Immediate effect of the MitraClip® procedure on mitral ring geometry in primary and secondary mitral regurgitation

Frank Patrick Schmidt*,†, Ralph Stephan von Bardeleben*†, Philipp Nikolai, Alexander Jabs, Nina Wunderlich, Thomas Münzel, Ulrich Hink, and Ascan Warnholtz*

Department of Medicine II, University Medical Center of Johannes Gutenberg-University Mainz, Langenbeckstr. 1, Mainz 55131, Germany

Received 28 July 2012; accepted after revision 24 November 2012; online publish-ahead-of-print 2 January 2013

Aims
Percutaneous treatment of mitral regurgitation (MR) has been shown to reduce MR severity and improve functional outcomes. Surgical treatment of MR usually includes mitral annulus reduction. The influence of the MitraClip® on annulus geometry is not clear. We wanted to investigate whether the procedure itself reduces annulus diameter and if there may be differences between secondary or functional (SMR) and primary (PMR) MR.

Methods and results
We retrospectively assessed 3D echocardiography (3D-TEE) data of 55 patients acquired during the procedure shortly before and after clip placement for changes in annulus diameter and area. Measurements were done with QLAB software. Patients were categorized as having either SMR (n = 41) or PMR (n = 14). In SMR, we were able to demonstrate a significant reduction in annulus area (mean Δ1.30 ± 1.44 cm²; P < 0.001), anterior-posterior (AP)-diameter (mean Δ 0.28 ± 0.32 cm; P < 0.001), tenting area (mean Δ 0.39 ± 0.49 cm²; P < 0.001). No significant change could be found for latero-medial (LM)-diameter. In contrast, we could not demonstrate significant changes in any of the parameters described above in patients with PMR.

Conclusion
Percutaneous treatment with the MitraClip® device can produce immediate reductions in mitral annulus size in SMR, probably supporting procedural success. It also reduces tenting, which may have prognostic implications. In contrast, these effects on mitral geometry cannot be demonstrated in PMR. Knowledge of this difference between SMR and PMR may be important to improve procedural strategies.

Keywords
Mitralseal geometry • MitraClip® • Mitral regurgitation • 3D echocardiography

Introduction
Interventional treatment for moderate-to-severe mitral regurgitation (MR) is an effective option for symptomatic patients with high operative risk. The MitraClip® procedure has shown its ability to reduce regurgitation severity and improve clinical symptoms. Although the EVEREST trials1,2 enrolled primarily patients with primary or degenerative MR (PMR), in current clinical practice, the majority of patients selected for MitraClip® therapy have functional or secondary MR (SMR).1,4 The surgical double-orifice technique that served as a model for the percutaneous procedure was initially developed for patients with mainly anterior leaflet degenerative MR.3 Although most surgical patients received annuloplasty in addition to leaflet suture, it has been demonstrated that double-orifice technique alone was able to produce acceptable results in selected patients,3 however, patients with additional annuloplasty appeared to have better mid-term results overall.6 Therefore, a number of interventional approaches have attempted to replicate annuloplasty but have not reached routine clinical practice yet.7

* Corresponding author. Tel: +49 6131 173641 (F.P.S.)/+49 6131 172892 (R.S.v.B.)/+49 6131 173746 (A.W.), Email: frank.schmidt@unimedizin-mainz.de (F.P.S.)/ralph_stephan.von_bardeleben@unimedizin-mainz.de (R.S.v.B.)/warnholt@uni-mainz.de (A.W.).
† F.P.S. and R.S.v.B. contributed equally to this manuscript.
Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2013. For permissions please email: journals.permissions@oup.com
In today’s practice, percutaneous edge-to-edge repair is predominantly used for functional MR.

Whereas annuloplasty is usually performed in addition to the Alfieri stitch, the MitraClip® procedure is not accompanied by a supporting ring device.

In order to improve outcomes and patient selection for percutaneous treatment, it is important to understand how the procedure achieves reductions in regurgitation severity and clinical improvement.

Effects of clipping may differ according to the aetiology of MR and mitral valve geometry. A more detailed understanding of MR mechanisms has been facilitated by the use of real-time three-dimensional transoesophageal-echocardiography (RT3D TEE) and will be necessary for improving percutaneous valvular interventions.

RT3D-TEE has more or less become the standard imaging technique for procedural guidance of MitraClip® implantation and its use is recommended by recent guidelines. Measurement of mitral annulus area by 3D-echocardiography is accepted as an accurate method and a comparator for other methods. We intended to use echocardiographic data recorded during interventional guiding to gain more insights into the immediate effects of Mitra-Clip® therapy on the mitral valve apparatus in different forms of pathology. Having noticed early changes to mitral valve geometry in patients undergoing the percutaneous intervention in our daily practice, we wanted to investigate whether this effect can be replicated for larger patient groups and if the MitraClip® can possibly produce a ‘small annuloplasty’ of its own.

**Methods**

We retrospectively assessed all patients treated with the MitraClip® at our centre in whom intra-procedural RT3D-TEE volume data sets were available in adequate quality immediately before and after placement of the device. All procedures were performed under general anaesthesia with a dedicated anaesthesiologist and intra-procedural haemodynamic monitoring. 3D-TEE imaging data were acquired as median and interquartiles, unless indicated otherwise). Measurement of mitral annulus area by 3D-echocardiography is accepted as an accurate method and a comparator for other methods. We intended to use echocardiographic data recorded during interventional guiding to gain more insights into the immediate effects of Mitra-Clip® therapy on the mitral valve apparatus in different forms of pathology. Having noticed early changes to mitral valve geometry in patients undergoing the percutaneous intervention in our daily practice, we wanted to investigate whether this effect can be replicated for larger patient groups and if the MitraClip® can possibly produce a ‘small annuloplasty’ of its own.

Clinical and echocardiographic data were obtained from electronic medical records. MR severity was graded by experienced examiners according to European guidelines, which emphasize vena contracta width. Grades were then translated into the four-grade system used in the EVEREST trials described elsewhere.

Systolic pulmonary artery pressure was estimated by transthoracic echocardiography using peak systolic tricuspid regurgitation velocity. Mitral annular calcification was rated by pre-procedural TTE or TEE as absent (0), spotty (1), confined to anterior or posterior ring (2), or involving both anterior and posterior ring (3).

Statistical analysis with t-tests and non-parametric testing for paired samples was performed using IBM SPSS Statistics Version 20. Additional testing and graphical rendering of results was done using GraphPad Prism version 5.0b for MacOS X. (GraphPad Software, San Diego, CA, USA). The Kolmogorov–Smirnov test was used to assess whether the data were normally distributed. T-test and one-factorial ANOVA testing was performed on normally distributed data (presented as mean ± standard deviation), the Mann–Whitney U-test or the Wilcoxon test were used for non-normally distributed data (presented as median and interquartiles, unless indicated otherwise). P-values <0.05 were considered significant.

**Results**

We identified 55 out of 64 patients with adequate data for analysis. Patient characteristics are shown in Table 1. Percutaneous mitral-valve intervention with the MitraClip® resulted in a median reduction of 2 grades of MR severity (0–4; mean 2.118) (Figure 2). Concomitantly, a reduction of invasively measured sPAP from a mean of 47.5 ± 16.7 mmHg to a mean sPAP of 41.7 ± 10.6 was achieved. Likewise estimated sPAP (by TTE) was reduced from 47 ± 13.6 mmHg to a mean of 39 ± 10.5 mmHg at discharge. Left-ventricular end-diastolic volume (LVEDV) was already slightly but significantly reduced at discharge (LVEDV post = 164.6 ± 82.8 vs. 174.4 ± 82.9, P = 0.039), while ejection fraction remained unchanged.

Statistical testing did not show significant differences in pre-discharge MR severity or MR reduction between SMR and PMR groups. Similarly, there was no difference in mean pulmonary capillary wedge pressure (mPCWP) after clip placement between the groups (P = 0.233). Compared with pre-interventional measurements, we found statistically robust reductions in annulus area
Effect of Mitra Clip procedure on Mitral geometry

(meanΔ 1.30 ± 1.44 cm²; P < 0.001), AP-diameter (meanΔ 0.28 ± 0.32 cm; P < 0.001), tenting area (meanΔ 0.39 ± 0.49 cm²; P < 0.001), and tenting height (meanΔ 0.074 ± 0.217; P = 0.04) for patients with SMR as shown in Figure 3. This corresponds to a mean relative reduction of 13.4% for annulus area, 9.8% for AP-diameter, and 21.4% for tenting area. There were no significant changes in LMDs.

In contrast, we could not find any significant changes in diameters or annulus area (P = 0.803) in patients with primary (mostly degenerative) aetiology (PMR). Comparing reduction in annulus area and AP-diameter, we could not find significant differences between patients with one or two clips in both PMR and SMR (Figure 4).

Similarly, we could not demonstrate a significant difference between more or less calcification of mitral apparatus despite numerically higher mean reduction in AP-diameter in non-calcified valves (0.40 ± 0.64 vs. 0.22 ± 0.34 cm). There was no significant correlation between reduction in annulus area or AP-diameter and post-interventional mean pressure gradients over the mitral valve (P = 0.813 and 0.116) as a measure of mitral stenosis. Development of gradients or of mitral stenosis seems to be more related to properties of the leaflets than to annulus size. In our cohort, we could not verify a correlation between achieved AP diameter reduction and reduction in MR severity (Figure 5). Also we could not find a significant correlation between initial annulus area and procedural success as expressed by reduction in MR grade (P = 0.293). No significant gender differences were seen in our analysis.

Comparing pre- and post-procedural mitral annular circumference measured with TomTec CardioView 4.1, we could not find a statistically significant difference in circumference (13.56 ± 1.34 vs. 13.42 ± 1.30; P = 0.355) (Figure 6). This can be seen as supporting evidence for the validity of our measurements by ruling out relevant differences in cutting planes due to temporal or spatial resolution constraints. In order to determine interobserver variability, measurement of AP- and LM-diameters was independently performed in 22 cases by two experienced readers. There were very good interobserver correlations for AP-diameter

(Figure 1 Measurement of mitral annulus diameters and area from 3D data. For measurements, an end-systolic volume was chosen, image settings (gain etc.) were adjusted, and image plains were aligned optimally. Measurements included tenting height (D4), tenting area (A1), AP-diameter (D1), LM-diameter (D2), and mitral annulus area (A2).)
Table 1  Patient characteristics and comorbidities in SMR and PMR

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total</th>
<th>SMR</th>
<th>PMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>55</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>Age, years</td>
<td>75.3±(49–86)</td>
<td>73.6</td>
<td>76.2</td>
</tr>
<tr>
<td>Sex ratio (m:f)</td>
<td>36:19</td>
<td>31:10</td>
<td>5:9</td>
</tr>
<tr>
<td>log EuroSCORE, %</td>
<td>35.7±(4–88)</td>
<td>38.3</td>
<td>13.4</td>
</tr>
<tr>
<td>MR severity 3:4, %</td>
<td>60.40</td>
<td>61.39</td>
<td>57.43</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35.6±(15–60)</td>
<td>30.6</td>
<td>51.3</td>
</tr>
<tr>
<td>LVEF ≤40% (%)</td>
<td>65.3</td>
<td>61.1</td>
<td>16.7</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>174.4±82.9</td>
<td>197.8±82</td>
<td>106.1±33.6</td>
</tr>
<tr>
<td>NYHA class (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10.9</td>
<td>2.4</td>
<td>35.7</td>
</tr>
<tr>
<td>III</td>
<td>65.5</td>
<td>73.2</td>
<td>42.8</td>
</tr>
<tr>
<td>IV</td>
<td>23.6</td>
<td>24.4</td>
<td>21.4</td>
</tr>
<tr>
<td>LBBB, %</td>
<td>16.1</td>
<td>22.0</td>
<td>0</td>
</tr>
<tr>
<td>CRT, %</td>
<td>14.3</td>
<td>19.5</td>
<td>0</td>
</tr>
<tr>
<td>CAD, %</td>
<td>75.5</td>
<td>83.8</td>
<td>50</td>
</tr>
<tr>
<td>PAD, %</td>
<td>26.5</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>AF, %</td>
<td>61.2</td>
<td>56.8</td>
<td>75</td>
</tr>
<tr>
<td>CKD, %</td>
<td>59.2</td>
<td>67.6</td>
<td>33.3</td>
</tr>
<tr>
<td>COPD, %</td>
<td>12.2</td>
<td>16.2</td>
<td>0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6±3.8</td>
<td>26.0</td>
<td>24.8</td>
</tr>
<tr>
<td>Annulus area, cm²</td>
<td>10.53±2.57</td>
<td>10.78±2.37</td>
<td>9.79±3.04</td>
</tr>
<tr>
<td>AP-diameter, cm</td>
<td>2.88±0.52</td>
<td>2.99±0.46</td>
<td>2.56±0.56</td>
</tr>
<tr>
<td>LM-diameter, cm</td>
<td>4.06±0.50</td>
<td>4.11±0.43</td>
<td>3.93±0.67</td>
</tr>
<tr>
<td>Tenting area, cm²</td>
<td>1.53±0.90</td>
<td>1.84±0.77</td>
<td>0.56±0.36</td>
</tr>
<tr>
<td>sPAP, mmHg</td>
<td>46.8±13.6</td>
<td>46.24±12.83</td>
<td>49.0±17.0</td>
</tr>
<tr>
<td>mPCWP, mmHg</td>
<td>18.4±7.86</td>
<td>19.9±7.80</td>
<td>13.77±6.26</td>
</tr>
</tbody>
</table>

LVEF, left-ventricular ejection fraction by echo; LVEDV, end-diastolic left-ventricular volume; NYHA, New York Heart Association functional class; LBBB, left bundle branch block; CRT, cardiac resynchronization therapy; CAD, coronary artery disease; PAD, peripheral arterial disease; AF, atrial fibrillation; CKD, chronic kidney disease stage 3 or more; COPD, chronic obstructive pulmonary disease; BMI, body mass index; sPAP, systolic pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure. Data are presented as mean±SD or as mean (minimum–maximum value), if more informative.

Discussion

We were able to demonstrate that the MitraClip® procedure does produce an immediate reduction in mitral annulus area in patients with secondary or functional MR. This reduction was mainly caused by a reduction of the anterior–posterior mitral-valve diameter. We did not find a significant change in latero-medial diameter, which seems to be in line with mechanistic considerations. Post-implantation tenting height and area were also significantly reduced compared with pre-implantation values, which may also be an important effect of the procedure.

In vitro as well as clinical studies of the surgical edge-to-edge repair have demonstrated decreased efficacy without reduction of annular dilatation. However, percutaneous edge-to-edge repair despite its similarities is a different procedure and the use of a clip has different mechanical effects compared with the suture technique. We have demonstrated that ‘clipping’ can by
itself reduce annular dilatation in SMR even before relevant ventricular remodelling can occur. The device can apparently create enough traction on the annulus–valve–papillary muscle apparatus to have immediate effects beyond the leaflets.

For the Alfieri technique, progressive dilatation of the annulus has been demonstrated in patients without additional annuloplasty. The tissue bridge that builds around the clip may stabilize the annulus in the percutaneous approach as suggested before. Although the reductions in area and diameter are small in absolute terms, their contribution to procedural success may be relevant. The extent of reductions varies widely, but in several cases reductions almost comparable to surgical or interventional annuloplasty of around 30% for AP-diameter and annulus area were achieved and seem possible in suitable patients.

Since remodelling or even left-ventricular volume reduction are unlikely causes of this immediate change in annular geometry, direct traction exerted by the clip on the mitral leaflets is most likely responsible for changes to the mitral apparatus. The forces involved can be expected to be higher than those exerted by the suture technique, which have been shown to correlate with annulus diameter. A hypothesis could be that if mitral geometry can be altered adequately, MR is reduced and ventricular remodelling will occur in SMR. The ability of the procedure to induce reverse remodelling has already been shown.

In contrast to those findings in SMR, we could not show a significant reduction of annulus size in patients with PMR, despite similar reduction in MR severity and no significant difference in mPCWP between both groups. This seems intuitive from a mechanistic standpoint since in the presence of excess tissue and leaflet length in most cases of PMR, the procedure will not exert significant traction on the annulus. It also supports the notion that the changes found in the SMR group are indeed a result of direct traction and not due to haemodynamic changes, since those should have occurred in the PMR group as well.

Differences in annulus geometry have been shown to produce different strain on mitral leaflet tissue, which may induce structural changes and affect durability. It is unclear if this may lead to different durability and long-term outcomes in functional vs. degenerative disease or if this only demonstrates differential mechanisms of the procedural effect.

We could not find a significant difference in annular reduction between cases in which one or two devices were placed. This suggests that the first device may already reduce annulus size and additional clips may have more of a stabilizing or modifying effect on the regurgitant orifice. However, since two or more clips are usually reserved for patients with inadequate reduction in MR with placement of one clip, this may represent a different patient subpopulation and within the individual patient, additional clips could lead to greater reduction in annulus size.

Recently, others have seen a non-significant trend linking initial annulus area to achieved reduction in MR. From our data, we could not support this link (P = 0.293). Therefore, patients with...
large annulus areas should not be excluded from percutaneous edge-to-edge repair at this time.

Other factors may influence the effects of percutaneous edge-to-edge repair on mitral geometry. In patients treated with the double-orifice technique, calcification of the mitral ring has been identified as a predictor of suboptimal results with edge-to-edge repair, an effect that we could not show in our data set possibly due to insufficient sample size.

The use of 3D-volumes in this study has advantages over conventional imaging in obviating the need for geometrical assumptions and allowing more accurate image plane selection for measurements. The ability to follow movements during the heart cycle makes measurement of the annulus area at defined time-points possible. Limitations are the retrospective evaluation of available images and the outcome-oriented nature of the procedure. The latter makes it difficult to demonstrate differences in acute results, e.g., MR reduction. Although we used state-of-the-art imaging equipment and analysis software, RT3DE still has some limitations with regard to spatial and temporal resolution. Especially with higher heart rates, time differences between frames/volumes are sometimes too large to compare exactly the same part of the heart cycle. This leads to differences in annulus geometry, which explains why we measured larger diameters after the procedure in a small number of study patients.

The findings of this study suggest different effects of Clip placement in PMR and SMR. The clip reduces hypermobility, straightens the leaflets, and preserves coaptation throughout systole in PMR, while it does not significantly alter the mitral annulus. In SMR, the device reduces tenting and annulus area, thereby enhancing coaptation and producing adequate coaptation length.

The procedure will reduce annular AP-diameter and area in most SMR-patients even before release of the device. These changes could be quickly assessed during the procedure and results would be available to guide decisions on location and number of clips to be placed for optimal results. Whether the immediate effects of clipping on mitral annulus geometry correlate to durable MR reduction and favourable clinical outcomes should be addressed in further studies. Data on the stability of observed mediates effects of clipping on mitral annulus geometry correlate to number of clips to be placed for optimal results. Whether the im-

ment in PMR and SMR. The clip reduces hypermobility, straightens the leaflets, and preserves coaptation throughout systole in PMR, while it does not significantly alter the mitral annulus. In SMR, the device reduces tenting and annulus area, thereby enhancing coaptation and producing adequate coaptation length.

The procedure will reduce annular AP-diameter and area in most SMR-patients even before release of the device. These changes could be quickly assessed during the procedure and results would be available to guide decisions on location and number of clips to be placed for optimal results. Whether the immediate effects of clipping on mitral annulus geometry correlate to durable MR reduction and favourable clinical outcomes should be addressed in further studies. Data on the stability of observed annulus changes over time and the association with MR reduction and clinical outcomes in follow-up is warranted. However, data from early trials of the device show stability in annulus diameter at 1 year and stable reduction in MR for the majority of patients.

The reduction in tenting area demonstrated in this study might also have prognostic implications. In a population of patients with SMR, tenting area has previously been shown to constitute a significant predictor of clinical outcomes such as death and hospitaliza-

Conflict of interest: none declared.

References


19. Aurichio A, Schilling W, Meyer S, Maisano F, Hoffmann R, Ussia GP et al. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy in SMR. The clip reduces hypermobility, straightens the leaflets, and preserves coaptation throughout systole in PMR, while it does not significantly alter the mitral annulus. In SMR, the device reduces tenting and annulus area, thereby enhancing coaptation and producing adequate coaptation length.

The procedure will reduce annular AP-diameter and area in most SMR-patients even before release of the device. These changes could be quickly assessed during the procedure and results would be available to guide decisions on location and number of clips to be placed for optimal results. Whether the immediate effects of clipping on mitral annulus geometry correlate to durable MR reduction and favourable clinical outcomes should be addressed in further studies. Data on the stability of observed annulus changes over time and the association with MR reduction and clinical outcomes in follow-up is warranted. However, data from early trials of the device show stability in annulus diameter at 1 year and stable reduction in MR for the majority of patients.

The reduction in tenting area demonstrated in this study might also have prognostic implications. In a population of patients with SMR, tenting area has previously been shown to constitute a significant predictor of clinical outcomes such as death and hospitalization.

Measuring tenting area after device implantation has not been sufficiently validated, however, it seems reasonable that tenting area reduction may be an indicator for the effect of the device on valve function in SMR. It may even be an additional objective of percutaneous intervention, if proved to be valid. In PMR, measuring tenting is of no conceivable value since there should be no tenting.

Despite being modelled after a procedure for the treatment of PMR, the device is doing remarkably well in SMR. We were able to demonstrate different effects of MitaClip® therapy in SMR and PMR in this study. Understanding the mechanisms behind the procedure is important when trying to improve patient selection and device placement.


Occlusion of persistent levoatrial cardinal vein without left heart hypoplasia utilizing an Amplatzer device

Paolo Ciliberti*, Andrew M. Taylor, Robert Yates, and Alessandro Giardini
Cardiorespiratory Unit, Great Ormond Street Hospital for Children, Great Ormond Street, London WC1N 3JH, UK
* Corresponding author. Tel: +44 207 4059200; fax: +44 207 7626728. Email: paolo.ciliberti@gosh.nhs.uk

An 18-year-old male was referred with a complaint of progressive exercise intolerance and systolic murmur. Echocardiography showed an atrio-ventricular septal defect with no atrial or ventricular component. There was no left atrio-ventricular valve stenosis, but mild regurgitation was present. Pulmonary venous drainage was normal but the modified parasternal short-axis view (Panel A; see Supplementary data online, Video S1) revealed a levoatrial cardinal vein (LACV) originating from the roof of the left atrium (LA) that ran parallel to the descending thoracic aorta and drained into the innominate vein (IV) (Panel B; see Supplementary data online, Video S2).

Cardiac magnetic resonance imaging (Panels C and D) confirmed the anomalous venous connection (arrow) between the roof of the LA and the IV, associated with a 1.5:1 pulmonary to systemic blood flow and mild right ventricular dilation. At angiography, the LACV measured 12 mm in diameter at the mid-course (Panel E; see Supplementary data online, Video S3). To minimize the risk of embolization, a 16 mm Amplatzer atrial septal defect occluder was used to block the LACV (Panel F, red arrow; see Supplementary data online, Video S4), with no complication.

Persistence of LACV has been associated with congenital mitral stenosis and other left-sided obstructive lesions, but it is rare in their absence. In this setting it is thought that the persistence of this embryonic connection between the embryonic pulmonary venous bed and the cardinal veins could act as ‘safety-valve’ able to drain the pulmonary venous blood into the systemic circulation, thus minimizing pulmonary venous congestion.

Percutaneous occlusion of the anomalous vein with a carefully selected Amplatzer device is a safe and effective option in this setting, and to the best of our knowledge it has been never reported before.

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.