Advanced echocardiography and clinical surrogates to risk stratify and manage patients with structural heart disease

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Chapter 6

Acute effect of MitraClip on valve geometry in functional mitral regurgitation: insights from 3-dimensional transesophageal echocardiography

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ABSTRACT

Objectives

Our aim was to evaluate the acute effects of transcatheter edge-to-edge mitral valve repair using the MitraClip device on mitral valve geometry in patients with functional mitral regurgitation (FMR).

Methods and Results

Forty-two patients (age 73 years [IQ range 66.1-78.0], 55% men, 62% ischaemic FMR) with moderate-to-severe and severe FMR treated with the MitraClip were included. Three-dimensional transoesophageal echocardiography was performed prior to and immediately after MitraClip implantation. Acute changes of mitral annular and leaflet geometry were assessed with dedicated mitral modelling software. FMR less than moderate grade was achieved in 36 (86%) patients. After MitraClip implantation, the mitral annulus became more elliptical (ellipticity from 122±17% to 129±18%; p=0.04) with a non-significant reduction in anteroposterior diameter (33±6 to 32±5 mm, p=0.08). The coaptation area increased from 350 mm^2 (IQ range 289-493 mm^2) to 434 mm^2 (IQ range 328-523 mm^2, p=0.008). In particular, a larger part of the anterior mitral leaflet was included in the coaptation, leaving a smaller exposed anterior leaflet length of the A2 segment (from 27±6 mm to 25±5 mm, p<0.05) while the exposed length of the posterior leaflet (P2 level) remained unchanged (12±4 mm pre- vs. 13±4 mm post-repair, p=0.15). There was no change in total leaflet area (1,811±582 mm^2 pre- vs. 1,870±506 mm^2 post-repair, p=0.18). Annular height to intercommissural width ratio and tenting volume remained unchanged, suggesting no increase in leaflet stress.

Conclusions

The MitraClip device affects MV geometry in FMR patients by increasing mitral annular ellipticity and coaptation area.

INTRODUCTION

Functional mitral regurgitation (FMR) is common in heart failure patients and is associated with poor clinical outcomes.[1-4] Surgical mitral valve repair has proven to be beneficial, providing significant improvement in symptoms and left ventricular (LV) function.[5,6] However, many patients with significant FMR are not referred for or are denied surgical intervention due to a high operative risk, related to advanced age and the presence of associated comorbidities.[7] Several minimally invasive and transcatheter based mitral valve repair techniques provide feasible alternative treatment options to conventional valve surgery for patients with a high operative risk. The transcatheter edge-to-edge mitral valve repair technique using the MitraClip system (Abbott Vascular-Structural Heart, Menlo Park, CA, USA) is designed to grasp the mitral valve leaflets at the middle scallops, creating a double orifice valve during diastole and maintaining closer apposition of the leaflets during systole to reduce the regurgitant volume. With more than 17,000 patients treated worldwide, the MitraClip device has demonstrated to be a feasible and safe procedure, also in patients with FMR, and to improve symptoms.[8,9] The effect of the MitraClip device on the geometry and function of the mitral valve, however, remains largely unexplored. Three-dimensional transesophageal (TEE) echocardiography allows for accurate measurements of mitral valve geometry.[10] Accordingly, the present study aimed at evaluating the acute effects of transcatheter edge-to-edge repair on mitral annular geometry and leaflet coaptation zones of patients with FMR using 3-dimensional TEE.

METHODS

Patient population and data collection

A total of 59 patients were treated with the MitraClip device at the Leiden University Medical Centre between January 2012 and July 2014. Thorough clinical and echocardiographic evaluation was performed prior to the procedure by an interdisciplinary team of cardiac surgeons and cardiologists. Patients had symptomatic moderate-to-severe or severe mitral regurgitation and were at high risk for conventional surgical mitral valve repair, defined by a logistic EuroSCORE>20% or the presence of specific risk factors associated with excessive morbidity and mortality. Evaluation of clinical symptoms included assessment of functional capacity according to the New York Heart Association (NYHA) functional class and the 6-minute walked distance test. Furthermore, a quality of life assessment was performed using the Minnesota Living With Heart Failure® questionnaire.[11] Transthoracic echocardiographic (TTE) and TEE assessment were routinely performed before the intervention to assess left ventricular (LV) dimensions and function, mitral valve morphology and mitral regurgitation grade and evaluation of factors that may contraindicate the procedure.[12] The procedure was guided with 3-dimensional TEE allowing acquisition of 3-dimensional data of the mitral valve. In the current analysis only patients with FMR and sufficient quality of peri-procedural 3-dimensional TEE data allowing for geometrical analysis of the mitral valve were included (n= 42).

Two-dimensional transthoracic echocardiographic evaluation

Pre-procedural TTE was performed using commercially available ultrasound systems (E9 or Vivid 7, GE Norway, Horten, Norway) equipped with an M5S transducer and 2-dimensional, M-mode and Doppler data were acquired with the patient in the left lateral decubitus position. LV dimensions and function were assessed according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.[13] From the apical 4- and 2-chamber views the LV end-diastolic and end-systolic volumes and LV ejection fraction were measured according to the biplane Simpson's method. LV diameters were assessed at end-diastole and end-systole from the parasternal long-axis view or M-mode recordings. From the apical 2-, 3- and 4-chamber views, colour and continuous wave Doppler data of the mitral valve were acquired and mitral regurgitation was quantitatively determined by the proximal isovelocity surface area method and by measuring the vena contracta according to current guidelines.[14]

Three-dimensional transesophageal echocardiographic data acquisition and evaluation

TEE was performed during the procedure using a commercially available ultrasound system (iE33, Philips Medical Systems, Andover, MA, USA) equipped with a fully sampled matrix-array TEE transducer (X7-2t Live 3D-TEE transducer, iE33, Philips Medical Systems, Andover, MA, USA) capable of acquiring both 2- and 3-dimensional images to guide implantation of the MitraClip device and to assess acute procedural success. Three-dimensional images were acquired during the intervention before and directly after implantation of the MitraClip device, using multi-beat (7-14 beats) full-volume or 1-beat 3-dimensional-zoom acquisitions encompassing a pyramid volume. The multi-beat full-volume images were acquired during respiratory breath-hold whenever possible to avoid stitch artefacts. In patients with atrial fibrillation, 1-beat 3-dimensional-zoom acquisitions with the sector adjusted to include the MV were performed. Furthermore, special care was taken to stabilize the probe during 3-dimensional data acquisition. All images were digitally stored for off-line analysis with the MVQ software (QLAB Cardiac 3DQ v.10.0; Philips Medical Systems, Andover, MA, USA), which allows semi-automated 3-dimensional quantification of the mitral valve geometry.[10] From 3-dimensional full-volume or zoomed datasets of the mitral valve, the software displays three orthogonal multiplanar reformation planes of the mitral valve. The planes are manually aligned across the mitral annulus in a selected end-systolic frame to obtain bicommissural, outflow tract and short-axis views of the mitral valve. The bicommissural view was used to indicate the antero-lateral and postero-medial points of the mitral annulus, whereas the outflow tract view was used to define the anterior and posterior points of the mitral annulus, the aortic annulus and the mitral leaflet coaptation point. The mitral leaflet commissural points were set on the short-axis plane and the mitral leaflets and coaptation length were traced on multiple cross-sections (18-30) in the outflow-tract view, orthogonal to the inter-commissural direction. The 3-dimensional rendered surgical en face view was used to correctly identify the coaptation point (Figure 1). Subsequently, the software automatically creates a 3-dimensional model of the mitral valve geometry and various measurements can be derived.

The measurements of the mitral valve performed with the MVQ software included anteroposterior and intercommissural annular diameters and area, and leaflet lengths, angles and areas. Mitral annular ellipsicity was calculated as the ratio between the anteroposterior annular diameter and the intercommisural diameter. Furthermore, to assess the effect of the MitraClip on mitral leaflet coaptation, the coaptation length at the middle scallops (A2P2) was measured and coaptation area was calculated by subtracting the exposed area of the anterior and posterior mitral leaflet (i.e. the area without the coapting part of the leaflets) from the total area of the anterior and posterior leaflet (i.e. the area including the coapting part of the leaflets). Moreover, the effect of the MitraClip on leaflet stress was analysed by assessing the annular-height-to-intercommissural-width ratio and the non-planarity angle. The non-planarity angle was determined as the angle between the two vectors from the anterior and posterior leaflet hinge points of the annulus to the centre of the intercommissural line. Additionally, tenting height at the A2P2 level, tenting volume and the angle between the mitral annulus and aortic annulus were measured. Three-dimensional TEE data were analysed by two experienced observers. An example of mitral geometry measurements performed before and after MitraClip implantation in a patient using MVQ software is displayed in Figure 2.

Procedural technique

The transcatheter edge-to-edge mitral valve intervention was performed as previously described using the MitraClip system and guided by fluoroscopy and 2- and

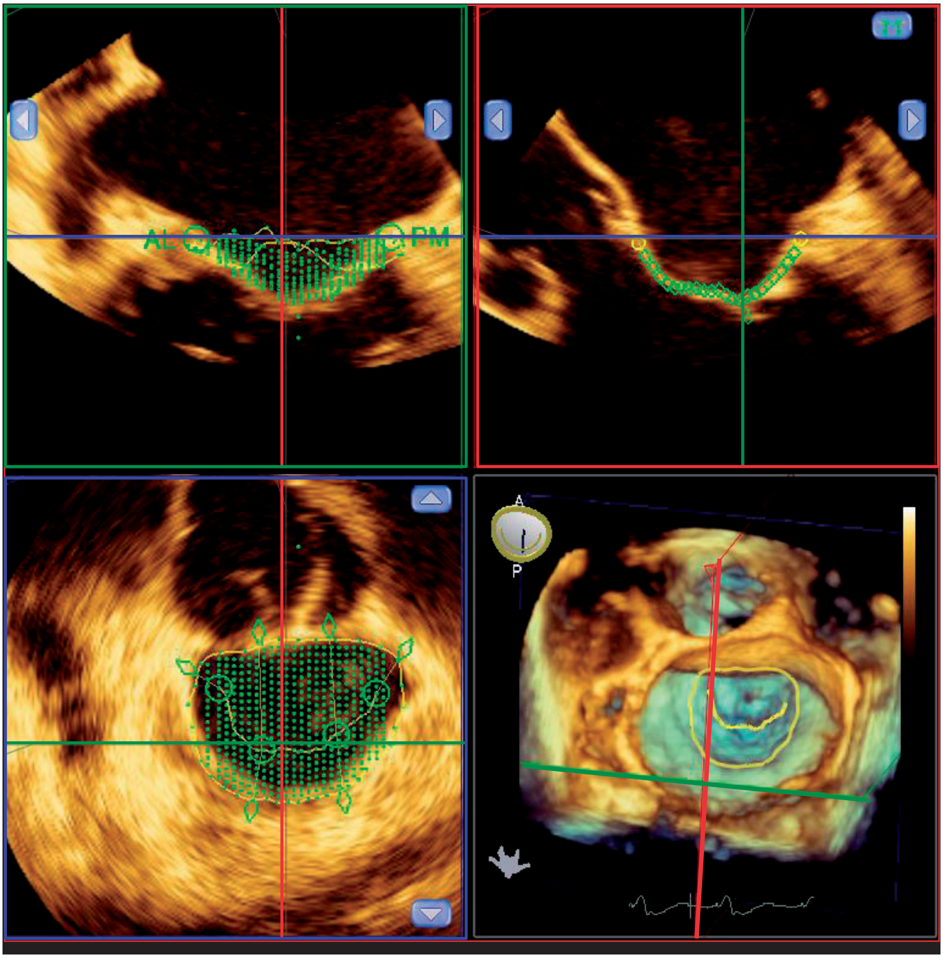

Figure 6.1
Identification of 3-dimensional landmarks on multiplanar reformation planes using Mitral Valve Quantification (MVQ) software. Using the multiplanar reformation planes, the MVQ software identifies the landmark points of the mitral annulus. The anterior, posterior, anterolateral and posteromedial points of the mitral annulus are identified on the 2- and 3-chamber views. The en face view provides the cross-sectional area of the mitral annulus and simultaneously the 3-dimensional full volume of the mitral valve can be visualised. Left upper panel: identification of leaflet insertion points, right upper panel: tracing the mitral leaflets and marking the leaflet coaptation point, left lower panel: tracing the coaptation line, right lower panel: 3-dimensional surgical view of the mitral valve with the manually traced lines visible.

3-dimensional TEE.[12,15] In brief, after transseptal punction, the clip delivery system was advanced into the left atrium and positioned above the mitral valve plane over the origin of the regurgitant jet. The device was oriented perpendicular to the line of coaptation and the system was advanced into the LV with the arms slightly opened. After ensuring good alignment of the device (just below the regurgitant orifice on the TEE bicommissural view of the mitral valve) and simultaneously visu-

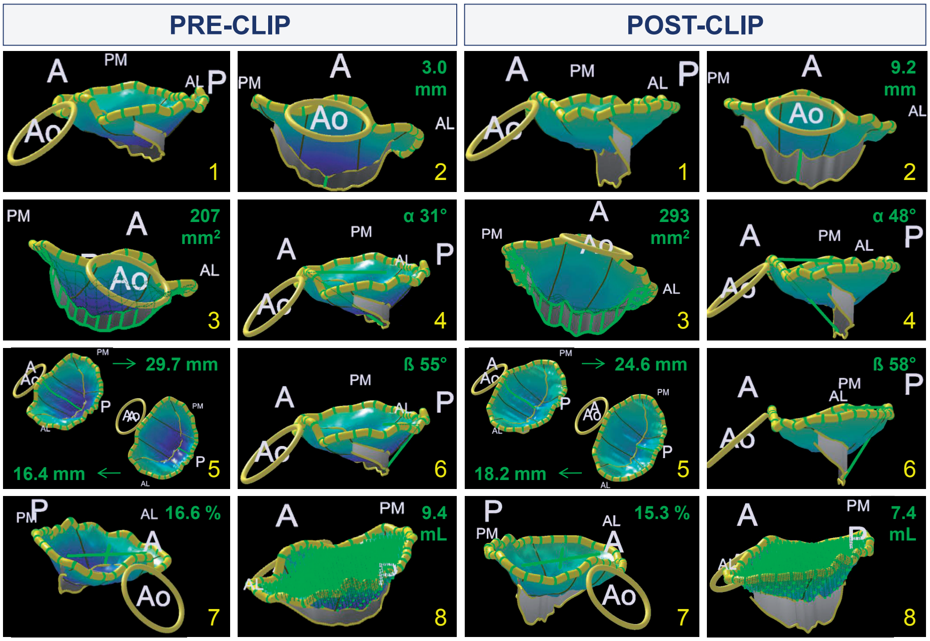

Figure 6.2
Example of changes in mitral valve geometry in a patient before and after MitraClip implantation with 3-dimensional model. 1: 3-dimensional model of the mitral valve, 2: Coaptation length at the A2P2 level pre- and post-MitraClip implantation, 3: Coaptation area pre- and post-MitraClip implantation, 4: Angle between anterior leaflet and mitral annulus aorta pre- and post-MitraClip implantation, 5: Length of the anterior (left) and posterior (right) leaflet at the A2 and P2 level respectively pre- and post-MitraClip implantation, 6: Angle between posterior leaflet and mitral annulus pre- and post-MitraClip implantation, 7: Ellipsicity pre- and post-MitraClip implantation, 8: Tenting volume pre- and post-MitraClip implantation. A = anterior, AL = anterolateral, Ao = Aorta, P = posterior, PM = posteromedial.

alizing the arms of the device opened in the perpendicular TEE view (120-150°, or LV outflow tract view) the system was pulled-back to grasp the mitral leaflets in the arms of the clip and create a double-orifice valve. The grade of MR was assessed during the procedure using color and continuous wave Doppler echocardiography. Procedural success was defined as reduction of MR to grade ≤ 2. If needed, a second clip was placed to ensure grade ≤ 2 MR without significant stenosis. The grade of residual MR was also evaluated at predischarge transthoracic echocardiogram using color flow Doppler and color flow jet area (MR jet area/ LA jet area).[16]

Statistical analysis

Distribution of the continuous data was tested by the Kolmogorov-Smirnov one-sample test and the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation, whereas non-normally distributed variables are presented as median and interquartile range. Categorical variables

Table 6.1
Baseline demographic, clinical and echocardiographic patient characteristics.

	n = 42
Male gender, n (%)	23 (55)
Age (years)	72.8 (IQ range 66.1-78.0)
Hypertension, n (%)	18 (43)
Hypercholesterolemia, n (%)	17 (42)
Positive family history of CVD, n (%)	8 (20)
(Ex-) smoker, n (%)	21 (50)
Diabetes Mellitus, n (%)	16 (38)
COPD, n (%)	6 (14)
Peripheral vascular disease, n (%)	11 (26)
Prior stroke, n (%)	5 (12)
Ischemic cardiomyopathy, n (%)	26 (62)
Prior myocardial infarction, n (%)	22 (52)
Location of myocardial infarction, n (%)	11 (50)
Anterior	6 (27)
Inferior	2 (9)
Anteroseptal	2 (9)
Posterolateral	1 (5)
Posterior	
NYHA class III-IV, n (%)	35 (83)
Logistic EuroSCORE (%)	17.7 (IQ range 10.9-27.4)
Glomerular filtration rate (ml/min/1.73m^2)	49.3 (IQ range 26.4-75.0)
Sinus rhythm, n (%)	14 (33)
CRT, n (%)	16 (38)
Medication, n (%)	
Betablockers	34 (81)
ACE-/ Angiotensin receptor II inhibitors	28 (78)
Diuretics	37 (88)
Digoxin	11 (26)
Statin	29 (69)
Calcium antagonist	4 (10)
Aspirin	13 (31)
Anticoagulants	40 (95)
LV end-diastolic diameter (mm)	63.2 ± 9.3
LV end-systolic diameter (mm)	52.7 ± 13.5
LV end-diastolic volume (ml)	176.5 (IQ range 133.8-243.8)
LV end-systolic volume (ml)	118.5 (IQ range 82.5-163.8)
LV ejection fraction (%)	33.7 ± 10.3
Mitral regurgitation	
Grade 3	20 (48)
Grade 4	22 (52)
Number of clips implanted	
1 clip	24 (57)
2 clips	15 (36)
3 clips	1 (2)
4 clips	2 (5)

ACE: Angiotensin Converting Enzyme, COPD: Chronic Obstructive Pulmonary Disease, CRT: Cardiac Resynchronization Therapy, CVD: cardiovascular disease; LV: left ventricular, NYHA: New York Heart Association functional class.

are expressed as numbers and percentages. Comparisons of MV geometry pre- and post-procedure were performed using the paired Student T-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. All statistical tests were 2-tailed and a $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 20.0.0 for windows (SPSS Inc., Chicago IL, USA).

RESULTS

Baseline characteristics

Baseline demographic, clinical and echocardiographic characteristics of the patients are listed in Table 1. Moderate-to-severe FMR was observed in 48% of patients and severe FMR in 52%. Ischemic heart failure was the most frequent underlying etiology of heart failure (62%).

Changes in 3-dimensional mitral valve geometry after MitraClip

FMR reduction to ≤grade 2 was achieved in 36 (86%) patients (Figure 3). Changes in mitral valve geometry post-MitraClip implantation are presented in Table 2. After the procedure, the mitral annulus became more elliptical indicated by an increase in ellipsicity (from 122±17% to 129±17%, $p<0.05$), increase in both the anterior (from 27±7º to 34±8º, $p<0.001$) and posterior mitral leaflet angle (from 49±14º to 56±10º, p=0.02) and a decrease in the antero-posterior mitral annular diameter (from 33±6 mm to 32±5 mm, p=0.08). Furthermore, an increase in both coaptation length at the A2-P2 level (from 50±11 mm to 53±9 mm, $p<0.001$) and total coaptation area (from 215 mm^2 (IQ range 164-264) to 281 mm^2 (IQ range 238-386), p=0.005) were observed. In addition, the exposed length of the anterior mitral leaflet (i.e. excluding the coapting part of the leaflet) at the A2 level (from 27±6 mm to 25±5 mm, p=0.03) and the exposed anterior leaflet area (from 795±277 mm^2 to 730±222 mm^2, p=0.04) decreased while the posterior leaflet length at the P2 level and total leaflet area remained unchanged, indicating that the improvement in leaflet coaptation is due to a larger area of the anterior mitral leaflet involved in the coaptation (Figures 4 and 5). The annular height-to-intercommissural-width ratio, non-planarity angle and tenting volume remained unchanged after MitraClip therapy, suggesting no increase in leaflet stress.

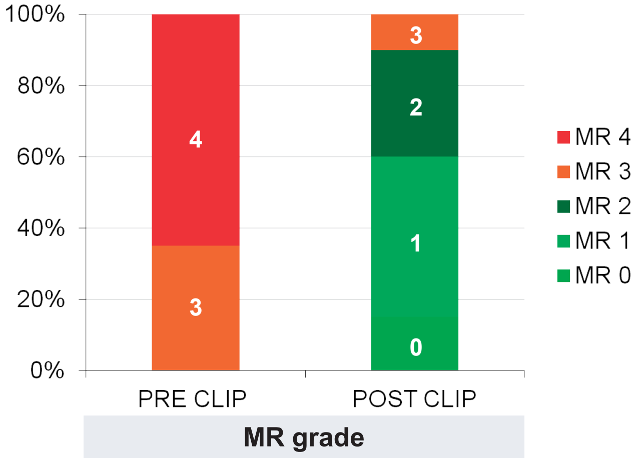

Figure 6.3
Mitral regurgitation grade reduction post-MitraClip implantation. MR: mitral regurgitation.

DISCUSSION

The results of this study demonstrate that the percutaneous edge-to-edge mitral valve repair procedure using the MitraClip device directly affects mitral valve geometry. By grasping the anterior and posterior leaflets, the coaptation length and area of the mitral leaflets significantly increase in end-systole. The contribution of the anterior mitral leaflet in the coaptation increases and the antero-posterior diameter of the mitral annulus is reduced leading to a more elliptical mitral annular shape.

Few studies have assessed the effect of surgical annuloplasty on mitral valve anatomy using 3D-TEE. Greenhouse *et al.* used intraoperative 3-dimensional TEE to examine the regional effects of surgical mitral annuloplasty on annular geometry and leaflet coaptation zones in patients with FMR.[17] A significant increase in mitral leaflet coaptation length after band annuloplasty was observed, particularly at the middle scallops of the anterior mitral leaflet (2.9±2.6mm at baseline vs 5.5±2.5mm post-surgery, $p<0.01$). The posterior annulus was displaced anteriorly leading to an increase of coaptation surface of the anterior leaflet and correction of the mitral regurgitation. Our findings are in agreement with this concept by showing that the exposed length and area of the anterior leaflet at the central scallop (i.e. the anterior leaflet length and area without the coapting part) decreased. These changes were not accompanied by changes in the total mitral leaflet area, indicating inclusion of a larger proportion of the anterior leaflet into the area of coaptation (Figure 4). Therefore, implantation of a MitraClip device seems to af-

Table 6.2
Echocardiographic mitral valve geometry parameters pre- and post- MitraClip implantation measured with 3-dimensional transesophageal echocardiography.

	Pre-MitraClip	Post-MitraClip	p-value
Annulus			
Anteroposterior diameter (mm)	33.2 ± 6.2	32.1 ± 5.3	0.08
Intercommissural diameter (mm)	39.9 ± 6.4	41.1 ± 6.5	0.15
Ellipsicity (%)	121.8 ± 17.3	129.4 ± 18.4	0.04
Circumference (mm)	124.5 ± 19	124.8 ± 17.4	0.88
Annular area (mm^2)	1178.0 ± 380.2	1170.7 ± 326.1	0.81
Annular height (mm)	5.5 ± 1.9	5.7 ± 1.9	0.62
Annular height to intercommissural width ratio (%)	20.2 ± 13.8	18.3 ± 6.3	0.41
Leaflets			
Anterior leaflet length exposed A2 segment (mm)*	27.2 ± 5.5	25.4 ± 5.0	0.03
Posterior leaflet length exposed P2 segment (mm)*	11.6 ± 4.1	12.5 ± 4.3	0.15
Anterior leaflet exposed area (mm^2)*	795.4 ± 277.0	729.8 ± 222.0	0.04
Posterior exposed leaflet area (mm^2)*	636.9 ± 257.0	666.3 ± 227.5	0.32
Total leaflet area (mm^2)	1811.2 ± 582.2	1870.3 ± 505.5	0.18
Anterior leaflet angle (º)	27.1 ± 7.4	33.6 ± 7.9	<0.001
Posterior leaflet angle (º)	49.0 ± 13.6	56.1 ± 10.3	0.02
Aortomitral angle (º)	134.8 ± 11.2	133.0 ± 11.3	0.39
Non-planarity angle (º)	122.6 ± 18.3	123.3 ± 18.4	0.82
Tenting height A2-P2 (mm)	8.1 ± 3.4	8.2 ± 3.0	0.65
Tenting volume (mL)	2.9 (IQ range 1.7-4.5)	3.3 (IQ range 2.5-4.5)	0.80
Coaptation			
Coaptation length A2P2 (mm)	5.0 ± 0.11	5.3 ± 0.87	<0.001
Coaptation area (mm^2)	349.6 (IQ range 289.0-492.8)	433.8 (IQ range 327.6-522.7)	0.008

*The exposed length and area of the leaflets does not include the coapting part of the leaflet.

fect mitral coaptation geometry similarly to surgical mitral annuloplasty, however, through a different mechanism.

In patients with FMR treated with the Mitraclip device, Schmidt *et al.*, reported significant reductions of the mitral annular area (mean difference 0.39±0.49cm^2, p<0.001) and antero-posterior annular diameter (mean difference 0.28±0.32cm, p<0.001) as well as a significant reduction in tenting area (mean difference 0.39±0.49cm^2, p<0.001).[18] The disparate results of the study by Schmidt et al and the present study may be explained by the different post-processing analysis. While Schmidt et al performed the measurements on the orthogonal multiplanar reformations of the 3-dimensional TEE volume set, in the present study the measurements were performed on 3-dimensional models that permit better assessment of the saddle shape of the mitral annulus. The current analysis did however show a change in the shape of the mitral annulus with an increase in annular ellipsicity and a decrease in anteroposterior diameter which is consistent

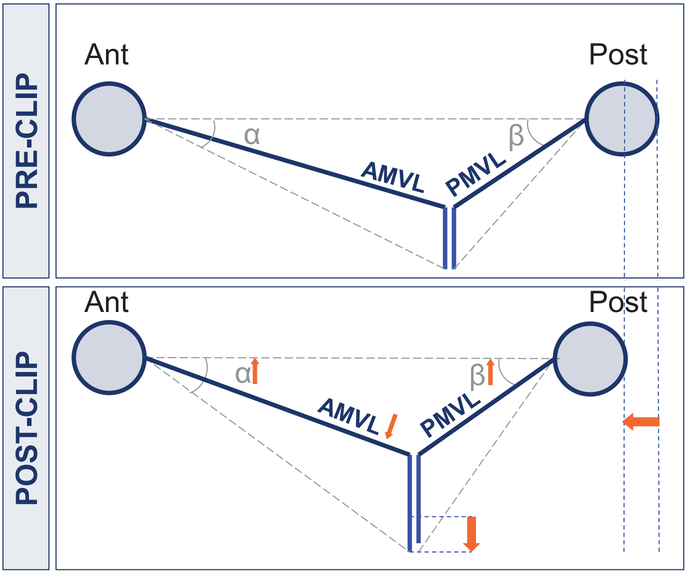

Figure 6.4
Schematic overview of acute effect of MitraClip device on mitral valve geometry. The MitraClip device leads to a decrease in exposed anterior leaflet length (AMVL) at the A2 level without change in overall mitral leaflet length and area, indicating a higher contribution of the AMVL into coaptation. Furthermore, the antero-posterior diameter tends to reduce with corresponding increases in the anterior and posterior mitral leaflet angle (α and β). AMVL = Anterior mitral valve leaflet, PMVL = Posterior mitral valve leaflet.

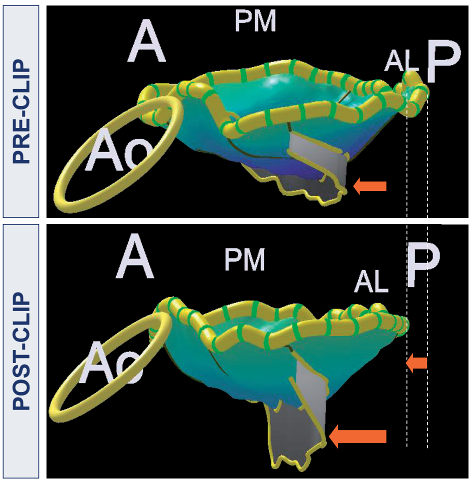

Figure 6.5
3-dimensional overview of acute effect of MitraClip therapy on mitral valve geometry showing an increase in coaptation area. The long-axis view of the 3-dimensional model is showed at baseline (upper panel) and after (bottom panel) MitraClip implantation with the arrow pointing the area of coaptation. A = anterior, AL = anterolateral, Ao = Aorta, P = posterior, PM = posteromedial.

with previous reports.[18-20] Recently, Schueler *et al.* showed that patients with FMR showed significant decreases in the anteroposterior diameter of the mitral annulus (from 4.0±0.6 cm to 3.6±0.6 cm, $p<0.001$), 3-dimensional mitral annulus area (from 14.4±3.9 cm^2 to 12.9±3.4 cm^2, $p<0.001$) and mitral valve sphericity index (from 0.9±0.1 to 0.8±0.1, $p<0.001$) whereas the intercommisural diameter remained unchanged.[20] Interestingly, these changes were not observed in patients with degenerative mitral regurgitation. Furthermore, patients in whom the antero-posterior diameter acutely reduced ≥6.4% had superior clinical response to MitraClip therapy after 6 months of follow-up compared with patients showing less acute annulus diameter reduction. However, an acute reduction in the antero-posterior diameter after MitraClip therapy would indicate significant traction on the mitral leaflets to reduce the distance between the anterior and posterior annulus. This high leaflet stress could affect the durability of the procedure. To assess leaflet stress, we analysed the annular-height to intercommissural-width ratio. In the present study, the annular-height to intercommissural-width ratio did not significantly reduce after MitraClip implantation, suggesting no acute increase in leaflet stress.[21] Understanding the effects of the MitraClip on the geometry of the mitral valve will eventually help to identify patients that will benefit most from this procedure.

Clinical implications

Evaluating the effects of MitraClip on 3-dimensional mitral valve geometry is important to understand its therapeutic efficacy and durability. The present study showed that MitraClip increases the coaptation length and area due to a larger contribution of the anterior mitral leaflet into the coaptation. Furthermore, the anteroposterior diameter tends to reduce with corresponding increases in the anterior and posterior mitral leaflet angles. Subsequent iterations of the device or development of newer systems may consider these findings to improve the efficacy of the repair. Although the effects of these geometrical changes on long-term durability were not evaluated in the present study, future investigations may shed light on this topic and help in the design of novel devices.

Limitations

There are several limitations inherent to this study. First, the study population was rather small. By recording both the pre- and postprocedural views during anaesthesia we aimed at creating a similar hemodynamic status for the pre- and postprocedural measurements of mitral annular geometry. However, the effects of the anaesthetics on patients' hemodynamic status must be considered. Furthermore, the clips caused shadowing artifacts and limited the evaluation of the coaptation point. By tracing the coaptation point in the body of the MitraClip after the procedure, which is the point where the leaflets are grasped by the clip, we aimed at reducing the effect of the artifacts on the outcomes.

CONCLUSION

Percutaneous MitraClip therapy affects mitral valve geometry in FMR patients by increasing coaptation length and area mainly due to a larger contribution of the anterior mitral leaflet into coaptation after the procedure.

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