ABBREVIATION LIST

MR, mitral regurgitation

MV, mitral valve

3D, three-dimensional

FMR, functional mitral regurgitation

DMR, degenerative mitral regurgitation

TEE, transesophageal echocardiography

2D, bi-dimensional

PVF, pulmonary vein flow

VC, vena contracta

MA, mitral annulus

AP, antero-posterior

CC, commissural

SI, sphericity index

AML, anterior mitral leaflet

PML, posterior mitral leaflet

AHCWR, annulus height to commissural width ratio

INTRODUCTION

The MitraClip System (Abbott Vascular, SA, California, USA) has emerged in the last decade as a valuable and safe treatment option for high-risk patients with symptomatic significant mitral regurgitation (MR). [1,2]

Despite the established clinical benefit of MitraClip procedure, [2,3] still little is known about how the device acts in modifying the anatomy of mitral valve (MV). Few studies have already examined acute changes occurring in MV apparatus after percutaneous repair, by three-dimensional (3D) echocardiography. [4,5,6,7,8,9] Of notice, these analysis were mainly limited to manual 3D assessment of annular and leaflets dimensions, ignoring the complexity of valvular apparatus geometry and dynamics.

Moreover, none of the above-mentioned studies has evaluated the outcome of third generation MitraClip XTR, released in 2018. The device, designed with longer clip arms and grippers, is meant to facilitate leaflet grasping even in complex valve anatomy. Compared with contemporary series of patients implanted with older versions (NTR, NT), the use of the new device has shown higher procedural success rate and comparable early 30-day outcomes. [10]

In our study we meant to understand the mechanisms behind the device's procedural outcome, evaluating the acute effect of MitraClip XTR implantation on mitral anatomy by 3D parametric quantification of valvular geometry and function. [11] Using a dedicated semiautomated software, it is possible to generate a 3D modelling of MV, deriving a number of quantitative measurements on mitral apparatus: annulus diameters, height and excursion during the cardiac cycle; leaflets' angle at annular hinge point and mitral non-planar angle. In literature there is already experience in using these new post-processing tool for diagnostic purposes, [12,11] but no data are still available for the use of the parametric analysis in the interventional field.

We hypothesized that mitral annular and leaflet parameters obtained by 3D parametric quantification will favour the correct understanding of changes occurring in mitral geometry after MitraClip device implantation.

The aim of this study was therefore threefold: (1) perform a prospective study, employing in clinical practice the new tool of MV 3D parametric analysis, (2) evaluate the effect of third generation MitraClip XTR implantation on valvular geometry, (3) searching for specific outcome in functional (FMR) and degenerative (DMR) cases.

METHODS

Study Population - From the consecutive series of 81 patients who underwent percutaneous mitral valve repair at our Institution between April 2018 and February 2020, we enrolled 59 patients implanted with at least one MitraClip XT_R device, in whom intra-procedural 3D transesophageal echocardiography (TEE) was adequate to perform parametric study of MV geometry prior and after MitraClip implantation. The Heart Team evaluated the patients' eligibility for procedure, as standard behaviour in our Institution. The recruited patients presented heart failure symptoms, with at least moderate-to-severe (3+) MR and high surgical risk according to EuroSCORE, STS score, elderly age and specific risk factors associated with excessive morbidity and mortality. Patients were affected by either FMR or DMR. In case of multiple mechanisms, we considered the predominant one as responsible for valve regurgitation. Qualifying inclusion and exclusion criteria, as well as the details of the MitraClip procedure, have been previously reported. [13]

Echocardiographic Protocol - An extensive transthoracic echocardiographic study was performed during patients' screening. Bi-dimensional (2D) and Doppler recordings were performed according to current Recommendations. [14] MR severity was graded following a four-step classification as "mild" (1+), "moderate" (2+), "moderate-to-severe" (3+) or “severe” (4+), integrating qualitative (Color Doppler jet characteristics and pulmonary vein flow pattern – PVF), semi-quantitative (Vena Contracta width – VC) and quantitative parameters (Regurgitant Volume and Effective Regurgitant Orifice Area). [15] In agreement with European Guidelines, different cut-off values for DMR and FMR cases were used. [16] Two-D and 3D TEE were performed just before and after device deployment, to evaluate patients’ immediate procedural results under stable hemodynamic conditions. We used a GE E95 (General Electrics Medical Systems, Barrington, IL, USA) ultrasound machine equipped with a 4D TEE matrix array probe. To grade post-procedural MR, a composite approach was employed, combining qualitative 2D and 3D parameters (3D VC area). [17] Three-D VC area was contoured at the level of cross-sectional plane through the VC, obtained from a multi-planar reconstruction, perpendicular to the largest regurgitant jet. [18] (**Figure 1**) Patients were therefore classified based on early procedural outcome, in two subgroups: optimal (residual MR ≤1+, residual jets ≤2, normalization of pulmonary vein flow pattern, 3D VC area <3 cm^2) vs. sub-optimal result (if at least one of the above-mentioned parameters was not present). Three-D images were acquired in *zoom* mode, taking as a reference MV inter-commissural mid-esophageal view. Multi-beat (3 to 5 beats) or single-beat acquisition was used, according to patients’ heart rhythm, possibility of inducing apnea on mechanical ventilation and image quality. [19] Only 3D dataset comprising both MV and aortic valve anulus and with a minimum frame rate of 12 FPS were considered adequate for off-line analysis using a dedicated semiautomated software (Mitral Valve Quantification, MVQ - GE EchoPAC v. 201). From the 3D dataset, each software automatically displays three orthogonal planes of the MV, which need to be manually aligned across the mitral annulus (MA) to establish the correct spatial orientation. Following, anatomical landmarks are placed in the reference end-systolic frame. For the post-procedural analysis, we considered as the coaptation point the MitraClip proximal extremity. Thereafter, the software automatically tracks MA and leaflets contour which the operator can run through and eventually fix manually and creates a 3D-rendered surgical *en face* view of the MV, used to evaluate major structural deformation in the annulus saddle-shape or abnormality in leaflet morphology. An example of MV 3D reconstruction performed using the GE software is displayed in **Figure 2**. The parametric quantification of MV geometry comprised the following indexes: AP and CC diameters, sphericity index (AP/ CC diameters ratio - SI), MA height and velocity, anterior (AML) and posterior leaflets (PML) angles (angles at which each leaflet met the MA plane), non-planar angle (subtended by two lines connecting the middle point of the CC diameter, respectively, with the anterior and the posterior annulus highest points). Furthermore, to estimate changes of MA saddle shape, we derived the ‘saddle index’ from annulus height to commissural width ratio (AHCWR), as previously described. [5,20] All 3D parameters were assessed at baseline and after device deployment; in case of more than one device used, 3D analysis was performed after the release of the last device (**Figure 3**).

Statistical Analysis - Categorical and dichotomous variables were expressed as absolute numbers and percentages and were compared by chi-square or Fisher exact tests, as appropriate. Continuous variables were analysed for distribution using the Shapiro-Wilk test. According to their normal or skewed distribution, continuous variables were expressed as mean ± standard deviation or median (25^{th} to 75^{th} interquartile range - IQR), as appropriate. Unpaired Student’s t-tests were used to compare continuous parameters following a normal distribution, while Mann-Whitney *U* tests were used to compare continuous variables with skewed distribution. Paired t-test was used to compare pre-procedural and post-procedural echocardiographic variables between FMR and DMR. Univariate and multivariate analysis was employed in order to define the association of pre-procedural echocardiographic variables with optimal or sub-optimal post-procedural result and to estimate corresponding odd ratios (OR) and 95% confidence intervals (CI). All the baseline echocardiographic variables were inserted in the univariate model. Just the variables with a p-value <0.10 in the univariate analysis were reported; then they were sequentially entered into the multivariate model. Parameters with a p value ≤0.05 were then considered significant in this model. The data were analysed with SPSS statistics software (version 25, IBM Corp., Armonk, N.Y., USA).

RESULTS

Baseline Characteristics - Baseline demographic, clinical and echocardiographic characteristics of the study population are listed in **Table 1**. Patient median age was 80 years (IQR 75-85), and 61% were male. Twenty-six patients (44.1%) were diagnosed with DMR, with the majority affected by fibro-elastic deficiency (15 cases of leaflet flail) or diffuse myxomatous degeneration (8 patients with multiple prolapse). The patients diagnosed with FMR (N= 33, 55.9%) presented higher incidence of previous myocardial infarction (51.5% vs. 11.5%; p=0.002), history of heart failure (66.7% vs. 38.5%, p=0.031) and critical bi-ventricular dysfunction, with consequent higher surgical risk according to EuroSCORE II (6% vs. 3%; p≤0.001), if compared to DMR. Severe MR was observed in 74.6% of patients, with equal distribution between the two cohorts. Nevertheless, patients with FMR presented higher left ventricle diameters and volumes, whereas patients with DMR revealed at MR quantification, greater regurgitant volume, larger VC and significantly bigger effective regurgitant orifice area.

Procedural Results – Twenty-four patients (40.7%) were successfully treated with the implantation of a single MitraClip XT_R, 32 patients (54.2%) with 2 clips and only 3 patients (5.1%) needed 3 devices. All patients had successful device implantation, with only one adverse event, represented by a major bleeding event during the hospital-stay. MR reduction to less than moderate grade (MR< 2+) was achieved in 40 patients (67.8%), with no significant difference between the two subgroups; all patients presented at least 1 grade reduction of MR severity (**Table 2**).

__**Three-D Echocardiographic Assessment**__ – Three-D echocardiographic parameters obtained intra-operatively before and after the MitraClip implantation are reported in **Table 3**. Regarding the baseline characteristics, the patients with FMR presented more severe MV deformation as indicated by bigger AML and PML angles (AML angle, 23.2° ± 10.8 vs. 15.9° ± 10.3, p value 0.015; PML angle, 36.3° ± 13.7 vs 19.8° ± 12.1, p value ≤0.001), while DMR patients revealed a more flexible annulus, with higher MA excursion velocity (maximum annular velocity, 26.3 mm/s ± 11.7 vs 35.0 mm/s ± 14.2, p value 0.038). No differences in annular diameters were found between FMR and DMR cohort (CC annulus diameter, 39.2 mm ± 6.8 vs 38.2 mm ± 4.2, p value 0.52; AP annulus diameter, 36.2 mm ± 5.7 vs 36.3 mm ± 6, p value 0.966).

Comparing the pre- and post-procedural data (**Table 3**), FMR patients experienced a significant reduction of SI, mainly driven by a critical shortening in AP diameter. Although not showing a significant variation in neither annular diameter, the DMR patients presented a significant decreased SI, as a proof of the immediate annular reshape after MitraClip implantation. We further appreciated distinctive geometrical changes for each MR sub-group. FMR patients emerged with significant narrowing of the non-planar angle and significant increase in MA height and AHCWR. On the other hand, DMR group revealed a reduction in MA velocity, as the annulus became more fixed because of the device deployment, and a significant increase in PML angle, possibly related to higher prevalence of posterior localization leaflet prolapse/ fail. Among the six 2D and 3D pre-procedural parameters statistically different at univariate analysis between optimal and sub-optimal groups, AML angle resulted the strongest independent predictor of procedural outcome at multivariate analysis (**Table 4**), next to end-diastolic volume (EDV).

Inter-Observer and Intra-Observer Variability – Three-D parametric MV measurements were found highly reproducible at both intra-observer and inter-observer variability analysis, with intra-class correlation coefficients ranging from 0.6 to 0.96 and 0.63 to 0.93, respectively (**Table 5**).

DISCUSSION

To the best of our knowledge, this is the first study evaluating acute changes in MV geometry after implantation of third generation MitraClip XT_R device, taking into account the underlying regurgitation mechanism (FMR vs DMR cases). Moreover, the novelty of our analysis, resides on the use of a dedicated semiautomated GE software that provides a detailed reconstruction of MV anatomy, thanks to a parametric quantification of its geometry (annular diameters, height, and angles) and dynamics (annular velocity).

Results of this study can be summarized as follows:

(1) MitraClip XT_R implantation induces acute MV remodelling, with distinctive effects in functional and degenerative cases: recovery of physiologic valvular saddle-shape in FMR cases, and normalization of annular dynamics in DMR patients

(2) 3-D derived parameters can be used as predictors of acute post-procedural result after percutaneous MV repair.

Three-D analysis of MV in the overall population – As regards baseline data, our study addressed a broad spectrum of patients, with quite heterogeneous MR etiology. Notably, the DMR group had a high prevalence of leaflet flail or multiple prolapse cases, usually judged as sub-optimal for percutaneous approach with older device versions. Nevertheless the early experience, MitraClip XT_R implantation demonstrated an optimal technical success rate even in these challenging cases, [21,22] with acute outcomes comparable between FMR and DMR cohorts [23] and resembling recent literature data on MitraClip performance. [2,10]

At baseline, FMR patients showed a greater angulation of both anterior and posterior leaflets, confirming leaflet displacement as the main determinant of valve regurgitation, [24] while degenerative affection (Fibroelastic deficiency and Barlow's disease) mainly produced an exaggeration of physiologic annular excursion during the cardiac cycle. [20] Mimicking surgical edge-to-edge repair, MitraClip implantation reduces MR severity primarily by narrowing the valve orifice. Recent evidence however demonstrated that acute changes also occur in MA dimensions and dynamics. Most studies identified the reduction of AP diameter as a crucial consequence of leaflets grasping, [7,9] with some investigators recognizing it as a specific behaviour of FMR cases. [6,8,25] Our findings agree with this concept by observing a reduction of AP diameter in both MR cohorts, with statistical significance in the FMR group. This observation comes in line with the mechanistic consideration that leaflets traction is primarily exerted along the antero-posterior direction; however, in degenerative valves the redundancy of fibrotic tissue may prevent major geometrical changes to occur. In addition to the reduction in size, our results demonstrated that MitraClip XT_R also alters the annular shape, restoring the physiological elliptical geometry, as indicated by a significant reduction of SI in both FMR and DMR patients. The reason why previous studies failed in demonstrating such change [9,25] could be probably recognized in the use of older devices.

Interestingly, the preliminary results of the ongoing EXPAND trial, presented during the American Collage of Cardiology Congress 2020, [26] revealed a higher frequency of post-procedural MR $\leq$1 achieved with new MitraClip NTR and XTR devices than previously reported in earlier trials. According to our analysis, we hypothesized two different mechanisms accounting for this improved procedural efficacy: (1) a larger portion of tissue grasped within MitraClip XTR system, and (2) a greater traction applied on valve leaflets, that is thereafter transmitted to the peripheral annulus, accomplishing the recovery of the original valve geometry.

FMR cohort - Looking into more detailed MA dynamics, we reported in the FMR group a significant narrowing of the non-planar angle, along with an increase of both annulus height and AHCWR. Taken together, these parameters suggest a critical improvement of annular flattening and leaflets tethering after the procedure, supporting the hypothesis that MitraClip XT_R may favour in FMR patients the recovery of the anatomical saddle-shape. Such data about annular dynamics after MitraClip procedure are lacking in previous reports. [5,8] Moreover, AHCWR can be used as an index of mechanical leaflet stress, which is minimal when MA saddle shape is preserved (AHCWR < 15-20%). [27] Our post-procedural data remain within this physiological range, suggesting no acute increase of leaflet stress exerted by MitraClip $XT_{R,}$ nonetheless the greater proportion of tissue grasping.

DMR cohort - On the other side, DMR patients presented a significant reduction of maximum annular velocity, indicating a predominant mechanical effect of the device that pulls down the leaflets and makes the MA more fixed. This effect has been already described in patients with DMR following surgical mitral ring annuloplasty. [28] Degenerative cases are not expected to show a significant annular reshape, since MA is nearly normal. Of relevance, the scallop eversion or prolapse over the annular plane may probably lead to an underestimation of the leaflet angle at the baseline analysis.

Considering the higher frequency of degenerative lesions affecting the posterior leaflet, the significant increase of post-procedural PML angle observed in DMR cases, could probably reflect the normalization of leaflet orientation, because of local MitraClip implantation.

Three-D predictors of acute procedural result - Previous studies have already suggested that AP diameter at baseline, [25] post-procedural reduction in AP diameter [7] and ventricular chamber size [29] might be possible determinants of MitraClip effectiveness. Consistent with the notion that ventricular and valvular remodelling negatively impact on procedural out-come, we found that ventricular end-diastolic volume and 3D-derived AML angle could predict residual MR after MitraClip implantation. Lower values of baseline AML angle are associated with optimal echocardiographic outcome, as previously defined in the manuscript. This finding is complementary with previous data from surgical experience that identified pre-operative PML angle as a predictor of long-term outcome after MV annuloplasty. [30]

CONCLUSIONS

Our investigation demonstrated that implantation of the new MitraClip XT_R device produces a significant and immediate remodelling of mitral geometry that extends far beyond the region of device deployment. Moreover, the 3D parametric analysis of MV, performed by semiautomated software, revealed new determinants of MitraClip procedural success, potentially useful for pre-procedural screening in the clinical practice.

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DISCLOSURES

All the authors have no conflict to report.