

# Early treatment with lisinopril and spironolactone preserves cardiac and skeletal muscle in Duchenne muscular dystrophy mice.

Paul M.L. Janssen, PhD, FAHA  
Dept. Physiology and Cell Biology  
The Ohio State University  
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OHIO STATE UNIVERSITY - NATIONWIDE CHILDREN'S HOSPITAL



RESEARCH FOR MUSCLE BIOLOGY AND DISEASE

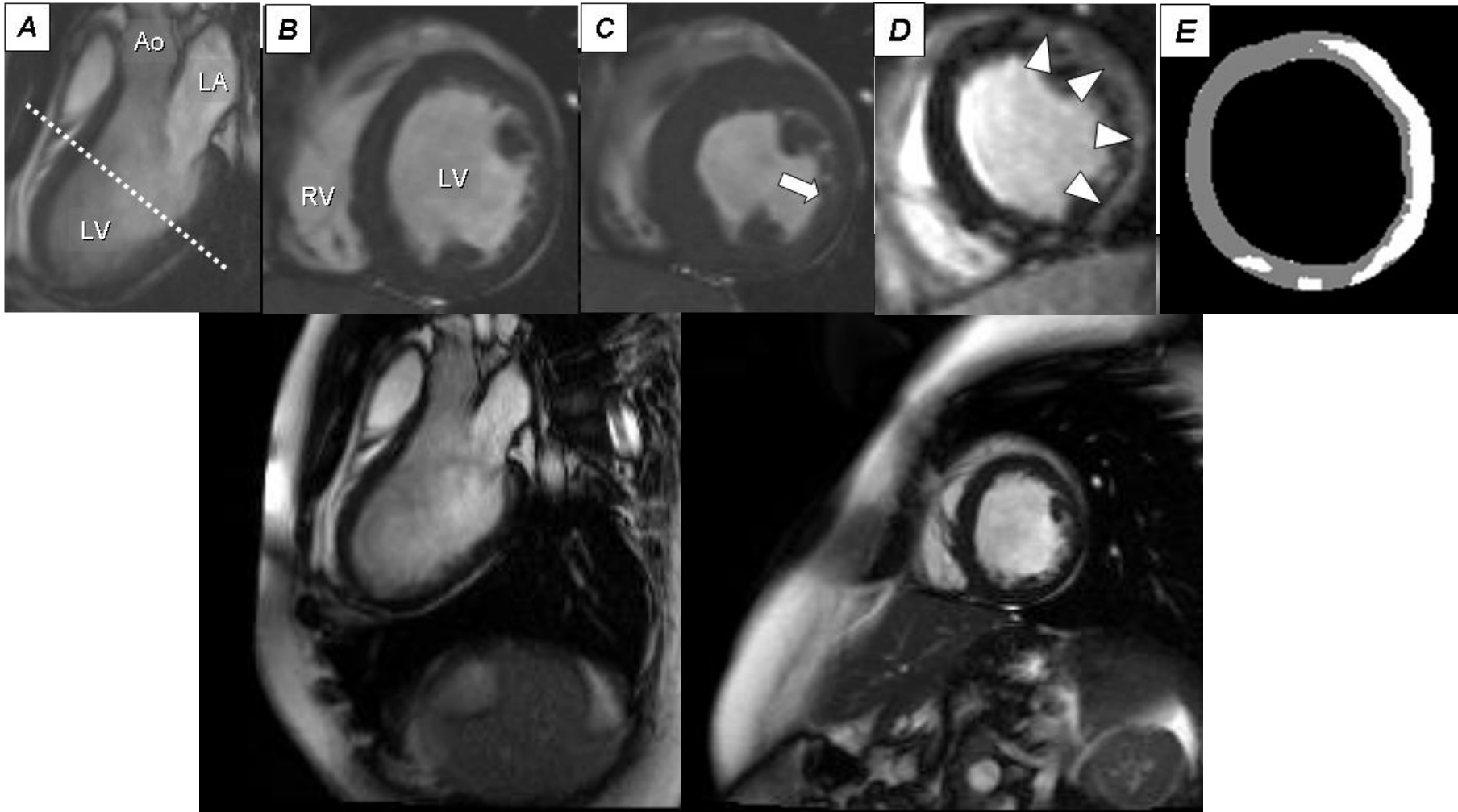
# Drug Re-Purposing

1/>3500 Incidence of Duchenne Muscular Dystrophy

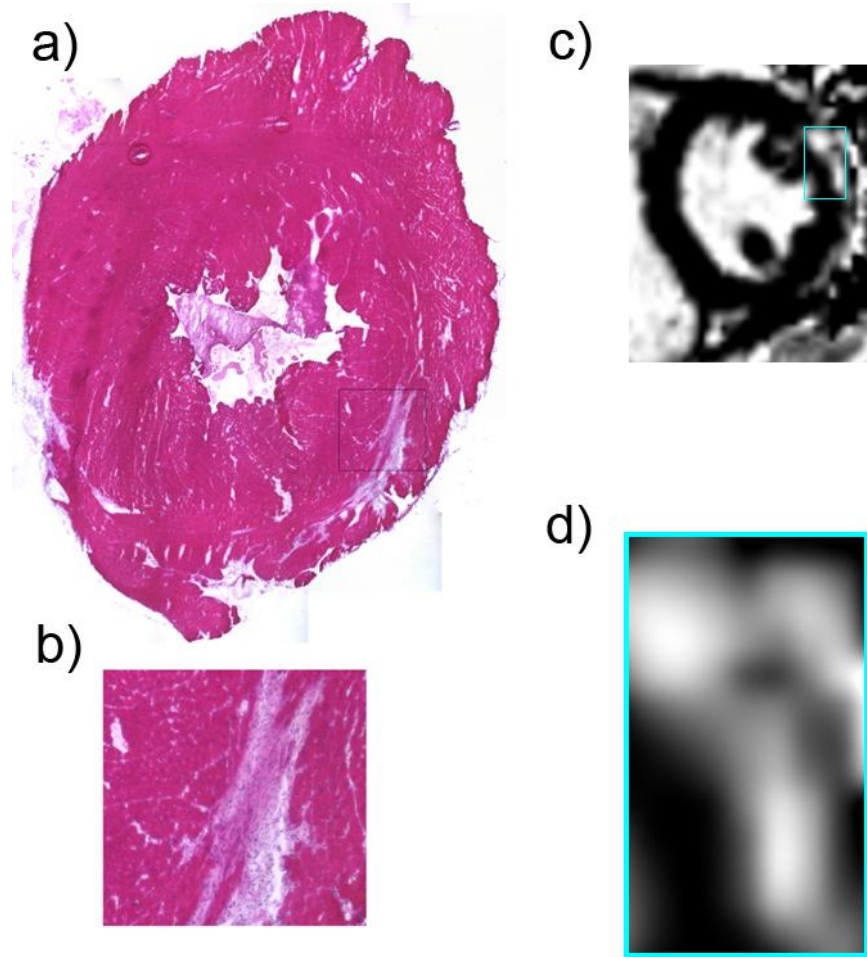
1/<10 Lifetime incidence of Cardiac-related disease

Extensive clinical trials of >1000 patients in cardiac field have yielded numerous treatment strategies

# Cardiac MRI, 14 year old DMD patient (Normal EF!)



# MRI/scarring comparison to mouse model



# Treatment with ACE inhibitor and Aldosterone antagonist

Anecdotal evidence:

- Stabilization of scarring
- Stabilization/maintenance of EF

# Study design I: DMD cardiomyopathy mouse models

*dko*  
Dystrophin/utrophin-deficient

- Dies 10-12 weeks-of-age
- mild skeletal muscle fibrosis
- severe cardiomyopathy



*Dko: Deconinck et al. Cell 1997,*

Het  
Dystrophin-  
deficient; missing  
1 copy of  
utrophin

- normal mouse lifespan (2 yrs)
- severe skeletal muscle fibrosis
- Cardiomyopathy progression more similar to DMD patients

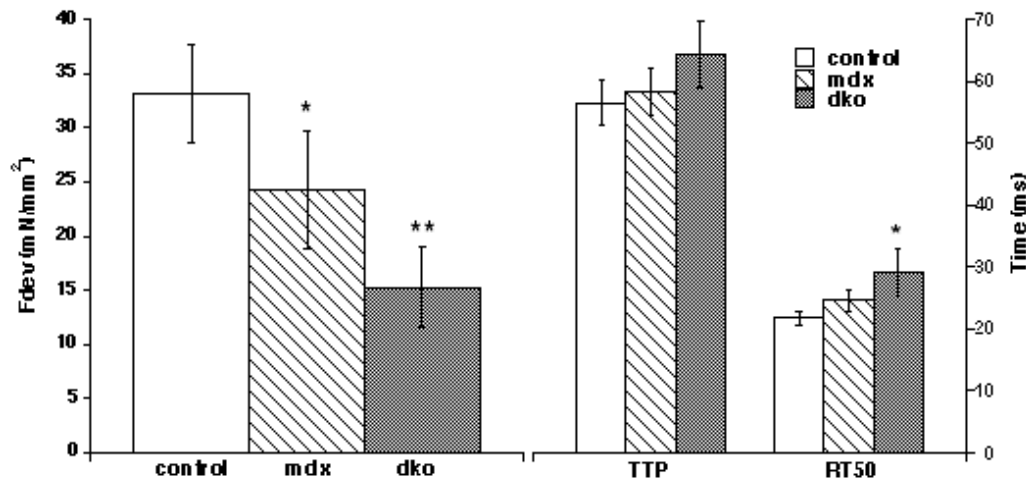
*Het: Zhou et al, J. Neurol Sci, 2008*

*mdx*  
Dystrophin-deficient

- normal mouse lifespan (2 yrs)
- mild skeletal muscle fibrosis
- mild cardiomyopathy



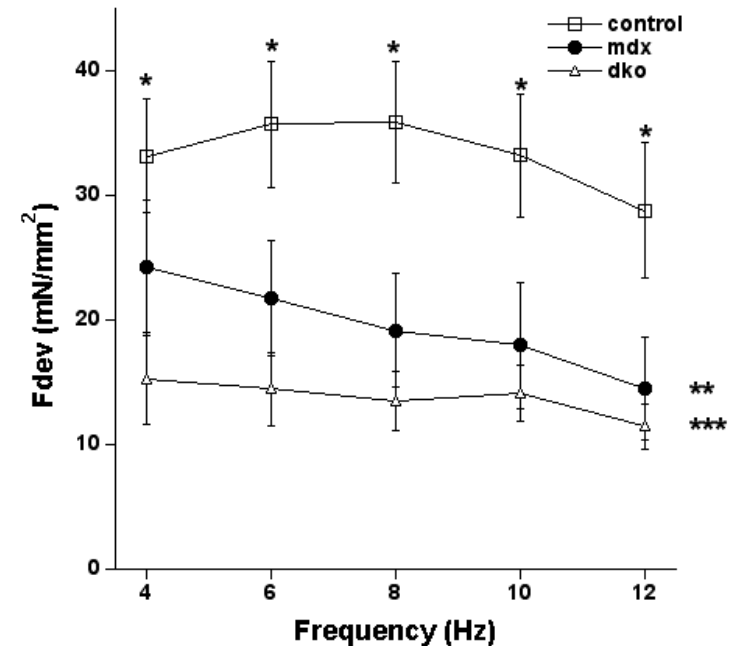
# Study design I: DMD cardiomyopathy mouse models



4 Hz

\* $P < 0.05$  compared with control

\*\* $P < 0.05$  compared with *mdx*



\* $P < 0.05$  compared with control

\*\*\* $P < 0.05$  compared with *mdx*

# Study design II: Drugs treatment

Spironolactone 250 mg/L in drinking water

Lisinopril 66 mg/L in drinking water

4 groups:

untreated “Het” mice

“Het” mice treated from 4 weeks-of-age

“Het” mice treated from 8 weeks-of-age

C57BL/10

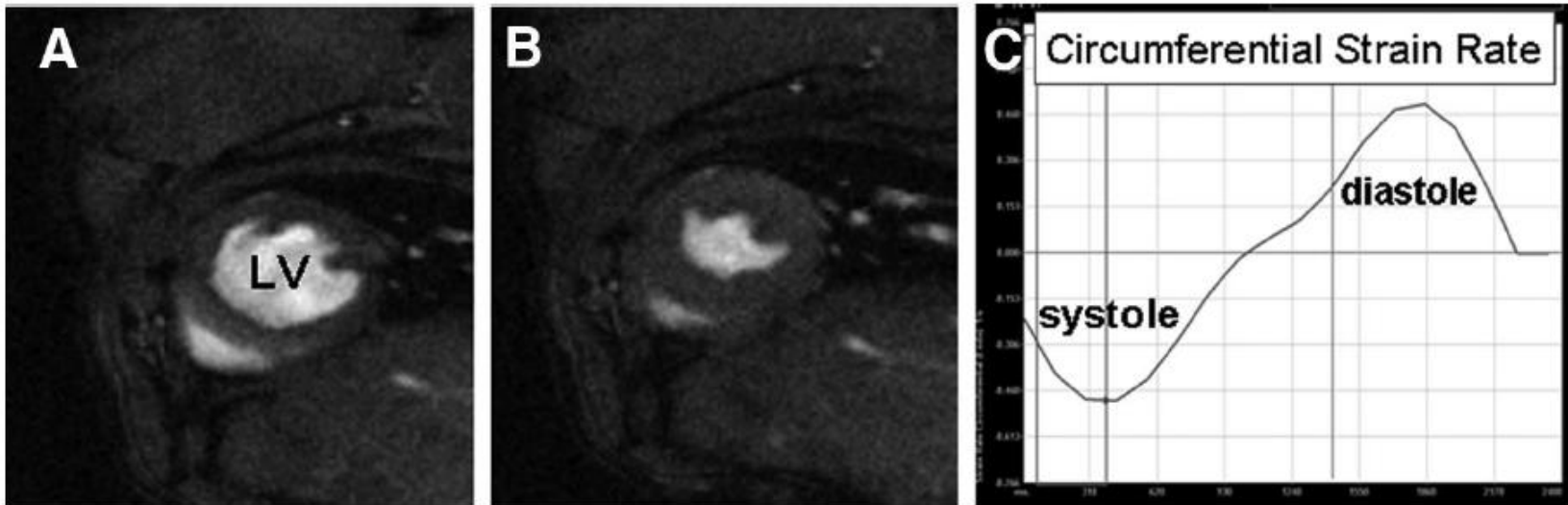
*First mouse into study on June 2010*

# Study design III: Assessment

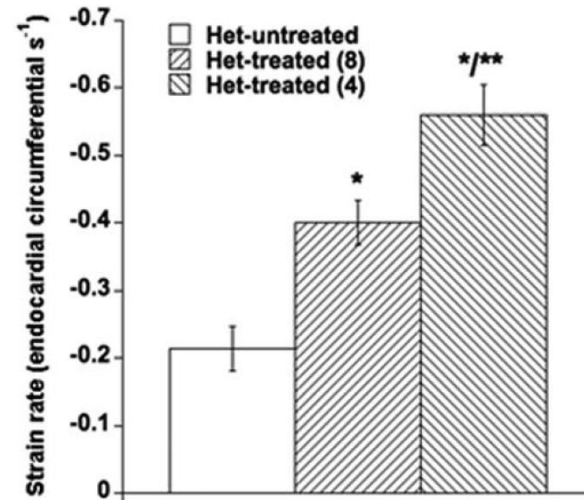
At 20 weeks of age:

- Cardiac MRI
- Unrestrained, conscious ECG
- Cardiac muscle contractility
- Diaphragm muscle contractility
- Skeletal muscle contractility
- Histology
- MMP analysis

# Results: Cardiac MRI

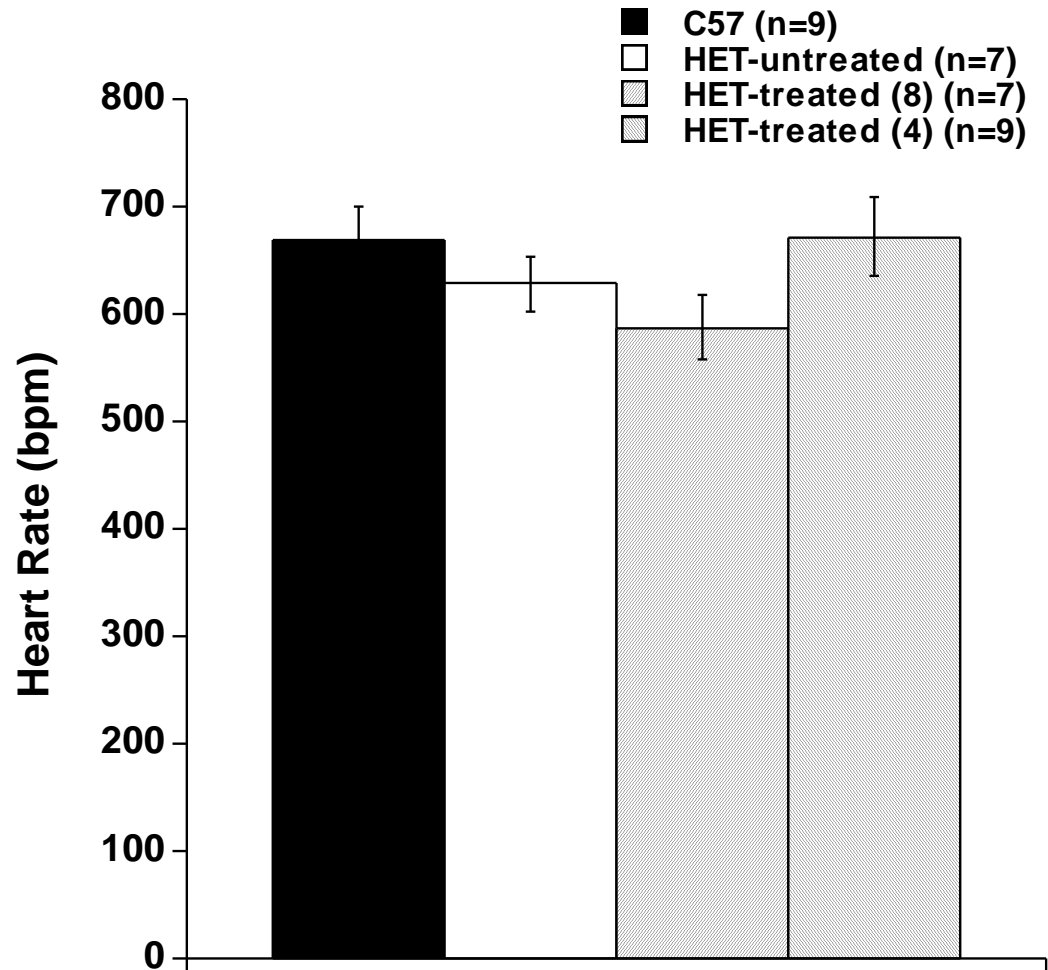


Strain Rate (circumferential LV base) shows significant improvement



# Results: Conscious unrestrained heart rate

HR is normal  
QT is not prolonged

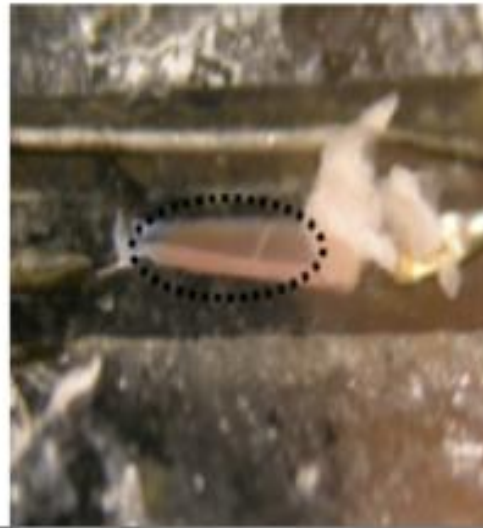


# Methods: Muscle contractile force

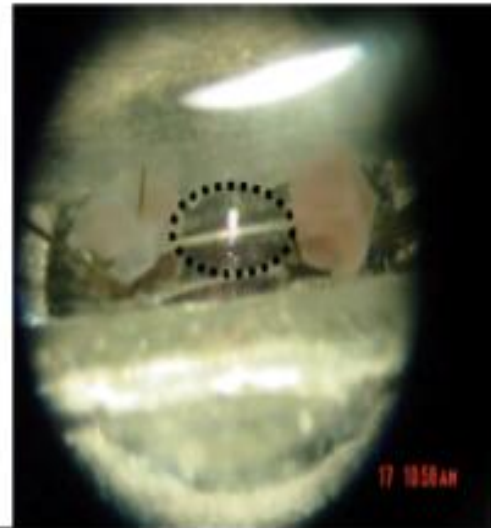
## Striated muscle preparations



EDL

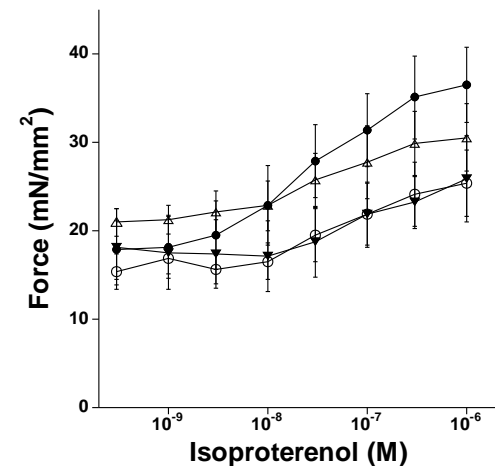
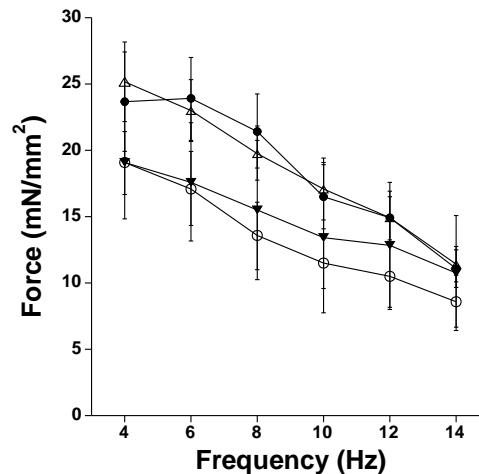
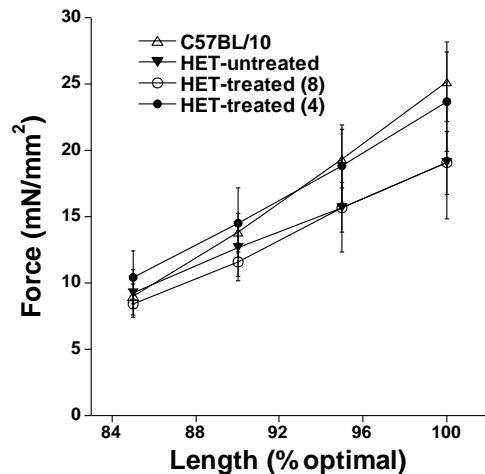
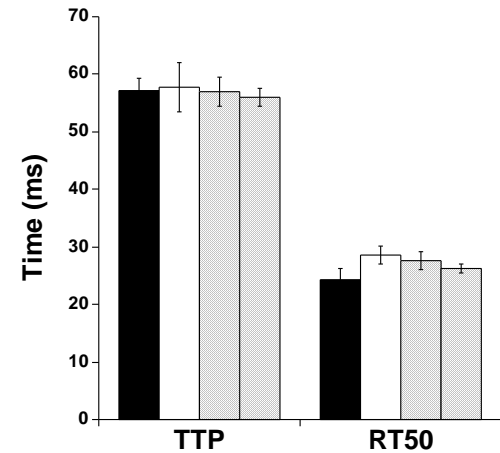
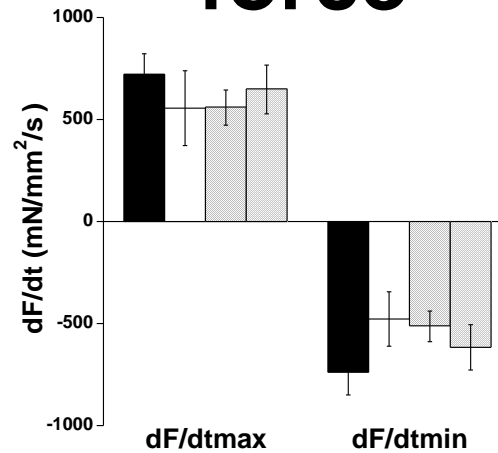
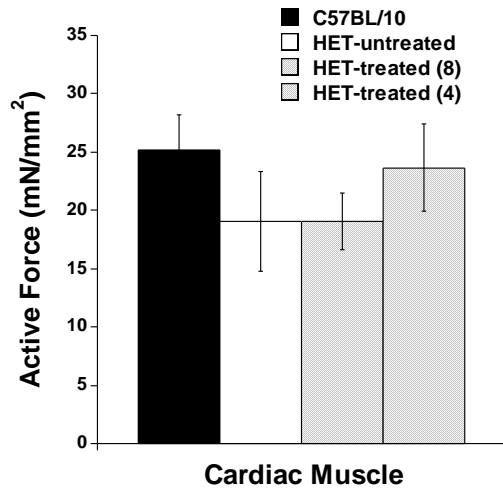


Diaphragm

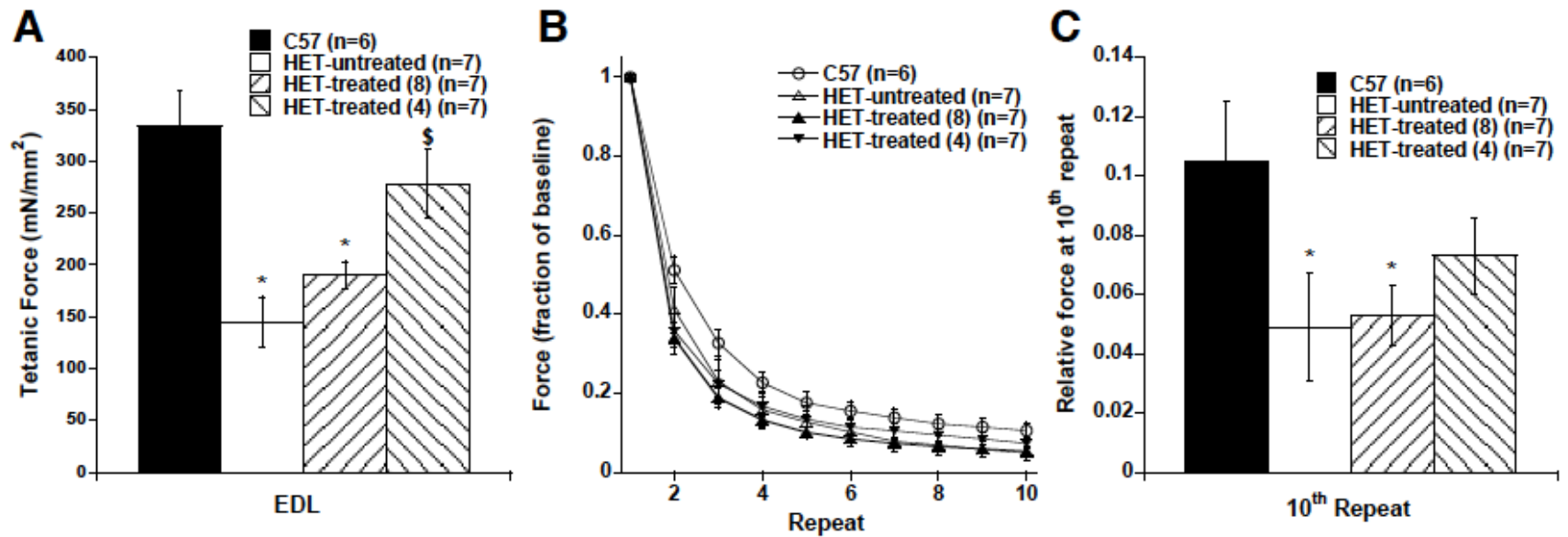


Cardiac trabecula

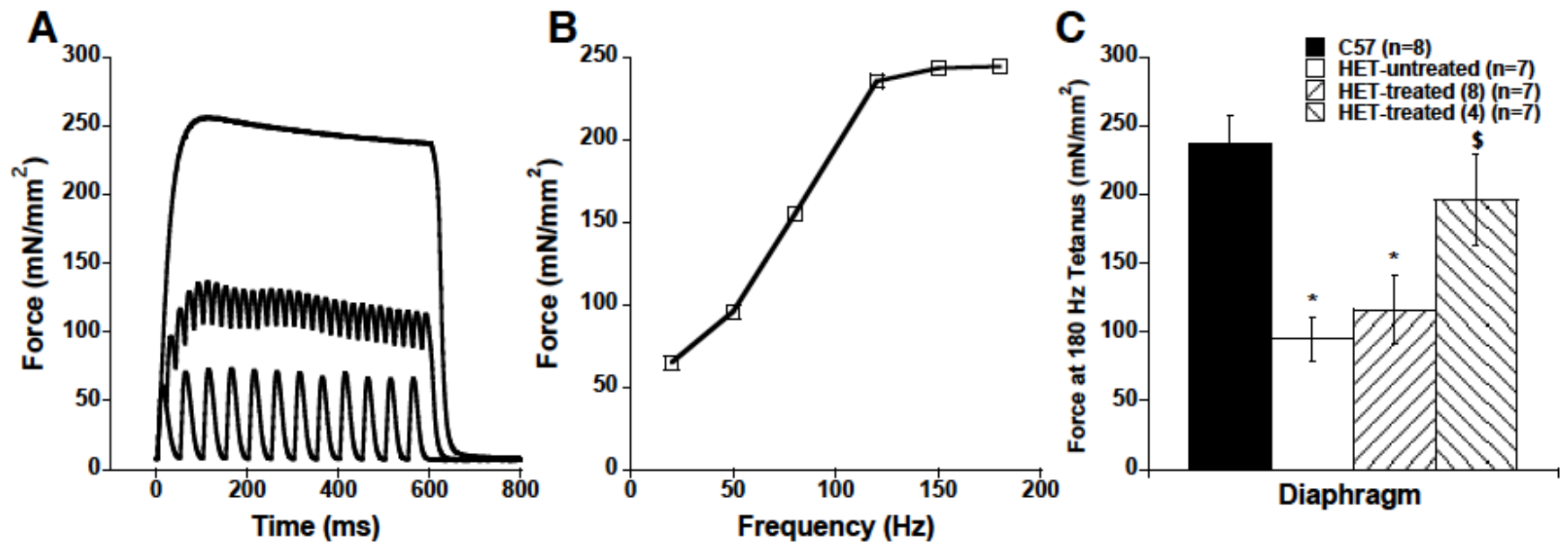
# Results: Cardiac muscle contractile force



# Results: EDL muscle contractile force

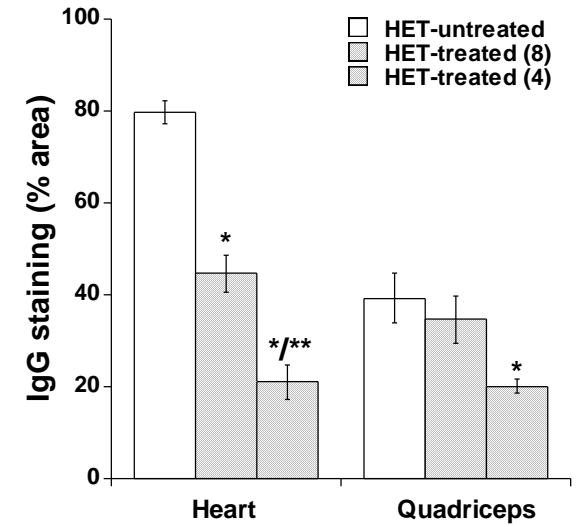
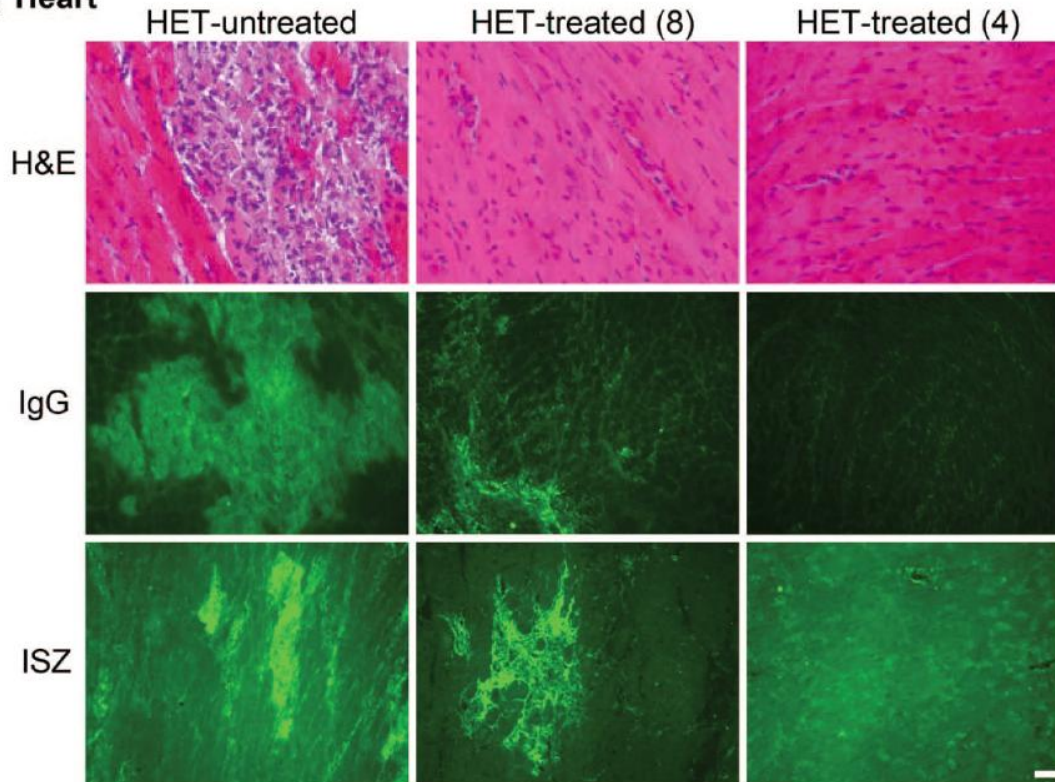


# Results: Diaphragm muscle contractile force

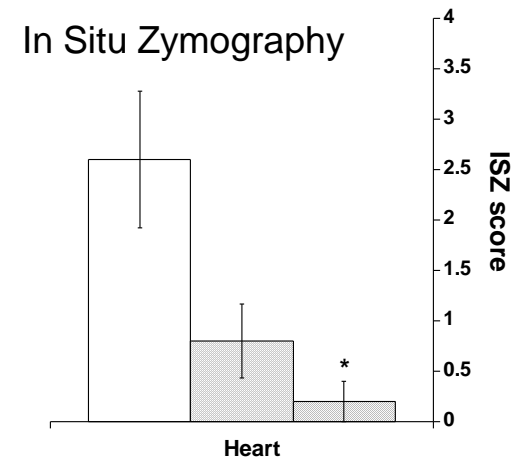
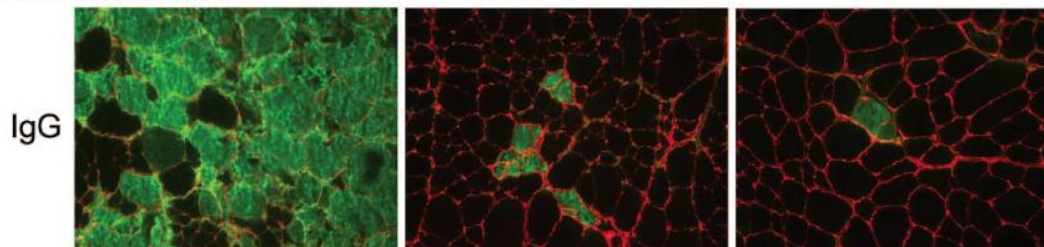


# Results: Histology

## A Heart



## B Skeletal Muscle

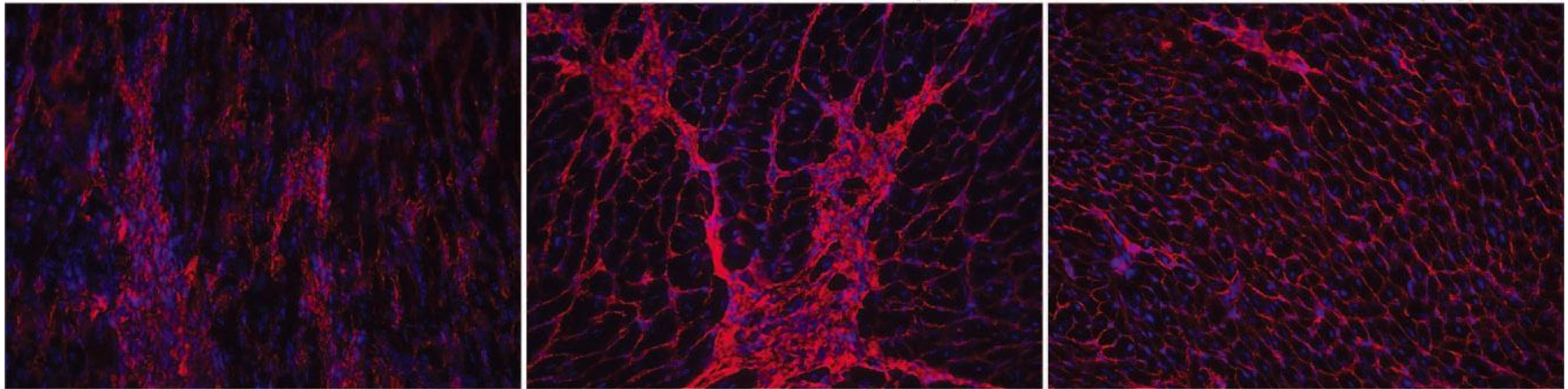


# Results: Fibroblast Marker

HET-untreated

HET-treated (8)

HET-treated (4)



Does not necessarily combat fibrosis,  
but prevents events leading to fibrosis

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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## **Early Treatment With Lisinopril and Spironolactone Preserves Cardiac and Skeletal Muscle in Duchenne Muscular Dystrophy Mice**

Jill A. Rafael-Fortney, Neeraj S. Chimanji, Kevin E. Schill, Christopher D. Martin, Jason D. Murray, Ranjit Ganguly, Jenna E. Stangland, Tam Tran, Ying Xu, Benjamin D. Canan, Tessily A. Mays, Dawn A. Delfín, Paul M.L. Janssen and Subha V. Raman

*Circulation* published online July 18, 2011

(.....First mouse treated June 2010)

# Next up....

- Determine basic mechanisms:
- How do these drugs work, could there be others?
- Can treatment halt, or even prevent a certain degree of dysfunction?
- How can contractile function improve without major changes in histopathology?
- Can we find biomarkers to track progression, or non-responders?
- Does this early treatment work in other myopathies?

# Two Clinical Trials

Planned for start early 2012:

- 1) Skeletal muscle function
- 2) Cardiac muscle function

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**Neeraj S. Chimanji**

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