The Pathophysiology and Management of Functional Mitral Regurgitation

What are the questions?

Banff 17
## Differences between Primary vs Secondary M. Regurgitation

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary (“Functional”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pathological abnormalities of the <strong>mitral apparatus</strong></td>
<td>• Normal or nearly normal mitral leaflets are prevented from proper coaptation by underlying LV dysfunction producing tethering, mitral annular dilation, or both</td>
</tr>
</tbody>
</table>
Normal Mitral Valve

- Mitral Annulus
- Papillary muscle
- Chordae

LV
LA
AO

Functional Mitral Regurgitation

- Ischemic LV Distortion
- Papillary muscle displacement
- Tethered Chordae
- Restricted Leaflet Closure
- Annular dilation

LV
AO
MR

Clinical Significance of *Mild* MR after MI

- 727 pts
- SAVE trial
- MI ≤16 days
- LVEF ≤40%

### M. Regurg. on Angiography

<table>
<thead>
<tr>
<th>Severity</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>141</td>
<td>19.4%</td>
</tr>
<tr>
<td>2+</td>
<td></td>
<td>4.5%</td>
</tr>
<tr>
<td>3+</td>
<td>2</td>
<td>2 pts</td>
</tr>
</tbody>
</table>

Lamas: Circ, 1997
Ischemic MR: Outcomes Stratified by the Degree of MR

- 303 patients
- Prior (>16 days) QMI
- Mayo Clinic

Survival Stratified by R. Vol

<table>
<thead>
<tr>
<th>RVol</th>
<th>Years</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>61±6</td>
</tr>
<tr>
<td>1-29</td>
<td>1</td>
<td>44±9</td>
</tr>
<tr>
<td>≥30*</td>
<td>2</td>
<td>35±7</td>
</tr>
</tbody>
</table>

P<0.0001

Survival Stratified by ERO

<table>
<thead>
<tr>
<th>ERO</th>
<th>Years</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>61±6</td>
</tr>
<tr>
<td>1-19</td>
<td>1</td>
<td>47±8</td>
</tr>
<tr>
<td>≥20**</td>
<td>2</td>
<td>29±9</td>
</tr>
</tbody>
</table>

P<0.0001

*P=0.002 on multivariate analysis

**P>0.004 on multivariate analysis

Grigioni Circ, 2001
Prognostic Impact of Functional MR

- Presence of MR
- Severity of MR

Surrogate? Causality?

Both
Management of Functional MR

In pts with moderate MR
- CABG alone vs CABG + mitral annuloplasty/repair

In pts requiring a mitral valve procedure (moderate to severe MR)
- Mitral valve repair
- Mitral valve replacement
Therapeutic Considerations for Ischemic MR in Patients With LV Dysfunction

Guideline based medical therapy to address LV dysfunction

- Pharmacologic
  - Beta blockers*
  - ACE/ARB*
  - Diuretics*
  - Isordil*
  - Aldosterone antagonists*

*Improvements documented

Coronary revascularization alone

Indications
- Extensive ischemia
- Angina
- Viability

Inconsistent effect on severity of MR

MV Replacement/Repair Surgery & Devices

LVAD/Cardiac transplantation
The results of mitral valve repair for functional mitral regurgitation are much inferior to those in patients with degenerative MR.
Durability of Ischemic Mitral Valve Repair

- 78 patients
- Ischemic MR
- Mean follow-up 28 mo

Recurrence of Severe MR After CABG ± Annuloplasty in Ischemic MR

- Recurrent MR (2+) – 32%
- Severe MR (3-4+) – 20%

- Recurrent severe MR lower with annuloplasty, but still 20% at 5 years

Jerri: JTCVS, 2006
Effect of Mitral Valve Annuloplasty in Patients With LVEF ≤30%

- 419 patients
- Retrospective analysis
- Consecutive series

Effectiveness of Surgical Mitral Valve Repair Versus Medical Treatment for People With Significant Mitral Regurgitation and Non-Ischemic Congestive Heart Failure (SMMART-HF)

This study has been terminated (unable to recruit sufficient numbers of patients)

Clinical Trials.gov NCT 00608140
Randomized Trials of Surgical Treatment in Moderate Ischemic Functional MR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pt (no.)</th>
<th>Follow-up (years)</th>
<th>Outcomes (CABG + MVR vs CABG alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fattouche e</td>
<td>102</td>
<td>5</td>
<td>↑ EF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Volumes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improved NYHA class</td>
</tr>
<tr>
<td>Chan (RIME Trial)</td>
<td>73</td>
<td>1</td>
<td>↓ LV reverse remodeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Peak $O_2$ consumption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ M regurgitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ BNP</td>
</tr>
<tr>
<td>Smith (CTS Network)</td>
<td>301</td>
<td>2</td>
<td>No change in LVESV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Moderate → severe MR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Bypass time and hospital stay</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Perioperative neurologic events</td>
</tr>
</tbody>
</table>

No trial powered for major clinical outcomes
Mitral Annuloplasty vs Replacement for Functional MR

↑ Periop. mortality and morbidity in some centers

Higher risk of persistent MR

Replacement

Impact on long-term clinical outcomes

Repair
Mitral Valve Repair vs Replacement for Severe Ischemic MR
CTS N Trial – 2-Year Outcomes (251 Patients)

Decrease in LVESV from Baseline

- Replacement
- Repair

Mortality

Moderate → Severe MR Recurrence

Repair patients - higher rate of serious heart failure, 24% vs 15% (P=0.05) and more CV readmissions 48.3 vs 32.2 (P=0.01)

Goldstein: NEJM, 2015
Should Moderate to Severe Functional MR be Corrected?

Intuitively– Yes

Caveats

• No concrete evidence that surgery alters natural history
• High risk of recurrence after MV Repair
• Significant morbidity and mortality with MV replacement in some series

Ongoing trials are important for both approaches

Surgery vs Medical

Percutaneous vs Medical

Percutaneous vs Surgery
Randomized Trial Data of Mitra-Clip vs Surgery in Functional vs Degenerative MR

EVEREST II Trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percutaneous Repair, %</th>
<th>Surgery, %</th>
<th>P value</th>
<th>Difference [95% CI]</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42.9</td>
<td>63.9</td>
<td>0.03</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Female</td>
<td>46.4</td>
<td>65.0</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥70 yrs</td>
<td>45.1</td>
<td>42.3</td>
<td>0.81</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Age &lt;70 yrs</td>
<td>43.4</td>
<td>83.3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of MR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional MR</td>
<td>40.5</td>
<td>28.6</td>
<td>0.43</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Degenerative MR</td>
<td>45.5</td>
<td>76.2</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;60%</td>
<td>44.1</td>
<td>41.2</td>
<td>0.83</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>LVEF ≥60%</td>
<td>44.1</td>
<td>74.4</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Feldman: JACC, 2015
ESC/EACTS Guidelines for Mitra-Clip

Class IIB  LOE-C
Approved for Both Primary and Secondary MR

MitraClip System for the Treatment of FMR:
Ongoing Randomized Trials vs Medical Therapy

<table>
<thead>
<tr>
<th>Design/location</th>
<th>COAPT</th>
<th>RESHAPE</th>
<th>MITRA-FR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multicentre and randomized; US</td>
<td>Multicentre and randomized; EU</td>
<td>Multicentre and randomized; France</td>
</tr>
<tr>
<td>No of patients</td>
<td>430</td>
<td>800</td>
<td>288</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>≥20%–≤50%</td>
<td>≥15%–≤40%</td>
<td>≥15%–≤40%</td>
</tr>
</tbody>
</table>
Functional Mitral Regurgitation – Conclusions

- FMR is primarily a disorder of the LV
- FMR is common in CHF and after MI
- FMR predicts increased mortality in a graded fashion
- Medical therapy including beta-blockers, ACE-1 ARB is effective
- CRT may be effective in some patients
- CABG alone can reduce FMR acutely in some patients – results unpredictable
Functional (Secondary) MR
“Evidence and Uncertainties”

- Does correcting FMR prolong or improve the quality of life?
  May depend upon presence of CHF symptoms

- Trials with Mitraclip / Devices will help inform the field

- If correcting FMR is demonstrated to help: then providing the most complete and durable correction is desirable

Predictors of recurrences after repair
- Severe tethering
- Inferobasal aneurysm
- Severe LV dilatation

Valve-sparing mitral valve replacement should be used more liberally in these patients
When to Intervene on the Mitral Valve in a Patient Undergoing CABG

- **Mild → moderate MR**
  - Dominant Symptom – Angina
  - CABG alone or CABG plus mitral annuloplasty

- **Severe MR**
  - Dominant symptom – CHF
  - Valve sparing MV replacement vs Repair

Trials suggest replacement is preferred over repair

- Annuloplasty
- Other techniques
Evolving Concepts in regard to the Management of Functional MR

We now understand much more about what we do not know
Existing Association Guidelines

Moderate Ischemic MR

A. MV repair may be considered at time of other cardiac surgery, including CABG (COR IIb, LOE B)

Mitral Valve Replacement (MVR) vs Repair

A. Not available

AATS Guidelines

Moderate Ischemic MR

A. MV replacement is reasonable in patients with severe IMR who remain symptomatic despite guideline directed medical and cardiac device therapy, and who have a basal aneurysm/dyskinesis, significant leaflet tethering, and/or severe LV dilation (EDD >6.5 cm) (COR IIa, LOE B)

Mitral Valve Replacement (MVR) vs Repair

A. MVR for IMR is performed with complete preservation of both anterior and posterior leaflet chords (COR I, LOE B)
B. MV repair for IMR is performed with small undersized complete rigid annuloplasty ring (COR IIa, LOE B)
Updated AATS Guidelines

Existing Association Guidelines

Severe Ischemic MR

A. MV surgery is reasonable at time of other cardiac surgery (eg, CABG, AVR) (COR IIa, LOE C)

B. MV surgery may be considered as an isolated procedure for treatment of patients with severe symptoms (NYHA III/IV) despite GDMT (COR II, LOE C)

AATS Guidelines

Severe Ischemic MR

A. MV replacement is reasonable in patients with severe IMR who remain symptomatic despite guideline directed medical and cardiac device therapy, and who have a basal aneurysm/dyskinesis, significant leaflet tethering, and/or severe LV dilation (EDD >6.5 cm) (COR IIa, LOE B)

B. MV repair with an undersized complete rigid annuloplasty ring may be considered in patient with severe IMR who remain symptomatic despite guideline directed medical and cardiac device therapy and who do not have a basal aneurysm/dyskinesis, significant leaflet tethering, or severe LV enlargement (COR IIb, LOE B)
Why is the Benefit of MR Reduction so Hard to Prove?

- MR recurrence ≥20%; perioperative mortality 1.5-15%
- The benefit may be limited to specific pt subgroups that have not been pre-defined in CV datasets
- Perhaps there is no benefit? – *MR is a surrogate not causally related to outcome?*
- “Things may not be as they seem”

Gersh And Frye NEJM 2008

M. Mack (Pers. Comm), 2016