Outcome Measures for the Heart

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Director, Cardiac Magnetic Resonance Imaging
Professor of Pediatrics
The Heart Center, Nationwide Children's Hospital
The Ohio State University

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

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

How do we know that our treatment is working?

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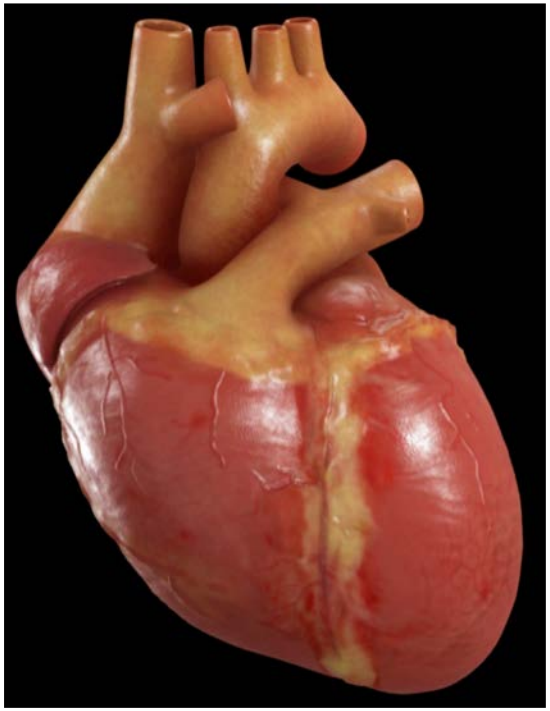
Objectives

- Defining Duchenne muscular dystrophy cardiac outcomes measure through the use of cardiac MRI
- Summary and application for cardiac disease staging
- Questions

Why are cardiologists interested in patients with neuromuscular disorders?

The Heart is the most active muscle

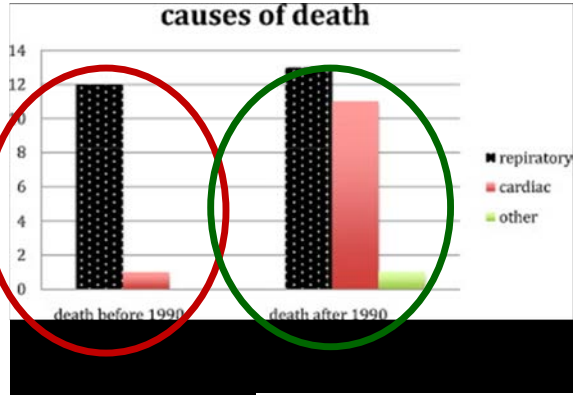


Lessons from the Past

- Treatment – offers hope
  - Over the last 2-3 decades, corticosteroids slow progression of skeletal muscle disease
  - Respiratory care improved survival
  - Leading cause of death from DMD-associated cardiomyopathy

Lessons from the Past

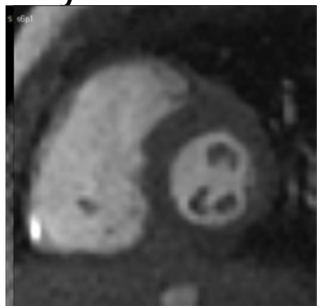
- Retrospective study of 119 patients with DMD at chronic care facility in France
- Life expectancy
  - 22 years without ventilation
  - 36 years with ventilation
- As respiratory management improves – cardiac disease will play a major role in disease related mortality
  - **Before 1990:** predominant respiratory cause of death
  - **After 1990:** predominant cardiac cause of death



P. Kieny, S. Chollet, P. Delanlande, M. Le Fort, A. Magot, Y. Pereon, B. Perrouin Verbe **Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper center between 1981 and 2011** Annals of Physical and Rehabilitation Medicine, Vol 56, Issue 6, 2013. 443-454

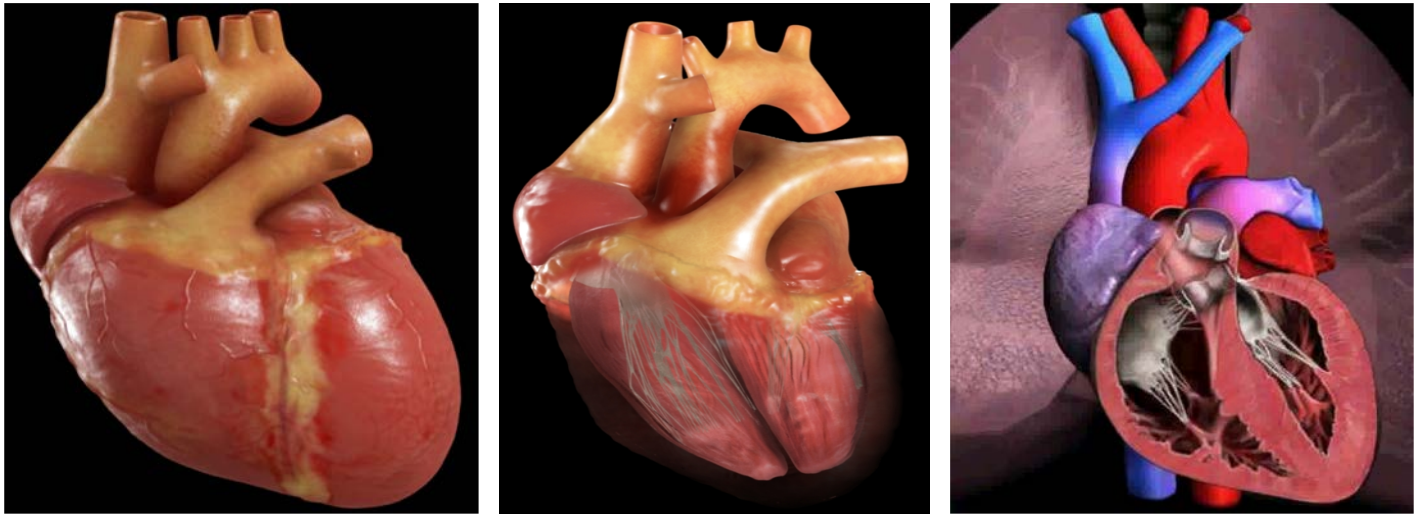
Defining DMD - Associated Cardiac Disease

- Past - clinical course characterized at a time when imaging was "*less sophisticated*"'
  - "Cardiomyopathy does not manifest until late teen to early adult years"
  - If we can't see it - must not be there
- Present - What we do know now…
  - The myocardium is dystrophin deficient
  - Cardiac disease is present at birth with abnormal EKG
  - Disease progresses with time and best assessed by non-invasive imaging
- *Cardiac disease is a significant contributor to disease related morbidity and mortality*



Defining DMD - Associated Cardiac Disease

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



Defining DMD - Associated Cardiac Disease

- Two common ways to obtain images of the heart:

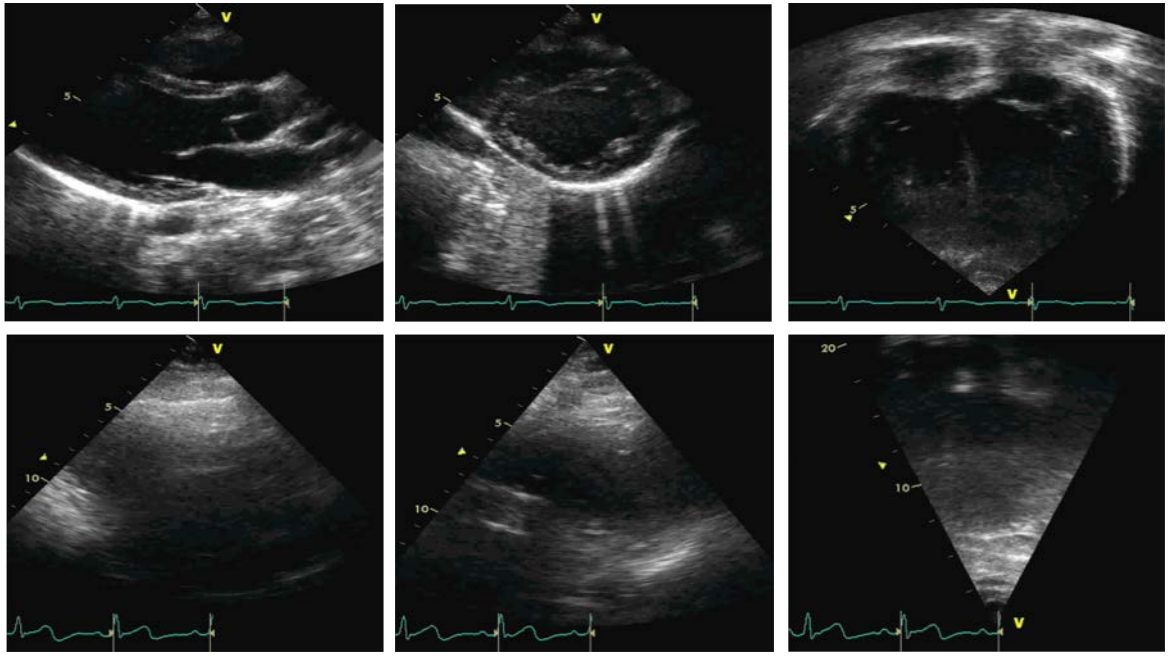
Echocardiogram

Cardiac MRI

Defining DMD - Associated Cardiac Disease: Echo

- Traditional assessment of cardiac function: echocardiography
  - Advantages
    - Readily available
    - Can be done quickly
    - Great first line tool
  - Disadvantages
    - Image quality worsen with age
    - Detection of global cardiac dysfunction

Defining DMD - Associated Cardiac Disease: Echo

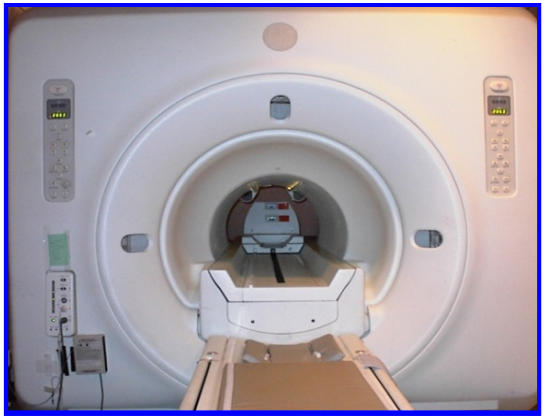


- Echocardiogram – good for global heart function
- Many times the heart is not well seen by ECHO when patients are older when we need it most

Defining DMD - Associated Cardiac Disease: MRI

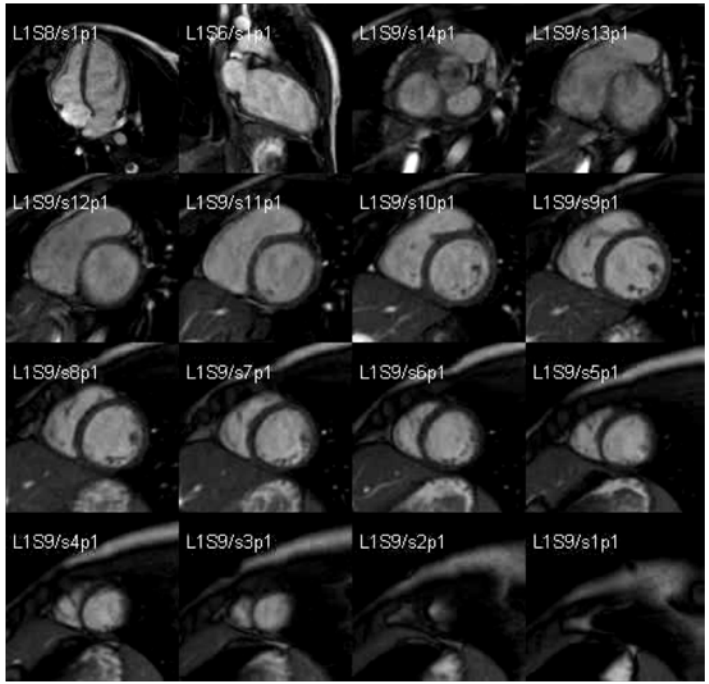
- Advantages: Accurate measurements
  - ***Traditional MRI Information***
    - *Function by ejection fraction*
    - *Late gadolinium enhancement (LGE)*

    Scar/Fibrosis assessment
  - **Newer MRI Techniques**
    - Myocardial strain for contractility
- Disadvantages:
  - IV placement for scar imaging
  - May take longer study - improving
  - Have to lay still
  - Not as readily available-changing

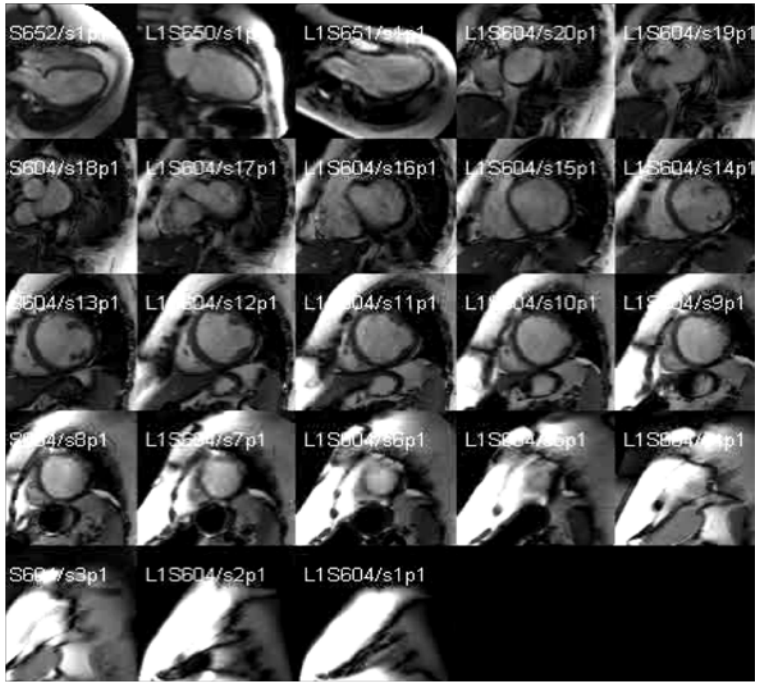


Defining DMD - Associated Cardiac Disease: MRI

- Good image quality regardless of age



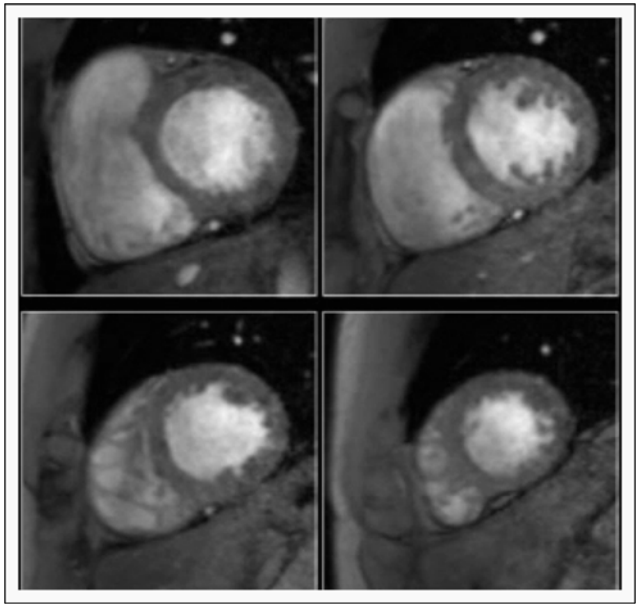
Normal Function

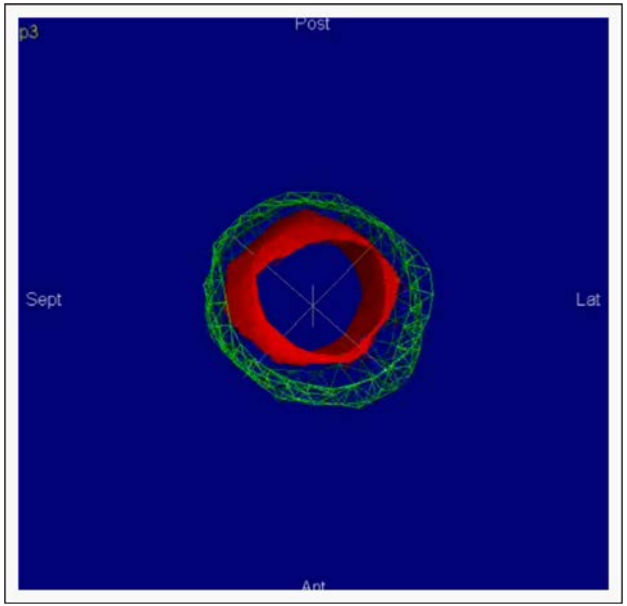


Abnormal Function

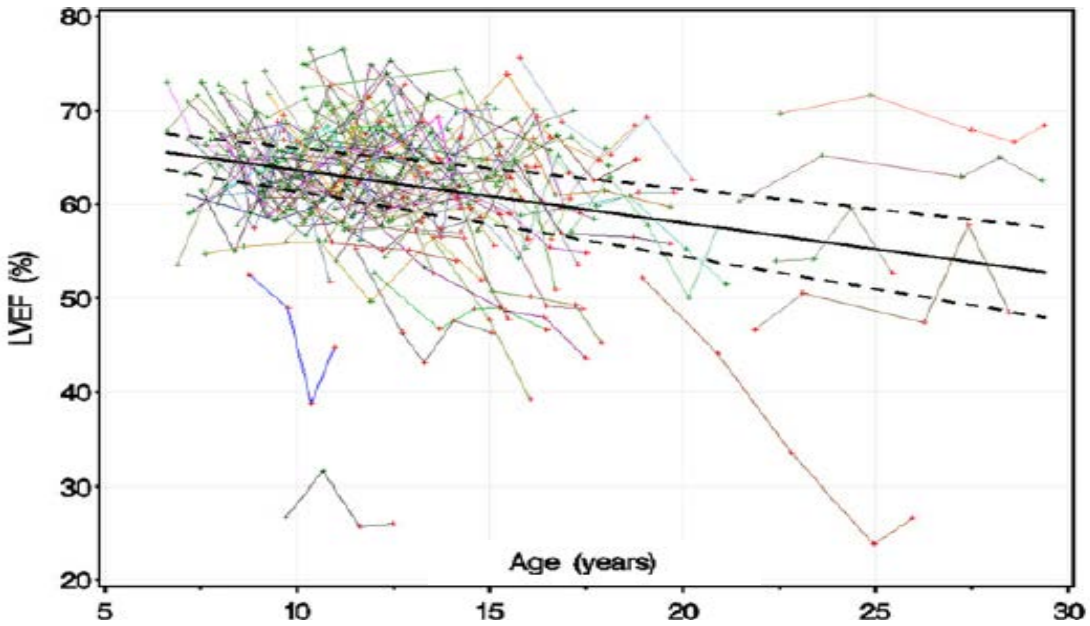
Defining DMD - Associated Cardiac Disease: MRI

- Ejection fraction by cardiac MRI measures the global state on how well the heart squeezes





Defining DMD - Associated Cardiac Disease: MRI



Cardiac Natural History by CMR

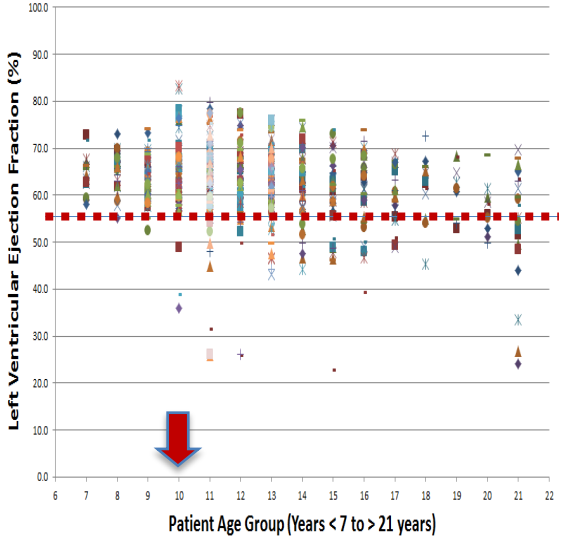
Graph of function by ejection fraction with age and over time individually and as a group

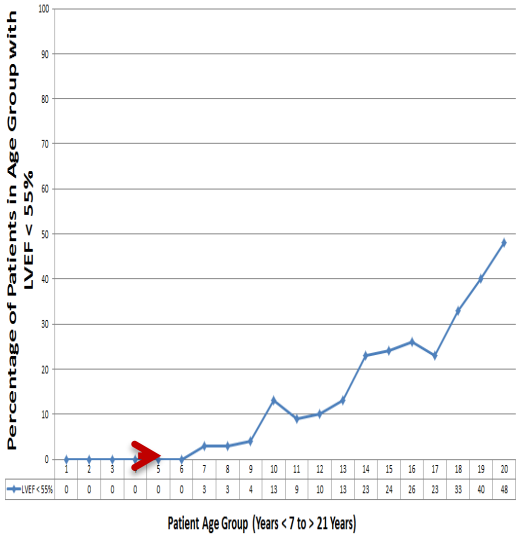
- Cardiac function by ejection fraction declines overtime and is worse with age

Tandon, Hor et al, JAHA 2015

Defining DMD - Associated Cardiac Disease: What we know using cardiac MRI

- Ejection fraction abnormalities (< 55%) starts around age **10 years** and progresses with time and age





Cardiac Natural History by CMR

Scatter Graph of function by ejection fraction with age and over time individually and as a group

Hor et al, Unpublished data

Defining DMD - Associated Cardiac Disease: What we know using cardiac MRI

- Cardiac MRI can track function by ejection fraction over time
- Provides a means to assess cardiac disease progression
- Provides a means to determine cardiac "natural history" while on traditional therapy
- Provides the ability to assess therapeutic efficacy

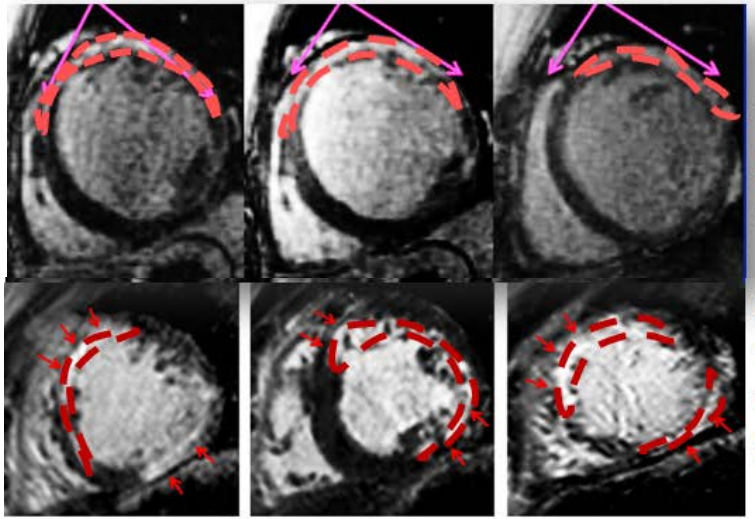
Defining DMD - Associated Cardiac Disease: Cardiac MRI

- Ejection fraction is currently gold standard tool for assessing cardiac function
- EF decline is a **late finding** in the disease process when the heart no longer squeezes normally
- Are there ways to look at DMD associated heart disease beyond squeeze?

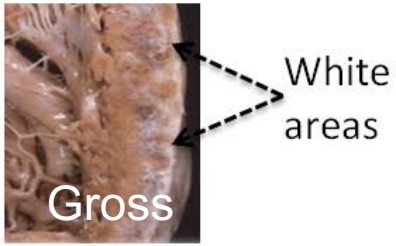
Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)

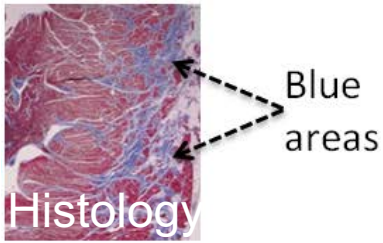
- Enhancement pattern **unique** to DMD (**sub-epicardial region = Pink**)
- Compared to Heart attack patients (**sub-endocardial = Red**)



DMD: white areas within pink (outer surface)



Heart Attack: white areas within **red** (inner surface)



Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)

- **Myocardial fibrosis/scar imaging**
  - Fibrosis associated with ventricular dysfunction BUT found ***few patients having fibrosis with normal function***

Int J Cardiovasc Imaging. 2009 January ; 25(1): 57–63. doi:10.1007/s10554-008-9352-y.

Late Gadolinium Enhancement: Precursor to Cardiomyopathy in Duchenne Muscular Dystrophy?

Michael D. Puchalski, M.D.*, Richard V. Williams, M.D., Bojana Askovich, Ph.D., C. Todd Sower, Kan H. Hor, M.D.#, Jason T. Su, D.O., Nathan Pack, BS, Edward Dibella, PhD, and William M. Gottliebson, M.D.#

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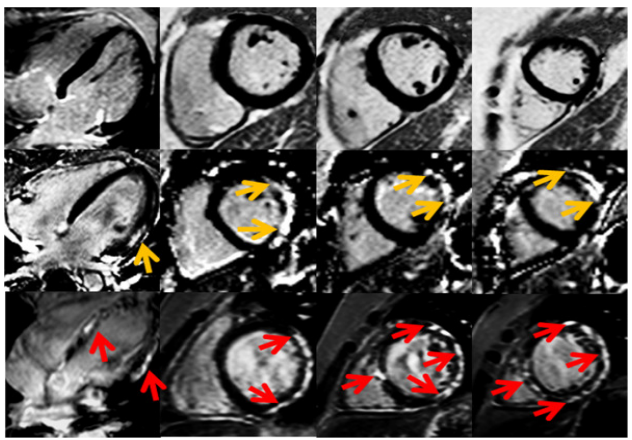
#Cincinnati Children's Hospital Medical Center 3333 Burnet Ave Cincinnati, OH 45229

Puchalski…Hor et al, Int J Cardiovasc Imaging, 2009 and Silva et al, JACC 2007

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)

- 17% of boys less 10 years of age has scar (youngest was 6.5 years old)
- 34% of boys 10-15 years of age has scar
- 59% of boys older 15 years have scar
- 30% of boys with **normal** heart function have scar
- 84% of boys with **abnormal** heart function have scar



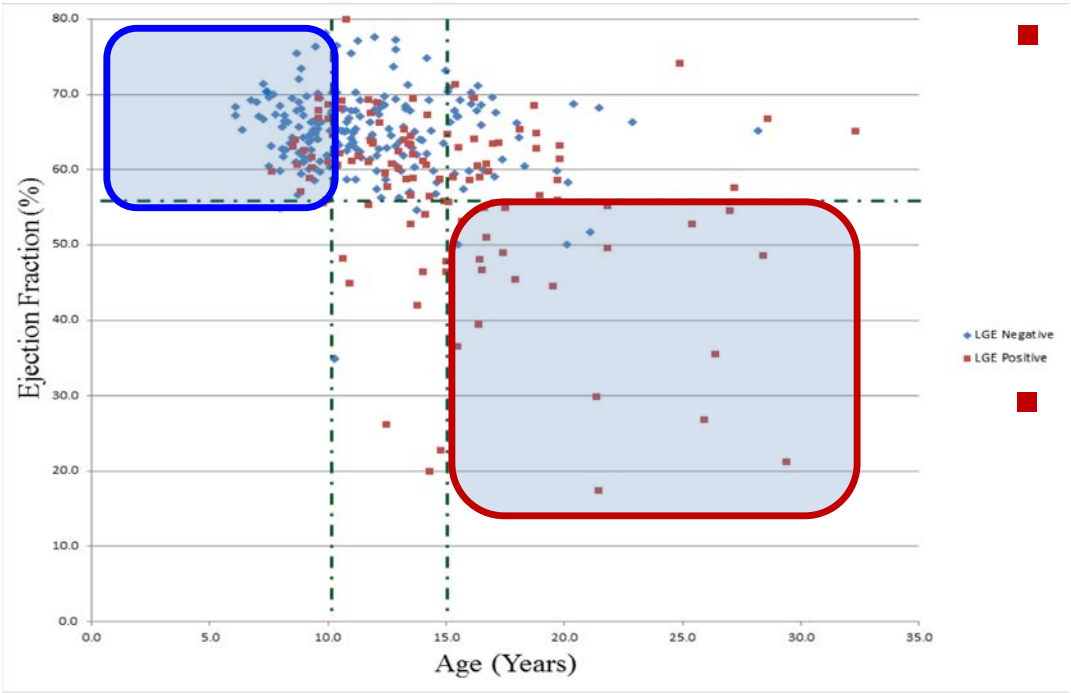
Age and EF	Patient	Heart Scar
Age < 10 years	83	14 (17%)
Age 10–15 years	149	52 (34%)
Age > 15 years	82	48 (59%)
LVEF ≥ 55%	277	82 (30%)
LVEF < 55%	37	31 (84%)

Hor et al, JCMR, 2013

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)

- Myocardial fibrosis: is a precursor to myocardial dysfunction.

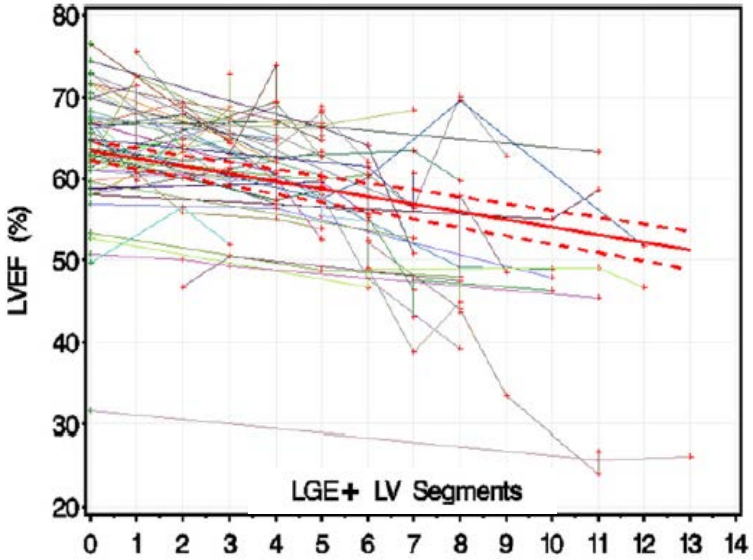


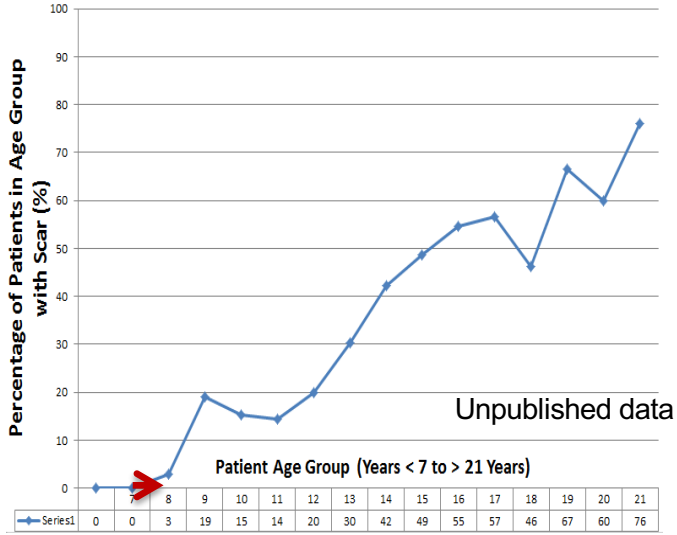
- LGE (red) is more prevalent with old age and abnormal EF
- LGE is present in young patients with normal EF (blue)

Hor et al, JCMR, 2013

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)





Cardiac Natural History by CMR

Scatter Graph of function by ejection fraction with age and scar burden

- Patients with myocardial fibrosis or scar have worse ejection fraction decline
- More areas with scar is associated with abnormal heart function (red) and increased with age

Defining DMD - Associated Cardiac Disease: MRI

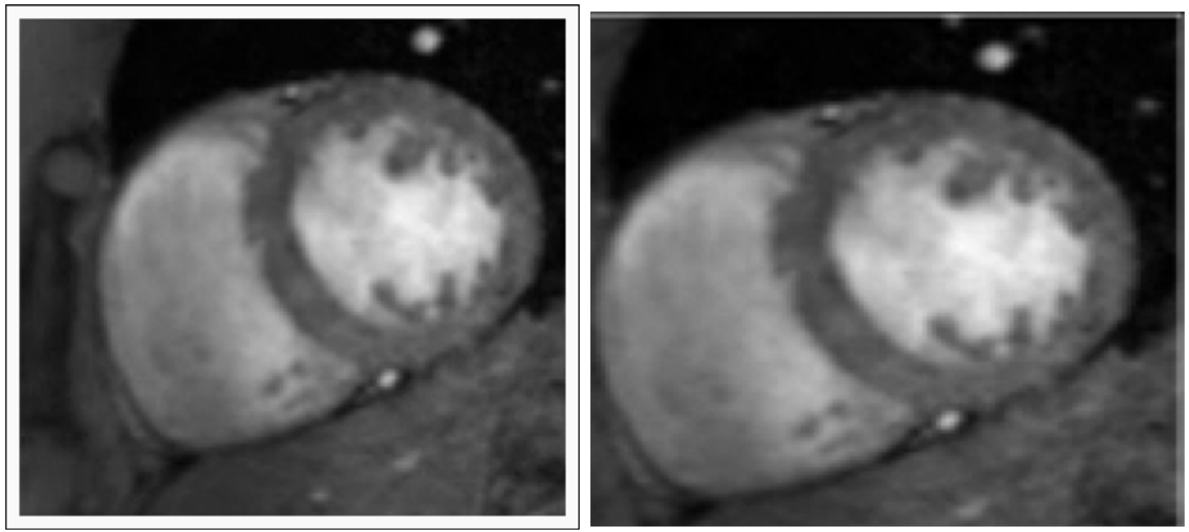
The Heart in DMD Beyond Squeeze (Myocardial Strain)

- LVEF - valuable for global ventricular function
- EF - insensitive to alterations in regional performance (conceal underlying regional dysfunction)
- Not an ideal index of contractility
- Lack of regional assessment – a major limitation

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (Myocardial Strain)

- More sensitive method beyond squeeze that can detect cardiac dysfunction earlier?
- Strain imaging - fundamentally important in assessing contractility and can detect cardiac disease earlier than appearance of scar or EF abnormality



Defining DMD - Associated Cardiac Disease: MRI

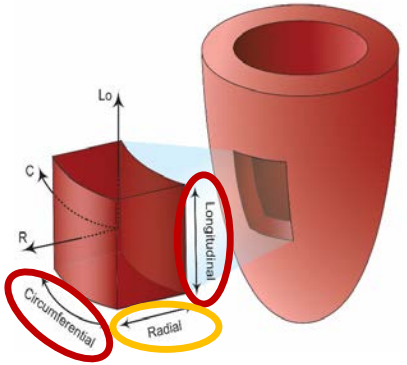
The Heart in DMD Beyond Squeeze (Myocardial Strain)

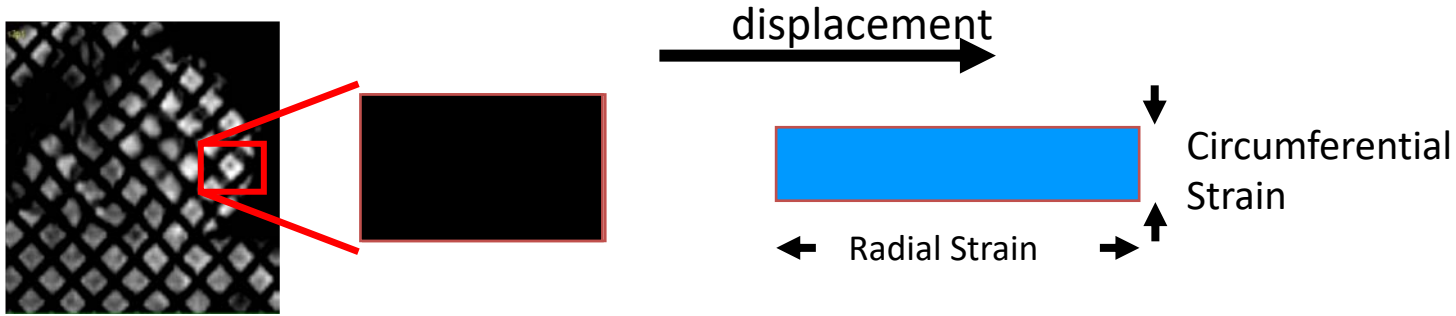
- **What is myocardial strain?**
  - Special technique that truly looks at heart muscle contractility beyond what ejection fraction can tell you
- **Why use strain?**
  - Detection of disease earlier will allow better understanding of disease manifestation and shift the paradigm from rescue to prevent

Mirsky et al, Circ Res, 1973, http://folk.ntnu.no/stoylen

Concept of Myocardial Strain

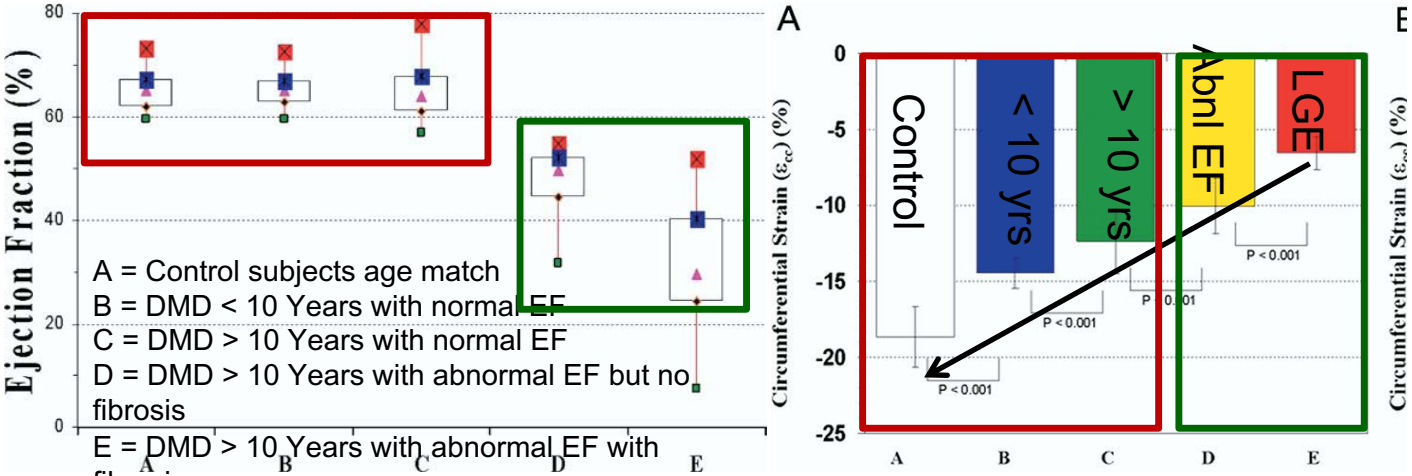
- **Displacement and Velocity = Motion**
- Strain analysis – detects myocardial contractility
  - *Positive strain = stretching*
  - *Negative strain = shortening*





Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (Myocardial Strain)



- Circumferential strain magnitude is lower and decline with age despite normal EF (red box)
- Strain magnitude further decline with disease progression (green box)

Hor et al, JACC 2009

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (Myocardial Strain)

- This study allowed us to overcome the barrier of treatment by finding **a more sensitive and earlier way to look at heart function beyond ejection fraction**

Circumferential Strain Analysis Identifies Strata of Cardiomyopathy in Duchenne Muscular Dystrophy: A Cardiac Magnetic Resonance Tagging Study

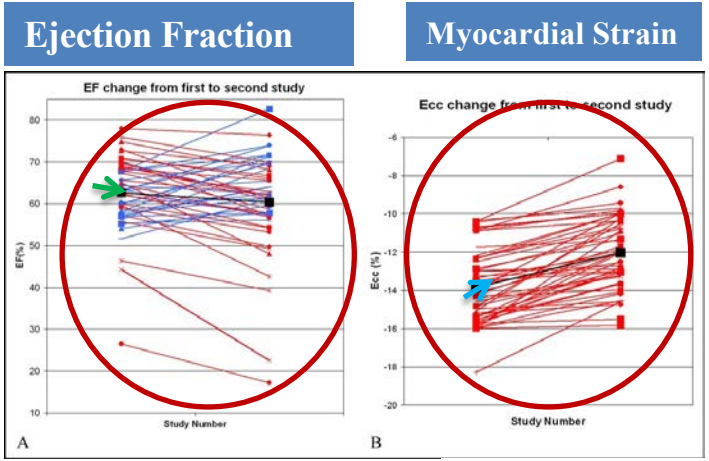
Kan N. Hor, Janaka Wansapura, Larry W. Markham, Wojciech Mazur, Linda H. Cripe, Robert Fleck, D. Woodrow Benson, and William M. Gottliebson

J. Am. Coll. Cardiol. 2009;53;1204-1210
doi:10.1016/j.jacc.2008.12.032

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (Myocardial Strain)

- We showed that the myocardial strain magnitude continue to decline
- In 35% of patients - ejection fraction increased despite no change in medication



Detection of Progressive Cardiac Dysfunction by Serial Evaluation of Circumferential Strain in Patients With Duchenne Muscular Dystrophy

Sean C. Hagenbuch, MD[a], William M. Gottliebson, MD, MS[a], Janaka Wansapura, PhD[b], Wojciech Mazur, MD[c], Robert Fleck, MD[b], D. Woodrow Benson, MD, PhD[a], and Kan N. Hor, MD[a,*]

Defining DMD - Associated Cardiac Disease: MRI

The Heart in DMD Beyond Squeeze (Myocardial Strain)

- Myocardial strain detect early cardiac abnormalities
- Further decline in strain magnitude with age despite normal global function by ejection fraction
- Reduce EF results in further decrease strain magnitude
- Development of myocardial fibrosis and EF decline resulted in further reduction in strain magnitude

Hor et al, JACC 2009

Defining DMD - Associated Cardiac Disease: MRI

What we know using Cardiac MRI

- **What we are Learning from Cardiac MRI?**
- Provides evidence of cardiac disease in a population with no routine way to assess heart failure symptoms
- Provides the potential to create biomarkers of disease before the heart no longer squeezes normally
- Provides a means to assess therapeutic efficacy
- Provides data for cardiac disease progression modeling

How About Heart Failure Symptoms?

- Traditional heart failure symptoms are listed above
- Application to NMD patients is challenging due to skeletal muscle myopathy

American College of Cardiology and American Heart Association Heart Failure Classification

- **Four Stages of Heart Failure**
  - **Stage A:** Presence of heart failure risk factors but no heart disease and no symptom
  - **Stage B:** Heart disease is present but there are no symptoms (structural changes in heart before symptoms occur)
  - **Stage C**: Structural heart disease is present AND symptoms have occurred
  - **Stage D**: Presence of advanced heart disease with continued heart failure symptoms requiring aggressive medical therapy

Yancy, C. W., et. al. "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." *Circulation* 128.16 (2013): n. pag. Print.

NYHA and AHA Heart Failure Classification: Utility

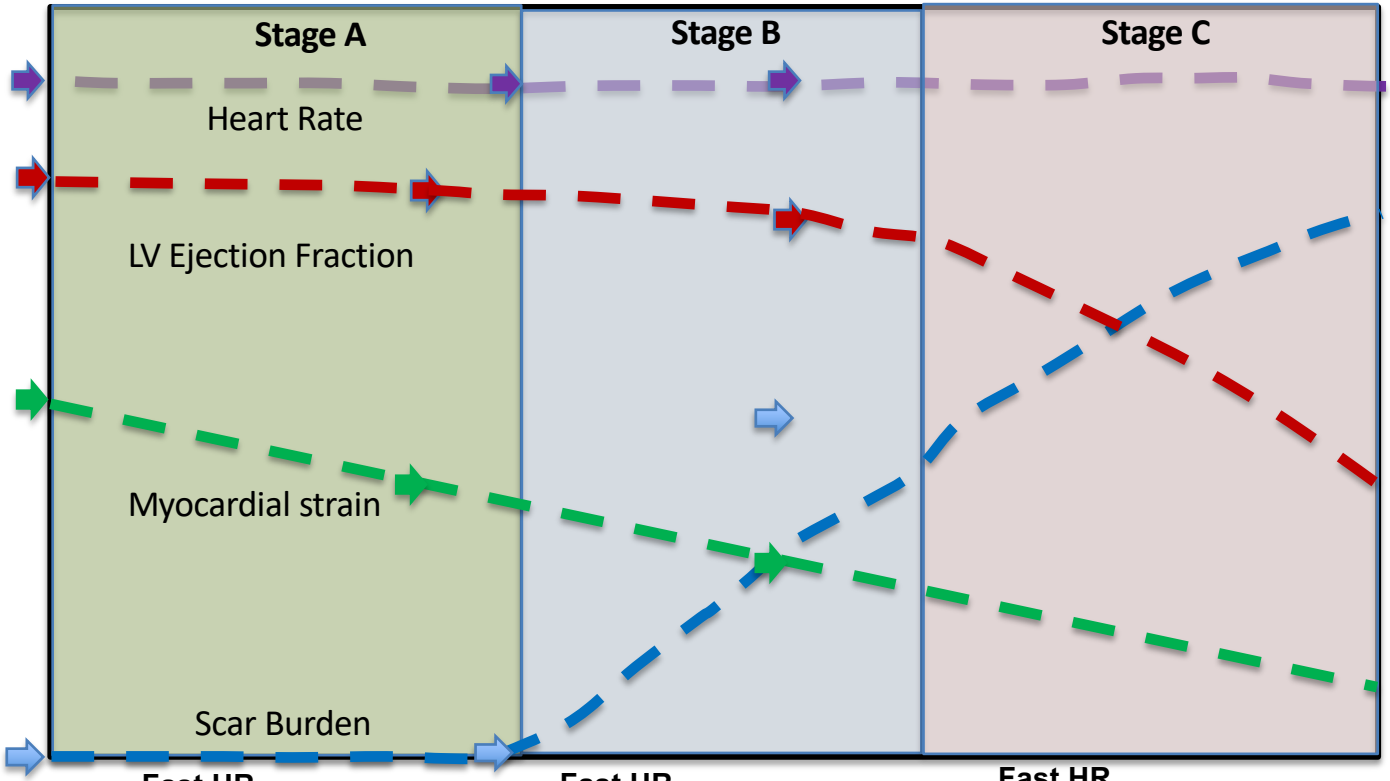
- Drives clinical practice in traditional heart failure treatment
- Trials frequently include the use of these classifications
- Neuromuscular disorders such as Becker and Duchenne muscular dystrophy - **universally** develop cardiomopathy and heart failure
- Utility in NMD is limited - lack traditional HF symptoms even in advance stages of heart failure due to skeletal myopathy

Defining DMD - Associated Cardiac Disease: MRI

Stage of DMD Heart Disease by Cardiac MRI?

- **AHA Heart Failure Stage A:** No symptoms but presence of risk factors
  - No scar
  - Normal heart function by ejection fraction ≥ 55%
  - ***Abnormal myocardial strain magnitude < 16%***
  - *No heart failure symptoms*
- **AHA Heart Failure Stage B:** No symptoms but structural changes present
  - **Subepicardial scar < 50% thickness and < 6/16 segments**
  - Normal heart function by ejection fraction ≥ 55%
  - ***Further decline myocardial strain magnitude < 14%***
  - *No heart failure symptoms*
- **AHA Heart Failure Stage C/D:** symptoms are evident
  - **Subepicardial scar ≥ 50% thickness and ≥ 6/16 segments involving apex and septum**
  - **Abnormal heart function by ejection fraction < 55%**
  - ***Further decline myocardial strain magnitude < 12%***
  - *No heart failure symptoms*

Cardiac MRI DMD-Associated Dystrophin Cardiomyopathy Staging



Stage A
Fast HR
Normal LVEF ≥ 55%
Abnormal Strain < 16%
No Scar
No HF symptoms

Stage B
Fast HR
Normal LVEF ≥ 55%
Abnormal Strain < 14%
Scar < 50% (< 6/16 seg)
No HF symptoms

Stage C
Fast HR
Abnormal LVEF < 55%
Abnormal Strain < 12%
Scar ≥ 50% (≥ 6/16 seg)
No HF symptoms

Takeaways

- Staging cardiac disease by non-invasive techniques such as cardiac MRI is important as traditional heart failure symptoms and current markers of disease are not sensitive enough
- A major barrier to treatment is understanding the cardiac disease natural history
- Surrogate cardiac MRI markers is **VITAL** to not only understand and better characterize cardiac disease progression but to assess treatment efficacy

Acknowledgements

- BMD, DMD patients and family for never ending quest to find the cure for NMD such as DMD
- Neurology and cardiology colleagues across centers
- Research teams at NCH and collaborators across the country and world wide
- Our sponsors and partners

Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE

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Questions

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