Iowa ACC FIT Series 05/16/2020: Hypertrophic Cardiomyopathy (HCM)

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Disclosures

- Research funding from MyoKardia
  - Will briefly discuss investigational drug
- Prior clinical research funding from Gilead Sciences
- Past consultant for Novartis and Janssen
- Compensation as senior associate editor of the *Journal of the American Heart Association*
Outline

• Epidemiology
• Genetics and Pathophysiology
• Clinical Features, Diagnosis, and Management
Remodeling in HCM

Normal  Asymmetric  Concentric

Epidemiology of HCM

- Prevalence up to 1/200, male = female
- 1.6 million patients are affected in the US
- Only 20% know of their diagnosis
- Annual mortality 1%, 3-6% in subgroups
- > 1500 patients will die from HCM every year, 10% of them under age 24 years
- HCM is highly underdiagnosed in African Americans
Annual deaths based on CDC database (1999-2006)

- Total deaths: 1565
- Under 54 yrs: 54%
- Under 44 yrs: 35%
- Under 24 yrs: 10% + 8% w/o under 1 yr.
Molecular Genetics of Hypertrophic Cardiomyopathy (HCM)
### Table 1  Summary of Hypertrophic Cardiomyopathy Susceptibility Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myofilament HCM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTN</td>
<td>2q24.3</td>
<td>Titin</td>
</tr>
<tr>
<td>MYH7</td>
<td>14q11.2–q12</td>
<td>Beta-myosin heavy chain</td>
</tr>
<tr>
<td>MYH6</td>
<td>14q11.2–q12</td>
<td>Alpha-myosin heavy chain</td>
</tr>
<tr>
<td>MYL2</td>
<td>12q23–q24.3</td>
<td>Ventricular regulatory myosin light chain</td>
</tr>
<tr>
<td>MYL3</td>
<td>3p21.2–p21.3</td>
<td>Ventricular essential myosin light chain</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>11p11.2</td>
<td>Cardiac myosin-binding protein C</td>
</tr>
<tr>
<td>TNNT2</td>
<td>1q32</td>
<td>Cardiac troponin T</td>
</tr>
<tr>
<td>TNNI3</td>
<td>19p13.4</td>
<td>Cardiac troponin I</td>
</tr>
<tr>
<td>TPM1</td>
<td>15q22.1</td>
<td>Alpha-tropomyosin</td>
</tr>
<tr>
<td>ACTC</td>
<td>15q14</td>
<td>Alpha-cardiac actin</td>
</tr>
<tr>
<td>TNNC1</td>
<td>3p21.3–p14.3</td>
<td>Cardiac troponin C</td>
</tr>
<tr>
<td><strong>Z-disc HCM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBD3</td>
<td>10q22.2–q23.3</td>
<td>LIM binding domain 3 (alias: ZASP)</td>
</tr>
<tr>
<td>CSRP3</td>
<td>11p15.1</td>
<td>Muscle LIM protein</td>
</tr>
<tr>
<td>TCAP</td>
<td>17q12–q21.1</td>
<td>Telethonin</td>
</tr>
<tr>
<td>VCL</td>
<td>10q22.1–q23</td>
<td>Vinculin/metavinculin</td>
</tr>
<tr>
<td>ACTN2</td>
<td>1q42–q43</td>
<td>Alpha-actinin 2</td>
</tr>
<tr>
<td>MYOZ2</td>
<td>4q26–q27</td>
<td>Myozenin 2</td>
</tr>
<tr>
<td><strong>Calcium-handling HCM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JPH2</td>
<td>20q12</td>
<td>Junctophilin-2</td>
</tr>
<tr>
<td>PLN</td>
<td>6q22.1</td>
<td>Phospholamban</td>
</tr>
</tbody>
</table>
HCM is a disease of the sarcomere.

Relative Contribution of HCM Genes

A background modifier gene alters left ventricular hypertrophy in αMHC Arg403Gln HCM mice.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Strain</th>
<th>No. of mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>129</td>
<td>4</td>
</tr>
<tr>
<td>WT</td>
<td>BS</td>
<td>2</td>
</tr>
<tr>
<td>403 +/-</td>
<td>129</td>
<td>6</td>
</tr>
<tr>
<td>403 +/-</td>
<td>BS</td>
<td>4</td>
</tr>
</tbody>
</table>

Semsarian et al. J Mol Cell Cardiol 2001;33:2055.
Mechanisms of Hypertrophic Cardiomyopathy (HCM)
Mechanisms of HCM

- \( \uparrow \) ATPase activity and energy consumption
- \( \uparrow \) Filament velocity
- \( \uparrow \) Force generation
- Perturbation of cellular \( \text{Ca}^{2+} \) homeostasis
  - Agents which affect myocyte \( \text{Ca}^{2+} \) can alter pathology of \( \alpha \)MHC Arg403Gln hearts
  - Myofibrillar preparations from mutant hearts are activated at lower \( \text{Ca}^{2+} \) concentrations
  - \( \text{Ca}^{2+} \) mobilization is upregulated compared to hearts from wild-type mice
HCM variants lead to hypercontractility by shifting myosin heads to the “on state.”

Clinical Features, Diagnosis, and Management of Hypertrophic Cardiomyopathy (HCM)
Main Clinical Concerns in HCM

• Symptoms (chest pain, shortness of breath on exertion)
  – Medications
  – Surgical septal myectomy
  – Alcohol septal ablation

• Sudden cardiac death
  – Implantable cardioverter defibrillator (ICD)

• Atrial fibrillation and stroke

• Screening of asymptomatic individuals
Prognosis profiles for HCM and targets for therapy.

Prognostic Profiles

- Sudden Death
- Heart Failure
- End Stage
- AF and Stroke

Benign/ Stable (Normal Longevity)

et al. Circulation 2011;124:2761-2796
Clinical Screening

Each Visit
• History (with special attention to ischemic and heart failure symptoms, arrhythmias, presyncope, and syncope)
• Physical examination (with special attention to the cardiac and skeletal muscle systems)
• Electrocardiogram
• Echocardiogram
• 48-hour Holter monitoring
• (Serum NT-proBNP, troponin)

Initial Evaluation and When Warranted on Subsequent Visits
• Magnetic resonance imaging (initial evaluation)
• Exercise treadmill testing (blood pressure response), preferably CPET combined with echocardiogram

Physical Examination

- Bisfiriens pulse
- Bifid apical impulse
- S4
- Systolic ejection murmur that increases with
  - Valsalva strain
  - Squat to stand
  - Exercise
Role of Imaging in HCM Care

- **Diagnosis**
  - **Echocardiography** (first-line)
  - **Cardiac MR** (no limitations of ultrasound windows or body habitus)

- **Risk stratification**
  - **Exercise stress echo testing**
    - Blood pressure response
    - Peak gradient
  - **Cardiac MR**
    - Can characterize fibrosis in myocardium (associated with increased VT)
LVOT Obstruction

Hypertrophic Cardiomyopathy

With Obstruction

Without Obstruction

Cardiovascular Division, Washington University
### Definitions of Dynamic Left Ventricular Outflow Tract Obstruction

<table>
<thead>
<tr>
<th>Hemodynamic State</th>
<th>Conditions</th>
<th>Outflow Gradient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal obstruction</td>
<td>Rest</td>
<td>$\geq 30$ mm Hg</td>
</tr>
<tr>
<td>Nonobstructive</td>
<td>Rest</td>
<td>$&lt; 30$ mm Hg</td>
</tr>
<tr>
<td></td>
<td>Physiologically provoked</td>
<td>$&lt; 30$ mm Hg</td>
</tr>
<tr>
<td>Labile obstruction</td>
<td>Rest</td>
<td>$&lt; 30$ mm Hg</td>
</tr>
<tr>
<td></td>
<td>Physiologically provoked</td>
<td>$\geq 30$ mm Hg</td>
</tr>
</tbody>
</table>

- Symptoms: peak gradient $> 40-50$ mmHg

LVOT Obstruction Worsens With:

- Increased contractility
- Decreased peripheral resistance
- Decreased left ventricular volume

- All of which occur with physical exertion
Severe symptoms in non-obstructive HCM are difficult to treat given the magnitude of pathology that may be present in the very symptomatic patient.

Shirani et al, JACC 2000
Management of Hypertrophic Cardiomyopathy (HCM)
Drug Doses in HCM

• Beta-blocker increased until heart rate 50-60 bpm (can go up to massive doses with pacemaker)
• Verapamil 80 mg - 480 mg / day
• Diltiazem 120 mg - 360 mg / day
• Disopyramide CR 250 mg or 300 mg BID
Changes in LVEDD z-Scores Over Time in HCM Subjects Randomized to Diltiazem or Placebo

Ho CY et al. JACC Heart Fail 2015;3:180.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>MYH7 Carriers (n = 21)</th>
<th></th>
<th>MYBPC3 Carriers (n = 12)</th>
<th>p for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diltiazem</td>
<td>Placebo</td>
<td>p Value</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Sample size (echocardiography), n</td>
<td>10</td>
<td>11</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Sample size (CMR), n</td>
<td>8</td>
<td>8</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Change in outcome measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo Max LVWT, mm*</td>
<td>+1.4 ± 0.60</td>
<td>+0.84 ± 0.70</td>
<td>0.49</td>
<td>-0.02 ± 0.60</td>
</tr>
<tr>
<td>Echo Max LVWT, z-score*</td>
<td>+0.92 ± 0.63</td>
<td>+0.78 ± 0.62</td>
<td>0.87</td>
<td>-0.02 ± 0.45</td>
</tr>
<tr>
<td>E/E’</td>
<td>+0.53 ± 0.20</td>
<td>-0.03 ± 0.17</td>
<td>0.04</td>
<td>-0.97 ± 0.15</td>
</tr>
<tr>
<td>CMR LV mass,† g</td>
<td>-1.8 ± 4.4</td>
<td>-8.8 ± 3.7</td>
<td>0.24</td>
<td>-13.4 ± 3.4</td>
</tr>
<tr>
<td>CMR LV mass index,† g/m²</td>
<td>-1.1 ± 3.1</td>
<td>-5.6 ± 1.6</td>
<td>0.21</td>
<td>-3.7 ± 2.3</td>
</tr>
<tr>
<td>Troponin I, pg/ml</td>
<td>+1.2 ± 1.2</td>
<td>-0.51 ± 0.59</td>
<td>0.24</td>
<td>-0.61 ± 0.70</td>
</tr>
</tbody>
</table>

Values are mean ± SE and are adjusted for age, sex, genotype, family relations, and baseline value. *Measured by echocardiography. †Measured by cardiac magnetic resonance (CMR) imaging.

E/E’ = mitral inflow E wave/E’; other abbreviations as in Table 1.
## Annual Death Rates

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>All death</th>
<th>Sudden death*</th>
<th>Cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong> N=373</td>
<td>6.4</td>
<td>3.8%</td>
<td>1.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td><strong>Diso</strong> N=153</td>
<td>4.4</td>
<td>2.7%</td>
<td>0.3%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

\*including ICD shock

- p=.16  
- p=.003  
- p=.03

- HR= .69  
- HR= .15  
- HR= .45
Fig. 1 MYK-461 inhibits myosin ATPase and contractility of cardiomyocytes.

Eric M. Green et al. Science 2016;351:617-621

Published by AAAS
Fig. 2 MYK-461 reduces cardiac contractility in mouse models of HCM and prevents or ameliorates LV hypertrophy.

Eric M. Green et al. Science 2016;351:617-621
Fig. 3 MYK-461 reduces the development of myocardial disarray and fibrosis in mouse models of HCM.

Eric M. Green et al. Science 2016;351:617-621

Published by AAAS
Effect of Mavacamten on left ventricular outflow tract (LVOT) Obstruction and left ventricular ejection fraction (LVEF) in human subjects with HCM.

Mavacamten 10-20 mg / day

Mavacamten 2-5 mg / day ± Beta Blockers

Drugs to Avoid in Obstructive HCM

- Nitrates
- ACE, (ARB?); ....prils and ....sartans
- Nifedipine, Amlodipine; ....pines
- Alpha blockers: Terazosin (Hytrin), Tamsulosin, (Flomax), Doxazosin (Cardura); ....sins
- Sildenafil (Viagra), Vardenafil (Levitra);....enafils
- Dobutamine, Dopamine
- Digoxin
Septal Myectomy
Symptoms before (Pre) (n=65) and 1 year after (Post) (n=61) surgical treatment of adult patients with hypertrophic obstructive cardiomyopathy

Survival Free from All-Cause Mortality

Survival Free from HCM-Related Death

![Graph showing survival free from HCM-related death with different groups: Myectomy, Nonobstructive, Nonoperated Obstructive.](image)

<table>
<thead>
<tr>
<th>Years</th>
<th>Myectomy</th>
<th>Nonobstructive</th>
<th>Nonoperated Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>289</td>
<td>820</td>
<td>228</td>
</tr>
<tr>
<td>2</td>
<td>249</td>
<td>587</td>
<td>146</td>
</tr>
<tr>
<td>4</td>
<td>179</td>
<td>490</td>
<td>106</td>
</tr>
<tr>
<td>6</td>
<td>108</td>
<td>355</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>244</td>
<td>42</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>201</td>
<td>28</td>
</tr>
</tbody>
</table>

P < 0.001

Surgery: Special Considerations

• Mitral valve repair
  – Leaflet repair
  – Ring
  – Artificial chordae
  – Alfieri stitch
• Mitral valve replacement
• MAZE procedure for atrial fibrillation
• Aortocoronary bypass surgery
Section of Hypertrophied Left Ventricle.
Role of Ablation

- Age > 60 years
- Comorbidities
- No concomitant reason for surgery (valve, ACBP, MAZE)
- Hemodynamically stable
- Free from severe pulmonary hypertension
Treatment algorithm.

HCM Patients

Treat comorbidities according to GL [HTN, Lipids, DM]

Obstructive Physiology

Yes

No

Heart Failure Symptoms or Angina

Yes

No

Avoid vasodilator therapy and high-dose diuretics

Annual clinical evaluation

No

LV EF <50%

Beta Blockade

Verapamil

Disopyramide

Therapy as outlined in Heart Failure GL

Persistent Symptoms

Yes

No

LV EF ≥50%

Beta Blockade

Verapamil

Diuretics

ACE inhibitor or ARB

Invasive Therapy

No

Acceptable surgical candidate

Yes

No

Acceptable candidate for alcohol ablation

Yes

No

Surgical Myectomy

Alcohol Ablation

Consider DDD Pacing

Legend

Class I

Class IIa

Class IIb
Risk Stratification for Sudden Cardiac Death in HCM
**Risk Factors for Sudden Death in HCM**

**Major**
- Cardiac arrest
- Spontaneous sustained VT
- Family history of premature sudden death
- Unexplained syncope
- LV thickness $\geq 3.0$ cm
- Abnormal exercise blood pressure
- Nonsustained VT

**Possible in Individual Patients**
- Atrial fibrillation
- Myocardial ischemia
- LV outflow obstruction
- Intense physical exertion

**Emerging**
- Fibrosis on cardiac MRI
- Sarcomere mutation
- Age at diagnosis
- Apical aneurysm

Relation between Extent of Late Gadolinium Enhancement (LGE) and Sudden Cardiac Death (SCD)


![Graph showing the relation between Extent of Late Gadolinium Enhancement (LGE) and Sudden Cardiac Death (SCD).](image)
Age at diagnosis is associated with burden of events.

Association between Sarcomere Mutations and Clinical Outcomes

Apical aneurysms are associated with adverse outcomes.

A Novel Clinical Risk Prediction Model (HCM Risk-SCD)

HCM Risk-SCD Calculator

<table>
<thead>
<tr>
<th>Age</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum LV wall thickness</td>
<td>mm</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>mm</td>
</tr>
<tr>
<td>Max LVOT gradient</td>
<td>mmHg</td>
</tr>
</tbody>
</table>

- **Age at evaluation**
- **Transthoracic Echocardiographic measurement**
- **Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation**
- **The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= 4V^2, where V is the peak aortic outflow velocity**
- **History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).**
- **3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.**
- **History of unexplained syncope at or prior to evaluation.**

<table>
<thead>
<tr>
<th>5-Y Risk</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4%</td>
<td>No</td>
</tr>
<tr>
<td>4 to &lt;6%</td>
<td>Maybe</td>
</tr>
<tr>
<td>≥ 6%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

## Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM

<table>
<thead>
<tr>
<th>Intensity Level</th>
<th>Eligibility Scale for HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Basketball (full court)</td>
<td>0</td>
</tr>
<tr>
<td>Basketball (half court)</td>
<td>0</td>
</tr>
<tr>
<td>Body building</td>
<td>1</td>
</tr>
<tr>
<td>Gymnastics</td>
<td>2</td>
</tr>
<tr>
<td>Ice hockey</td>
<td>0</td>
</tr>
<tr>
<td>Racquetball/squash</td>
<td>0</td>
</tr>
<tr>
<td>Rock climbing</td>
<td>1</td>
</tr>
<tr>
<td>Running (sprinting)</td>
<td>0</td>
</tr>
<tr>
<td>Skiing (downhill)</td>
<td>2</td>
</tr>
<tr>
<td>Skiing (cross-country)</td>
<td>2</td>
</tr>
<tr>
<td>Soccer</td>
<td>0</td>
</tr>
<tr>
<td>Tennis (singles)</td>
<td>0</td>
</tr>
<tr>
<td>Touch (flag) football</td>
<td>1</td>
</tr>
<tr>
<td>Windsurfing</td>
<td>1</td>
</tr>
</tbody>
</table>

# Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM

<table>
<thead>
<tr>
<th>Intensity Level</th>
<th>Eligibility Scale for HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
</tr>
<tr>
<td>Baseball/softball</td>
<td>2</td>
</tr>
<tr>
<td>Biking</td>
<td>4</td>
</tr>
<tr>
<td>Hiking</td>
<td>3</td>
</tr>
<tr>
<td>Modest hiking</td>
<td>4</td>
</tr>
<tr>
<td>Motorcycling</td>
<td>3</td>
</tr>
<tr>
<td>Jogging</td>
<td>3</td>
</tr>
<tr>
<td>Sailing</td>
<td>3</td>
</tr>
<tr>
<td>Surfing</td>
<td>2</td>
</tr>
<tr>
<td>Swimming (laps)</td>
<td>5</td>
</tr>
<tr>
<td>Tennis (doubles)</td>
<td>4</td>
</tr>
<tr>
<td>Treadmill/stationary bicycle</td>
<td>5</td>
</tr>
<tr>
<td>Weightlifting (free weights)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td></td>
</tr>
<tr>
<td>Bowling</td>
<td>5</td>
</tr>
</tbody>
</table>

Special Considerations in Adolescents

- Single risk factor—nonsustained VT
  - Age 15—relative risk 6
  - Age 50—relative risk 2
<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Relative Risk of Sudden Death</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18</td>
<td>8.07</td>
<td>0.003</td>
</tr>
<tr>
<td>18 – 39</td>
<td>0.69</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 39</td>
<td>0.68</td>
<td>NS</td>
</tr>
</tbody>
</table>
Incidence of AF 3%

Incidence of thromboembolism without anticoagulation 3.75%

Independent of CHA$_2$DS$_2$-VASc score
### Management of Atrial Fibrillation in HCM

<table>
<thead>
<tr>
<th>Issue</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate control</td>
<td>Beta-blockers and CCBs for acute and chronic rate control (class I)</td>
<td>Caution in patients with LV systolic dysfunction and cardiogenic shock.</td>
</tr>
<tr>
<td>Rhythm control</td>
<td>Amiodarone followed by disopyramide (class IIa)</td>
<td>In clinical practice, sotalol is preferred due to long-term side effects with other drugs.</td>
</tr>
<tr>
<td>Catheter ablation</td>
<td>Consider in patients with drug-refractory symptomatic AF, or unable to take antiarrhythmic (class IIa)</td>
<td>Early ablation strategy might be useful in young patients with normal-sized left atrium and/or paroxysmal AF.</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Unless contraindicated, oral anticoagulation with VKA (INR 2–3) to prevent thromboembolism (class I)</td>
<td>Direct oral anticoagulant can be used a second-line therapy. CHA2DS2-VASc score is not validated and does not effectively predict stroke risk.</td>
</tr>
</tbody>
</table>

Approach to the Family

- Careful family history for ≥ 3 generations
- Clinical screening for cardiomyopathy in asymptomatic first-degree relatives

Proposed Clinical Screening Strategies With Echocardiography (and 12-Lead ECG) for Detection of Hypertrophic Cardiomyopathy With Left Ventricular Hypertrophy in Families

Age < 12 y

Optional unless

Malignant family history of premature death from HCM or other adverse complications

Patient is a competitive athlete in an intense training program

Onset of symptoms

Other clinical suspicion of early LV hypertrophy

Age 12 to 18 y

Every 12–18 mo

Age > 18–21 y

At onset of symptoms or at least every 5 y. More frequent intervals are appropriate in families with a malignant clinical course or late-onset HCM