SYSTEMIC DISORDERS IN HEART DISEASE

Cardiac involvement in muscular dystrophy: advances in diagnosis and therapy

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The term muscular dystrophy (MD) comprises various neuromuscular disorders that are characterised by progressive muscle weakness affecting certain muscle groups, which are specific for the respective genetic disorder. Muscular dystrophy type Duchenne (DMD) and type Becker (BMD) represent the most common X-linked genetic diseases: DMD is believed to affect one in 3500 male births whereas BMD is less frequent (one in 18 450 male births).[w1 w2] However, due to the longer life expectancy of BMD patients, the prevalence of DMD and BMD is rather similar and at least 2.4/100 000.[w1] Apart from progressive proximal skeletal muscle weakness and wasting, DMD and BMD are characterised by cardiac muscle involvement. Indeed, progressive cardiomyopathy has become a major cause of morbidity and mortality in these patients since progressive respiratory failure—the former number one cause of death—can be better managed due to advances in respiratory therapy today.[w3 w4] Hence, cardiologists should be familiar with the distinctiveness of cardiac pathophysiology, the challenges and state-of-the-art methods in diagnosing cardiomyopathy, and the respective therapeutic options in patients with DMD and BMD.

CLINICAL FEATURES OF DMD AND BMD

The specific clinical features of DMD and BMD in comparison to other forms of muscular dystrophy, such as limb girdle muscular dystrophy, have been described in detail previously.[1 2] Briefly, initial symptoms in DMD start in early childhood and are characterised by difficulties in running and later climbing stairs caused by progressive weakness and wasting of the proximal skeletal muscles. Ambulation is lost in most DMD patients by the age of 12 years and only a few patients survive until the third decade of life. Respiratory failure constitutes one of the main causes of mortality in DMD patients, whereas BMD patients demonstrate a later onset and a similar, although slower, progression of the disease. BMD patients may survive until the sixth decade of life and cardiomyopathy represents the number one cause of death.[3] Since MD patients suffer from progressive skeletal muscle weakness, their physical activity continuously decreases and/or is quite limited. Hence, clinical cardiac symptoms such as dyspnoea or palpitations mostly do not arise until cardiac involvement is already advanced and rather severe. Moreover, previous studies have shown that there is no correlation between the extent and severity of skeletal myopathy and the degree and onset of cardiomyopathy in MD patients.[4 w5]

DYSTROPHIN GENE AND PROTEIN FEATURES

Both DMD and BMD are caused by mutations in the dystrophin gene which is located on chromosome Xp21.1. The dystrophin protein is an essential structural member of the proteoglycan–dystrophin complex, and has both mechanical stabilising and signalling roles in mediating interactions between the cytoskeleton, the cell membrane, and the extracellular matrix (figure 1). In the case of DMD, the most common mutations are exon deletions or duplications (together in ~70% of DMD cases), whereas the remaining mutations comprise small insertions or deletions and point mutations.[w6] Although exon deletions or duplications are even more common in BMD (~85% of BMD cases), the remaining mutations are primarily point mutations or mutations affecting splicing.[w6] In 1988, Monaco *et al* postulated the 'reading-frame rule' as a possible explanation for differences in clinical phenotype between DMD and BMD patients: in DMD patients, mutations in the dystrophin gene lead to a shift in the reading frame ('out-of-frame') which in turn is associated with either a total absence of dystrophin protein expression or a truncated, dysfunctional dystrophin; whereas in BMD 'in-frame' mutations enable the expression of somewhat truncated, but still functional, dystrophin.[6] However, large database analyses have shown that approximately 90% of cases are in agreement with this rule with respect to the skeletal muscle phenotype.[w6]

CARDIAC FEATURES OF DMD AND BMD

ECG

In the 1960s and '70s, when imaging modalities such as echocardiography and cardiovascular magnetic resonance were not available, ECG recordings attracted great interest, and their correlation to postmortem histopathological findings revealed interesting insights into the distinct features of cardiomyopathy in DMD and BMD patients. Typical ECG abnormalities for both DMD and BMD comprise an R:S ratio ≥1 in lead V1, deep

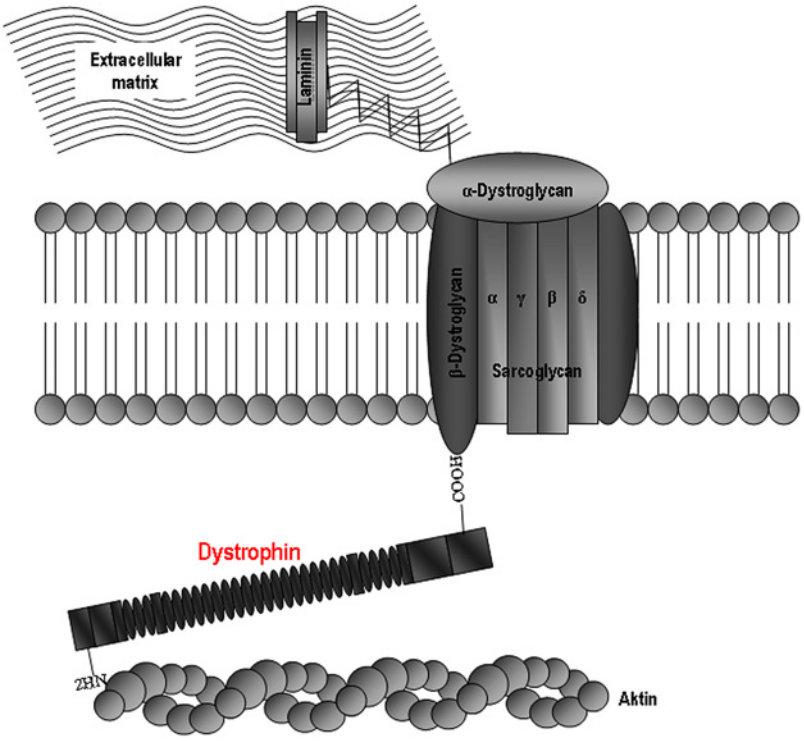

Figure 1 Diagram showing the constitution of a cardiomyocyte cell membrane and demonstrating the connection between intramembraneous sarcoglycan complex and the intracellular dystrophin complex. Reproduced with permission from Yilmaz *et al*.[5]

Q waves in leads I, aVL, V5–V6, sinus tachycardia, right axis deviation or a complete right bundle branch block.[7 8] Postmortem histopathology revealed a distinct pattern of myocardial damage, starting from the epicardial third of the infero-lateral wall with possible extension in contiguous segments (figure 2).[7–9] Hence, the aforementioned typical ECG findings are believed to reflect a reduction in electromotive forces in the posterobasal and contiguous lateral wall.[7 11] Surprisingly, in a former study comprising 84 DMD patients and a median follow-up of 76 months with a high mortality rate of 27% in the follow-up period, ECG abnormalities and ventricular arrhythmias (during Holter monitoring) did not have any prognostic value regarding prediction of mortality.[12] In contrast, in a recent study ECG abnormalities preceded cardiac dysfunction and the presence of ventricular tachycardia (during Holter monitoring) was associated with a poor outcome.[13]

Echocardiography

The first comprehensive echocardiographic studies in MD patients were based on two dimensional echocardiography and revealed progressive left ventricular (LV) expansion and impaired systolic function, with a rapid and lethal development in some cases (within 4 years).[w7 w8] Wall motion abnormalities were predominantly described in posterior and lateral wall segments, confirming previous ex vivo findings and clearly suggesting that myopathic changes in the myocardium cause regional wall motion abnormalities and LV dilation, which in turn may result in heart failure and cardiac death (figure 3 and movie 1A,B).[w7 w8] Moreover, echocardiographic evaluation of LV diastolic function demonstrated the presence of impaired diastolic function even in MD patients with normal systolic function.[w9 14] Therefore, evaluation of diastolic function is recommended, since it may reveal initial stages of cardiomyopathy in MD patients before the occurrence of systolic dysfunction.

In addition, advanced echocardiographic techniques such as myocardial velocity and deformation imaging were applied in MD patients with normal systolic function and showed significant reductions in radial and longitudinal peak systolic strain, and

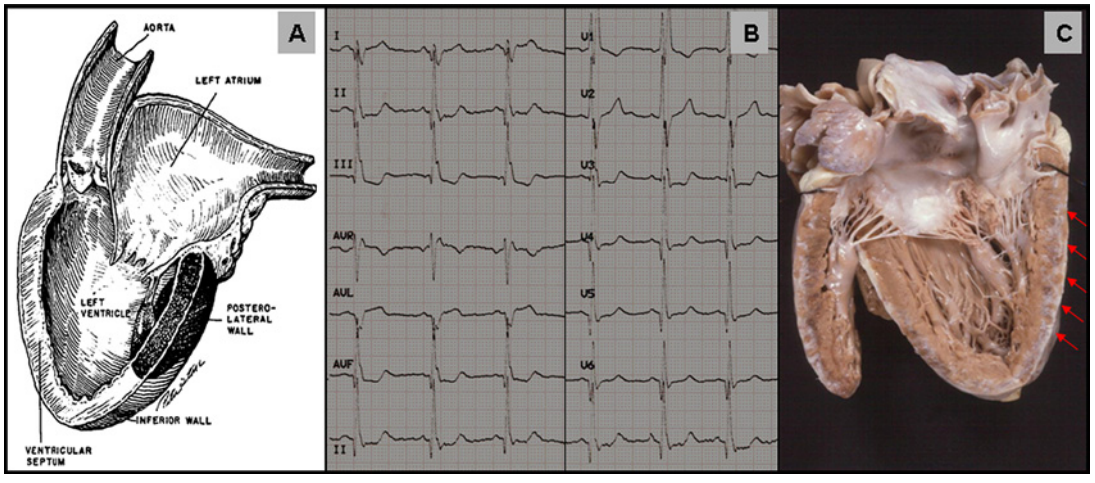

Figure 2 (A) Diagram of the left side of the heart illustrating the distribution of the fibrous scarring in Duchenne muscular dystrophy (DMD) patient drawn by Joseph K Perloff in 1967. Reproduced with permission from Perloff *et al*.[7] (B) Typical resting ECG of a muscular dystrophy patient demonstrating R:S ratio ≥1 in lead V1, deep Q waves in leads I, aVL, V4–V6, and a complete right bundle branch block. (C) Exemplary macroscopic image of the heart of a patient with DMD. Extensive fibrous tissue replacement (red arrows) is typically confined to the outer-mid subepicardial layer of the left ventricular free wall. Reproduced with permission from Yilmaz *et al*.[10]

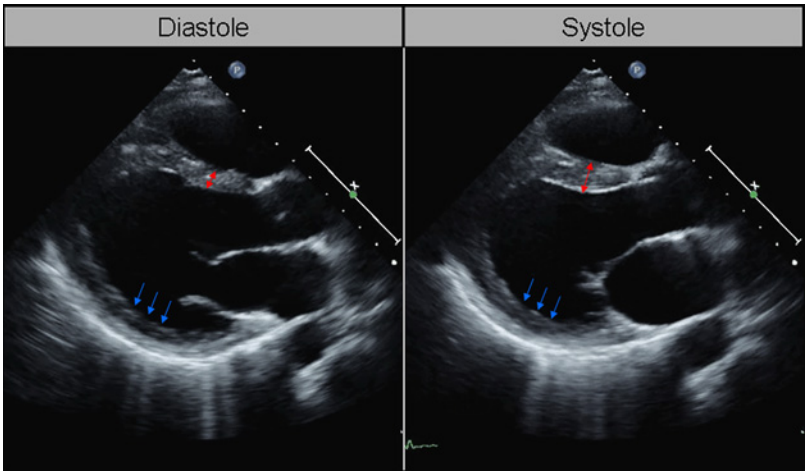

Figure 3 Two dimensional echocardiography images of a Becker muscular dystrophy (BMD) patient in the parasternal long axis in diastole (left) and systole (right). While normal systolic thickening is observed in the anteroseptal wall (red arrows), typical impaired systolic thickening is seen in the inferolateral segments (blue arrows).

decreased early diastolic myocardial velocities in the lateral LV wall segments (figure 4 and movie 1E).[15] Hence, more detailed echocardiographic work-up of these patients may reveal subtle or severe cardiac abnormalities suggestive of cardiac involvement, even at early disease stages. Moreover, unlike ECG abnormalities, the echocardiographic finding of LV systolic dysfunction was shown to provide adverse prognostic information in DMD patients.[12]

Nevertheless, since the majority of MD patients becomes wheelchair bound and develops thoracic scoliosis and/or kyphosis, successful echocardiographic studies may be challenging due to a poor acoustic window and limitations in patient positioning.

Cardiovascular magnetic resonance imaging

In recent years, cardiovascular magnetic resonance imaging (CMR) has gained wide acceptance for non-invasive evaluation of ischaemic as well as non-ischaemic cardiomyopathies. In particular, multi-parametric CMR enables the assessment of functional as well as morphological parameters in a single session without any radiation burden and independent of the acoustic window (movie 1C,D and movie 2A–C).

The first prospective CMR study on patients with MD was performed by Ashford *et al*.[16] In this study, DMD patients underwent routine cine-imaging and CMR tagging which enabled accurate and rapid measurement of regional transmural myocardial deformation over the entire cardiac cycle (figure 5). Despite normal LV volumes and systolic function, reduced midventricular and basal cross-sectional global circumferential strain was documented. Consequently, the authors concluded that occult regional cardiac dysfunction may be diagnosed with CMR tagging before the development of global systolic dysfunction, which is in line with the aforementioned echocardiographic data.

Today, contrast enhanced CMR (ceCMR) is widely used for non-invasive evaluation of morphological abnormalities in the myocardium. Silva *et al* were the first to publish their findings on the use of ceCMR (in addition to functional cine-imaging) in MD, primarily in DMD patients.[17] Presence of late gadolinium enhancement (LGE), which is indicative of myocardial damage, was found in seven out of 10 patients, and the free LV lateral wall was most commonly involved. Another study involving 15 patients with BMD showed that cardiac involvement in terms of myocardial damage predominantly begins at the subepicardium of the inferolateral wall in the third decade of life, with an age dependent increase in its extent (figure 6A–C).[10] Moreover, there was a substantial agreement between the presence of myocardial damage and regional wall motion abnormalities, suggesting that a progressive reduction in LV ejection fraction is primarily due to the extent of myocardial damage. In addition, these study results indicated that cardiac evaluation based on CMR is more sensitive in detecting pathological findings compared to ECG and conventional echocardiography, respectively.

Hor *et al* were the first to compare ceCMR and CMR tagging results in the same MD patients.[w10] Myocardial peak circumferential strain (PCS) was

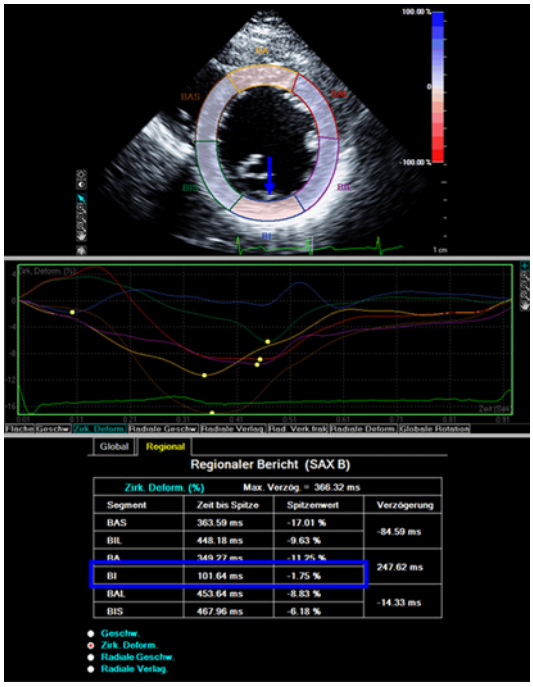

Figure 4 A three-beat cine loop selected from a two dimensional parasternal short-axis echocardiographic view using high frame rate harmonic imaging (iE33, Philips system). Endocardial and epicardial contours were manually traced with avoidance of papillary muscles and trabeculations (upper image). After definition of six in-slice segments, the peak circumferential strain was analysed for each segment using a two dimensional speckle tracking software (middle image; TMQ, QLab software, Philips systems). The calculated percentage values of peak circumferential strain for the respective segments are shown in the lower image. The inferolateral wall segment (indicated by the abbreviation BI and contoured in blue colour; marked by a blue arrow) demonstrated the lowest peak circumferential strain.

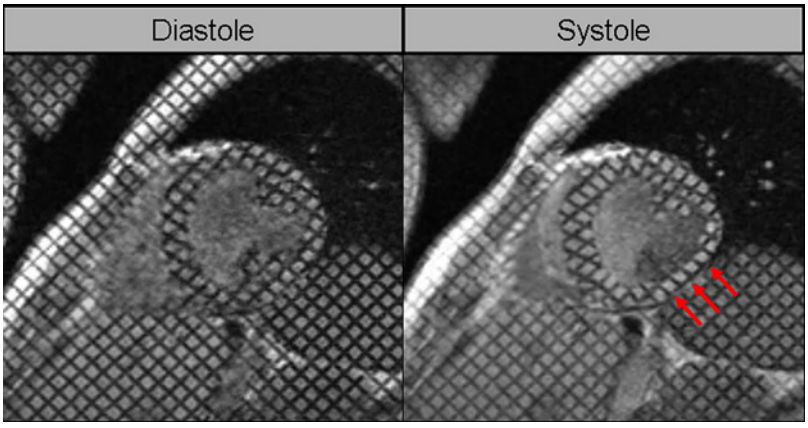

Figure 5 Short axis cine tagged images of a Becker muscular dystrophy (BMD) patient in diastole (left) and systole (right). Absence of tag deformation indicating impaired circumferential strain was observed in the left ventricular inferolateral wall segments (red arrows).

reduced even in young DMD patients aged <10 years compared to healthy controls. A further decrease in myocardial PCS was observed in older DMD patients and in those with reduced LV systolic function. The most severe reduction in myocardial PCS was found in those patients with both impaired LV systolic function and LGE. Moreover, in a subsequent study the same authors suggested that serial measurements of myocardial PCS may provide a highly accurate tool in order to monitor cardiac disease progression in DMD patients, since changes in myocardial PCS were observed in a relatively short period of time while systolic function remained unchanged.[w11]

Taken together, multi-parametric CMR enables the detection of even subtle functional as well as morphological abnormalities in patients with MD, and in principle seems to be ideally suited for both accurate evaluation of cardiac disease progression and therapy monitoring based on serial studies. However, the prognostic value of CMR data in patients with MD still needs to be evaluated.

EXTENT AND TIMING OF CARDIAC STUDIES

In previous reports, cardiac evaluations in DMD patients—comprising ECG and echocardiography—were recommended at diagnosis and every 2 years to age 10, and annually after age 10.[18] Based on our

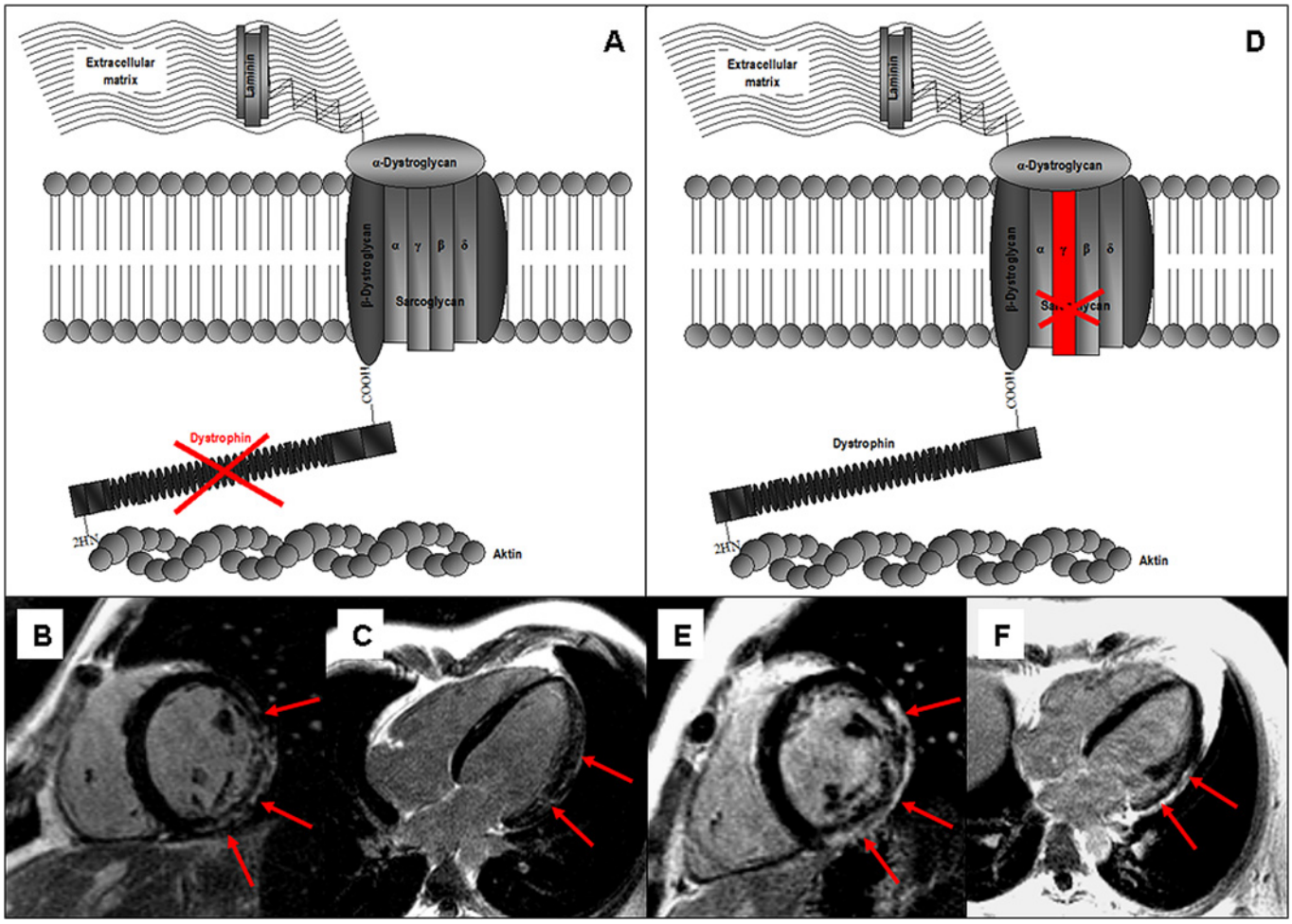

Figure 6 (A and D) Diagrams showing the constitution of a cardiomyocyte cell membrane and demonstrating the connection between intramembraneous sarcoglycan complex and the intracellular dystrophin complex in a case of a dystrophinopathy (A) and sarcoglycanopathy (D). (B, C and E, F) Short and long axis cardiac magnetic resonance contrast images of a patient with Becker muscular dystrophy (BMD) (B and C) and γ-sarcoglycanopathy (LGMD-2C), each showing late gadolinium enhancement in the inferolateral wall (red arrows). Reproduced with permission from Yilmaz *et al*.[5]

experience in serial examinations in more than 100 patients with DMD or BMD, such intervals are sufficient to capture major changes in LV ejection fraction over the course of the disease. However, if possible, based on the age, body weight and physical status of the patient, we would recommend an additional CMR study including cine-CMR, CMR tagging and ceCMR, since CMR enables an earlier and more accurate and detailed diagnosis of cardiac abnormalities. However, performance of CMR studies (in particular of ceCMR) in patients aged <6 years and/or with a body weight of <20 kg may be quite challenging due to limited patient cooperation and severe motion, as well as partial volume artefacts and subsequent difficulties in image interpretation. Since early detection of cardiomyopathy and timely initiation of heart failure therapy may improve LV systolic function or at least retard progressive cardiac dysfunction in MD patients,[19 w12] follow-up CMR studies enabling early diagnosis of cardiomyopathy and/or accurate therapy monitoring should be scheduled, depending on previous CMR findings.

In the case of BMD patients, previous reports suggested cardiac evaluations—comprising ECG and echocardiography—at diagnosis and thereafter at least every 5 years in the case of normal findings.[18] Considering recent diagnostic and therapeutic data in MD patients, we would recommend cardiac evaluations in BMD patients without cardiomyopathy also beginning with a comprehensive CMR study at diagnosis, and schedule follow-up examinations depending on the initial findings, but at least every second year even in the case of normal findings.

Moreover, since female carriers of MD are also prone to cardiomyopathy,[w13] cardiac examinations are recommended at diagnosis and at least every 5 years thereafter or even more frequently in patients with pathological findings. As shown recently, CMR is a well-suited tool to diagnose and identify the pattern of cardiomyopathy in female carriers of MD.[20] However, more experience in this group of patients regarding CMR based therapy implementation as well as monitoring will be necessary to substantiate this recommendation.

UNDERLYING PATHOPHYSIOLOGY OF CARDIAC INVOLVEMENT IN MD

As previously discussed, the detailed molecular pathomechanism leading to cardiac contractile dysfunction in MD patients is still not known, although the underlying genetic dystrophin defect can be identified easily by appropriate mutation screening.[10] Early alterations in cell metabolism and signal transduction associated with a defect in the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway were suggested based on preclinical studies in dystrophin deficient animal models.[21] Moreover, excessive intracellular calcium signalling and reactive oxygen species (ROS) generation with breakdown of the mitochondrial membrane potential were described in in vitro studies and may constitute the link between the initial sarcolemmal injury due to dystrophin deficiency and mitochondrial dysfunctions.[w14] In addition, Yasuda *et al*[w15] demonstrated that even intact dystrophin deficient cardiomyocytes have reduced compliance and increased susceptibility to stretch mediated calcium overload, which in turn lead to cardiomyocyte contracture and cell death. Hence, the fragility of the cell membrane caused by deficient sarcolemmal dystrophin may predispose cardiomyocytes to metabolic dysfunctions, which in turn may be enhanced by an excessive susceptibility to mechanical stress. However, nuclear imaging studies in MD patients documented changes in regional myocardial metabolism at early disease stages, when regional wall motion abnormalities or myocardial fibrosis were still absent.[11]

When patients with DMD are studied by positron emission tomography (PET) ^{18}F-2FDG (in order to study regional myocardial metabolism) and PET ^{13}N-NH3 (in order to evaluate regional myocardial perfusion),[11] most DMD patients demonstrate a regionally 'increased' ^{18}F-2FDG activity in the posterolateral wall segments suggestive of an increased regional glucose utilisation. However, ^{13}N-NH3 activity is 'decreased' in 87% of these DMD patients in the same posterolateral wall segments, suggesting either a regionally reduced myocardial blood flow and/or regional metabolic alterations in the uptake of ^{13}N-NH3. Based on these results, Perloff *et al* reasonably concluded that DMD patients demonstrate myocardial metabolic abnormalities in the posterolateral wall segments[11] reminiscent of the findings of viable myocardium seen in coronary artery disease (CAD) patients. Concordant to these findings of a substrate reminiscent of viable myocardium in CAD patients, Nishimura *et al*[w16] found a rest-redistribution pattern in ^{201}Tl-SPECT studies in seven DMD patients who died at a later date and in whom histopathological heart muscle analyses were available at autopsy. Both severe but scattered myocardial fibrosis and myocardial fatty infiltration was histopathologically documented in—but not limited to—the posterolateral wall segments (figure 7).

Finally, there are new interesting data on this issue that were presented at the American Heart Association congress.[w17] Suttie *et al* performed ^{31}P and ^{1}H magnetic resonance spectroscopy (MRS) on a 3T MR scanner in DMD and BMD patients. Even in patients with normal LV ejection fraction, abnormal energetics (decreased PCr/ATP ratio based on ^{31}P-MRS) and presence of myocardial lipidosis (based on ^{1}H-MRS) were detected. Hence, the authors suggested that impaired fat utilisation may play a central role in the development of cardiomyopathy in MD patients. This interesting issue is further illustrated in figure 8. Based on T1 weighted spin echo CMR images 'with' and 'without' fat suppression techniques, the regionally accentuated presence of myocardial fatty infiltration in the inferolateral wall segments in MD patients is highlighted.

Taken together, the underlying genetic dystrophin defect may cause (global or regional)

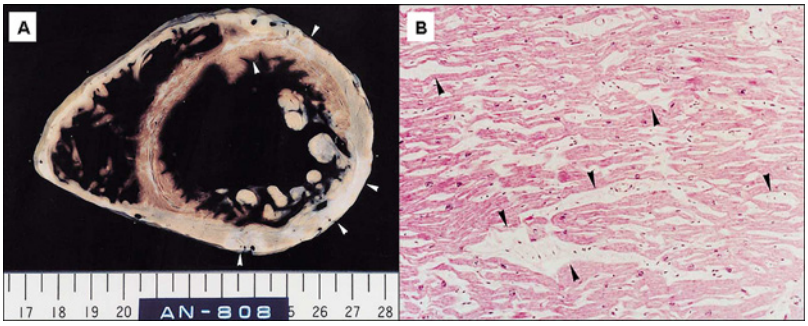

Figure 7 Macroscopic and microscopic findings from a Duchenne muscular dystrophy (DMD) patient. In panel A, myocardial fibrosis is seen in the anterior, lateral, and posterior walls of the left ventricle (white arrows). In panel B, a microscopic image of the lateral wall is seen. Slight interstitial fibrosis and intermuscular oedema (arrows), thinning of myofibrils, and eosinophilic degeneration are observed. Adapted with permission from Nishimura *et al*.[w16]

metabolic and structural abnormalities in the myocardium, which predispose to morphological changes comprising early cardiomyocyte cell death and replacement fibrosis. These morphological changes seem to begin in the posterolateral wall potentially aggravated by additional mechanical stress, but may involve other myocardial regions at a later stage. Early diagnosis is now possible using modern imaging modalities.

Theoretically, one would expect a rather diffuse and random distribution of deficient dystrophin throughout the whole myocardium. Unfortunately, histopathological data addressing the myocardial distribution of dystrophin deficiency in MD patients with early stages of cardiomyopathy are scarce. Numerous former studies have evaluated the distribution of myocardial scarring and fibrosis—but not the distribution in dystrophin expression—and consistently demonstrated that the posterolateral wall segments represent the most extensive sites of myocardial fibrosis.[8 9] In one smaller study, the distribution of myocardial dystrophin expression was assessed in four BMD patients and a variable distribution with continuous, discontinuous or absent immunostaining patterns was documented.[w18] Hence, we believe that cardiomyopathy in MD patients is a diffuse (genetically determined) disease process with ubiquitous or randomly distributed alterations in cell metabolism and signal transduction. These alterations precede functional impairment and lead to myocardial damage preferentially—but not only—in the posterolateral wall due to exaggerated mechanical stress in this region. This notion is further supported by recent findings demonstrating a similar pattern of myocardial damage in patients with different missing or deficient components of the proteoglycan-dystrophin complex (figure 6D–F).[5 22]

GENOTYPE AND PHENOTYPE CORRELATIONS

In several previous studies an association between the underlying dystrophin gene mutation and the clinical phenotype (regarding skeletal muscle status) was suggested. In one study, the relationship between dystrophin protein structure and function was evaluated in comparison to the domain of mutation in BMD patients.[w19] Deletions effecting the amino-terminal domain (which binds to the actin filaments) of the dystrophin protein were associated with a more severe phenotype, while mutations in the central rod domain resulted in more variable phenotypes (figure 9) suggesting that—apart from the gene defect itself—epigenetic and environmental factors essentially determine the clinical phenotype. In another study, BMD patients with mutations involving exon 9 (amino-terminal domain) of the dystrophin gene demonstrated a worse clinical phenotype with an earlier onset of myopathy and a faster progression rate.[w20]

Regarding the cardiac phenotype, in the 1990s Nigro *et al* described a higher frequency of cardiac involvement in MD patients with deletion mutations involving exons 48-49 of the dystrophin gene with a concurrent earlier onset of cardiomyopathy.[w5] However, other studies could not confirm these results.[4] A decade later, Jefferies *et al* described a potential association between the underlying dystrophin gene defect and the occurrence of cardiomyopathy in MD patients.[19] They studied 62

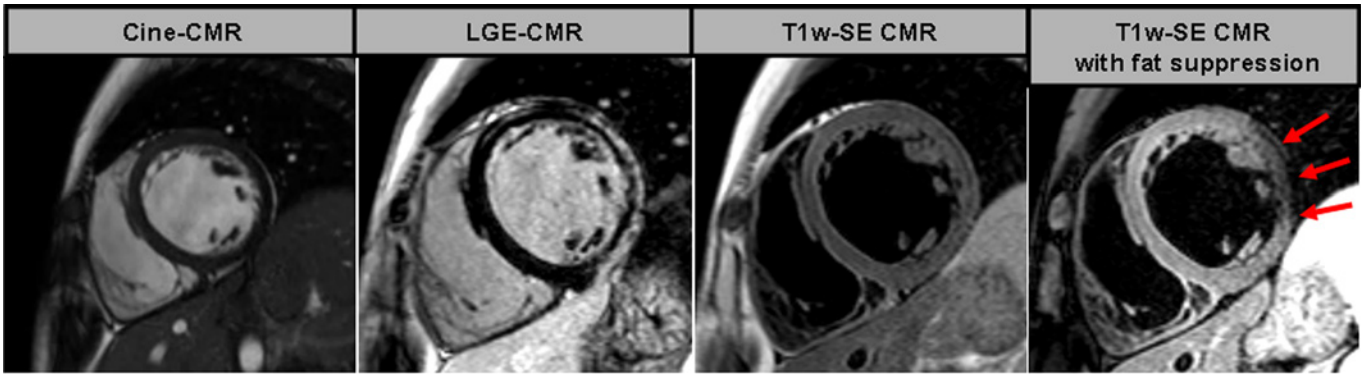

Figure 8 Cine, late gadolinium enhancement (LGE), and T1 weighted spin echo cardiac magnetic resonance (CMR) images 'without' and 'with' fat suppression techniques of a patient with Becker muscular dystrophy (BMD) and advanced cardiomyopathy. Fatty infiltration (red arrows) in the lateral wall segments of the myocardium was documented by comparison of T1 weighted spin echo CMR images 'without' and 'with' fat suppression. Moreover, the area of myocardial fatty infiltration corresponds to the area of positive LGE.

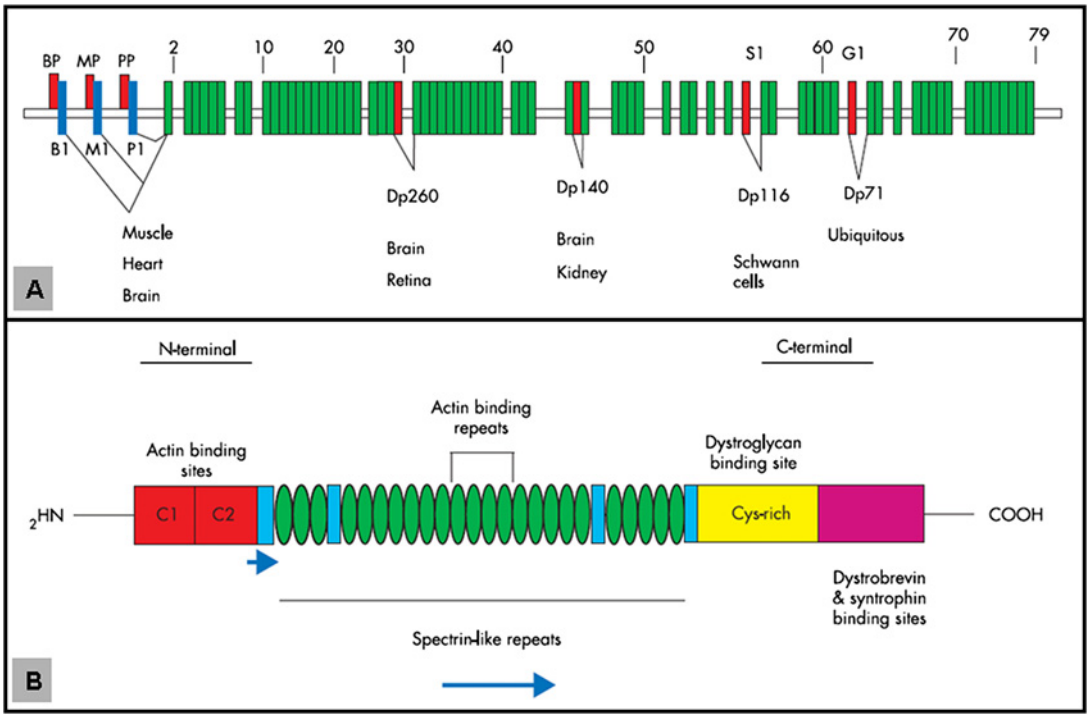

Figure 9 (A) Physical map of the dystrophin gene. Green boxes indicate exons, blue boxes indicate exons specific for each promoter (B1, first brain exon; M1, first muscle exon; P1, first Purkinje exon), and red boxes indicate promoters (BP, brain promoter; G1, general type promoter; MP, muscle promoter; PP, Purkinje promoter; S1, Schwann cell promoter). (B) Domains of the dystrophin protein. The N-terminus contains the primary actin binding sites, whereas the C-terminus contains the β-dystroglycan, dystrobrevin, and syntrophin binding sites. The N- and C-terminal domains are connected by 24 spectrin-like repeats, some of which have been shown to bind actin. The four 'hinge' regions are shown as blue boxes. The blue horizontal arrows indicate regions of the gene that have been suggested to have a role in the function and interaction of dystrophin in the heart. Both images reproduced with permission from Cohen *et al*.[w27]

boys with DMD and seven with BMD and found: (1) an association between mutations involving exons 12 and 14 to 17 and onset of dilated cardiomyopathy; (2) a trend towards a significant association between mutations involving exons 31 to 42 and heart disease; and (3) a decreased risk of cardiac involvement in case of mutations involving exons 51 or 52. However, this study suffered from severe statistical limitations.

More recently, Kaspar *et al* elegantly demonstrated: (1) that the locus of dystrophin gene mutation is associated with the time of onset (early vs late) of cardiomyopathy, indicating that deletions affecting the amino-terminal domain of the dystrophin protein are associated with early onset dilated cardiomyopathy in BMD patients; and (2) that genetic dystrophin mutations which result in the disruption of spectrin repeat phasing (located in the rod domain of the dystrophin protein) lead also to early onset of cardiomyopathy—despite the absence of any differences in myocardial dystrophin expression compared to those with dystrophin mutations without spectrin repeat phasing disruption.[23] Hence, this study demonstrates the importance of integrating protein structure information in genotype–phenotype correlation studies.

Taken together, the underlying dystrophin gene mutation seems to be associated with the time of onset and potentially the severity and progression rate of cardiomyopathy in MD patients. Therefore, genetic findings have to be taken into consideration regarding optimal timing and aggressiveness of treatment.

THERAPEUTIC OPTIONS FOR THE TREATMENT OF CARDIOMYOPATHY IN MUSCULAR DYSTROPHY

Since cardiomyopathy in patients with MD is caused by a genetically determined dystrophin deficiency, therapeutic options for treatment of this cardiomyopathy are unfortunately still quite limited. The majority of MD patients continues to be asymptomatic in spite of advanced cardiomyopathy due to limited physical activity. The first clinical symptoms consist of dyspnoea and palpitations (primarily on exercise/efforts) due to the reduced systolic LV function and often tachyarrhythmias.

Previous studies have shown that timely onset of heart failure treatment, including ACE inhibitors, ß-blockers and diuretics, may result in beneficial ventricular remodelling with improvement in LV systolic function or at least in retardation of progressive cardiac dysfunction.[19 w12] In particular, one study suggested that early treatment with an ACE inhibitor in DMD patients aged 9 years and older may have beneficial effects when therapy is implemented even before LV dysfunction occurs.[24] This observation may be explained and is supported

Cardiac involvement in muscular dystrophy: key points

- Muscular dystrophy type Duchenne (DMD) and type Becker (BMD) represent the most common X-linked genetic diseases.
- Differences in the clinical phenotype between DMD and BMD patients may be explained in ~90% of cases by the 'reading-frame rule' (out-of-frame vs in-frame mutation).
- Progressive cardiomyopathy has become a major cause of morbidity and mortality in these patients.
- Cardiac involvement is characterised by a distinct pattern of myocardial damage starting from the epicardial third of the inferolateral wall, with possible extension in contiguous segments, and may result in dilated cardiomyopathy or sudden cardiac death.
- Due to their limited physical activity, clinical cardiac symptoms such as dyspnoea or palpitations do not usually arise until cardiac involvement is already advanced and rather severe.
- Typical ECG abnormalities comprise an R:S ratio ≥1 in lead V1, deep Q waves in leads I, aVL, V5—V6, sinus tachycardia, right axis deviation or a complete right bundle branch block.
- Echocardiography using myocardial velocity and deformation imaging may reveal subtle cardiac abnormalities suggestive of cardiac involvement at early disease stages and may provide important prognostic information.
- Multi-parametric CMR enables the detection of both subtle functional as well as morphological abnormalities in patients with MD, and may thus be ideally suited for both accurate evaluation of cardiac disease progression and therapy monitoring.
- Heart failure treatment comprising ACE inhibitors, ß-blockers, and diuretics may result in beneficial ventricular remodelling with improvement in left ventricular systolic function.
- Medical treatment with steroids, cardiac resynchronisation, ICD implantation, and cardiac transplantation should be considered in those patients with rapidly worsening cardiac function.

by recent CMR results which demonstrated that myocardial fibrosis and/or impaired myocardial deformation may be present before the reduction of LV systolic function.[10 w10] Accordingly, recently published American College of Cardiology/American Heart Association guidelines on the diagnosis and treatment of heart failure suggest that heart failure treatment should principally be begun even in the absence of clinical symptoms if there is evidence of structural abnormalities and reduced LV function.[w21]

Treatment with steroids has been shown to prolong ambulation and improve respiratory muscle strength in MD patients. In a large retrospective study, Markham *et al* evaluated the effect of steroid treatment with respect to cardiomyopathy in DMD patients[w22] and demonstrated that steroid treatment prevents or at least retards progressive cardiac dysfunction. Moreover, these authors showed that the effect of steroid treatment is sustained beyond the duration of treatment. More recently, Mavrogeni *et al* compared CMR based functional values in DMD patients with and without deflazacort treatment and showed that treatment with deflazacort resulted in improved LV systolic function.[w23] Hence, medical treatment with steroids should be considered in those patients with rapidly worsening cardiac function, and implemented with close clinical monitoring for side effects.

Cardiac resynchronisation therapy (CRT) is a relatively new additional treatment option. However, this rather invasive therapeutic approach is limited to patients with: (1) ongoing dyspnoea (New York Heart Association functional class III–IV) despite optimal medical treatment; (2) a severely reduced LV ejection fraction; and (3) an intraventricular excitation delay (QRS ≥120 ms) preferably with a left bundle branch block. Although CRT implantation in MD patients with advanced myopathy may be technically challenging and the data in this specific subgroup of patients are limited, this therapeutic alternative should be offered to those MD patients fulfilling the aforementioned criteria. Moreover, an implantable cardioverter-defibrillator (ICD) should be considered, particularly in those patients with documented ventricular arrhythmias.

Heart transplantation is an important treatment option in selected MD patients with advanced and therapy resistant cardiomyopathy. As demonstrated recently, the clinical outcomes after heart transplantation (regarding survival, infection, rejection, and transplant vasculopathy rates) seem to be similar between MD and non-MD patients with non-ischaemic cardiomyopathy.[25] Wu *et al* performed a comprehensive retrospective review comprising 29 transplant centres in the USA over the period from 1990 to 2005.[25] They identified 29 transplanted patients with MD and compared the post-cardiac transplant outcome with 275 non-MD patients with non-ischaemic cardiomyopathy who were matched for age, body mass index, race, and sex. Interestingly, the clinical outcomes in patients with MD were similar to those age matched non-MD patients with non-ischaemic cardiomyopathy. Hence, at least a rapid recurrence of cardiomyopathy (affecting predominantly the posterolateral wall segments) seems to be unlikely in post-cardiac transplant MD patients.

Finally, some new experimental approaches are noteworthy. Exon skipping based on antisense oligonucleotide therapy aims at restoring the reading frame in DMD patients (with exon deletions) by removing specific exons from the altered dystrophin transcript, thereby enabling the expression of a shortened but functional dystrophin protein. Previous studies in animal models of MD showed promising results at least with respect to improvement of skeletal myopathy. Whether cardiomyopathy will also benefit from exon skipping is still under investigation.[26] Another promising approach is the use of viral vectors with incorporated cDNA of micro- or mini-dystrophin. Successful gene transfer and subsequent in vivo micro-dystrophin expression was demonstrated in animal models and resulted in improved cardiac function and histopathology.[w24] Sildenafil has been shown to have positive effects on the heart of dystrophin deficient mdx mice that develop cardiomyopathy comparable to BMD patients.[w25 w26] The ability of dystrophin deficient mice hearts to resist

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sarcolemmal damage induced in vivo by increasing the cardiac workload acutely (with isoproterenol) was enhanced by inhibiting cGMP breakdown using sildenafil. Hence, enhancing cGMP signalling using sildenafil may improve contractile performance, myocardial metabolic status, and sarcolemmal integrity. Since sildenafil is already approved for clinical use, appropriate clinical trials with MD patients for the treatment of cardiomyopathy are expected.

CONCLUSIONS

Cardiac involvement is prevalent in patients with DMD and BMD, and may also occur in female carriers of MD. Cardiomyopathy in MD is characterised by metabolic and structural abnormalities which predispose the myocardium to morphological changes resulting in cardiomyocyte cell death and replacement fibrosis. Cardiac involvement is characterised by a distinct pattern of myocardial damage starting from the epicardial third of the inferolateral wall, with possible extension in contiguous segments, and may result in dilative cardiomyopathy or sudden cardiac death. Although ECG and conventional echocardiography may also reveal signs of cardiomyopathy with potential prognostic value, more sophisticated techniques such as myocardial velocity and deformation imaging by echocardiography or multi-parametric CMR enable the diagnosis to be made more early and reveal more subtle cardiac abnormalities. In particular, ceCMR and CMR tagging are optimally suited to detect even minor foci of myocardial fibrosis and mild wall motion abnormalities, respectively. Since timely onset of heart failure therapy may result in beneficial ventricular remodelling, optimised imaging techniques enabling diagnosis of early cardiac abnormalities may be of essential clinical and prognostic value. Moreover, in consideration of new treatment options for cardiomyopathy that are currently under investigation, multi-parametric CMR may become an important tool for disease surveillance and appropriate therapy monitoring.

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