Care of the Heart in Duchenne Muscular Dystrophy

Parent Project Muscular Dystrophy’s End Duchenne Tour
March 24, 2018
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Chicago, IL

#PPMDConnect
Why the Heart is important in Duchenne Muscular Dystrophy

- Significant advances in respiratory care are unmasking cardiomyopathy as a leading cause of death in DMD.

- The incidence of cardiomyopathy increases with age:
  - 25% of patients with DMD affected by cardiomyopathy by 6 years of age
  - 59% affected between the ages of 6 and 10 years.
  - By adulthood, 100% of patients have cardiac involvement

- Early detection is important because institution of cardio-protective medical therapies may slow adverse cardiac remodeling and attenuate heart failure symptoms in these patients

Dystrophin-Deficient Cardiomyopathy
*Journal of the American College of Cardiology*, Volume 67, Issue 21, Pages 2533-2546
Forum Kamdar, Daniel J. Garry
What is Cardiomyopathy?

Normal Heart:
- Left Venticles
- Right Venticles
- Chambers relax and fill, then contract and pump.

Heart with Dilated Cardiomyopathy:
- Muscle fibers have stretched.
- Heart chambers enlarge.
Objectives

• Review Dystrophinopathies
• Review Pathophysiology of Cardiomyopathy in Duchenne Muscular Dystrophy
• Discuss Diagnosis of Cardiomyopathy
• Discuss Treatment Strategies
Dystrophinopathies

- The first historical account of muscular dystrophy appeared in 1830, when Sir Charles Bell wrote an essay about an illness that caused progressive weakness in boys.

- Duchenne’s muscular dystrophy (DMD) is named after the French neurologist Guillaume Benjamin Amand Duchenne (1806–1875), who first described the disease in 1861.

- In 1986, MDA-supported researchers identified the gene that causes DMD.

- In 1987, the protein associated with this gene was identified and named dystrophin.
What is the Dystrophin Gene?

- There are 79 exons: which makeup 0.6% of the entire gene.
- There are 8 promoters (binding sites).
- Introns: make up 99.4% of the entire gene.
- Genomic DNA: 2.2 million base pairs.
- N-terminal or actin binding sight: binds dystrophin to membranes surrounding striated muscle fiber.
- Rod Domain: contains 24 proteins that repeat and maintain molecular structure.
  - It is thought to give the rod its flexibility.
  - The main rod is interrupted by 4 hinge regions.
- The cysteine-rich domain: regulates ADAM protease which are cell membrane anchors that are important in maintaining cell shape and structure.
- The C-terminal: contains the syntrophin binding sight (for binding internal cellular components).

(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 \( \beta \)-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.
Dystrophin Related Diseases

- Duchenne (DMD) and type Becker (BMD) represent the most common X-linked genetic diseases.
  - DMD affects one in 3500 male births
  - BMD affects one in 18,450 male births.

- Both diseases result from mutations in the dystrophin gene located on chromosome Xp21.1.

- DMD and BMD are related disorders differing in severity due to the amount of and quality of expressed dystrophin.

- Female Carriers
- X linked Dilated Cardiomyopathy
DMD Mutations

- Deletion of 1 or more exons are found in approximately 60 to 65% of patients
- Duplications are found in 9% cases
- Nonsense or splice site mutations in 16% and 5% cases, respectively
- Although there is no clear correlation found between the extent of the deletion and the severity of the disorder, DMD deletions usually result in out-of-frame shift mutations
A. Normal situation

pre-mRNA
1-48 49 50 51 52 53-79

mRNA
1-48 49 50 51 52 53-79

Intact reading frame

transcription

extracellular matrix

functional dystrophin protein

actin cytoskeleton

B. Duchenne muscular dystrophy

pre-mRNA
1-48 49 50 51 52 53-79

mRNA
1-48 49 50 52 53-79

Reading frame disrupted

translation

extracellular matrix

non-functional dystrophin protein

actin cytoskeleton

C. Becker muscular dystrophy

pre-mRNA
1-48 49 deletion exon 50-51 52 53-79

mRNA
1-48 49 52 53-79

Reading frame stays intact

translation

extracellular matrix

shorter, functional dystrophin protein

actin cytoskeleton
Becker Muscular Dystrophy

- Becker Muscular Dystrophy is named after the German doctor Peter Emil Becker
- Also known as Benign pseudohypertrophic muscular dystrophy
- In BMD, the disease is milder and more heterogeneous, compared to DMD.
- Muscle weakness often is first noticed in adolescence or young adulthood.

- The frequency of cardiac involvement in BMD is 60% to 75%
- The average age of onset of cardiac involvement is $28.7 \pm 7.1$ years. Severe dilated cardiomyopathy (DCM) in patients less than 20-year-old is rare.
- Cardiac involvement in BMD may precede the skeletal muscle decline, with death due to cardiomyopathy often occurring before the age 60 years

- Presence of cardiac involvement has been associated with exon 49 deletion and exon 48 deletion
Duchenne Muscular Dystrophy Carriers

- Genetic screening of mother and potential female carriers should be offered
- Carriers should be made aware of the risk of developing cardiomyopathy
- X-inactivation is the mechanism where 1 of the 2 X chromosomes in female cells randomly becomes transcriptionally inactive. It is postulated that carriers can become symptomatic on the basis of the extent of random X-inactivation of the normal X chromosome versus the dystrophic X chromosome.
- Carriers should have screening in late adolescence or early adulthood
- Should have screening at least every 5 years
X linked Dilated Cardiomyopathy (XLDCM)

- First described in 1987
- Rare cardiomyopathy resulting from mutations in the DMD gene that affects teenage males and their mothers
- Patients with XLDCM have normal dystrophin levels in skeletal muscle, but a complete loss of dystrophin in cardiac muscle, thus making it a distinct phenotype (i.e., cardiomyopathy without overt skeletal muscle disease) from DMD or BMD
- The rapidly progressive cardiomyopathy associated with XLDCM results in death between 10 and 20 years of age.
Why is Dystrophin Important?

Metabolic and structural abnormalities in the myocardium, which predispose to morphological changes comprising early cardiomyocyte cell death and replacement. 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. 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. 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.

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. 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 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. 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. However, other studies could not confirm these results. A decade later, Jefferies et al described a potential association between the underlying dystrophin gene defect and the occurrence of cardiomyopathy in MD patients. They studied 62 patients and found that patients with mutations involving exon 9 of the dystrophin gene demonstrated a worse clinical phenotype with an earlier onset of myopathy and a faster progression rate. However, other studies could not confirm these results.
Pathophysiology of Dystrophin Deficiency in the Heart

Progression of Cardiomyopathy

How is Cardiomyopathy Diagnosed?

- Physical Exam, signs and Symptoms
- Electrocardiogram
- ECHOCARDIOGRAM
- Cardiac MRI
- HOLTER
- Lab work
  - B type Natriuretic Peptide
  - Lipids
Signs & Symptoms of Cardiac Dysfunction

• Some children do not have symptoms early on.
• Cardiac symptoms typically appear late because boys with DMD are wheelchair bound and physically inactive.
• Some may have palpitations, difficulty breathing, and some may have postural nocturnal dyspnea.
• Heart rate and respiratory rate may be elevated
• Hypotension
• Impaired cough and speech
Electrocardiogram

• Typical ECG abnormalities for both DMD and BMD
  - 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.

Study of 150 boys with DMD
ECG abnormalities often preceded the development of DCM by a significant period of time (3.7 +/- 2.6 yrs)
Ambulatory Holter monitoring

- Used to detect arrhythmias
- Holter analysis has shown impaired automaticity with sinus tachycardia, loss of circadian rhythm, and reduced heart rate variability
- In one study of 150 boys:
  * Arrhythmias were common with 11% of the cohort being affected.
  * Those with cardiomyopathy were more likely to have an arrhythmia, with 16 of 64 (25%) of that group being affected (P < .01).
  * The presence of ventricular tachycardia was a poor prognostic indicator

ECHOCARDIOGRAPHY

- Specific imaging recommendations include:
  - Echocardiogram beginning at diagnosis and by at least 6 years of age, then
  - Subsequent echo studies every 1 to 2 years, depending on age and function
  - After 10 years of age, it is recommended that boys undergo at least annual echocardiograms.

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**FIGURE 3.** Echocardiographic images of a 16-year-old DMD patient with cardiomyopathy. 

(A) Two-dimensional apical four-chamber view of a dilated left ventricle (LV) showing thin and rounded lateral myocardial wall and septum.

(B) Measurement of the left ventricle end-diastolic volume (LVEDV) in the apical four-chamber view used to calculate ejection fraction. The ejection fraction in this patient was severely decreased at 20% (normal 55–65%).

(C) M-mode image of the left ventricle showing decreased movement of the interventricular septum at the top of the image and the lateral free wall at the bottom of the image. The left ventricular internal diameter in diastole (LVIDd: green line) and the left ventricular internal diameter in systole (LVIDs: blue line) are measured to derive the shortening fraction (LVIDd/C0LVIDs / LVIDd). This image shows a severely decreased shortening fraction of 9% (normal 28–40%).

(D) Color tissue Doppler image of the left ventricle (LV). The coloring of the ventricular myocardium corresponds to myocardial velocities that are measured to evaluate diastolic function and myocardial strain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Cardiac MRI

- Study of 314 DMD boys
  - 36% of DMD subjects showed LGE positivity suggesting fibrosis & scar
    * 17% of patients <10 years to
    * 34% of those aged 10–15 years
    * 59% of those >15 years-old.

- Patients with LVEF ≥55% were LGE positive in 30% of cases →
  this increased to 84% for LVEF <55%.

- Patterns of LGE: LGE was more prevalent in the free wall vs. septal segments

- Patients with septal involvement were significantly older and had lower LVEF than those with isolated free wall LGE.

- Patients who died had higher heart rate, larger left ventricular volume and mass, greater number of positive LGE segment and increase incident of septal LGE compared to those who remained alive.

*Hor et al. Journal of Cardiovascular Magnetic Resonance 2013, 15:107*
Treatment Strategies

- Based on symptoms and degree of dysfunction
- Goal is to decrease symptoms and prolong quality of life
Medical Management

- The use of ACE inhibitors or ARBs has now become more mainstream in the DMD population
  - age at which such therapy should begin remains an important question
  - this should be a discussion with the cardiologist

- Opinion of the 2014 NHLBI Working Group that ACE inhibitor/ARB use in DMD should begin by 10 years of age, but the relatively low risk of ACE inhibitors and ARBs should not discourage the consideration of earlier therapy.

- The use of β-adrenergic blockers remain variable,
  - Common practice to begin after the onset of ACE inhibitor/ARB use, usually on the basis of ventricular dysfunction or elevated heart rate.
Effect of Perindopril on the Onset and Progression of Left Ventricular Dysfunction in Duchenne Muscular Dystrophy

Denis Duboc, MD, PhD,* Christophe Meune, MD,* Guy Lerebours, MD,† Jean-Yves Devaux, MD, PhD,* Guy Vaksman, MD,* Henri-Marc Bécane, MD*

Paris, France

• Aim of study was to examine effects of perindopril on cardiac function in boys with DMD
• Phase I → 57 children with DMD and a left ventricular ejection fraction (LVEF) 55% (mean 65.0 +/- 5.4%), 9.5 to 13 years of age (mean 10.7 +/-1.2 years), were enrolled in a three-year multicenter, randomized, double-blind trial of perindopril, 2 to 4 mg/day (group 1), versus placebo (group 2)
• Phase II → all patients received open-label perindopril for 24 more months
  LVEF was measured at 0, 36, and 60 months
• At the end of phase I, mean LVEF was 60.7 +/- 7.6% in group 1 versus 64.4 +/- 9.8% in group 2, and was 45% in a single patient in each group (p = NS).
• At 60 months, LVEF was 58.6 +/- 8.1% in group 1 versus 56.0 +/- 15.5% in group 2 (p = NS). A single patient had an LVEF <45% in group 1 versus eight patients in group 2 (p = 0.02).

JACC, 2005
Early initiation of treatment with perindopril is associated with a lower mortality in patients with DMD with normal LV ejection fraction.
Beta Adrenoreceptor Blockade

- Literature contains scant and conflicting data concerning the efficacy of carvedilol or other beta-blockers for patients with DCM secondary to muscular dystrophy.
- One study assessed use in 22 patients with DCM and LVEF <50% ages 14 to 46 years
  - Carvedilol up-titrated over 8 weeks then was administered at the maximum or highest tolerated dose for 6 months.
  - Baseline and post-treatment cardiac magnetic resonance imaging (CMR), echocardiography, and Holter monitoring were recorded.
Results

- Carvedilol therapy also was associated with modest improvement in ventricular function.
- Significant improvements were detected in the left ventricular ejection fraction

*secondary to an increase in left ventricular end-diastolic volume with no change in end-systolic volume), mean dP/ dt, and MPI.


Table 2 Effect of carvedilol on indices of left ventricular function

<table>
<thead>
<tr>
<th>Index</th>
<th>Before</th>
<th>After</th>
<th>% Change</th>
<th>n</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (mL)</td>
<td>183 ± 76</td>
<td>195 ± 77</td>
<td>+6.6</td>
<td>20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>113 ± 62</td>
<td>115 ± 61</td>
<td>+1.8</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>41.0 ± 8.3</td>
<td>43.2 ± 8.3</td>
<td>+5.4</td>
<td>20</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>70 ± 18</td>
<td>80 ± 22</td>
<td>+14.3</td>
<td>20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MPI</td>
<td>0.54 ± 0.16</td>
<td>0.43 ± 0.15</td>
<td>−20.4</td>
<td>18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>dP/dt (mmHg/s)</td>
<td>804 ± 216</td>
<td>947 ± 276</td>
<td>+17.8</td>
<td>21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E/E’ ratio</td>
<td>10.1 ± 6.3</td>
<td>8.8 ± 4.1</td>
<td>−12.9</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>IRT (ms)</td>
<td>115 ± 35</td>
<td>106 ± 38</td>
<td>−7.8</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>SF</td>
<td>0.21 ± 0.08</td>
<td>0.23 ± 0.08</td>
<td>+9.5</td>
<td>16</td>
<td>NS</td>
</tr>
</tbody>
</table>

Before, before initiation of carvedilol; After, 6-month follow-up value; n, number of patients who completed pre- and posttreatment studies; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NS, not significant; EF, ejection fraction; SV, stroke volume; MPI, myocardial performance index; dP/dt, mean change in left ventricular pressure during isovolumetric contraction; IRT, isovolumetric relaxation time; SF, shortening fraction
Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial

- Addition of eplerenone to ACEI or ARB therapy attenuates the decline in left ventricular systolic function over 12 months
- Earlier use warrants consideration but further studies are needed

Lancet Neurology; 2015 Feb 14(2) 153-161
Glucocorticoids

- Most patients with DMD now are being treated with corticosteroids
  - most commonly prednisone or deflazacort
  - therapy begins in early life while boys still are ambulatory.

- One recent study:
  Eighty-six patients:
  9.1 ± 3.5 years of age, followed for 11.3 ± 4.1 years.

- Seven of 63 patients (11%) receiving steroid therapy died compared with 10 of 23 (43%) not receiving steroid therapy (p = 0.0010)

- Annual rates of decline in left ventricular ejection fraction (-0.43% vs. -1.09%, p = 0.0101) and shortening fraction (-0.32% vs. -0.65%, p = 0.0025) were less steep in steroid-treated patients

- Patients were on a renin-angiotensin aldosterone inhibitor already

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**Table 1. Patient Characteristics at Last Follow-Up**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Steroid Therapy</th>
<th>No Steroid Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initiation, yrs</td>
<td>12.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Initial weight, kg</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Baseline LV ejection fraction, %</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Baseline LV end-diastolic dimension, mm</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Baseline LV end-systolic dimension, mm</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Baseline corrected QT interval, ms*</td>
<td>404 (400, 416)</td>
<td>404 (400, 418)</td>
</tr>
</tbody>
</table>

**Figure 1. Overall Survival in Patients With and Without Steroids**

**Figure 2. Freedom From Cardiomyopathy in Patients With and Without Steroid Therapy**

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**Schram, All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy et al JACC 2013**
antagonists of the renin-angiotensin-aldosterone system alone, or in combination with a beta-blocker, delay the course of progressive left ventricular dysfunction (11, 17, 18).

Corticosteroids (i.e., namely prednisone and deflazacort) are commonly used to treat musculoskeletal and respiratory complications in DMD, with no perceived differences in efficacy between the 2 agents (2, 19, 20, 33). To our knowledge, our study is the first to explicitly assess the impact of steroids on all-cause mortality. In multivariate propensity-adjusted analyses that controlled for factors such as age, concomitant pharmacological therapy, echocardiographic parameters, and electrocardiographic metrics, steroid therapy was associated with a statistically significant 76% lower mortality rate. These findings are consistent with those of a previous study of 74 patients with DMD, 40 of whom were treated with deflazacort for an average of 5.5 years (2). Twelve of 34 boys (35%) who did not receive deflazacort died in their second decade of life compared with to 2 of 40 boys (5%) treated with deflazacort. A mortality analysis was not specifically performed, and concomitant medications were not reported.

The mortality reduction observed in our study appeared to be driven by significantly fewer heart failure–related deaths, as evidenced by the analysis of modes of death. Consistently, steroid therapy was associated with a 62% lower rate of new-onset cardiomyopathy, defined by a left ventricular ejection fraction \(< 45\%\). This finding was independent of the left ventricular ejection fraction at baseline and other clinical, electrocardiographic, and echocardiographic parameters.

### Table 4 Patient Characteristics at Last Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 86)</th>
<th>Steroid Therapy (n = 63)</th>
<th>No Steroid Therapy (n = 23)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last follow-up, yrs</td>
<td>20.4 ± 5.7</td>
<td>19.8 ± 5.5</td>
<td>22.1 ± 5.8</td>
<td>0.0910</td>
</tr>
<tr>
<td>Height, cm</td>
<td>153 ± 15</td>
<td>149 ± 14</td>
<td>167 ± 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>54 ± 18</td>
<td>54 ± 16</td>
<td>54 ± 24</td>
<td>0.9284</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23 ± 7</td>
<td>24 ± 6</td>
<td>19 ± 7</td>
<td>0.0017</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>104 ± 14</td>
<td>104 ± 14</td>
<td>102 ± 13</td>
<td>0.5509</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67 ± 11</td>
<td>67 ± 11</td>
<td>66 ± 11</td>
<td>0.5404</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>89 ± 17</td>
<td>89 ± 14</td>
<td>89 ± 22</td>
<td>0.9796</td>
</tr>
<tr>
<td>RAASa treatment duration, yrs</td>
<td>7.9 ± 3.2</td>
<td>8.1 ± 3.4</td>
<td>7.3 ± 2.9</td>
<td>0.2900</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>50 ± 10</td>
<td>53 ± 7</td>
<td>42 ± 13</td>
<td>0.0008</td>
</tr>
<tr>
<td>Normal</td>
<td>30 (35)</td>
<td>27 (43)</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>35 (41)</td>
<td>29 (46)</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>15 (17)</td>
<td>6 (10)</td>
<td>9 (39)</td>
<td></td>
</tr>
<tr>
<td>Severely impaired</td>
<td>6 (7)</td>
<td>1 (2)</td>
<td>5 (22)</td>
<td></td>
</tr>
<tr>
<td>LV shortening fraction, %</td>
<td>27 ± 6</td>
<td>29 ± 5</td>
<td>23 ± 7</td>
<td>0.0043</td>
</tr>
<tr>
<td>Normal</td>
<td>67 (80)</td>
<td>56 (90)</td>
<td>11 (50)</td>
<td></td>
</tr>
<tr>
<td>Mildly abnormal</td>
<td>8 (9)</td>
<td>2 (3)</td>
<td>6 (27)</td>
<td></td>
</tr>
<tr>
<td>Moderately abnormal</td>
<td>5 (6)</td>
<td>3 (5)</td>
<td>2 (9)</td>
<td></td>
</tr>
<tr>
<td>Severely abnormal</td>
<td>4 (5)</td>
<td>1 (2)</td>
<td>3 (14)</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>47 ± 8</td>
<td>46 ± 7</td>
<td>51 ± 11</td>
<td>0.0341</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>35 ± 9</td>
<td>32 ± 7</td>
<td>40 ± 12</td>
<td>0.0146</td>
</tr>
<tr>
<td>PR interval, ms*</td>
<td>120 (112, 134)</td>
<td>120 (112, 134)</td>
<td>120 (114, 124)</td>
<td>0.9565</td>
</tr>
<tr>
<td>QRS duration, ms*</td>
<td>90 (84, 100)</td>
<td>90 (84, 100)</td>
<td>90 (88, 100)</td>
<td>0.4966</td>
</tr>
<tr>
<td>Corrected QT interval, ms*</td>
<td>415 (401, 429)</td>
<td>420 (405, 429)</td>
<td>409 (392, 415)</td>
<td>0.1182</td>
</tr>
<tr>
<td>Follow-up duration, yrs</td>
<td>11.3 ± 4.0</td>
<td>11.3 ± 3.6</td>
<td>11.3 ± 5.1</td>
<td>0.9671</td>
</tr>
</tbody>
</table>

Values shown are mean ± SD or n (%). *Non-normally distributed continuous variables are summarized by median and interquartile range (25th, 75th percentile).

Abbreviations as in Table 1.
Emerging Cardiac Treatments

- Dystrophin gene replacement
- Implantable cardioverter defibrillators
- Gene Editing with CRISPR
- Exon Skipping
- Polaxamer 188
- Phosphodiesterase Inhibition
- Cardiac Resynchronization therapy
- Heart Transplantation
- Mechanical Circulatory Support
- Cardiac Stem Cell Therapy : CAP -1002
Implantable Cardioverter Defibrillator (ICD)

- A slight increase in sudden cardiac death among patients with DMD has been reported, although this has never been documented in prospective studies.
- The indications for ICD implantation are based on recommendations given for patients with HF.
- The indication for ICD implantation is usually given for EF ≤35%.
Cardiac Resynchronization therapy

- Cardiac resynchronization therapy (CRT) is a relatively new additional treatment option.
- It is limited to patients with:
  1. ongoing dyspnea (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 is being considered, particularly in those patients with documented ventricular arrhythmias.

- However, it is not established in DMD or BMD patients, but is limited to single case reports.
Ventricular Assist Device (VAD)

- LVAD as destination therapy for end-stage heart failure
- Paucity of literature
- Case Reports:
  - 3 patients in Italy had Jarvik 2000
  - 2 patients in US: one with Heart mate & one with Heart Ware
Heart Transplantation

• Wu et al performed a comprehensive retrospective review comprising 29 transplant centers in the USA over the period from 1990 to 2005.
  - 29 transplanted patients with MD were identified and compared with 275 non-MD patients with non-ischemic cardiomyopathy who were matched for age, body mass index, race, and sex.
  - Becker's muscular dystrophy was present in 52% of the patients.

• Survival in the muscular dystrophy patients was similar to the controls at 1 year (89% vs 91%; \( p = 0.5 \)) and at 5 years (83% vs 78%; \( p = 0.5 \)).

• The differences in rates of cumulative infection, rejection, or allograft vasculopathy between the 2 groups were not significant (\( p > 0.5 \) for all comparisons).

Emerging Cardiac Strategies

- **Phosphodiesterase Inhibition with Sildenafil**
  - Sildenafil has been shown to have positive effects on the heart of dystrophin deficient mdx mice that develop cardiomyopathy comparable to BMD patients.
  - The ability of dystrophin deficient mice hearts to resist
  - Enhancing cGMP signaling using sildenafil may improve contractile performance, myocardial metabolic status, and sarcolemmal integrity.
  - Studies with tadalafil have not shown benefit

- **Polaxamer 188 (CARMA SEAL)**
  - non-ionic tri-block copolymer of poly(ethylene oxide)\(_{80}\)-poly(propylene oxide)\(_{27}\)-poly(ethylene oxide
  - a surfactant that helps seal membrane ruptures
  - In mdx mice, it improved compliance in response to stretch and acute dobutamine induced heart failure
Non-Cardiac Considerations that Affect the Heart

- Respiratory Care
  - Use of Non-invasive positive Pressure ventilation: BIPAP, CPAP
- Anesthesia considerations:
  - Prior cardiac evaluation is necessary before anesthesia or procedural sedation
  - Avoidance of certain anesthetics such as Succinylcholine and volatile anesthetics
- Exercise
- Nutrition
- Mental Health
Conclusion

• Cardiomyopathy is a leading cause of death in the DMD population.
• However, with early detection, consideration for medical intervention, and multidisciplinary care, quality of life can be improved.

Thank you!
Genotype- Phenotype Correlation

- Genetic Predictors and Remodeling of Dilated Cardiomyopathy in Muscular Dystrophy ¹
  - 67 boys with DMD and seven with BMD
    * an association between mutations involving exons 12 and 14 to 17 and onset of dilated cardiomyopathy
    * trend towards a significant association between mutations of exons 31 to 42 and dilated cardiomyopathy
    * a decreased risk of dilated cardiomyopathy in mutations in exons 51 or 52.

- Analysis of dystrophin deletion mutations predicts age of cardiomyopathy onset in Becker Muscular Dystrophy ²
  - 118 patients
    * deletions affecting the amino-terminal domain of the dystrophin protein are associated with early onset cardiomyopathy in BMD patients
    * that genetic dystrophin mutations which result in the disruption of spectrin repeat phasing are also associated with dilated cardiomyopathy