Heart failure and mitral regurgitation: clip it, band it or leave it?

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Functional MR is one of many components of the CHF constellation

- Ischemia - stunning
- Hybernation
- Fibrosis
- Dilatation - Remodeling
- Functional MR
- Atrial Fibrillation
- LV Dyssynchrony
- Malignant arrhythmias
- Neurohumoral status
Functional mitral regurgitation
Valve structure is preserved
Left ventricular function and shape is impaired

- Dilated Idiopathic cardiomyopathy
- Ischemic cardiomyopathy
- IMR with preserved global LV function
- FMR in Ao Stenosis
Rationale for interventional treatment of FMR in HF

- To reduce symptoms by reducing LA pressure under resting conditions
- To prevent acute HF by reducing the chance of flash pulmonary edema
- To improve compliance to therapy by increasing cardiac output
- To initiate reverse remodeling by reducing volume overload
Medical therapy can improve FMR (by reverse remodeling, reducing preload, reducing afterload)

Reverse remodeling achieved by beta-blocker is associated with reduction in MR in selected patients

Waagstein, EJHF, 2003
CRT therapy can improve MR in selected patients

MIRACLE trial (450 pts with LVEF < 35% and QRS>130 sec)

St John Sutton et al, Circulation 2000
Non responder to CRT are at high risk of mortality if MR remains untreated
MitraClip in patients with Heart Failure and FMR

- After about 40000 patients treated, anatomical eligibility for MitraClip is not a limitation:
  - most patients can be efficiently treated with satisfactory acute outcomes
- Clinical indications and management need improvement
  > Timing
  > When MitraClip is a futile excercise?
MitraClip therapy is not an alternative to ECMO, VAD or HTx
MitraClip therapy as a bridge to Heart transplantation

Mitraclip Procedure as a Bridge Therapy in a Patient With Heart Failure Listed for Heart Transplantation
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Cardiac Surgery and Heart Failure Units, IRCCS Policlinico San Donato, Milan, Italy

Functional mitral regurgitation (MR) is frequently detected in patients with dilated cardiomyopathy and advanced heart failure, worsening quality of life and predicting poor survival. However, the optimal treatment of patients with advanced heart failure and severe MR has been controversial. We present the case of a 55-year-old man with previous aortic valve replacement, severe MR with high-grade pulmonary hypertension, and refractory heart failure (HF). He was listed for cardiac transplant and underwent percutaneous MitraClip implantation as bridge therapy. The postoperative course was uneventful, with significant improvement in New York Heart Association functional class. The patient underwent a successful heart transplant 8 months after the procedure.

Table 1. Changes Over Time of Left Ventricular Echocardiographic Parameters Between Preoperative and Transplantation

<table>
<thead>
<tr>
<th>Echocardiographic Parameters</th>
<th>Preoperative</th>
<th>At Discharge</th>
<th>3-Month Follow-Up</th>
<th>At Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDD (mm)</td>
<td>73</td>
<td>69</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>LV ESD (mm)</td>
<td>64</td>
<td>66</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>EDV (mL)</td>
<td>277</td>
<td>260</td>
<td>265</td>
<td>262</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>217</td>
<td>200</td>
<td>205</td>
<td>200</td>
</tr>
<tr>
<td>EF (%)</td>
<td>22</td>
<td>23</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>PaPs (mm Hg)</td>
<td>57</td>
<td>48</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Severe</td>
<td>Mild</td>
<td>Mild/moderate</td>
<td>Mild/moderate</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>Severe</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
</tr>
</tbody>
</table>

EDD = end diastolic diameter; EDV = end diastolic volume; LV = left ventricle; EF = ejection fraction; ESD = end systolic diameter; ESV = end systolic volume; PaPs = systolic pulmonary artery pressure.
Rationale of MitraClip as Bridge to Transplantation

- Improvement of symptoms
- Reduction of Pulmonary hypertension
- Minimally invasive therapy without sternotomy

|’Brien et al, JTCVS 1997 |

<table>
<thead>
<tr>
<th>Baseline strata</th>
<th>Low risk</th>
<th>Average risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk stratum range</td>
<td>&lt;2 WU</td>
<td>2-3 WU</td>
<td>&gt;3 WU</td>
</tr>
<tr>
<td>SSLR&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.46 (0.26-0.83)</td>
<td>0.97 (0.55-1.71)</td>
<td>1.62 (1.24-2.10)</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>9/177 (5.1%)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>10/94 (10.6%)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>28/158 (17.7%)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>PVRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk stratum range</td>
<td>&lt;4 WU·m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4-7 WU·m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&gt;7 WU·m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>SSLR&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.52 (0.30-0.87)</td>
<td>1.58 (0.78-1.79)</td>
<td>1.64 (1.14-2.37)</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>11/194 (5.7%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>16/124 (12.9%)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>20/111 (18.0%)&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>TPG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk stratum range</td>
<td>&lt;10 mm Hg</td>
<td>10-14 mm Hg</td>
<td>&gt;14 mm Hg</td>
</tr>
<tr>
<td>SSLR&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.44 (0.27-0.74)</td>
<td>1.28 (0.81-2.03)</td>
<td>1.95 (1.38-2.75)</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>11/226 (4.9%)&lt;sup&gt;‡‡&lt;/sup&gt;</td>
<td>14/100 (14.0%)&lt;sup&gt;‡‡&lt;/sup&gt;</td>
<td>22/103 (21.4%)&lt;sup&gt;‡‡&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
MitraClip therapy in FMR

Feasibility and learning curve

Overall efficacy

Outcome optimization


First Implant

EVEREST I (Feasibility Study) (55 Patients Enrolled)

High Risk Study (78 Patients Enrolled)

ACCESS Europe (Commercial Registry) (567 Commercial Patients Enrolled)

COAPT (Currently Enrolling)

RESHAPE-HF (Currently Enrolling)

EVEREST II (Randomized Controlled Trial) (279 Patients Enrolled)

CE Mark

REALISM (Continued Access) (815 Patients Enrolled)
Significant clinical benefits have been reported in Severe Heart Failure despite optimal medical therapy

- 94% successful implant rate (cohort of 50 patients)
- Improved short-term survival related to NYHA functional class
- Significant improvements in 6-minute walk test, MLHFQ score, and NT-proBNP plasma levels, as well as EF, LV ESV and LVEDV which supports reverse remodeling of the LV

**CLINICAL IMPROVEMENTS at 6 months**

- MR GRADE 87% less than or equal to 2+
- NYTHA CLASS 72% in class I or II
- MLHFQ SCORE Mean improvement of -22 points

**6 MINUTE WALK TEST**

- Median of 311 meters at 6 months
- 81 meters
- Median of 230 meters at baseline
- (P < 0.0005) 19 patients

*THERAPY OUTCOMES*

- 94% Success
- IMPLANT RATE*

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NEED FOR REHOSPITALIZATION
propensity matched cohorts of MitraClip vs Controls
(IN-HF registry) heart failure patients with FMR>3+

- Treated patients: 232 patients enrolled in 2 centres located in different regions (san raffaele, milano – HSR- with 105 patients and ferrarotto, catania –HFC- with 127 patients).
- Untreated patients were observed in 32 centres and data were extracted from the in-hf database from ANMCO.

Source: CERGAS (Dr Tarricone)
KM observed vs predicted survival following MitraClip therapy in FMR pts

3C-HF Score
57% (52%-62%, 95% CI)

Seattle Score
1y: 79% (75%-84%, 95% CI)
2y: 69% (63%-74% 95% CI)

Observed 1y 89% (86%-92% 95% CI)

San Raffaele Hospital FMR population
Unpublished data
Current RCT for MitraClip therapy

- MitraClip vs OMT in HF
  - COAPT trial
  - RESHAPE
  - MITRA-HF

- MitraClip vs Surgery in HF
  - MATTEHORN

- MitraClip vs Surgery in intermediate and high risk patients with DMR
  - HIRIDE
Subgroup analysis of survival following MitraClip therapy

Pro-BNP ad admission

Survival

<table>
<thead>
<tr>
<th>Pro-BNP &lt;1,600 pg/ml</th>
<th>100% at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-BNP ≥1,600 pg/ml</td>
<td>83.9±5.7% at 1 year</td>
</tr>
</tbody>
</table>

Residual MR at discharge

Survival (%)

MR>2+

MR≤2+

Same cohort, unpublished data


Clinical outcomes of MitraClip for the treatment of functional mitral regurgitation
Relation of predicted change in left ventricular end-diastolic volumes (LVEDV) to residual mitral regurgitation (MR) severity.

Edge-to-edge surgical mitral valve repair in the era of MitraClip: what if the annuloplasty ring is missed?

Mechanism of MR:
- bileaflet prolapse in 46%
- anterior leaflet prolapse in 18%
- posterior leaflet in 36%

The omission of annuloplasty was due to important annular calcification in 59%.

In the remaining patients, annuloplasty was intentionally avoided because of the presence of only mild annular dilatation/deformation.

Freedom from reoperation & recurrence of MR 3-4+ with initial residual MR 0-1+ at discharge.

Michele De Bonis, Elisabetta Lapenna, Alberto Pozzoli, Andrea Giacomini, and Ottavio Alfieri. Curr Opin Cardiol 2015, 30:155–160
Percutaneous Direct Annuloplasty by Cardioband

A SURGICAL BAND IMPLANTED PERCUTANEOUSLY

Trans-femoral venous access (transeptal)
Delivered without interference to mitral and LV function
Surgical-like annular fixation
Significant Reduction of Annular dimensions
Keeps future options open
Watch How Cardioband Works
Reduction of Septo Lateral (A-P) Diameter by Cinching

Reduction in A-P

Cincing performed on Cadaveric Heart (TVT 2012)
Reduction of MR

Baseline

Final size Post Adjustment

[Images of medical scans and diagrams demonstrating the reduction of MR]
90% patients with MR≤2+ At 12 Months By Core Lab*

88% MR ≤ 2+ 84% MR ≤ 2+ 91% MR ≤ 2+ 90% MR ≤ 2+
at Discharge at 1 Month at 6 Months at 12 Months

*Dr. Paul Grayburn – Baylor University
Where Core Lab data was not available, clinical site data was used
Annular Reconstruction by Significant Reduction in Septo Lateral (A-P) Dimension

30% average reduction in A-P (N=39)

*P<0.01
Delivering Surgical repair through a catheter
Fusion imaging allows expedited complex procedures mimicking surgical grade valve repair
The promises of transcatheter mitral valve implantation

- More similar to TAVI (over the wire, angio-based, stent implant concept..)
- One device for all
- Predictable MR reduction
- Easier to learn and to implement in clinical practice
Clinical and technological challenges

- **Fixation**
  - No calcifications
  - Large anatomy
  - Non-circular and dynamic anatomy

- **Sealing**
  - Complex and dynamic structure
  - High pressure environment
  - Risk of LVOT obstruction

- **Delivery**
  - More than just a stent
  - Need for orientation
  - Additional fixation and sealing features

- **Imaging**
  - Patient selection
  - Planning
  - Guidance

- **Indications**
  - TMVI vs repair
  - Timing
  - Anticoagulation

- **Durability**
  - Stent durability
  - Leaflet degeneration
  - Fixation elements
Not always replacement is the best option
FMR and heart failure

- neurohumoral
- LV remodeling
- ischemia
- dissynchrony
Determinant of reverse remodeling following correction of MR
Synergistic approach

MitraClip + Medical Therapy
Mitraclip + CRT
Mitraclip + PCI
Mitraclip + TAVI
Mitraclip + annuloplasty
Mitraclip + Cell therapy
......

neurohumoral
LV remodeling
ischemia
dissynchrony
Timing of the intervention is the most challenging issue in PMVR

MR is fluctuant
HF symptoms respond to medical therapy
Reccomendations for PMVR therapy are not yet established
Timing

NYHA

I

II

III

IV

Outpatient clinic

Hospitalization

Inotrope use

Time from diagnosis
Vicious circle

MR

Anular-Ventricular dilatation

Volume overload
Timing

NYHA

I

II

III

IV

Outpatient clinic

Hospitalization

Inotrope use

Time from diagnosis
Late Repair of Ischemic Mitral Regurgitation Does Not Prevent Left Ventricular Remodeling

Integrated density from Western blot normalized for α-actin.
Timing for FMR

Conservative

- Severe symptomatic patients with severe MR after multiple hospitalizations
- End stage patients
- Acute pulmonary edema with preserved EF

Expanded

- Severe MR patients after first hospitalization for APE
- Less than severe MR (fluctuant) in patients with recurrent hospitalizations
- CRT non responders with FMR
The complementary role of transcatheter techniques

- Stand-alone Annuloplasty: early treatment FMR
- Stand-alone Mitraclip: FMR with asymmetric tethering (IMR)
- Stand-alone Mitraclip: DMR
- Combined Annuloplasty and MitraClip: DMR and Advanced FMR
- MV Replacement: advanced DMR and Advanced FMR
conclusions

- MitraClip and Cardioband are effective methods to treat FMR
- MR reduction can be achieved in most patients, but reverse remodeling is more difficult to achieve
- Every effort should be made to reduce MR to a minimum at the time of the procedure
- Timing is crucial: treating end-stage DCM is not efficient
- A synergistic approach between transcatheter therapy and other HF therapies is recommended
Modern management of HF
multidisciplinary team approach

- Total artificial heart
- Medical therapy
- Assist devices
- CRT
- Cell therapy
- FMR repair and replacement
- Transplant