Assessment of Mitral Valve Area during Percutaneous Mitral Valve Repair using the MitraClip™ System: Comparison of Different Echocardiographic Methods

Biaggi et al: Assessment of MV Area During MitraClip Repair

Patric Biaggi, MD;* Christian Felix, MD*; Christiane Gruner, MD, Bernhard A. Herzog, MD; Sabine Hohlfeld, MD; Oliver Gaemperli, MD; Barbara E. Stähli, MD; Michaela Paul, PhD, Leonhard Held, PhD; Felix C. Tanner, MD; Jürg Grünenfelder, MD; Roberto Corti, MD and Dominique Bettex, MD

From the Echocardiography (PB, CG, BH, SH, FCT) and the Andreas Grüntzig Cardiac Catheterization Laboratories (OG, BS, RC), Cardiology; from Cardiovascular Surgery (JG), University Hospital Zurich, Switzerland, and the Institute for Social and Preventive Medicine (MP, LH), University of Zurich; Zurich, Switzerland

*Both authors equally contributed to this manuscript.

Correspondence to
Patric Biaggi, MD
Echocardiography Laboratory
Cardiology, Cardiovascular Center
University Hospital Zurich
Ramistrasse 100
8091 Zurich
Switzerland
Tel: +41 44 255 3979
Fax: +41 44 255 4401
Email: pbiaggi@gmx.ch

DOI: 10.1161/CIRCIMAGING.113.000620

Journal Subject Code: Treatment:[23] Catheter-based coronary and valvular interventions:other
Abstract

Background—Quantification of the mitral valve area (MVA) is important to guide percutaneous mitral valve repair using the MitraClip™ system. However, little is known how to best assess MVA in this specific situation.

Methods and Results—Immediately pre and post MitraClip implantation, comprehensive three-dimensional transesophageal echocardiography (3D TEE) data were acquired for MVA assessment by pressure half-time method (MVA_{PHT}) and by two 3D quantification methods (mitral valve quantification software (MVA_{MVQ}) and 3D quantification software (MVA_{3DQ})). In addition, transmitral gradients by continuous-wave Doppler (dP\text{mean}_\text{CW}) were measured to indirectly assess MVA. Data are given as median (interquartile range). 33 patients (39% women) with a median age of 77.1 (12.4) years were studied. Pre intervention, the median MVA by PHT, MVQ and 3DQ were 4.4 (2.0) cm\(^2\), 4.7 (2.4) cm\(^2\) and 6.2 (2.4) cm\(^2\), respectively (p < .001). Post intervention the MVA was reduced to 1.9 (0.7) cm\(^2\), 2.1 (1.1) cm\(^2\) and 2.8 (1.1) cm\(^2\), respectively (p = .001). The median values for dP\text{mean}_\text{CW} pre and post intervention were 1.0 (1.0) and 3.0 (3.0) mmHg (p < .001). At discharge, the median dP\text{mean}_\text{CW} was 4.0 (3.0) mmHg. In multivariate regression analyses including body surface area, the three different MVA methods and dP\text{mean}_\text{CW}, a post dP\text{mean}_\text{CW} \geq 5\text{mmHg} was the best independent predictor of an elevated transmitral gradient at discharge.

Conclusions—Transmitral gradients by continuous-wave Doppler are quick, feasible in all patients and superior to direct peri-interventional assessment of MVA. A post-interventional transmitral gradient by continuous-wave Doppler of \geq 5\text{mmHg} best predicted elevated transmitral gradients at discharge.

Key Words: mitral valve regurgitation, mitral stenosis, percutaneous mitral valve repair, transesophageal echocardiography, 3-dimensional, MitraClip
Percutaneous mitral valve repair (MVR) using the MitraClip™ system has emerged as an alternative treatment option for patients with severe mitral regurgitation and a high surgical risk for surgical MVR. The EVEREST II trial has demonstrated that percutaneous MVR is effective in reduction of mitral regurgitation (MR), improvement of clinical symptoms and induction of reverse left ventricular remodeling. As an intended side effect, percutaneous MVR using the MitraClip™ system leads to a reduction of the mitral valve orifice area (MVA). In order to prevent post-procedural mitral valve stenosis, the presence of a MVA < 4cm² was an exclusion criteria in the EVERST trial.

The assessment of MVA is crucial for the detection of a mitral stenosis and hence for decision-making during percutaneous MVR. While the 2009 European and American guidelines recommend two-dimensional (2D) planimetry and the use of the pressure half-time (PHT) method to assess MVA in native mitral stenosis, the 2011 recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease do not specify how to assess MVA during percutaneous MVR. Three-dimensional transesophageal echocardiography (3D TEE) has the potential of becoming the method of choice for MVA assessment. Historically however, invasive measurements were used for the validation of the PHT method for assessment of MVA in stenotic native valves.

The aim of this study was to compare different 2D and 3D echocardiographic methods of MVA assessment as well as invasive MVA calculations and to define which of these measurements best predicts an elevated transmitral gradient at discharge.

Methods

Patient population

We included consecutive patients undergoing percutaneous MVR using the MitraClip™ system at the University Hospital Zurich, Switzerland. Patients were selected for the
procedure according to the current guidelines on valvular heart disease and as previously published.\textsuperscript{1, 10, 11} The clinical patient data were obtained by chart review. All patients gave written informed consent for inclusion in a prospective MitraClip registry (MitraSwiss registry). The protocol of the MitraSwiss registry was approved by the local institutional review board.

**Echocardiography**

TEE was performed using a Philips iE33 platform and an X7-2t real-time 3D transesophageal echocardiography probe (Philips Medical Systems, Andover, MA). A 2D TTE was performed in all patients at the time of discharge. All measurements were performed according to the guidelines.\textsuperscript{12} Mitral regurgitation was graded mild (1+), moderate (2+), moderate to severe (3+) and severe (4+).\textsuperscript{11} Mitral stenosis was defined by a MVA less than 2cm\textsuperscript{2}: mild (1.5-1.99cm\textsuperscript{2}), moderate (1.0-1.49cm\textsuperscript{2}), and severe (< 1cm\textsuperscript{2}). In addition, a mean transvalvular gradient $\geq$ 5mmHg was considered as stenosed mitral valve.\textsuperscript{4, 13} Immediately before the start of the procedure and after the last clip was placed, continuous wave (CW) Doppler of mitral valve inflow was used for assessment of the mean gradient across the mitral valve ($dP_{\text{mean,CW}}$) and of the MVA by PHT (MVA\textsubscript{PHT}).\textsuperscript{9} The beam of the continuous wave Doppler was located in the center of the largest orifice after clipping in order to obtain a good quality Doppler spectrum. In addition full volumes (median frame rate = 23 Hz (9Hz)) or 3D zoom loops (median frame rate = 12 Hz (3Hz)) of the mitral valve were acquired (Figure 1 A/B). Two different methods were used for 3D measurement of the MVA: the **Mitral Valve Quantification** software (MVA\textsubscript{MVQ}, Figure 1 C/D) and **3D Quantification** software (MVA\textsubscript{3DQ}, Figure 1 E/F), both by Philips Medical Systems, Andover, MA. MVQ is a specific software for 3D quantification of the mitral valve, and its use has previously been described.\textsuperscript{14, 15} We used 28 landmarks to delineate the annulus and analyzed the mitral
leaflets using up to 22 intersections per patient. The version 8.1 used in this study works identically to previous versions, with the addition of measuring MVA when the analysis is performed in diastole at the time of the peak valve opening (usually early diastole, Figure 1C/D). 3DQ is widely used for quantitation in 3D but is not a specific mitral valve quantification software (Figure 1 E/F). The mitral valve can be displayed using three orthogonally orientated planes. In order not to overestimate the MVA, the plane in which the measurement is performed is orientated perpendicularly to the valve leaflets.\textsuperscript{16,17} Post clipping, we adjusted the measurement plane separately for each orifice if necessary.

**Invasive measurements:**

In a subset of 14 patients, invasive measurements were performed immediately before MitraClip\textsuperscript{TM} implantation and repeated after deployment of the last clip as previously described.\textsuperscript{10,11} A Swan-Ganz catheter was used to measure mean pulmonary capillary wedge pressure (mPCWP), systolic pulmonary artery pressure (sPAP) and pulmonary artery oxygen saturation. The left atrial pressure (LAP) was measured through the transseptal needle sheath (8F, at the beginning of procedure) and through the 24F MitraClip sheath after the procedure. A pigtail catheter was placed into the left ventricle for measurement of the left ventricular end-diastolic pressure (LVEDP), the transmitral gradients (dPmean\textsubscript{INV}) and for measurement of systemic artery oxygen saturation as previously described.\textsuperscript{10,11} The cardiac output and the MVA area were calculated using the Fick principle\textsuperscript{18} and according to the Gorlin formula (MVA\textsubscript{Gorlin}), respectively.\textsuperscript{19}

**Statistical analyses:**

Continuous data are expressed as median and interquartile range (IQR), and categorical data as number and percentage (%). Continuous data were compared using the Wilcoxon signed-
rank test, and categorical data were analyzed using the chi-Square or Fisher’s exact test, as
appropriate. We used the Bland-Altman method and one factorial ANOVA with Kruskal-
Wallis test for the comparison of the different MVA methods. We fitted univariable and
multivariable linear regression models with dPmeanCW at discharge as outcome variable.
Three different models of multivariable analyses were considered by inclusion of the
clinically most meaningful factors of the univariable linear regression analysis (body surface
area, the three different methods of measuring MVA as well as dPmeanCW). An optimal cutoff
for predicting an elevated transmitral gradient at discharge has been selected using the
minimal p-value approach.20 The ability of post-interventional dPmeanCW to predict elevated
dPmeanCW at discharge was quantified by calculation of the receiver operating characteristic
(ROC) analysis and calculation of the area under the curve (AUC) as well as sensitivity,
specificity, positive and negative predictive values for the determined cut-off value. A
smoothed ROC curve and 95% (bootstrap) confidence intervals for the AUC were obtained
using a binormal model.21 We used intraclass correlation coefficient (ICC) to test for inter-
and intraobserver variability. A p-value of < .05 was considered statistically significant
without adjustment for multiple testing. Statistical analyses were performed using R, version
2.15.2 (R Development Team, Vienna, Austria, 2011) and SPSS software (release 21.0, SPSS

Results

Patient population

Of the 58 patients screened and undergoing percutaneous MVR, 33 were included in this
study. The patients of this study partially overlap with the populations recently published.10,
11 The main exclusion criteria were insufficient peri-procedural 3D image quality (n= 22) and
missing dPmeanCW at discharge (n = 3). The median age of patients included was 77.1 (12.4) years, and 39% were women (Table 1).

**Peri-procedural data**

Blood pressure, heart rate and sPAP did not change significantly during the intervention (Figure 2). 19 patients (58%) received 2 clips, while 9 patients (27%) received 1 clip and 5 patients (15%) 3 or more clips. The number of clips did not differ significantly between those developing stenosis and those without stenosis. The procedure resulted in significant reduction of mitral regurgitation, leaving 27 patients (75%) with only mild mitral regurgitation (Figure 3). However, the procedure led to a MVA < 2cm² in 61% of patients if assessed by PHT, in 39% if measured by MVQ and in 21% when quantified by 3DQ (Figure 3). Accordingly, the dPmeanCW increased from median (IQR) 1.0 (1.0) mmHg to 3.0 (3.0) post intervention (p <.001), leaving 11 patients (33%) with a mean gradient between 5mmHg and 10mmHg.

**Comparison of MVA by the different methods**

The MVA assessed by 3DQ method resulted in larger absolute valve size compared to assessment by PHT or MVQ (p < .001 pre and p = .001 post intervention, Figure 4). However, the percentage of change measured by the three methods was almost identical (between 54% and 56%, Figure 2). Post intervention, the bias [in brackets: limits of agreements] according to the Bland-Altman analysis were smallest for comparison of $MVA_{MVQ}$ with $MVA_{PHT}$ (0.0cm², [1.39]) and slightly greater for $MVA_{3DQ}$ with $MVA_{MVQ}$ (0.74cm², [1.23]) and $MVA_{3DQ}$ with $MVA_{PHT}$ (0.74cm², [1.49]). Intra-observer variability by ICC for MVA by MVQ and 3DQ was 0.996 (0.990 to 0.998) and 0.998 (0.996 to 0.999),
respectively. Inter-observer variability by ICC for MVQ and 3DQ were 0.991 (0.978 to 0.997) and 0.992 (0.980 to 0.997), respectively.

In a subset of 14 patients, MVA and transmitral gradients were assessed by invasive measurements in addition to all other parameters (Table 2). In contrast to the entire study population, the mean LAP pre and post clipping did not significantly change in the subgroup, while all other parameters performed comparably. Cardiac output increased significantly by 1.1 l/min (p = .02), however, the MVA_{Gorlin} and dPmean_{inv} did not show significant peri-interventional changes.

**Predictors of elevated transmital gradients at discharge**

Compared to immediately post intervention, the dPmean_{CW} at discharge increased from 3.0 (3.0) to 4.0 (3.0) mmHg (p<0.001), with 4 additional patients having elevated transmitral gradients. Univariable regression output for response to transmitral gradient at discharge are shown in Table 3. While heart rate and hemoglobin levels significantly changed from pre to discharge values (Figure 5), this did not significantly influence dPmean_{CW} at discharge. In the three multivariable models testing the different MVA methods, all regression coefficients are in the expected direction with decreasing BSA, decreasing MVA measurement and increasing post-interventional dPmean_{CW} predicting an increase in dPmean_{CW} at discharge. The effect of immediate post-interventional dPmean_{CW} was significant (p<.001) in all three formulations whereas there was only some evidence for the predictive value of BSA and any of the three post MVA measurements (Table 4). In the ROC analysis, the best cut-off values for predicting an elevated transmital gradient at discharge was a post-interventional dPmean_{CW} ≥ 5 mmHg (Figure 6).
Discussion

In this study on a prospective cohort of patients undergoing percutaneous MVR we compared MVA immediately pre and post intervention measured invasively and non-invasively by three different echocardiographic modalities. While the three echocardiographic modalities measured very similar relative reductions of MVA (between 53% and 56%), the absolute values varied considerably among the different techniques. In a multivariable linear regression analysis, the only consistent predictor of an elevated transmitral gradient at discharge was a post-interventional transmitral gradient by CW-Doppler of ≥5mmHg. No pre-interventional parameter was prognostic for the creation of a mitral stenosis, and invasive MVA measurements appeared invalid in this specific setting.

What is the best method to assess MVA during percutaneous MVR?

For invasive MVA calculations and adequate hemodynamic measurements, the setting of percutaneous mitral valve repair is unique: (1) Left ventricular and left atrial pressures and volumes change completely within a few heart beats after clip placement.10 (2) The patient is intubated and ventilated, leading to a reduction in left ventricular afterload, supra-normal oxygen saturation in the pulmonary artery and thus overestimation of left ventricular stroke volumes calculated using the Fick principle.11,18 (3) The procedure is associated with the creation of an atrial septal defect (ASD), further influencing stroke volume calculations due to left-to-right shunt. (4) Mitral regurgitation is not accounted for in the Gorlin formula and leads to overestimation of the degree of mitral stenosis.22 (5) Continuous measurement of left atrial pressure is not possible by the current generation of devices. Post-interventional left atrial pressure measurements can only be performed once the steering catheter is retrieved, hence after the release of a clip. These circumstances explain why invasive measurements of transmitral gradients and MVA using the Gorlin formula have lead to erroneous
measurements in our study and, due to the technical limitation, can not be used for decision making.

Assessment of MVA by echocardiography has a longstanding tradition, and has been validated in various settings. In our study, MVA_{PHT} pre and post intervention was very similar to that measured by MVQ method, but both measurements appeared to underestimate the true orifice. By PHT method, 20 (61%) patients had a post-interventional MVA < 2cm², whereas only 11 (33%) patients had elevated post-interventional transmitral gradients. The PHT method is validated in stenotic mitral valves as well as in patients with combinations of mitral stenosis and mitral regurgitation and is relatively flow independent. However, it is largely dependent of the left ventricular compliance, and its accuracy is lower in subjects with relevant diastolic dysfunction. In addition, it should not be used immediately after creation of an ASD by transseptal puncture as this overestimates the valve area. Furthermore, measuring MVA by PHT has been found to be a source of error immediately after mitral valvuloplasty and surgical MVR due to the acute change in loading conditions and change of valve geometry. All our patients had a combination of these conditions that limit the accuracy of the PHT method, which may explain the overall underestimation of MVA by PHT. The overestimation of MVA due to the ASD might be less relevant as long as the guidance catheter is in place. The underestimation of MVA_{MVQ} is technically driven as the software limits the tracing of the opening area near the commissures. While MVA_{MVQ} independently predicted mitral stenosis at discharge and thus might be closest to the ‘true’ MVA, the technique cannot be used for intra-procedural decision-making as advanced operator skills in 3D reconstruction are needed and the reconstruction is rather time intensive. Compared to MVA_{PHT} and MVA_{MVQ}, MVA_{3DQ} was larger both before and after intervention. Our results for MVA_{3DQ} are very similar to those recently published in the only other study using the same technique for MVA assessment. The 3DQ method tends to overestimate
MVA if the two or more orifices resulting from clipping are not calculated separately (Figure 7). While we followed this rule for measurement, we cannot exclude that slight overestimation of the MVA area has occurred due to relatively low spatial resolution of 3D datasets.

The degree of change during the procedure was very similar in all three methods, representing a good consistency in measurements. However, in the absence of a reference method for assessment of the MVA during and post percutaneous MVR and based on our results, we cannot determine the best method to directly assess MVA in this specific setting.

**Continuous wave Doppler is an alternative to MVA measurements**

An indirect way of assessing MVA or the risk of stenosis is measuring the transvalvular gradient by continuous wave Doppler. Values of 5mmHg or higher are associated with a moderate mitral stenosis in native valves, and CW Doppler measurements are valid in both single and double-orifice area mitral valves. Our results of post-interventional dPmeanCW were comparable to those published in the EVERST population and two European studies.

One of the limitations of CW Doppler measurements is its dependency of hemodynamic parameters such as hemoglobin levels and heart rate. In our study, the dPmeanCW measurements at discharge were higher than post-procedurally, but according to the univariate analysis the CW Doppler values at discharge were not influenced by the increase in heart rate and or the decrease in hemoglobin levels.

Can CW Doppler be used instead of direct peri-interventional MVA assessment to prevent mitral stenosis during percutaneous MVR? This question cannot be answered by our study. However, the post-interventional dPmeanCW was consistently the best predictor of an elevated transmitral gradient at discharge, with a positive predictive value of 100% at a
cutoff-level of $\geq 5$mmHg. We also noted that factors influencing transmitral gradients by CW Doppler undergo significant changes between the end of the procedure and discharge: hemoglobin decreases and the heart rate increases. Considering these changes it comes as no surprise that the transmitral gradient at discharge was higher compared to immediately post interventional. In the light of these results it is however noteworthy that the predictor of an elevated transmitral gradient at discharge was not lower than 5mmHg.

Currently there is no gold-standard method to measure MVA (and hence mitral stenosis) during MitraClip procedure. Furthermore we do not know whether a transmitral gradient $\geq 5$mmHg truly represents mitral stenosis, and whether the creation of a mitral stenosis has a prognostic impact in this population. Until we know, a peri-interventional transmitral gradient $\geq 5$mmHg should at least be of concern.

**Limitations**

We have to acknowledge a relative small sample size and a large number of excluded patients due to insufficient 3D TEE image quality. While the 3D images were sufficient for procedure guidance, they were of insufficient quality for the use of the 3D reconstruction software in the excluded patients.

We used the pre-discharge transmitral gradient as endpoint of the study instead of a measured MVA since 3D TTE has insufficient image resolution for the assessment of MVA in most post-interventional patients. We did not use 2D TTE measurement since they tend to overestimate the MVA$^{16,17}$, and performing another 3D TEE before discharge was not justifiable. Also, it should be expected that with normalization of the hemoglobin level, the transmitral gradients should slightly decrease over time. However, in the study of Herrmann et al. the transmitral gradients did not change significantly within 24 months of follow up.$^{27}$
The lower frame rate of 3D zoom acquisitions used in patients with atrial fibrillation may have limited the accuracy of this study. As the frame-rate gets low, the chances raise that the frame with the largest valve opening is missed, leading to an underestimation of the MVA. This could have influenced the comparison with the PHT method, but not the correlation between MVQ and 3DQ since they are based on the same dataset.

Conclusion

In the absence of a reference method for assessment of MVA changes during percutaneous MVR and based on our results we cannot determine the best method to directly assess MVA in this specific setting. However, a post-interventional transmitral gradient by CW-Doppler echocardiography of ≥ 5mmHg consistently predicted elevated transmitral gradients at discharge. CW Doppler measurements are quick, feasible in all patients and should be used for indirect peri-interventional assessment of MVA.

Sources of Funding

X2022: Funding: Drs Gruner and Herzog were supported by a research Grant of Valtech Ltd, Israel.

Disclosures

Drs Biaggi, Gaemperli, and Corti have received speaker’s or consultant honoraria from Abbott Vascular and Philips.

References


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### Table 1. Baseline characteristics of the study population (n = 33)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 33)</th>
<th>Normal gradient at discharge (n = 18)</th>
<th>Elevated gradient at discharge (n = 15)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>77.1 (12.4)</td>
<td>76.2 (11.7)</td>
<td>83.5 (11.5)</td>
<td>.14</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>20 (61)</td>
<td>14 (78)</td>
<td>6 (40)</td>
<td>.027</td>
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<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- Body surface area (m²)</td>
<td>1.8 (0.3)</td>
<td>1.9 (0.3)</td>
<td>1.7 (0.2)</td>
<td>.008</td>
</tr>
<tr>
<td>- Body mass index (kg/m²)</td>
<td>25.0 (6.4)</td>
<td>25.9 (5.7)</td>
<td>24.0 (8.5)</td>
<td>.33</td>
</tr>
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<td>- NYHA* class II / III / IV</td>
<td>6 / 20 / 7</td>
<td>3 / 13 / 2</td>
<td>3 / 7 / 5</td>
<td>.24</td>
</tr>
<tr>
<td>- VO₂ max (ml/min*kg) †</td>
<td>10.7 (6.4)</td>
<td>10.7 (6.4)</td>
<td>11.0 (8.8)</td>
<td>.75</td>
</tr>
<tr>
<td>- 6 minutes walking test (m)</td>
<td>293 (206)</td>
<td>325 (161)</td>
<td>212 (134)</td>
<td>.15</td>
</tr>
<tr>
<td>- Regular rhythm (sinus or paced), n (%)</td>
<td>17 (52)</td>
<td>7 (39)</td>
<td>10 (67)</td>
<td>.11</td>
</tr>
<tr>
<td>- Heart rate (beats per minute)</td>
<td>62 (18)</td>
<td>59 (20)</td>
<td>65 (14)</td>
<td>.19</td>
</tr>
<tr>
<td>- Systolic blood pressure (mmHg)</td>
<td>102.5 (14.2)</td>
<td>102 (14)</td>
<td>103 (22)</td>
<td>.97</td>
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<tr>
<td><strong>Laboratory findings</strong></td>
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<tr>
<td>- NT-proBNP (ng/l)</td>
<td>3388 (7330)</td>
<td>3388 (5077)</td>
<td>4444 (13516)</td>
<td>.58</td>
</tr>
<tr>
<td>- Glomerular filtration rate (ml/min*kg)</td>
<td>42.5 (30.0)</td>
<td>42.5 (21)</td>
<td>44.5 (38)</td>
<td>.67</td>
</tr>
<tr>
<td>- Hemoglobin (mg/dl)</td>
<td>12.5 (2.6)</td>
<td>12.6 (2.2)</td>
<td>11.5 (3.6)</td>
<td>.45</td>
</tr>
<tr>
<td><strong>Echocardiographic findings</strong></td>
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<td></td>
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<tr>
<td>- LV EDVi (ml/m²) ‡</td>
<td>81.0 (36.0)</td>
<td>88 (50)</td>
<td>62 (39)</td>
<td>.006</td>
</tr>
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<td>- LV ejection fraction (%)</td>
<td>46.5 (34.8)</td>
<td>43.5 (31.0)</td>
<td>63.0 (33.0)</td>
<td>.07</td>
</tr>
<tr>
<td>- Left atrial volume index (ml/m²)</td>
<td>74 (30)</td>
<td>70 (33)</td>
<td>77.5 (39.0)</td>
<td>.35</td>
</tr>
<tr>
<td>- RV/RA pressure gradient (mmHg) §</td>
<td>41 (29)</td>
<td>42 (17)</td>
<td>39 (20)</td>
<td>.98</td>
</tr>
<tr>
<td>- EVEREST criteria fulfilled, n (%),</td>
<td></td>
<td></td>
<td>14 (42)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>- Degenerative etiology, n (%)</td>
<td>14 (42)</td>
<td>7 (39)</td>
<td>7 (47)</td>
<td>.65</td>
</tr>
<tr>
<td>- MVA &gt;4cm² by PHT, n (%) #</td>
<td>20 (61)</td>
<td>12 (67)</td>
<td>8 (53)</td>
<td>.44</td>
</tr>
<tr>
<td>by MVQ, n (%) **</td>
<td>20 (61)</td>
<td>14 (78)</td>
<td>6 (40)</td>
<td>.027</td>
</tr>
<tr>
<td>by 3DQ, n (%) ††</td>
<td>30 (91)</td>
<td>18 (100)</td>
<td>12 (80)</td>
<td>.08</td>
</tr>
<tr>
<td><strong>Congestive heart failure medication §§</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>- ACI, n (%) §§</td>
<td>15 (45)</td>
<td>7 (39)</td>
<td>8 (53)</td>
<td>.41</td>
</tr>
<tr>
<td>- ARB, n (%) #§§</td>
<td>9 (27)</td>
<td>5 (28)</td>
<td>4 (27)</td>
<td>1.00</td>
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<tr>
<td>- Beta-blockers, n (%)</td>
<td>16 (48)</td>
<td>9 (50)</td>
<td>7 (47)</td>
<td>.85</td>
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<tr>
<td>- Diuretics, n (%)</td>
<td>26 (79)</td>
<td>13 (72)</td>
<td>13 (87)</td>
<td>.41</td>
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<tr>
<td><strong>History of</strong></td>
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<td></td>
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<tr>
<td>- Systemic hypertension, n (%)</td>
<td>27 (82)</td>
<td>14 (78)</td>
<td>13 (87)</td>
<td>.66</td>
</tr>
<tr>
<td>- Coronary artery disease, n (%)</td>
<td>17 (52)</td>
<td>8 (44)</td>
<td>9 (60)</td>
<td>.37</td>
</tr>
<tr>
<td>- Diabetes mellitus, n (%)</td>
<td>6 (18)</td>
<td>4 (22)</td>
<td>2 (13)</td>
<td>.66</td>
</tr>
<tr>
<td>- COPD, n (%)</td>
<td>3 (9)</td>
<td>2 (11)</td>
<td>1 (7)</td>
<td>1.00</td>
</tr>
<tr>
<td>- Previous device implantation, n (%)</td>
<td>5 (15)</td>
<td>4 (22)</td>
<td>1 (7)</td>
<td>.35</td>
</tr>
<tr>
<td>- Previous mitral valve repair, n (%)</td>
<td>5 (15)</td>
<td>2 (11)</td>
<td>3 (20)</td>
<td>.64</td>
</tr>
</tbody>
</table>

Abbreviations: * NYHA; New York Heart Association, † VO₂ max; maximal oxygen consumption during exercise, ‡ LV EDVi; left ventricular end diastolic volume indexed to body surface area, § RV/RA pressure gradient; pressure gradient
across tricuspid valve, ¶ EVEREST criteria, according to Feldman et al.³, # PHT; pressure half time, ** MVQ, mitral valve
quantiﬁcation software, †† 3DQ; three-dimensional quantiﬁcation software, §§ ACI; Angiotensin converting enzyme
inhibitor, ## ARB, Angiotensin II receptor blockers.
Table 2. Invasive and echocardiographic hemodynamic measurements in subset of 14 patients

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>99 (19.5)</td>
<td>106 (15.8)</td>
<td>.16</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>60 (19.5)</td>
<td>60 (18)</td>
<td>.94</td>
</tr>
<tr>
<td>Mean left atrial pressure (LAP, mmHg)</td>
<td>10 (11)</td>
<td>11.5 (5.25)</td>
<td>.72</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (LVEDP, mmHg)</td>
<td>12 (6)</td>
<td>10 (3.5)</td>
<td>.72</td>
</tr>
<tr>
<td>MVA by PHT (cm²)</td>
<td>4.4 (1.7)</td>
<td>2.0 (0.7)</td>
<td>.001</td>
</tr>
<tr>
<td>MVA by MVQ (cm²)</td>
<td>4.8 (2.8)</td>
<td>2.4 (1.0)</td>
<td>.001</td>
</tr>
<tr>
<td>MVA by 3DQ (cm²)</td>
<td>7.0 (1.6)</td>
<td>2.9 (1.4)</td>
<td>.001</td>
</tr>
<tr>
<td>MVA invasively (by Gorlin formula), cm²</td>
<td>6.2 (3.0)</td>
<td>6.4 (4.6)</td>
<td>.48</td>
</tr>
<tr>
<td>Cardiac output (by Fick formula), l/min</td>
<td>4.6 (3.2)</td>
<td>5.7 (3.6)</td>
<td>.020</td>
</tr>
<tr>
<td>Systolic pulmonary arterial pressure (mmHg)</td>
<td>44 (22)</td>
<td>45 (30)</td>
<td>.38</td>
</tr>
<tr>
<td>dPmean&lt;sub&gt;INV&lt;/sub&gt; mitral valve, (mmHg) *</td>
<td>5.8 (2.1)</td>
<td>5.2 (2.1)</td>
<td>.53</td>
</tr>
<tr>
<td>dPmean&lt;sub&gt;CW&lt;/sub&gt; mitral valve, (mmHg) †</td>
<td>1 (1)</td>
<td>3 (3.5)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Abbreviations: * dPmean<sub>INV</sub>: transmitral gradient by invasive measurement, † dPmean<sub>CW</sub>: transmitral gradient by continuous wave (CW) Doppler measurement, LVEDP: left ventricular end-diastolic pressure. Other abbreviations as in Table 1.
Table 3. Univariable regression output for response to dPmean<sub>CW</sub> at discharge

<table>
<thead>
<tr>
<th>Univariate linear regression analysis</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>-2.26</td>
<td>3.83 to -0.69</td>
<td>.006</td>
</tr>
<tr>
<td>Functional mitral regurgitation</td>
<td>-1.2</td>
<td>-2.90 to 0.50</td>
<td>.16</td>
</tr>
<tr>
<td>Previous mitral valve repair</td>
<td>1.47</td>
<td>-0.89 to 3.82</td>
<td>.21</td>
</tr>
<tr>
<td>EVEREST criteria met</td>
<td>-0.29</td>
<td>-2.04 to 1.46</td>
<td>.74</td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>-0.03 to 0.17</td>
<td>.17</td>
</tr>
<tr>
<td>Body surface area</td>
<td>-4.39</td>
<td>-8.53 to -0.25</td>
<td>.38</td>
</tr>
<tr>
<td>LV EDVi</td>
<td>-0.023</td>
<td>-0.04 to 0.00</td>
<td>.018</td>
</tr>
<tr>
<td>Hemoglobin at discharge</td>
<td>-0.30</td>
<td>-0.90 to 0.31</td>
<td>.33</td>
</tr>
<tr>
<td>Change of hemoglobin pre intervention to discharge</td>
<td>-0.19</td>
<td>-1.33 to 0.94</td>
<td>.72</td>
</tr>
<tr>
<td>Heart rate at discharge</td>
<td>0.02</td>
<td>-0.04 to 0.09</td>
<td>.50</td>
</tr>
<tr>
<td>Change of heart rate post intervention to discharge</td>
<td>-0.01</td>
<td>-0.08 to 0.05</td>
<td>.65</td>
</tr>
<tr>
<td>pre intervention MVA&lt;sub&gt;PHT&lt;/sub&gt;</td>
<td>-0.62</td>
<td>-1.30 to 0.06</td>
<td>.074</td>
</tr>
<tr>
<td>pre intervention MVA&lt;sub&gt;MVQ&lt;/sub&gt;</td>
<td>-0.67</td>
<td>-1.44 to -0.20</td>
<td>.007</td>
</tr>
<tr>
<td>pre intervention MVA&lt;sub&gt;DQ&lt;/sub&gt;</td>
<td>-0.77</td>
<td>-1.21 to -0.33</td>
<td>.001</td>
</tr>
<tr>
<td>post intervention MVA&lt;sub&gt;PHT&lt;/sub&gt;</td>
<td>2.27</td>
<td>-3.15 to -1.40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>post intervention MVA&lt;sub&gt;MVQ&lt;/sub&gt;</td>
<td>2.02</td>
<td>-2.86 to -1.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>post intervention MVA&lt;sub&gt;DQ&lt;/sub&gt;</td>
<td>-1.71</td>
<td>-2.42 to -1.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>post intervention dPmean&lt;sub&gt;CW&lt;/sub&gt;</td>
<td>0.96</td>
<td>0.73 to 1.19</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1
Table 4. Multivariable regression output for response to dPmean\textsubscript{CW} at discharge

<table>
<thead>
<tr>
<th></th>
<th>Model 1: MVA\textsubscript{PHT}</th>
<th>Model 2: MVA\textsubscript{MVQ}</th>
<th>Model 3: MVA\textsubscript{3DQ}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coefficient 95% CI p-value</td>
<td>coefficient 95% CI p-value</td>
<td>coefficient 95% CI p-value</td>
</tr>
<tr>
<td>Body surface area</td>
<td>-2.78 -4.94 to -0.61 .014</td>
<td>-2.38 -4.57 to -0.20 .033</td>
<td>-1.98 -4.55 to 0.59 .13</td>
</tr>
<tr>
<td>Post MVA\textsubscript{PHT}</td>
<td>-0.72 -1.46 to 0.02 .057</td>
<td>-0.74 -1.38 to -0.11 .023</td>
<td>-0.56 -1.19 to 0.07 .078</td>
</tr>
<tr>
<td>Post MVA\textsubscript{MVQ}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post MVA\textsubscript{3DQ}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post dPmean\textsubscript{CW}</td>
<td>0.78 0.53 to 1.03 &lt;.001</td>
<td>0.79 0.57 to 1.02 &lt;.001</td>
<td>0.81 0.57 to 1.05 &lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1
Figure Legends

Figure 1.
Heading: Mitral valve area assessment by mitral valve quantification software (MVQ) and Three-dimensional quantification software (3DQ) before and after percutaneous mitral valve repair.
Legend: The orientation of all 6 images is identical, with the aortic valve at 12 o’clock.
Figure 1A and 1B: 3D TEE image in diastole with maximal opening of the mitral valve before (A) and after implantation of two clips (B, arrows point to area of clip insertion). Figure 1C/D and 1E/F demonstrate the reconstruction of the same valve with MVQ and 3DQ, respectively. Abbreviations: MVA; mitral valve area, AV; aortic valve, AML; anterior mitral leaflet, PML; posterior mitral leaflet.

Figure 2.
Heading: Peri-procedural relative changes of hemodynamic parameters and mitral valve area.
Legend: Abbreviations: BP syst; systolic blood pressure, MR; mitral regurgitation, sPAP; systolic pulmonary artery pressure, mLAP; mean left atrial pressure, dPmeanCW; mean transmitral gradient measured by continuous wave Doppler echocardiography, MVA PHT, MVQ and 3DQ; mitral valve area calculated by pressure half time, MVQ or 3DQ software, respectively.

Figure 3.
Heading: Reduction of mitral regurgitation and creation of mitral stenosis by MitraClip procedure
Legend: Assessment of Mitral regurgitation by visual estimation. Measurement of mitral valve area and hence degree of mitral stenosis using the 3DQ method. Abbreviations: pre and post; before and after percutaneous mitral valve repair, Degree of mitral regurgitation: 1+: mild, 2+: moderate, 3+:
moderate to severe, 4+: severe. Degree of mitral stenosis: none (mitral valve area ≥ 2cm²), mild (1.5 to 1.99cm²), moderate (1.0-1.49cm²).

**Figure 4.**

Heading: Comparison of mitral valve area measurements using different methods

Legend: Numbers in columns represent median (inter quartile range). Abbreviations as in figure 1.

**Figure 5.**

Heading: Changes of relevant hemodynamic parameters.

Legend: Abbreviations: Pre, post and discharge; measurements before and immediately after clipping as well as at the time of discharge, BP; blood pressure, Hb; haemoglobin level, dPmean CW; transmitral gradient by continuous wave Doppler.

**Figure 6.**

Heading: ROC curve and performance of cut-off value for prediction of an elevated transmitral gradient at discharge.

Legend: The numbers printed on the red line indicate the corresponding value. The blue line corresponds to a smooth ROC curve from a binormal model. Abbreviations: post dPmean CW ≥ 5mmHg; post-interventional transmitral gradient measured by continuous wave Doppler, AUC, area under the curve.
Figure 7.

Heading: Post-interventional mitral valve area by three-dimensional quantification software (3DQ): Source of error.

Legend: Panel (A): The mitral valve area is obtained by using a single plane (blue) through the mitral valve. Panel (B): The mitral valve area is obtained by three optimized planes (blue) through the medial, central and lateral orifice of the repaired mitral valve. The valve area obtained this way, i.e. by respecting the orifice orientation in the third space, is smaller than the MVA obtained by using a single (two-dimensional) plane.
**Before**

- MVA in 3D TEE image
- MVA by MVQ software
- MVA by 3DQ software

**After Implantation of 2 MitraClips**

- MVA 7.0 cm²
- MVA 7.8 cm²
- MVA 2.4 cm²
- MVA 2.3 cm²

Figure 1
Figure 3

Mitral regurgitation

- Pre: 4+
- Post: 3+
- Pre: 3+
- Post: 1+

Mitral stenosis (by MVA$_{3DQ}$)

- Pre: no stenosis
- Post: no stenosis
- Pre: moderate
- Post: mild
Figure 4

MVA (cm²)

Pre MitraClip

Post MitraClip

by PHT  

4.4  

(2.0)

by MVQ  

4.7  

(2.4)

by 3DQ  

6.2  

(2.4)

by PHT  

1.9  

(0.7)

by MVQ  

2.1  

(1.1)

by 3DQ  

2.8  

(1.1)

p = .430

p < .001

p = .715

P = .001
Figure 6

Performance of cut-off value (post dPmean, of ≥ 5mmHg) for prediction of an elevated transmitral gradient at discharge

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.73 (0.48 to 0.89)</td>
</tr>
<tr>
<td>Specificity</td>
<td>1.00 (0.82 to 1.00)</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>1.00 (0.74 to 1.00)</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.82 (0.61 to 0.93)</td>
</tr>
</tbody>
</table>
Figure 7

(A) Single plane through MV

(B) 3 individually optimised planes

<table>
<thead>
<tr>
<th>Medial orifice</th>
<th>Central orifice</th>
<th>Lateral orifice</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA 3.8cm²</td>
<td>MVA 3.2cm²</td>
<td>MVA 3.2cm²</td>
</tr>
</tbody>
</table>
Assessment of Mitral Valve Area during Percutaneous Mitral Valve Repair using the MitraClipTM System: Comparison of Different Echocardiographic Methods
Patric Biaggi, Christian Felix, Christiane Gruner, Bernhard A. Herzog, Sabine Hohlfeld, Oliver Gaemperli, Barbara E. Stähli, Michaela Paul, Leonhard Held, Felix C. Tanner, Jürg Grünenfelder, Roberto Corti and Dominique Bettex

Circ Cardiovasc Imaging. published online October 17, 2013;
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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