Chronic Primary Mitral Regurgitation

The Case For Early Surgical Intervention

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DISCLOSURES

Relevant Financial Relationship(s)
None

Off Label Usage
None
Watchful Waiting . . .

. . . Is Looking for Trouble
Quantitative Determinants of Outcome of Asymptomatic MR
Initial Patient Characteristics

- 456 Asymptomatic patients with MR
- Mean age 63 ± 14 yrs
- MR regurgitant volume 66 ± 40 cm$^3$, ERO 40 ± 27 mm$^2$; (Gr IV/IV in 54%)
- LVEF: 70 ± 8%, LVESD: 34 ± 6 mm
- Systolic PAP: 38 ± 11 mmHg
Quantitative Determinants of Outcome of Asymptomatic MR

Patient Follow-up

- Follow-up: 5.1 ± 2.9 yrs
- 5 Yr freedom from surgery: 46 ± 3%
- 5 Yr freedom from surgery/death: 36 ± 3%

Triggers for mitral valve surgery
- Cardiac symptoms: 41%
- LVESD ≥ 40 mm: 39%
- Other: 20%

Sarano ME et al: NEJM 352:875, 2005
Quantitative Determinants of Outcome of Asymptomatic MR Events: Cardiac Death, CHF, New Atrial Fibrillation

Sarano ME et al: NEJM 352:875, 2005
Quantitative Determinants of Outcome of Asymptomatic MR Death From Cardiac Causes

**Cardiac Death (%)**

- **ERO**
  - <20 mm²
  - 20-39 mm²
  - ≥40 mm²

**Years**

- 0
- 1
- 2
- 3
- 4
- 5

- **P<0.01**
- **36±9%**
- **20±6%**
- **3±2%**

Sarano ME et al: NEJM 352:875, 2005
Waiting for Symptoms... Is Asking for Trouble
Early Surgery vs Conservative Therapy For Severe MR
Impact of Preoperative Symptoms

Adjusted survival from diagnosis (%)

NYHA I-II

NYHA III-IV

Years

Early surgery

Conservative Rx

P < 0.02

Ling et al: Circulation 1997; 96: 1819
Cardiopulmonary Exercise Testing in “Asymptomatic” MR: Is the Patient Truly Asymptomatic?

- 134 Asymptomatic patients; 63 ± 14 yrs
- MR regurgitant volume 68 ± 24 cm$^3$, ERO 35 ± 14 mm$^2$; LVEF 73±6%
- Reduced functional capacity (<84% predicted) related to MR in 19% 
  Peak VO$_2$ 22 ± 5  (74 ± 8% Predicted)

Messika-Zeitoun D, et al. JACC 2006; 47: 2521
Cardiopulmonary Exercise Testing in “Asymptomatic” MR Events: Death, Heart Failure, Surgery, AFib

Patients with cardiac events or surgery (%)

Functional capacity
- Reduced
- Normal

Years

P=0.001

“Asymptomatic” MR: Exercise Induced Pulmonary Hypertension
Is the Patient Truly Asymptomatic?

- 49 Asymptomatic patients with MR
- MR ERO 0.40 ± 0.14 cm², RVSP 30 ± 7 mmHg
- LVEF 67 ± 7 %, LVESD 31 ± 6 mm
- Symptom limited exercise echo VO₂ stress
- 24% with <80% functional aerobic capacity (FAC)
- Exercise induced pulmonary hypertension (RVSP ≥ 60 mmHg) the strongest multivariate predictor of poor FAC and onset of symptoms

"Asymptomatic" MR: Exercise Induced Pulmonary Hypertension
Is the Patient Truly Asymptomatic?

Sensitivity

1-specificity

Systolic PAP

Exercise* C = 0.88
Exercise C = 0.52
Resting

*Adjusted for age and gender

"Asymptomatic" MR: Exercise Induced Pulmonary Hypertension

Is the Patient Truly Asymptomatic?

“Asymptomatic” MR: Exercise Induced Pulmonary Hypertension
Post-Op Events: Heart Failure, Stroke, Death

• 104 Patients; mean age 64 ± 12 yrs
• MR ERO 0.40 ± 0.07 cm², RVSP 36 ± 7 mmHg
• LVEF 71 ± 5 %, LVESD 34 ± 6 mm
• Preoperative exercise echo: 58% of patients had exercise induced pulmonary HTN (RVSP ≥ 60 mmHg)
• Mitral surgery for isolated primary MR directed by ACC/AHA guideline triggers

“Asymptomatic” MR: Exercise Induced Pulmonary Hypertension
Post-Op Events: Heart Failure, Stroke, Death

Patients at Risk
- No Exercise Pulmonary HTN
  - Months 0: 43
  - Months 12: 37
  - Months 24: 26
  - Months 36: 6
  - Months 48: 2

- Exercise Pulmonary HTN
  - Months 0: 59
  - Months 12: 48
  - Months 24: 37
  - Months 36: 15
  - Months 48: 4

P = 0.003

And we must be wary . . .

... of the ultimate end-point
Sudden Death in Severe MR Due to Flail Leaflet

- 348 Patients with flail MV leaflet
- Mean age: 67 ± 12 yrs; 48 ± 41 mo. F/U
- Under medical therapy: 99 deaths
  Sudden death: 25 patients (7.2%)
- Sudden death multivariate predictors:
  - NYHA functional class
  - LVEF (mean initial EF 63 ± 10%)
  - Atrial fibrillation

Grigioni F, et al. JACC 1999; 34:2078
Sudden Death in Severe MR Due to Flail Leaflet

Grigioni F, et al. JACC 1999; 34:2078
Sudden Death in Severe MR Due to Flail Leaflet: Relation to NYHA Functional Class

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Yearly Rate of Sudden Death (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>$1.0 \pm 0.3$</td>
</tr>
<tr>
<td>NYHA II</td>
<td>$3.1 \pm 1.0$</td>
</tr>
<tr>
<td>NYHA III-IV</td>
<td>$7.8 \pm 3.2$</td>
</tr>
</tbody>
</table>

Grigioni F, et al. JACC 1999; 34:2078
Sudden Death in Severe MR Due to Flail Leaflet: Relation to LVEF

Grigioni F, et al. JACC 1999; 34:2078
Sudden Death in Severe MR Due to Flail Leaflet:
Sinus Rhythm vs. Atrial Fibrillation

Grigioni F, et al. JACC 1999; 34:2078
Sudden Death in Severe MR Due to Flail Mitral Leaflet

In patients NYHA Class I-II, in sinus rhythm, LVEF ≥ 60%, and no history of CAD:

Rate of sudden death = 0.8% / yr

Grigioni F, et al. JACC 1999; 34:2078
If There Are No Randomized Controlled Trials . . .

. . . Perform a Meta - Analysis
Early Surgical Intervention vs. Watchful Waiting for Asymptomatic MR
A Meta-Analysis

- Observational studies; tertiary referral
- Asymptomatic patients without Class I Guideline triggers for surgery
- All primary (degenerative) MR etiology
- All included a watching waiting cohort

### Timing of Surgical Intervention for Asymptomatic MR (No Class I Trigger) All Cause Mortality (1,823 Patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang (2014)</td>
<td>0.509</td>
<td>0.241</td>
<td>1.076</td>
<td>-1.769</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>Suri (2103)</td>
<td>0.520</td>
<td>0.346</td>
<td>0.781</td>
<td>-3.149</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Montant (2009)</td>
<td>0.190</td>
<td>0.093</td>
<td>0.388</td>
<td>-4.566</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

0.38 0.206 0.708 -3.057 0.002

Timing of surgical intervention for asymptomatic MR (no class I trigger) all cause mortality (1,823 patients).

## Timing of Surgical Intervention for Asymptomatic MR (No Class I Trigger)
### Mitral Repair Rate (1,631 Patients)

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<tr>
<th>Study</th>
<th>HR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang (2014)</td>
<td>1.155</td>
<td>1.047</td>
<td>1.273</td>
<td>2.879</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Suri (2013)</td>
<td>1.069</td>
<td>1.019</td>
<td>1.122</td>
<td>2.718</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.10</td>
<td>1.022</td>
<td>1.179</td>
<td>2.559</td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

0.5 1 2
Favors Watchful waiting Favors early surgery

A Stitch in Time . . .

. . . Saves Nine
# Surgery for MR: The Importance of Experience and Volume

**STS Database (13,614 MV operations)**

<table>
<thead>
<tr>
<th>Hospital Mitral Procedures / Year</th>
<th>Operative Mortality</th>
<th>MV Repair Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 35</td>
<td>3.1%</td>
<td>48%</td>
</tr>
<tr>
<td>36-70</td>
<td>2.3%</td>
<td>55%</td>
</tr>
<tr>
<td>71-140</td>
<td>2.0%</td>
<td>65%</td>
</tr>
<tr>
<td>&gt; 140</td>
<td>1.1%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Elective Mitral Repair For Severe MR vs. Risk of Sudden Death

Risk of Sudden Death (0.8%/yr)

Operative Mortality* (0 - 0.5%)

* High volume, tertiary referral surgical centers

Grigioni F, et al. JACC 1999; 34:2078
DeBonis M, et al Eur Heart J 2013;34;13
Suri RM et al. JAMA 2013; 310:609
Are we delaying surgery too long....

... with the current guideline triggers to intervention?
Current (2014) Guideline Indications
Triggering Surgery for Severe MR
Is There an Outcome Penalty?

1,512 Patients: Surgery for Primary MR

**Class I Triggers:**
Cardiac Symptoms, LVEF < 60%,
or LVESD > 40 mm (n = 794)

**Class II Triggers:**
Clinical complications: New AFib,
or pulmonary HTN (n = 195)

**Class II Triggers:**
Early Asymptomatic: Gr 4/4 MR, High probability of MV Repair only (n = 523)


Post-op survival (%)

Patients at Risk

Guideline Indication Triggers for Surgery in Severe MR: Impact on Outcome

**Heart Failure**

- Class II - High Prob Repair
- Class II - New AFib, PHTN
- Class I - Sxs, LVEF, LVESD

**Death or Heart Failure**

- P<0.0001

Patients at Risk:

- Years 0: 478, 155, 592
- Years 5: 383, 110, 383
- Years 10: 61, 33, 107
- Years 15: 65±2, 55±4, 37±3

Left Ventricular End-Systolic Dimension (LVESD) in Severe MR

MIDA Database: 739 Patients with Flail Leaflet

Watchful Waiting

Surgical Intervention

Overall survival (%)

LVESD (mm)

P < 0.001

P = 0.04

Left Ventricular End-Systolic Dimension (LVESD) in Severe MR
Risk of Mortality With Watchful Waiting

Indexed cut-point for increased mortality: LVESD ≥ 22 mm/m²

Severe MR: The Fallacy of “Normal” Preoperative LV Function

<table>
<thead>
<tr>
<th></th>
<th>≥ 50% (n = 1,391)</th>
<th>&lt; 50% (n = 314)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEF (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Op</td>
<td>66.8 ± 4.8</td>
<td>65.3 ± 4.0</td>
</tr>
<tr>
<td>Post-Op</td>
<td>59.2 ± 5.8</td>
<td>41.8 ± 6.2</td>
</tr>
<tr>
<td><strong>LVESD (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Op</td>
<td>34.2 ± 4.6</td>
<td>37.7 ± 4.4</td>
</tr>
<tr>
<td>Post-Op</td>
<td>33.4 ± 5.1</td>
<td>41.9 ± 5.4</td>
</tr>
</tbody>
</table>

Severe MR: Predictors of Early Postoperative LVEF < 40% *

OR (± 95% CI)

RVSP > 49 mmHg

4.40 (2.35-8.23)

LVESD > 36 mm

6.46 (3.31-13.61)

* Post-Operative Death  HR = 1.74 (1.03-2.92)

Severe Primary Mitral Regurgitation: The Case for Early Surgical Intervention

Conclusions

• Unoperated severe MR has serious clinical consequences, even if asymptomatic
• Clinical symptom status is often unreliable
• Stress testing discriminates elusive functional status and prognosticates
• Early surgical intervention improves outcome
• Selection of surgical center and surgeon is critical
• Current ACC/AHA guideline triggers to surgery may delay intervention, resulting in suboptimal outcome
• Why wait for the inevitable, and increase patient risk?