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# Impact of interventional edge-to-edge repair on mitral valve geometry☆

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ABSTRACT

*Background/objectives:* The acute and long-term effects of interventional edge-to-edge repair on the mitral valve (MV) geometry are unclear.
We sought to assess MV-annular geometry and the association of changes in MV-diameters with functional response one year after MitraClip implantation.
*Methods:* Consecutive patients ($n = 84$; age 81.2 ± 8.3 years, logistic EuroSCORE 21.7 ± 17.9%) with symptomatic moderate-to-severe mitral regurgitation (MR) underwent MitraClip-procedure. MV-annular geometry was assessed with 3D TOE before, immediately and one year after clip implantation.
*Results:* 96.7% of secondary mitral regurgitation (SMR) patients presented with moderate-to-severe MR, 3.3% with severe SMR, respectively. 66.7% of primary MR (PMR) patients had moderate-to-severe MR, and 33.3% severe PMR respectively. When analyzing immediate effects of MitraClipC on mitral geometry, only patients with SMR ($n = 60$, 71.4%) experienced significant reductions of the diastolic MV anterior-posterior diameters (AP: 3.9 ± 0.5 cm, 3.5 ± 0.7 cm; $p < 0.001$), and annulus-areas (2D: 12.9 ± 3.8 cm2, 12.6 ± 3.7 cm2; $p < 0.001$; 3D: 13.4 ± 3.8, 13.1 ± 3.2 cm2; $p < 0.001$). All measures on MV annular geometry were not significantly altered in patients with PMR ($p > 0.05$).
After one year of follow-up, MV annular parameters remained significantly reduced in SMR patients ($p < 0.05$) and remained unchanged in subjects with PMR ($p > 0.05$).
Only SMR patients experienced significant increase in 6 min walking distances ($p = 0.004$), decrease in pulmonary pressures ($p = 0.007$) and functional NYHA-class ($p < 0.001$); in patients with PMR only NYHA class improved after one year ($p < 0.001$).
*Conclusion:* Edge-to-edge repair with the MitraClip-system impacts on MV-geometry in patients with SMR with stable results after 12 months. Reduction of MV-annular dimensions was associated with higher rates of persisting MR reduction and better functional status in patients with SMR.


## 1. Introduction

Despite the fact that transcatheter mitral valve repair (TMVR) with the MitraClip system is an established alternative treatment option to surgery in high-risk patients with severe symptomatic primary and/or secondary mitral regurgitation (PMR, SMR), clinical research aims for an interventional device mimicking the surgical approach: To reduce anterior-posterior (AP) mitral valve (MV) diameters and, thus, reconstructing the MV annular geometry. All of the current annuloplasty devices are objects to clinical or pre-clinical testing, and therefore not yet available in broad daily routine [1].

The MitraClip procedure has been shown effective for the reduction of mitral regurgitation in up to 80% of cases with improvement of MR related clinical symptoms [1]. Due to the fact that the Clip device does not directly address MV annular pathology, a debate is still ongoing concerning the durability of interventional edge-to-edge repair with the MitraClip in SMR patients [2,3]. We and others were able to show that MitraClip implantation acutely reduces MV annular diameters in patients with SMR [4,5] and the amount of AP diameter reduction was associated with clinical changes after TMVR [4]. These results suggest, that interventional edge-to-edge repair of MR with the MitraClip system creates significant tension on the MV annulus via the anterior and posterior MV leaflets.

*Abbreviations:* 2DTOE, two-dimensional transesophageal echocardiography; 3DTOE, three-dimensional transesophageal echocardiography; AP, anterior-posterior; FU, follow up; LM, lateral-medial; LVEF, left ventricular ejection fraction; MV, mitral valve; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TMVR, transcatheter mitral valve repair.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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In this study we sought to assess the durability of acute changes in MV annular geometry after MitraClip implantation with 3D transesophageal echocardiography (TOE) and to determine the association of MV diameter reduction with clinical outcomes after one year of follow up (FU).

## 2. Methods

### 2.1. Patients

All patients presenting at the Heart Centre of the University Hospital of Bonn with symptomatic, more than moderate MR were evaluated for TMVR or surgery. Following current guidelines, patients with SMR and moderate MR were considered for MR treatment when having an effective regurgitation orifice area (EROA) of >20 $mm^2$, NYHA functional class III–IV, concomitant AF and/or elevated pulmonary pressure despite optimized medical and/or device therapy [6]. TMVR was planned after heart team decision when a patient was deemed high-risk for open-heart surgery or inoperable.

The study was approved by the Ethics Committee of the University of Bonn and in concordance with the Declaration of Helsinki and all patients had to provide written informed consent before study inclusion.

### 2.2. 2D and 3D TOE image acquisition

Echocardiographic assessment before, during and after TMVR was done following current recommendations and guidelines with determination of proximal isovelocity surface area (PISA), EROA, as well as vena contracta width and regurgitant volume [6]. MR was graded according to the recommendations of the European Society of Cardiology as "mild", "moderate", "moderate to severe" or "severe" [6–8]. Moderate-to-severe SMR was defined as vena contracta width > 3–6 mm, EROA 0.15–0.19, regurgitant volume 15–29 ml/beat. Severe SMR was defined as EROA ≥ 0.20 $cm^2$, vena conctracta width ≥ 7 mm, regurgitant volume ≥ 30 ml/beat. Moderate-to-severe PMR was defined as EROA 0.3–0.39 $cm^2$, vena contracta width > 3–6 mm or regurgitant volume 45–59 ml/-beat. Severe PMR was defined as EROA ≥ 0.4 $cm^2$, vena contracta width ≥ 7 mm and regurgitant volume ≥ 60 ml/beat according to current guidelines. 3DTOE was performed with a commercially available echocardiographic system (iE 33, Philips Medical Systems, Andover, Massachusetts) and a TOE probe (X7-2t) allowing acquisition of 2D and 3DTOE data sets. All patients underwent transthoracic echocardiography 1 to 2 days prior to clip implantation and at FU.

3D full volume data sets were acquired in all patients directly before MitraClip implantation, immediately after clip deployment and 1 year after clip implantation, derived from an optimized 2D intercomissural view on the MV by scanning 2D planes from 50 to 90°. MV diameters were measured off-line by using a dedicated analysis software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany), which enables a stepwise multiplanar approach for the delineation of the MV annulus and leaflets (Fig. 1). For the definition of MV annular geometry we assessed AP diameters, lateral/medial (LM) diameters, 2D and 3D areas, MV annulus circumference and the MV annular sphericity index (defined as AP-/LM-diameter) in diastole and systole in each case. After delineation of the mitral apparatus, the MV annulus was tracked automatically during the heart cycle and realigned manually when and where necessary.

TOE images were obtained by a single experienced echocardiographer. A second echocardiographer, blinded to functional outcomes, etiology of MR (as far as possible) and the patient characteristics, performed the offline analysis of the 3D volume data sets. FU evaluation was carried out by trained study nurses, unattended by the echocardiographers.

### 2.3. Definition of MR etiology

Patient cohorts were divided according to the underlying etiology of mitral regurgitation. SMR was defined as mostly central mitral regurgitation with global (symmetric) or regional (eccentric) left ventricular (LV) dilatation and reduced LV ejection fraction (LVEF) despite structurally normal MV leaflets. Pathological changes in MV annular geometry or pathologic tension on the valve leaflets due to ventricular dilatation causing asymmetric or symmetric MV tenting and tethering led to SMR in the study patients.

In patients with primary pathologies of the MV leaflets, such as flail leaflets or MV prolapse, and/or MV apparatus MR was deemed to be primary [7].

### 2.4. Interventional edge-to-edge repair of MR

All procedures were performed under general anesthesia using fluoroscopy and TOE guidance. No contrast agent was used in all cases. TMVR by using the MitraClip system has been described in detail previously [1].

In short: The right atrium is accessed via the right femoral vein. After transseptal puncture a guidewire is passed into the left atrium to allow for guide catheter introduction. After introducing the guide in the left atrium the clip delivery system is advanced. With echocardiographic and fluoroscopic guidance, the clip device is moved until it is centered over the mitral valve. The clip-arms are opened and oriented perpendicular to the mitral leaflets and the clip is advanced into the left ventricle. The clip is then closed to approximately 120° and pulled back until the leaflets are captured in the arms of the clip, then the grippers are lowered and the clip is closed. The degree of MR reduction and is checked with (color-Doppler) echocardiography. If functional results are appropriate and relevant MV stenosis is excluded, the clip will be released and the delivery system and guide catheter are withdrawn. The number of clips that were implanted was left to the discretion of the treating physician.

### 2.5. Statistical analysis

Normal distribution of continuous variables was examined using the Kolmogorov–Smirnov test. Continuous data were expressed as mean values ± standard deviation. Two-tailed $p$-values were calculated and considered to be significant if ranging below 0.05. Comparisons between PMR and SMR groups at 1 year were done using chi-square test or Kruskal-Wallis-test. Further comparisons were performed with the paired $t$-test (for continuous variables) or Friedman test (for categorical data).

Correlation of variables was tested using bivariate correlations test with calculation of Pearson's correlation coefficient. Intraclass correlation coefficients (ICC) for absolute agreement was used for the assessment of method agreement, with good agreement defined as >0.80. For the assessment of intra-observer variability, 10 randomly chosen patients of each group (PMR, SMR) were analyzed by the same investigator twice and by a second investigator, who was blinded to the results of the first investigator, to determine inter-observer variability. Mean values and standard deviations between the measurements were obtained, and absolute agreement among the observation was calculated using ICC analysis. Statistics were performed using SPSS for Windows (PASW statistic, Version 22.0.0.0, SPSS Inc., Chicago, Illinois, USA) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium).

## 3. Results

### 3.1. Baseline data and acute clinical and procedural outcomes

We included 84 patients (age 81.2 ± 8.3 years) at high surgical risk (logistic EuroSCORE 21.7 ± 17.9%) for mitral valve replacement or annuloplasty. 60 (71.4%) patients were treated for SMR and 24 (28.6%) patients had primary causes of MR (Table 1). All patients completed TOE-FU one year after the procedure. The procedure was successfully completed in all patients with implantation of more than one clip in 42% of cases with a mean procedural time of 78.7 ± 38.5 min (28–168 min).

Patients with SMR had a significantly lower LVEF (38.8 ± 14.7%, 56.7 ± 12.4%; $p = 0.001$); they did more often suffer from hyperlipidemia ($p = 0.05$) and diabetes ($p = 0.03$). Patients with PMR were significantly older than patients with SMR (85.6 ± 5.1 years, 79.6 ± 8.7 years; $p = 0.031$) (Table 1). With regard to baseline functional status there was no difference between SMR and PMR patients concerning 6MWD (230 ± 104 m, 285 ± 142 m; $p = 0.76$), N-terminal pro brain natriuretic peptide (NT pro-BNP) (7125.1 ± 1502.7 pg/ml, 7922.1 ± 1474.9 pg/ml; $p = 0.88$), or functional NYHA class ($p = 0.07$) (Table 2).

### 3.2. Echocardiographic measures after follow-up

After one year of FU, echocardiography revealed sustained reduction of mitral regurgitation < 2 + in 100% of patients with SMR and in 91.7% of subjects with PMR. We found no reduction in echocardiographic determined systolic pulmonary arterial pressures (sPAP) (44.5 ± 13.8 mm Hg, 38.9 ± 14.7 mm Hg; $p = 0.15$) in the overall cohort. However, when separating the groups according to MR etiology, patients with SMR had significantly decreased sPAP values (43.2 ± 13.9 mm Hg, 34.0 ± 10.4 mm Hg; $p = 0.007$), and in patients with PMR sPAP was non-significantly higher as compared to baseline measurements (48.4 ± 13.2 mm Hg, 53.3 ± 17.6 mm Hg; $p = 0.21$). LV volumes (endsystolic [ESV]/enddiastolic volume [EDV]) and EF improved in both groups, albeit not reaching statistical significance.

Mean MV pressure gradients increased significantly in both groups after the procedure (SMR: $p < 0.001$; PMR: $p = 0.007$) and this increase was unchanged after one year (SMR: 1.4 ± 1.1 mm Hg, 3.3 ± 1.6 mm Hg, $p = 0.003$; PMR: 1.9 ± 1.1 mm Hg, 4.0 ± 1.8 mm Hg, $p = 0.01$) (Table 3, Supplemental Table 1).

### 3.3. Clinical outcomes after 12 months

We found a significant improvement of functional NYHA class (SMR: $p < 0.001$; PMR: $p < 0.001$) in both groups. 6MWD were significantly

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