Cardiac Health in Duchenne: What we are Learning from Cardiac MRI

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#PPMDDConference
Why are cardiologists interested in patients with neuromuscular disorders?
The Heart is a Muscle Too!!!
Cardiac Health in Muscular Dystrophy

Background

- Becker and Duchenne muscular dystrophy - universally develop cardiomyopathy – time course variable
- Deficiency in dystrophin protein leads to skeletal, respiratory and cardiac disease
Cardiac Health in Muscular Dystrophy

Background

- Treatment – offers hope
  - Over the last 20 years, corticosteroids slow progression of skeletal muscle disease
  - Respiratory care improved survival
  - Leading cause of death from DMD-associated cardiomyopathy
Cardiac Health in Muscular Dystrophy
Background

- **WHY the need to understand cardiac natural history?**
  - Cardiac care currently lagging – mortality relates to cardiomyopathy
  - Improved outcomes requires better proactive treatment strategy
  - Barrier is a lack of sensitive and specific tool to assess efficacy of treatment
Cardiac Health in Muscular Dystrophy

Background

What we currently know...

- The myocardium is dystrophin deficient
- Cardiac disease is present at birth with abnormal ECG (James, Cripe et al)
- Disease progresses with time and best assessed by non-invasive imaging

Cardiac disease is a significant contributor to disease related morbidity and mortality

James, Cripe et al, Neuromusc Disord, 2011
How will the heart function be checked?

- Images of the heart will be obtained to evaluate structure and function.
Heart Function Assessment
How will the heart function be checked

Two common ways to obtain images of the heart:

Echocardiogram
Cardiac MRI
Heart Function: Echocardiography

- 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
Echocardiography: The Heart in DMD
How the Heart Squeeze

- 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
Heart Function: Cardiac MRI (CMR)

**Advantages:**
- Accurate measurements
  - *Traditional MRI Information*
    - Function by ejection fraction
    - (LGE) Scar/Fibrosis assessment
  - *Newer MRI Techniques*
    - (T2) Edema/inflammation
    - Myocardial strain for contractility
    - (T1) Diffuse microscopic scar

**Disadvantages:**
- IV placement for scar imaging
- May take longer study - improving
- Have to lay still
- Not as readily available-changing
Cardiac MRI (CMR): The Heart in DMD
How the Heart Squeeze

Normal Function

Abnormal Function
Cardiac MRI (CMR): The Heart in DMD
How the Heart Squeeze

- Ejection fraction by cardiac MRI measures the global state on how well the heart squeezes
Cardiac MRI (CMR): The Heart in DMD
How the Heart Squeeze

- PPMD Natural History Grant: Preliminary Data

- The purpose of this study:
  - Collect and make available comprehensive CMR data
  - To inform the naturally history of DMD cardiac disease
  - To allow cardiac disease progression modeling and potential development of surrogate biomarker cardiac disease
Cardiac MRI (CMR): The Heart in DMD
How the Heart Squeeze

Cardiac Natural History
Graph of function by ejection fraction with age and over time

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

Tandon, Hor et al, JAHA 2015
Ejection fraction abnormalities (< 55%) starts around age 10 years and more common with age.
Cardiac MRI (CMR): The Heart in DMD
Cardiac Natural History

- Cardiac MRI can track function by ejection fraction over time
- Provides a means to assess cardiac disease progression
- Provides the ability to assess therapeutic efficacy
- Provides a means to determine cardiac “natural history” while on traditional therapy
Cardiac MRI (CMR): The Heart in DMD
Beyond Squeeze

- EF 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?
Cardiac MRI (CMR): 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)
Cardiac MRI (CMR): The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)

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


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

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Puchalski...Hor et al, Int J Cardiovasc Imaging, 2009 and Silva et al, JACC 2007
Cardiac MRI (CMR): 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

<table>
<thead>
<tr>
<th>Age and EF</th>
<th>Patient</th>
<th>Heart Scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 10 years</td>
<td>83</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Age 10–15 years</td>
<td>149</td>
<td>52 (34%)</td>
</tr>
<tr>
<td>Age &gt; 15 years</td>
<td>82</td>
<td>48 (59%)</td>
</tr>
<tr>
<td>LVEF ≥ 55%</td>
<td>277</td>
<td>82 (30%)</td>
</tr>
<tr>
<td>LVEF &lt; 55%</td>
<td>37</td>
<td>31 (84%)</td>
</tr>
</tbody>
</table>

Hor et al, JCMR, 2013
Cardiac MRI (CMR): 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
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
Cardiac MRI (CMR): The Heart in DMD
Beyond Squeeze (Myocardial Strain)

- EF - 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
Cardiac MRI (CMR): 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.
Cardiac MRI (CMR): 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

Concept of Myocardial Strain

- Displacement and Velocity = Motion
- Strain = Myocardial Deformation
  - Strain analysis – detects myocardial contractility
    - Positive strain = stretching
    - Negative strain = shortening
Cardiac MRI (CMR): 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
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
We also showed that the myocardial strain magnitude continue to decline while in some ejection fraction increased despite no change in medicine.
Cardiac MRI (CMR): The Heart in DMD
Beyond Squeeze (Myocardial Strain): Summary

- 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
What we are Learning from 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
What we are Learning from Cardiac MRI?
PPMD Natural History Grant: Preliminary Data

- What is the plan for this data?
  - Work with Parent Project Muscular Dystrophy and other patient organizations to allow access
  - Work with academic and industry partners to standardize cardiac disease assessment
  - Work with industry to provide tools to assess treatment efficacy
  - Does the new drug improve cardiac disease compared to standard treatment only
What we are Learning from Cardiac MRI?
PPMD Natural History Grant: Preliminary Data

What is the plan for this data?

- Imagine that one day you can access the PPMD or other websites
  - Plug in your child’s age, perhaps genetic information and current treatment
  - Imagine being able to know how severe your child’s cardiac disease is compared to DMD boys of the same age, same type of mutation and treatment
What we are Learning from Cardiac MRI?
PPMD Natural History Grant: Preliminary Data

- What is the plan for this data?
  - If all goes as plans – it allows you and your son to actively manage his cardiac disease
  - It gives you and your doctor information on the effectiveness of your treatment compared to other DMD patients
  - It gives you knowledge that can change the disease outcomes
Acknowledgements

- BMD, DMD patients and family for never ending quest to fine the cure for DMD
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- Research teams at NCH and collaborators across the country and world wide
- Our sponsors and partners
Thank you!

Questions?