Cardiac Care for Boys with Duchenne Muscular Dystrophy

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• Why should your son with Duchenne muscular dystrophy have a cardiologist?

• The heart is a muscle, too
• Care of the child with DMD is a team sport
• Your team should include a cardiologist
Questions we will answer today

1. What does “cardiomyopathy” mean?
2. What does “heart failure mean”?
3. Who should care for the heart?
4. When should cardiac care begin?
5. How will the heart be checked?
6. What should I watch for?
7. What treatment is available?
8. Should carriers have their hearts checked?
1. What does cardiomyopathy mean?

- Cardio – heart
- Myo – muscle
- Pathy – pathology/abnormality

- Cardiomyopathy is abnormality in the muscle of the heart
Cardiomyopathy

Normal heart

Dilated CM heart
Cell injury > cell death > dilation > wall thinning > scar, fibrosis > function declines

Dilated heart
(systolic heart failure)
Cardiomyopathy

DMD heart showing evidence of extensive fibrosis.
Differences between skeletal and cardiac muscle

- **Cellular architecture** – looks different under a microscope

- **Calcium handling**

- **Regenerative capacity**
  - *When injured:*
    - Skeletal muscle
      - can regenerate from immature muscle cells
    - Cardiac muscle
      - limited regenerative capacity
      - injury results in increased connective tissue or scar
2. What does “Heart Failure” mean?

- Scary sounding term
- The heart fails to meet the demands of the body
- Does **NOT** mean the heart has failed (stopped working)
- Heart failure typically occurs when cardiac function is poor but can occur with good function and increased demand
- Body’s response at first helpful but eventually causes harm

**PEOPLE CAN LIVE LONG LIVES WITH HEART FAILURE**
3. Who should care for the heart?

- **Cardiologist** is a “heart doctor”
  - Pediatric cardiologists
    - Pediatrics and cardiology
    - Pediatric patients should have a pediatric cardiologist, if possible
  - Adult cardiologists
    - Adult medicine and cardiology
- Some cardiologists have special interests
  - Heart failure/transplantation
  - Neuromuscular disorders
  - Talk to your son's doctor about finding an expert in treating “heart failure”
4. When should care begin?

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107th ENMC International Workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy. 7th–9th June 2002, Naarden, the Netherlands

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Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management

Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula Clemens, Linda Cripe, Ajay Kaul, Kathi Kinnett, Craig McDonald, Shree Pandya, James Poysky, Frederic Shapiro, Jean Tomezsko, Carolyn Constantin, for the DMD Care Considerations Working Group*

Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care

Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula Clemens, Linda Cripe, Ajay Kaul, Kathi Kinnett, Craig McDonald, Shree Pandya, James Poysky, Frederic Shapiro, Jean Tomezsko, Carolyn Constantin, for the DMD Care Considerations Working Group*

Stage 1: Presymptomatic
- Echocardiogram at diagnosis or by age 6 years

Stage 2: Early ambulatory
- Maximum 24 months between investigations until age 10 years, annually thereafter

Stage 3: Late ambulatory
- Assessment same as in the younger group
- Increasing risk of cardiac problems with age; requires intervention even if asymptomatic

Stage 4: Early non-ambulatory

Stage 5: Late non-ambulatory

Cardiac management

Use of standard heart failure interventions with deterioration of function
4. When should cardiac care begin?

Summary of Consensus Statements

Cardiac investigation should:

- **Begin at diagnosis**
- **Repeat investigation:**
  - At least biannually until age 10
    - Or with the onset of cardiac signs and symptoms
  - Annually after the age of 10
    - Or more frequently based on cardiac signs and symptoms
  - Prior to any major surgery

Minimum recommendations generated by interested individuals
5. How will the heart be checked?

- **Imaging**
  - Look at structure and function

- **Electrical Activity**
  - Record the heart rhythm
5. How will the heart be checked?

Two common ways to obtain images of the heart:
Neither one involves radiation
5. How will the heart be checked?

- **Echocardiogram**
  - Ultrasound evaluation of heart
    - Evaluate anatomy and function
  - **Advantages:**
    - Readily available
    - Quick
  - **Disadvantages:**
    - Operator dependent
    - Image quality changes over time
    - Not accurate for RV function
5. How will the heart be checked?

- **Cardiac MRI**
  - Magnetic resonance imaging
    - “Radio tuned to hydrogen”
  - Evaluate anatomy and function
  - **Advantages:**
    - Detailed cardiac information
    - Accurate measurements
    - Additional information
      - Fibrosis
      - Metabolism
  - **Disadvantages:**
    - Usually involves IV placement
    - One hour in duration
    - Claustrophobic
    - Expensive
    - Sedation (younger children)
MRI delayed enhancement and fibrosis

MRI short axis view of the left ventricle utilizing Gadolinium delayed enhancement

A. DMD – 9 year old normal diastolic and systolic function and no fibrosis
B. Dystrophinopathy extensive ring of subepimyocardial or midwall fibrosis (arrow)
C. Subendomyocardial fibrosis (arrows) associated with ischemic heart disease

(A. performed at CCHMC; B. Heart, 2004; C. JACC, 2005)
5. How will the heart be checked?

1. Electrocardiogram (ECG) -
   a. Heart Rate
   b. Heart Rhythm
2. Holter monitor
3. Event monitor
Electrocardiogram (ECG)

- Abnormal at an early age
- Early abnormality not predictive of phenotype
- Type of abnormality changes with age
  - Likely represents disease progression
- HR often elevated 10-15 bpm above “normal”
  - True tachycardia (>95th %ile) comes with dysfunction
- Important to watch for changes with time
- Baseline important to obtain at diagnosis

N = 105
ECGs 503
Holter findings in DMD patient

**FIGURE 2.** Holter monitor tracing of an 18-year-old DMD patient. The tracing shows a non-sustained run of ventricular tachycardia at a rate of approximately 160 beats per minute. The patient was asymptomatic during the recording. N, normal sinus beat; V, abnormal ventricular beat.
6. What signs and symptoms should I watch for?

- Know your son’s baseline
  - Learn to take his pulse
    - At rest, when busy, when sleeping
    - Consider buying a stethoscope
  - Make sure his blood pressure is being checked at visits
- Be aware of his activity level
  - Is it changing? Why?

- Develop a relationship with your care provider before you need them
6. What signs and symptoms should I watch for?

- Heart failure symptoms often are difficult to identify in DMD patient
  - *Rapid weight gain (or loss)*
  - *Swelling of feet or overall puffiness*
  - *Heart racing/skipping beats or fainting (syncope)*
  - *Sometimes GI symptoms – nausea, vomiting (not otherwise ill)*
- Chest pain (common)
  - *Usually musculoskeletal*
  - *Rarely cardiac cause*
    - Coronary occlusion
    - Myocarditis
  - *Check cardiac enzymes to help tell if the heart is involved*
  - *Consider additional imaging*
7. What treatment is available?

- Currently, standard HF treatment
  - *Taken from adult HF experience*
- Treatment
  - *Based on limited pediatric data*
  - *Not dystrophin specific*
- Goals:
  - *Alleviate symptoms*
  - *Slow disease*
  - *Improve survival*
7. What treatment is available?

- **Standard HF drugs – Cardiac “cocktail”**
  - *ACE inhibitors*
    - enalapril, lisinopril, perindopril
  - **Angiotensin-receptor blockers**
    - Losartan
  - **β-blockers**
    - metoprolol, carvedilol
  - **Diuretics**
    - furosemide, thiazides
  - **Aldosterone receptor antagonists**
    - Spironolactone, eplerenone
  - **Anti-coagulation**
    - Coumadin, Aspirin

NEJM 2003
7. What treatment is available – When to start?

- We know patients will develop cardiac dysfunction at some point
  - We don’t know when

- **Should cardiac meds be started at dx?**
  - No data exists to suggest benefit
  - Limited data to suggest ACE may be beneficial if started before echo changes are seen

- **Definitely start ACE inhibitors when**
  - Left ventricular enlargement
  - Ventricular dysfunction
  - Myocardial fibrosis

- **Consider starting ACE earlier**
  - Talk to your son’s cardiologist
Do steroids benefit the heart in DMD?
7. What treatment is available?

- **Steroids**
  - Started early in disease
    - Use dependent on institution
    - Use dependent on country
  - Has been shown to change the time course of the disease
    - Mechanism unknown
    - More than simply the anti-inflammatory effect

- **Side effects**
  - Hypertension
  - Obesity
  - Delayed puberty
  - Behavioral problems
  - Short stature
Steroid Treatment

Kaplan-Meier Estimate of Freedom from DCM, steroid treatment

Follow up, days

Hazard ratio = 0.16 (0.037 - 0.70 95% CI)
Log rank = 0.005
7. What treatment is available?

• **What about the future?**
  
  – Heart rhythm problems
    
    • Pacemakers in some cases
    • AICD
      
      Implanted defibrillator
  
  – At end stage HF
    
    • Continuous IV milrinone
    • Cardiac Transplantation
      
      – Few DMD patients transplanted
      – More BMD patients transplanted
      – Problems
        
        » Donor hearts scarce
        » Still a chronic disease
  
  – **Left ventricular assist devices**
    
    – Very new but may be beneficial
      
      » Bridge to transplant?
      » “Destination” therapy?
7. What treatment is available?

- Always a risk/benefit analysis
  - If there is abnormal function (+/- symptoms)
    - Benefits established
  - Normal function – unclear
    - *Role for research to answer: when, what agent, what dose, how long?*
- Risks:
  - All drugs have side effects
  - Drugs untested in patients with DMD
8. Should carriers have their hearts checked?

- Often cardiac disease only manifestation

- Cardiomyopathy risk increases with age
  - *Approximately 350 DMD/BMD carriers*
    - age < 16 yrs: all normal
    - age 16-30 yrs: 6%; 31-50 yrs: 9%; > 50 yrs: 16% DCM

- Baseline evaluation as young adult
  - *Frequency unclear (≈ every 5 years)*
  - *Be aware of symptoms*
  - *Take care of yourself*
    - minimize other CV risks
      - smoking, HTN, cholesterol
Conclusions

• Cardiac care should start at diagnosis

• Ongoing cardiac follow-up is important and the best way to insure long term cardiac health
Conclusions

• When there is evidence of abnormal function, treatment is recommended

• Early treatment prior to onset of dysfunction is unproven and controversial
  – Important to consider risks and benefits
Conclusions

• Get to know your cardiologist
  – Maintain an open dialog
  – He/she is working for you and with you to benefit your child
Conclusions

YOU AND YOUR FAMILY

are essential to the health care team!
Conclusions

- Need to use common sense AT ALL TIMES
There are differences between skeletal and cardiac muscle

- **Skeletal muscle**
  - Elongated multi-nucleated cells
  - Organized into fascicles
  - Multiple nuclei located on the periphery of the cell

- **Cardiac muscle**
  - Rectangular shape
  - Mono-nucleated or bi-nucleated
  - Nuclei located centrally in the cell
  - Often branched

- **Important to note:**
  - Not every neuromuscular disorder manifests both skeletal and cardiac disease
“Typical” DMD ECG

FIGURE 1. Electrocardiogram tracing of an 8-year-old DMD patient. This shows common features of DMD including resting tachycardia with a heart rate of approximately 90 beats per minute, increased R-wave amplitudes in leads V1, V2, and V3, and Q waves in the lateral and inferior leads (II, III, aVF, V4, V5, V6).
5. How will the heart be checked?

- MRI allows you to obtain information about:
  - **Cardiac function**
    - Left ventricular ejection fraction
      - In DMD does not decline until late in the disease
  - **Left ventricular morphology**
    - DMD is not a “true” dilated cardiomyopathy
    - Normal LV remodeling index at end stage with only modest chamber enlargement
5. How will the heart be checked?

- **Left ventricular myocardial tissue characterization**
  - Evidence of left ventricular non-compaction (LVNC)
    - Unlikely primary LVNC but likely represents disease progression
  - Utilize late gadolinium enhancement for myocardial fibrosis/scar
    - Fibrosis in DMD is sub-epicardial and sub-endocardial in ischemic cardiomyopathy

- **Left ventricular mechanics**
  - Myocardial tagging for myocardial strain analysis
7. What treatment is available?

- **Ventricular Assist Devices**
  - Cutting edge technology
  - Many devices currently under development
- Possible benefit for sub-population of DMD/BMD patients
  - Useful as
    - Bridge to transplantation
    - Destination therapy
7. What treatment is available?

- Pacemakers
  - Cardiac re-synchronization therapy
  - Successful in adult heart failure population
  - Preliminary data suggest DMD population may not be good candidates
  - No evidence of dys-synchrony
Cardiomyopathy in a female Duchenne carrier.
Conclusions

- Cardiac evaluation should begin at diagnosis