Ischemic/Functional Mitral Regurgitation: Mechanism, Treatment and New Trials

Judy Hung, MD
Cardiac Ultrasound Laboratory
Massachusetts General Hospital
Boston, MA

NO DISCLOSURES

Age, Gender and Prevalence of Moderate-Severe VHD
Population-Based Studies

Nkomo et al. Lancet 2006;368:1005–1011
Age and Prevalence of Mitral Regurgitation Framingham Heart Study

PAUCITY OF RANDOMIZED TRIAL DATA FOR VALVULAR DISEASE

"...unlike many other forms of cardiovascular disease, there is a scarcity of large-scale multicenter trials addressing the diagnosis and treatment of patients with valvular disease from which to derive definitive conclusions...."


VALVULAR HEART DISEASE BASED ON....

- Level of Evidence A: Data derived from multiple randomized clinical trials.
- Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.
- Level of Evidence C: Only consensus opinion
- Level of Evidence D:
The Problem: ischemic mitral regurgitation

Patient with remote inferior myocardial infarction and aneurysm formation

Inferior wall aneurysm

Ischemic Mitral Regurgitation

Mitral regurgitation resulting from changes in the mitral valve apparatus secondary to abnormal left ventricular function from coronary artery disease

- Normal leaflet morphology
- Occurs after chronic remodeling
- Very small percentage: “acute ischemia” leading to development of mitral regurgitation

Mechanism: Ischemic Mitral Regurgitation

Ischemic MR: It’s the Ventricle!
“Development of significant FMR is associated with insufficient leaflet area relative to that demanded by tethering geometry. The varying adequacy of leaflet area may explain in part the heterogeneity of this disease in patients.”
• 49 year old male with no CAD
• Presents with heart failure

Functional Mitral Regurgitation: General term describing MR associated with ventricular dilation. Could be ischemic or nonischemic (often refers to latter case)

Survival post myocardial infarction: Dose Related Influence of MR

We know that developing MR after myocardial infarction is bad for you….
But we don’t know what to do about it.

Data on therapies for IMR whether CABG alone or CABG plus MV surgery impacts negatively on survival is conflicting.

No randomized clinical data on therapy for IMR; Studies are retrospective.


Compared Matched Patients without MR (N=210) and with moderate MR (N=210) undergoing CABG. Mean f/u 3.6 years

Patients with MR had decreased survival (p=0.0003) at 5 years.


Test : Patients with moderate IMR N=58
Control: Matched Group of patients without MR

Survival of Patients with Moderate IMR Post CABG Only vs Patients Post CABG with No IMR

Late survival of patients with moderate MR who underwent CABG only.

Test : Patients with moderate IMR N=58
Control: Matched Group of patients without MR

No Difference in Survival
No randomized data that demonstrates improvement in survival or CV morbidity following ring annuloplasty in patients with ischemic mitral regurgitation.

**Beneficial Effects of MV annuloplasty (LVEDD <65 mm)**

Restrictive Mitral Annuloplasty Cures Ischemic Mitral Regurgitation and Heart Failure

Jerry Braun, MD, Nico R. van de Veire, MD, Robert J. M. Klautz, MD, PhD, Michel I. M. Versteegh, MD, Eduard R. Holman, MD, PhD, Jeroen J. Bax, MD, PhD, Ernst E. van der Wall, MD, PhD, and Robert A. E. Dion, MD, PhD


100 pts: For preop LVEDD of < 65 mm: (mean f/u 4.3 yrs)

- Improved survival compared to LVEDD > 65 mm: 80% vs 49%
- Improved NYHA: 2.9 to 1.6
- Decreased degree of MR: mean 0.8 grade

**CABG alone compared to CABG/MV Ring**

Retrospective analysis comparing patients with 3 or 4+ MR who either underwent CABG alone (N=100) or CABG plus MV annuloplasty (N=290).

No difference in survival or long term functional class between the two groups.

Mihaljevic T. and Lytle B et al. JACC 2007;49:2191-211
Rings do not directly address the ventricle and leaflet tethering.

**Current Therapy - Mitral Ring Annuloplasty**

**Limitations**
- Recurrence Rate of Ischemic MR Approximately 30%
- Does not directly address Fundamental Mechanism (Ventricle)
- Doesn’t directly prevent further ventricular remodeling

**Mechanism of Action**
- AP dimensional reduction at the mitral valve annulus

**Incidence of Recurrent MR after MV Ring**

Larger series show ~ 30% recurrence rate of IMR (Moderate or greater)

Magne: Cardiology 2009;112:244-259
Mitral Valve Repair  OR  Mitral Valve Replacement

Preservation of leaflets and chordal apparatus

St. Jude Valve

Overall Survival Post Mitral Valve Surgery for Ischemic MR:
Retrospective Study of 482; MV repair (N=397) vs MV replacement (N=85)

Most patients (70%) benefited from repair. In sickest group: no difference whether MV repair or replacement

Therapy for Ischemic MR: Is There Consensus? What are the Issues?

Therapy for Ischemic MR: Is There Consensus? What are the Issues?

- Mitral regurgitation is associated with reduced survival in patients with coronary disease.
- Significant mitral regurgitation remains following CABG.
- No trial showing improved survival with MV surgery performed at time of CABG.
- Data suggests MV repair with CABG associated with improved LV remodeling with decrease in LV volumes, some studies show greater improvement in functional status with MV repair.
- Data supporting a 30 to 40% recurrence rate with MV annuloplasty.
- MV repair versus MV replacement for IMR controversial but data suggests that better outcomes with MV repair (Retrospective data).
- We need randomized trials!

Cardiothoracic Surgical Network (CTSN)

- Network of surgical sites whose mission is to conduct collaborative clinical protocols to evaluate surgical and minimally invasive interventional strategies in the treatment of cardiovascular disease in adult populations.
- Funded by NIH/NHLBI

CTSN TRIAL: Randomized Clinical Trial: Patients undergoing CABG with either moderate or severe ischemic MR:

<table>
<thead>
<tr>
<th>Moderate MR</th>
<th>Severe MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>CABG plus</td>
</tr>
<tr>
<td></td>
<td>MV repair</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>MV Repair</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>MV Replacement</td>
</tr>
</tbody>
</table>

Endpoint: Decrease in ESVindex
Trial is underway
Severe MR group has completed enrollment target
Moderate MR is 70% enrollment target
Ischemic MR: What to do now?

“Patients with severe ischemic MR usually have significant LV dysfunction, and the decision to perform revascularization and MV repair is based on symptoms, severity of CAD, LV dysfunction, and inducible myocardial ischemia.”


Thank You

Current Therapy - Mitral Ring Annuloplasty at time of CABG

Mechanism of Action:
• AP dimensional reduction at the mitral valve annulus
Survival post myocardial infarction: Dose Related Influence of MR

Ischemic Mitral Regurgitation

Mitral regurgitation resulting from changes in the mitral valve apparatus secondary to abnormal left ventricular function (CAD or myopathy)
- Normal leaflet morphology

Ischemic mitral regurgitation results from an imbalance between tethering forces and closing forces

- Apical displacement of the papillary muscles increases tethering forces.
- Decreased LV function decreases closing forces.
Ischemic Mitral Regurgitation

- Mitral regurgitation resulting from changes in the mitral valve apparatus secondary to abnormal left ventricular function (CAD or myopathy)
  - Normal leaflet morphology

Functional Mitral Regurgitation: General term describing MR associated with ventricular dilation: Could be ischemic or nonischemic (often refers to latter case)

- 49 year old male with no CAD
- Presents with heart failure

Is There Adequate Leaflet Area in FMR?

Leaflet Area


**FMR: Insufficient Leaflet Adaptation?**

Mitral leaflet area (LeafA) adjusted for closure area (ClosA) and annular area (AnnA) in different patient groups

“Development of significant FMR is associated with insufficient leaflet area relative to that demanded by tethering geometry. The varying adequacy of leaflet area may explain in part the heterogeneity of this disease in patients.”


**Mitral ring annuloplasty**

- Standard therapy for ischemic MR is ring annuloplasty, typically placed at time of concurrent coronary artery bypass grafting
- Rings decrease the mitral annular area by bringing in the posterior annulus
Significant IMR post ring annuloplasty

One month post-op: LVID=58  One year post-op: LVID=75

Further ventricular remodeling

There is approximately 30 to 40% recurrence rate of IMR following ring annuloplasty

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>% with significant MR (moderate)</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liel-Cohen et al.; Circulation 1997</td>
<td>31</td>
<td>58%</td>
<td>6 yrs</td>
</tr>
<tr>
<td>Calafiore et al.; Ann Thorac Surg. 2001</td>
<td>16</td>
<td>78%</td>
<td>2 yrs</td>
</tr>
<tr>
<td>Tata et al.; J. Heart Valve Dis. 2002</td>
<td>100</td>
<td>30%</td>
<td>3 yrs</td>
</tr>
<tr>
<td>McGee and Cosgrove; J. Thorac Cardiovasc Surg 2004</td>
<td>422</td>
<td>28%</td>
<td>6 mo</td>
</tr>
<tr>
<td>Gelsomino et al; EHJ 2007 (Restrictive Annuloplasty)</td>
<td>251</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>
It's the ventricle!

We apply a surgical repair method that was applied originally for repair of degenerative mitral valve disease, to a ventricular problem....
Chordal Cutting: Patient Example

Tethered Leaflet at Basal Chord Insertion
Decreased Tethering Post Chordal Cutting

Before Chordal Cutting
After Chordal cutting and Normal Size Ring

Courtesy of Dr. Emmanuel Messas

Chordal Cutting Approach; N=43

Ring Only
Ring + Chordal Cutting


Direct Remodeling of Papillary Muscles

Mitral Regurgitation from nonischemic etiology

MV arm on Corcap Trial (Acorn-passive restraint device)

193 pts: 102 with MVR alone and 91 with MVR with Corcap. 93% nonischemic etiology
30 day survival 1.6%; 2 yr survival 85%; Reduction in MR from Grade 2.6 to 0.5
End to side coaptation in Ischemic MR:
Results from asymmetry of tethering and hence coaptation and eccentric jet


End to side coaptation in Ischemic MR:
Results from asymmetry of tethering and hence coaptation and eccentric jet


Does Coronary Artery Bypass Grafting Alone Correct Moderate Ischemic Mitral Regurgitation?

136 patients with moderate MR undergoing CABG alone
Distribution of MR severity on intraoperative (Intra-op) TEE and postoperative (Post-op) TTE

Akog, L. et al. Circulation 2001;104:166-170
Unadjusted and adjusted survival estimates for the 3 patient cohorts: no/trace MR, mild MR, and moderate MR.

Decreased survival in patients with MR in a dose related manner.

TABLE 2: Echocardiographic Findings in 773 Patients Who Underwent Echocardiography Within 30 Days After MI

<table>
<thead>
<tr>
<th></th>
<th>No MR (n=387)</th>
<th>Mild MR (n=297)</th>
<th>Moderate/Severe MR (n=89)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %, mean±SD</td>
<td>49±13</td>
<td>45±14</td>
<td>40±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV enlargement, n (%)</td>
<td>87 (28)</td>
<td>118 (40)</td>
<td>49 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMSI, median (Q1–Q3)</td>
<td>1.4 (1.1–1.7)</td>
<td>1.5 (1.2–1.9)</td>
<td>1.6 (1.3–2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV systolic pressure, mm Hg</td>
<td>38±9</td>
<td>45±11</td>
<td>49±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time, ms, mean±SD</td>
<td>209±48</td>
<td>210±57</td>
<td>178±63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular EF; WMSI, left ventricular wall-motion score index; and RV, right ventricular.

Subgroup analysis suggests that pts with Class 3-4 had better survival with MV surgery.