Hypertrophic Cardiomyopathy: beyond gradient and wall thickness

Michael H. Picard, M.D.
Massachusetts General Hospital
Harvard Medical School

no disclosures special thanks to A. Baggish
Hypertrophic cardiomyopathy (HCM)

- Unexplained LV hypertrophy (15 mm) associated with non-dilated ventricles in the absence of a cardiac or systemic disease that could produce the magnitude of hypertrophy.
- Autosomal dominant mutations in genes encoding components of the sarcomere and myofilament elements (> 1400 mutations in at least 8 genes identified).
- Prevalence 0.2% (1 in 500).
- Variation in morphologic expression + natural history:
  - Concentric LVH, Asymmetric LVH with or without LVOT obstruction, mid LV obstruction, apical hypertrophy, etc.
- Diagnosis made by echo (cMR).
HCM: Genetics

A disease of sarcomeric protein genes:

- myosin heavy chain (MYH7)
- myosin binding protein C (MYBPC3)
- cardiac troponin T (TNNT2)
- cardiac troponin I (TNNI3)
- cardiac actin (ACTC)
- alpha-tropomyosin (TPM1)
- essential myosin light chain (MYL2)

Identifiable in 60-70% of familial HCM

Limited value in disease management
HCM presents in all age groups

• Diverse clinical presentations
  – Many asymptomatic
  – SCD due to VT
    • Young (including athletes)
  – Heart failure
    • Exertional dyspnea
      – Diastolic HF
      – LVOT obstruction
  – Ischemia
    • Chest pain
  – AF and stroke
Pathophysiology

• LVH (myocardial disarray)
• Dynamic LVOT obstruction
  – Sensitive to load and contractility
  – Mechanical obstruction from SAM
    • Mitral-septal contact
• Diastolic dysfunction
• Mitral regurgitation
• Altered papillary muscle position
• Myocardial ischemia/fibrosis
• Arrhythmias
# HCM: Heterogeneous Clinical Presentation and Heterogeneous Symptom Burden

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Mild Symptoms</th>
<th>Severe Symptoms</th>
<th>Refractory CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Life Expectancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Education</td>
<td>Pharmacotherapy</td>
<td>Septal Reduction Therapy</td>
<td>Transplant</td>
</tr>
</tbody>
</table>

_Sudden Cardiac Death Always on the Radar Screen_
HCM: Role of Echocardiography

5. Echocardiography

Class I
1. TTE is recommended in the initial evaluation of all patients with suspected HCM. (Level of Evidence: B)
2. TTE is recommended as a component of the screening algorithm for family members of patients with HCM unless the family member is genotype negative in a family with known deleterious mutations. (Level of Evidence: B)
3. Periodic (12 to 18-month) TTE screening is recommended for children of patients with HCM, starting by age 10 or earlier if a growth spurt or signs of pathology are evident and/or when there are plans for engaging in intense competitive sports or there is a family history of sudden death. (Level of Evidence: C)
4. Periodic TTE is recommended for the evaluation of patients with HCM with a change in clinical status or new cardiovascular events. (Level of Evidence: B)
5. A transthoracic echocardiogram (TTE) is recommended for the preoperative guidance of surgical myectomy. (Level of Evidence: B)

Class IIa
No benefit

6. TEE or TEE with intracoronary contrast injection of the candidate's septal perforator(s) is recommended for the intraprocedural guidance of alcohol septal ablation. (Level of Evidence: B)
7. TTE should be used to evaluate the effects of surgical myectomy or alcohol septal ablation for obstructive HCM. (Level of Evidence: C)

Class IIb
No benefit

1. TTE studies should not be performed more frequently than every 12 months in patients with HCM when it is unlikely that any changes have occurred that would have an impact on clinical decision-making. (Level of Evidence: C)
2. Routine TEE and/or contrast echocardiography is not recommended when TTE images are diagnostic of HCM and/or there is no suspicion of fixed obstruction or intrinsic mitral valve pathology. (Level of Evidence: C)
HCM: Role of Echocardiography

- Establish / confirm diagnosis of LVH
- Identify LVH factors suggestive of dx other than HCM
- Identify corollary findings that explain sxs
- Provide data that may guide therapy
- Openly acknowledge the limitations of echo
Diagnosis of HCM variants by Echo

- LVH, non dilated LV
- Obstructive variant
  - Systolic anterior motion of MV
  - Late systolic LVOT pressure gradient (cw Doppler)
    - Change with maneuvers that alter load
- Apical variant
Other causes of increased LV wall thickness

• Familial
  – Glycogen storage ds (Pompe, Danon)
  – Lysosomal storage ds (Fabry)
  – Mitochondrial myopathies
  – Friedrich’s ataxia
  – Noonan’s syndrome

• Acquired
  – Exaggerated hypertrophy response to HTN
  – Athlete’s heart
  – Infiltration (amyloid, sarcoid)
61 yo F with dyspnea
52 yo M with abnormal ECG detected in ER after MVA (no prior ECGs)
Increase in peak gradient from 36 mm Hg to 127 mm Hg with Dobutamine

64 yo F with intractable dyspnea referred to MGH pulmonologist; has syncopal spells and 3 first degree relatives have died suddenly

? HCM on exam, echo ordered

Importance of provocation when refractory symptoms and low resting LVOT gradient
Clinical management

- Symptom management
- Risk stratification for sudden cardiac death
- Counseling/screening
  - Exercise and lifestyle recommendations
  - Family screening
  - Genetic counseling
Treatments for HCM (symptoms)

• ICDs for those at risk of SCD

• Pharmacologic
  – Beta blockers for angina or dyspnea (caution with bradycardia or conduction ds)
    • Verapamil, disopyramide second line agents (potential contraindications)

• Septal reduction therapy
  – Severe drug refractory symptoms and LVOT obstruction (peak > 50 mm Hg)
    • Surgical myectomy
    • Catheter based alcohol septal ablation
      – When surgery contraindicated or surgical risk unacceptable
        » Advanced age, serious co-morbidities
      – Patient preference
Rarer treatments (continued)

- Mitral valve replacement
- Transplant
  - Advanced HF not responsive to other treatments
Surgical myectomy
Transaortic approach

• Traditional (Morrow) procedure
  – ~ 3 cm long resection

• Extended myectomy
  – ~ 7 cm long resection

• Additional possible procedures
  – MV repair if anterior leaflet elongated
  – Shaving of papillary muscles, incising off LV wall, or repositioning PM
    • if enlarged or malpositioned
Other modifications to myomectomy

Fifer and Vlahakes, Circ 2008;117:429-439

Iacovini et al, Eur Hrt J 2012; epub
Percutaneous alcohol septal ablation therapy for HOCM

NEJM Oct 2002
Roles of echo in percutaneous septal ablation

- Identifying appropriate patients
- Identifying proper artery
- Confirming gradient reduction, LVOT remodeling
- Understanding mechanism of action
- Follow-up to determine etiology of recurrent symptoms
Using echo to select cases for alcohol septal ablation

- NYHA/CCS II-IV despite optimal medical therapy
- Upper septal thickness ≥ 16 mm
- Resting LVOT gradient ≥ 30 mm Hg
- If resting gradient low, LVOT gradient ≥ 50 mm Hg with exercise or dobutamine infusion
- Appropriate coronary anatomy
  - Contrast injection (diluted) into septal perforator prior to alcohol infusion to assess
    - Territory at risk
    - Insure perfusion bed does not involve RV, LV free walls
Echo contrast for selection of proper septal

• Perfusion bed should fill out the LV side of the upper septum
• look for collaterals
  – change imaging planes to examine RV free wall and inferior, posterior and lateral walls of LV
• an infusion speed of contrast that is identical to alcohol infusion speed
Echo contrast guidance

RV free wall perfusion from second branch of S1

Optimum perfusion from first branch of S1
Contrast echo guidance

S1 does not perfuse LV side of upper septum

S2 better perfusion territory
Monitoring results

**Pre-ablation**
105 mm Hg

**Post-ablation**
34 mm Hg
Echo Gradient Response
Yoerger et al, Am J Cardiol 2006;97:1511-1514

• The positive predictive value of an acute gradient reduction in the cath lab is high

• A sizable portion of patients in whom acute success is achieved in the cath lab subsequently re-develop a significant gradient at discharge, but go on to demonstrate echocardiographic relief of gradient at 3 months.

• The negative predictive value of an early increase in echo gradient after septal ablation is low.
Pre-ablation and 4 months post
Reduction in MR post-ablation

Pre-ablation

4 months post-ablation
Surgical myectomy vs. percutaneous alcohol ablation

• In experienced hands
  – Both improve hemodynamics, symptoms, exercise tolerance

• Similar morbidity/ mortality
  – Higher rates of pacer and incomplete gradient reduction with septal ablation
  – Higher rates of AI with myectomy

• No data to justify treating asymptomatic obstructions
ICD for SCD prevention in HCM

Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

HCM: What’s New and in the Future?

• Natural history studies
• Roles for cMR
• Genotype phenotype relations
• Myocardial mechanics – rest/ exercise
• Genotype / imaging / outcomes correlates
• Pre-phenotypic imaging clues
• How to deal with G+ P-
• Improved LVH discriminants
Prognosis with contemporary treatments

**ARTICLE IN PRESS**

*What Do Patients With Hypertrophic Cardiomyopathy Die from?*

Barry J. Maron, MD*•*, Ethan J. Rowin, MD'$, Susan A. Casey, RN', Ross F. Garberich, MSc', and Martin S. Maron, MD$*

Am J Cardiol

1,902 consecutive cases of HCM

Deaths due to non-HCM causes substantially exceeded HCM-related causes by 2.6 X (178 vs 71)
**HCM: Sudden Cardiac Death**

**Risk Stratification and Outcome of Patients With Hypertrophic Cardiomyopathy ≥60 Years of Age**

Barry J. Maron, MD; Elhan J. Rovin, MD; Susan A. Clancy, RN; Timothy S. Shau, RN; Raymond H.M. Chie, MD; James E. Udelson, MD; Ross P. Camerich, MD; John E. Lesser, MD; Evan Appelbaum, MD; Wayne J. Manning, MD; Martin S. Maron, MD

Figure 3. Kaplan-Meier survival curves describing total mortality (death resulting from any cause, including hypertrophic cardiomyopathy [HCM]), at ≥60 years of age among 429 HCM patients, compared with that expected in the US general population after adjustment for age and sex. Dotted lines represent 95% confidence intervals for survival probability.

Figure 2. Clinical outcome of hypertrophic cardiomyopathy (HCM) patients first evaluated at ≥60 years of age. SD indicates sudden death. Graph excludes 2 HCM-related operative deaths and 27 others resulting from indeterminate causes. *Includes 1 surviving patient with heart transplantation. †Includes 3 surviving patients with aborted ventricular tachycardia/ventricular fibrillation. ‡Associated atrial fibrillation in 5 of 6 patients.
Myocardial extracellular volume expansion (profibrotic) is increased in HCM mutation carriers even in absence of LVH?

? ECV expansion precedes phenotypic expression?
Impaired perfusion reserve and tissue oxygenation are key pathophysiologic attributes of overt HCM (SCD)

Relative ischemia may precede phenotypic expression due to intrinsic increase in energy required for contractile function

Mechanism of SCD in overt HCM and perhaps pre-clinical disease…..more work to be done.
HCM: Prognosis

Prognostic Significance of Myocardial Fibrosis in Hypertrophic Cardiomyopathy

Kerr O'Hanlon, MD,* Agata Grazioso, MD,* Michael Roughton, MSc; James C. Moon, MD,§ Susan Clark, RN,* Ricardo Warg,§ Jessica Webb, MD,§ Meghana Kulkarni, MD,* Dana Dawson, MD, PhD,* Lerna Sulabekk, MD,* Badi Changaezekraun, MD,* Chirar Buciarini-Duca, MD,* Fernando Pasqualo, MD,§ Martin R. Cowie, MD,§ William J. McKenna, MD,§ Mary N. Sheppard, MD,§ Peter M. Elliott, MD,§ Dudley J. Pennell, MD,* Srijay K. Prasad, MD*

Table 3 Breakdown of Events Contributing to Overall MACE Rate in 217 HCM Patients With and Without Fibrosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Fibrosis (n = 81)</th>
<th>Fibrosis (n = 136)</th>
<th>Total (n = 217)</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>6 (7.4)</td>
<td>24 (18.4)</td>
<td>30 (13.8)</td>
<td>3.367</td>
<td>1.406-8.083</td>
<td>0.008</td>
</tr>
<tr>
<td>CV mortality</td>
<td>1 (1.2)</td>
<td>8 (6.0)</td>
<td>9 (4.2)</td>
<td>4.452</td>
<td>0.548-36.204</td>
<td>0.163</td>
</tr>
<tr>
<td>Unplanned CV hospital stay</td>
<td>5 (6.2)</td>
<td>24 (17.7)</td>
<td>29 (13.4)</td>
<td>2.626</td>
<td>1.072-7.448</td>
<td>0.036</td>
</tr>
<tr>
<td>VVF</td>
<td>1 (1.2)</td>
<td>8 (6.0)</td>
<td>9 (4.2)</td>
<td>4.573</td>
<td>0.622-39.762</td>
<td>0.218</td>
</tr>
<tr>
<td>ICD discharge</td>
<td>0 (0)</td>
<td>2 (1.5)</td>
<td>2 (0.9)</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1 (1.2)</td>
<td>1 (0.7)</td>
<td>2 (0.9)</td>
<td>0.648</td>
<td>0.042-10.300</td>
<td>0.759</td>
</tr>
<tr>
<td>HF death</td>
<td>0 (0)</td>
<td>6 (4.4)</td>
<td>6 (2.8)</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CV death</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>1 (0.4)</td>
<td>NA</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

O = outcome; CV = cardiovascular; DM = diastolic murmur; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; VVF = ventricular tachycardia/ventricular fibrillation.

Myocardial Scar Visualized by Cardiovascular Magnetic Resonance Imaging Predicts Major Adverse Events in Patients With Hypertrophic Cardiomyopathy

Olivier Bruder, MD,* Anja Wagens, MD,§ Christoph J. Siewers, MD,§ Steffen Schneider, PhD,* Peter Ong, MD,§ Eva-Maria Luebert, RN,§ Kai Nussmeier, MD,§ Thomas Schloesser, MD,§ Georg V. Sahin, MD,* Udo Sechtmann, MD,§ Heiko Mahrholdt, MD*

Eisen, Ludwigshafen, and Stuttgart, Germany, and Philadelphia, Pennsylvania

Figure 4 Bar Graph Plotting the Number of Sudden Cardiac Death Risk Factors and All-Cause and Cardiac Mortality Versus the Amount of Scarring.
**HCM: Prognosis**

Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy

Maekawa Saku, Motoki Ohguma, Tomohiro Yatoki, Haruhiko Higashi, Hiroe Morioka, Go Hisata, Takumi Sumimoto, Shoji Inaba, Kazuhisa Nishimura, Katsumi Inoue, Akioshi Ogimoto, Yuji Shigematsu, Masumi Hamada, and Jitsuo Higashi

**Table 3** Correlation between %LGE and study parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.009</td>
<td>0.953</td>
</tr>
<tr>
<td>Left atrial volume index</td>
<td>0.220</td>
<td>0.151</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>-0.171</td>
<td>0.268</td>
</tr>
<tr>
<td>E/A</td>
<td>0.080</td>
<td>0.604</td>
</tr>
<tr>
<td>e'</td>
<td>-0.378</td>
<td>0.011</td>
</tr>
<tr>
<td>Vp</td>
<td>-0.352</td>
<td>0.045</td>
</tr>
<tr>
<td>LV pressure gradient</td>
<td>0.045</td>
<td>0.773</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.563</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP</td>
<td>0.042</td>
<td>0.832</td>
</tr>
<tr>
<td>GLS</td>
<td>0.595</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 2** Kaplan–Meier event-free curves of patients with HCM stratified in two groups according to the median level of GLS. HCM, hypertrophic cardiomyopathy; GLS, global longitudinal strain.
Role of echo in HCM

• Diagnosis
• Etiology of symptoms
• Selection for appropriate treatment
• Selecting proper vessel for septal ablation
• Monitoring of ablation procedure
• Follow up of treatments
• Understanding mechanism of treatment