The Heart Is A Muscle Too!

The Cardiomyopathy In Duchenne Muscular Dystrophy

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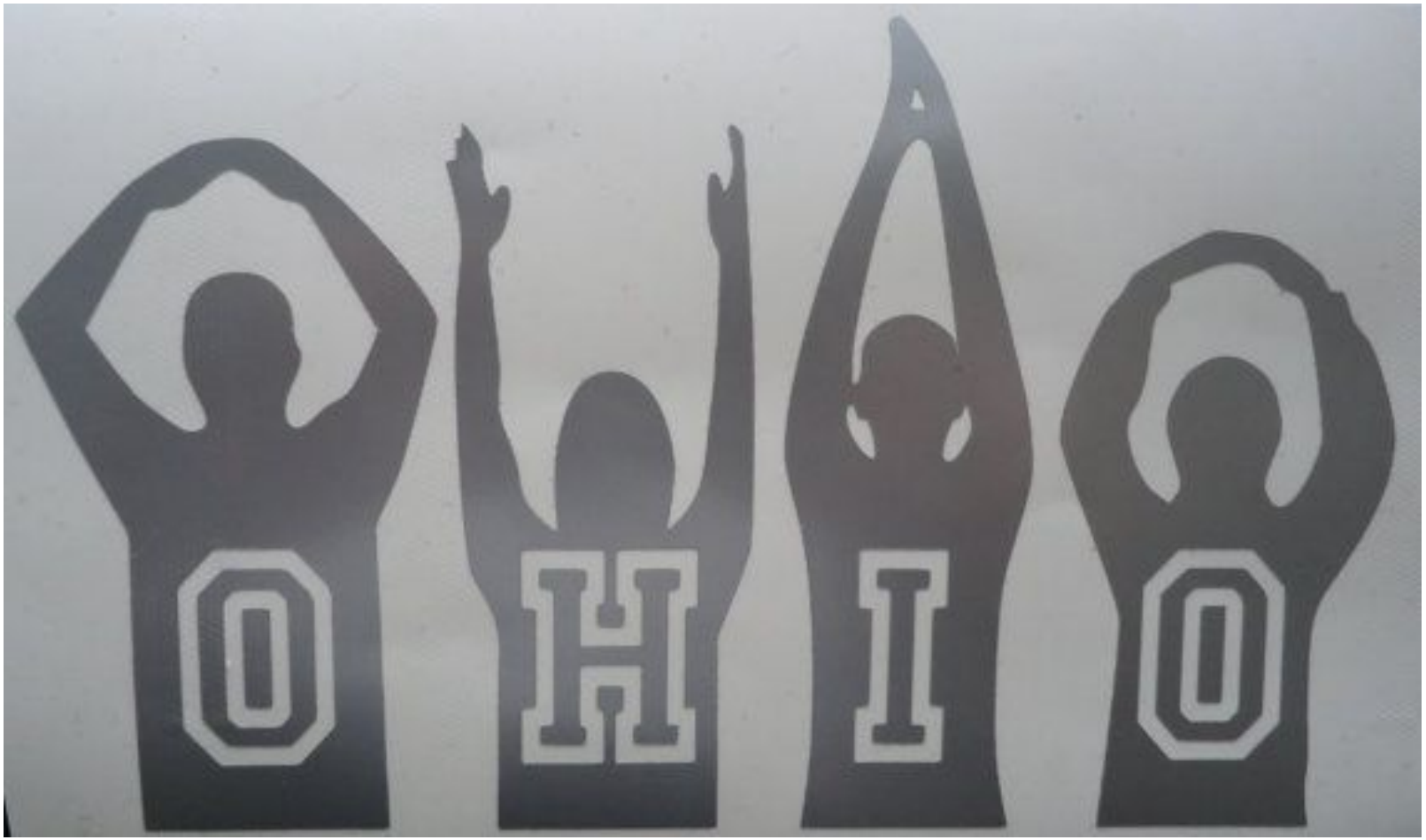
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Why are cardiologists interested in caring for patients with neuromuscular disorders?

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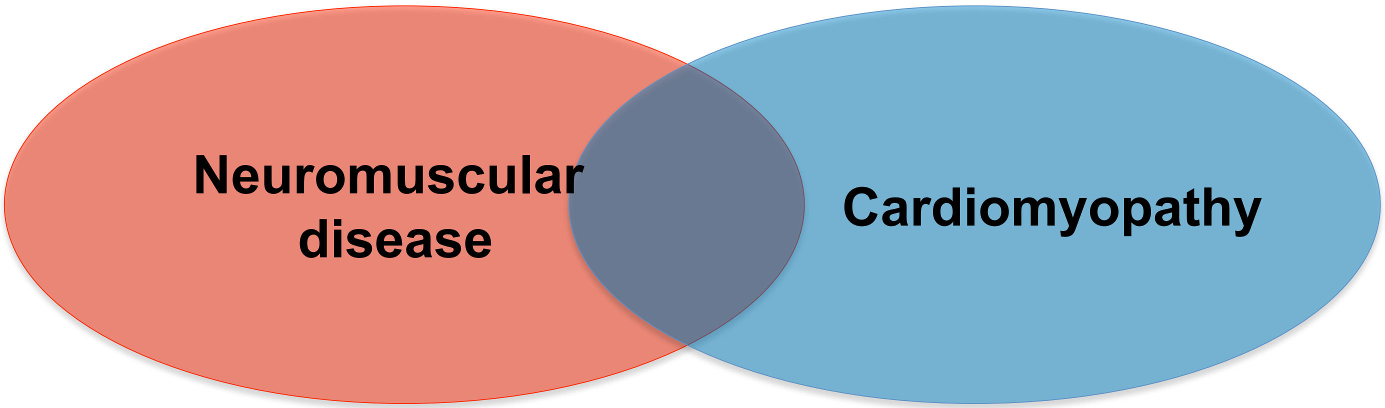
Cardiologists are interested in neuromuscular disorders

- Improve quality/duration of life of patients with:
  - Neuromuscular as well as cardiovascular disease



  - Many neuromuscular diseases such as DMD have an associated cardiomyopathy and vice versa
- Understanding DMD cardiomyopathy will likely improve understanding of DMD skeletal muscle disease
- This will ultimately improve duration and quality of life for our patients

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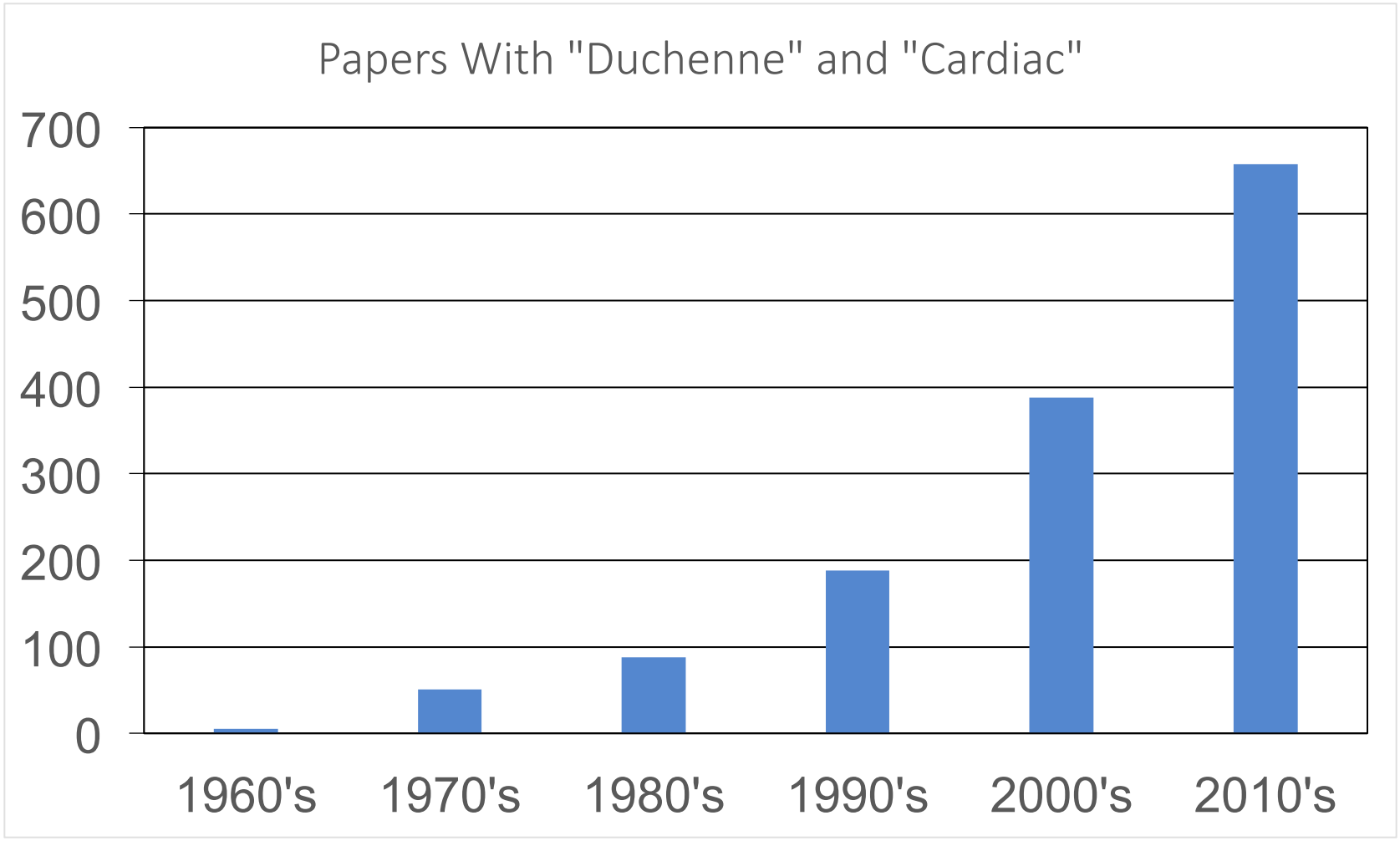
Interest in DMD cardiomyopathy has experienced an exponential increase



Hot topics in DMD cardiomyopathy

- Current cardiac standards of care
- Cardiac magnetic resonance imaging (CMR)
- New insights into DMD chest pain
- Novel treatments employing cardiac devices
- Cardiomyopathy in female carriers

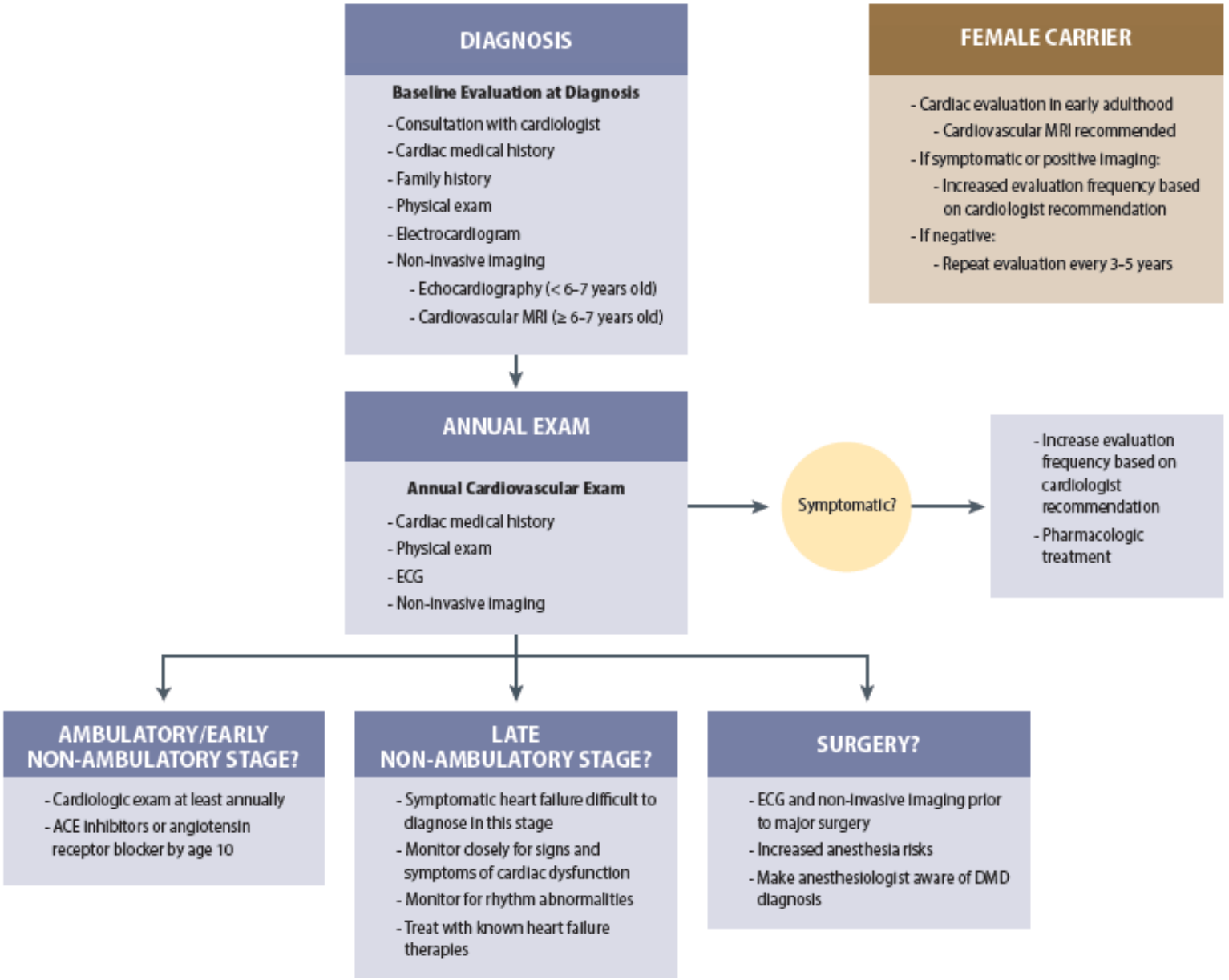
Current cardiac care standards

Lancet Neurol. 2018 Apr;17(4):347-361. doi: 10.1016/S1474-4422(18)30025-5. Epub 2018 Feb 3.

Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management.

Birnkrant DJ[1], Bushby K[2], Bann CM[3], Alman BA[4], Apkon SD[5], Blackwell A[3], Case LE[6], Cripe L[7], Hadjiyannakis S[8], Olson AK[9], Sheehan DW[10], Bolen J[11], Weber DR[12], Ward LM[8]; DMD Care Considerations Working Group.

Author information



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Current cardiac care standard-summary

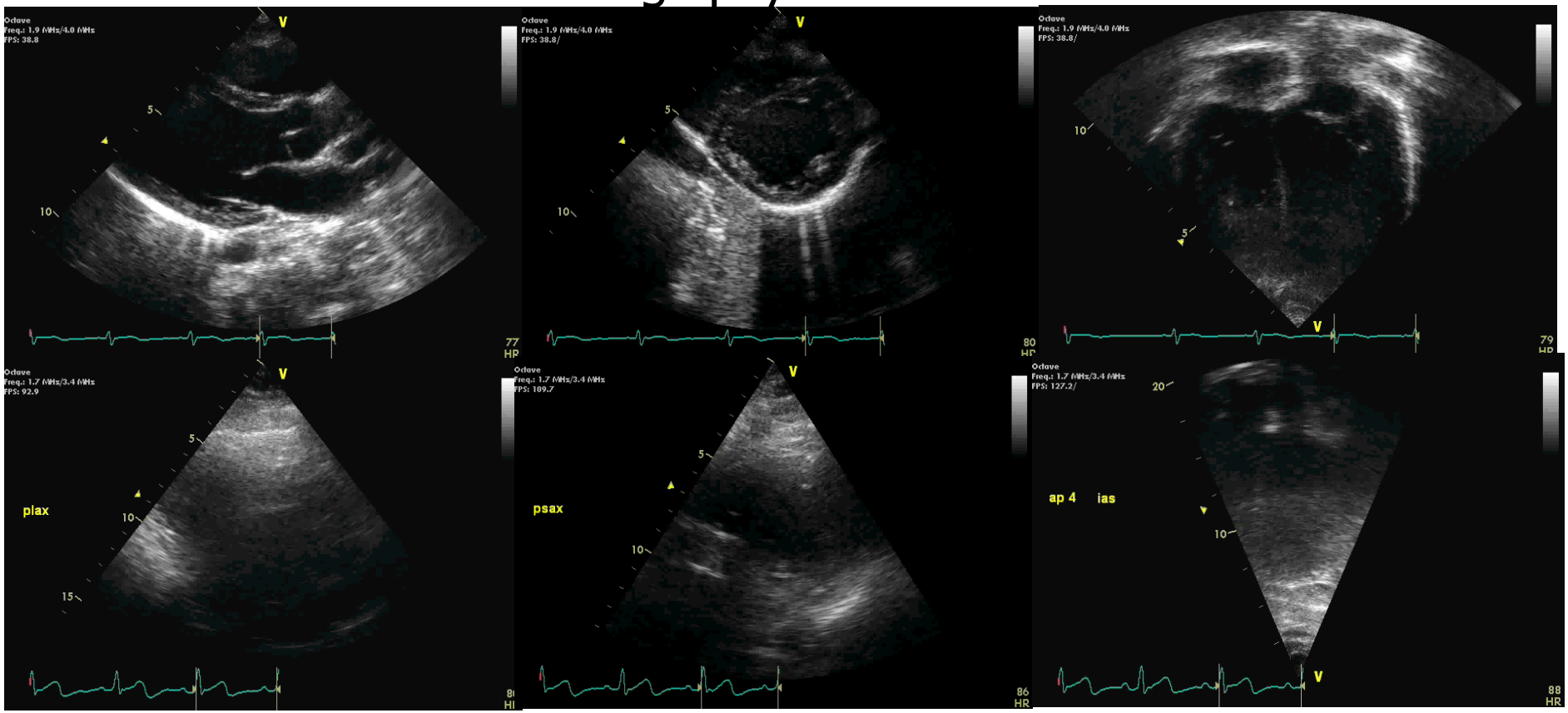
- Cardiology should be involved at diagnosis
- Yearly evaluations while the patient is asymptomatic
  - ECG and cardiac imaging (MRI preferred)
- Increase in frequency as symptoms develop
- ACE inhibitors started by age 10 years
- Cardiac evaluation before major surgery
- Female carriers should be evaluated

Cardiac imaging is revealing a great deal about the disease

Cardiac imaging is important because…

- Help us to better understand the natural history of the disease
  - As imaging modalities improve we see the disease with new eyes
    - Era of echocardiography: Cardiomyopathy not present until late teen years
    - Now with CMR: know disease present much earlier
- Improved understanding will
  - Guide clinical care
  - Provide better clinical trial endpoints

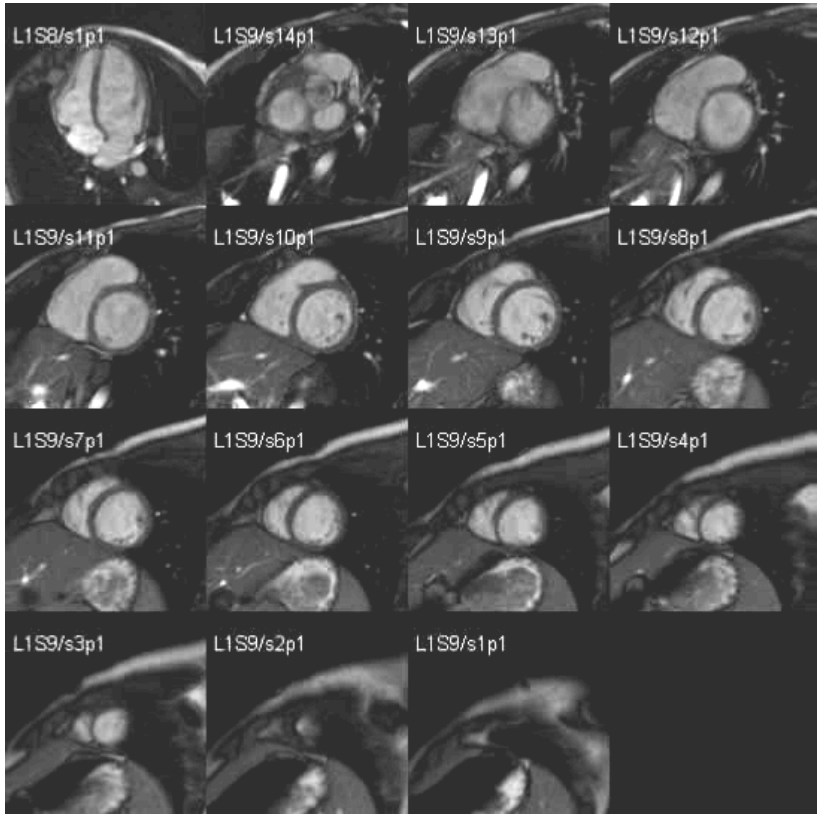
Echocardiography has limitations



- Image quality is poor in many DMD patients (especially in non-ambulatory patients)
- Sub-optimal images result in poor clinical decision making and poor clinical trial data

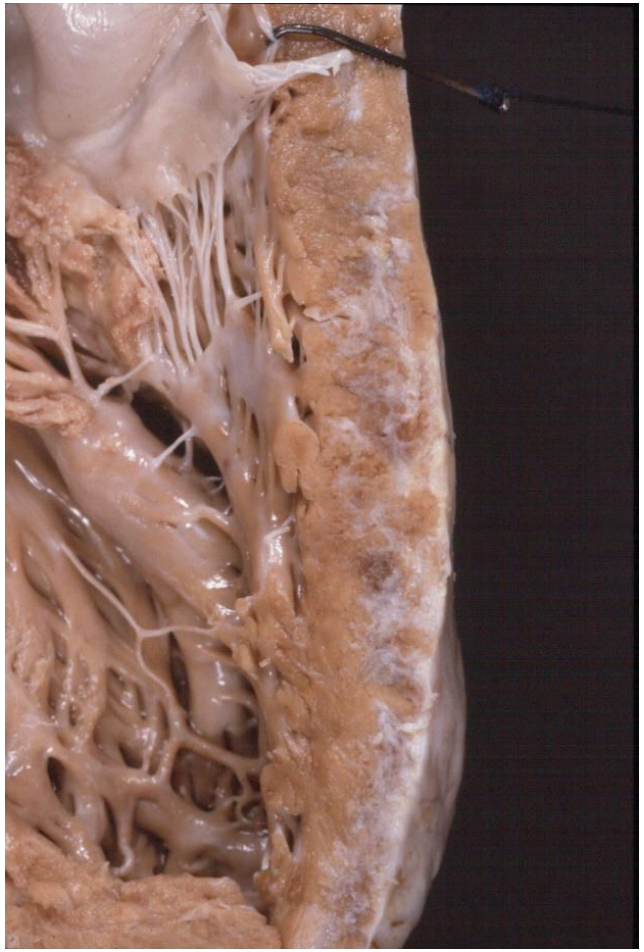
CMR offers advantages in DMD/BMD

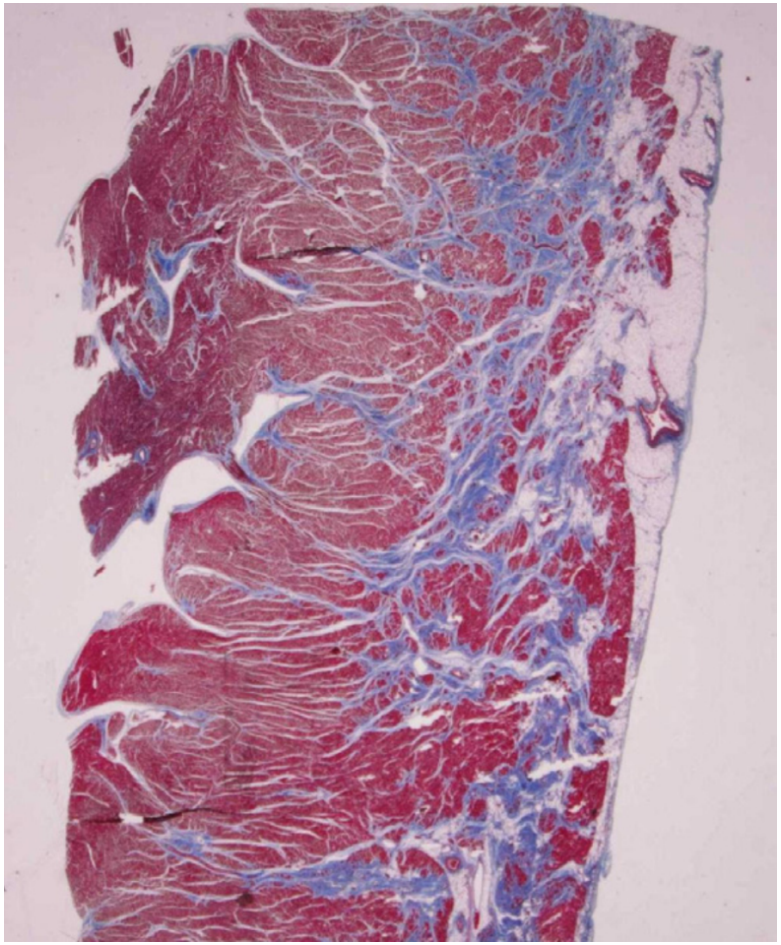
- Advantages
  - Lack of radiation exposure
  - Provides detailed information:
    - Myocardial mass
    - Volume
    - LV and RV function
    - Fibrosis quantification
    - Edema/inflammation
    - Myocardial strain
- Disadvantages
  - IV placement required for fibrosis quantification
  - Longer scan times
  - Pediatric patients are not cooperative
  - Lack of global availability



A key concept in understanding DMD cardiomyopathy

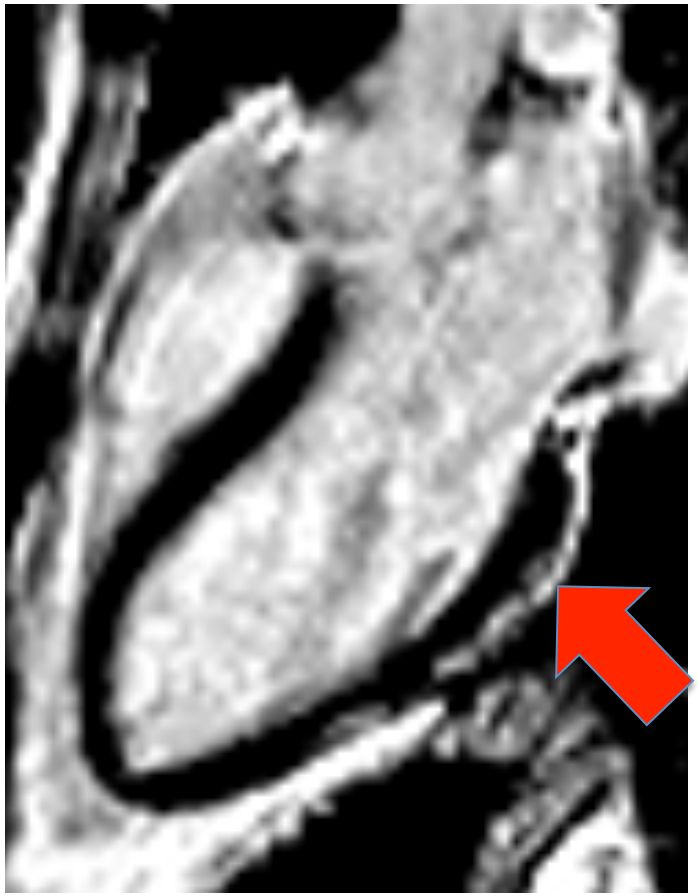
Cardiomyopathy in Duchenne muscular dystrophy is characterized by extensive sub-epicardial fibrosis



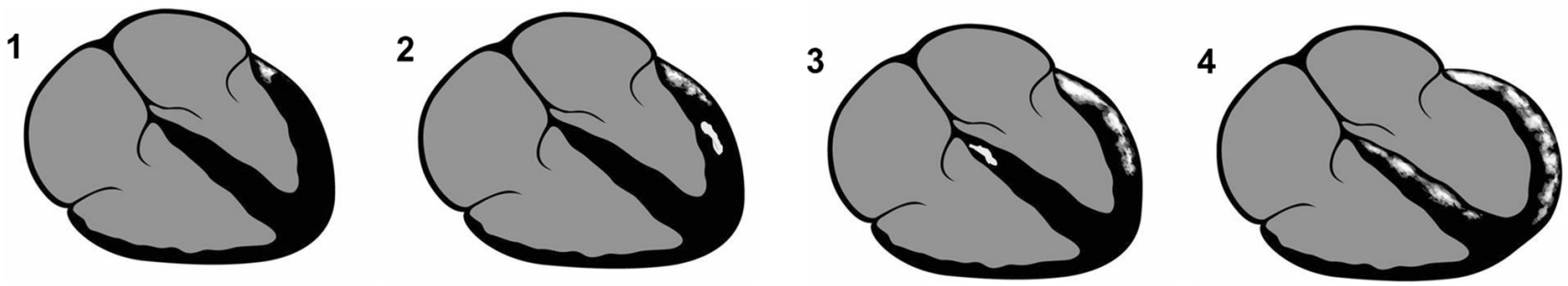


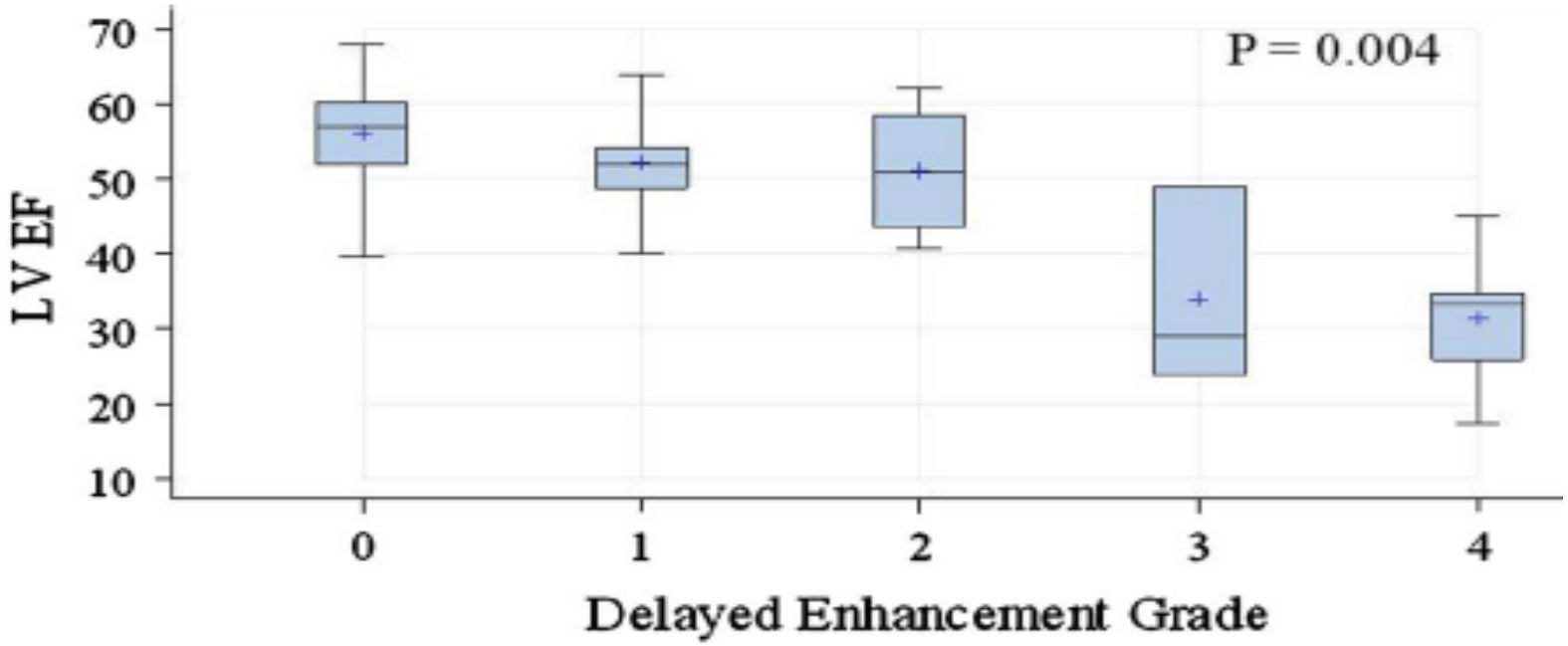
CMR has expanded our understanding of DMD cardiomyopathy

- Sub-epicardial fibrosis is easily identified easily on CMR
  - Fibrosis starts in the sub-epicardium of the basolateral or inferolateral wall and progresses to apex and then septum
  - Importantly, it is present
    - Prior to decline of LV function
    - Early in the disease
- Of note, sub-epicardial enhancement is seen in myocarditis
  - Represents inflammatory infiltrate
- Begs the question:
  - Are similar pathophysiological mechanisms at work in DMD and myocarditis?



Late gadolinium enhancement (fibrosis) in DMD Cardiomyopathy





Menon SC *et al*. Ped Cardiol 2014.

Natural history data (NCH)

- Fibrosis incidence (314 patients)
  - 17% <10 years
    - Youngest patient 6 years
  - 34% 10-15 years
  - 59% >15 years

  - 30% with normal cardiac function
  - 84% with abnormal cardiac function

Utilizing CMR to help us look at common problems differently-pediatric chest pain

Chest pain in the DMD patient

- FREQUENT and typically attributed to the musculoskeletal system
- Often dismissed in a pediatric ER
- Formal cardiac evaluation rarely undertaken
  - ECG is sometimes obtained
  - Troponin I (cTnI) rarely obtained
    - cTnI is a sensitive and reliable marker of cardiac muscle tissue injury
    - cTnI is normal or minimally elevated at baseline in DMD
    - Not thought to be predictive of disease progression

Our patient had elevated troponins did your patient have MRI changes?

What do you think is going on?

We have seen that too!

We had 3 patients present like that last year !

How did you treat them?

What have you noticed on follow-up?

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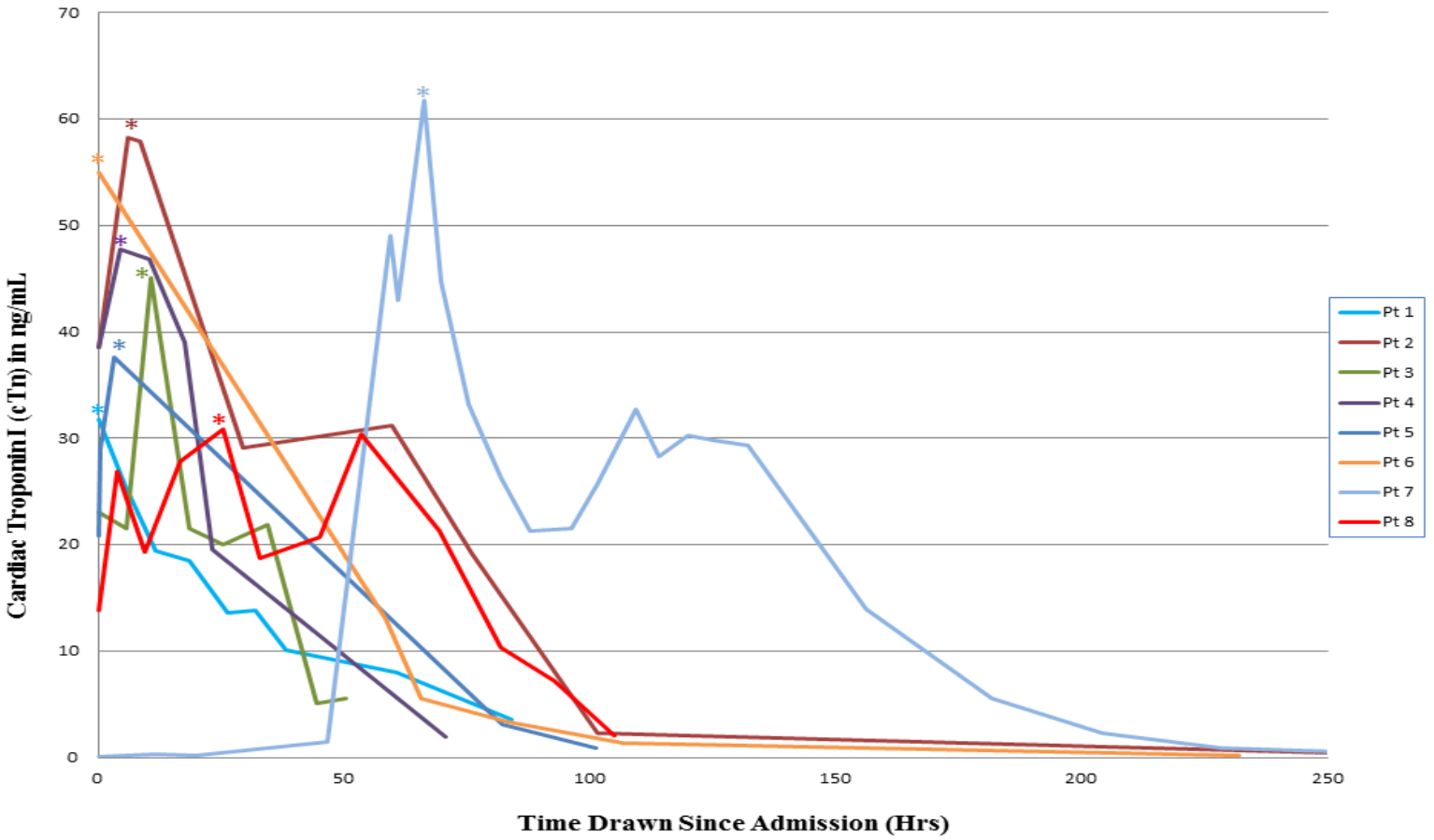
Chest pain in the DMD patient

- Case series of 8 DMD patients (NCH; 2013-2017)
  - Acute chest pain and transient elevations of cTnI
  - Average age of 15 years (range 9-23 years)
- Clinical characteristics
  - 8/8 acute chest pain, ECG changes and elevation of cTnI
    - ECG demonstrated diffuse ST segment elevation
    - NOT a ST-elevation myocardial infarction (STEMI) pattern thus not consistent with coronary ischemia
  - 5/8 no antecedent illness
  - 3/8 concurrent illness
    - Pneumonia, gastroenteritis, and sepsis
  - 8/8 were on an ACE inhibitor
  - 5/8 were on corticosteroid

Troponin course



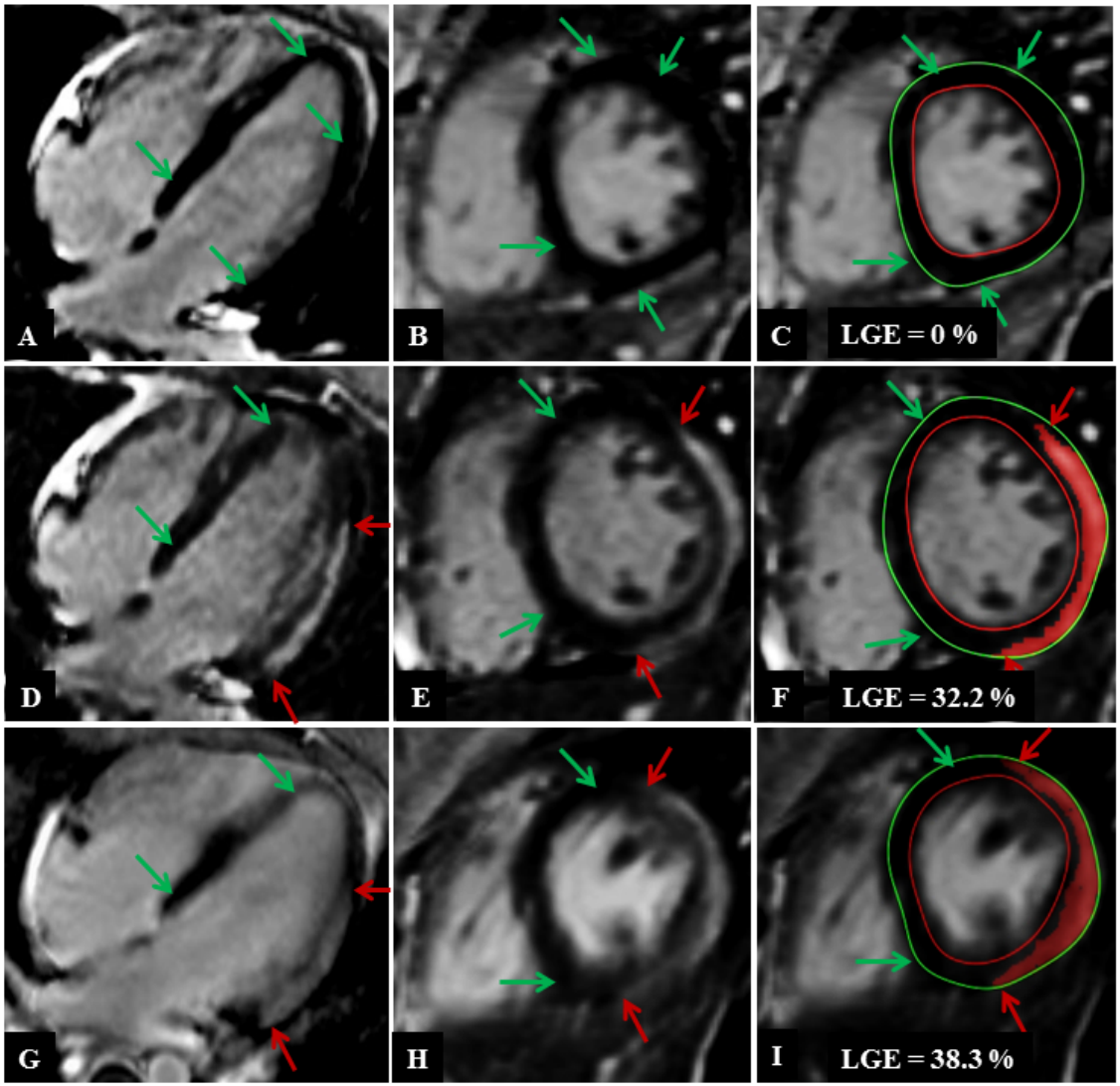
- 7/8 cTnI was elevated on admission and normalized within 4 days
- 1/8 presented with sepsis and late cTnI elevation which persisted >200 hours
  - Mean peak cTnI level of 44.1 (range 31-62 ng/ml)

CMR findings for patient 6

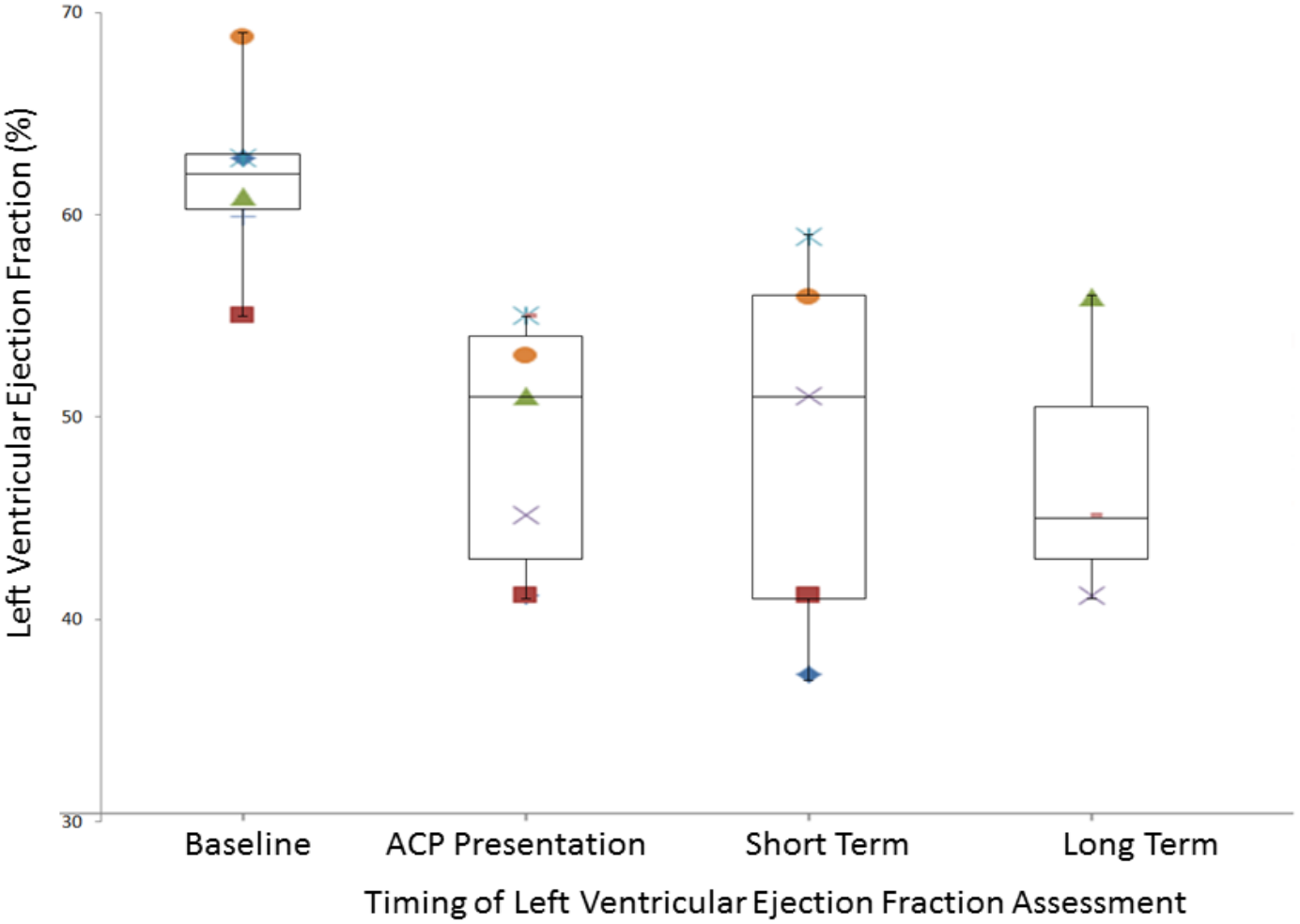
baseline

acute phase of event

follow-up



Serial LVEF assessment by CMR



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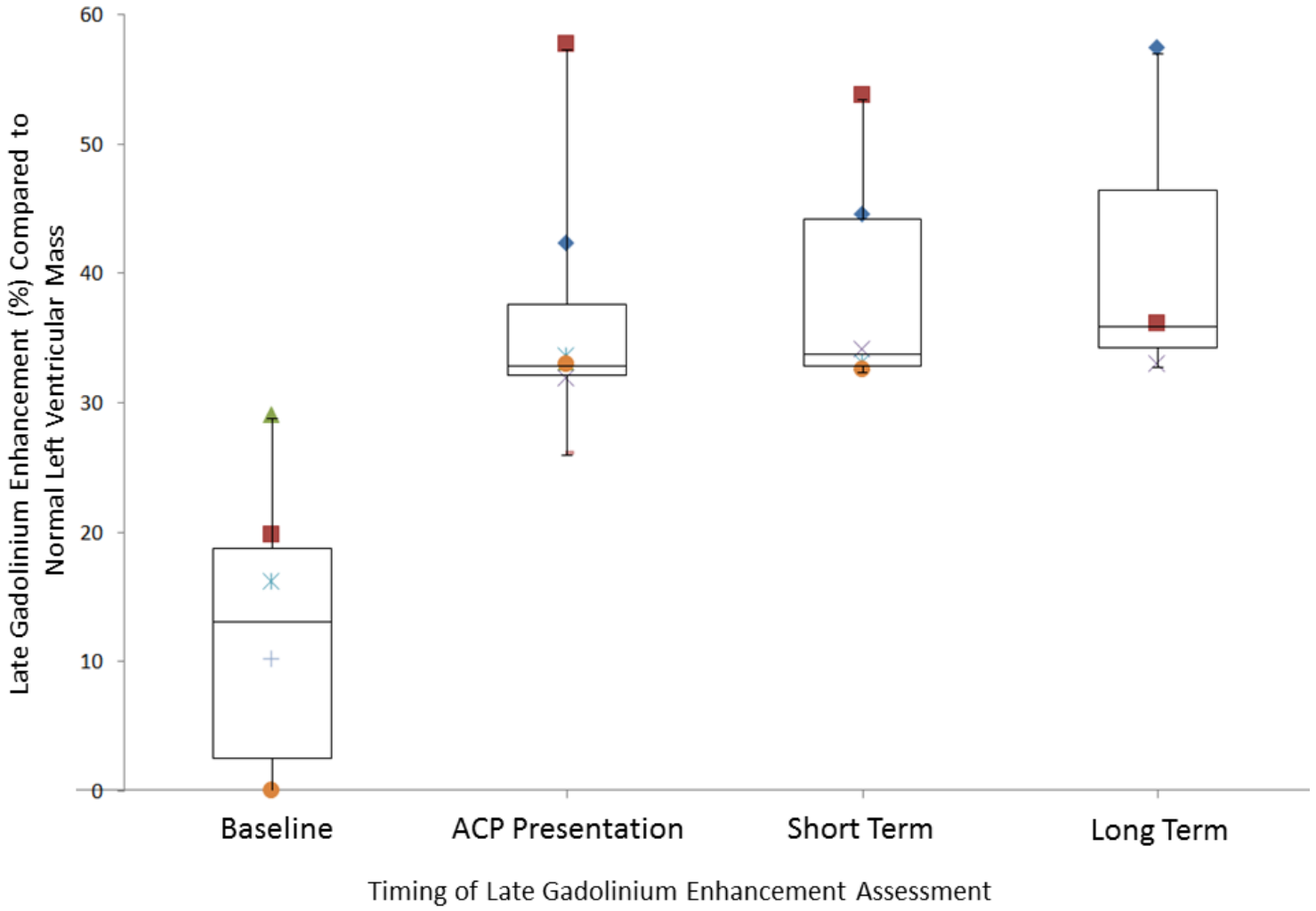
Serial LGE (fibrosis) evaluation by CMR



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Clinical course

- 4/8 patients underwent coronary artery evaluation
  - 2/4 cardiac CT and 2/4 cardiac cath
  - NO coronary abnormalities identified
- All viral studies were negative
- Patients received supportive care with traditional cardiac medications
- Ongoing follow-up continues on all patients

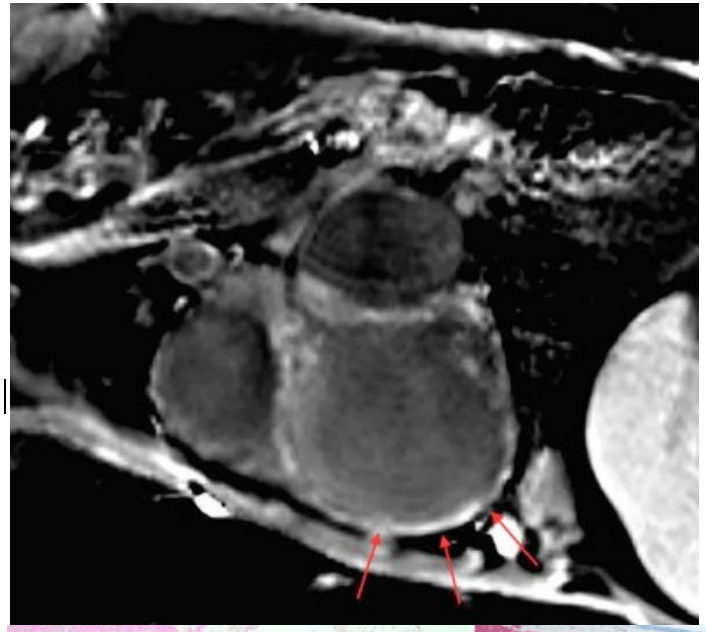
Chest pain discussion

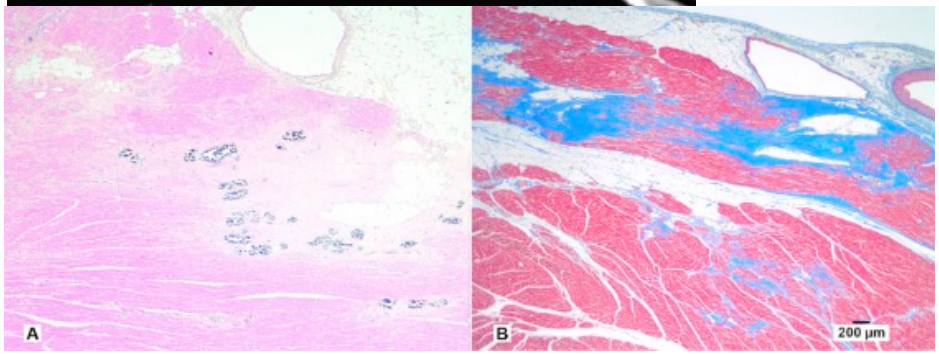
- We hypothesize that progression of DMD associated cardiomyopathy results in part from episodic myocardial injury rather than exclusively from continuous ongoing injury
  - Silent and recurrent events lead to cumulative injury
  - Process similar to that which occurs in skeletal muscle
  - Suggests a step wise model of disease progression as opposed to a linear one
- Unknown if there could there be external triggers
  - Viral infection
  - Physiological stress
  - Other intercurrent illness
- Role of inflammatory cytokines given that 3/8 patients presented with infection

Suspected acute myocardial infarction in a dystrophin-deficient dog

Sarah Morar Schneider [a,1], Amanda Erickson Coleman [b,1,2], Lee-Jae Guo [c,d], Sandra Tou [b], Bruce W. Keene [b], Joe N. Kornegay [a,c,d,e,f,*]

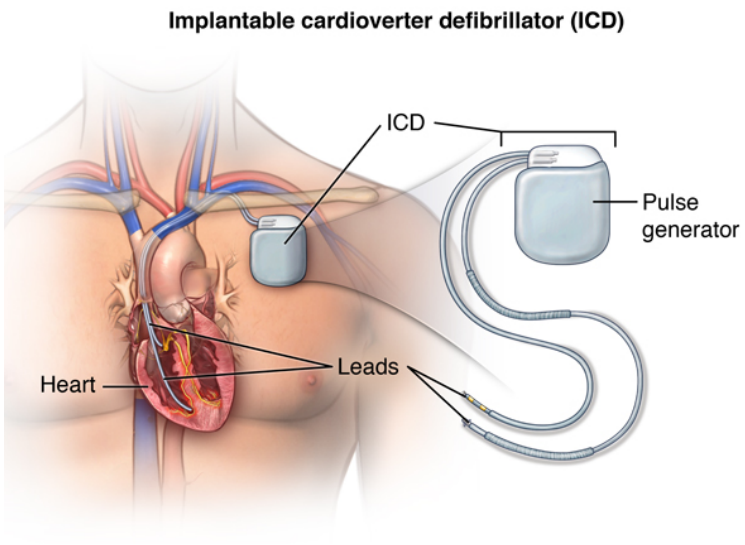
- 7 mo old GRMD dog with acute onset of cardiac decompensation consistent with a myocardial infarction
- Died suddenly at 45 months with induction of anesthesia
  - Serum biomarkers, including cTnI were markedly increased
  - Echo evidence of regional wall dysfunction
  - Sub-epicardial myocardial fibosis and decreased LVEF noted on CMR
  - Sub-epicardial fibrosis noted on pathology



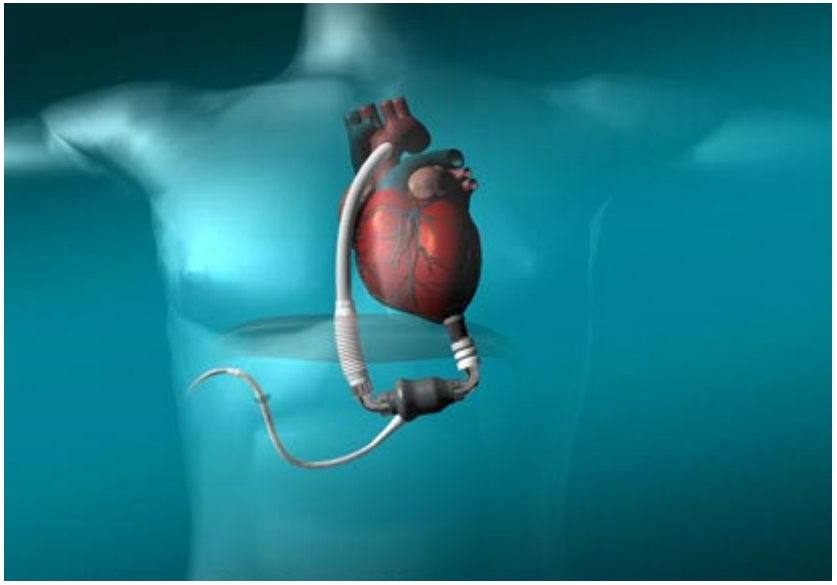


Neuromuscul Disord. 2016 Jun;26(6):361-6.

Cardiac devices in the treatment of Duchenne muscular dystrophy



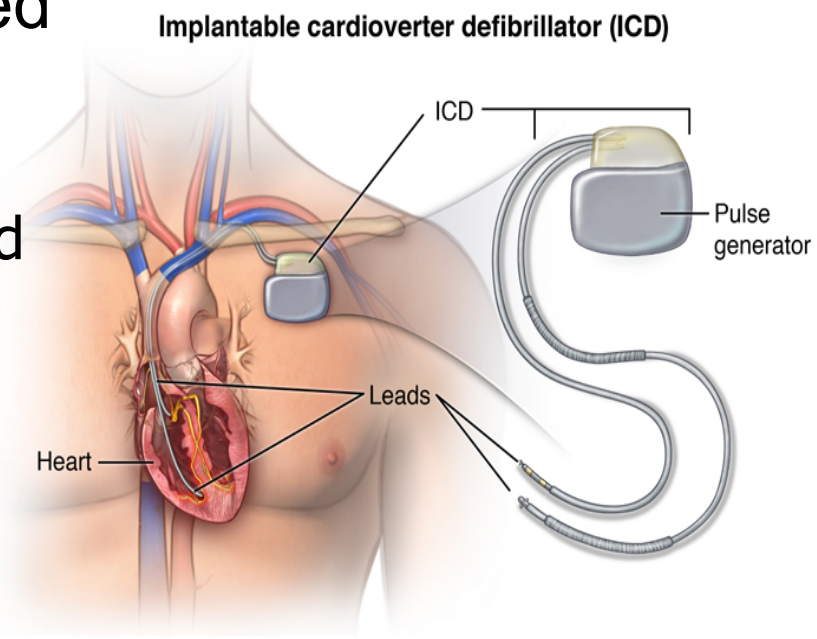
ICD



Left ventricular assist device

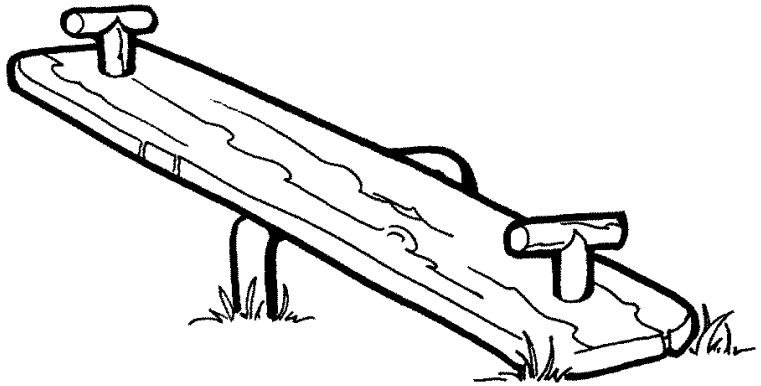
(ICD) Implantable cardioverter defibrillator

- Battery-powered device placed under the skin
  - Monitors heart rate
  - Provides a shock when sustained ventricular tachycardia or fibrillation is detected
- Newer-generation ICDs
  - Dual pacemaker function
  - Pacemaker feature paces the heart when bradycardia is detected



ICDs are great when needed, but come with complications

Prevent sudden death



May cause complications

- Inappropriate shocks
- Lead dislodgement
- Lead failure
- Psychological impact

What are the indications for ICD placement in DMD?

- NO significant data for ICD placement in patients with DMD

- Look to other patient populations for guidance
- Several important trials conducted in adults with cardiomyopathy
  - SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)
    - ICD therapy reduced overall mortality *for both ischemic and non-ischemic cardiomyopathy* by 23% compared to placebo

- As a result, current class I indications for ICD placement in adult cardiomyopathy are:
  - LVEF <35% and
  - NYHA functional class II or III (mild to moderate CHF)

Bardy et al. NEJM 2005;352:225

So where does that leave us….

- Individuals with cardiomyopathy are at risk of sudden cardiac death
- ICD's prevent sudden cardiac death

Hmmmmm…….

- Pts with DMD develop cardiomyopathy
- Therefore everyone with DMD who is symptomatic with a LVEF<35% should get an ICD
- Or should they…..?

- What is the incidence of sudden cardiac death in DMD?

To answer this question, we must know more about the natural history of rhythm problems in DMD.

What is the natural history of rhythm problems in DMD?

- Villa et al retrospectively reviewed 442 holters of 235 pts (2010-2014)
  - Mean age 14 ± 4 years (88% were for routine screening)

	EF ≥ 55%	EF 35-54%	EF ≤ 35%
Number of patients	184	46	5
Non-sustained VT	2%	2%	40%
Death	3 (non-cardiac)	0	0

- Conclusions:
  - Clinically significant holter recordings were rare in patients with LVEF>35%
  - Sudden cardiac death is also rare in DMD patients with LVEF >35%
  - Holter monitoring has highest yield in DMD patients with dysfunction

Villa et al. J Am Heart Assoc 2016; 5:e002620

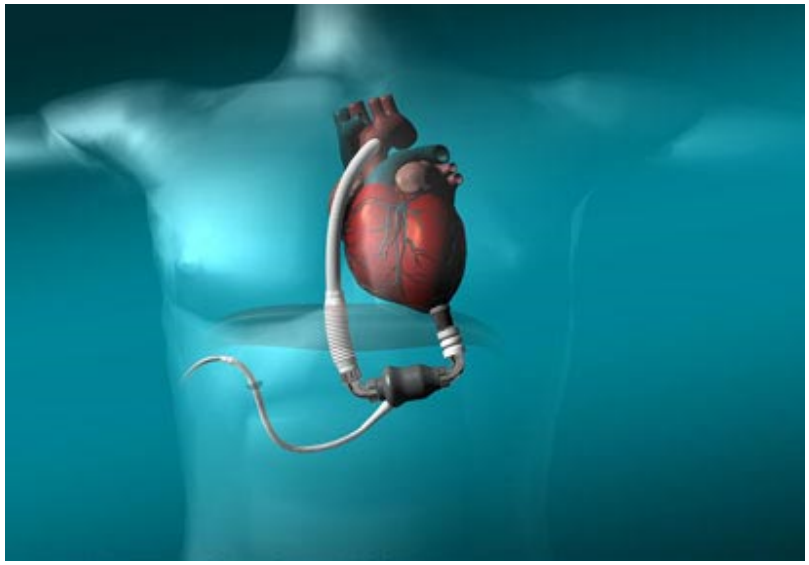
What is the incidence of sudden cardiac death in DMD?

- Nationwide Children's Hospital Sudden Cardiac Death Registry
  - International ongoing study
  - Identified 90 subjects with EF <55%
  - Average age 21 years
  - Average LVEF of 37% (range 8%-54%)
- 14/90 patients had significant arrhythmias
- 9 non sustained VT, 2 atrial tachycardia, 3 atrial flutter and 2 SVT
- 9/90 patients had ICDs implanted with **0 appropriate fires**
- One ICD patient died suddenly
  - Device interrogation demonstrated no tachyarrhythmia
  - Death was likely a respiratory event

Suggests ICD placement for EF <35% may not be indicated, in contrast to adult guidelines

Mechanical Circulatory Support

- Use of a mechanical pump/s to support a weakened heart muscle.
  - Ventricular Assist Device (VAD) to assist a single weakened ventricle
  - Total Artificial Heart (TAH) to replace a failing biventricular heart
- Three indications:
  - Bridge to transplant (BTT)
  - Bridge to Recovery
  - Destination therapy (chronic therapy)



- Transplantation is not typically considered an option in DMD
  - Limited donor availability
  - Complex ethical issues
    - Patients develop progressive respiratory failure and skeletal myopathy

LVAD use in DMD

- Limited case reports in the literature regarding use of LVAD in DMD
  - Largest series (7 patients) reported by Bambino Gesu Children's Hospital in Rome
    - 6 with DMD and 1 with β2 sarcoglycan deficit
    - Median follow-up of 21.7 months (range 3-45 months)
    - 3 non cardiac deaths

- Challenges exist for the use of LVAD devices in DMD
  - Multi-disciplinary evaluation required
  - Candidate selection critical
  - Delayed wound healing secondary to muscle wasting
  - Device placement must not disrupt diaphragm function

- Unclear if use will prolong duration and quality of life

Perri G et al J Thorac Surg 2017 Mar; 153(3) 669-674

Lastly…….

…Cardiac Findings in Carriers

Female carriers

- To date majority of carrier studies focused on cardiac manifestations
  - Psychosocial and skeletal muscle disease not extensively studied
- Believed that cardiac abnormalities are not present until adulthood
  - Incidence is variable and dependent on imaging modality
    - Echocardiographic studies (8%-38%)
    - Single recent CMR study (Florian et al)
      - 36 DMD/BMD carriers (44 $\pm$ 14 years)
      - 4% had a reduced LVEF
      - 44% had evidence of fibrosis
    - Suggests that carriers may be at higher risk than previously believed

Florian Eur Heart J Cardiovasc Imaging. 2016 Mar;17(3):326-33.

Nationwide Children's female carrier study

- Recruitment ongoing (aim 100 carriers/50 non-carriers)
  - Functional skeletal muscle evaluation
  - Psychological evaluation
  - Cardiac evaluation (CMR and exercise testing)

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Treadmill Exercise Testing

- Typically used to:
  - Define functional capacity in patients
  - Exclude ischemic heart disease
    - Which is not expected to be more prevalent in female carriers
- Carriers are highly functional individuals
  - treadmill exercise testing add information beyond the traditional 6-minute walk test
  - define those “with” and “without” manifestations of disease

Results:

- Full efforts were given by 100% of participants
- Maximal oxygen consumption (VO2 max)
  - Recognized as an indication of a person's fitness level
- No difference between somatic and non-somatic DMD moms with regards to VO2
- Significant difference between DMD moms and controls
- Translation: being a DMD mom meant that you had a lower general fitness level compared to age-matched control mothers

Results:

- PVC's are a marker of myocardial "irritability" in non-DMD (dilated) cardiomyopathy studies
- PVC's were noted during exercise in 50% of somatic carrier patients (25/49)

Preliminary thoughts about results

- While our DMD moms did not appear as physically conditioned as our age-matched control moms
  - Deconditioning is multifactorial and was still at a respectable level
  - Exercise appears safe for DMD moms
    - No mom has had a cardiac evaluation (exercise or MRI finding) which would preclude exercise
  - While arrhythmias were more common in carrier moms, they were a very benign type of arrhythmia (PVCs) and none demonstrated a sustained rhythm abnormality

Nationwide Children's female carrier study-CMR results

	Carrier	Non-carrier
Average age (yrs)	42 ± 8 (29-63)	40 ± 10 (28-65)
LVEDVi > 100 ml/m^2 (chamber enlargement)	3/34 (8%)	0/12 (0%)
LVEF < 55%	5/34 (15%)	0/12 (0%)
Fibrosis	17/34 (50%)	0/12 (0%)

- These very preliminary data suggest a significant incidence of low LVEF and fibrosis
- We need to better understand the morbidity associated with carrier status

Conclusions

- The heart is an important muscle, too
- CMR is a valuable and informative tool to evaluate the cardiomyopathy in DMD
- Chest pain in the DMD patient may signal acute cardiac injury
  - cTnI levels and ECG should be obtained
- Cardiac devices have an evolving but uncertain role in management of DMD patients
- Carriers may be at elevated risk for cardiac disease
- Finally…

We can all achieve better patient outcomes with breakdown of clinical silos.

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THANK YOU

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