Integrated reverse left and right ventricular remodelling after MitraClip implantation in functional mitral regurgitation: an echocardiographic study

Cristina Giannini*, Anna Sonia Petronio, Marco De Carlo, Fabio Guarracino, Lorenzo Conte, Francesca Fiorelli, Andrea Pieroni, and Vitantonio Di Bello

Cardiac Thoracic and Vascular Department, University of Pisa, Pisa, Italy

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Aims
The aim of the present study was to investigate the changes of left and right ventricular (RV) dimensions and function after MitraClip implantation in high-risk surgical patients with severe functional mitral regurgitation (MR).

Methods and results
Study population included 35 patients with functional MR. All the patients underwent clinical and echocardiographic evaluation at baseline, before discharge and at 6-month follow-up. The mean age was 75 years (63–81), 65.7% (n = 23) was male with a mean logistic EuroSCORE of 20%. Percutaneous mitral valve repair acronym (PMVR) resulted in significantly reduced MR and improved in New York Heart Association functional class. Echocardiography revealed improvement in left ventricular (LV) size and function since discharge with further improvement at 6 months. During the follow-up, a significant improvement in RV function was also observed by the baseline values. At baseline, before discharge and 6 months, respectively, the tricuspid annulus plane systolic excursion (TAPSE) was 16.8 ± 3.9, 18.7 ± 3.4, and 19.3 ± 4.5 mm (P = 0.001); the systolic pulmonary artery pressure (SPAP) was 50.1 ± 6.8, 41.2 ± 6.8, and 38.1 ± 6.8 mmHg (P < 0.0001); and the systolic velocity at the tricuspid annular (RV-Sm) was 8.8 ± 2.9, 10.4 ± 3.5, and 17.7 ± 3.1 cm (P < 0.0001).

Conclusion
MitraClip implantation induces a significant reverse remodelling of LV, with reduction in both diastolic and systolic LV volumes and an increase in the cardiac index. The concomitant reduction in LV filling pressure, obtained after MitraClip implantation, reflects nearly immediately on the haemodynamics of the right sections. In fact, since discharge, we observed both a reverse remodelling of the right sections, with a significant reduction in SPAP, and a significant increase in longitudinal RV systolic function as shown by the increase in TAPSE and RV-Sm.

Keywords
Percutaneous mitral valve repair

Introduction
Mitral regurgitation (MR) represents the second most common valvular disease in Europe. This pathology evolves, over many years, allowing the heart to adapt to a chronic volume overload, leading to significant haemodynamic, and structural changes. In chronic severe MR, the remodelling of left heart may lead to the development of a significant pulmonary hypertension in almost half of the patients. The increase in right ventricular (RV) afterload at first induces to the remodelling of RV and right atrial (RA) and afterwards leads to decreased contractile performance and to RV dysfunction that affects patient prognosis. Percutaneous mitral valve repair (PMVR) has been shown to be associated with a favourable left ventricular (LV) reverse remodelling and with clinical outcomes in high-risk patients with severe MR. However, nowadays, no data on right cardiac chambers reverse remodelling and function, after PMVR, are available.

In the present study, LV and RV integrated reverse remodelling after PMVR with the MitraClip system (Abbott, Abbott Park, IL, * Corresponding author. Tel: +39 050995330; Fax: +39 050995325, Email: crigiannini@hotmail.it
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Methods

Patient population and study design
This was a prospective observational study of 43 consecutive high surgical risk patients with moderate-to-severe or severe functional MR who underwent PMVR with the MitraClip system at our institution from November 2009 to August 2012. The indication for MR treatment according to current guidelines in combination with a high surgical risk was assessed by a multi-specialist team composed by cardiac surgeons, interventional and clinical cardiologists, and cardiac anaesthesiologists. The team also assessed valve anatomy to check the suitability for MitraClip treatment according to the EVEREST anatomic eligibility criteria.6,7 Patients were on stable optimized individual target heart failure medication and were treated with percutaneous angioplasty and stent implantation, implantable cardioverter defibrillator, and cardiac resynchronization devices prior to MitraClip therapy, if applicable. Patients who did not undergo acute procedural success (n = 3), those who experienced partial clip detachment without re-MitraClip device implantation before discharge (n = 2) and those who died before 6-month follow-up (n = 3), were excluded from the study (Figure 1). Therefore, the study population was constituted of 35 patients. Clinical follow-up through office visits was carried out at 1 and 6 months and every 6 months afterwards. B-type natriuretic peptide (BNP) was measured both at baseline and 6-month follow-up in 27 patients. Furthermore, results of the Minnesota Living with Heart Failure (MLHF) score were available at baseline and 6-month follow-up in 13 patients.

The study protocol was approved by the ethics committee of our institution, and all the patients gave informed consent.

MitraClip procedure and definitions
The MitraClip procedure was performed with the patient under general anaesthesia using transoesophageal echocardiography and fluoroscopic guidance in the cardiac catheterization laboratory, as previously described.6,8 The MitraClip system was introduced into the left atrium via the trans-femoral venous route and trans-septal puncture. The device was steered until it was aligned over the origin of the regurgitant jet and advanced into the left ventricle. The mitral leaflets were grasped, and the device was closed to approximate the leaflets. Once the resulting MR reduction was deemed satisfactory, the clip was deployed. If the reduction in MR was inadequate with one device, a second clip was placed. Acute procedural success was defined as placement of one or more clips resulting in MR reduction at least one-grade, as determined by Echocardiography Laboratory.

Echocardiographic assessment
All enrolled patients underwent transthoracic two-dimensional echocardiography (Philips i33, Philips Ultrasound, Andover, MA, USA) before, at hospital discharge, and 6 months after the procedure. All measures were assessed according to ASE recommendations guidelines.9,10 LV volumes and ejection fraction (EF) were calculated from apical two- and four-chamber views using the modified Simpson’s rule. Stroke volume (SV) and the cardiac output (CO) were measured by echocardiography in the LV outflow tract and were indexed for the body surface area (SVi and COi, respectively). LV internal dimensions, end-diastolic diameter, and end-systolic diameter were measured at the level of the LV minor axis, approximately at the mitral valve leaflet tips, in the parasternal view, using two-dimensional-targeted M-mode echocardiography. Left atrial (LA) chamber was evaluated using LA volume, measured from a single-plane apical imaging window. MR severity was visually estimated by colour Doppler and grading by the vena contracta width and the PISA (proximal isovelocity surface area) method, according to the following score: 1+ (mild), 2+ (mild to moderate), 3+ (moderate to severe), or 4+ (severe). To evaluate the possible development of MV stenosis, the mitral valve area was measured by planimetry. After PMVR, each of the two orifices was planimetred at the level of the clip and summed. Pulsed wave Doppler mitral velocity curves were not evaluated because they had not been validated for a double-orifice valve.

The modified apical four-chamber view was performed to obtain ‘the right ventricle-focused view’ to evaluate the RV changes in size and function. Therefore, the following parameters were measured at end diastole: RV free wall thickness, basal, mid, and RV base to apex diameter. The RV global function was evaluated in apical four-chamber view by tracing the RV area, both in systole and diastole, and calculating fractional area changes (FACs) using the following formula: \( \text{FAC} = \frac{(end-diastolic area - end-systolic area)}{end-systolic area}, \) reported in percentage. The RV longitudinal function was obtained, in apical four-chamber view, placing an M-mode cursor through the tricuspid annulus and measuring tricuspid annulus plane systolic excursion (TAPSE). RA chamber was evaluated using the RA area, measured from a single-plane apical imaging window. Pulsed wave Doppler tricuspid velocity curves were obtained from the apical four-chamber view by positioning a 1- to 2-mm sample volume between the tips of the tricuspid valve leaflets. Peak early (E) and late (A) flow velocities, their ratio E/A, and E wave deceleration time were measured by tricuspid velocity tracings.

Pulsed Doppler tissue imaging, at the mitral lateral site and at tricuspid annulus respectively, was acquired from the apical four-chamber view to measure the following parameters: systolic velocity (Sm), early diastolic (Em), and atrial contraction peak velocities. All measurements were performed on three consecutive cycles if the patient was in sinus rhythm and on 10 consecutive cycles in case of atrial fibrillation and the mean value was calculated.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Baseline clinical and echocardiographic profile</th>
<th>All patients (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>75 (63–81)</td>
<td>Male gender</td>
</tr>
<tr>
<td>Male gender</td>
<td>23 (65.7)</td>
<td>Logistic EuroSCORE (%)</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>20 (11–44)</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (27.5)</td>
<td>Hypertension</td>
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<tr>
<td>Hypertension</td>
<td>19 (54.2)</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>7 (20.0)</td>
<td>History of congestive heart failure</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>31 (88.5)</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>22 (62.8)</td>
<td>Prior myocardial infarction</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>17 (48.5)</td>
<td>Previous coronary artery bypass</td>
</tr>
<tr>
<td>Previous coronary artery bypass</td>
<td>15 (42.8)</td>
<td>Previous percutaneous coronary angioplasty</td>
</tr>
<tr>
<td>Previous percutaneous coronary angioplasty</td>
<td>9 (25.7)</td>
<td>History of cerebrovascular disease</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>1 (2.8)</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18 (51.4)</td>
<td>Serum creatinine &gt;2 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine &gt;2 mg/dL</td>
<td>5 (14.2)</td>
<td>NYHA functional class III/IV</td>
</tr>
<tr>
<td>NYHA functional class III/IV</td>
<td>24 (68.5)</td>
<td>SPAP &gt;60 mmHg</td>
</tr>
<tr>
<td>SPAP &gt;60 mmHg</td>
<td>8 (22.8)</td>
<td>Pacemaker or ICD implant</td>
</tr>
<tr>
<td>Pacemaker or ICD implant</td>
<td>17 (48.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%), mean ± SD, or median (inter-quartile range).
The myocardial performance index, defined as the ratio of the total isovolumic time (isovolumic contraction time (IVCT) and the isovolumic relaxation time (IVRT)) divided by the RV ejection time (ET), was calculated as follows: \((\text{IVRT} + \text{IVCT})/\text{ET}\). All indices were obtained by pulsed tissue Doppler velocity of the lateral tricuspid annulus.

Systolic pulmonary artery pressure (SPAP) was determined from peak tricuspid regurgitation jet velocity, using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure: \(\text{SPAP} = 4 \times (V)^2 + \text{RA pressure}\), where \(V\) is the peak velocity (in m/s) of the tricuspid valve regurgitation jet, and RA is right atrial pressure estimated from inferior vena cava diameter and with respiratory changes according to the guidelines.

**Statistical analysis**

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean ± SD. For continuous variables, paired comparison between baseline and 6-month follow-up was performed with a Wilcoxon signed-rank test. The comparison of a single group over different points of time was achieved by the Friedman two-way ANOVA with Bonferroni’s post-tests. Correlations between the echocardiographic measurements were tested, and only those statistically significant have been reported, providing the Spearman correlation coefficient. A P-value of <0.05 was considered statistically significant. All data were processed using the Statistical Package for Social Sciences, version 15 (SPSS, Chicago, IL, USA).

**Results**

**Patient population**

Baseline characteristics are detailed in (Table 1, Figure 1). The mean age of patients was 75 years (63 – 81), 65.7% (n = 23) was male and the mean logistic EuroSCORE was 20% (11 – 44). All the patients had a history of congestive heart failure with 24 patients (68.5%) in III to IV New York Heart Association (NYHA) class. The mechanism of MR was functional in all cases with an ischaemic aetiology in 23 (65.7%) patients. One clip was implanted in 27 patients (77.1%), with two clips used in the remaining patients.

**MR improvement**

MR of grade 2+ or less was achieved in all the patients (P < 0.0001) (Table 2). Overall distributions of MR severity at
baseline and before discharge as well as at 6-month follow-up are shown in Figure 2A. In relation to the baseline MR grade, 2 patients were discharged with MR severity reduced from 4+ to 3+, 15 patients from 4+ to 2+, 4 patients from 4+ to 1+, 11 patients from 3+ to 2+, and 3 patients from 3+ to 1+, respectively.

At 6-month follow-up, 30 patients maintained the MR grade achieved by the intervention, 3 improved (from MR 2+ to MR 1+), and 2 worsened (from MR 2+ to MR 3+).

In terms of MR severity as a continuous variable, a decrease from 3.6 ± 0.4 at baseline to 1.9 ± 0.5 before discharge and to 1.8 ± 0.6 at follow-up was noted (P < 0.0001).

Table 2  LV results at baseline, discharge and follow-up using ANOVA test with Bonferroni adjustment

<table>
<thead>
<tr>
<th>M-mode and 2D LV measurements</th>
<th>Baseline (n = 35)</th>
<th>Discharge (n = 35)</th>
<th>6 Months (n = 35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>66.1 ± 11.2</td>
<td>63.6 ± 10.8</td>
<td>61.6 ± 11.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>51.7 ± 13.1</td>
<td>49.1 ± 12.6</td>
<td>45.4 ± 12.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL)</td>
<td>191.4 ± 73.7</td>
<td>174.2 ± 72.3</td>
<td>152.9 ± 73.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic volume (mL)</td>
<td>124.6 ± 62.5</td>
<td>111.1 ± 57.6</td>
<td>93.3 ± 60.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>36.6 ± 11.3</td>
<td>39.2 ± 9.7</td>
<td>41.8 ± 10.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>56.7 ± 17.0</td>
<td>67.3 ± 26.7</td>
<td>65.6 ± 31.2</td>
<td>0.036</td>
</tr>
<tr>
<td>Stroke volume index (mL m⁻³)</td>
<td>32.8 ± 10.6</td>
<td>39.0 ± 15.3</td>
<td>37.8 ± 17.8</td>
<td>0.035</td>
</tr>
<tr>
<td>Cardiac output (L min)</td>
<td>3.99 ± 1.3</td>
<td>4.93 ± 1.9</td>
<td>4.62 ± 2.2</td>
<td>0.052</td>
</tr>
<tr>
<td>Cardiac output index (L min m⁻³)</td>
<td>2.32 ± 0.8</td>
<td>2.84 ± 1.1</td>
<td>2.67 ± 1.29</td>
<td>0.052</td>
</tr>
<tr>
<td>MR ≤2</td>
<td>0 (0%)</td>
<td>33 (94.2%)</td>
<td>31 (88.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA volume (mL)</td>
<td>112.3 ± 27.3</td>
<td>92.1 ± 26.5</td>
<td>100.1 ± 27.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MVA (cm²)</td>
<td>4.9 ± 1.8</td>
<td>2.6 ± 0.7</td>
<td>2.7 ± 0.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Tissue Doppler LV measurements

| Em (cm)                        | 6.7 ± 3.1        | 7.2 ± 2.6         | 5.8 ± 3.3       | 0.09    |
| Am (cm)                        | 7.4 ± 3.4        | 6.9 ± 3.3         | 7.0 ± 2.4       | 0.88    |
| Sm (cm)                        | 5.9 ± 1.7        | 6.4 ± 1.9         | 6.7 ± 2.1       | 0.13    |

Values are n (%), mean ± SD. LV, left ventricular; MR, mitral valve regurgitation; LA, left atrial volume; MVA, mitral valve area; Em, peak early diastolic velocity at the lateral mitral annulus; Am, peak late diastolic velocity at the lateral mitral annulus; Sm, systolic velocity at the lateral mitral annulus.

*P < 0.0001 baseline vs. discharge.

P < 0.0001 baseline vs. 6 months.

*P = 0.001 baseline vs. discharge.

**P = 0.001 discharge vs. 6 months.

#P = 0.001 baseline vs. discharge.

§P = 0.05 baseline vs. discharge.

^P = 0.05 baseline vs. 6 months.

& P = 0.05 discharge vs. 6 months.

Table 2  LV results at baseline, discharge and follow-up using ANOVA test with Bonferroni adjustment

Figure 2  Distributions of mitral regurgitation severity (A) and of New York Heart Association functional class (B) at baseline, before discharge and 6 months after MitraClip implantation.
The mitral valve area (planimetry) was 4.9 \pm 1.8 \text{ cm}^2 at baseline, 2.6 \pm 0.7 \text{ cm}^2 at discharge, and 2.7 \pm 0.8 \text{ cm}^2 at 6 months (P < 0.0001).

**Change in LV size and function**

Table 2 reports all data. At discharge, LV end-diastolic and end-systolic volumes and dimensions significantly improved, as well as LVEF (P < 0.0001). Between discharge and 6 months, a further significant improvement in LV size (P < 0.0001), and LVEF (P = 0.05) was also observed. At discharge, both SV indexed and CO indexed showed a mild significant increase without further improvement at 6 months (respectively, P < 0.03 and P < 0.05).

Furthermore, a significant reduction in LA volume was found after the procedure (P < 0.0001) and during the follow-up (P = 0.05) compared with baseline values. No significant changes regarding pulsed Doppler tissue velocity parameters were found.

**Change in RV size and function**

Table 3 reports all data. No significant differences in RV size were observed after the procedure and during the follow-up, except for a significant reduction in the RA area from baseline to discharge (22.2 \pm 3.8 vs. 19.2 \pm 3.9 \text{ cm}^2; P < 0.0001) which returned to be same as baseline after 6 months. Otherwise, a significant improvement in RV global function was observed in terms of TAPSE (P = 0.001) and systolic velocity at the tricuspid annular (RV-Sm; P < 0.0001) (Figures 3 and 4). In particular, these parameters increased significantly both from baseline to discharge (TAPSE: 16.8 \pm 3.9 vs. 18.7 \pm 3.4 \text{ mm}, P = 0.05; RV-Sm: 8.8 \pm 2.9 vs. 10.4 \pm 3.5 \text{ cm}, P = 0.05) and from baseline to 6-month follow-up (TAPSE: 16.8 \pm 3.9 vs. 19.3 \pm 4.5 \text{ mm}, P = 0.001; RV-Sm: 8.8 \pm 2.9 vs. 11.7 \pm 3.1 \text{ cm}, P < 0.0001) without significant improvement between discharge and 6 months.

SPAP reduced significantly before discharge and during the follow-up compared with baseline values (50.1 \pm 6.8 vs. 41.2 \pm 6.8, P < 0.0001 and 50.1 \pm 6.8 vs. 38.1 \pm 6.8, P < 0.0001, respectively) (Figures 3 and 4). In addition, a further significant improvement of SPAP was observed between discharge and 6-month follow-up (41.2 \pm 6.8 vs. 38.1 \pm 6.8 \text{ mmHg}, P = 0.05).

Finally, we did not find significant differences in the RV size and function according to MR aetiology (ischaemic vs. non-ischaemic cardiomyopathy) or according to the number of implanted clips.

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**Table 3  RV results at baseline, discharge, and follow-up using ANOVA test with Bonferroni adjustment**

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 35)</th>
<th>Discharge (n = 35)</th>
<th>6 Months (n = 35)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M-mode and 2D RV measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV free wall thickness (mm)</td>
<td>4.4 \pm 0.7</td>
<td>4.3 \pm 0.5</td>
<td>4.6 \pm 1.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Basal RV diameter (cm)</td>
<td>3.7 \pm 0.6</td>
<td>3.7 \pm 0.6</td>
<td>3.9 \pm 0.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Mid RV diameter (cm)</td>
<td>2.8 \pm 0.7</td>
<td>2.7 \pm 0.8</td>
<td>2.9 \pm 0.7</td>
<td>0.25</td>
</tr>
<tr>
<td>RV diameter base-to-apex (cm)</td>
<td>8.1 \pm 0.8</td>
<td>7.8 \pm 0.9</td>
<td>8.1 \pm 0.8</td>
<td>0.20</td>
</tr>
<tr>
<td>RV FAC (%)</td>
<td>34.8 \pm 7.8</td>
<td>36.7 \pm 9.8</td>
<td>40.4 \pm 11.2</td>
<td>0.09</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>16.8 \pm 3.9</td>
<td>18.7 \pm 3.4</td>
<td>19.3 \pm 4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>RA area (cm²)</td>
<td>22.2 \pm 3.8</td>
<td>19.2 \pm 3.9</td>
<td>22.7 \pm 4.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Standard RV Doppler measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>50.1 \pm 6.8</td>
<td>41.2 \pm 6.8</td>
<td>38.1 \pm 6.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak E (cm/s)</td>
<td>6.4 \pm 1.5</td>
<td>5.9 \pm 1.8</td>
<td>5.9 \pm 1.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Peak A (cm/s)</td>
<td>3.9 \pm 0.8</td>
<td>5.1 \pm 1.1</td>
<td>4.5 \pm 1.4</td>
<td>0.75</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3 \pm 0.2</td>
<td>1.2 \pm 0.4</td>
<td>1.1 \pm 0.4</td>
<td>0.64</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>208.0 \pm 40.1</td>
<td>217.1 \pm 32.3</td>
<td>223.3 \pm 35.6</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Tissue Doppler RV measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Em (cm)</td>
<td>7.9 \pm 3.1</td>
<td>7.9 \pm 3.0</td>
<td>7.7 \pm 2.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Am (cm)</td>
<td>12.9 \pm 3.5</td>
<td>11.8 \pm 4.2</td>
<td>8.6 \pm 3.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Sm (cm)</td>
<td>8.8 \pm 2.9</td>
<td>10.4 \pm 3.5</td>
<td>11.7 \pm 3.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV MPI</td>
<td>0.35 \pm 0.1</td>
<td>0.36 \pm 0.1</td>
<td>0.34 \pm 0.2</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Values are n (%), mean \pm SD.

RV, right ventricular; FAC, fractional area change; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annulus plane systolic excursion; DT, deceleration time; IVRT, isovolumetric relaxation time; MPI, myocardial performance index; Em, peak early diastolic velocity at the tricuspid annular; Am, peak late diastolic velocity at the tricuspid annular; Sm, systolic velocity at the tricuspid annular.

*p < 0.0001 baseline vs. discharge.

*p < 0.0001 baseline vs. 6 months.

*p < 0.001 baseline vs. discharge.

+p = 0.001 baseline vs. discharge.

+p = 0.01 discharge vs. 6 months.

+p = 0.01 baseline vs. 6 months.

+p = 0.05 baseline vs. discharge.

+p = 0.05 baseline vs. 6 months.

+p = 0.05 discharge vs. 6 months.

+p = 0.05 discharge vs. 6 months.
Heart failure and quality of life

The favourable ventricular changes were associated with a better functional status, according to the NYHA class, with 8.7% of patients in NYHA class ≥ 3 at 6 months vs. 85.8% at baseline; \( P < 0.0001 \) (Figures 2B and 3). In particular, 30 (58.7%) patients improved their NYHA class from baseline to follow-up (5 patients from NYHA III or IV to NYHA I, 22 patients from NYHA III or IV to NYHA II, and 3 patients from NYHA II to NYHA I). Five patients showed no functional improvement from baseline values at follow-up despite MR being reduced at least 1 grade. In terms of NYHA functional class as a continuous variable, patients improved from \( 3.0 + 0.5 \) at baseline to \( 1.9 + 0.6 \) at follow-up \( (P < 0.0001) \).

BNP plasma levels were available at baseline and follow-up in 27 patients and revealed a statistically significant overall decrease (from \( 900.1 \pm 144.9 \) to \( 478.9 \pm 54.37 \) pg/mL; \( P < 0.0003 \) (Figures 3–5A). Among the 13 patients who completed the MLHF at baseline and at follow-up, a significant score reduction was also noted (from \( 61.1 \pm 16.5 \) to \( 32.9 \pm 18.4 \); \( P < 0.0001 \) (Figures 3–5B).

A significant reverse correlation was observed between baseline NYHA class and baseline TAPSE \( (r = -0.36, P = 0.03) \) while a significant positive correlation resulted between baseline MR grade and 6 months TAPSE \( (r = 0.44, P = 0.03) \). Furthermore, the 6 months TAPSE improvement correlated significantly with improvements in NYHA class \( (r = -0.41, P = 0.05) \).

Discussion

The present work has demonstrated that PMVR with the MitraClip system is able to induce:

(i) LV and LA reverse remodelling both at discharge and after 6-month follow-up;

(ii) progressive significant reduction in SPAP since discharge;

(iii) improvement of the longitudinal systolic RV function, evidenced both by the significant increase in TAPSE and by RV-Sm wave, linked to RA reverse remodelling;
(iv) a better quality of life of the patients as shown by a progressive significant reduction in NYHA class and of MLHF score;
(v) a significant reduction in BNP at 6 months as expression of a better haemodynamic equilibrium of these patients.

The MitraClip device has evolved as a promising interventional tool for MV repair in selected high surgical risk patients or patients with severely reduced LV function. This procedure has been demonstrated to be feasible and safe leading to reduction in MR severity and improvement in clinical status and quality of life.6,7 The present study selected symptomatic patients with moderate-to-severe or severe functional MR at high risk of MV surgery. In accordance with previous studies, our results have demonstrated that these patients, who were not considered suitable for surgery, could be successfully treated with the MitraClip System to reduce the degree of MR with significant reduction in LV volume and dimensions and significant improvement in LVEF at 6 months.11–13 It has to be noted that, as previously demonstrated, the acute reduction in MR severity is also accompanied at 6 months by significant improvements in NYHA functional class and MLHF as well as significant reductions in BNP plasma levels.11,12,14 Furthermore, for the first time, we evaluated the impact of PMVR with the MitraClip System on RV chamber in patients with functional MR.

LV sections after PMVR with MitraClip system

In this study, we report increased clinical outcome and structural cardiac reverse remodelling after MitraClip implantation in high surgical risk patients with symptomatic functional MR and reduced LVEF. PMVR with the MitraClip, reducing instantly the acronym MV regurgitation, induces a significant reduction in volume overload with the reverse remodelling of both end-diastolic and end-systolic LV dimensions, already at discharge, confirming these adaptations also at 6 months, as a result of favourable effects of chronic LV unloading. LVEF in our series undergoes significant improvement, such as a mild significant improvement for both SV and acronym CO index. Previous studies have shown similar results demonstrating a significant cardiac structural reverse remodelling after 12 months, even in patients with an LVEF < 30%.5 Our data are in line with Tamburino et al., which have confirmed the positive LV reshaping effects after mitral valve repair with the MitraClip system, showing significant improvements in LV size and function.6

Figure 5 Follow-up of BNP (A) and MLHF questionnaire (B), at baseline and 6 months after MitraClip implantation.

RV sections after PMVR with the MitraClip system

The RV reverse remodelling after PMVR with the MitraClip system has not been extensively explored. The present study has been specifically designed to add further insights on this topic, also evaluating RV remodelling in a cohort of high surgical risk patients with moderate-to-severe or severe functional MR. The concomitant reduction in LV filling pressure, obtained after MitraClip implantation, reflected nearly immediately on clinical profile and on haemodynamics of the right sections. In fact, since discharge, we observed both a significant reduction in SPAP and a significant increase in longitudinal RV systolic function as shown by the increase in TAPSE and RV-Sm. Otherwise, no significant differences in the RV size were observed after the procedure and during the follow-up. In fact, correct size determination of the RV is difficult by two-dimensional echocardiography due to the complexity of the RV anatomy. Unfortunately, we did not perform three-dimensional echocardiography that can accurately quantify RV cavity volumes and SVs without geometric assumptions.15 Furthermore, we reported a positive LA remodelling both at discharge and 6-month follow-up, with minor changes regarding the RA dimensions. Volume overload, in chronic MR, progressively leads to LV and LA remodelling.16 The increased LA compliance for a long time is able to maintain a low average atrial pressure, which gives an account of the long asymptomatic period present in these patients. However, as the disease advances, there is a progressive increase in left filling pressures, which ultimately involves the development of a significant pulmonary hypertension in almost half of the patients.3 In healthy subjects, systolic function of the RV is much more sensitive to volume overload than to pressure overload.17–21 Indeed, RV may tolerate volume overload for a long time without a significant decrease in RV function. In contrast to volume-overload states,
moderate-to-severe chronic increased in the RV afterload at first induces the remodelling of RV and RA and afterwards leads to RV dilatation and failure. In patients with severe MR, the RV dysfunction (given mainly by impairment of the longitudinal shortening of the ventricular fibres) is associated with increased morbidity and mortality.22–25

Percutaneous and surgical mitral valve repair (MitraClip), decreasing the LV volume overload, has been shown to result in reverse LV remodelling and LA remodelling.4,7,12,14,26

Both the improvement in the haemodynamic state and the reverse remodelling of the LV should be associated with a substantial reduction in the RV afterload. This should increase RV systolic function, already in the acute phase, and progressively should lead to favourable RV remodelling as well as demonstrated by surgical mitral valve repair.23

According to these findings, we demonstrated a significant mild correlation between the TAPSE improvement and NYHA class improvement ($r = -0.41, P = 0.05$).

Furthermore, the evaluation of RV chamber function is crucial in patients with severe MR at end-stage heart failure. Recently, Neuss et al. have demonstrated that a TAPSE $< 15$ mm at baseline is a negative predictor of combined events after PMVR ($P < 0.001$).27 In these patients, with reduced RV function, the indication for PMVR should be reconsidered.

**Global haemodynamic effects of MitraClip implantation**

According to the two studies which performed invasive haemodynamic monitoring with a Swan Ganz catheter, in the present work, the SV and the cardiac index significantly increased after MitraClip implantation, in parallel with a reduction in pulmonary artery and wedge pressure, which are predictive of an improved clinical outcome after 7–8 months.28,29 In these studies, there is a discrepancy about the behaviour of LV end-systolic pressure, in fact in Gaemperli study, LV end-systolic pressure does not reduce while Siegel et al. documented a significant reduction in LV end-systolic pressure. Also, in our study, LV-Em (expression of LV end-systolic pressure) does not significantly change before and after MitraClip procedure; a possible explanation could be that eliminating regurgitant flow into the LA reduces pulmonary pressures, while the acute increase in afterload (due to the removal of the low impedance regurgitant flow) imposed on a compromised LV was responsible for the lack of change in left ventricular end-diastolic pressure. According to these two studies, cardiac index increased in our study indicating that the positive effect of reducing regurgitant flow out-weighted the potentially harmful increase in afterload and thereby improved cardiac forward output.

**Study limitations**

The major limitations of the present study included its observational nature and relatively small sample size. However, a comparison with a surgical cohort was missing, and this will be the objective of future investigations. We did not perform calculations of the effective regurgitant orifice area using the PISA method before and after PMVR with MitraClip. This method has not been validated for double-orifice mitral valves and therefore the validity of results after PMVR would have been questionable.

**Conclusions**

It has been demonstrated that the surgical or PMVR, decreasing the LV volume overload, can lead LV chambers reverse remodelling. Our study have confirmed that the positive LV remodelling after PMVR with the MitraClip system, showing significant improvements in LV size and function. The concomitant reduction in LV filling pressure, obtained after MitraClip implantation, reflected nearly immediately on clinical profile and on haemodynamics of the right sections. In fact, since discharge, we observed both a significant reduction in SPAP and a significant increase in longitudinal RV systolic function as shown by the increase in TAPSE and RV-Sm. Future larger studies are needed to confirm our findings.

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**References**

10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellika PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440–63.
on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J 2010;31:1373–81.


