocardium is gradually replaced by fibrous and adipose tissue, a process that usually starts in the atria (leading to atrial arrhythmias), often involves the atrioventricular node (leading to conduction abnormalities sometimes requiring pacemaker implantation) and eventually affects the ventricles (causing progressive dilatation and systolic failure)[43,

[44]. Because sudden death may be the presenting symptom in this disease, cardiac screening of relatives (including female carriers with X-linked EDMD) has been recommended[7, 44].

II.2 Cardiac Magnetic Resonance Imaging Phenotype

In EDMD, CMR data are limited due to the rarity of the disease but also because of the frequent need for pacemaker implantation in this population (particularly in the more advanced stages of the disease). A study by Smith *et al*.[45] in 8 patients with the AD subtype of EDMD (EDMD2; LMNA gene mutation at 1q21) showed that early stage disease does not display apparent fibrosis, despite the presence of more subtle myocardial abnormalities including a decrease in systolic circumferential strain in the inferior segment. This suggests a different pathogenesis of cardiac involvement in EDMD compared to DMD/BMD, where fibrosis typically precedes systolic dysfunction.

III. Limb Girdle Muscular Dystrophies

III.1 Clinical and Genetic Features

Limb-girdle muscular dystrophy (LGMD) refers to a group of disorders with great clinical and genetic heterogeneity, all characterized by weakness affecting the proximal musculature. AD and AR inheritance patterns have been identified. The more common AR subtypes usually have an earlier age of onset, and show more rapid disease progression compared to AD variants. The subtypes mostly associated with cardiac involvement (manifest as conduction disorders and/or myocardial disease) are those associated with a defect in the genes encoding for the α-(LGMD2D), β-(LGMD2E), γ-(LGMD2C) or δ-(LGMD2F) subunits of the dystrophin-associated sarcoglycan complex in heart and skeletal muscle (Fig. 1)[46]. Cardiomyopathy is also very common in LGMD2I, caused by a mutation in fukutin-related protein (FKRP). FKRP is an enzyme involved in the glycosylation of α-dystroglycan, a peripheral membrane component of the dystrophin-associated glycoprotein complex. Post-translational glycosylation by FRKP allows α-dystroglycan to bind with the extracellular matrix, making it an important component in the link among cytoskeleton, sarcolemmal dystrophin-associated glycoprotein complex and extracellular matrix.

The AD subtype LGMD1B is also caused by a defect in the LMNA gene encoding for lamin A/C, resulting in a phenotype similar to autosomal dominant EDMD but with a different distribution of muscle involvement. The pelvic girdle weakness in LGMD1B is slowly progressive, sparing the lower muscles. Additionally, contractures and cardiac disease manifestations (atrioventricular block, sudden death, atrial paralysis, atrial fibrillation/flutter and dilated cardiomyopathy) tend to occur later compared to autosomal dominant EDMD[47, 48].

Different mutations involving the LMNA gene have been described, resulting in a clinically heterogeneous group of disorders (laminopathies) spanning muscular dystrophy, progeria, familial partial lipodystrophy and Charcot-Marie-Tooth disease. The muscular dystrophies associated with LMNA gene mutation that cause cardiac disease include the autosomal variants of EDMD, LGMD1B, and a third disorder commonly referred to as dilated cardiomyopathy with conductive system disease. The last, although initially linked to chromosome 1p1-1q1[49] was later associated with mutations in the lamin A/C gene (1p1-q21 locus)[50]. Patients with this defect develop sinus node dysfunction, atrioventricular node dysfunction, ventricular arrhythmias and adult-onset cardiomyopathy with little clinical evidence of skeletal myopathy. The inheritance pattern is autosomal dominant with high penetrance, and patients have a high risk of sudden death[50].

III.2 Cardiac Imaging Phenotype

In lamin A/C cardiomyopathy, we have demonstrated midmyocardial scarring of the basal interventricular septum by LGE that occurs well before the onset of ventricular dilatation and systolic dysfunction (Fig. 4), and which may herald conduction system disease[51]. This midwall fibrosis is similar in distribution to that observed at autopsy, and in our experience is often associated with diastolic dysfunction. Further studies are needed to define the prognostic significance of midwall fibrosis in this population, as it may represent substrate for potentially fatal ventricular arrhythmias seen in these patients as reported in other cardiomyopathies[52–54]. While skeletal muscle disease may not be readily apparent clinically, we have detected clear alterations involving the medial head of the gastronemius muscles by magnetic resonance imaging (Fig. 5), similar to that described in patients with EDMD2[55]. This suggests the presence of a continuum between phenotypes with predominant cardiac involvement and phenotypes with cardiac and skeletal muscle compromise[56].

IV. Myotonic Dystrophy

IV.1 Clinical and Genetic Features

Myotonic dystrophy (DM) is an autosomal dominant muscular dystrophy that produces progressive skeletal muscle wasting and cardiac conduction abnormalities; multisystem manifestations include cataracts, testicular failure, hypogammaglobulinemia and insulin resistance. As shown in the Table, two types of DM have been identified. DM1 is the most common form and is associated with an abnormal expansion of a CTG-trinucleotide repeat sequence in the DMPK gene that codes for myotonic dystrophy protein kinase, a protein mainly expressed in smooth, cardiac and skeletal muscle cells. Disease severity and age of onset in DM1 correlates with CTG expansion length, and the number of repeats can increase from one generation to the next (anticipation). DM2 on the other hand is associated with an expanded CCTG-tetranucleotide repeat in a totally unrelated gene, coding for zinc finger protein. In both cases, the gene including the abnormal repeat sequences is transcribed into RNA but not translated. The mutant RNA accumulates in the nucleus[57] and disturbs the function of RNA-binding proteins that normally participate in splicing of pre-messenger RNA into mature mRNA. This eventually results in abnormal function of different genes, including those encoding for the muscle-specific chloride channel ClC-1 and insulin receptor, at least partially explaining the features of myotonia and insulin resistance in patients with DM[58].

Atrioventricular and intraventricular conduction defects are common in both DM1 and DM2. Infra-hisian block is likely an important cause of sudden death in these patients[59, 60]. As in many other types of muscular dystrophy, cardiac arrhythmias may occur early in the disease course i.e. in the absence of severe neuromuscular impairment. Structural heart disease is also frequently observed in DM, with LV dilatation or hypertrophy observed in approximately 20% of patients, and LV systolic dysfunction in 14%[61]. Clinical heart failure, however, is less common—2% according to that same report.

IV.2 Cardiac Imaging Phenotype

Gaul *et al*. recently described the CMR findings in 9 patients with LGMD2I (due to a mutation in the FKRP gene)[62]. They found CMR to be more sensitive than conventional diagnostic investigations (ECG and echocardiography) for detecting cardiac involvement, which was manifest as a decrease in ejection fraction and/or an increase in LV volumes and mass. Unfortunately, no results from late gadolinium-enhancement imaging were reported in that study. Our own experience with CMR in patients with LGMD2I suggests that at an

early stage, when LV size and function are still normal, midmyocardial scarring may be observed. As cardiomyopathy advances, extensive myocardial fibrosis is apparent (Fig. 6).

A similar pattern of fibrosis was recently reported by Yilmaz *et al*. in a patient with LGMD2C[63]. Taken together, these findings suggest that different abnormalities within the dystrophin-sarcoglycan-dystroglycan complex may all lead to cardiomyocyte instability and damage, eventually resulting in a characteristic (but non-specific) pattern of fibrosis.

Patients with DM may present with cardiomyopathy, which usually is more benign in DM2 compared to DM1. CMR may help define the LV abnormalities of the disease: dilatation, systolic dysfunction, hypertrophy, and occasionally non-compaction[64, 65]. Typical LGE patterns have not been reported in DM. In our experience, mild midwall fibrosis involving the septum is occasionally present; the clinical significance of this finding in DM remains uncertain.

V. Beyond LGE

V.1 Myocardial Strain Analysis

The assumption that cardiac dysfunction can be prevented (or at least be attenuated) in patients with MD has led to the belief that therapy should be initiated at an early stage of the disease, rather than delayed until ventricular dilatation or systolic dysfunction become apparent. CMR has been proposed as a sensitive screening tool for that purpose by its ability to show myocardial fibrosis, even when the LV is otherwise structurally normal. Another means of revealing occult cardiac dysfunction in patients with MD may be provided by strain analysis. Ashford *et al*. used CMR tagging to show that boys with DMD exhibit abnormal global and segmental circumferential strain compared to age- and gender-matched controls, despite similar LV volumes and ejection fraction[66]. Similar findings were recently reported by Hor *et al*., who showed abnormalities in myocardial strain preceded both the age-dependent decline in ejection fraction *and* the appearance of myocardial fibrosis in DMD patients[67]. This group recently showed that strain analysis better captures serial decline in LV function compared to EF[68]. The sensitivity of strain imaging analysis by CMR could potentially be used not only to reveal occult cardiac dysfunction, but also to assess the efficacy of existing or novel therapeutic agents. Some questions remain, however, regarding these tools, particularly in terms of their accuracy for measuring strain on a segmental (rather than global) level, but also with respect to the reproducibility of strain measurements among centers. Prospective and multicenter studies that randomize patients to therapeutic decision making with or without strain imaging analysis are therefore critically needed before these new techniques can become adopted into the clinical management of patients with muscular dystrophy[69].

V.2 Fat vs. Water Imaging

Histological studies of autopsy hearts from DMD patients suggest a component of fat infiltration, described as “predominantly epimyocardial” in a small case series[32]. CMR may distinguish fat using either cine or LGE imaging techniques that take advantage of the consistent difference in resonant frequency of water vs. fat protons[70]. Studying 3 DMD dogs with these techniques, Kellman *et al*. demonstrated that extensive epicardial hyperenhacement on LGE imaging that at least in part was attributable to fat[71]. Our experience in one patient with early myocardial disease using the same technique suggests that LGE in patients with dystrophin-associated cardiomyopathy may also demonstrate a component of fatty infiltration (Fig. 7, Movie File 3). T2-weighted CMR, which depicts myocardial water’s distribution, may provide additional insights into the myocardial disease of DMD[72].

VI. Suggested CMR Protocol and Clinical Implications of Findings

VI.1 Suggested CMR Protocol

When designing a CMR examination for the patient with muscular dystrophy, the key clinical questions should be addressed: What is the degree of LV dysfunction? What evidence is there for myocardial disease? What pattern of disease is present? What is the likelihood of functional recovery? Acquisitions should include cine imaging in all standard long axis and contiguous short axis planes; real-time cine techniques may be necessary in patients who have difficulty breathholding. Fat-suppressed or fat-only cine imaging if available may help delineate the extent of myocardial fat infiltration. Finally, LGE acquisition forms the cornerstone of any CMR protocol in patients with cardiomyopathy, and the same is true in evaluating the MD patient. While the optimal contrast dose and acquisition timing have not been specifically interrogated in MD cardiomyopathy LGE imaging, our experience suggests that values similar to those used for other nonischemic cardiomyopathies (save amyloidosis) perform well. If fat and water can be distinctly imaged with specialized LGE sequences, these may shed further insight into the extent of fibrosis vs. fatty infiltration of the myocardium. While absence of hyperenhancement has established value in predicting response to, for instance, medical and resynchronization therapies in other cardiomyopathy populations, the predictive value in MD-associated myocardial disease remains to be established. Given evidence that subclinical abnormalities in regional strain may precede overt contractile dysfunction, strain analysis may be included at centers where robust postprocessing affords reproducible results.

VI.2 Clinical Implications of Findings

Increased recognition of subclinical myocardial changes with advanced imaging raises challenging management questions. Evidence-based guidelines for patients with cardiomyopathy advocate initiation of drugs like angiotensin converting enzyme inhibitors (ACEI) and beta-blockers in stage B cardiomyopathy, defined in the adult guidelines as “impaired left ventricular (LV) function, hypertrophy, or geometric chamber distortion”[73]. Pediatric guidelines also advocate ACEI therapy for subclinical LV dysfunction[74]; notably, neither document addresses management of myocardial fibrosis that may be present in the absence of structural and functional changes. Our approach is to initiate ACEI and occasionally aldosterone antagonist therapy, given the proven antifibrotic effect of both in other cardiomyopathy populations[75], if CMR demonstrates myocardial fibrosis in the muscular dystrophy patient and particularly in the lamin A/C mutation-positive patient. While one prospective, randomized trial in children with DMD supports a possible long-term benefit with ACEI even if the initial LV ejection fraction by echocardiography is normal[76], it is unknown if any of these patients had subclinical fibrosis in the absence of CMR data. A strategy of fibrosis-guided initiation of cardioprotective drug therapy requires prospective, randomized trial data before it can be widely advocated.

Electrophysiological testing should be considered in muscular dystrophy-associated cardiomyopathies known to affect conduction system such as DM and lamin A/C. Timing of such may be informed by symptoms suspicious for conduction system disease or conduction abnormalities by electrocardiography[77]. We have observed longer PR intervals in lamin A/C patients with septal fibrosis by CMR relative to those of mutation-positive patients without evident fibrosis[51]; longitudinal studies are suggested to test the predictive value of hyperenhancement for pacemaker requirement in appropriate DM and lamin A/C patients.

VII. Cardiac Disease in MD: Genotype vs. Phenotype

One of the major problems for clinicians dealing with the cardiovascular complications of MD is that clear correlations between genotype and phenotype have been difficult to

achieve. It remains unclear why distinct mutations may result in a clinically indistinguishable phenotype, while strikingly different phenotypes may result in carriers of identical gene mutations or even among affected siblings. In this respect, MD-associated cardiomyopathies are no different from other heritable cardiomyopathies (hypertrophic cardiomyopathy, for instance). Although there is little doubt that genotype plays a central role in initiating the cardiomyopathic process, the ultimate cardiovascular phenotype is likely also determined by multiple other interacting factors, including genetic background effects, biomechanical stress pathways (with loss of functional myocardium creating additional stress on remaining viable heart muscle) and modifying effects of calcium cycling and signaling[78, 79].

A better understanding of clinical variability in MD-associated myocardial disease will, therefore, require identification of modifying genes and improved knowledge of gene-protein function and protein interactions. Importantly, it will also benefit from continued advances in cardiac phenotyping; lack of sensitivity in the armamentarium of diagnostic tests has previously impaired detection of early cardiac involvement in many of these patients. The greater sensitivity and reproducibility of CMR to demonstrate early abnormalities or subtle changes in serial assessment offers the promise of better defining the natural history, and offers significant value in developing novel therapeutic approaches for these disorders. It is hoped that this review's demonstration of limitations of current state-of-the-art in imaging phenotype prompts synergistic efforts among geneticists, molecular biologists and CMR specialists to eventually generate new insights into the pathogenesis and expression of cardiac disease in muscular dystrophy, which is critically needed to help reduce the burden of heart disease in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dennis Mathias, BA, for his graphical assistance with Figure 1.

Sources of Funding

BallouSkies, NIH

References

1. Bach JR. Update and perspective on noninvasive respiratory muscle aids. Part 2: The expiratory aids. Chest 1994;105:1538–1544. [PubMed: 8181348]
2. Duboc D, Meune C, Lerebours G, Devaux JY, Vaksmann G, Becane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. J Am Coll Cardiol 2005;45:855–857. [PubMed: 15766818]
3. Ishikawa Y, Bach JR, Minami R. Cardioprotection for Duchenne's muscular dystrophy. Am Heart J 1999;137:895–902. [PubMed: 10220639]
4. Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation 2005;112:2799–2804. [PubMed: 16246949]
5. Kajimoto H, Ishigaki K, Okumura K, Tomimatsu H, Nakazawa M, Saito K, Osawa M, Nakanishi T. Beta-blocker therapy for cardiac dysfunction in patients with muscular dystrophy. Circ J 2006;70:991–994. [PubMed: 16864930]

6. Ramaciotti C, Heistein LC, Coursey M, Lemler MS, Eapen RS, Iannaccone ST, Scott WA. Left ventricular function and response to enalapril in patients with duchenne muscular dystrophy during the second decade of life. Am J Cardiol 2006;98:825–827. [PubMed: 16950195]
7. Bouhouch R, Elhouari T, Oukerraj L, Fellat I, Zarzur J, Bennani R, Arharbi M. Management of cardiac involvement in neuromuscular diseases: review. Open Cardiovasc Med J 2008;2:93–96. [PubMed: 19337361]
8. Emery AE. The muscular dystrophies. Lancet 2002;359:687–695. [PubMed: 11879882]
9. Silva MC, Meira ZM, Gurgel Giannetti J, da Silva MM, Campos AF, Barbosa Mde M, Starling Filho GM, Ferreira Rde A, Zatz M, Rochitte CE. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. J Am Coll Cardiol 2007;49:1874–1879. [PubMed: 17481447]
10. Yilmaz A, Gdynia HJ, Baccouche H, Mahrholdt H, Meinhardt G, Basso C, Thiene G, Sperfeld AD, Ludolph AC, Sechtem U. Cardiac involvement in patients with Becker muscular dystrophy: new diagnostic and pathophysiological insights by a CMR approach. J Cardiovasc Magn Reson 2008;10:50. [PubMed: 18983659]
11. Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 1987;51:919–928. [PubMed: 3319190]
12. Monaco AP, Bertelson CJ, Liechti-Gallati S, Moser H, Kunkel LM. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. Genomics 1988;2:90–95. [PubMed: 3384440]
13. Rafael JA, Cox GA, Corrado K, Jung D, Campbell KP, Chamberlain JS. Forced expression of dystrophin deletion constructs reveals structure-function correlations. J Cell Biol 1996;134:93–102. [PubMed: 8698825]
14. Corrado K, Rafael JA, Mills PL, Cole NM, Faulkner JA, Wang K, Chamberlain JS. Transgenic mdx mice expressing dystrophin with a deletion in the actin-binding domain display a “mild Becker” phenotype. J Cell Biol 1996;134:873–884. [PubMed: 8769413]
15. Kaspar RW, Allen HD, Ray WC, Alvarez CE, Kissel JT, Pestronk A, Weiss RB, Flanigan KM, Mendell JR, Montanaro F. Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in becker muscular dystrophy. Circ Cardiovasc Genet 2009;2:544–551. [PubMed: 20031633]
16. Feng J, Yan JY, Buzin CH, Sommer SS, Towbin JA. Comprehensive mutation scanning of the dystrophin gene in patients with nonsyndromic X-linked dilated cardiomyopathy. J Am Coll Cardiol 2002;40:1120–1124. [PubMed: 12354438]
17. Menke A, Jockusch H. Extent of shock-induced membrane leakage in human and mouse myotubes depends on dystrophin. J Cell Sci 1995;108:727–733. [PubMed: 7769014]
18. Pasternak C, Wong S, Elson EL. Mechanical function of dystrophin in muscle cells. J Cell Biol 1995;128:355–361. [PubMed: 7844149]
19. Franco-Obregon A Jr, Lansman JB. Mechanosensitive ion channels in skeletal muscle from normal and dystrophic mice. J Physiol 1994;481:299–309. [PubMed: 7537813]
20. Fong PY, Turner PR, Denetclaw WF, Steinhardt RA. Increased activity of calcium leak channels in myotubes of Duchenne human and mdx mouse origin. Science 1990;250:673–676. [PubMed: 2173137]
21. Jung C, Martins AS, Niggli E, Shirokova N. Dystrophic cardiomyopathy: amplification of cellular damage by Ca2+ signalling and reactive oxygen species-generating pathways. Cardiovasc Res 2008;77:766–773. [PubMed: 18056762]
22. Bia BL, Cassidy PJ, Young ME, Rafael JA, Leighton B, Davies KE, Radda GK, Clarke K. Decreased myocardial nNOS, increased iNOS and abnormal ECGs in mouse models of Duchenne muscular dystrophy. J Mol Cell Cardiol 1999;31:1857–1862. [PubMed: 10525423]
23. Sander M, Chavoshan B, Harris SA, Iannaccone ST, Stull JT, Thomas GD, Victor RG. Functional muscle ischemia in neuronal nitric oxide synthase-deficient skeletal muscle of children with Duchenne muscular dystrophy. Proc Natl Acad Sci U S A 2000;97:13818–13823. [PubMed: 11087833]

24. Wheeler MT, Allikian MJ, Heydemann A, Hadhazy M, Zarnegar S, McNally EM. Smooth muscle cell-extrinsic vascular spasm arises from cardiomyocyte degeneration in sarcoglycan-deficient cardiomyopathy. J Clin Invest 2004;113:668–675. [PubMed: 14991064]
25. Hainsey TA, Senapati S, Kuhn DE, Rafael JA. Cardiomyopathic features associated with muscular dystrophy are independent of dystrophin absence in cardiovasculature. Neuromuscul Disord 2003;13:294–302. [PubMed: 12868498]
26. Grain L, Cortina-Borja M, Forfar C, Hilton-Jones D, Hopkin J, Burch M. Cardiac abnormalities and skeletal muscle weakness in carriers of Duchenne and Becker muscular dystrophies and controls. Neuromuscul Disord 2001;11:186–191. [PubMed: 11257476]
27. Hoogerwaard EM, van der Wouw PA, Wilde AA, Bakker E, Ippel PF, Oosterwijk JC, Majoor-Krakauer DF, van Essen AJ, Leschot NJ, de Visser M. Cardiac involvement in carriers of Duchenne and Becker muscular dystrophy. Neuromuscul Disord 1999;9:347–351. [PubMed: 10407858]
28. Nolan MA, Jones OD, Pedersen RL, Johnston HM. Cardiac assessment in childhood carriers of Duchenne and Becker muscular dystrophies. Neuromuscul Disord 2003;13:129–132. [PubMed: 12565910]
29. Politano L, Nigro V, Nigro G, Petretta VR, Passamano L, Papparella S, Di Somma S, Comi LI. Development of cardiomyopathy in female carriers of Duchenne and Becker muscular dystrophies. JAMA 1996;275:1335–1338. [PubMed: 8614119]
30. McNally EM. New approaches in the therapy of cardiomyopathy in muscular dystrophy. Annu Rev Med 2007;58:75–88. [PubMed: 17217326]
31. Melacini P, Fanin M, Danieli GA, Villanova C, Martinello F, Miorin M, Freda MP, Miorelli M, Mostacciuolo ML, Fasoli G, Angelini C, Dalla Volta S. Myocardial involvement is very frequent among patients affected with subclinical Becker's muscular dystrophy. Circulation 1996;94:3168–3175. [PubMed: 8989125]
32. Frankel KA, Rosser RJ. The pathology of the heart in progressive muscular dystrophy: epimyocardial fibrosis. Hum Pathol 1976;7:375–386. [PubMed: 939536]
33. Badorff C, Knowlton KU. Dystrophin disruption in enterovirus-induced myocarditis and dilated cardiomyopathy: from bench to bedside. Med Microbiol Immunol 2004;193:121–126. [PubMed: 12920582]
34. Yilmaz A, Gdynia HJ, Ludolph AC, Klingel K, Kandolf R, Sechtem U. Images in cardiovascular medicine. Cardiomyopathy in a Duchenne muscular dystrophy carrier and her diseased son: similar pattern revealed by cardiovascular MRI. Circulation 2010;121:e237–239. [PubMed: 20231539]
35. Bione S, Maestrini E, Rivella S, Mancini M, Regis S, Romeo G, Toniolo D. Identification of a novel X-linked gene responsible for Emery-Dreifuss muscular dystrophy. Nat Genet 1994;8:323–327. [PubMed: 7894480]
36. Bengtsson L, Wilson KL. Multiple and surprising new functions for emerin, a nuclear membrane protein. Curr Opin Cell Biol 2004;16:73–79. [PubMed: 15037308]
37. Bonne G, Di Barletta MR, Varnous S, Becane HM, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizberea JA, Duboc D, Fardeau M, Toniolo D, Schwartz K. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat Genet 1999;21:285–288. [PubMed: 10080180]
38. Burke B, Stewart CL. Life at the edge: the nuclear envelope and human disease. Nat Rev Mol Cell Biol 2002;3:575–585. [PubMed: 12154369]
39. Gruenbaum Y, Margalit A, Goldman RD, Shumaker DK, Wilson KL. The nuclear lamina comes of age. Nat Rev Mol Cell Biol 2005;6:21–31. [PubMed: 15688064]
40. Holaska JM. Emerin and the nuclear lamina in muscle and cardiac disease. Circ Res 2008;103:16–23. [PubMed: 18596264]
41. Mounkes L, Kozlov S, Burke B, Stewart CL. The laminopathies: nuclear structure meets disease. Curr Opin Genet Dev 2003;13:223–230. [PubMed: 12787783]
42. Sakata K, Shimizu M, Ino H, Yamaguchi M, Terai H, Fujino N, Hayashi K, Kaneda T, Inoue M, Oda Y, Fujita T, Kaku B, Kanaya H, Mabuchi H. High incidence of sudden cardiac death with

conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. Circulation 2005;111:3352–3358. [PubMed: 15967842]

43. Buckley AE, Dean J, Mahy IR. Cardiac involvement in Emery Dreifuss muscular dystrophy: a case series. Heart 1999;82:105–108. [PubMed: 10377322]
44. Fishbein MC, Siegel RJ, Thompson CE, Hopkins LC. Sudden death of a carrier of X-linked Emery-Dreifuss muscular dystrophy. Ann Intern Med 1993;119:900–905. [PubMed: 8215002]
45. Smith GC, Kinali M, Prasad SK, Bonne G, Muntoni F, Pennell DJ, Nihoyannopoulos P. Primary myocardial dysfunction in autosomal dominant EDMD. A tissue doppler and cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2006;8:723–730. [PubMed: 16891232]
46. Norwood F, de Visser M, Eymard B, Lochmuller H, Bushby K. EFNS guideline on diagnosis and management of limb girdle muscular dystrophies. Eur J Neurol 2007;14:1305–1312. [PubMed: 18028188]
47. Kitaguchi T, Matsubara S, Sato M, Miyamoto K, Hirai S, Schwartz K, Bonne G. A missense mutation in the exon 8 of lamin A/C gene in a Japanese case of autosomal dominant limb-girdle muscular dystrophy and cardiac conduction block. Neuromuscul Disord 2001;11:542–546. [PubMed: 11525883]
48. Muchir A, Bonne G, van der Kooi AJ, van Meegen M, Baas F, Bolhuis PA, de Visser M, Schwartz K. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). Hum Mol Genet 2000;9:1453–1459. [PubMed: 10814726]
49. Kass S, MacRae C, Graber HL, Sparks EA, McNamara D, Boudoulas H, Basson CT, Baker PB 3rd, Cody RJ, Fishman MC, Cox N, Kong A, Wooley CF, Seidman JG, Seidman CE. A gene defect that causes conduction system disease and dilated cardiomyopathy maps to chromosome 1p1-1q1. Nat Genet 1994;7:546–551. [PubMed: 7951328]
50. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Muehle G, Johnson W, McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 1999;341:1715–1724. [PubMed: 10580070]
51. Raman SV, Sparks EA, Baker PM, McCarthy B, Wooley CF. Mid-myocardial fibrosis by cardiac magnetic resonance in patients with lamin A/C cardiomyopathy: possible substrate for diastolic dysfunction. J Cardiovasc Magn Reson 2007;9:907–913. [PubMed: 18066751]
52. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol 2006;48:1977–1985. [PubMed: 17112987]
53. Hsia HH, Marchlinski FE. Characterization of the electroanatomic substrate for monomorphic ventricular tachycardia in patients with nonischemic cardiomyopathy. Pacing Clin Electrophysiol 2002;25:1114–1127. [PubMed: 12164454]
54. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Watkins SP, Dickfeld TL, Meininger GR, Roguin A, Calkins H, Tomaselli GF, Weiss RG, Berger RD, Lima JA, Halperin HR. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. Circulation 2005;112:2821–2825. [PubMed: 16267255]
55. Mercuri E, Counsell S, Allsop J, Jungbluth H, Kinali M, Bonne G, Schwartz K, Bydder G, Dubowitz V, Muntoni F. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery-Dreifuss muscular dystrophy. Neuropediatrics 2002;33:10–14. [PubMed: 11930270]
56. Carboni N, Mura M, Marrosu G, Cocco E, Marini S, Solla E, Mateddu A, Maioli MA, Piras R, Mallarini G, Mercuro G, Porcu M, Marrosu MG. Muscle imaging analogies in a cohort of patients with different clinical phenotypes caused by LMNA gene mutations. Muscle Nerve 2010;41:458–463. [PubMed: 19882644]
57. Cooper TA. A reversal of misfortune for myotonic dystrophy? N Engl J Med 2006;355:1825–1827. [PubMed: 17065646]
58. Ranum LP, Cooper TA. RNA-mediated neuromuscular disorders. Annu Rev Neurosci 2006;29:259–277. [PubMed: 16776586]

59. Babuty D, Fauchier L, Tena-Carbi D, Poret P, Leche J, Raynaud M, Fauchier JP, Cosnay P. Is it possible to identify infrahissian cardiac conduction abnormalities in myotonic dystrophy by non-invasive methods? Heart 1999;82:634–637. [PubMed: 10525524]
60. Melacini P, Buja G, Fasoli G, Angelini C, Armani M, Scognamiglio R, Dalla Volta S. The natural history of cardiac involvement in myotonic dystrophy: an eight-year follow-up in 17 patients. Clin Cardiol 1988;11:231–238. [PubMed: 3365873]
61. Bhakta D, Lowe MR, Groh WJ. Prevalence of structural cardiac abnormalities in patients with myotonic dystrophy type I. Am Heart J 2004;147:224–227. [PubMed: 14760317]
62. Gaul C, Deschauer M, Tempelmann C, Vielhaber S, Klein HU, Heinze HJ, Zierz S, Grothues F. Cardiac involvement in limb-girdle muscular dystrophy 2I: conventional cardiac diagnostic and cardiovascular magnetic resonance. J Neurol 2006;253:1317–1322. [PubMed: 16786213]
63. Yilmaz A, Suttie J, Petersen SE. Letter regarding article, “analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in Becker muscular dystrophy”. Circ Cardiovasc Genet 2010;3:e1. author reply e2. [PubMed: 20407095]
64. Finsterer J, Stolberger C, Kopsa W. Noncompaction in myotonic dystrophy type 1 on cardiac MRI. Cardiology 2005;103:167–168. [PubMed: 15785023]
65. Wahbi K, Meune C, Bassez G, Laforet P, Vignaux O, Marmursztejn J, Becane HM, Eymard B, Duboc D. Left ventricular non-compaction in a patient with myotonic dystrophy type 2. Neuromuscul Disord 2008;18:331–333. [PubMed: 18395448]
66. Ashford MW Jr, Liu W, Lin SJ, Abraszewski P, Caruthers SD, Connolly AM, Yu X, Wickline SA. Occult cardiac contractile dysfunction in dystrophin-deficient children revealed by cardiac magnetic resonance strain imaging. Circulation 2005;112:2462–2467. [PubMed: 16216964]
67. Hor KN, Wansapura J, Markham LW, Mazur W, Cripe LH, Fleck R, Benson DW, Gottliebson WM. Circumferential strain analysis identifies strata of cardiomyopathy in Duchenne muscular dystrophy: a cardiac magnetic resonance tagging study. J Am Coll Cardiol 2009;53:1204–1210. [PubMed: 19341862]
68. Hagenbuch SC, Gottliebson WM, Wansapura J, Mazur W, Fleck R, Benson DW, Hor KN. Detection of progressive cardiac dysfunction by serial evaluation of circumferential strain in patients with Duchenne muscular dystrophy. Am J Cardiol 2010;105:1451–1455. [PubMed: 20451693]
69. Simonetti OP, Raman SV. Straining to justify strain measurement. JACC Cardiovasc Imaging 2010;3:152–154. [PubMed: 20159641]
70. Hernando D, Haldar JP, Sutton BP, Ma J, Kellman P, Liang ZP. Joint estimation of water/fat images and field inhomogeneity map. Magn Reson Med 2008;59:571–580. [PubMed: 18306409]
71. Kellman P, Hernando D, Shah S, Hoyt RF Jr, Kotin RM, Keene BW, Kornegay JN, Aletras AH, Arai AE. Myocardial fibro-fatty infiltration in Duchenne muscular dystrophy canine model detected using multi-echo Dixon method of water and fat separation imaging. Proc of Int Soc for Magn Res Med 2009;17:3761.
72. Wansapura JP, Hor KN, Mazur W, Fleck R, Hagenbuch S, Benson DW, Gottliebson WM. Left ventricular T2 distribution in Duchenne muscular dystrophy. J Cardiovasc Magn Reson 2010;12:14. [PubMed: 20298602]
73. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112:e154–235. [PubMed: 16160202]
74. Rosenthal D, Chrisant MR, Edens E, Mahony L, Canter C, Colan S, Dubin A, Lamour J, Ross R, Shaddy R, Addonizio L, Beerman L, Berger S, Bernstein D, Blume E, Boucek M, Checchia P, Dipchand A, Drummond-Webb J, Fricker J, Friedman R, Hallowell S, Jaquiss R, Mital S, Pahl E, Pearce FB, Rhodes L, Rotondo K, Rusconi P, Scheel J, Pal Singh T, Towbin J. International

Society for Heart and Lung Transplantation: Practice guidelines for management of heart failure in children. J Heart Lung Transplant 2004;23:1313–1333. [PubMed: 15607659]

75. Chan AK, Sanderson JE, Wang T, Lam W, Yip G, Wang M, Lam YY, Zhang Y, Yeung L, Wu EB, Chan WW, Wong JT, So N, Yu CM. Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. J Am Coll Cardiol 2007;50:591–596. [PubMed: 17692742]
76. Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, Berard C, Vaksmann G, Weber S, Bécane H. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. Am Heart J 2007;154:596–602. [PubMed: 17719312]
77. Prystowsky EN, Pritchett EL, Roses AD, Gallagher J. The natural history of conduction system disease in myotonic muscular dystrophy as determined by serial electrophysiologic studies. Circulation 1979;60:1360–1364. [PubMed: 498462]
78. Chien KR. Stress pathways and heart failure. Cell 1999;98:555–558. [PubMed: 10490095]
79. Chien KR. Genotype, phenotype: upstairs, downstairs in the family of cardiomyopathies. J Clin Invest 2003;111:175–178. [PubMed: 12531871]

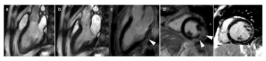

Figure 1. Proteins implicated in the muscular dystrophies

Dystrophin is located inside the cell and bound to actin at its N-terminus and to a large oligomeric complex of membrane glycoproteins at its C-terminus. This complex, referred to as the dystrophin-glycoprotein complex (DGC) consists of dystrophin, sarcoglycans (α, β, γ and δ subunits), α- and β dystroglycan, sarcospan and syntrophins. Mutations in the dystrophin gene lead to Becker and Duchenne muscular dystrophy. Mutations in the sarcoglycan subunits cause limb-girdle muscular dystrophy (LGMD). LGMD2I is a distinct form of LGMD caused by a mutation in the FKRP gene, encoding a Golgi apparatus protein. FKRP is involved in the glycosylation of α dystroglycan, necessary for its binding to laminin-α2 and the extracellular matrix.

Mutations in the genes encoding emerin and lamin A/C cause a spectrum of “nuclear envelopathies”. X-linked and autosomal dominant Emery-Dreifuss muscular dystrophy belong to this group of diseases, and are both characterized by skeletal muscle wasting, cardiac conduction defects and cardiomyopathy. Distinct LMNA gene mutations have also been associated with autosomal dominant limb-girdle muscular dystrophy (LGMD1B) and with isolated cardiomyopathy and conductive system disease (lamin A/C cardiomyopathy).

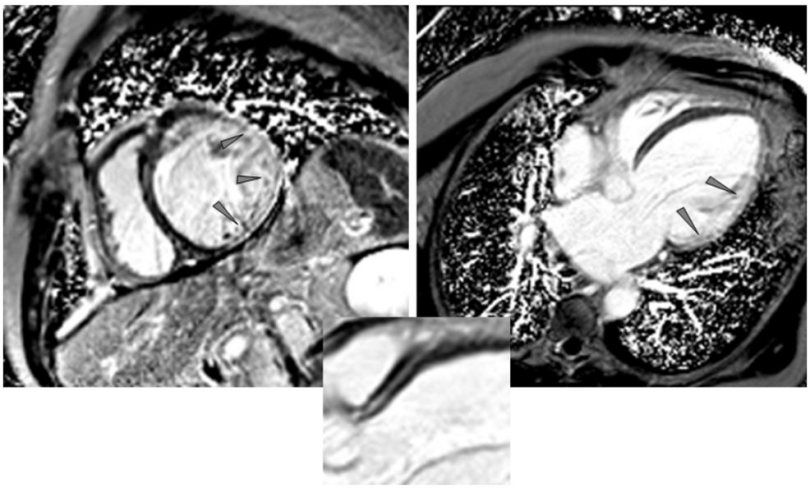

Figure 2. CMR findings in Duchenne muscular dystrophy at different stages of the disease

End-diastolic and end-systolic frames (A, B) from a three-chamber long-axis cine acquisition (Supplemental Movie I) show preserved LV systolic function in this 28 year-old male with DMD. Late gadolinium-enhancement images (C: three-chamber view, D: mid-ventricular short-axis view) in the same patient show that despite preserved global LV systolic function, myocardial injury is evident as subepicardial fibrosis of the inferolateral wall (arrowheads). E: LGE in a 14-year old boy with DMD shows more advanced cardiomyopathy with profound LV dilatation and systolic dysfunction (Supplemental Movie II), and more extensive subepicardial scarring as well as septal fibrosis in this patient (arrowheads).

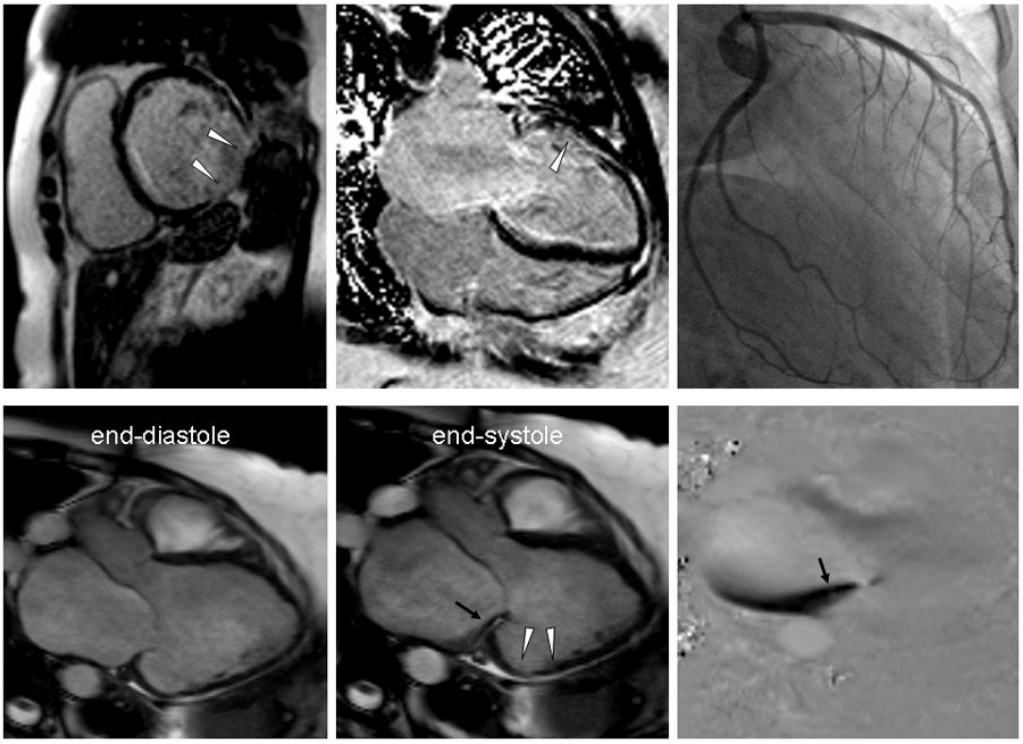

Figure 3. LGE findings in Becker MD

The pattern of myocardial injury in patients with Becker MD is similar to that seen in DMD, starting at the subendocardium of the inferolateral wall with an age-dependent increase in the extent of fibrosis and progressive decline in systolic function. The left and right upper panels (short-axis and horizontal long-axis views, respectively) show almost transmural hyperenhancement of the entire anterolateral and inferolateral walls, consistent with advanced disease. In addition, this patient had also evidence of septal midwall fibrosis (lower middle panel), also seen in myocarditis and other non-ischemic cardiomyopathies.

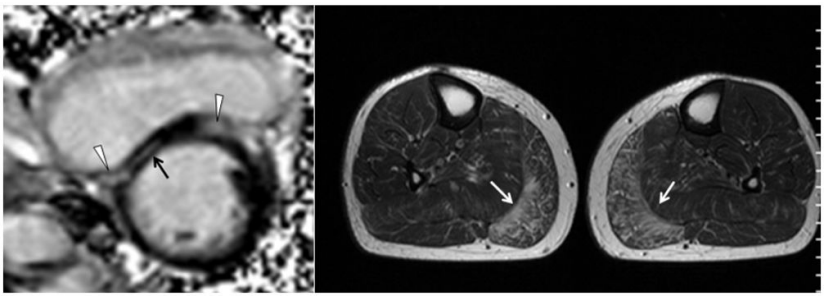

Figure 4. Cardiomyopathy in a female Duchenne carrier

Coronary angiography and CMR findings in a 58-year old female patient with Duchenne carrier status and chronic heart failure. *Upper panels*: In spite of normal findings by coronary angiography, transmural scarring of the inferolateral wall is evident by LGE (yellow arrowheads). *Lower panels*: CMR cine imaging showed severe global biventricular systolic dysfunction, with severe LV dilatation and akinesis of the inferolateral walls. Displacement of the papillary muscles due to global LV dilatation and segmental bulging of the inferolateral wall (white arrowheads) caused severe mitral regurgitation (green arrows, velocity-encoded cine image, lower right panel).

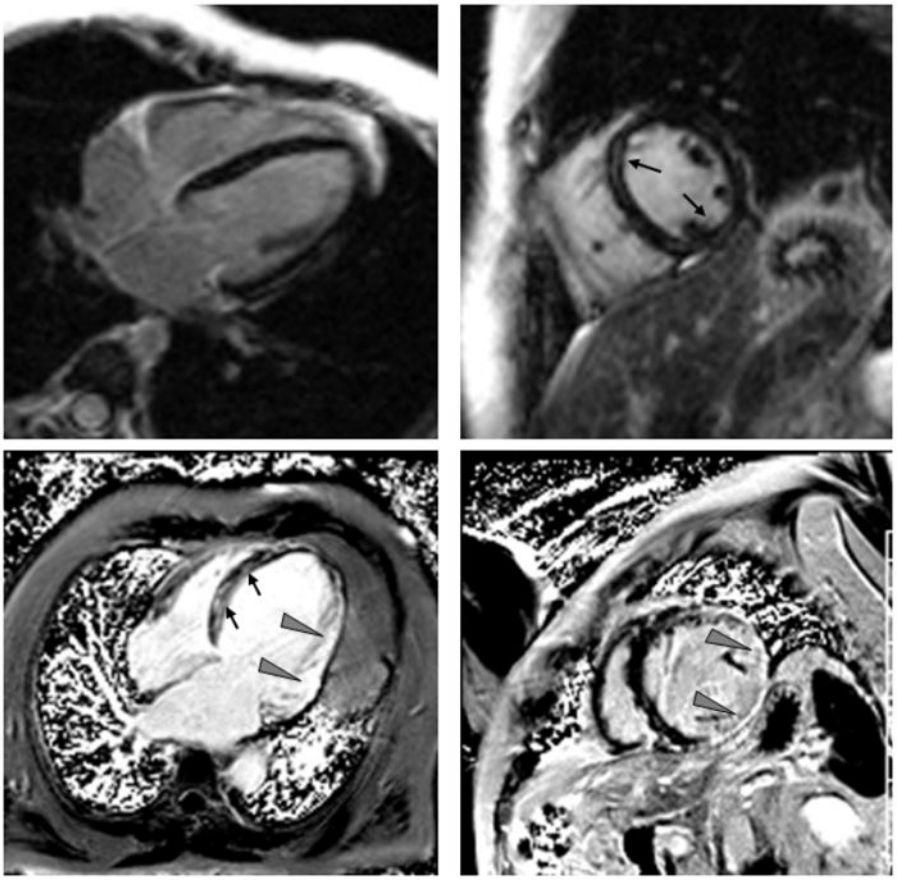

Figure 5. CMR findings in lamin A/C cardiomyopathy

Lamin A/C cardiomyopathy has been associated with midwall fibrosis of the mid-ventricular septum (left panel, red arrow) at an early stage of the disease. Note also the presence of fibrosis at the RV-LV septal insertion sites (yellow arrowheads) in this patient. Unlike patients with different types of LMNA-mutations (EMDM, LGMDB1), lamin A/C cardiomyopathy does not typically produce apparent skeletal muscle weakness. Nevertheless, muscle imaging in these patients may reveal fibrosis of the gastrocnemius muscles (right panel, arrows), suggesting a continuum in the LMNA-gene disorders between phenotypes with selective cardiac involvement and phenotypes with both cardiac and skeletal muscle abnormalities.

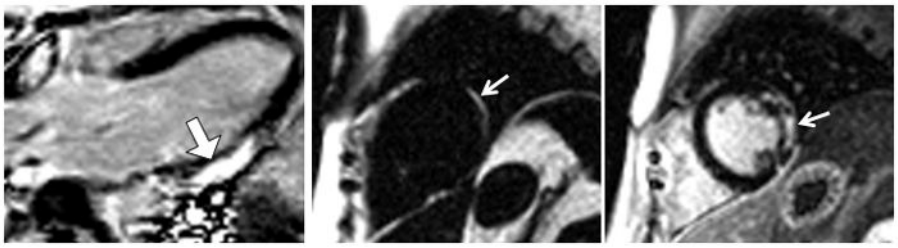

Figure 6. Late gadolinium-enhancement findings in LGMD2I

Upper panels: LGE in an 11-year old boy with FKRP mutation. Despite normal LV systolic function, midwall fibrosis of the septum and inferior wall was seen, consistent with early cardiac involvement.

Lower panels: LGE in 57-year old patient with FKRP mutation. At an advanced stage of the disease, patients with LGMD2I may develop cardiomyopathy with severe systolic dysfunction and extensive scarring of the lateral walls (yellow arrowheads). The septum is affected as well in this patient (red arrows).

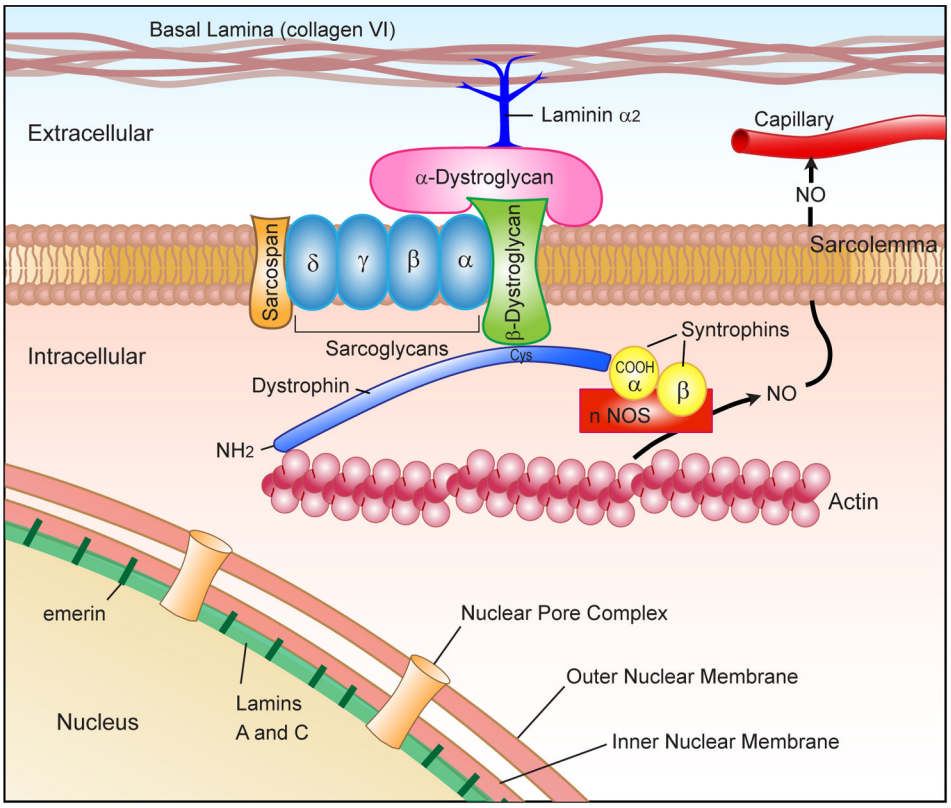

Figure 7. Fat infiltration vs. gadolinium enhancement in dystrophin-associated cardiomyopathy

Left: Late gadolinium enhancement image acquired in the three-chamber plane shows prominent enhancement of the basal inferolateral wall in a patient with Duchenne muscular dystrophy. Middle: Fat-only reconstruction using the multi-echo Dixon method of water and fat separation magnetic resonance imaging shows a thin rim of epimyocardial fat, whereas the corresponding water-only reconstruction shows more extensive hyperenhancement; together, these images suggest a combination of fibrofatty replacement of normal myocardium in this disorder.

Table

Dystrophy	Genetics	Incidence/Prevalence	Age of Onset	Clinical Features/Progression	Cardiac Complications	Recommended cardiac screening [7]
Duchenne Muscular Dystrophy (DMD)	X-linked recessive (Xp21)	incidence 1/3000 (boys)	3–7 years	Proximal skeletal muscle weakness with loss of ambulation between 7 and 13 years Respiratory failure and death in 2nd–3rd decade of life Mild cognitive impairment	DCM; symptoms often masked by severity of skeletal myopathy Ventricular arrhythmias	boys: ECG+TTE every 2 years until age 10; then once a year girls: when asymptomatic: ECG + TTE every 5 years after age 16
Becker Muscular Dystrophy (BMD)	X-linked recessive (Xp21)	prevalence 1/30,000	Teenage years	Similar distribution of muscle wasting as DMD, but more benign course Death in 4th–5th decade, usually due to cardiac complications	50–70% eventually developing DCM Ventricular arrhythmias	boys: ECG+TTE every 5 years girls: when asymptomatic: ECG+TTE after age 16
Emery- Dreifuss Muscular Dystrophy (EDMD)	X-linked recessive (Xq28 in EDMD1, Xq26 in EDMD 6) Autosomal dominant (EDMD2; LMNA gene at 1q21) Rarely autosomal recessive (EDMD3, also involving the LMNA gene at 1q21)	combined prevalence of X- linked and autosomal EDMD estimated at 1-2/100,000	bimodal distribution: (often 1st or 2nd decade, sometimes adult onset)	Onset, severity and progression of disease highly variable Disease usually starts with contractures (elbows, Achilles tendons, posterior cervical muscles, spine) Subsequent slowly progressive weakening and wasting of humeroperoneal musculature Eventually proximal limb-girdle musculature becomes affected	DCM Atrioventricular conduction abnormalities Atrial standstill, atrial flutter, atrial fibrillation Sudden death, occasionally in patients with minimal skeletal myopathy	ECG+Holter+TTE annually in affected patients Screening of family members indicated after age 10 (irrespective of symptoms) Consider need for pacemaker and/or defibrillator (particularly for EDMD2 patients with DCM) Consider need for anticoagulation in case of atrial dysfunction
Limb Girdle Muscular Dystrophy (LGMD)	Usually autosomal recessive (LGMD2C. 2D, 2E & 2F: sarcoglycanopathies; LGMD2I: mutation of fukutin-related protein gene; 19q) Rarely autosomal dominant (LGDM1; 1B due to mutation of the LMNA gene encoding lamin A/C)	unknown, usually sporadic (autosomal recessive)	variable (early childhood to adulthood)	Variable; autosomal dominant forms generally less severe. Slowly progressive weakness of shoulder and pelvic muscles; elevated serum creatine kinase	Cardiac involvement most common in LGMD1B (laminopathy) and LGMD 2E and 2I DCM; RV and LV fatty infiltration, conduction disorders In heterozygotes, cardiac dysfunction may be the only sign of disease	No formal guidelines; ECG +Holter+TTE probably indicated every 2–5 years
Myotonic Dystrophy (DM)	autosomal dominant:	prevalence 1/8,000 (DM1 + DM2)	DM1:	DM1:	-DCM	Asymptomatic patients: annual

Dystrophy	Genetics	Incidence/Prevalence	Age of Onset	Clinical Features/Progression	Cardiac Complications	Recommended cardiac screening [7]
	• type 1 (DM1, Steinert's disease): unstable expansion of CTG the myotonic dystrophy protein kinase gene (DMPK) on chromosome 19q13.3, • type 2 (DM2): CCTG tetranucleotide repeat expansion in intron 1 of the zinc finger protein 9 gene (ZNF9) on chromosome 3q21.3		• early childhood to adulthood • rarely during infancy (congenital form) DM2: -adult onset, usually 4th decade	• skeletal muscle weakness and wasting (facial, distal forearm, intrinsic hand and ankle dorsiflexors) • myotonia (slowed relaxation following muscle contraction) • muscle pain • cataracts, baldness, infertility, mental and endocrine abnormalities DM2: proximal muscle weakness (particularly hip girdle)	Left ventricular hypertrophy Conduction disturbances (atrioventricular & intraventricular) Atrial fibrillation and flutter Sudden cardiac death (most commonly DM1)	ECG, TTE+Holter every 2 years Electrophysiologic testing in case of syncope, dizziness, palpitations, documented arrhythmias or family history of sudden death or ventricular arrhythmias Consider need for pacemaker or defibrillator depending on ECG, Holter and EP findings

Abbreviations: DCM: dilated cardiomyopathy, ECG: electrocardiogram, TTE: transthoracic echocardiography, EP study: electrophysiologic study, DMD: Duchenne muscular dystrophy, BMD: Becker muscular dystrophy, EDMD: Emery-Dreifuss muscular dystrophy, LGMD: limb-girdle muscular dystrophy, DM: myotonic dystrophy.