

Cardiac Care in patients with Duchenne muscular dystrophy



Linda Cripe, M.D.
Professor of Pediatrics
The Heart Center

Why are cardiologists interested
in patients with Duchenne
muscular dystrophy?

The Heart is a Muscle TOO!!!

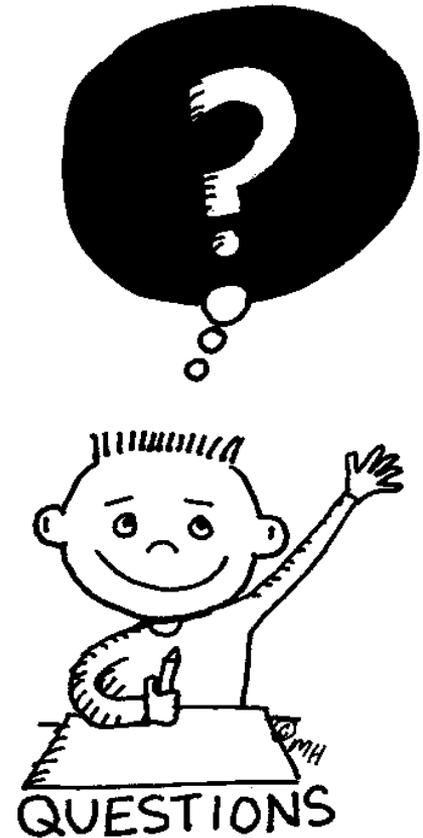


Care of the individual with DMD is a team sport

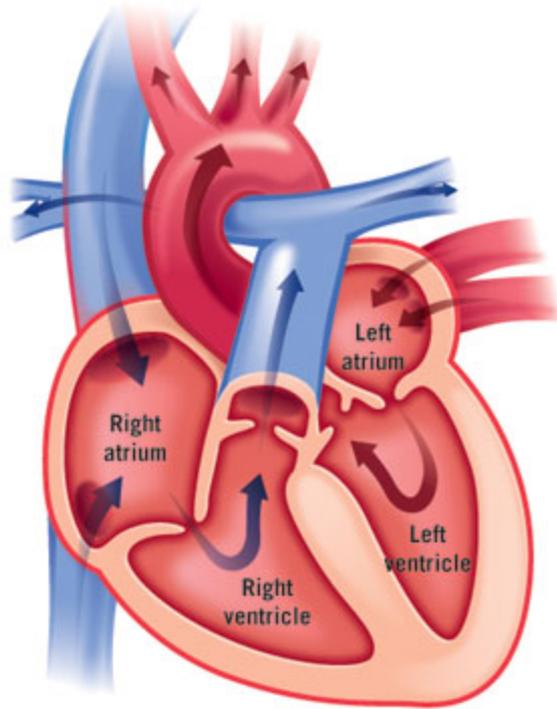


Questions we will answer today

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?



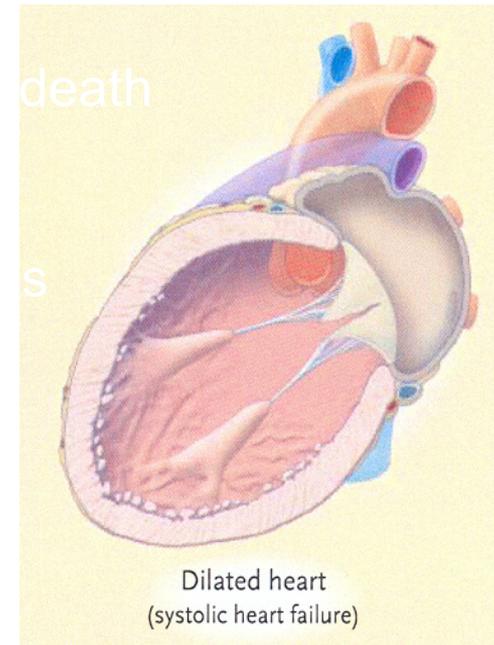
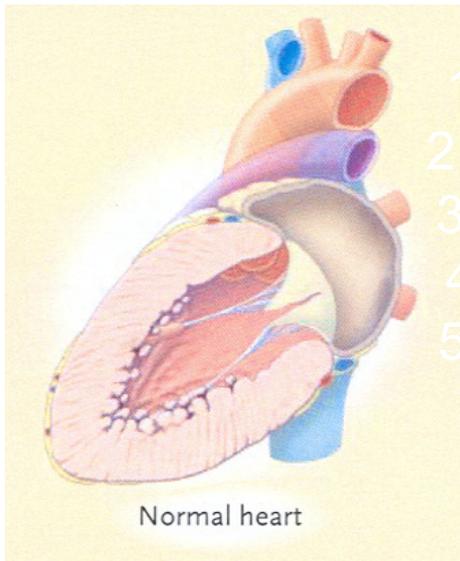
The normal heart



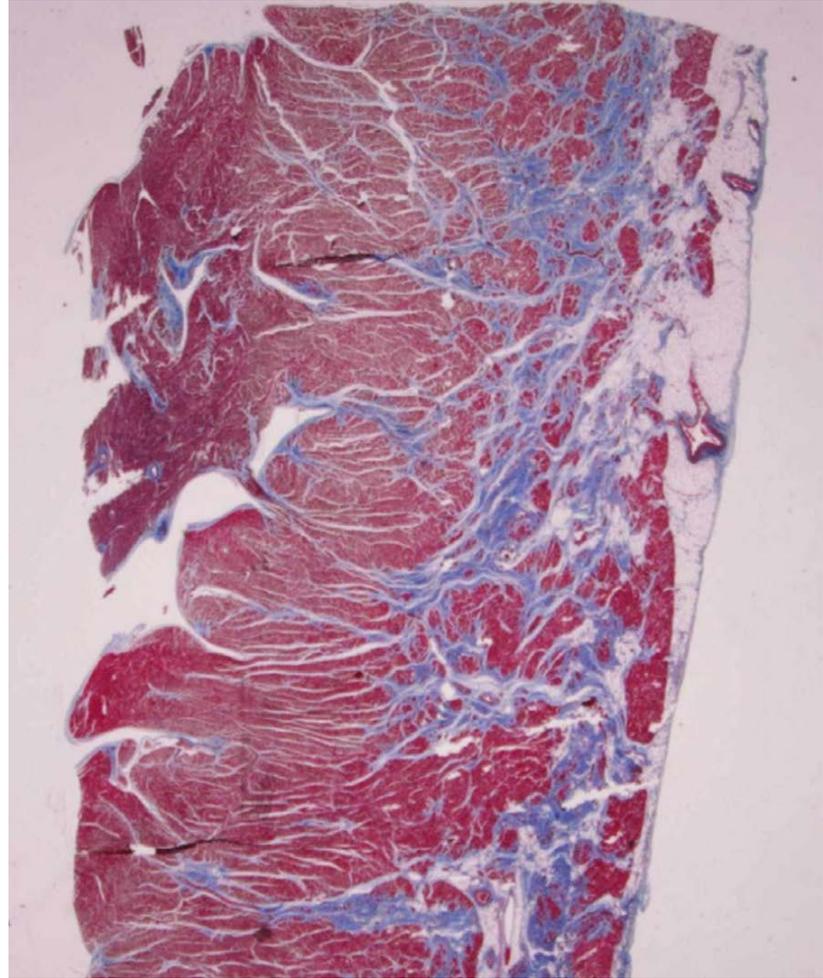
NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.™

1. What does “cardiomyopathy” mean?

Disease of heart muscle



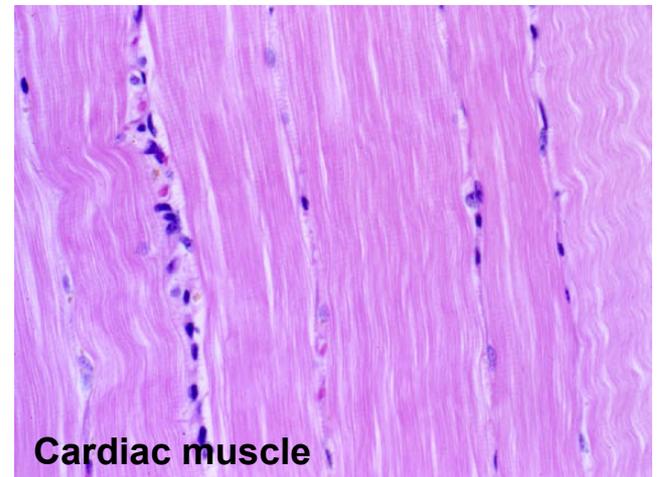
Cardiomyopathy



DMD heart showing evidence of extensive fibrosis.

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



There are differences between skeletal and cardiac muscle

- Cellular architecture
- Calcium handling
- Regenerative capacity
 - When injured:
 - Skeletal muscle
 - regenerates from fusion of mononucleated myoblasts to the syncytium of the myofiber
 - Cardiac muscle
 - limited regenerative capacity
 - injury results in increased connective tissue or scar

3. Who should care for the heart?

- **Cardiologist** is a “heart doctor”
 - Pediatric **cardiologists**
 - Pediatrics and cardiology
 - Adult **cardiologists**
 - Adult medicine and cardiology
- Some **cardiologists** have special interests
 - Heart failure/transplantation
 - Neuromuscular disorders
 - Talk to your sons doctor about finding an expert in treating “heart failure”



4. When should care begin?

Cardiovascular Health Supervision for Individuals Affected by Duchenne or Becker Muscular Dystrophy

Section on Cardiology and Cardiac Surgery

Pediatrics 2005;116;1569-1573

DOI: 10.1542/peds.2005-2448

PERGAMON

Neuromuscular Disorders 13 (2003) 166–172


www.elsevier.com/locate/nmd

Workshop report

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

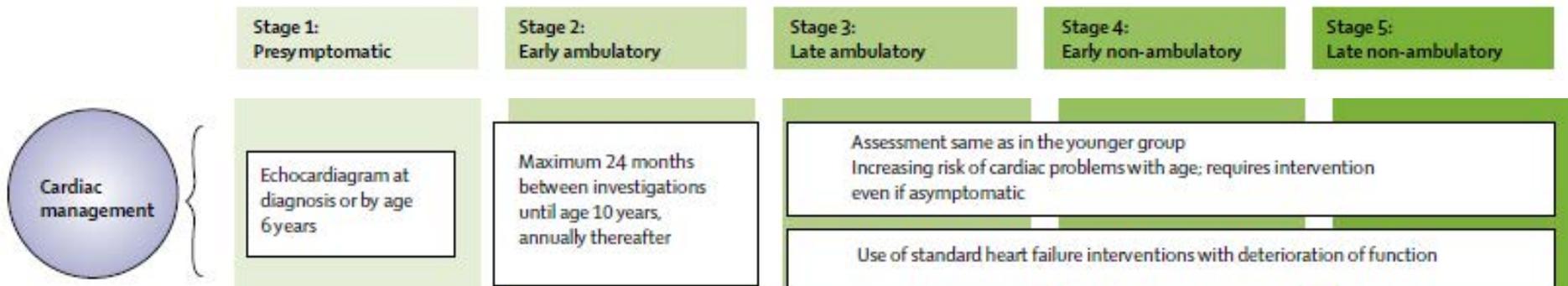
K. Bushby*, F. Muntoni, J.P. Bourke

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*



4. When should cardiac care begin?

Summary of Consensus Statements

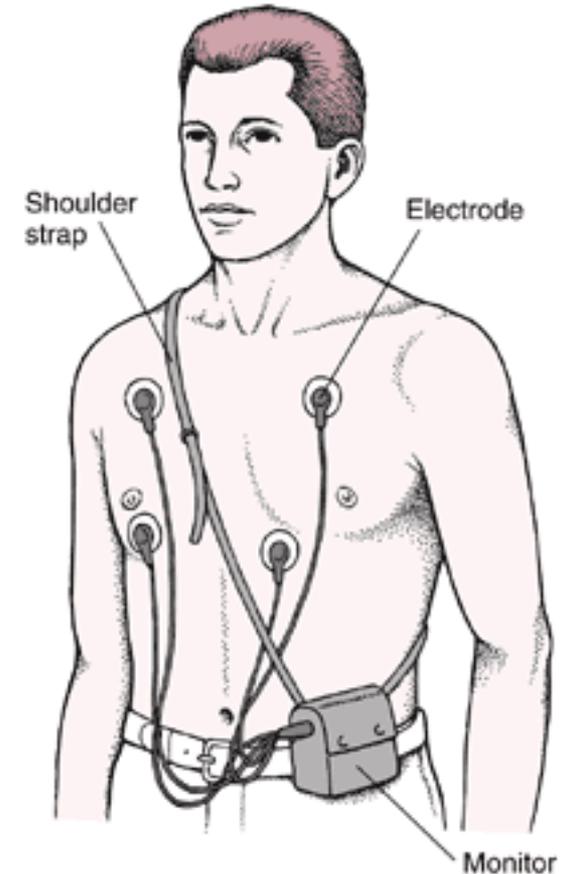
Cardiac investigation should:

- **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

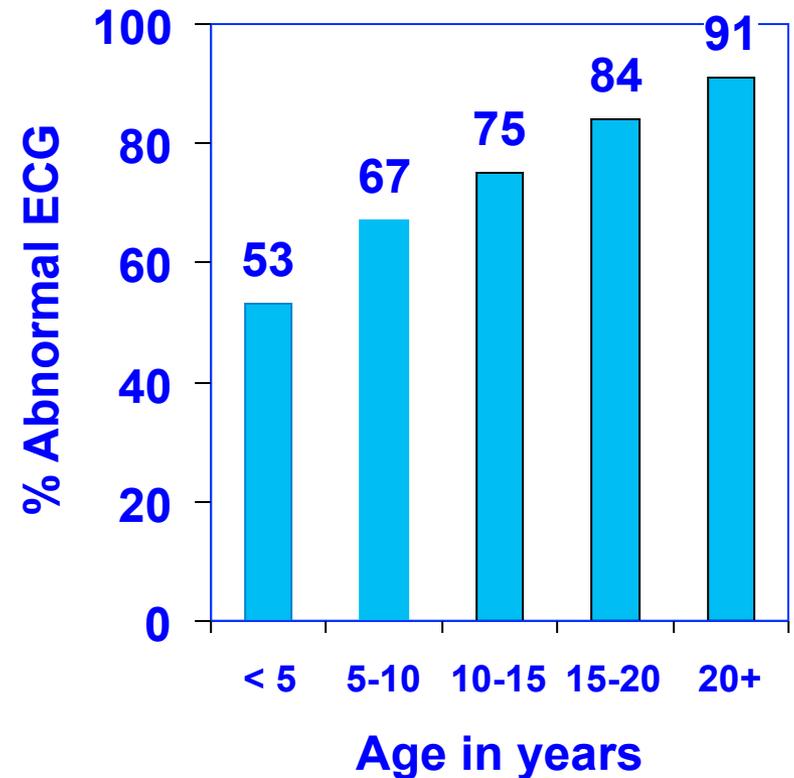
5. How will the heart be checked?

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 percentile) comes with dysfunction
- Important to watch for changes with time
- Baseline important to obtain at diagnosis



N = 105
ECGs 503

“Typical” DMD ECG

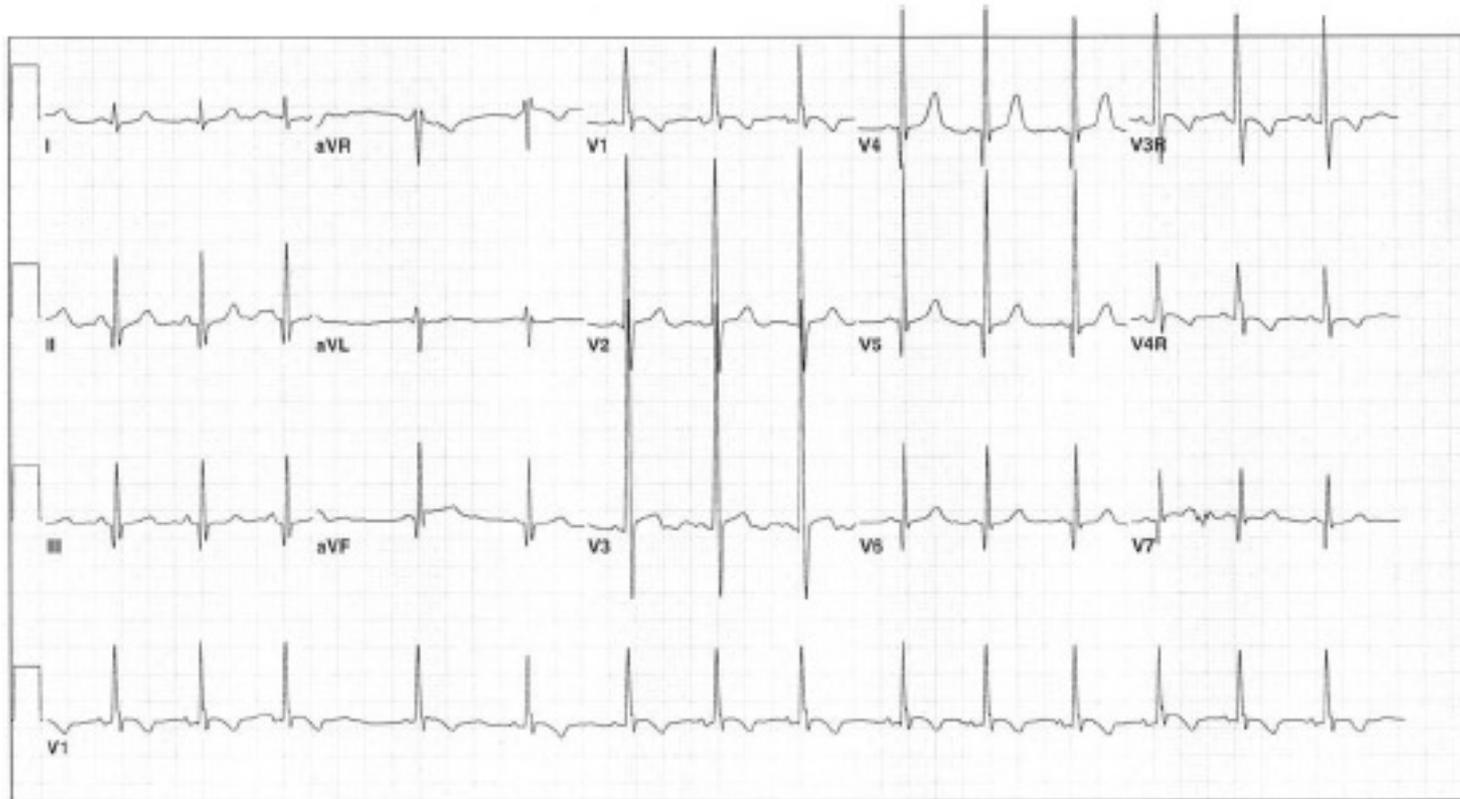


FIGURE 1. Electrocardiogram tracing of an 8-year-old DMD patient. This shows common features of DMD including resting tachycardia with a heart rate of approximately 90 beats per minute, increased R-wave amplitudes in leads V1, V2, and V3, and Q waves in the lateral and inferior leads (II, III, aVF, V4,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

Holter findings in DMD patient

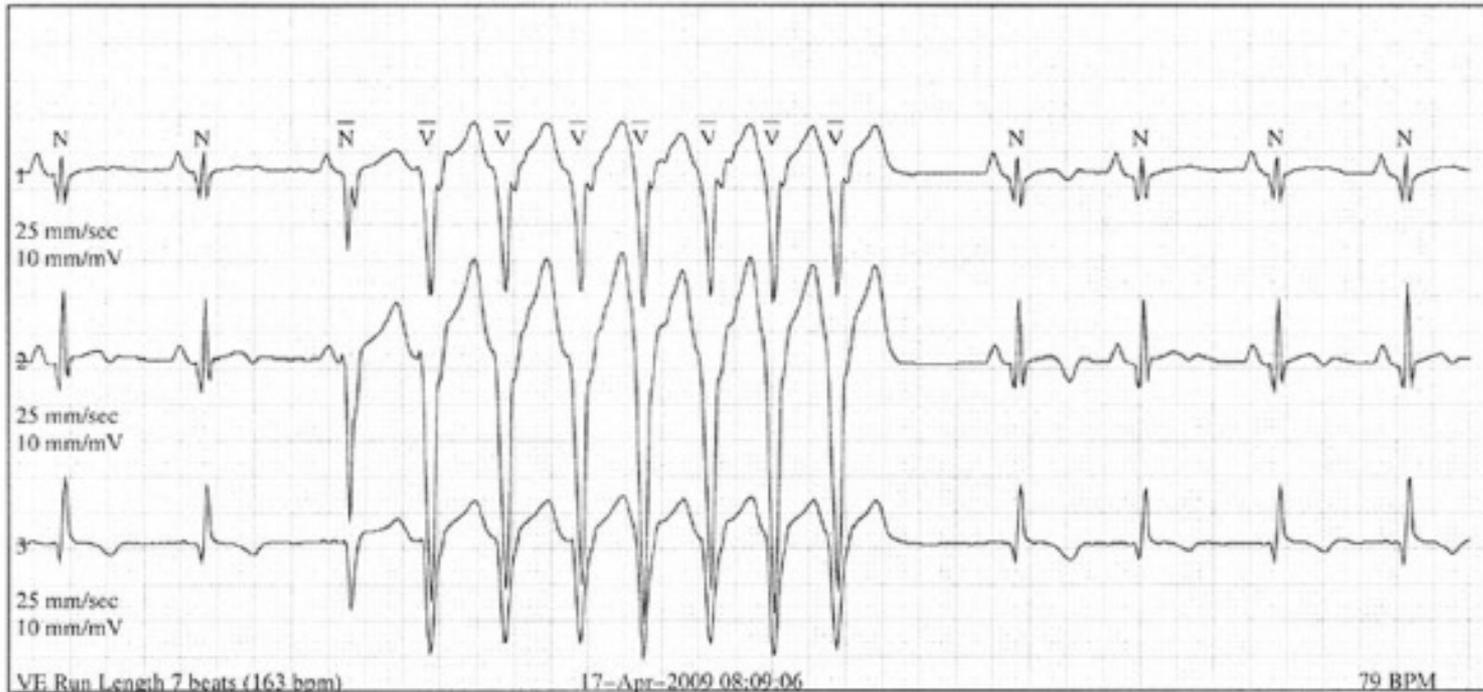
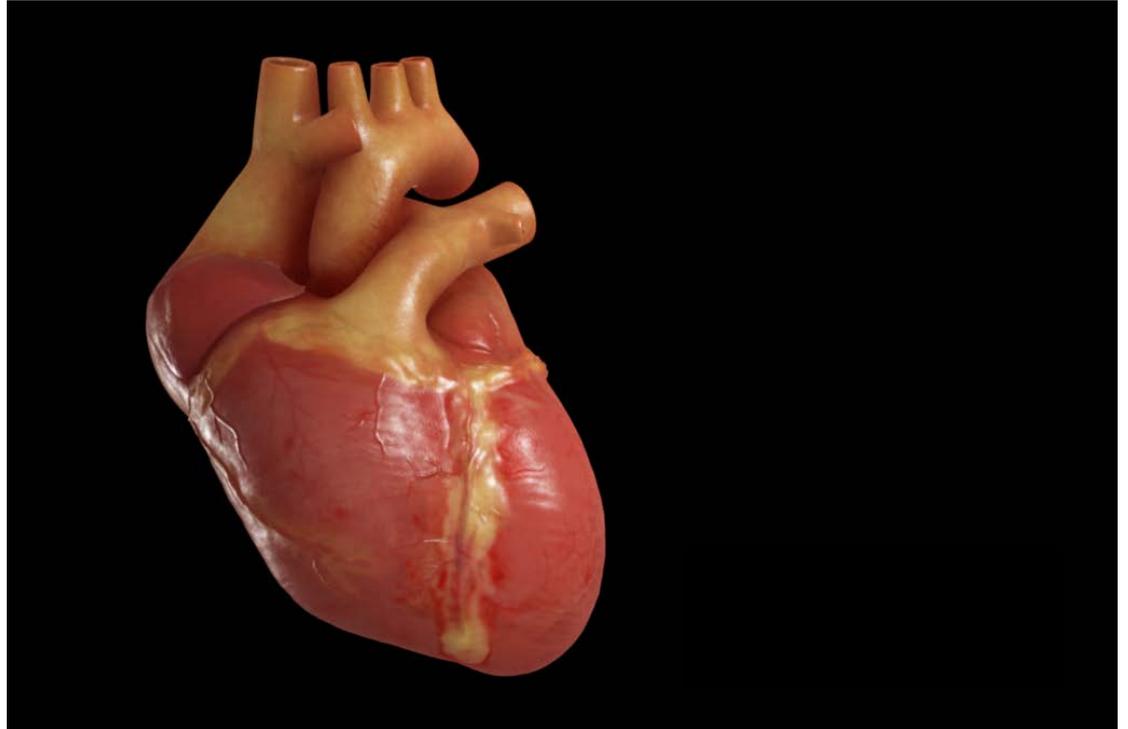


FIGURE 2. Holter monitor tracing of an 18-year-old DMD patient. The tracing shows a non-sustained run of ventricular tachycardia at a rate of approximately 160 beats per minute. The patient was asymptomatic during the recording. N, normal sinus beat; V, abnormal ventricular beat.

5. How will the heart be checked ?

- Images of the heart will be attained to evaluate structure and function



5. How will the heart be checked?

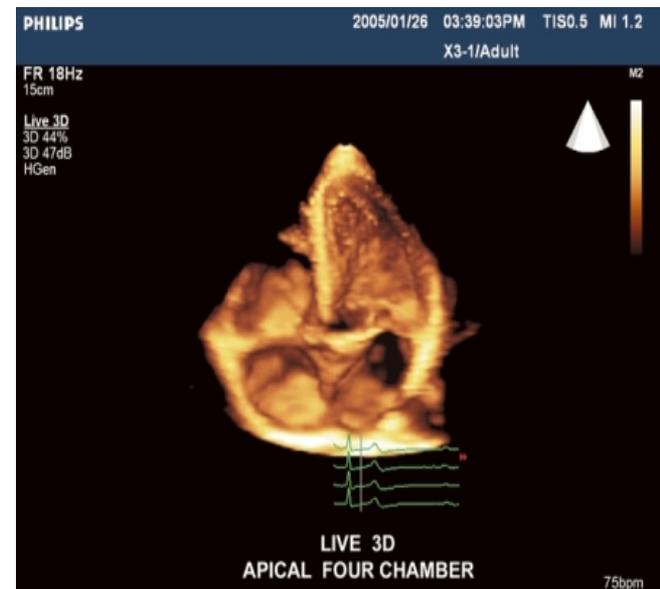
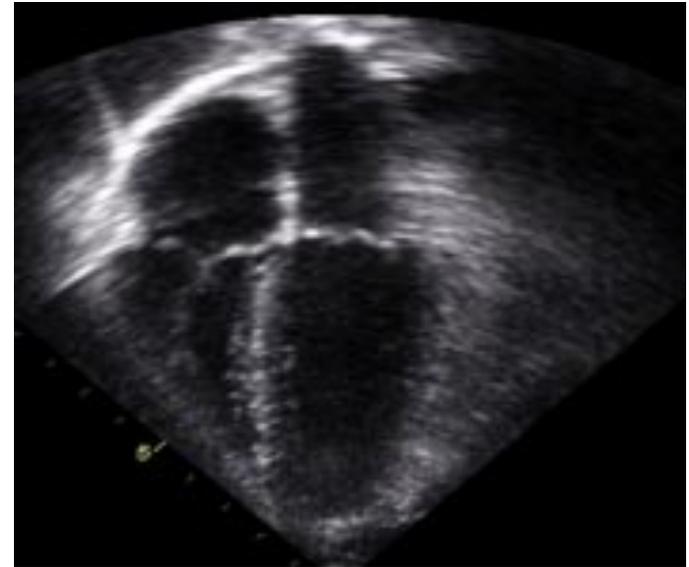
Two common ways to obtain images of the heart:



5. How will the heart be checked?

- **Echocardiogram**

- Ultrasound evaluation of heart
 - Evaluate anatomy and function
 - Contraction (systole)
 - Relaxation (diastole)
 - Advantages:
 - Readily available
 - Quick
 - Disadvantages:
 - Image quality unreliable
 - Scoliosis
 - Weight and position
 - Not accurate for RV function



5. How will the heart be checked?

- Cardiac MRI
 - Advantages:
 - No radiation exposure
 - Detailed cardiac information
 - Accurate measurements
 - Additional information
 - Fibrosis
 - Metabolism
 - Disadvantages:
 - May involve IV placement
 - One hour in duration
 - Claustrophobic
 - Expensive
 - Sedation (younger children)



5. How will the heart be checked?



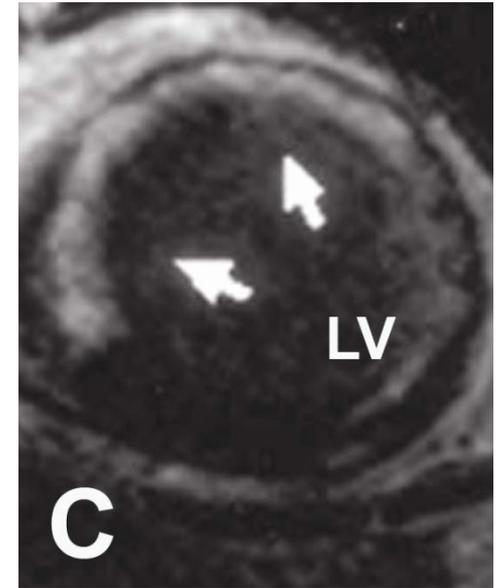
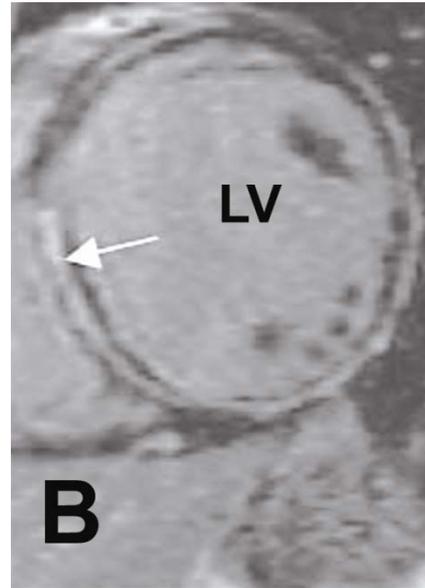
- MRI allows you to obtain information about:
 - Cardiac function
 - Left ventricular ejection fraction
 - In DMD does not decline until late in the disease
 - Left ventricular morphology
 - DMD is not a “true” dilated cardiomyopathy
 - Normal LV remodeling index at end stage with only modest chamber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

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)

6. What signs and symptoms should I watch for?

- Know your sons baseline
 - Learn to take his pulse
 - At rest
 - While busy
 - Sleeping
 - Buy a stethoscope
- Develop a relationship with your care provider *before* you need them



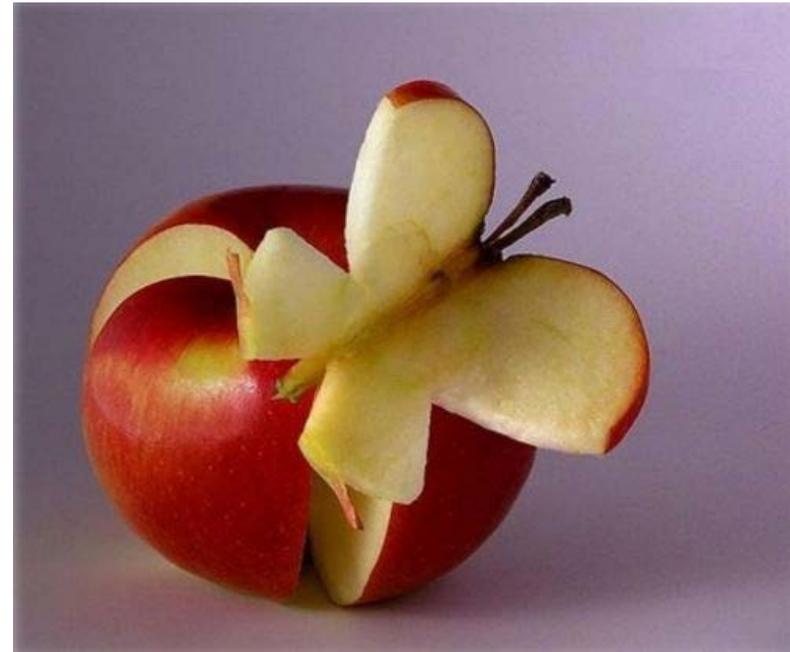
6. What signs and symptoms should I watch for?

- 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)
- Chest pain (common)
 - Usually musculoskeletal
 - Coronary occlusion
 - Myocarditis
 - Check cardiac enzymes
 - consider additional imaging



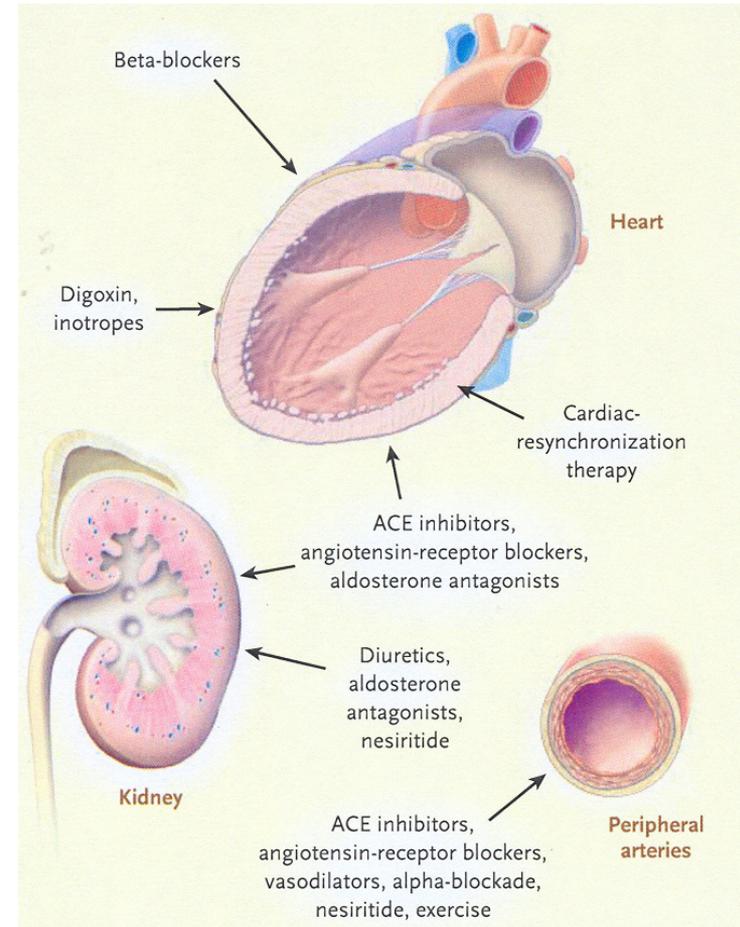
7. What treatment is available?

- Currently, standard HF treatment
 - Taken from adult HF experience
- Treatment
 - Not based on pediatric data
 - Not dystrophin specific
- Goals:
 - Improve survival
 - Slow disease
 - Alleviate symptoms



7. What treatment is available?

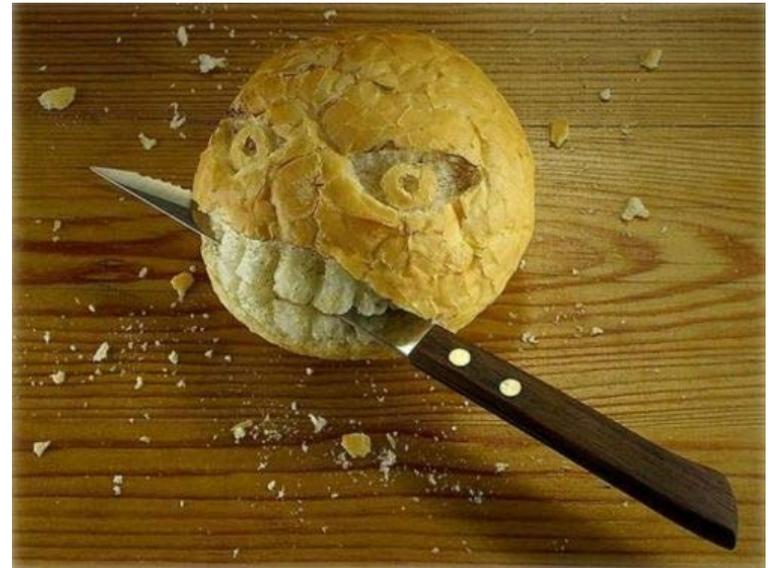
- Standard HF drugs
 - ACE inhibitors
 - enalapril, lisinopril, perindopril
 - Angiotensin- receptor blockers
 - Losartan
 - β -blockers
 - metoprolol, carvedilol
 - Diuretics
 - furosemide, thiazides
 - Aldosterone receptor antagonists
 - Spironolactone, eplerenone
 - Anti-coagulation
 - Coumadin, Aspirin



NEJM 2003

7. What treatment is available-When to start?

- We know patient **will** develop cardiac dysfunction at diagnosis
- Should cardiac meds be started at dx?
 - No data exists to suggest benefit
- Families exert significant pressure to do something
- Start ACE inhibitors when evidence of
 - Left ventricular enlargement
 - Ventricular dysfunction
 - Myocardial fibrosis



Do steroids benefit the heart in DMD?



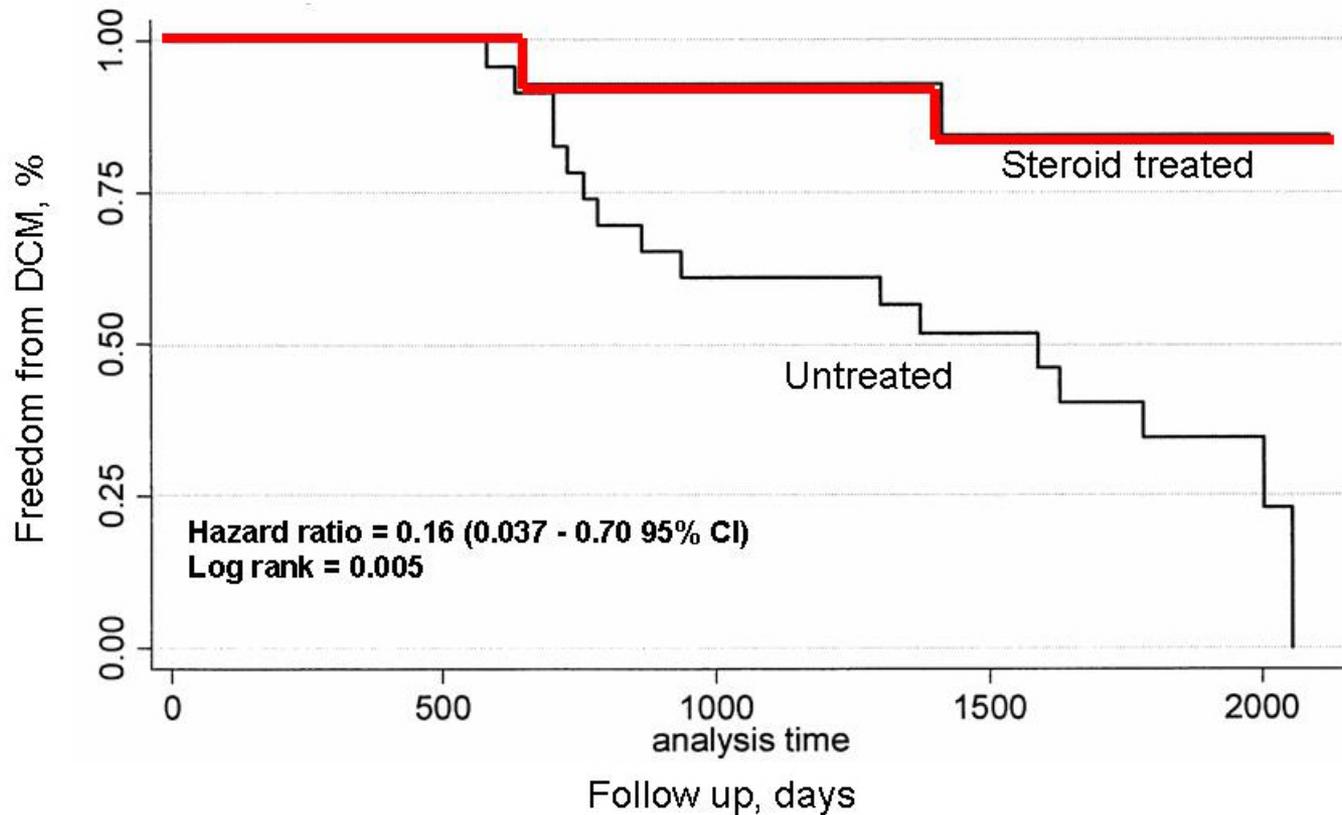
7. What treatment is available?

- 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



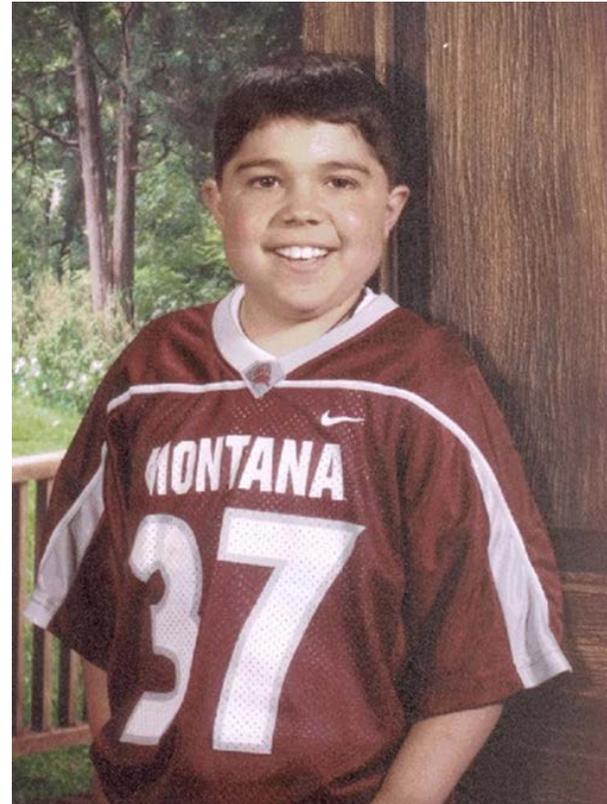
Steroid Treatment

Kaplan-Meier Estimate of Freedom from DCM, steroid treatment



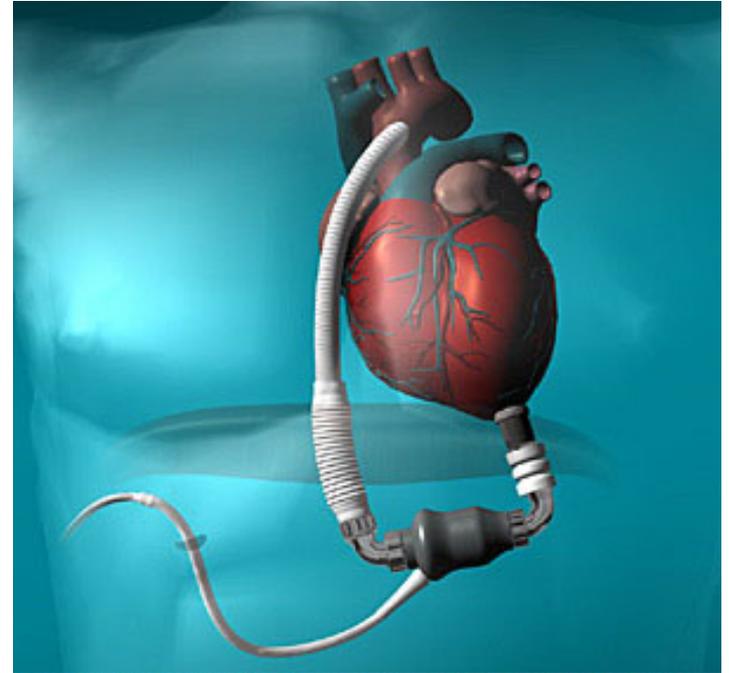
7. What treatment is available?

- At end stage HF
 - Continuous IV milrinone
 - Cardiac Transplantation
 - Few DMD patients transplanted
 - More BMD patients transplanted
 - Problems
 - Limited donor availability
 - Trading one disease for another
 - Quality of life issues



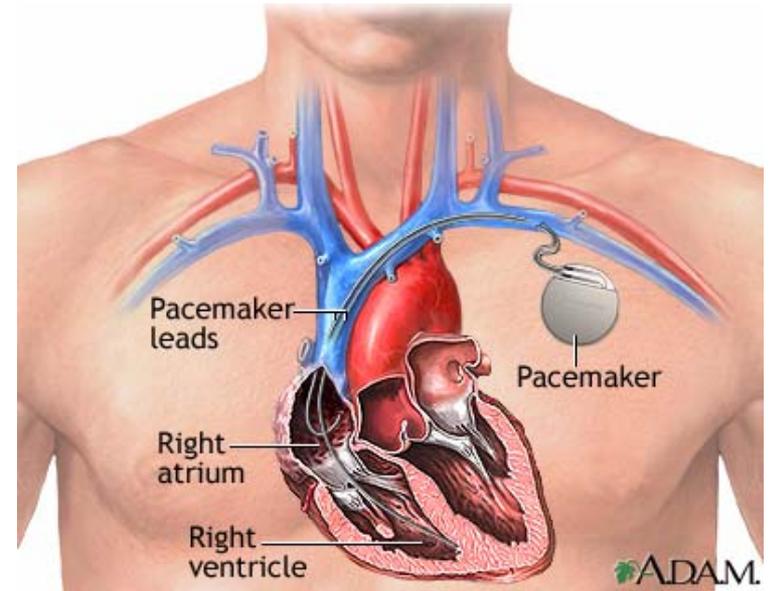
7. What treatment is available?

- **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



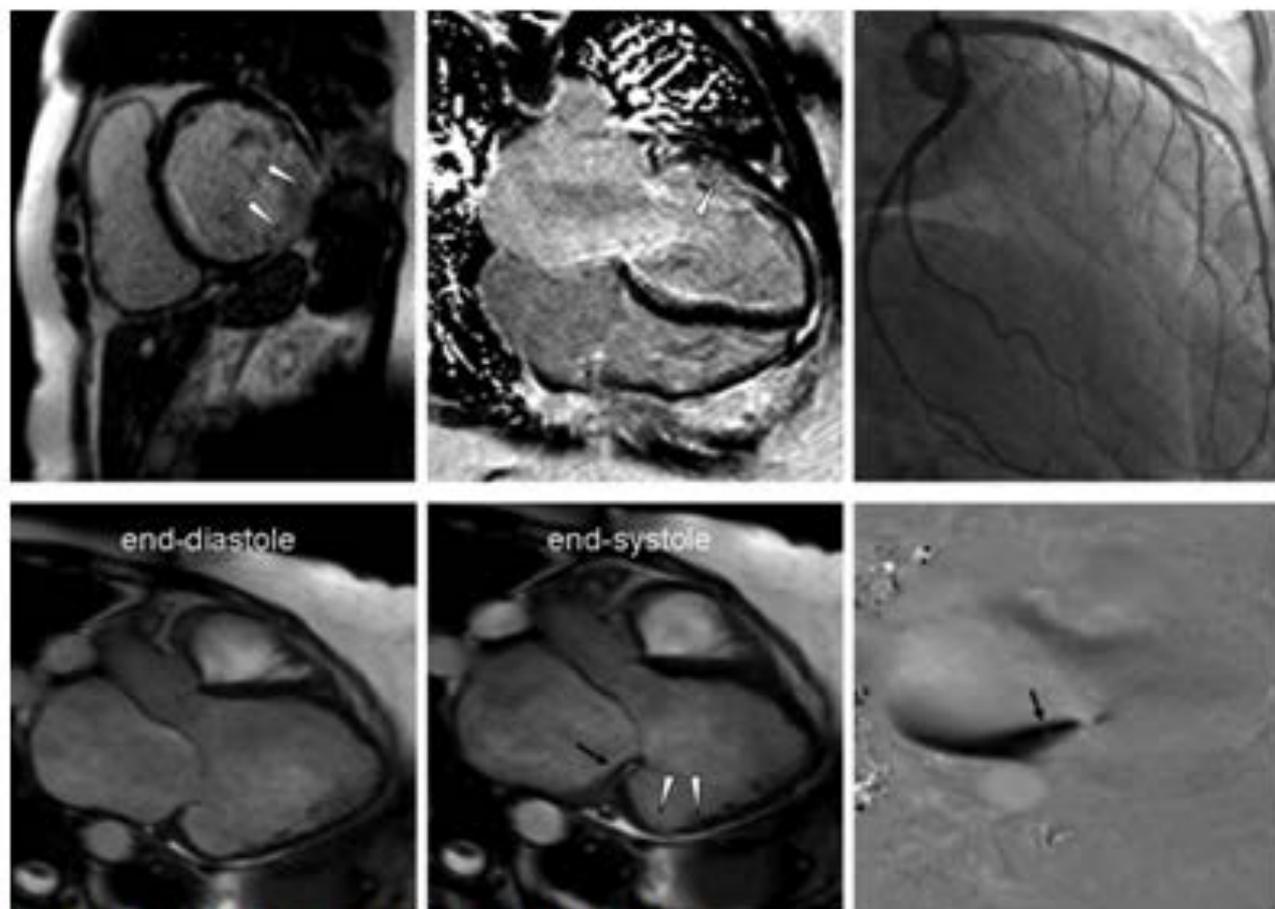
7. What treatment is available?

- 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

Cardiomyopathy in a female Duchenne carrier.



Verhaert D et al. *Circ Cardiovasc Imaging* 2011;4:67-76

Conclusions

- Cardiac evaluation should begin at diagnosis



Conclusions

- 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



Conclusions

- Early treatment prior to onset of dysfunction is unproven and controversial
 - Important to consider risks and benefits



Conclusions

- Need to use common sense AT ALL TIMES



Conclusions

- Maintain an open dialog with all care providers
 - They are working FOR YOU



Conclusions

YOU AND YOUR FAMILY

are the most important members of the health care team



THANK YOU

