Severe mitral regurgitation recurrence after successful percutaneous mitral edge-to-edge repair by Mitraclip: Insights from a three-dimensional echocardiography study

Running title: Mitral regurgitation recurrence after Mitraclip

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Abstract

Background: The sustainability of the results of mitraclip procedures is a source of concern.

*Aims***:** To investigate risk factors of severe mitral regurgitation (MR) recurrence after Mitraclip in primary MR.

Methods and results: Eighty-three patients undergoing successful Mitraclip procedures were retrospectively included. Valve anatomy and Mitraclips placement were comprehensively analyzed by post-processing 3D echocardiographic acquisition. The primary composite endpoint was the recurrence of severe MR. Mean age was 83±7 years-old, 37 (44%) were female. Median follow-up was 381 days (IQR 195-717) and 17 (20%) patients reached the primary endpoint. Main causes of recurrence of severe MR were relapse of a prolapse (64%) and single leaflet detachment (23%). Posterior coaptation line length (HR 1.06 95%CI 1.01-1.12 p=0.02), poor imaging quality (HR 3.84, 95%CI1.12-13.19; p=0.03), and inter-clip distance (HR 1.60, 95%CI 1.27-2.02; p<0.01) were associated with the occurrence of the primary endpoint.

Conclusions: Recurrence of severe MR after a MitraClip procedure for primary MR is common and results from a complex interplay between anatomical (tissue excess) and procedural criteria (quality of ultrasound guidance and MitraClips spacing).

Keywords

Mitral regurgitation, Three-dimensional echocardiography, Percutaneous intervention

Abbreviations

CI: confidence intervals

HR: hazards ratios

MR: Mitral regurgitation

PMVR: percutaneous mitral valve repair

TEE: transesophageal echocardiography

Introduction

Mitral regurgitation (MR) is one of the most common valve diseases. (1),(2). It is usually categorized into primary MR, an organic valvular impairment, and secondary MR, related to left ventricle and mitral annulus dilatation. Clinical consequences of untreated severe MR are represented by heart failure, pulmonary hypertension, atrial fibrillation, and death(3). Cardiac surgery, especially mitral valve repair, is the gold standard treatment for PMR(4). Due to their frailty or comorbidities, many patients are contraindicated or considered having a prohibitive risk for conventional surgery (5). In consequence, percutaneous techniques have been in rapid development over the past decade. Among the latter, the percutaneous mitral valve repair (PMVR) by edge-to-edge approach, mainly represented by the Mitraclip technique (6) (Abbott Vascular, Abbott Park, Illinois), is the one that accumulates the most evidence and experience. It is based on the surgical technique first described by Alfieri(7) that creates a double-orifice mitral valve by approximation of the free edges of at the site of regurgitation and thus promotes a coaptation bridge between the mitral leaflets. In brief, it is safe(6), equivalent to surgical treatment in the treatment of inoperable patients with primary MR (8) and superior to optimal medical therapy for secondary MR(9).

Durability and the reoperation rate have been pointed out as the Achilles heel of this technique(8). Indeed, while the rate of patients with MR ≤ grade 2 is excellent in the immediate post-procedural period, it tends to decrease over time(10) (e.g. success rate of 91% at 30 days versus 79% at one year in the ACESS-EU registry)(11). MR recurrence after Mitraclip has been associated with an increased risk of death and re-hospitalization for heart failure during follow-up(12). Anatomical considerations such as coaptation length,

coaptation gap are key actors for immediate post procedural success and eligibility criteria have been advanced for patients and valves selection (13). Nevertheless, pre, per and post procedural factors associated with long-term MR recurrence are not as well identified.

The purpose of this study was to characterize and determine the risk factors for severe MR recurrence, among patients with primary MR treated by PMVR with Mitraclip, with an initial good results (MR ≤ grade 2).

Methods

Study design and objectives

The study was designed to include retrospectively all consecutive patients who underwent PMVR with MitraClip therapy (Abbott Vascular, Abbott Park, Il, USA) for primary MR, between October 2016 and April 2020 at the university hospital of Toulouse, France.

Patients who have experienced an unsuccessful procedure, as defined by a MR over grade 2 of 4, assessed by the intraprocedural TEE immediately after edge-to-edge repair, were excluded.

The study is conformed to the principles outlined in the Declaration of Helsinki. According to French law on ethics, patients were informed that their codified data will be used for the study According to the French ethic and regulatory law (public health code) retrospective studies based on the exploitation of usual care data shouldn't be submit at an ethic committee but they have to be declare or cover by reference methodology of the French National Commission for Informatics and Liberties. A collection and computer processing of personal and medical date was implemented to analyze the results of the research. Toulouse University Hospital signed a commitment of compliance to the reference methodology MR-004 of the French National Commission for Informatics and Liberties. After evaluation and validation by the data protection officer and according to the General Data Protection Regulation, this study completing all the criteria, it is register in the register of retrospective study of the Toulouse University Hospital and cover by the MR-004 (French National Commission for Informatics and Liberties number: 2206723 v 0). This study was approved by Toulouse University Hospital and confirms that ethic requirements were totally

respected in this report.

Data collection

Clinical data as past medical history, symptoms status were collected from the institutional database. All patients were considered unsuitable for surgery or with a high risk for cardiac surgery by the heart team.

All procedures were guided by TEE using a commercially available 3D TEE machine (6VT-D transducer, e95 Vivid system, GE Vingmed Ultrasound AS, Horten, Norway). Echocardiographic follow-up of patients was performed by transthoracic echocardiography (4V-D transducer, e95 Vivid system, GE Vingmed Ultrasound AS, Horten, Norway). All intraprocedural and follow-up images were stored on a dedicated workstation, EchoPAC V.202 (Advanced Analysis Technologies; GE Medical Systems) for the offline analysis.

Follow-up was assessed in June 2020 by electronic chart review or by phone interview of the patient's general practitioner/cardiologist, patient, or family.

Echocardiographic specific measurements

All exams were blindly reviewed by a single (YLB) experienced operator (over 150 Mitraclip procedures) on a dedicated EchoPAC workstation.

Intra-procedural TEE data were analyzed as follows:

-Mitral valve analysis immediately after anesthetic induction: use of a 3D modeling of the mitral valve obtained with a dedicated application (4D Auto MVQ, GE Vingmed Ultrasound AS, Horten, Norway) from a 3D zoom acquisition. From the latter, a comprehensive analysis of the measurements of the mitral valve was carried out (Figure 1 and online data supplement video 1).

-Analysis of the mitral valve at the end of the procedure. Based on a 3D volume acquisition and the use of a multiplanar reconstruction software (Flexi Slice, GE Vingmed Ultrasound AS, Horten, Norway), a comprehensive analysis of the Mitraclips position in relation to the main mitral axes was made (Figure 2 and online data supplement video 2). If more than one Mitraclip was used, the largest distance between the two clips was measured.

In addition, the quality of the ultrasound image and of the patient selection were evaluated. Poor image quality was defined by the inability to correctly visualize the grasping of the leaflets (both leaflets, both Mitraclip's arms and grippers simultaneously visible). Regarding patient selection, the valve morphology was defined as optimal, conditionally suitable and unsuitable according to Everest criteria(13). Optimal valve morphology was defined by a central pathology in segment 2, non-leaflet calcifications, a mitral valve opening aera > 4 cm^2, a mobile length of the posterior leaflet ≥ 10 mm, a normal leaflet strength and mobility, a flail width <15 mm, and a flail gap <10mm. Conditionally suitable valve

morphology was defined by a pathology in segment 1 or 3, mild calcifications outside of the grasping zone, a mitral opening > 3 cm2, a mobile length of the posterior leaflet of 7-10 mm, a leaflet restriction in systole, and a flail width > 15 mm. Unsuitable morphology was defined by a perforated mitral valve leaflet or a cleft, severe calcifications, a significant mitral stenosis, a rheumatic leaflet thickening and restriction in systole and diastole and a Barlow's syndrome.

All patients underwent a transthoracic echocardiography check-up within 3 days after the procedure and regularly every 6 months afterward. These data were reviewed to determine the occurrence of severe residual regurgitation. Grading of residual MR was conducted according to the American Society of Echocardiography guidelines(14). In practical terms, if the patient met ≥ 4 specific criteria for mild MR, the MR was considered mild. Specific criteria for mild MR were a small, narrow central jet, a vena contracta ≤ 0.3 cm, a vena contracta aera < 0.2 cm, no or small flow convergence, a mitral A wave dominant inflow, a soft or incomplete jet by continue doppler. If the patient met ≥ 4 specific criteria for severe MR, the MR was considered severe. Specific criteria for severe MR were an abnormal device morphology or a flail leaflet, a vena contracta ≥ 0.7 cm or ≥ 2 moderate jets, a vena contracta aera ≥ 0.4 cm or ≥ 2 moderate jets, a large flow convergence, a central large jet > 50% of left atrium area, and a pulmonary vein systolic flow reversal. In other cases, quantitative volumetric methods were performed. Regurgitant volume ≥ 60 mL or regurgitation fraction ≥ 50% were used to define severe MR.

Endpoints

The primary endpoint was the recurrence of severe mitral valve regurgitation during the follow-up.

Early occurrence of severe mitral valve regurgitation was defined by its appearance within the first three days post-procedure and late occurrence of mitral valve regurgitation was defined by its appearance at one year after the procedure.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Nominal values were expressed as numbers and percentages. Comparisons were made using Chi2 test for categorical variables or Fisher exact test when appropriate, while Student t test or Mann-Whitney test were used for continuous variables. Univariate Cox regression analysis were performed to assess the association of the variables with the primary endpoint.

Results of the Cox regression analysis were reported with hazards ratios (HR) and 95% confidence intervals (CI). A value of $p<0.05$ was considered significant. Statistics were analyzed using XLSTAT v2019.1 (Addinsoft, Paris, FR).

Results

Patients characteristics

A total of 85 patients underwent a PMVR with Mitraclip for primary MR during the study period. Among them, 2 (2%) had unsuccessful procedures, with a final MR over grade 2 of 4 (1 leaflet tear and 1 grasping failure due to high flail gap) and were therefore excluded. Finally, 83 patients were included.

Mean age was 83±7 years-old, 37 (44%) were female. All patients (100%) had a preprocedural severe MR. Regarding patient screening, 40 (48%) had optimal valve morphology, 33 (40%) had conditionally suitable valve morphology and 10 (12%) had unsuitable morphology for MitraClip technique. All patients with unsuitable morphology were Barlow diseases. The main valve pathology was P2 prolapse (n=65, 78%). Baseline demographic and clinical characteristics of patients are summarized in Table 1.

Procedural data

The mean procedure time was 124±40 minutes, and the mean fluoroscopy time was 30±18 minutes. The mean postprocedural transmitral gradient was 3.4±0.9 mmHg and an average of 1.7±0.6 MitraClips were used. NTR or NT Clip Delivery System were used for 57 (69%) patients, XTR Clip Delivery System was used for 15 (18%) patients, and 11 (13%) had both XTR and NTR in same procedure.

A complete MR correction was achieved in 12 (14%) patients, 67 (81%) had a post-procedural MR grade 1 and 4 (5%) a post-procedural MR grade 2.

No intra-procedural death occurred, and there was no immediate conversion to surgery.

Follow-up and primary endpoint

The median follow-up was 381 days (IQR 195-717). Seventeen (20%) patients reached the primary endpoint. Regarding the delay of occurrence of severe MR, 9 (53%) were early and 8 (47%) were late. The median delay for the primary endpoint to occur was 35 (IQR 2-471) days. There were 6 (7%) reoperations by PMVR and 1 (1%) by cardiac surgery. The main causes of recurrence of severe MR after PMVR (figure 3) were relapse of a prolapse adjacent to the MitraClip (29%) (online data supplement video 3) or between two MitraClips (35%) (online data supplement video 4), single leaflet detachment (23%) (online data supplement video 5), infective endocarditis (6%) and appearance of a coaptation gap alongside the MitraClip (6%). The mechanisms of recurrence of severe MR after PMVR, according to their chronology of onset are presented in table 2.

Factors associated with the primary endpoint

The anatomical conditions associated with the occurrence of the primary endpoint were posterior closure line length (HR 1.06 95%CI 1.01-1.12 p=0.02), and, only in the case of procedures using one MitraClip, Barlow disease (HR 7.67; 95% CI, 1.4 to 39.69; p = 0.01) (Table 3). For information, the posterior closure line length was measured in three

dimensions by the post-processing software and was the true length of the free edge of the posterior leaflet (figure 1G).

Procedural factors associated with the occurrence of the primary endpoint were poor imaging quality (HR 3.84, 95%CI 1.12-13.19; p=0.03), and, only in the case of procedures using more than 1 Mitraclip, inter-clip distance (HR 1.60, 95%CI 1.27-2.02; p<0.01).

Discussion

In this retrospective study that included 83 patients who had undergone PMVR by MitraClip technique for primary MR,with initial procedural success, we described causes, prevalence, and risk factors for severe MR recurrence. The main results can be summarized as follows: 1) severe recurrent MR were common, representing 20% of the population 2) The most common cause of MR recurrence was the prolapse reformation, and contributing factors are anatomical (excess tissue) and procedural (number and position of mitraclips); 3) The second most frequent cause of MR recurrence was Mitraclip's single leaflet detachment.

In our study, severe recurrent MR after Mitraclip therapy was frequent as it concerned 20% of the patients. It was, however, consistent with data from other studies: 18% in Everest 2 and 21% in ACESS-EU at one year (11)(15). The discrepancy between immediate post-procedural and long-term results, in terms of MR reduction, appears to be multifactorial. Indeed, our study seems to demonstrate that it is a complex phenomenon that involves valve anatomy, procedural data, and operators' experience.

In our study, the most common cause of recurrent MR was the prolapse reformation. Contributing factors were anatomical and procedural. From an anatomical point of view, one of the strengths of this study is to have been able to achieve 3D valve modelling of all the patients and thus to have had access to a comprehensive analysis. The main risk factor for severe recurrent PMR was the length of the coaptation line of the posterior leaflet, which reflected excess valvular tissue. It is reasonable to hypothesize that a significant excess of tissue increases the risk of MR relapse since the coaptation area to be stabilized is larger. This observation seems to be confirmed when considering the procedural parameters. Indeed, the use of a single Mitraclip in cases of significant excess tissue (Barlow's disease) was strongly associated with MR relapse. Also, when using two or more Mitraclips, the distance between the clips seemed to be critical, as the more they were spaced, the more patients tended to develop a new prolapse between the Mitraclips. In addition, there was a trend towards the occurrence of the primary endpoint in case of a different orientation between two MitraClips with respect to the antero-posterior axis. While the MitraClip orientation with respect to the medial-lateral axis is purely related to the clip delivery system orientation during grasping and had no impact in our study, its orientation with respect to the anterograde-posterior axis is mainly related to the quantity of valvular tissue. Indeed, only a significant tissue excess allows a different anteroposterior-posterior movement between two adjacent MitraClips along the cardiac cycle. If using multiple clips and minimizing their spacing seems to be the key to obtain a durable result, it is reasonable to think that mitral valve diseases with significant excess tissue are poor candidates for the technique. It is likely that the use of transcatheter mitral valve implantation in these patients would be preferable.

In our study, the second most frequent cause of recurrent MR was Mitraclip's single leaflet detachment. This is a known complication, as it has been observed in 9% of the patients in the EVEREST I study (6). Several factors can explain this phenomenon. From an anatomical point of view, partial clip detachment occurs when the load applied to the clipped parts of both leaflets and the MitraClip overcome the tissue resilience. Indeed, tension over the Mitraclip becomes maximum in the diastolic phase. As it is deployed in the systolic phase, increased tension forces over the clipped part in an anterior-posterior direction during diastole can be expected to have a graded impact on single leaflet detachment occurrence (16). Quality of echocardiographic guidance was also associated with recurrent MR. Since the procedure is exclusively guided by ultrasound, it is consistent that in the case of poor vision, the procedural results are less durable. Poor visualization of the leaflets' insertion into the Mitaclip during the grasping phase may promote single leaflet detachment. Indeed, the quality of ultrasound guidance, such as the possibility of offering 4D views, has already been associated with a decrease in the rate of single leaflet detachment. (17)

Therefore, important lessons can be learned from these observations: 1) in case of significant excess tissue (e.g. Barlow disease), alternative techniques such as percutaneous mitral replacement should be considered and, if not feasible, the use of a single Mitraclip should be avoided. 2) the gap between two Mitraclips should be minimized in multiple clips procedures 3) a poor acoustic window should be carefully considered as a contraindication to the procedure.

Limitations

Some limitations should be noted. First, the study was limited by its retrospective nature, which has a relatively low quality of evidence. Secondly, there are also potential limitations of assessing MR itself. We know that the anesthesia alters hemodynamics, even more in FMR which is known to be fluctuant and load-dependent, intraprocedural MR assessment is therefore difficult to standardize and quantitative methods not well validated for TEE. Additionally, MR grading after a double orifice repair is challenging. However, the MR severity after MitraClip was estimated according to the integrative method recommended by the guidelines(18), allowing a better reproducibility.

Conclusion

Recurrence of severe MR after a MitraClip procedure for primary MR results from a complex interplay between anatomical (tissue excess) and procedural criteria (quality of ultrasound guidance and MitraClips spacing). These results emphasize the critical importance of teamwork between imaging and interventional cardiologists to adapt the Mitraclips position to individual valvular anatomy.

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Conflict of interest statement

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Author contributions

Conception/design, data analysis, interpretation, drafting article: YLB

Data analysis, drafting article: FV

Critical revision of article, Approval of article, Statistics: RI, SC, PF, EC, VB, MG, DC, OL, FB and TL

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Figure legends:

Figure 1: Figure illustrating the key 3D measures obtained from the mitral valve's modeling before PMVR (4D Auto MVQ, GE Vingmed Ultrasound AS, Horten, Norway).

A Example of mitral valve modeling with P2 prolapse. The red zone corresponds to the prolapsed surface in relation to the mitral annulus plane.

B The yellow area represents the anterior leaflet surface

C The yellow area represents the posterior leaflet surface

D The yellow area represents the 3D annular surface

E The yellow line represents the annular perimeter

F The yellow line represents the anterior closure line length

G The yellow line represents the posterior closure line length

Figure 2: Figure illustrating the main measurements related to the position of the clips

1) Mitral valve in surgical view ("en face"). The green line represents the antero-posterior axis, the orange line represents the medial-lateral axis and the yellow line represents the coaptation line.

2)Two chambers (commissural) view showing the clips' position with respect to the medial-lateral axis. Clip "A" is perpendicular, Clip "B" is not. Clip "A" and "B" have different orientation with respect to the Medial-lateral axis

3)"En face" mitral view showing the clips' position with respect to the coaptation line. Clip "A" is perpendicular, Clip "B" is not. Clip "A" and "B" have different orientation with respect to the coaptation line.

4)Three chambers view showing the clips' position with respect to the antero-posterior axis. Clip "A" is perpendicular, Clip "B" is not. Clip "A" and "B" have different orientation with respect to the Anteroposterior axis

Figure 3: Figure illustrating the main etiologies of recurrence of severe leakage after MitraClip treatment

A Surgical view of the mitral valve showing a prolapse of the posterior leaflet between two MitraClips

B Biplane TEE view showing a de novo prolapse of the posterior leaflet alongside a Mitraclip

C Surgical view of the mitral valve showing a coaptation gap alongside a Mitraclip

D 3D TEE surgical view showing a single leaflet detachment of a Mitraclip

Online data supplement:

Video 1: example of 3D modeling of the mitral valve (P2 prolapse)

Video 2: example of a multiplanar reconstruction software with analysis of the Mitraclips position in relation to the main mitral axes

Video 3: example of relapse of a prolapse adjacent to one MitraClip

Video 4: example of relapse of a prolapse between two MitraClips

Video 5: example of Mitraclip single leaflet detachment

Tables:

Table 1 Patients' characteristics

	n = 83
Mean age *(years)*	83±7
Female gender	37 (44)
BMI *kg/m²*	24±5
GFR *mL/min/1.73 m²*	50±20
Diabetes	12 (14)
History of coronary artery disease	28 (34)
Previous CABG	6 (7)
Previous aortic surgery	11 (13)
AF	56 (67)
NYHA class III-IV	44 (53)
Congestive heart failure	46 (55)
Euroscore 2	4.6±3,4
STS score	4.0±4.4
LVEF *(%)*	68±11
MR ERO *mm²*	59+/-19
MR RVol *ml*	82+/-30
Mean transmitral gradient *mmHg*	3.4±0.9
Number of Mitraclips used	1.73±0.6
No residual MR	12 (14)
Early recurrence of severe MR	8 (9)
Late recurrence of severe MR	8 (9)
Reoperation by PMVR	6 (7)
Reoperation by surgery	1 (1)
Primary Endpoint	17 (20)

AF: atrial fibrillation, BMI: body mass index, CABG: Coronary Artery Bypass Grafting, ERO: Effective Regurgitant Orifice GFR: glomerular filtration rate, LVEF: left ventricular ejection fraction; MR: mitral regurgitation, NYHA: New York Heart Association; RVol: Regurgitant Volume; STS: Society of Thoracic Surgeons

Table 2: Detailed causes of recurrence of severe MR after PMVR, according to their chronology of onset

	Early recurrence of severe MR n=9	Late recurrence of severe MR n=8
Single leaflet detachment	4 (44)	0 (0)
New prolapse close to the clip	2 (22)	3 (37)
New prolapse between two Mitraclips	3 (33)	3 (37)
Coaptation gap close to the Mitraclip	0 (0)	1 (12)
Infective endocarditis	0 (0)	1 (12)

Table 3 Results of the univariate Cox regression analysis to predict the occurrence of severe mitral valve regurgitation recurrence after percutaneous mitral valve repair (MitraClip system), in patients with primary mitral regurgitation (n = 83).

	Hazard ratio	95% confidence interval	*P value*
Patients' Characteristics			
Age	0.97	0.92-1.03	0.39
Female gender	0.67	0.24-1.81	0.43
LVEF	1.03	0.98-1.08	0.20
Mitral anatomy			
Ideal anatomy according to Everest criteria	1.01	0.38-2.69	0.98
Barlow disease	1.61	0.55-4.66	0.37
Barlow disease *(for procedures that have used a unique clip)*	7.67	1.48-39.69	**0.01**
Mitral valve area	0.84	0.56-1.23	0.396
P1 prolapse	0.55	0.07-4.16	0.56
P2 prolapse	1.37	0.39-4.79	0.61
P3 prolapse	1.35	0.38-4.71	0.63
Anterior leaflet prolapse	0.87	0.25-3.06	0.83
Flail gap	1.04	0.89-1.22	0.61
Flail width	0.98	0.87-1.10	0.82
More than 1 scallops involved	0.56	0.16-2.01	0.764
3D annular surface	0.99	0.93-1.06	0.96
Annular perimeter	1.15	0.85-1.56	0.34
Antero-posterior diameter	1.31	0.50-3.39	0.57
Medio-lateral diameter	1.73	0.75-4.02	0.19
Anterior leaflet surface	1.20	0.82-1.75	0.34
Posterior leaflet surface	1.07	0.90-1.28	0.42
Anterior closure line length	1.52	0.72-3.19	0.26
Posterior closure line length	1.06	1.01-1.12	**0.02**
Procedure related data			
Number of clips (for one more)	0.55	0.24-1.25	0.15
Only one clip used	2.00	0.76-5.23	0.15
Use of MitraClip XTR vs NTR/NT Clip Delivery System	0.43	0.09-1.93	0.27
Non-perpendicular position with respect to the antero-posterior axis	1.78	0.49-6.39	0.37
Non-perpendicular position with respect to the medial-lateral axis	2.62	0.58-11.75	0.20
Non-perpendicular position with respect to the coaptation line	0.87	0.30-2.54	0.81
Different orientation between the clips with respect to the Medial-lateral axis*	4.26	0.52-34.68	0.17
Different orientation between the clips with	7.89	0.97-64.22	0.05

respect to the antero-posterior axis*			
Clips divergent with respect to the coaptation line*	0.84	0.20-3.55	0.94
Inter-clip distance (for 1 mm more) *	1.60	1.27-2.02	**<0.01**
Operators related data			
Experience (for ten procedures more)	0.91	0.77-1.06	0.25
Poor imaging quality	3.84	1.12-13.19	**0.03**

* Results on procedure using two or more clips (n=52).

LVFE, left ventricular ejection fraction

In bold, P value<0.05