Phenotypes and Genotypes in HCM

Steve R. Ommen, MD
Director, Mayo Hypertrophic Cardiomyopathy Clinic
Phenotypes

Obstructive

Non-obstructive

Apical
Prevalence of Obstruction

All-Time Mayo Data

Maron, Circ 2006

Non-Obstructive \(~30\%\)

Obstructive Physiology

\(~70\%\)
LV Outflow Obstruction
What is significant obstruction?

Peak Gradient > 30 at rest

Obstructive HCM

Peak Gradient > 40-50

Sufficient to result in symptoms
1. Show extent and distribution of LVH
2. Show mitral valve and apparatus
3. Show SAM
4. Show MR jet
5. CW of LV Outflow
6. CW of MR jet
7. Use provocation if resting gradient < 50 mmHg and repeat all steps
Provocation

- PVC
- Standing
- Valsalva
- Amyl Nitrite
- Dobutamine
- Isoproterenol
- Exercise
Provocation

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Preload

Afterload

Contractility
Provocation

• PVC
• Standing
• Valsalva
• Amyl Nitrite
• Dobutamine
• Isoproterenol
• Exercise
Provocation

- PVC
- Standing
- Valsalva
- Amyl Nitrite
- Dobutamine
- Isoproterenol
- Exercise

Reproduces the situation related to the patients’ symptoms
Provocation Pitfalls

- PVC: Serendipity
- Standing: Tough to acquire
- Valsalva: Unreliable but Specific
- Amyl Nitrite: Obliteration / RN
- Dobutamine: Obliteration / RN
- Isoproterenol: Obliteration / Cath
- Exercise: Can be tough to acquire
Pursuit of Obstruction

If suggestive symptoms

Rest Gradient > 50 ?
No

Valsalva Gradient > 50 ?
No

Amyl Gradient > 50 ?
No

Stress Gradient > 50 ?
No

Cath Gradient > 50 ?
Yes

44%

14%

37%

1%

Yes

4%

Yes

Obstructive Physiology
To Decrease Obstruction ...

Avoid These

- Increased contraction
- Decreased resistance
- Decreased volume

Do These

- Decrease contraction
- Increase resistance
- Increase volume
To Decrease Obstruction ...  

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Do These</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive intropes</td>
<td>Decrease contraction</td>
</tr>
<tr>
<td>Pure vasodilators</td>
<td>Increase resistance</td>
</tr>
<tr>
<td>High-dose diuretic</td>
<td>Increase volume</td>
</tr>
</tbody>
</table>
To Decrease Obstruction ...

- Beta-blockers
  - Verapamil
  - Diltiazem
  - Disopyramide
  - Decrease contraction

- Avoid vasodilators
- Increase resistance
- Hydration
- Increase volume
Success in Medical Therapy

Success is determined by the patient....

If they feel better then medical therapy has been successful

1,500 Consecutive HCM Patients

- Meds only
- Myectomy
- Ablation
Apical

Diastole

Systole
Apical HCM

Apical HCM with outpouching, no aneurysm

Apical HCM with aneurysm

LV
LA
Apical Myectomy

Diagram showing a before (A) and after (B) comparison with a graph plotting pressure (mm Hg) against volume (ml). The graph includes data for both preoperative (Preop) and postoperative (Postop) conditions, with a notable increase in stroke volume (SV) and end-diastolic pressure (EDP) postoperatively.
Genotypes
# HCM Cohort (n = 1053)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>629/424</td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>44.4 ± 19</td>
</tr>
<tr>
<td>MLVWT (mm)</td>
<td>21.0 ± 6</td>
</tr>
<tr>
<td>No. patients with resting LVOTO (%)</td>
<td>500 (47)</td>
</tr>
<tr>
<td>Positive family history of HCM</td>
<td>32%</td>
</tr>
<tr>
<td>Positive family history of SCD</td>
<td>20%</td>
</tr>
<tr>
<td>Positive family history of HCM, SCD or both</td>
<td>37%</td>
</tr>
<tr>
<td>Myectomy</td>
<td>45%</td>
</tr>
</tbody>
</table>
**Results**

- **Genotype negative (67%)**
  - MYBPC3 (51%)
  - MYH7 (32%)
  - Other (11%)
    - TNNI3 13 (3.7%)
    - MYL2 9 (2.6%)
    - TPM1 6 (1.7%)
    - TNNC1 4 (1.1%)
    - TNNT2 3 (0.9%)
    - ACTC1 2 (0.6%)
    - MYL3 1 (0.3%)
- **Genotype positive (33%)**
- **Multiple (6%)**
Genotype-Phenotype Relationships

(*) p < 0.05

- Age at Diagnosis (yrs)
- Left Ventricular Wall Thickness (mm)
- Family History of SCD (%)
- Family History of HCM (%)
- Family History of SCD (%)

Genotype negative vs. Genotype positive
Follow-Up after Genetic Testing (Yrs)

Free of CV Death, Ischemic Stroke and Progression to NYHA Class III/IV (%)

Myofilament-Negative

Myofilament-Positive

\[ p = 0.002 \]

Myofilament-Negative

Myofilament-Positive

\[ p = 0.021 \]

Free of Systolic Dysfunction (%)

Free of Restrictive LV Filling (%)

Myofilament-Negative

Myofilament-Positive

\[ p = 0.018 \]

\[ * p < 0.05 \]

Double Heterozygous

Thin Filament

Thick Filament

Free of Systolic Dysfunction and Restrictive LV Filling (%)

Double Heterozygous

* * *
Clinical Markers for Positive Genetic Test

<table>
<thead>
<tr>
<th>Marker</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Dx &lt; 45 yrs</td>
<td>1</td>
</tr>
<tr>
<td>MLVWT ≥ 20 mm</td>
<td>1</td>
</tr>
<tr>
<td>FH of HCM</td>
<td>1</td>
</tr>
<tr>
<td>FH SCD</td>
<td>1</td>
</tr>
<tr>
<td>Reverse-curve HCM</td>
<td>1</td>
</tr>
<tr>
<td>Hx of Hypertension</td>
<td>-1</td>
</tr>
</tbody>
</table>

Scoring range: -1 to 5 pts

Thank you