*MVIMG 7470: Fundamentals of Muscle Biology, Spring Semester 2014*

# Cardiomyopathy in Duchenne Muscular Dystrophy

February 5, 2014

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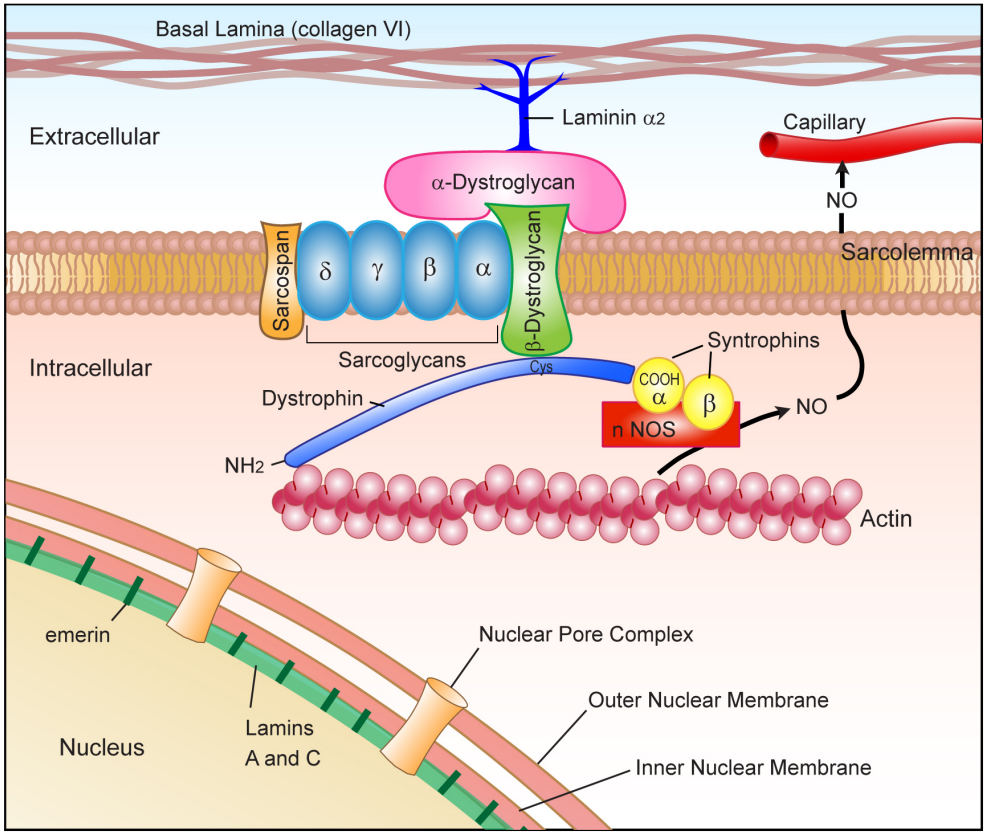
Medical Director, CMR/CT
The Ohio State University

# Outline

- Why cardiomyopathy develops in DMD
- Clinical presentation and outcomes
- Current guidelines for diagnosis and treatment
- Can we do better?

# Why Cardiomyopathy in DMD?

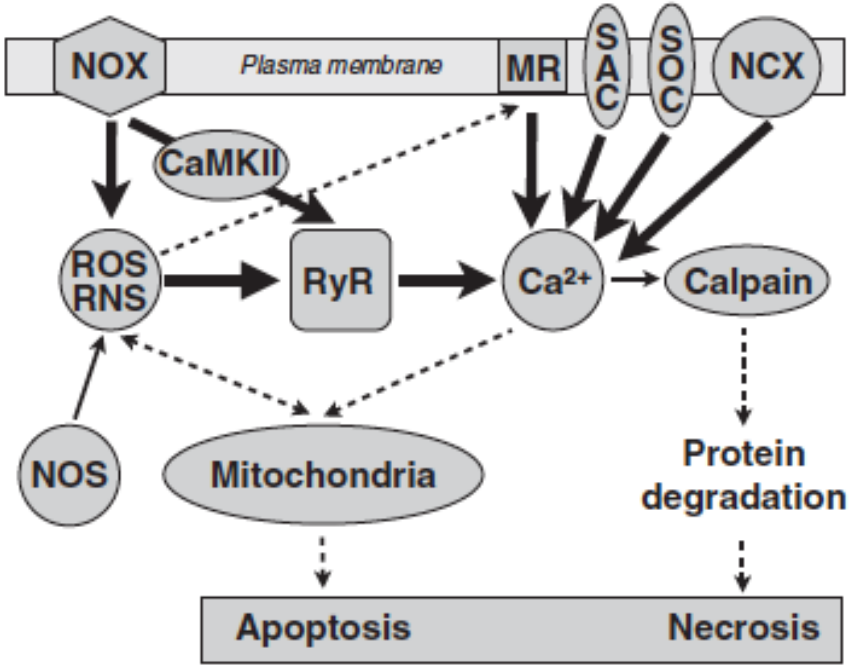
*Dystrophin is crucial for cardiomyocyte integrity*




Verhaert D *et al*. Circ Im 2011

# Damage and Cell Death Pathways

- Sarcolemmal fragility without stabilizing effect of dystrophin
- Intracellular calcium accumulation → protease activation, increased ROS
- Neuronal NOS mislocalizes to cytosol → impaired NO diffusion to μvasculature




Shirokova and Niggli. JMCC 2013.

ELSEVIER

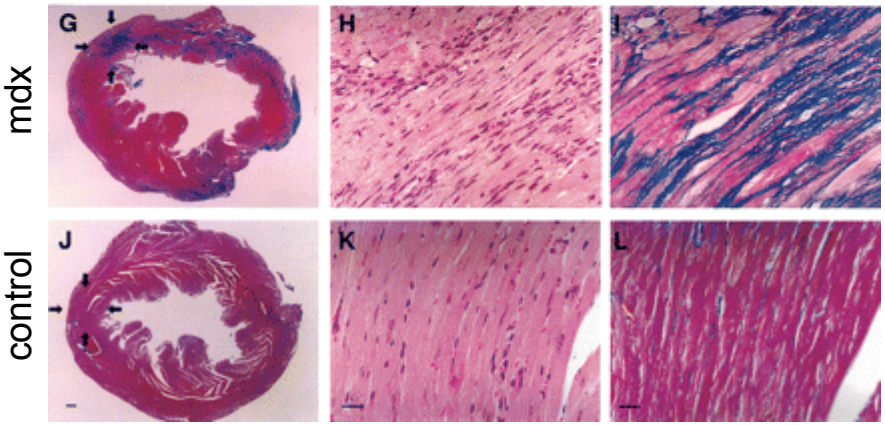
Cardiovascular Research 50 (2001) 509–515

Cardiovascular Research

www.elsevier.com/locate/cardiores
www.elsevier.nl/locate/cardiores

# Dystrophin-deficient myocardium is vulnerable to pressure overload in vivo

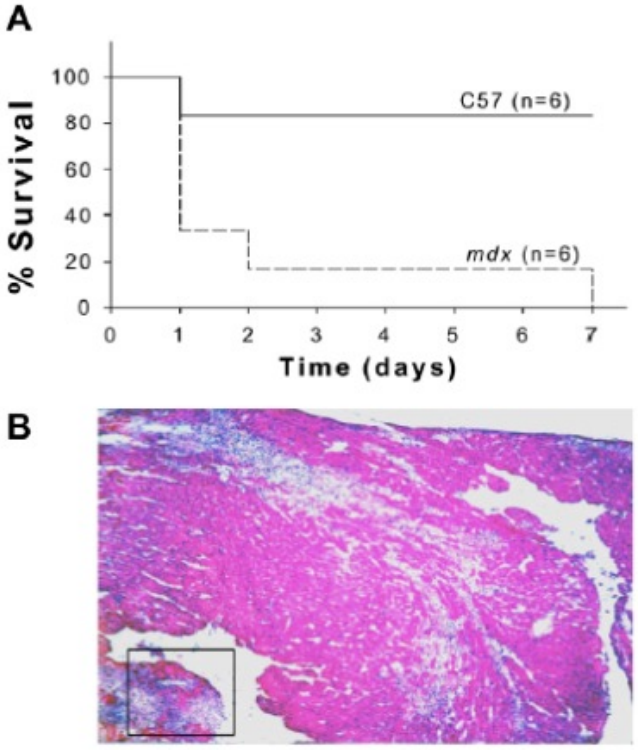
Yasuyuki Kamogawa[a], Sadatoshi Biro[a,*], Masato Maeda[a], Manabu Setoguchi[a], Tatsumi Hirakawa[a], Hiroki Yoshida[b], Chuwa Tei[a]




*The FASEB Journal* express article 10.1096/fj.01-0030fje. Published online May 29, 2001.

# Dystrophin-deficient cardiomyocytes are abnormally vulnerable to mechanical stress-induced contractile failure and injury

Gawiyou Danialou*, Alain S. Comtois[†], Roy Dudley*, George Karpati[‡], Geneviève Vincent[§], Christine Des Rosiers[§], and Basil J. Petrof*[,‡]



PERGAMON

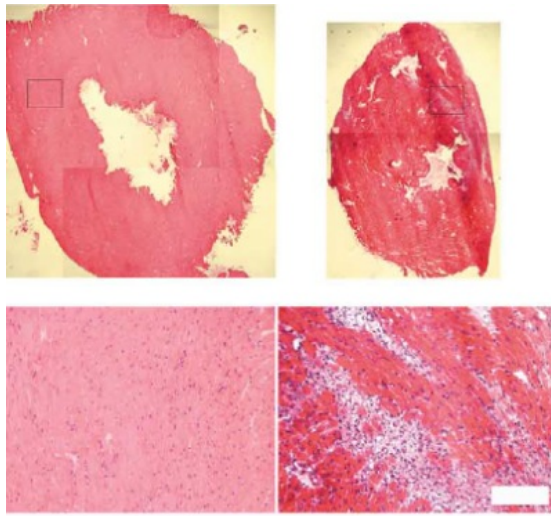
Neuromuscular Disorders 13 (2003) 294–302

www.elsevier.com/locate/nmd

# Cardiomyopathic features associated with muscular dystrophy are independent of dystrophin absence in cardiovasculature

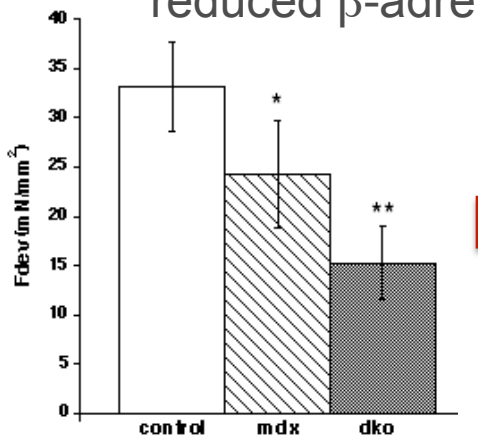
T.A. Hainsey, S. Senapati, D.E. Kuhn, J.A. Rafael*

- Studied dko mice with transgenes that restore dystrophin to cardiomyocytes but not cardiovasculature
- Cardiomyopathic features prevented by presence of dystrophin in cardiomyocytes, but not in cardiovasculature

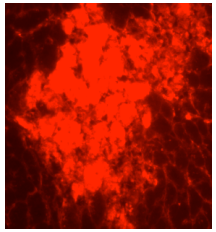


# Putting It All Together

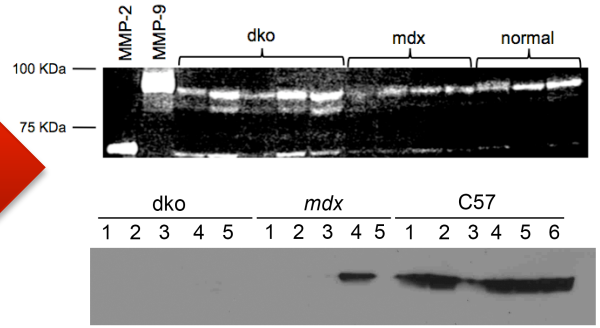
Step 1: Cardiac contractile dysfunction / reduced β-adrenergic response



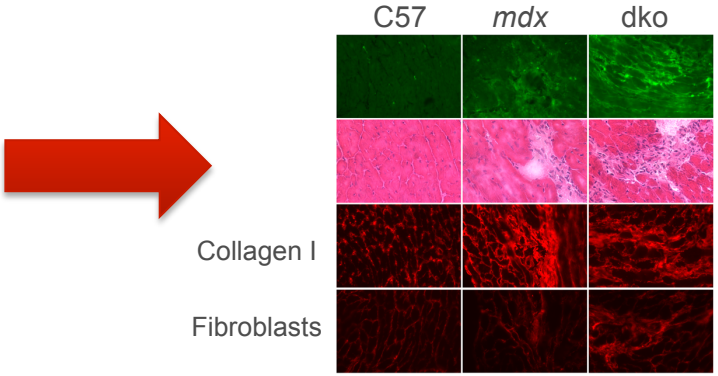

Step 2: Heart muscle damage



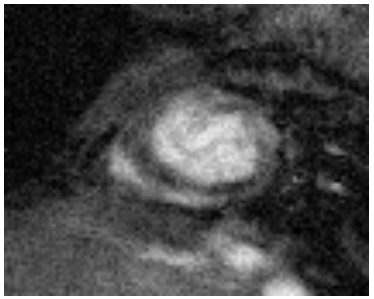
Step 3: Unregulated MMP remodeling




Step 4: Collagen scarring




*All While Ejection Fraction (EF) Is Normal*



*Courtesy Jill Rafael-Fortney, PhD*

# Outline

- Why cardiomyopathy develops in DMD
- Clinical presentation and outcomes
- Current guidelines for diagnosis and treatment
- Can we do better?

# Natural History

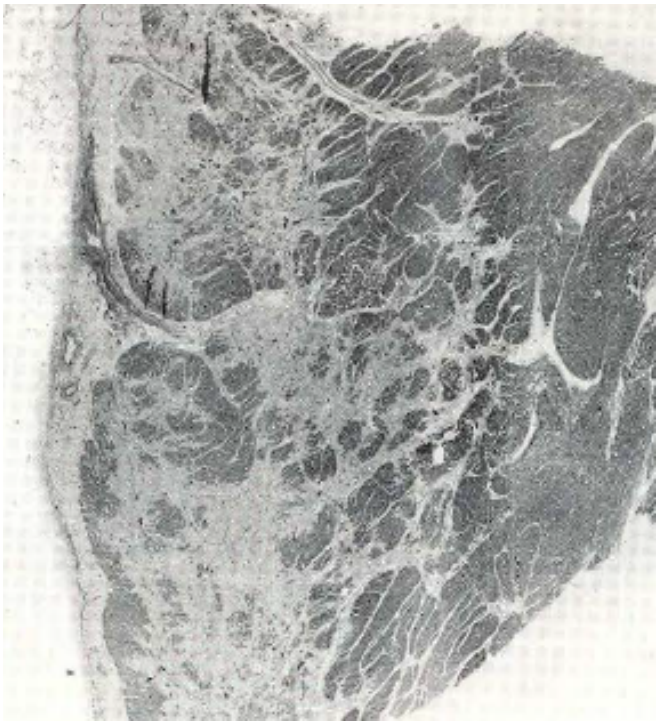
| NYHA Functional Classification (46) | |
|---|---|
| None | |
| I | No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. |
| I | No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. |
| II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. |
| III | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF. |
| IV | Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest. |

- Diagnosis of DMD made ~age 5-7 years
- Full-time use of wheelchair between ~10-12 years
- Signs/symptoms of cardiomyopathy:
  - Typical exertional symptoms may not be present
  - Vague/nonspecific symptoms of LV dysfunction: abdominal discomfort, nausea, palpitations, etc.
  - Overlap with those of pulmonary disease
  - Chest pain with acute episodes of cardiac damage
  - Cardiac complications during noncardiac illness
  - Sudden death/arrhythmias
- Death due to cardiopulmonary disease in 3$^{rd}$ to 4$^{th}$ decades of life

Romfh and McNally. Curr Heart Fail Rep 2010

# Prevalence in Humans by Autopsy: ~100% By 3rd Decade of Life

- Muscle replacement with fibrosis & some fat
- From basal inferolateral epicardium to diffuse disease



Frankel and Rosser. Human Pathol 1976.

# Cardiomyopathy Detection *In Vivo*: ECG

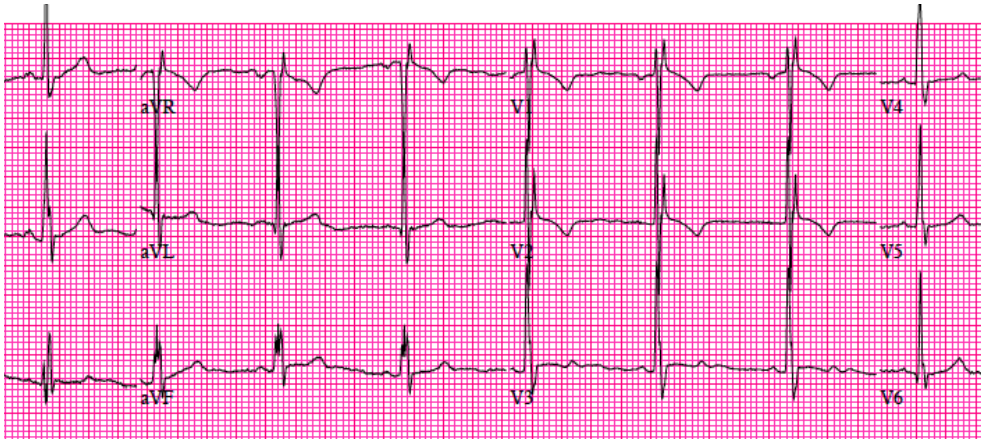
'LV'

- R (V6) > 98th percentile ✓
- S (V1) > 98th percentile ✓
- R (V6)+S(V1) > 98th percentile ✓
- Q (III or V6) > 98th percentile
- R/S ratio (V6) > 50th percentile ✓
- ST segment depression (V5 or V6) > 0.5 mm
- Total mid-precordial voltage (V3 or V4) > 60 mm

'RV'

- R (V1) > 98th percentile
- S (V6) > 98th percentile
- R/S ratio (V1) > 98th percentile
- Right axis deviation
- qR pattern (V1)
- Upright T wave (V1)
- rSR′ pattern with R′ > 10 mm (V1)
- ST segment depression (V1, V2 or V3) > 0.5 mm

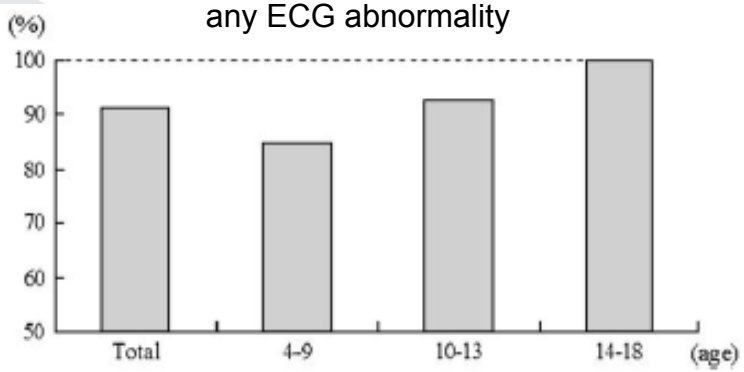
James…Cripe. Neuromusc Disord 2011.



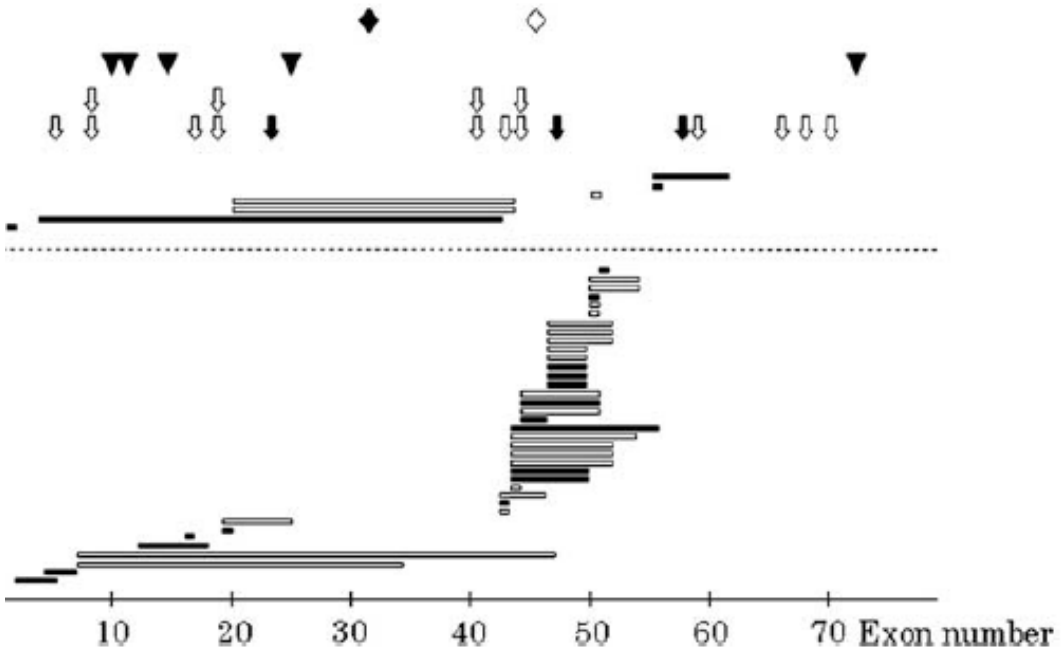

DMD age 19; HR 73 (on beta-blocker)

# High Prevalence of ECG Abnormalities

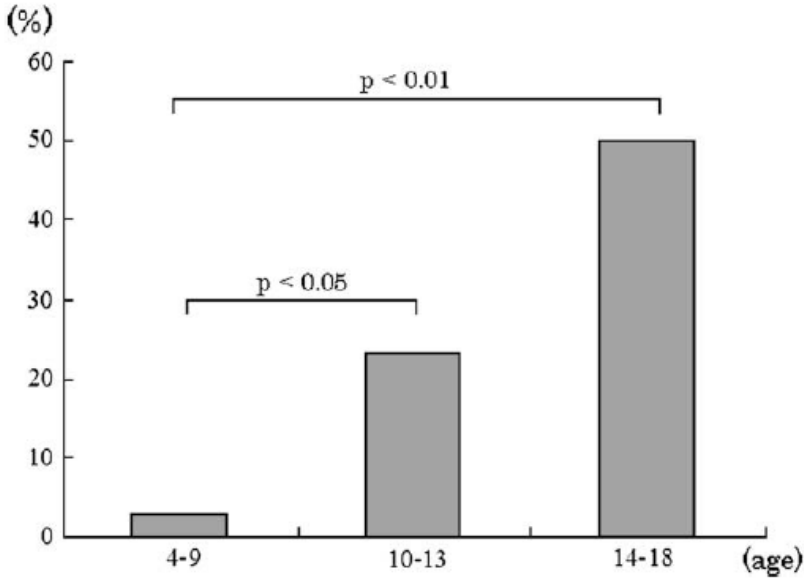
any ECG abnormality




Open symbols: ECG abnormalities present;
Filled-in symbols: ECG abnormalities absent




Q wave >0.4 mV; R in V5 plus S in v1 <2nd %ile

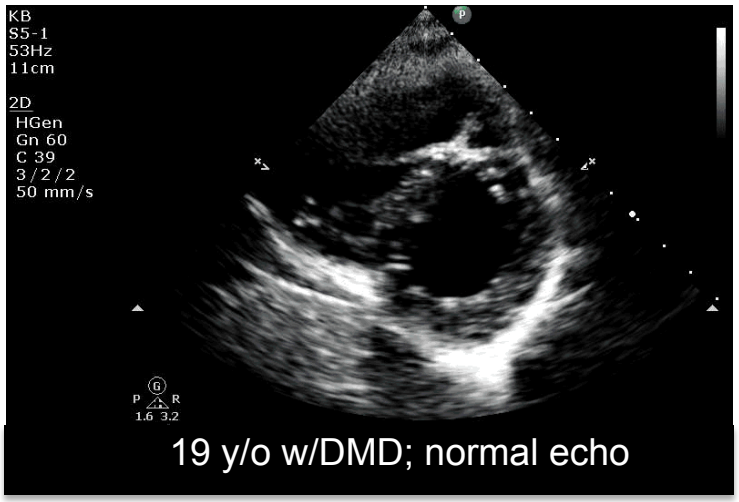



Takami Y *et al.* Pediatr Neurol 2008.

# Cardiomyopathy detection *In Vivo*: Echocardiography (Ultrasound)

| | DMD (N = 25) |
|---|---|
| Age (y) | 14.8 ± 3.1 |
| Heart rate (bpm) | 87 ± 17 |
| LV diastolic dimension (mm) | 44 ± 5 |
| Shortening fraction (%) | 34 ± 3 |
| Ejection fraction (%) | 62 ± 7 |
| Wall thickness of IVS (mm) | 7.0 ± 2.0 |
| % thickening of IVS (%) | 42.7 ± 13.0 |
| Wall thickness of PW (mm) | 8.3 ± 1.0 |
| % thickening of PW (%) | 59.6 ± 12.7 |
| E (cm/sec) | 88 ± 16 |
| A (cm/sec) | 55 ± 17 |
| A/E | 0.61 ± 0.17 |
| A (% of normal)* | 117 ± 27 |
| A/ E (% of normal)* | 105 ± 20 |
| Tei index | 0.38 ± 0.07 |
| Pulsed TDI | |
| IVS Sw (cm/sec) | 2.6 ± 1.0 |
| Ew (cm/sec) | 3.6 ± 1.7 |
| Aw (cm/sec) | 1.7 ± 0.6 |
| LVPW Sw (cm/sec) | 3.1 ± 1.0 |
| Ew (cm/sec) | 5.5 ± 2.8 |
| Aw (cm/sec) | 1.9 ± 1.2 |

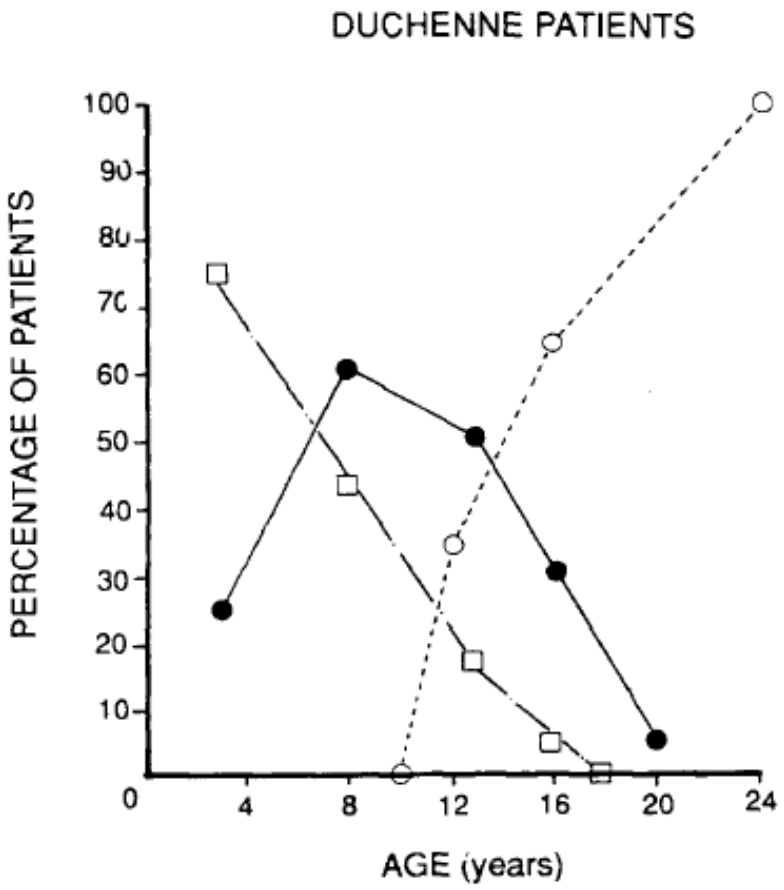
Mori K *et al.* Echocardiography 2007.




19 y/o w/DMD; normal echo

# Cardiomyopathy Detection *in vivo*: ECG and Echocardiography

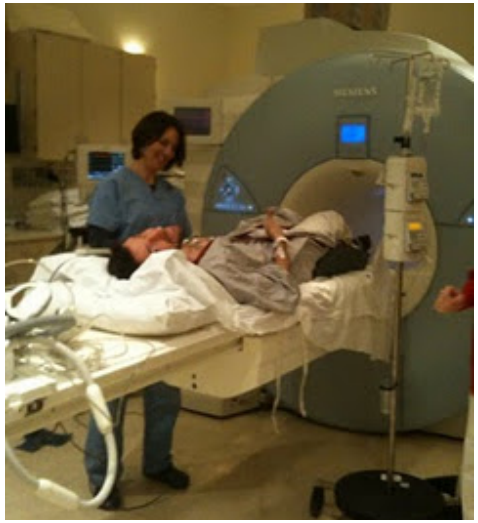
- Serial data in 326 DMD patients
- Abnormal ECGs in bo< 6 years
- Increasing clinically-apparent CMP (e.g. echo EF <45%) with age

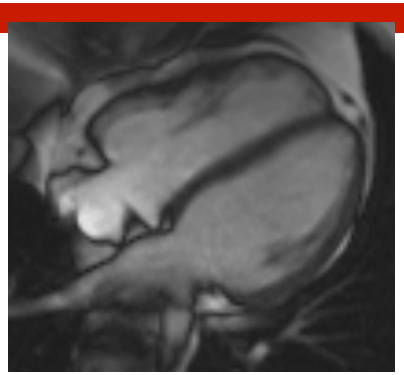


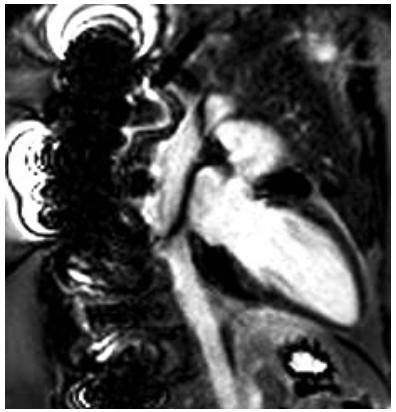

Nigro G *et al.* Int J Cardiol 1990.

# Cardiomyopathy Detection *In Vivo*: Cardiac MRI

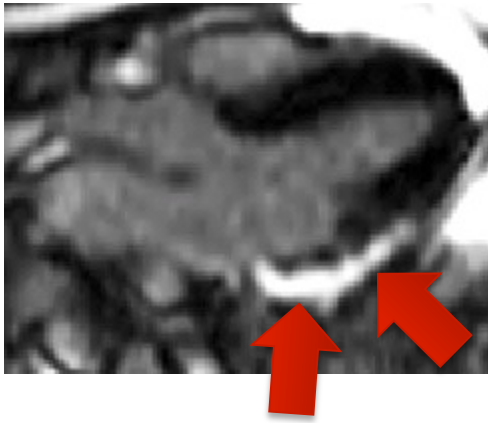
- Gold standard for LV structure & function
- Shows myocardial damage *in vivo*







| Echo Measure | Correlation with CMR | P-value |
|---|---|---|
| M-mode FS | 0.59 | 0.04 |
| 2D FS | 0.79 | 0.03 |
| Biplane LVEF | -0.07 | 0.53 |
| 4-chamber LVEF | 0.50 | 0.09 |
| 3D LVEF | 0.28 | 0.17 |
| Ecc | 0.52 | 0.04 |

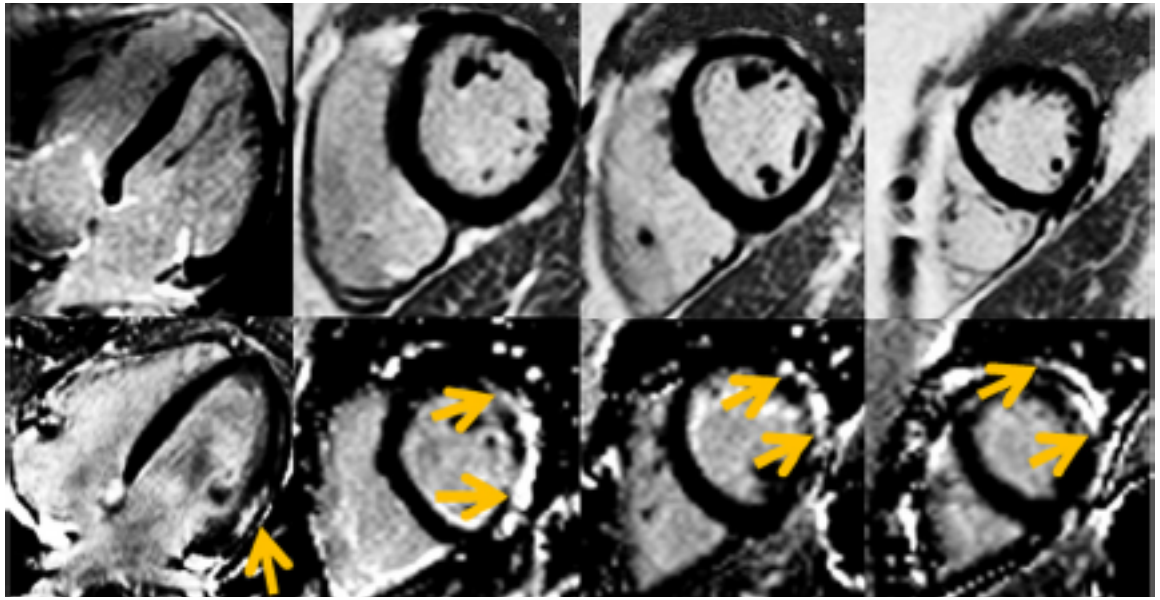


19 year-old with DMD

Soslow JH *et al.* JCMR 2014 (abstract)

# Better Sense of Prevalence with Greater Precision in Diagnosis

- LGE-positive prevalence 17% in patients <10



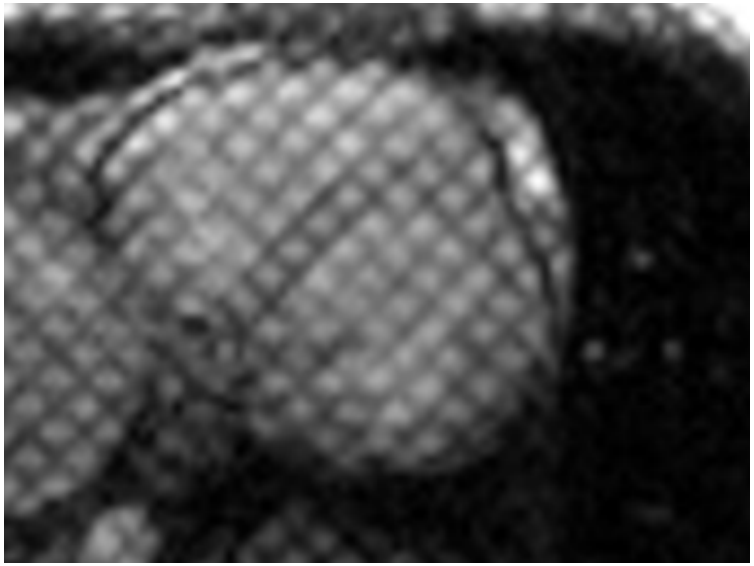
12 y/o

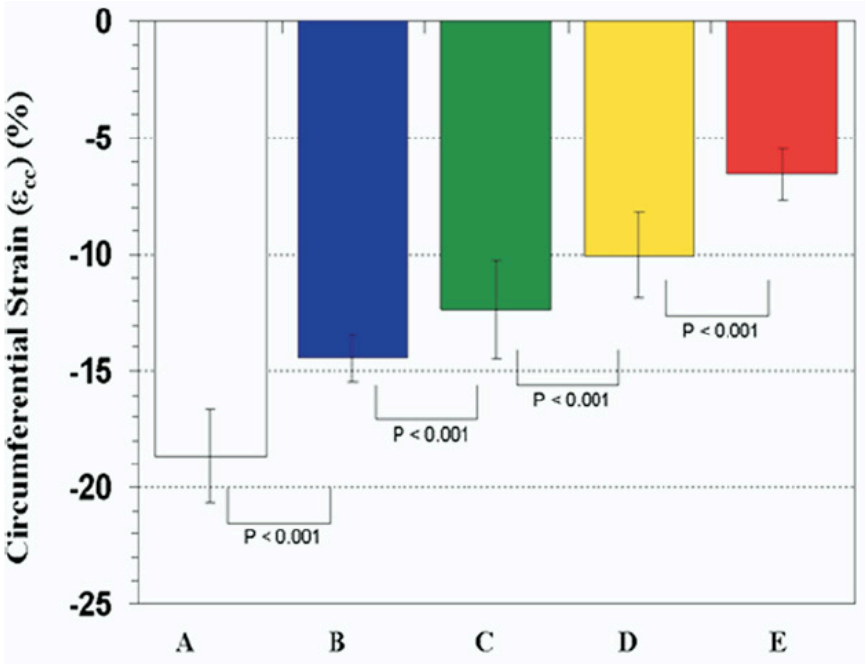
8.5 y/o

| Patient groups | LGE negative (n = 201) | LGE positive (n = 113) | P-value |
|---|---|---|---|
| Age (years) | 11.8 ± 3.4 (6–28) | 15.2 ± 5.1 (7–32) | <0.0001 |
| Heart rate (bpm) | 100.8 ± 14.1 (55–143) | 98 ± 15.7 (48–149) | 0.056 |
| BSA ($m^2$) | 1.2 ± 0.33 (0.8-2.6) | 1.4 ± 0.3 (0.9-2.4) | <0.0001 |
| Height (cm) | 135.5 ± 16.9 (108–191) | 147.3 ± 16.8 (117–191) | 0.0004 |
| Weight (kg) | 42 ± 19.2 (19–136) | 52 ± 18.1 (24–106) | <0.0001 |
| LVEF (%) | 64.8 ± 5.4 (35–78) | 57 ± 11.6 (17–79) | <0.0001 |
| LVEDV/BSA (mL/m2) | 67.9 ± 13.9 (31–107) | 76.9 ± 26.4 (35–207) | 0.0004 |
| LVM/BSA (g/m2) | 46.3 ± 9.9 (24–78) | 51.7 ± 13.2 (29–109) | <0.0001 |

Hor K *et al.* J Cardiovasc Magn Res 2013.

# Strain Imaging Detects Subtle Changes in Contractile Function (before EF↓)

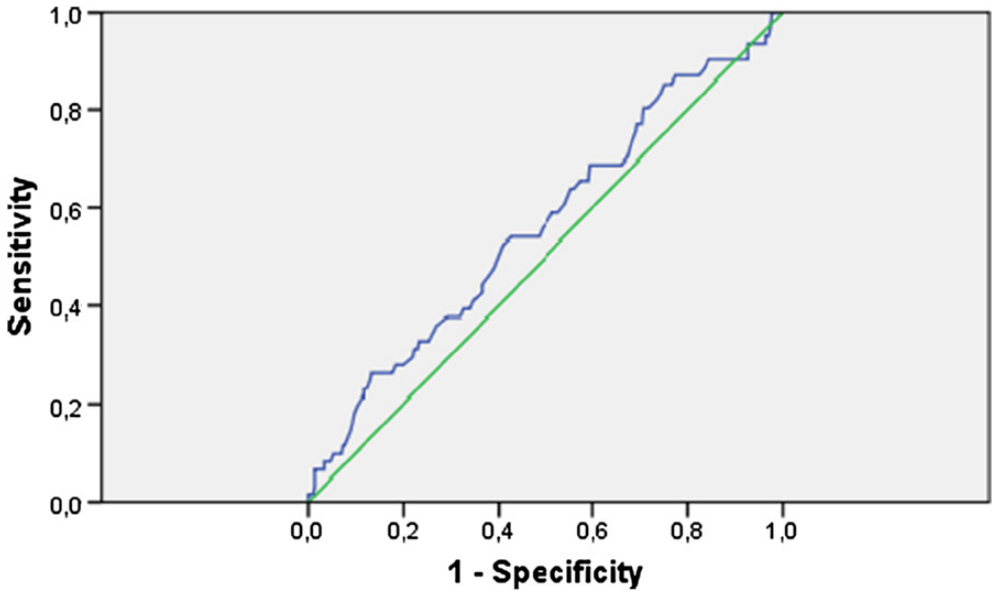





Hor K *et al.* JACC 2009.

# How About a Blood Test?

- NT-pro BNP measured in 55 DMD patients age 8-44 years
- DCM presence/absence based on echocardiography

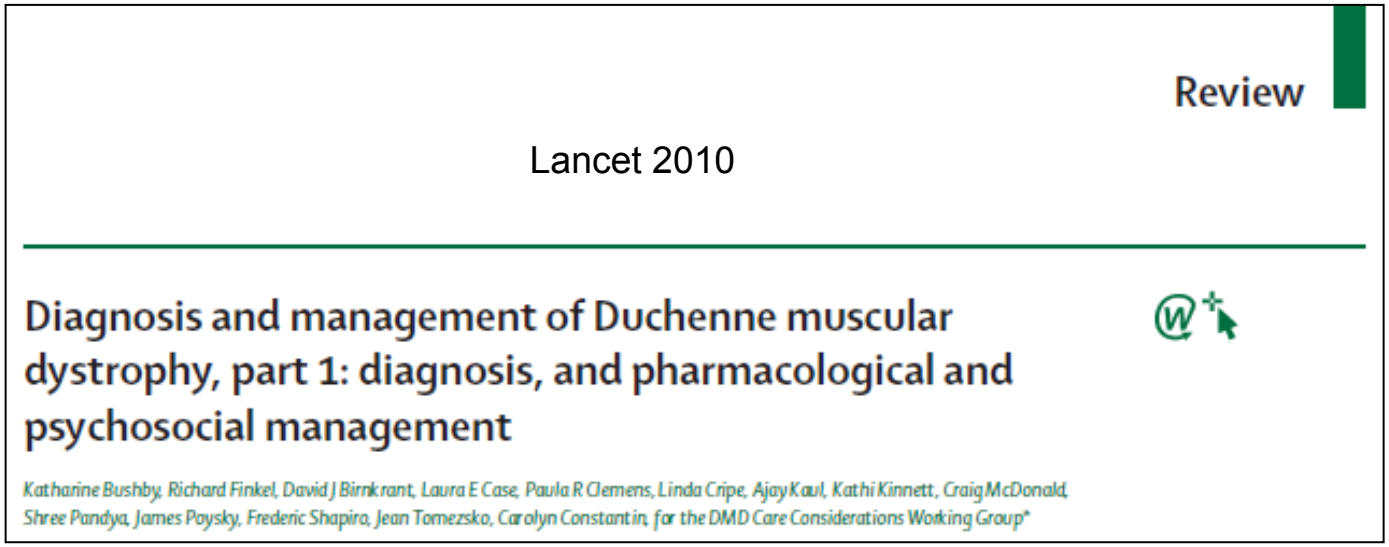



Schade van Westrum S *et al.* BMC Neurol 2013.

# Outline

- Why cardiomyopathy develops in DMD
- Clinical presentation and outcomes
- Current guidelines for diagnosis and treatment
- Can we do better? Clinical trials in progress

# Screen for Cardiac Disease



Review

Lancet 2010

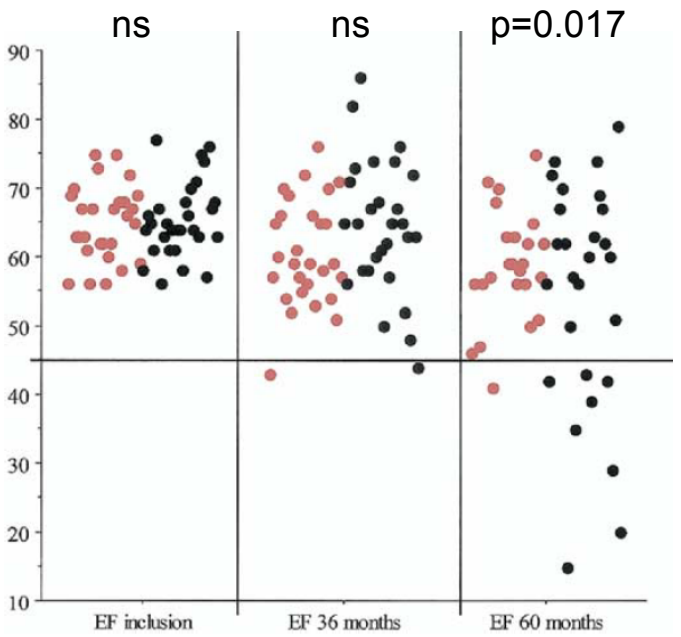
Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management

Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula R 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*

- Echocardiogram
  - At diagnosis or by age 6
  - Every 2 years until age 10, then annually
  - At onset of signs & symptoms (*Pediatrics* 2005)

# Drug Treatment for Subclinical Cardiac Disease: ACE Inhibitors

- 57 DMD boys 9-13 yrs with EF >55 by radionuclide imaging
  - 12-month placebo-controlled RCT of perindopril
  - Another 24 months of open-label therapy
  - Less progression to EF<45% with initial assignment to ACEI
- Continued follow-up showed 93% vs. 66% survival at 10 years in group 1 vs. group 2

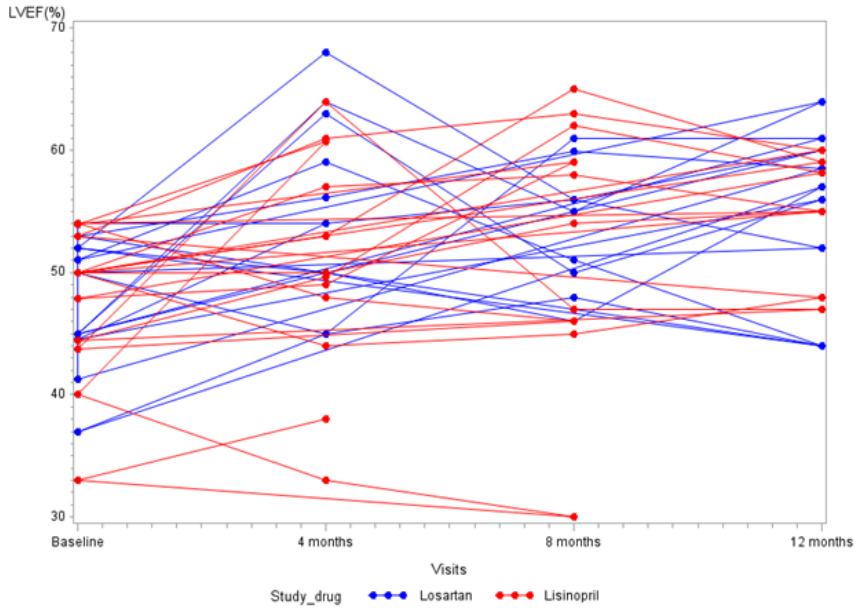



Red – initially assigned to ACEI (Group 1)
Black – initially assigned to placebo (Group 2)

Duboc D *et al.* JACC 2005; Duboc D *et al.* Am Heart J 2007.

# ACE Inhibitors vs. Angiotensin Receptor Blockers (ARBs)

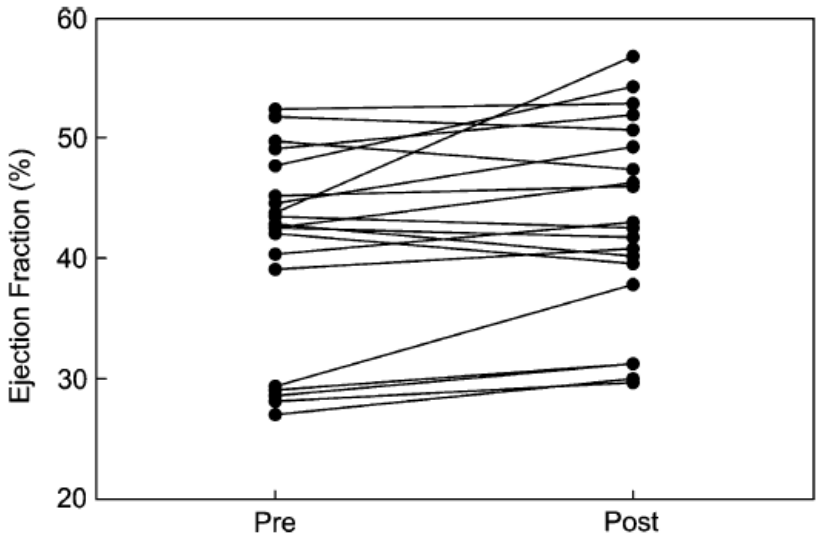
- 22 boys age 7 to 27 years with echo EF <55%
- 2 week washout if already taking ACEI or ARB
- Echo 4-chamber LV EF improved from ~48 to 55% in both groups




Allen HD, Flanigan KM…Mendell JR. PLoS Currents 2013.

# Beta-Blockers

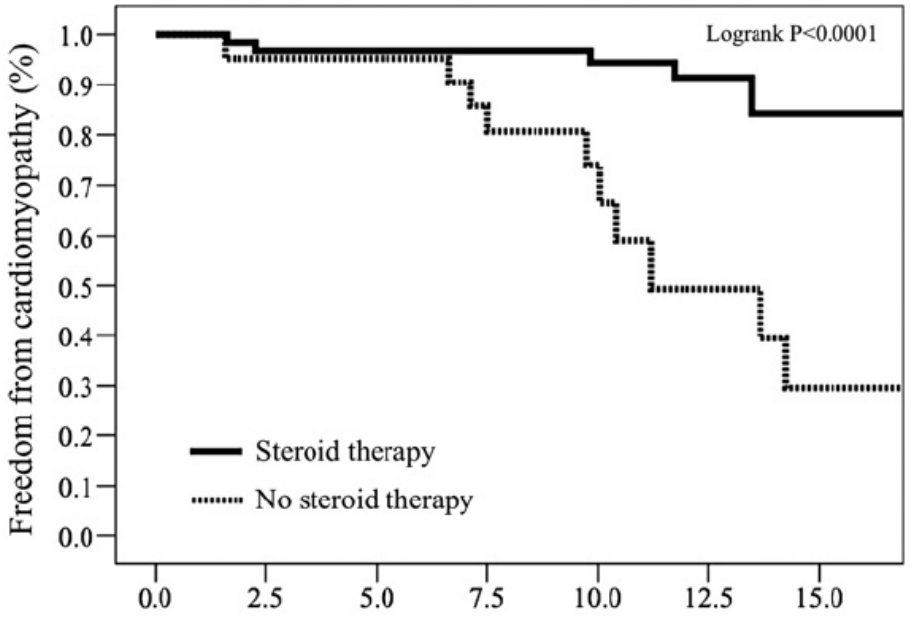
- Prospective, unblinded clinical trial in 22 DMD or BMD patients age 14 to 46 with EF <50% by CMR
- Carvedilol titrated up to 50 mg/d produced a small, significant improvement in EF (41 ± 8 → 43 ± 8%, p<0.02)
- Small, statistically insignificant decline in spirometry measurements




Rhodes J *et al*. Ped Cardiol 2008.

# Corticosteroids

- Prospective, observational study of 86 DMD boys age ~9 years at baseline, followed for ~11 years
- Heart failure-related deaths: 0/63 boys on prednisone or deflazacort vs. 5/23 of those not on steroid at baseline (p=0.001)
- Trend toward younger age in steroid tx group (20 vs. 22 years at last follow-up, p=0.09)




Schram G *et al*. JACC 2013.

# Symptomatic Cardiac Disease: ACCF/AHA Guidelines

- **Size of treatment effect:**
  - **Class I**: benefit >>> risk
    - procedure/treatment should be done
  - **Class IIa**: benefit >> risk
    - reasonable to perform procedure/tx
  - **Class IIb**: benefit ≥ risk
    - procedure/treatment may be considered
  - **Class III** – no benefit or harm
- **Estimate of certainty (precision) of treatment effect:**
  - **Level A** – multiple populations evaluated; data from RCTs or meta-analysis
  - **Level B** – limited populations evaluated; single RCT or nonrandomized studies
  - **Level C** – limited data from consensus opinion, case studies, ‘standard of care’

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**PRACTICE GUIDELINE**

# 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

*Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation*

*Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation*

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## ACCF/AHA Stages of Heart Failure

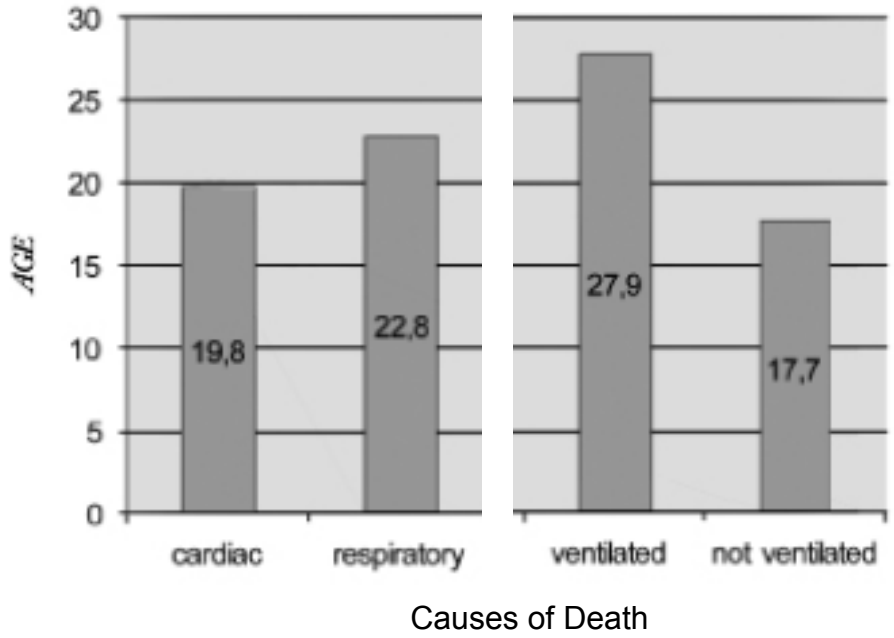
| | |
|---|---|
| A | At high risk for HF but without structural heart disease or HF symptoms |
| B | Structural heart disease but without signs/symptoms of HF |
| C | Structural heart disease with prior/current HF symptoms |
| D | Refractory HF requiring specialized interventions |

Table 12: Recommendations for Treatment of Stage B HF/Cardiomyopathy

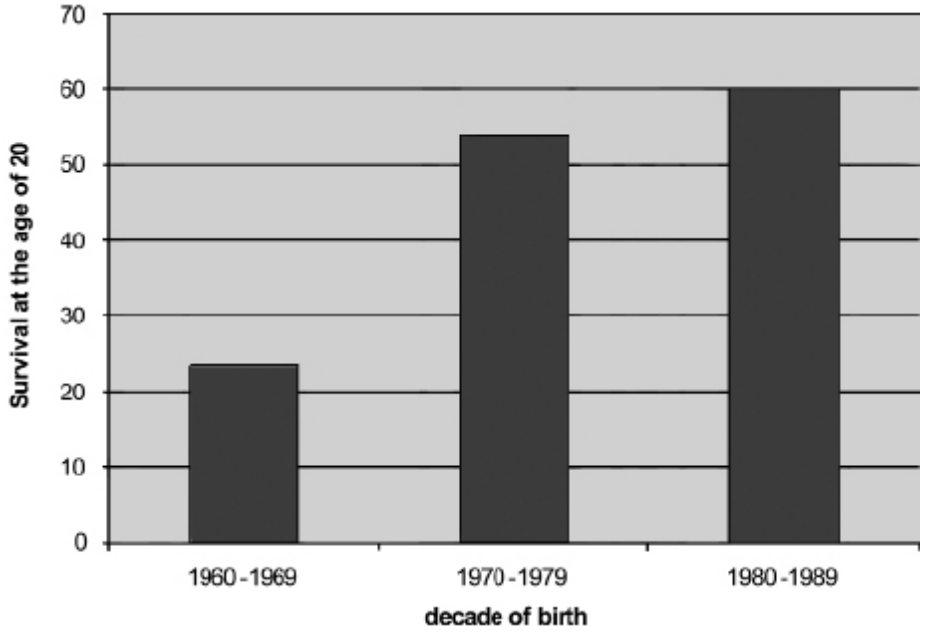
| | | |
|---|---|---|
| ACE inhibitors should be used in all patients with a reduced EF to prevent HF | I | A |
| Beta blockers should be used in all patients with a reduced EF to prevent HF | I | C |
| An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT | IIa | B |
| Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF | III: Harm | C |

# Better Survival with Current Management

- Retrospective review of 516 patients with confirmed DMD in Naples from 1961 to 2006
- Cause of death primarily respiratory until the ‘80s



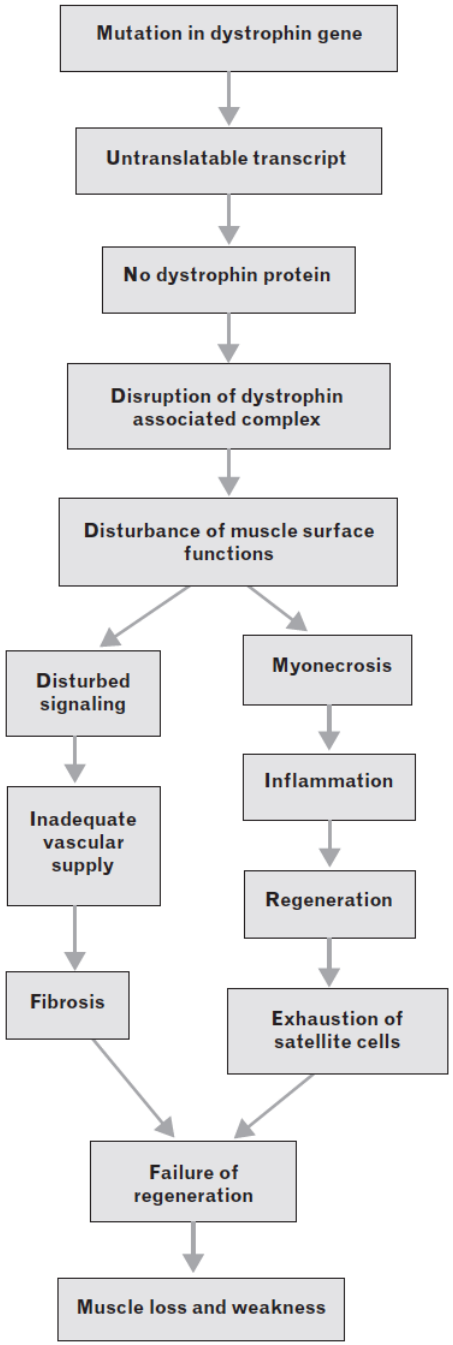

Causes of Death




Passamano L *et al*. Acta Myologica 2012

# Outline

- Why cardiomyopathy develops in DMD
- Clinical presentation and outcomes
- Current guidelines for diagnosis and treatment
- Can we do better?




**1. Repair or replace* mutated gene**

**2. Rescue translation**

- **Exon skipping***
- **Stop-codon read through***

**3. Substitute other proteins**

- **Increase utrophin* expression**
- **Over-express adhesive* molecules**
- **Enhance NOS activity***

**4. Ameliorate downstream pathology**

**4a. Modulate inflammation**

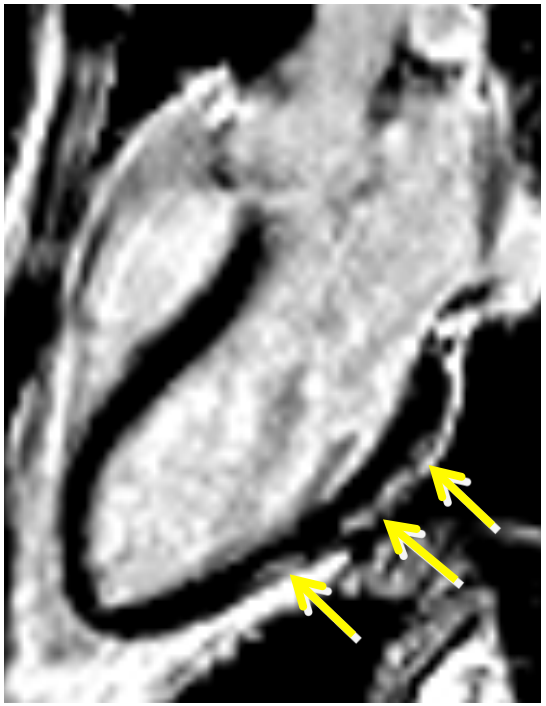
- **Modulate inflammation***
- **Modulate collagen production**

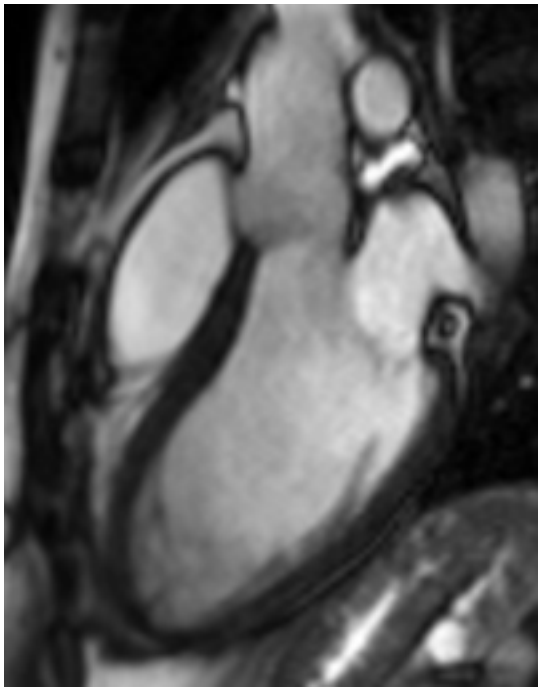
**4b. Enhance regeneration**

- **Induce muscle hypertrophy***

Partridge TA.
Curr Op Neurol 2011.

# One approach: prompted by an encounter with a young man and his father in 2007





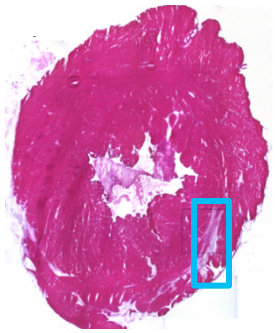
# Observation → Insight

- Old drugs with *anti-fibrotic effect* (ACEI plus aldosterone antagonist) might help protect the heart in DMD
- What would it take to test this idea?

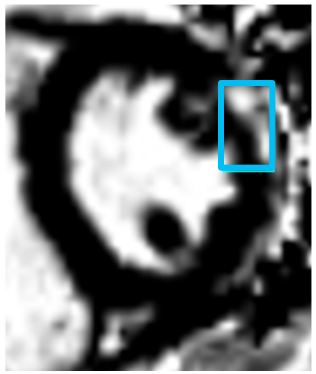
## 1st – see if it works in mice

- Het mouse: dystrophin-deficient and missing 1 copy of utrophin
- Severe skeletal muscle fibrosis
- Cardiomyopathy progression similar to DMD patients

Het Mouse Heart



DMD Patient's Heart



Treatment w/ACEI and aldosterone antagonist:

Het – untreated

Het treated (8) – treatment started at 8 weeks-of-age

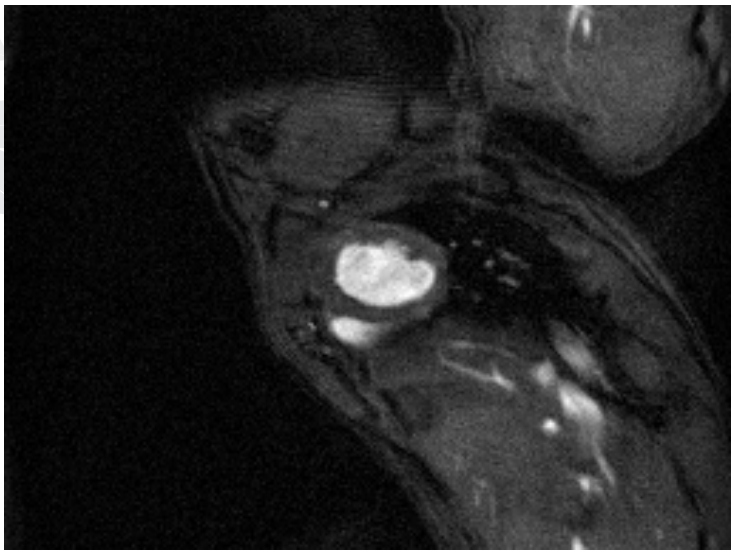
Het treated (4) – treatment started at 4 weeks-of-age

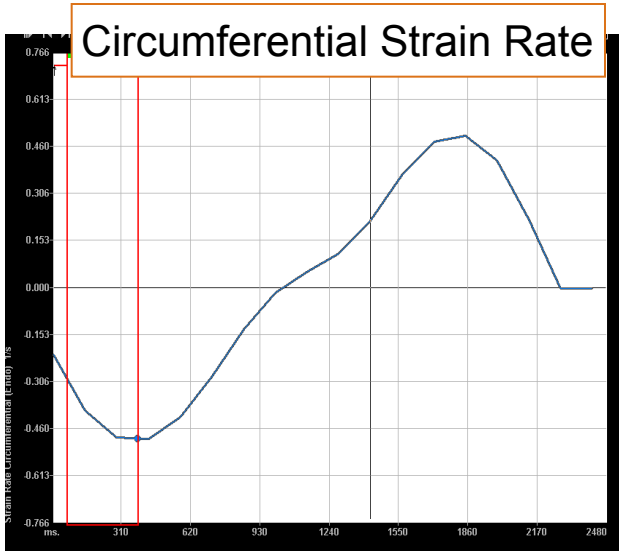
Analysis at 20 weeks-of-age:

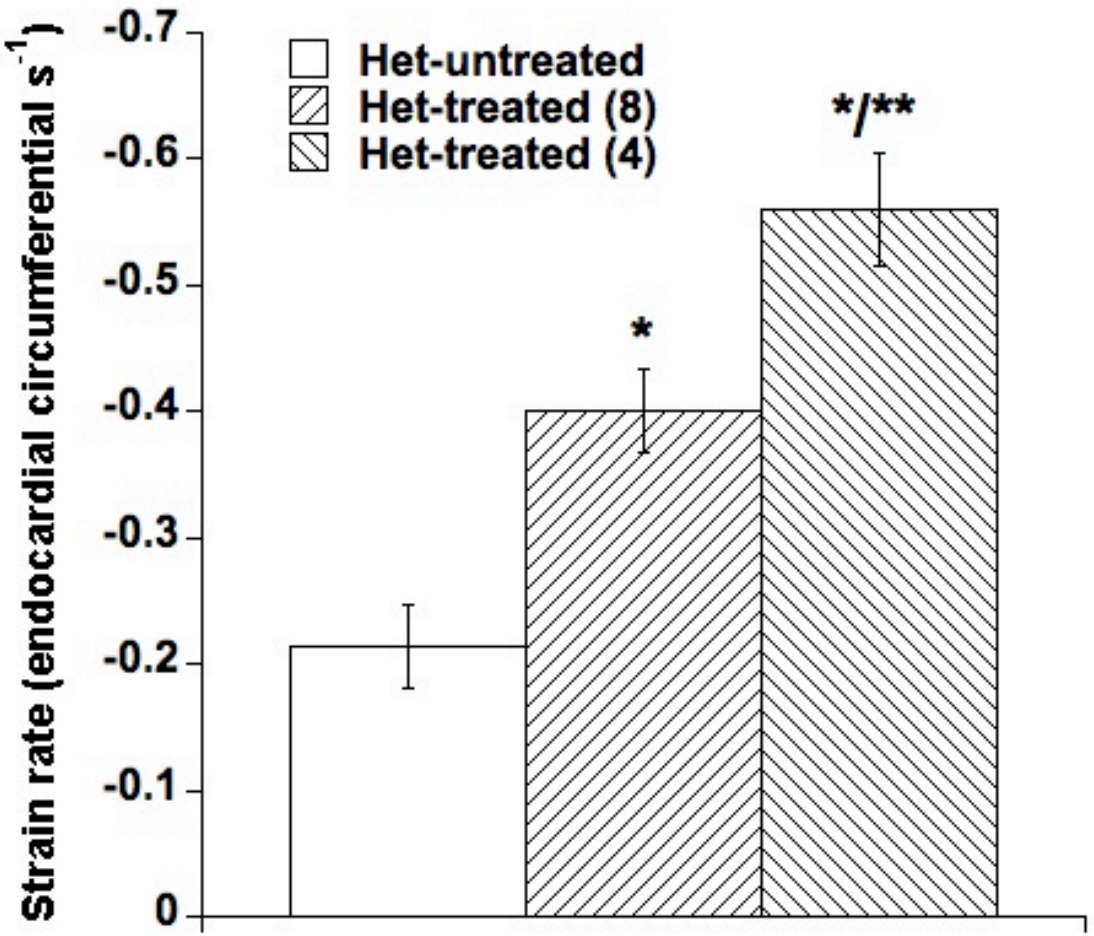
*in vivo* cardiac MRI

*in vitro* muscle force measurements (heart, EDL, diaphragm)

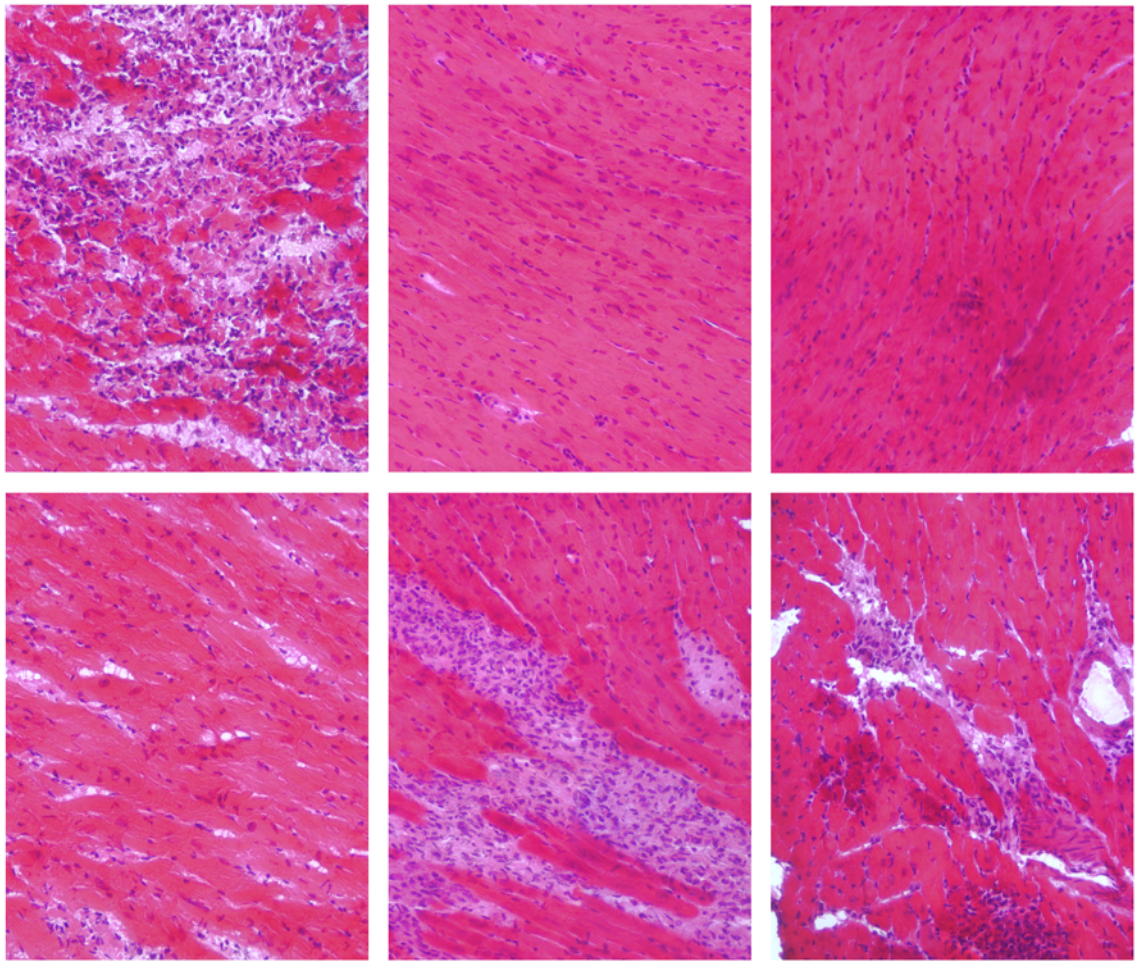
heart and skeletal muscle histological analysis




Circumferential Strain Rate
0.766
0.613
0.460
0.306
0.153
0.000
-0.153
-0.306
-0.460
-0.613
-0.766
ms.
310
620
930
1240
1550
1860
2170
2480

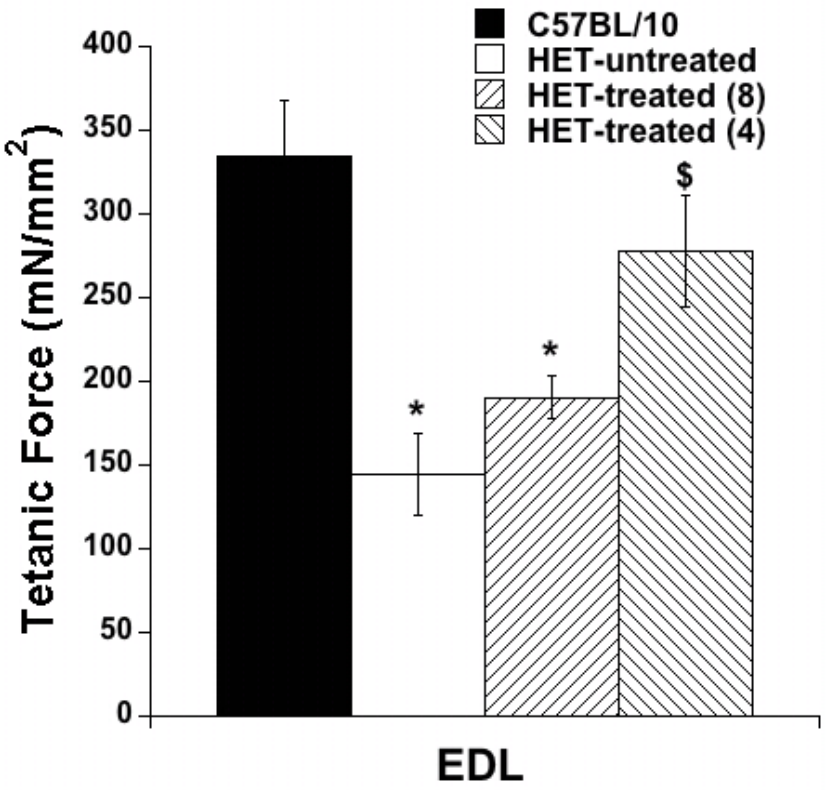

Strain rate (endocardial circumferential s-1)
-0.7
-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0
Het-untreated
Het-treated (8)
Het-treated (4)
*
*/**

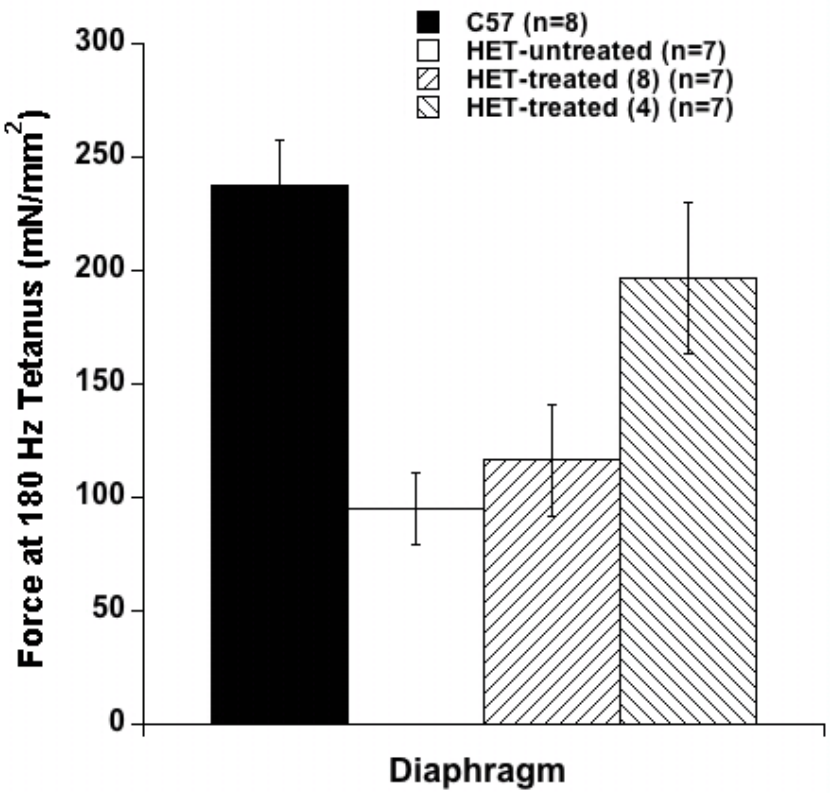
# Cardiac Muscle Histology



untreated treated (8wk) treated (4wk)

# Drugs Also Improves Skeletal Muscle




Circulation 2011.

# Clinical Trial Organized, Underway

- Baseline enrollment is **done**
  - 40 boys with evidence of heart muscle injury but preserved EF by cardiac MRI
  - ACEI/ARB started or continued
  - Randomized to receive aldosterone antagonist or placebo in addition to ACEI/ARB
- Should finish 12-month follow-up in July 2014
- Goal: present initial findings in 2014/2015
- Timeline tempered by reality of peer review, etc. (Life According to Sam)

# Next Steps

- Open-label 24-month extension study
- Additional mouse experiments
  - Comparing 2 types of aldosterone antagonists (spironolactone & eplerenone)
  - Look more closely at how the drugs work, in what combinations
- Subsequent clinical trial based on these results will begin **~January 2015**

# Summary

- Cardiomyopathy develops at some point to some degree in all patients with DMD
- In the absence of typical signs and symptoms, screening can identify early myocardial changes
- Timely institution of treatment bends the natural history curve, improves outcomes
- Synergies between basic and clinical research → better treatment & prevention


***There is much yet to do – can you help?***

# The Team


- OSU
  - Drs. Rafael-Fortney, Janssen, Kissel
  - Beth McCarthy, Tam Tran, Suzanne Smart
- Nationwide Children's
  - Drs. Cripe, Hor, Flanigan
- Boys with DMD, their families & friends from around the world

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