A Little Background

Some Diagnostic Testing

Clinical Considerations

Treatment Considerations

A rose by any other name would smell as sweet

Courtesy of Barry Maron

Asymmetrical hypertrophic cardiomyopathy
Asymmetrical hypertrophy of the heart
Asymmetrical septal hypertrophy
Brock's disease
Diffuse muscular subaortic stenosis
Diffuse subvalvular aortic stenosis
Dynamic hypertrophic subaortic stenosis
Dynamic muscular subaortic stenosis
Familial hypertrophic subaortic stenosis
Familial hypertrophic cardiomyopathy
Familial muscular subaortic stenosis
Familial myocardial disease
Functional aortic stenosis
Functional hypertrophic subaortic stenosis
Functional obstructive cardiomyopathy
Functional obstruction of the left ventricle
Functional obstructive subvalvular aortic stenosis
Functional subaortic stenosis
Hereditary cardiovascular dysplasia

HYPERTROPHIC CARDIOMYOPATHY (HCM)
Hypertrophic constrictive cardiomyopathy
Hypertrophic hyperkinetic cardiomyopathy
Hypertrophic infundibular aortic stenosis
Hypertrophic nonobstructive cardiomyopathy
Hypertrophic obstructive cardiomyopathy (HOCM)
Hypertrophic stenosing cardiomyopathy
Hypertrophic subaortic stenosis
Idiopathic hypertrophic cardiomyopathy
Idiopathic hypertrophic obstructive cardiomyopathy
Idiopathic hypertrophic subaortic stenosis (HSS)
Idiopathic muscular hypertrophic subaortic stenosis
Idiopathic muscular subaortic stenosis of the left ventricle
Idiopathic myocardial hypertrophy
Idiopathic stenosis of the flushing chamber of LV
Idiopathic ventricular septal hypertrophy
Irregular hypertrophic cardiomyopathy
Left ventricular muscular stenosis
Low subvalvular aortic stenosis
Muscular aortic stenosis
Muscular hypertrophic stenosis of LV
Muscular stenosis of the left ventricle
Muscular subaortic stenosis
Muscular subvalvular aortic stenosis
Non-dilated cardiomyopathy
Nonobstructive hypertrophic cardiomyopathy
Obstructive cardiomyopathy
Obstructive hypertrophic aortic stenosis
Obstructive hypertrophic cardiomyopathy
Obstructive hypertrophic myocardial stenosis
Obstructive myocardiaopathy
Pseudoaortic stenosis
Stenosing hypertrophy of the left ventricle
Stenosis of the ejection chamber of LV
Subaortic hypertrophic stenosis
Subaortic idiopathic stenosis
Subaortic muscular stenosis
Subvalvular aortic stenosis of the muscular type
Teare's disease

Courtesy of Barry Maron
Definition

Morphologic diagnosis

Thick walls
>15mm (adult)
> 2 SD (ped)

Non-dilated LV

No cause for LVH
Elevated wall stress
Athletic conditioning

Histopathologic diagnosis

Normal Architecture

Myocyte Disarray
Histopathologic diagnosis

Interstitial Fibrosis
β-myosin Heavy Chain 25-30%

Myosin-binding protein C 20-30%

Trop T - 3-5%
Trop I - < 5%
Tropomyosin 1α
Reg. myosin light chain 2 - <5%
Exo. myosin L-chain 3
α-Cardiac actin 1
Titin
Troponin C
α-Myosin heavy chain
Muscle LIM protein
Myosin light chain kinase 2
LIM binding domain 3
Telethonin
Vinculin/metavinculin
α-Actinin 2
Phospholamban
Myozenin 2
Junctophilin 2
The Mitral Valve in HCM

- SAM
- MAC
- Elongation of leaflets
- Decreased mobility of the posterior leaflet
- Abnormal papillary muscle
Not all hypertrophy is HCM.
Presentation

SCD
• < 35 yrs
• Asymptomatic

CHF
• Exertional
• Progressive

AF
• CHF
• CVA

Benign

Clinical Features

0.2%

Quintessential Phenotype
Obstruction to LV outflow is dynamic, varying with loading conditions and contractility of the ventricle.

- **Valsava**
- **Inotropes**
- **Dehydration**
- **Decrease afterload**

**Increased Murmur**

**Downward** LV Cavity
- Volume or
- **Contractility**

**Increased Murmur**

**Upward** LV Cavity
- Volume or
- **Decrease** Contractility

**Decreased Murmur**

- **Hand-grip**
- **Negative inotropes**
- **Increase** afterload

**CHF**

**LVOTO**

**Diastolic HF**

**Systolic HF**
Not all HCM has LVOTO
LVOTO


Physical Findings
Valvular Aortic Stenosis

IHSS

Brockenbrough’s Sign

LVOTO


Treatment of LVOTO

Medical

- β-blocker
- Ca++-blocker
- Dysopirimide

Septal Reduction

- Surgical Myectomy
- Mitral Valve Plication
- Pap Realignment
- ETOH Septal Ablation

Pacemaker

Induction of Septal Dyssynchrony
Medical Therapies

β-blockers

Non-dihydropyridine Ca++-blockers

Verapamil Diltiazem

Disopyramide

Morrow Procedure


Obstructive HCM with rest or provokable gradient ≥ 50 mm Hg and symptoms refractory to optimal medical therapy

- Frailty, Contraindication to surgery, Aged
- Valvular Calcification
  - ASA
  - MVR
- Anomalous papillary muscle inserting directly into the mid anterior mitral leaflet
  - Extended myectomy and resect or thin anomalous papillary muscle

- Septal thickness ≤ 18 mm and AML > 30 mm or > 17 mm/m²
  - Less aggressive myectomy, Plication of the AML*, Release/resection of papillary muscles/or chordae
  - "Plicate, Release"

- Septal thickness > 18 mm and AML > 30 mm or > 17 mm/m²
  - Extended myectomy, Plication of the AML*, Release/resection of papillary muscles†
  - "Resect, Plicate, Release"

- Septal thickness > 18 mm and AML ≤ 30 mm or ≤ 17 mm/m²
  - Extended myectomy, Release/resection of papillary muscles‡, +/- Plication of AML as per surgical inspection for slack
  - "Resect, Release"


**Table 3** Survival Rate After Alcohol Septal Ablation

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival Rate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.968</td>
<td>0.956</td>
<td>0.981</td>
</tr>
<tr>
<td>2</td>
<td>0.943</td>
<td>0.924</td>
<td>0.963</td>
</tr>
<tr>
<td>3</td>
<td>0.936</td>
<td>0.915</td>
<td>0.968</td>
</tr>
<tr>
<td>4</td>
<td>0.905</td>
<td>0.872</td>
<td>0.938</td>
</tr>
<tr>
<td>5</td>
<td>0.866</td>
<td>0.809</td>
<td>0.950</td>
</tr>
<tr>
<td>6</td>
<td>0.830</td>
<td>0.774</td>
<td>0.891</td>
</tr>
<tr>
<td>7</td>
<td>0.812</td>
<td>0.738</td>
<td>0.883</td>
</tr>
<tr>
<td>8</td>
<td>0.812</td>
<td>0.748</td>
<td>0.883</td>
</tr>
<tr>
<td>9</td>
<td>0.742</td>
<td>0.638</td>
<td>0.863</td>
</tr>
</tbody>
</table>

**Figures**

- LVOTO
- Alcohol Septal Ablation
- Comparison of LVOT gradient before and after ablation
- Table showing survival rates after ablation

Systolic HF

- β-blocker
- ACE-I or ARB
- Aldosterone Blocker
- Diuretic
- ICD +\- CRT

Transplantation

Diastolic HF

- Careful Diuresis

Transplantation
SCD

• Paucity of data
• Relative infrequency of HCM and SCD
• Cumulative Morbidity of living with an ICD

ICD for 1° Prevention

• Personal Hx of SCD/VT/VF
• Documented NSVT
• Family Hx of SCD
• Unexplained Syncope
• Wall thickness >30mm
• Abnormal exercise BP response

Established Risk Markers

ICD

http://www.doc2do.com/hcm/webHCM.html

HCM Risk-SCD Calculator

Age at evaluation

Trans-thoracic Echocardiographic measurement

- Maximum LV wall thickness
- Left atrial size
- Max LVOT gradient

- Family History of SCD
- 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).

- Non-sustained VT
- 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.

- Unexplained syncope
- History of unexplained syncope at or prior to evaluation.

Risk of SCD at 5 years (%): 0.32
ESC recommendation: ICD should be considered

Does # of Risk Factors Matter?

RF Matters

# RF Doesn’t Matter

Elliott, Lancet 2001

Maron, JAMA 2007

SCD Events

ICD Events

Complications

Cumulative %

(3.7+/-.8 years)

Appropriate

Inappropriate

Lead dysfunction

Infection

Bleeding/Clothing

Maron et al. JAMA 2007
Common - about 1/4 patients will develop AF

2/3 patients are symptomatic

Associated with a worse survival

All patients should be anti-coagulated unless contraindicated

Clinical Trials at OHSU

<table>
<thead>
<tr>
<th>Eleclazine</th>
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</thead>
<tbody>
<tr>
<td>Perherhexilineexiline</td>
</tr>
<tr>
<td>B-myosin HC inhibitor</td>
</tr>
<tr>
<td>Exercise in HCM</td>
</tr>
<tr>
<td>Novel predictors HCM</td>
</tr>
</tbody>
</table>

Thank You

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DAM that SAM

**Genotype Guided Therapy**

**TABLE 4** Change in Cardiac Measurements after 3 Years of Treatment With Diltiazem, by Genotype

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MYH7 Carriers (n = 21)</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>
</tr>
<tr>
<td>Sample size (echocardiography), n</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Sample size (CMR), n</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Change in outcome measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo Max LVWT, mm*</td>
<td>$+1.4 \pm 0.60$</td>
<td>$+0.84 \pm 0.70$</td>
<td>0.49</td>
</tr>
<tr>
<td>Echo Max LVWT, z-score*</td>
<td>$+0.92 \pm 0.63$</td>
<td>$+0.78 \pm 0.62$</td>
<td>0.87</td>
</tr>
<tr>
<td>E/E'</td>
<td>$+0.53 \pm 0.20$</td>
<td>$-0.03 \pm 0.17$</td>
<td>0.04</td>
</tr>
<tr>
<td>CMR LV mass, g</td>
<td>$-1.8 \pm 4.4$</td>
<td>$-8.8 \pm 3.7$</td>
<td>0.24</td>
</tr>
<tr>
<td>CMR LV mass index, g/m²</td>
<td>$-1.1 \pm 3.1$</td>
<td>$-5.6 \pm 1.6$</td>
<td>0.21</td>
</tr>
<tr>
<td>Troponin I, pg/ml</td>
<td>$+1.2 \pm 1.2$</td>
<td>$-0.51 \pm 0.59$</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Ho, CY, et al., Diltiazem Treatment for Pre-Clinical Hypertrophic Cardiomyopathy Sarcomere Mutation Carriers: A Pilot Randomized Trial to Modify Disease Expression. JACC Heart Fail. 2014.
Phenotypic Heterogeneity

Lack of Consistent Biological Effect of Current Therapies

Need for Individualized/Targeted Therapies
Biomechanical Stress Sensing

Altered Calcium Trafficking

Energy Homeostasis

Fibrosis

Sarcomeric Mutation

Structural
Mechanical
Biochemical
Metabolic

Stress
Potential Therapeutic Targets

- Calcium Trafficking: Diltiazem
- Oxidative Stress: Atorvastatin, NAC
- Myocardial Energetics: Perhexiline
- Fibrosis: RAAS Modulation
- BioMechanical Stress: M-band and Z-disc