Update on Evaluation and Nonsurgical Treatment Strategies for the Symptomatic Patient with HCM

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## DISCLOSURE

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Astra-Zeneca, Eli Lilly, Gilead, GSK, Merck</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria</td>
<td>Lilly, Novo Nordisk</td>
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<tr>
<td>Major Stock Shareholder/Equity</td>
<td>None</td>
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<td>Royalty Income</td>
<td>None</td>
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<td>Ownership/Founder</td>
<td>None</td>
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<td>Intellectual Property Rights</td>
<td>None</td>
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<td>Other Financial Benefit</td>
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Hypertrophic Cardiomyopathy (HCM)
Hypertrophic Cardiomyopathy

- Approximately 70% of pts with HCM have significant resting or provicable left ventricular outflow tract obstruction
Hypertrophic Cardiomyopathy: Clinical Manifestations

- Heart Failure
- Angina
- Syncope
- Sudden Death
Hypertrophic Cardiomyopathy

Treatment Goals

Symptom Relief

Prevent Sudden Death
Evaluation and Treatment Algorithm for HCM Patients

Asymptomatic

Mild-Moderate Symptoms
NYHA Class I/II

Severe Symptoms
NYHA Class III/IV

Referral to HCM Center

Refractory Symptoms

Clinical Assessment
Echocardiogram
CMR

Echocardiogram
Stress Echo

Beta-blocker
Verapamil

Beta-blocker
Verapamil
Disopyramide
Diuretic

Severe LVOT Obstruction

Septal Myectomy
Alcohol Septal Ablation

Nonobstructive

Heart Transplantation

SCD
Sx’s
QOL

SCD
Sx’s
QOL

SCD
Sx’s
QOL

Referral to HCM Center

Adapted from Maron and Nishimura, Circ, 2014;130:1617
Evaluating the Symptomatic Patient with HCM

- Specialized Evaluation
  - Stress Echocardiography
  - Cardiac Cath
  - Cardiac MRI
  - TEE
Patient A: History

• 29 yr old male
  • SOB/chest discomfort on exertion increasing in frequency and severity over the last several months
  • SOB with walking < 1 block
  • chest pressure at rest after heavy meals
  • multiple episodes of lightheadedness and near syncope.

• Social History
  • Former construction worker, now on disability

• Exam
  • Regular S1 and S2, harsh III/VI systolic murmur that increases with Valsalva maneuver, otherwise unremarkable.
Echocardiogram

“Asymmetric Septal Hypertrophy”

“Systolic Anterior Motion”

Septum 2.57 cm
Post Wall 1.6 cm
LA 5.7 cm
SAM Present
Patient A

Resting CW Doppler in Outflow Tract

- 29 yr old WM
- Severe DOE
  - Pre-syncope
  - CP after meals
- CHF NYHA Class III
- Angina Class III-IV

Peak Outflow Velocity = 4.9 m/s
Resting LVOT Gradient = 96 mmHg
Patient A: Treatment Algorithm

• 29 yr old male with HCM
  • Severe LVOT obstruction
  • Class III CHF
  • Class III-IV angina

• Treated with metoprolol…

• Only minor improvement in symptoms…
Disopyramide for HCM

- 118 Patients with HCM and Severe LVOT Obstruction
- Treated with disopyramide and followed for 3 years

Effect on LVOT Gradient
Effect on Symptoms (NYHA Class)

Patient A: History

- 29 yr old male with HCM
  - Severe LVOT obstruction
  - Class III CHF
  - Class III-IV angina

- Treated with metoprolol…
- Only minor improvement in symptoms…
- Treated with disopyramide…
- Did not tolerate due to dry mouth, malaise…
HCM Center

- Imaging
  - Echo
  - CMR
- EP
  - Afib, VT, ICDs
- Genetics
  - Genetic Testing, Family Screening
- Interventional Cardiology
  - Alcohol Ablation
- Cardiac Surgery
  - Myectomy
- Advanced Cardiac Support
- Transplantation
Evaluating the Patient with HCM
For Symptomatic Patients:

I. Specialized HCM-Protocol Stress Echo

• Resting 2D Imaging
  - LV shape, wall thickness, ASH, SAM
  - Tissue Doppler
  - LVOT Velocity
    • At rest
    • + Valsalva
    • + Amyl nitrite
    • Peak exercise
Patient A

Specialized HCM-Protocol Echocardiogram

- Treadmill Exercise Study
  - Bruce Protocol
    - 3 min 56 sec
    - 5 METS
  - Stopped due to SOB, chest heaviness and lightheadedness
- BP 120/60 → 90/50

Peak Exercise Velocity = 7.1 m/s
Peak LVOT Gradient = 202 mmHg
Dx:
- HCM with Severe LVOT Obstruction
- Congestive Heart Failure, NYHA Class III
- Angina, CCS Class III-IV
- Sxs refractory to medical therapy...

Treatment Recommendation?
Further Evaluation?
Evaluating the Patient with Suspected HCM
For Patients with LVOT Obstruction:

II. Specialized HCM-Protocol TEE

- Assess the LVOT:
  - Exclude fixed LVOT obstruction
- Assess Mitral regurgitation
Evaluating the Patient with Suspected HCM Patients with LVOT Obstruction:

TTE with Severe (3-4+) MR

- Valve Morphology
- MR Jet Direction*
- MR Timing*
- Valve Motion
- Dynamic Drug Suppression Test

Evaluating the Patient with Suspected HCM

- Specialized TEE Evaluation
Evaluating the Patient with Suspected HCM

- MR: Posteriorly directed
- Related to SAM
Before and After IV Phenylephrine

Systolic BP = 120

Systolic BP = 203
Before and After IV Phenylephrine

Systolic BP = 120

Systolic BP = 203
Before and After IV Phenylephrine

Systolic BP = 120

Systolic BP = 203
Before and After IV Phenylephrine

Systolic BP = 120

Systolic BP = 203
Evaluation for Candidacy for Septal Reduction is Key: Not ALL LVOT Obstruction is Due to HOCM!

- Mayo Clinic Experience
  - 4 cases referred to Mayo Clinic with presumed dx HOCM found to have fixed LVOT obstruction
    - 1 subaortic fibrous ring + accessory mitral valve
    - 2 fixed tunnel stenoses
    - 1 subaortic ridge

- Washington University Experience
  - 175 pts with dx HCM referred for alcohol septal ablation
  - 8 pts (4.5%) with unexpected fixed cause of LVOTO
    - 6 subaortic membrane or tunnel lesions
    - 2 accessory mitral valves
    - Of these, 4 had classic TTE features of HCM with ASH and SAM...diagnosed at TEE
Evaluation for Candidacy for Septal Reduction is Key: Not ALL LVOT Obstruction is Due to HOCM!

Obstructive

Drug Therapy

- β Blocker
- Verapamil
- Disopyramide

Refractory Sxs

Surgery

Alternative to Surgery

Alcohol Septal Ablation
Patient A

• Treatment by Alcohol Septal Ablation
Treatment of Drug-Refractory HOCM
Septal Reduction by Transcatheter Alcohol Septal Ablation
Contrast Echo Guidance for Alcohol Septal Ablation
Low Mechanical Index Real Time Imaging

Second Septal vs. First Septal
Echo Follow-Up 3 Months After Alcohol Septal Ablation

Parasternal Long Axis View
Patient A - 3 Months Post-Septal Ablation

Treadmill Exercise Study

- Bruce Protocol
  - 7 min 24 sec
  - 9 METS

- Stopped due to fatigue

- BP 130/70 → 170/60

Peak Exercise CW Doppler

Resting LVOT Gradient = 12 mmHg
Peak Exercise LVOT Gradient = 33 mmHg
Effect of Alcohol Septal Ablation on LVOT gradient

- Baseline
- Post-alcohol ablation

Resting Post-PVC

Gradient (mmHg)

- p<0.001
- p<0.0001

12% required PPM implantation for 3° AVB
Alcohol Septal Ablation for HOCM at Washington University
100 Patients: NYHA Functional Class

Procedural Success: 100%
Procedural Deaths: None
Permanent PM for AV Block: 12 (12%)

92% Class I or II at 1 Year
Alcohol Septal Ablation: 5-Year Follow-Up
Reduction of LVOT Gradient by Alcohol Septal Ablation

N = 130 pts; 2 (1.5%) deaths, 17 (13%) PPM for AVB
Cardiac mortality 0.6% per year

Fernandes VL et al., Clin Cardiol 2005; 28:124-130
Alcohol Septal Ablation: 5-Year Follow-Up
Symptomatic Response

Baseline

<table>
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<tr>
<th>Months</th>
<th>CCS Angina Class</th>
<th>NYHA Class</th>
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<tr>
<td>Baseline</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3 Months</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>1 Year</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>2 Years</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>3 Years</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>4 Years</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>5 Years</td>
<td>1.2</td>
<td>1</td>
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Fernandes VL et al., Clin Cardiol 2005; 28:124-130
Alcohol Septal Ablation: 5-Year Follow-Up

Improvement in Exercise Capacity

Exercise Treadmill Time

Fernandes VL et al., Clin Cardiol 2005; 28:124-130
# Long Term Outcomes of Alcohol Septal Ablation

<table>
<thead>
<tr>
<th>AUTHOR, et al.</th>
<th>CENTER</th>
<th>PRESENTED/PUBLICATION</th>
<th>N</th>
<th>F/U</th>
<th>%NYHA Class I/II</th>
<th>CARD MORT/yr</th>
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<tr>
<td>Fernandes, et al.</td>
<td>MUSC+Baylor Charleston, SC Houston, TX</td>
<td>Clin Cardiol 2005</td>
<td>137</td>
<td>5 yrs</td>
<td>96%</td>
<td>0.6%</td>
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<tr>
<td>Welge, et al.</td>
<td>Ruhr U Bochum Bad Oeynhausen Germany</td>
<td>ACC 2008 Dtsch Med Wochen</td>
<td>347</td>
<td>5 yrs</td>
<td>89%</td>
<td>1%</td>
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<td>Sorajja, et al.</td>
<td>Mayo Clinic Rochester, MN</td>
<td>AHA 2007 Circ</td>
<td>140</td>
<td>5 yrs</td>
<td>81%</td>
<td>2%</td>
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<td>Chawla, et al.</td>
<td>Institut CV Paris Massy, France</td>
<td>ACC 2008</td>
<td>104</td>
<td>3 yrs</td>
<td>&gt;90%</td>
<td>1.5%</td>
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<td>ten Cate, et al.</td>
<td>Thoraxcenter Rotterdam, Netherlands</td>
<td>Circ Hrt Fail 2010</td>
<td>91</td>
<td>5.4 yrs</td>
<td>NR</td>
<td>4.4%* (*or ICD shock)</td>
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<td>Kuhn, et al.</td>
<td>Bielefeld, Germany</td>
<td>Clin Res Cardiol 2008</td>
<td>644</td>
<td>1.4 yrs</td>
<td>NR</td>
<td>3.2%</td>
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Multicenter North American Registry

- Prospective, Initiated in 2000
- Uniform Criteria for Case Selection,
- Standardized Procedural and Follow-up Protocols
- 9 Institutions, 874 patients
  - Methodist Debakey Heart & Vascular Center.............. Nagueh, Buergler
  - Medical University of South Carolina..................... Spencer, Nielson
  - University of Colorado....................................... Groves
  - Washington University in St. Louis....................... Bach
  - University of Florida.......................................... Smith
  - Loyola University Medical Center......................... Leya
  - Duke University Medical Center............................. Wang
  - Heartland Regional Medical Center......................... Rowe
  - University of Toronto........................................ Schwartz, Woo

Nagueh SF, et al, JACC 2011; 58:2322-8
Long Term Outcomes of Alcohol Septal Ablation
Multicenter North American Registry

- 874 Patients, 2000 to 2010, 78% NYHA Class III/IV
  - Mean Duration of F/U: 2.1 ± 0.1 yrs
  - NYHA Class I or II: 95%
  - Total Deaths: 81 (9.3%); 25 cardiac, 25 noncardiac, 31 unknown
  - Survival:
    @ 1 yr: 97% (95% CI, 96%, 98%)
    @ 5 yr: 86% (95% CI, 81%, 91%)
    @ 9 yr: 74% (95% CI, 64%, 86%)

“...compared with HCM pts who did not undergo septal reduction therapy included in other series, survival appears better after alcohol septal ablation...(9-10 yrs, 74% vs. 61%)”

Nagueh SF, et al, JACC 2011; 58:2322-8
Long-Term Survival for Patients with Septal Ablation

Mayo Clinic Experience


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Long-Term Survival for Patients with Septal Ablation Compared with Myectomy

Mayo Clinic Experience

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Long Term Outcomes of Alcohol Septal Ablation

Conclusions

• For severely symptomatic patients with HCM and LVOT obstruction, ASA results in early and sustained hemodynamic and symptomatic improvement.

• ASA, like myectomy, carries risks of death and significant morbidity, mandating careful patient selection and meticulous technique by experienced operators; for appropriately selected patients, long term results of ASA support a highly favorable risk-benefit balance.
Schematic Representation of the Differing Effects of Septal Reduction Therapies
Decreasing Mortality Due to HCM

Graph showing HCM mortality rates over time, with a decrease from early referral cohorts (3%-6%/yr) to present cohorts (0.8%/yr) due to interventions like ICD, Heart Transplant, OHCA/Defibrillation/Hypothermia.
• Novel late sodium channel inhibitor
• Favorable effects on action potential duration, Ca^{++} overload
Heart & Vascular Center

Barnes Jewish Hospital BJC HealthCare

Washington University in St. Louis Physicians

National Leaders in Medicine