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Surgical revision of failed percutaneous edge-to-edge mitral valve repair: lessons learned

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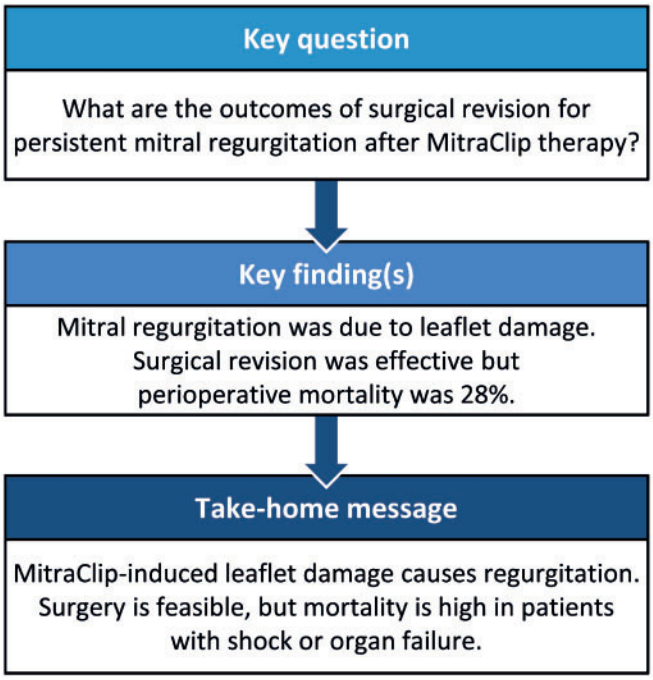

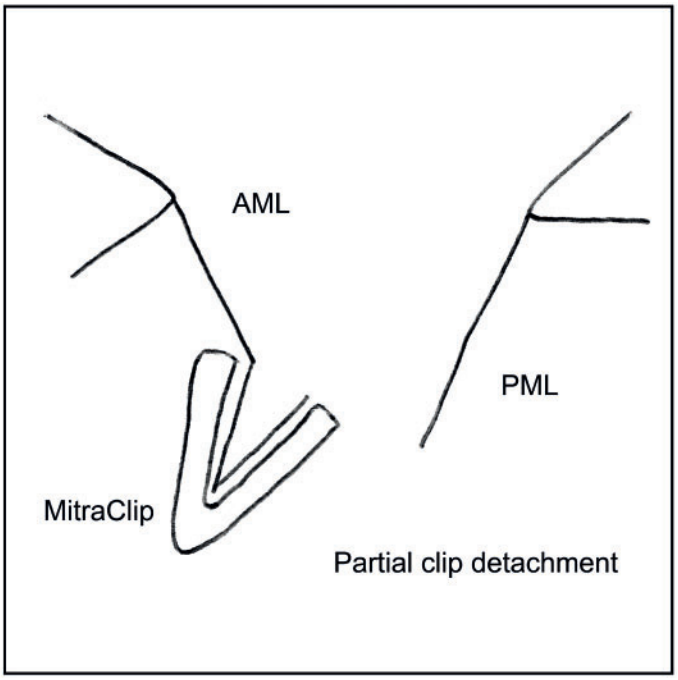

Abstract

OBJECTIVES: Although percutaneous edge-to-edge mitral valve repair with the MitraClip system is becoming widely adopted in clinical practice, surgical experience on how to correct failed MitraClip therapy is limited. We aimed to analyse the surgical and pathological outcomes after surgical revision of the failed MitraClip therapy.

METHODS: Between January 2011 and January 2018, 25 patients (age 73 ± 9 years; men 48%; New York Heart Association class 3.4 ± 0.49) were admitted for severe mitral regurgitation at a median of 54 days (range 1–1496 days) after MitraClip edge-to-edge repair. Perioperative variables were analysed for their association with surgical outcomes.

RESULTS: All patients underwent explantation of the MitraClip system and subsequent mitral valve replacement. Perioperative mortality was as high as 28%, mainly due to pre-existing cardiogenic or septic shock. The Kaplan–Meier analysis revealed a 53% overall 1-year survival. Among preoperative variables, the logistic European System for Cardiac Operative Risk Evaluation score, left ventricular ejection fraction and liver dysfunction had a significant influence on in-hospital survival. Intraoperatively, the predominant pathology included mitral

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valve leaflet damage due to tear, degeneration or infection. Although leaflet tears or MitraClip detachment mainly occurred within the first 6 months after MitraClip therapy, leaflet infections and degeneration mainly occurred later during follow-up.

CONCLUSIONS: The surgical revision of failed MitraClip therapy is feasible but has high perioperative mortality, especially among patients with cardiogenic shock, septic shock or liver failure. Mitral regurgitation after the MitraClip therapy is mainly caused by mitral valve leaflet damage due to tear, degeneration or infection, all related to the MitraClip itself.

Keywords: Percutaneous edge-to-edge mitral valve repair • MitraClip • Revision surgery • Mitral valve replacement • Mortality • Mitral regurgitation

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INTRODUCTION

Percutaneous edge-to-edge mitral valve repair with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) is becoming widely adopted in clinical practice due to its reported safety in elderly and other high-risk patients, providing an acute success rate of 92% [1], acceptable in-hospital mortality of 2.5–2.7% [2–5] and acceptable 1-year survival free from cardiac depression of 14–23% [6–8]. Meanwhile, ∼2.3–6.3% of patients require surgical repair and mitral valve replacement (MVR) due to various complications within 1 year after MitraClip therapy [6]. As few studies have described the outcomes of patients with surgical revision after failed MitraClip implantation [9, 10], the optimal surgical strategy for open-heart operations after failed MitraClip therapy is not well defined. In this study, we evaluated the postoperative clinical outcomes and intraoperative pathological findings of patients who underwent surgical revision for failed MitraClip therapy. We believe that this analysis will contribute immensely to future practice involving the MitraClip system and to the development of a suitable surgical strategy for open-heart operations after failed MitraClip therapy.

MATERIALS AND METHODS

Study design

With approval from the Institutional Review Board of the Sana Heart Center, we retrospectively reviewed the records of consecutive patients who, between January 2011 and January 2018, underwent MVR for recurrent or uncontrolled mitral regurgitation (MR) despite adequate medical therapy after percutaneous MitraClip therapy. Clinical data were collected. Information about the follow-up status was obtained by phone and fax from the treating general physician or from the patients themselves. The study end points were death and cardiac-related death. A heart team consisting of a cardiologist, cardiac surgeon, perfusionist and cardioanaesthesiologist discussed the surgical revision. All patients provided written informed consent for undergoing the revision operation.

Surgical procedures

MVR was performed to reduce the duration of aortic cross-clamping and cardiopulmonary bypass. All procedures were performed via the median sternotomy or right thoracotomy approach, at the discretion of the surgical team. Full sternotomy was chosen for critically ill patients and for those undergoing redo surgery. After sternotomy, cardiopulmonary bypass was established through direct cannulation of the ascending aorta and right atrium vein (20 patients, 80%). Following right anterolateral thoracotomy at the fourth intercostal space, cardiopulmonary bypass was established through cannulation of the femoral artery and vein (5 patients, 20%). After transthoracic aortic cross-clamping, myocardial arrest was obtained with antegrade warm blood cardioplegia (18 patients, 72%) or Bretschneider cardioplegia (7 patients, 28%). The mitral valve was exposed via the standard left atriotomy or the transseptal approach, depending on the need for tricuspid valve repair and atrial septal defect closure. The failure characteristics of the implanted clips and the degree of tissue damage to the mitral valve were assessed. The clips were cut using scissors and removed, and standard MVR was performed.

Follow-up

We evaluated data collected at 48 h, 30 days, 6 months and up to 5 years postoperatively. Follow-up data were complete in all patients.

Statistical analysis

Data are expressed as mean ± standard deviation or median [range and/or interquartile range (IQR)] for continuous variables, and as frequency (%) for categorical variables. Univariable comparisons were performed using the Student's unpaired *t*-test for continuous, normally distributed data, the Mann–Whitney *U*-test for non-parametric continuous data and the Fisher's exact test for categorical data. The Kaplan–Meier analysis was used to compute 1-year survival. The statistical significance was set at a *P*-value <0.05. All reported *P*-values are 2-sided. The statistical analysis was performed by a statistician using SPSS for Windows, version 22.0 (IBM Japan, Tokyo, Japan).

RESULTS

Study population

Between January 2011 and January 2018, 25 patients (age 73 ± 9 years; age range 52–85 years; men 48%) underwent MVR for severe MR at a median of 54 days (range 1–1496 days) after MitraClip edge-to-edge repair. During the study period, MVR was conducted in 8 (3.21%) of 249 patients who underwent the original intervention at our hospital and in 17 patients who underwent the original intervention at another hospital. Among the 8 patients originally treated at our hospital, the average MR grade after the MitraClip procedure was 2.

Table 1: Preoperative characteristics of 25 patients who underwent surgical revision for failed MitraClip therapy

Characteristics	Values
Age (years)	73 ± 9
Male gender	12 (48)
Body mass index (kg/m^2)	28 ± 5
Hypertension	23 (92)
Chronic obstructive pulmonary disease	12 (48)
Diabetes mellitus with insulin dependence	5 (20)
NYHA functional class	3.4 ± 0.5
Aetiology of mitral valve disease	
Degenerative	2 (8)
Functional	22 (88)
Combined	1 (4)
Implanted MitraClips	2.2 ± 0.9
Previous open cardiac surgery	7 (28)
Prior percutaneous coronary intervention	11 (44)
Atrial fibrillation	20 (80)
Coronary artery disease	15 (60)
Dilated cardiomyopathy	6 (24)
Ischaemic cardiomyopathy	4 (16)
CRTD implantation	7 (28)
Left ventricular ejection fraction (%)	0.44 ± 0.12 (range 0.17–0.55)
MR grade at surgery	3.0 ± 0.5
Systolic pulmonary artery pressure (mmHg)	50 ± 14
Time since clipping (days)	54 (IQR 13–257; range 1–1496)
Shock	6 (24)
Sepsis	2 (8)
Preintubation	3 (12)
Emergent MVR	3 (12)
Urgent MVR	8 (32)
Elective MVR	14 (56)
EuroSCORE II (%)	12.9 (IQR 6.7–24.3; range 1.9–81.6)
Logistic EuroSCORE (%)	35.2 (IQR 15.7–57.9; range 4.5–96.6)

Data are shown as mean ± standard deviation or frequency (%), unless otherwise specified.

CRTD: cardiac resynchronization therapy defibrillator; EuroSCORE: European System for Cardiac Operative Risk Evaluation; IQR: interquartile range; MR: mitral regurgitation; MVR: mitral valve replacement; NYHA: New York Heart Association.

Preoperative characteristics

The preoperative New York Heart Association (NYHA) functional class was III or IV (mean 3.4 ± 0.49) in all patients. An average of 2.2 ± 0.93 clips had been implanted per patient (IQR 1.5–3; range 1–4). Disease aetiology at the time of MitraClip implant included primarily functional MR ($n = 22$, 88%), followed by degenerative MR ($n = 2$, 8%) and combined degenerative and functional MR ($n = 1$, 4%). No echocardiographic indication of leaflet calcification or mitral annular calcification was noted at the time of MitraClip implantation. One patient had undergone redo clipping after unsatisfactory results of the original MitraClip procedure. Nine patients (36%) received some preoperative treatment including placement of an implantable defibrillator or cardiac resynchronization therapy defibrillator. Six patients (24%) had previous cardiac surgery including aortic valve replacement and coronary artery bypass grafting. Six patients were admitted with cardiogenic shock, and an intra-aortic balloon pump was implanted in 2 patients. Three patients (16%) were operated on within 24 h after admission (emergent MVR), whereas 8 patients (26%) were operated on within 24–48 h after admission (urgent MVR). The median logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 35.9% (IQR 15.7–57.9%; range 4.53–96.6%) (Table 1).

Operative data

Most patients (24/25, 96%) received a biological valve, whereas 1 patient (4%) received a mechanical valve. The duration of cardiopulmonary bypass and aortic cross-clamping was 117 ± 57 and 61 ± 24 min, respectively. Concomitant procedures included tricuspid valve repair in 7 patients, aortic valve replacement in 2 patients, coronary artery bypass grafting in 1 patient and cryoablation of atrial fibrillation in 4 patients. In 11 patients, the artificial atrial septal defect created due to the transseptal approach for the MitraClip therapy was closed with a suture from the right atrium side. According to the guidelines, 2 patients received an intra-aortic balloon pump and 2 received extracorporeal membrane oxygenation. Nitric oxide gas was used in 1 patient (Table 2).

Early clinical outcomes

One patient died during surgery because of severe low cardiac output. There were 7 in-hospital deaths (28%), all among patients at very high surgical risk (logistic EuroSCORE: median 58.8%; IQR 34.6–92.3%; range 21.2–96.6%) (Table 2). In 6 of 7 cases, death occurred mainly because of the pre-existing cardiogenic shock or septic shock within 30 days after surgery. Among the 8 patients undergoing urgent surgery, 1 with logistic EuroSCORE 56.9% died due to multiorgan failure (MOF) within 48 h postoperatively despite intraoperative implantation of extracorporeal membrane oxygenation. Among the 3 patients undergoing emergent surgery, 2 patients died because of MOF caused by systemic inflammatory response syndrome resulting in septic shock, renal failure or liver failure. All 3 patients with liver complications died because of MOF within 48 h after surgery. One patient received a left ventricular assist device at 3 days postoperatively but died because of sepsis and MOF at 33 days postoperatively.

Among the 18 survivors, 2 required re-exploration for bleeding, 1 required reintubation for pulmonary pneumonia and 1 developed new atrioventricular block requiring pacemaker implantation. Two patients were transferred to the neurology department due to a transient cerebrovascular event. All other patients were discharged to rehabilitation homes or home at a median of 12.5 days (IQR 8.8–28.8; range 1–80 days), with no residual MR or endocarditis noted on thoracic echocardiography at discharge.

Variables related to in-hospital survival

There was a significant association with in-hospital survival for several preoperative variables including logistic EuroSCORE at surgery, left ventricular ejection fraction and liver dysfunction. No such association was noted for age, sex, acute or chronic renal failure, MR grade, cardiogenic shock, NYHA functional class, operative situation (emergent versus urgent versus elective) and time between MitraClip therapy and revision cardiac surgery (Table 3).

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Table 2: Intraoperative data and findings of patients who received surgical revision for failed MC therapy

Case	Time to MVR (days)	No. of clips	Indication for surgery	Mitral valve surgery	Concomitant procedures	Intraoperative findings of valve lesion	ACC duration (min)	CPB duration (min)
Survivors								
1	1454	3	MR II, MS II	MVR	TAP, ablation, ASD closure	Myxomatous mitral valve, MC *in situ*, moderate MS	57	87
2	41	2	MR III	Redo-urgent MVR	N	Partial MC detachment from the AML	30	42
3	61	4	MR III, MSII, TR III	Redo-urgent MVR	TAP	Pronounced annular dilation, MC *in situ*, moderate MS	65	111
4	122	2	MR III	Redo-MVR	ASD closure	Pronounced annular dilation, MC *in situ*	31	45
5	1496	1	IE, MR III	MVR	N	Vegetation around MC	88	116
6	8	3	MR III	Urgent MVR	N	Tear of the chordae tendineae, MC *in situ*	42	61
7	54	2	MR IV, MS II, TR III	MVR with RAMT	N	Endothelialized MC *in situ*, severe MR, moderate MS	44	105
8	434	2	IE, MR III, TR IV	Urgent MVR	TAP, LAA occlusion, ablation, ASD closure	Vegetation around MC	73	149
9	275	2	MR III, MS II	MVR	N	Partial detachment from the PML with leaflet tear, calcification (AML and PML)	23	33
10	36	3	MR III	Urgent MVR with RAMT	ASD closure	Pronounced annular dilation, MC *in situ*, PML with tear	58	85
11	1	3	MR IV, posterior prolapse	Emergent MVR	N	AML and PML with tear, MC *in situ*	41	61
12	87	2	MR III	MVR with RAMT	N	One MC *in situ* (A3–P3) with leaflet tear (PML), second MC only with A2 attachment	48	124
13	51	3	AS III, MR III	MVR	AVR, ASD closure	Pronounced annular dilation, MC *in situ*	72	88
14	5	3	MR III	Redo-urgent MVR	ASD closure	Pronounced annular dilation, MC *in situ*, with leaflet tear	108	156
15	503	1	MR III, MS II	MVR with RAMT	ASD closure	Severe degenerative changes of the AML and PML, MC *in situ*, severe MR, moderate MS	52	128
16	11	1	MR III	MVR with RAMT	Ablation	Partial detachment from the PML (P2–3)	64	137
17	22	1	MR IV	MVR	Ablation, ASD closure	Partial detachment from the PML	91	133
18	14	1	MR III	Urgent MVR	N	AML (A2–3) with tear, MC *in situ*, pronounced annular dilation	51	103
Non-survivors								
1	9	3	MI III	Redo-MVR	ASD closure, ECMO implantation	MC-related MV perforation, MC *in situ*	78	137
2	48	2	MI III, AS III, TI III	MVR	AVR, TAP, CABG ASD closure	Severe MR, MC *in situ*	90	259
3	239	4	MR IV, MS III, TR II	Redo-MVR	TAP, NO use	Pronounced annular dilation, MC *in situ*, severe MR, moderate MS	63	146
4	12	1	Acute IE, MR III, septic shock	Emergent MVR	ASD closure	Vegetation around MC with leaflet tear, annular dilation	115	167
5	76	3	MR III, TR III	MVR	TAP, IABP implantation	Pronounced annular dilation, MC *in situ*	39	85
6	358	2	MR III, MS II	Urgent MVR	AsAo replacement, ECMO implantation	Pronounced annular dilation, MC *in situ*, severe MR, severe MS	62	265
7	83	2	MR III, TR III, cardiogenic shock, MOF	Emergent MVR	TAP, IABP implantation	One MC completely detached from the PML, attached only to the AML	47	111

ACC: aortic cross-clamping; AML: anterior mitral valve leaflet; AMR: anterior mitral leaflet; AS: aortic stenosis; AsAo: ascending aorta; ASD: atrial septal defect; AVR: aortic valve replacement; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; IE: infective endocarditis; LAA: left atrial appendage; MC: MitraClip; MI: myocardial infarction; MOF: multiple organ failure; MR: mitral regurgitation; MS: mitral stenosis; MVR: mitral valve replacement; NO: nitric oxide; PML: posterior mitral valve leaflet; PMVR: percutaneous mitral valve repair; RAMT: right anterior minithoracotomy; TAP: tricuspid annuloplasty; TR: tricuspid regurgitation.

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Table 3: Factors associated with perioperative mortality after surgical revision for failed MitraClip therapy

Risk factor	Survivors ($n = 18$)	Non-survivors ($n = 7$)	P-value
Preoperative characteristics			
Age (years)	73.0 ± 8.6	73.1 ± 11.1	0.97
Sex			>0.10
Female	9 (50)	4 (57)	
Male	9 (50)	3 (43)	
Body mass index (kg/m^2)	28.6 ± 4.9	26.6 ± 6.1	0.40
Chronic obstructive pulmonary disease	8 (44)	4 (57)	0.67
Acute renal failure	2 (11)	1 (14)	>0.10
Chronic renal failure	9 (50)	5 (71)	0.41
Liver failure	0 (0)	3 (43)	0.015
Ischaemic heart disease	11 (61)	4 (57)	>0.10
Previous cardiac surgery	4 (22)	2 (29)	>0.10
Sepsis	1 (6)	1 (14)	0.49
Cardiogenic shock	3 (17)	3 (43)	0.30
Emergent MVR	1 (6)	2 (29)	0.18
Urgent MVR	7 (39)	1 (14)	0.36
Elective MVR	10 (56)	4 (57)	>0.10
MR grade	3.1 ± 0.5	2.9 ± 0.4	0.37
Tricuspid regurgitation grade	1.8 ± 0.73	2.3 ± 0.29	0.13
Left ventricular ejection fraction (%)	50 (44–55)	37 (20–50)	0.012
Systolic pulmonary artery pressure (mmHg)	48 (40–63)	50 (35–60)	0.47
EuroSCORE II at surgery (%)	8 (5.8–21.5)	24 (13.8–62.1)	0.013
Logistic EuroSCORE at surgery (%)	28.7 (9.7–47.8)	58.8 (34.6–92.5)	0.015
Time after MitraClip (days)	53 (13–315)	76 (12–239)	>0.10
Aortic cross-clamping time (min)	58 ± 23	71 ± 26	0.23
Cardiopulmonary bypass time (min)	98 ± 38	167 ± 70	0.0038
Pathology			
Partial clip detachment	5	1	0.64
Leaflet tear without clip detachment	4	0	>0.10
Leaflet infection	1	2	>0.10
Leaflet degeneration	1	2	0.53

Data shown as mean ± standard deviation, median (IQR), number or frequency (%).
EuroSCORE: European System for Cardiac Operative Risk Evaluation; IQR: interquartile range; MR: mitral regurgitation; MVR: mitral valve replacement.

Late clinical outcomes and survival

The median follow-up was 13 months (IQR 7–32; range 2–76 months). During follow-up, 8 patients died. One patient died after 10 months due to bladder cancer, whereas another patient died of sepsis within 6 months after surgery. The cause of death was unknown in 6 patients. On Kaplan–Meier overall survival analysis, the 6-month, 1- and 2-year survival rates were 68%, 53% and 47%, respectively. There was no stroke, prosthesis dysfunction or endocarditis. No patients received redo surgery.

Intraoperative pathological and microbiological findings associated with the MitraClip system

Recurrent MR was caused by mitral valve leaflet damage due to tear ($n = 10$), degeneration ($n = 3$) or infection ($n = 3$) associated with the MitraClip system and by uncontrolled mitral annulus dilation ($n = 7$) (Fig. 1, Table 2). Although complete detachment of the clip did not occur, partial detachment (defined as detachment of the clip from a single leaflet) occurred in 6 of 10 patients with mitral leaflet tear. In 5 patients (83%) with partial detachment, the posterior mitral valve leaflet was torn and the MitraClip had partially migrated onto the anterior mitral valve leaflet. MR due to leaflet tear or clip detachment occurred within 6 months of MitraClip therapy in 9 patients (90%) and later in 1 patient (10%) (Fig. 2).

In 3 patients, vegetation was noted near the MitraClip (Table 2). Blood cultures were positive for *Staphylococcus aureus* (acute phase), *Enterococcus faecalis* (chronic phase) and *Staphylococcus epidermidis* (subacute phase), respectively. In 2 patients, the infection-related tissue damage had led to tears in the mitral valve leaflet. These patients did not have chordae rupture, and the infection did not reach the mitral annulus or the other valves.

Mitral valve degeneration included myxomatous and endothelialization changes around the MitraClip implantation areas (fibrous encapsulation of the clip, with extension over adjacent mitral leaflets and tissue bridge formation), which were noted in 3 patients at 2, 17 and 49 months, respectively. Perioperative mortality was not influenced by the time interval between MitraClip therapy and revision surgery or by pathological findings noted intraoperatively (Table 3).

DISCUSSION

Overview of findings

In the past 7 years, 25 patients including those with sepsis and cardiogenic shock state received the bail-out therapy for patients at our centre for recurrent severe MR after MitraClip therapy. In this series, the 30-day mortality was 24%, which we consider acceptable in a population with high surgical risk. Geidel *et al.* [10] reported a 30-day mortality of 9.1% in a case series that did not include patients presenting with sepsis or undergoing cardiopulmonary resuscitation.

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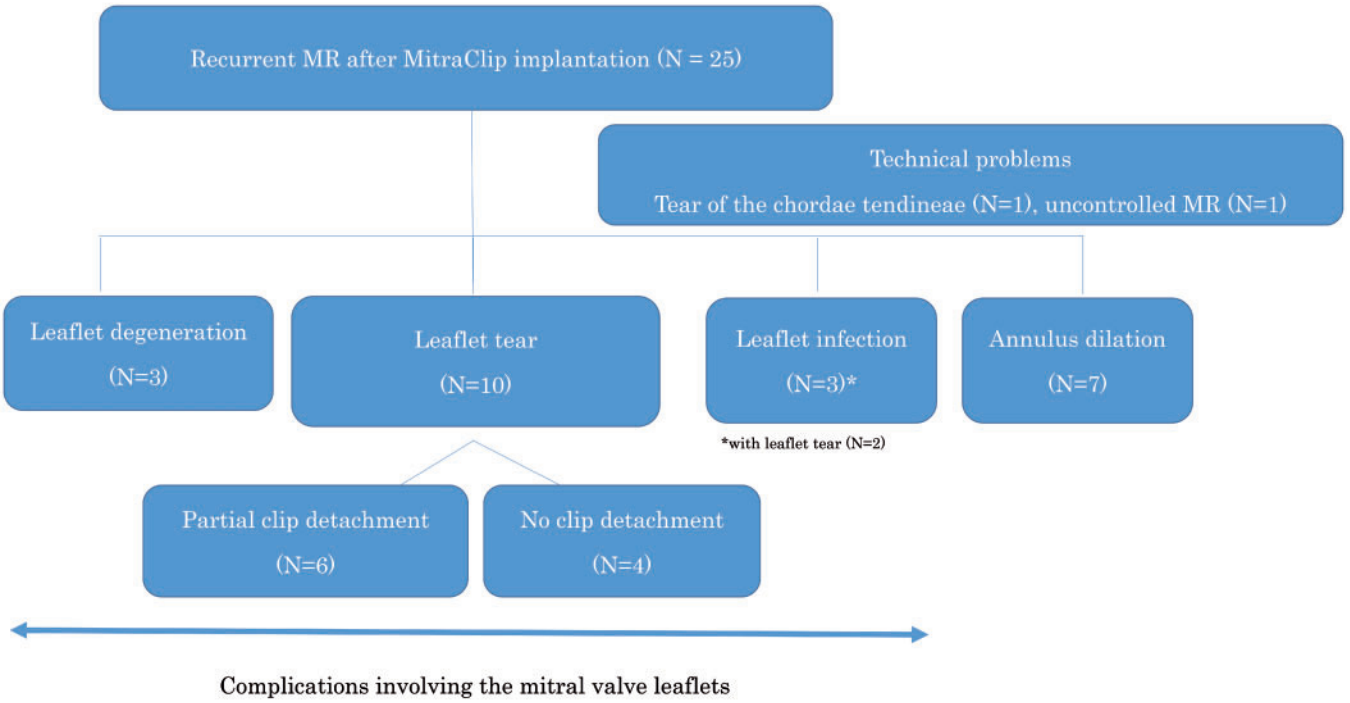

Figure 1: Intraoperative pathological findings in patients with MR after MitraClip therapy. MR: mitral regurgitation.

The most important findings of this study were as follows: (i) surgical revision after failed MitraClip therapy is a feasible option even in high-risk patients; (ii) patients presenting with liver failure, cardiogenic shock or septic shock are at extremely high risk for in-hospital mortality; and (iii) the predominant pathology underlying MR after failed MitraClip therapy is mostly related to mitral valve leaflet damage due to tear, degeneration or infection associated with the clip itself.

Survival predictors

Variables predicting postoperative survival (in particular, in-hospital survival) are used for risk stratification and represent important factors in the decision to perform surgery. In the present series, 6 patients (24%) died within the first 48 h due to MOF. All non-survivors had a logistic EuroSCORE >35% plus one or more risk factors including shock of either aetiology, age >80 years or severe left ventricular dysfunction. Elhmidi *et al.* [11] also suggested that the combination of preoperative cardiogenic shock with severe left ventricular dysfunction represents a high risk for in-hospital death. A recent study reported that the conservative therapy is advisable in patients with logistic EuroSCORE >30% [10]. In our present series, the average logistic EuroSCORE at the time of surgery was 62% among patients who died before discharge; however, 8 patients (44%) who survived until discharge also had a logistic EuroSCORE >30% at surgery. In addition, all patients with severe liver dysfunction died within 48 h after surgery. In 2 such patients, liver failure occurred due to shock. Of the patients requiring mechanical support with extracorporeal membrane oxygenation or intra-aortic balloon pump implantation, none survived (survivor versus non-survivor, $P < 0.0001$). Taken together, our findings suggest that the decision to perform surgery should take into consideration not only the value of the logistic EuroSCORE but also other factors reflecting MOF (in particular, liver failure).

Leaflet tears

Leaflet tears typically occurred within 6 months after MitraClip therapy. Clip detachment likely occurred due to substantial tension in the repaired leaflet, causing leaflet tear secondary to progressive mitral annulus dilation or valve disruption due to hypertension or atrial fibrillation. In 1 patient, leaflet tear occurred later than 6 months after MitraClip therapy and echocardiography revealed mild mitral stenosis. Partial clip detachment may have been caused by pressure overload of the MitraClip-implanted valve in the chronic phase. Therefore, mild mitral valve stenosis during follow-up after MitraClip therapy represents a very important clinical finding.

In all cases, partial detachment was caused by posterior leaflet tears. In functional MR due to left atrial dilation and mitral annulus dilation, the posterior wall of the left atrium expands posteriorly, whereas the posterior wall of the left ventricle bends anteriorly, causing the posterior leaflet to bend and expand according to the movement of the posterior wall of the left ventricle. The anterior leaflet flattens out during valve opening. Thus, as posterior leaflets that shift posteriorly tend to be shorter, MitraClip therapy increases the risk of tear at this location.

Leaflet infection

In this study, infective endocarditis was found in 3 patients (mean MR grade 3), of whom 2 had clip-related leaflet tear. Infective endocarditis with *S. aureus* occurred in the acute phase (12 days) after MitraClip therapy in a patient with severe progressive MR (EuroSCORE II, 81.6%) who underwent emergent MVR

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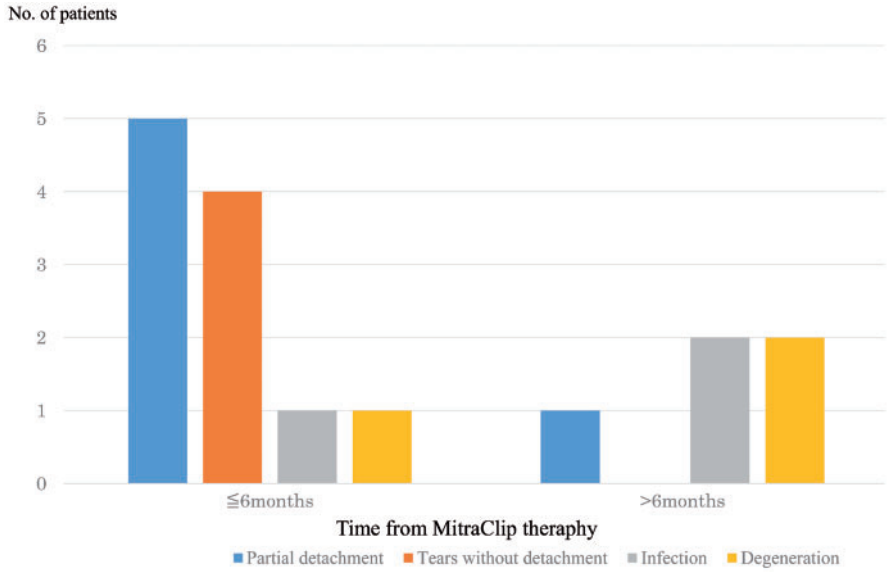

Figure 2: Leaflet damage in patients with recurrent mitral regurgitation after MitraClip therapy. The patients were stratified according to whether revision surgery was performed within 6 months of MitraClip therapy or later.

but died due to septic shock. Meanwhile, infective endocarditis with *S. epidermidis* and *E. faecalis*, respectively, occurred in the subacute (13 months) and chronic phase (49 months) after clip implantation and these patients had progressive MR (EuroSCORE II: 6.2% and 21.1%, respectively) but survived.

Prosthetic valve endocarditis, mostly due to *S. aureus* infection, has been reported for up to 30% of all patients with infective endocarditis [12]. However, the incidence of MitraClip-related endocarditis is unknown. Frerker *et al.* [13] were the first to report a case of *S. aureus*-related endocarditis after MitraClip therapy. In our hospital, none of the other ∼250 patients implanted with MitraClips developed endocarditis over a follow-up of 5 years, suggesting that infective endocarditis in MitraClip-implanted patients is extremely rare. However, patients with severe circulatory compromise preoperatively have extremely high risk of postoperative mortality, especially if the causal agent is *S. aureus*. MitraClip implantation may increase the risk of infective endocarditis because residual MR is common after MitraClip therapy and the clip itself is a foreign object that can serve as a suitable habitat for bacteria. Therefore, although the risk of prosthetic valve endocarditis is low, the patients should be carefully monitored for signs of infective endocarditis in both the acute and late phase after MitraClip therapy.

A recent review reported a 42% rate of postoperative mortality associated with MitraClip-related infection, with *S. aureus* as the most frequent (60%) causal micro-organism [14]. We believe that acute infective endocarditis with *S. aureus*, and the subacute or chronic infective endocarditis may follow acute haemodynamic alteration due to tear or deterioration of the mitral valve. The rate of infective endocarditis following MitraClip therapy appears to be lower than that associated with the implantation of mechanic or bioprosthetic valves.

Leaflet degeneration

In our series, 3 patients (12%) had degenerative changes in the leaflet region around the MitraClip. The healing response to the MitraClip device in humans is currently not well understood. According to Stephens *et al.* [15], regurgitation alone can result in leaflet remodelling characterized by increased matrix degeneration, collagen synthesis and abundance of elastin in the spongiosa and fibrosa layers following mitral valve deterioration. We hypothesize that the MitraClip system may trigger aggressive inflammatory reactions leading to formation of fibrotic tissue around the implanted clip, which sometimes results in mitral stenosis.

Interestingly, 2 of 3 patients with MitraClip-related degeneration had mediastinal radiation therapy due to mammary carcinoma before MitraClip therapy. Cardiac valve disease associated with mediastinal radiation therapy is characterized by valve fibrosis and calcification, often with progression to heart failure and death. Our 2 patients presented obvious mitral leaflet degeneration at 1454 and 503 days after MitraClip therapy, respectively. The MitraClip itself may have stimulated the progress of degeneration caused by mediastinal radiation therapy. In another patient, progressive endothelialization around the MitraClip was noted at 54 days after MitraClip therapy. The reason for this acute healing reaction around the clip is unknown. Although the pathology associated with leaflet remodelling appeared to differ according to the time after the MitraClip procedure, the type of pathological findings had no significant influence on perioperative mortality (Table 3). Further studies are warranted to clarify the characteristics and clinical relevance of leaflet remodelling in response to MitraClip implantation in humans.

Limitations

The baseline characteristics in this case series were heterogeneous, the sample size was small, and our experience relates only to a single institution. Moreover, 60% of patients were transferred from other interventional hospitals, suggesting that not all patients with failed MitraClip therapy may have been referred for surgical revision. Therefore, selection bias could not be excluded. Multicentre studies with large sample size and long follow-up are required to confirm the mitral valve alterations associated with the MitraClip therapy.

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CONCLUSION

Open-heart surgery after unsuccessful MitraClip treatment is acceptable at any time in patients with high surgical risk. However, it may be too late to operate in patients with established MOF due to shock. Based on our experience of 7 years, we recommend the following: (i) MitraClip-implanted patients should be regularly followed-up by a heart team to monitor for MitraClip-associated infection or degenerative alterations of mitral valve leaflets, even if no partial detachment is noted in the early phase; and (ii) patients with recurrent MR after MitraClip therapy should be operated before MOF establishment, with shock-induced liver failure carrying a very high risk of perioperative mortality.

Conflict of interest: none declared.

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