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Original Article

Operative Timing and Feasibility of Mitral Valve Repair in Active Infective Endocarditis

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Purpose: We studied the association between operative timing and the feasibility of mitral valve (MV) repair in active infective endocarditis (IE).
Methods: Forty-nine active IE patients who underwent MV operation were classified according to operative timing: within 48 hours (Term I: n = 7), between 3 and 14 days (Term II: n = 22), and ≥15 days (Term III: n = 20). Patient profiles, operative outcomes, and feasibility of MV repair were evaluated. Complexity score and severity score were used to define the feasibility of MV repair depending on the extent of infected lesion and technical difficulties.
Results: There were no differences in basic profile in the three groups. Rate of major complications was higher in Term I (86%) than II (41%, p = 0.031) and III (25%, p = 0.005). In-hospital mortality was also higher in Term I (43%) than II (9%, p = 0.039) and III (5%, p = 0.015). The three groups did not differ by feasibility of MV repair calculated by the two-score system or by frequency of MV repair (I: 57%, II: 59%, and III: 55%).
Conclusions: Morbidity and mortality were high in urgent cases. Feasibility of MV repair is associated with the extent of infected lesion and technical difficulties, and not with operative timing.

Keywords: mitral valve repair, infective endocarditis

Introduction

Despite advances in diagnosis, infectious control, and surgical techniques, infective endocarditis (IE) still carries high mortality and morbidity. In patients with medically uncontrollable heart failure, surgical intervention is required. The recent American Heart Association/American College of Cardiology 2021 guidelines recommend early surgical intervention in patients with IE, including heart failure, persistent infection, abscess, heart block, infection with highly resistant organisms, or recurrent emboli (with persistent vegetation). Cerebral embolic events are not a contraindication unless extensive neurological damage or intracranial hemorrhage occurs.[1)]

Although mitral valve (MV) repair is the preferred surgical approach in patients with IE,[2,3)] early MV repair in a highly infectious state may be inappropriate due to the presence of tissue edema or inflammation. The purpose of this study was to clarify the association between the timing of operation and the feasibility of MV repair, as well as surgical outcomes.

Materials and Methods

In this retrospective study, 119 patients with active IE who underwent surgical intervention between December 2004 and August 2021 were reviewed of whom 49 patients with native MV endocarditis were enrolled. If

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surgical intervention was required before completion of a standard course of antibiotics, endocarditis was defined as active IE.[4,5] Preoperative head and whole-body computed tomography imaging was performed in all patients. IE was diagnosed based on the modified Duke criteria.[6]

Surgery in our institution during the active phase of IE is performed in the following three categories:

1) Emergent or urgent (within 48 hours): Patients with circulatory collapse and respiratory failure that cannot be controlled by medical therapy or with very large mobile vegetation.
2) Acute phase (3–14 days): Patients with progressive hemodynamic compromise, uncontrolled infection despite the use of appropriate antibiotics, or with mobile (although not gigantic) vegetation.
3) Subacute phase (from 15 days): Patients without heart failure following medical therapy, and with well-controlled infection and valvular regurgitation.

Surgery was not delayed or suspended in patients with cerebral infarction if intracranial hemorrhage was not detected.

Patient profiles, operative outcomes, and feasibility of MV repair were compared between these three operative timings: within 48 hours (Term I: n = 7), between 3 and 14 days (Term II: n = 22), and from 15 days (Term III: n = 20). Major complication was defined as cerebrovascular, cardiac (heart failure, complete atrioventricular block), respiratory (pneumonia, respiratory failure), renal (new onset of hemodialysis), and gastrointestinal (requiring surgical intervention). In order to assess the feasibility of MV repair, two types of scoring system were used, namely "complexity score" and "severity score." Complexity score, first advocated by Mount Sinai Hospital, assigns a score to each valve based on the following: prolapsing segments (weight 1 for each posterior segment; weight 2 for each anterior and commissural segment), presence of valve restriction (weight 2), presence of calcification (weight 3 if the annulus is involved; otherwise, weight 2), and prior MV repair (weight 3).[7] In patients with both MV repair and replacement, severity score was assessed according to the feasibility of MV repair. "Severity score" was developed by our institute and assigns a score derived from two aspects, namely 1) extensiveness of valvular destruction and 2) technical difficulties.[8,9] In this scoring system, a cutoff value of 8 points by the receiver operating curve had the best balance of specificity and sensitivity for predicting the feasibility of MV repair.[8,9] Severity score, ischemic time, rate of major complication, and in-hospital mortality were compared between patients who underwent MV repair and replacement.

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Showa University School of Medicine (IRB No. 3123, approved on 2022.5.7). Patients have been given an opt-out information regarding this study.

Statistical analysis

Continuous variables were expressed as mean with standard deviation and categorical variables as a proportion (%). Assessment of differences in baseline characteristics and preoperative patient profiles in each of three categories was performed using analysis of variance, Bonferroni correction for normally distributed continuous variables, and Pearson's $\chi 2$ analysis for categorical variables.

We used multiple logistic regression analysis to identify independent predictors of major complications and in-hospital mortality. All statistical analysis was performed using JMP Pro 15 (SAS Institute Inc., Cary, NC USA), and values of $p < 0.05$ were considered to indicate statistical significance.

Results

Patient profiles

Preoperative patient characteristics are listed in **Table 1**. There were no significant differences in age, female gender ratio, height, weight, diabetes mellitus, preoperative ejection fraction, frequency of preoperative cerebral infarction, and frequency of concomitant procedures. Preoperative day in Term I, II, and III was 1.4 ± 3.0, 8.7 ± 1.7, and 29.3 ± 1.8 days, respectively. Preoperative C-reactive protein was higher in Term I than II ($p = 0.0086$) and tended to be higher in Term II than III ($p = 0.0509$) (**Fig. 1**).

With regard to surgical procedure, median sternotomy was used for 45 patients and a right chest small thoracotomy incision was used for 4 patients. There was no redo operation. Exposure of the MV was through a left atrial incision in the interatrial groove in all patients. MV repair consisted of leaflet resection, annular plication, artificial chordae implantation, and autologous pericardial patch. Ring annuloplasty was applied in 48/49 patients. There was no statistical difference in concomitant procedures between the three groups (**Table 1**) and no significant differences in operative time or aortic cross-clamping time between the three groups.

Table 1 Preoperative, intraoperative, and postoperative patient data

	≤48 hours (I) n = 7	3–14 days (II) n = 22	≥15 days (III) n = 20	p-value		
				I vs. II	II vs. III	I vs. III
Age (year)	66.9 ± 18.2	56.1 ± 18.5	63.6 ± 13.6	0.161	0.246	0.524
Female gender	3/7 (43%)	7/22 (32%)	5/20 (25%)	0.593	0.625	0.373
Height (cm)	159 ± 12	165 ± 9	165 ± 9	0.306	0.860	0.361
Weight (kg)	64.7 ± 8.1	56.0 ± 10.3	57.0 ± 10.5	0.234	0.989	0.319
Preop. EF (%)	60.5 ± 4.4	62.0 ± 9.6	61.8 ± 9.0	0.594	0.814	0.610
DM	1/7 (14%)	4/22 (18%)	2/10 (10%)	0.812	0.449	0.756
Preop. cerebral infarction	3/7 (43%)	5/22 (23%)	7/20 (35%)	0.299	0.379	0.711
Concomitant procedure	5/7 (71%)	9/22 (41%)	9/20 (45%)	0.452	0.554	0.745
	AVR (4)	AVR (8)	AVR (7)			
	MAZE (1)	CABG (1)	MAZE (1)			
			CABG (1)			
Ischemic Time (min)	126 ± 36	126 ± 36	111 ± 39	0.858	0.072	0.306
MV repair	13/22 (59%)	13/22 (59%)	11/20 (55%)	0.927	0.789	0.922
Severity score	8.5 ± 3.4	8.5 ± 3.4	8.1 ± 3.2	0.938	0.869	0.889
Ischemic time of MV repair	121 ± 24	121 ± 24	122 ± 46	0.651	0.622	0.695
Autologous pericardial patch	8/13 (62%)	8/13 (62%)	5/11 (45%)	0.091	0.188	0.013
Repair for the anterior mitral leaflet	8/13 (62%)	8/13 (62%)	7/11 (64%)	0.622	0.912	0.697
Repair for the commissure leaflet	5/13 (38%)	5/13 (38%)	2/11 (18%)	0.031*	0.276	0.004
More than moderate postoperative MR	1/4 (25%)	2/8 (25%)	1/5 (20%)	0.659	0.642	0.423
In-hospital Mortality	3/7 (43%)	2/22 (9%)	1/20 (5%)	0.039	0.607	0.015
Major complication	6/7 (86%)	9/22 (41%)	5/20 (25%)	0.039	0.275	0.005
Neurological	3/7 (43%)	3/22 (14%)	1/20 (5%)	0.097	0.341	0.015
Cardiac	2/7 (29%)	1/22 (5%)	1/20 (5%)	0.069	0.945	0.088
Respiratory	1/7 (14%)	3/22 (14%)	1/20 (5%)	0.965	0.341	0.419
Gastro intestinal	1/7 (14%)	1/22 (5%)	2/20 (10%)	0.376	0.493	0.756
Renal	0/7 (0%)	2/22 (9%)	0/20 (0%)	0.408	0.167	0.000

*p <0.05. DM: diabetes mellitus; preop.: preoperative; EF: ejection fraction; AVR: aortic valve replacement; MAZE: Cox-Maze procedure; CABG: coronary artery bypass graft; MV: mitral valve; MR: mitral regurgitation

Feasibility of MV repair (Table 1 and Fig. 2)

There were no significant differences in complexity score in Terms I, II, and III (4.1 ± 1.7, 4.2 ± 2.0, and 4.2 ± 1.6, respectively). Further, there were no significant differences in severity score in Terms I, II, and III (8.7 ± 2.3, 8.5 ± 3.4, and 8.1 ± 3.2, respectively) or in the frequency of MV repair in the three groups, at 57%, 59%, and 55%, respectively (**Table 1, Fig. 2**). Repair involving the commissure leaflet was more frequently performed in Term I (4/4, 100%) than in Term II (5/13, 38%, p = 0.003) and Term III (2/11, 18%, p = 0.004). Also, autologous pericardial patch repair was more frequently used in Term I (4/4, 100%) than in Term III (5/11, 45%, p = 0.013).

Major complications and in-hospital mortality

There were no differences in occurrence of postoperative more than moderate MV regurgitation after MV repair (1/4, 2/8, and 1/5 in Term I, II, and III, respectively), and two of them required redo-surgery. One patient in Term II, with severity score 8, underwent MV repair, and redo MV repair was performed 4 weeks after the first operation. One patient in Term I with severity score 13 underwent MV replacement 6 months after the first operation. The rate of major complications was significantly higher in Term I (86%) than in Term II (41%, p = 0.031) and Term III (25%, p = 0.005). In-hospital mortality was also higher in Term I (43%) than in Term II (9%, p = 0.039) and Term III (5%, p = 0.039).

There were no differences between patients who underwent MV repair (n = 28) and MV replacement (n = 21) in ischemic time (123 ± 39 min vs. 116 ± 40 min, p = 0.419), as well as in the rate of major complications and in-hospital mortality (**Table 2**).

	≦48 hours	3-14 days	≧15 days
CRP(mg/dl)	11.5 ± 9.7	5.1 ± 3.8	2.9 ± 2.1

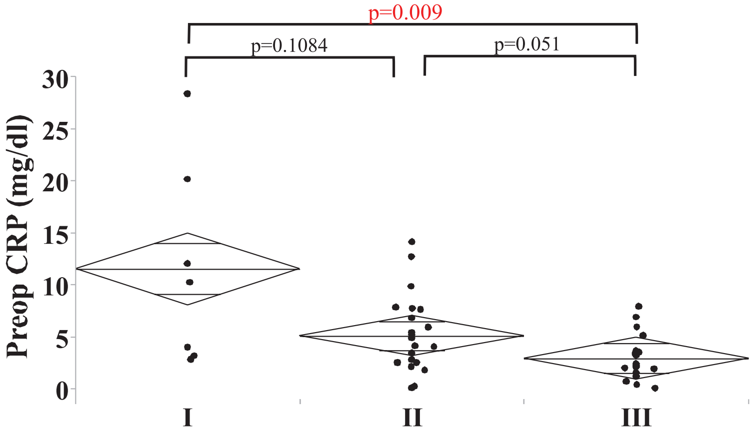

Fig. 1 Preoperative C-reactive protein.

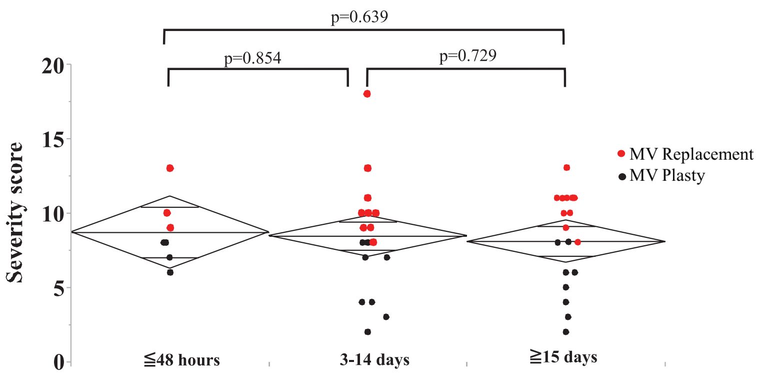

Fig. 2 Feasibility of MV repair in each operative timing. MV: mitral valve

Multiple regression analysis was used to identify variables associated with postoperative major complication and in-hospital mortality (**Table 3**). Of these, body surface area and preoperative C-reactive protein were shown to be risk factors for major complications. Age, the operative day, or preoperative C-reactive protein was not predictive of in-hospital mortality.

Discussion

This study has two major findings. First, patients who underwent operation within 48 hours had poor operative outcomes. Second, the frequency of MV repair did not increase in patients who underwent operation after more than 2 weeks of antibiotic therapy.

Although the optimal timing of surgery for patients with active IE has long been discussed, the answer is unclear. Cardiac surgeons face a dilemma in deciding whether to perform early surgery to prevent the risk of emboli and severe cardiac insufficiency or to delay surgical intervention until the state of infection is controlled and the risk of operation is accordingly reduced. In our study, patients who underwent surgery within 48 hours consisted of cases with deteriorating respiratory function or worsening hemodynamic status, which was previously demonstrated as a major predictor of in-hospital outcome,[10] and the surgical schedule could not be delayed.

MV repair has been preferred for patients with IE, and the possibility of MV repair has been considered high with surgery in the healed stage. In 1998, Lee and colleagues reported 71 consecutive patients who underwent operation for mitral endocarditis. In that study, MV repair was performed in 17% in the active stage versus 59% and 63% in the partially treated and healed stages of IE, respectively.[11] We previously agreed with Feringa et al.[12] that "during the early stages of the disease, reconstructive surgery in inflammatory tissue may be difficult" and that a delay in surgical schedule may be beneficial to successful repair. Nevertheless, our present study demonstrated

Table 2 MV repair vs. replacement

	MV repair n = 28	MV replacement n = 21	p-value
Severity score	6.9 ± 3.0	10.2 ± 2.2	<0.0001*
Ischemic time	164 ± 48	141 ± 35.6	0.120
Major complications	10 (36%)	10 (48%)	0.401
In-hospital mortality	4 (14%)	2 (10%)	0.615

*p <0.05. MV: mitral valve

Table 3 Multiple regression analysis of major complication and in-hospital mortality

	Odds ratio	95% CI	p-value
Major complications			
Ischemic time ≥120 min	421.0	0.827–5.216	0.007
Body surface area <1.55	3777	0.859–7.377	0.013
Preop. CRP >4.0 mg/dl	48.8	0.242–3.647	0.025
MV replacement	188.2	0.229–5.008	0.032
In-hospital mortality			
Age ≥75 year	39.66	0.160–3.840	0.030
MV replacement	16.45	3.284–0.484	0.100
Body surface area <1.55	3.062	0.846–1.965	0.430
Preop. cerebral infarction	2.824	0.816–1.860	0.444
Preop. CRP >4.0 mg/dl	2.223	1.599–0.798	0.504
Ischemic time ≥120 min	1.452	0.980–1.353	0.754

CI: confidence interval; preop: preoperative; MV: mitral valve; CRP: C-reactive protein

that the feasibility of MV repair does not depend on timing of the operation, and the frequency of MV repair did not increase the delayed, subacute phase of IE.

Even in patients who delayed surgery to after 2 weeks of antibiotic therapy and improved C-reactive protein value, the feasibility of MV repair was low in those with extensive valvular destruction and a technically complex repair (**Fig. 2**). In our previous study, we introduced "severity score" to predict successful MV repair.[8,9] We found that patients with a severity score less than 7 were good candidates for MV repair, whereas repair was likely to fail in those with a severity score higher than 9. In patients with a severity score of 8, in contrast, decision making depends on the benefits of repair in the patient. In our present study, severity score was 8.1–8.7 and the frequency of MV repair was 55%–59% with no difference by operative timing. The complexity score has also demonstrated equal repair difficulty among the three operative timings, at around 4 points.

Although there were no differences in the feasibility of MV repair between three operative timings, emergent/urgent cases had lesions including commissure leaflet more frequently than acute or subacute phase (**Table 1**). High occurrence of commissure leaflet involvement might have been associated with progressive circulatory deterioration. Although severity score was not different between the emergent/urgent group and the subacute group (8.7 ± 2.3 vs. 8.1 ± 3.2, p = 0.889), autologous pericardial patch was more frequently used (100% vs. 45%) in the emergent/subacute group. In cases with commissure lesions, a sliding annuloplasty could be applied; however, use of autologous pericardial patch is also an effective repair technique to avoid suture dehiscence and coaptation adjustment.

Several limitations of this study warrant mention. First, clinical studies of active IE are characteristically hampered by consistently small patient numbers, and the ability to draw definitive conclusions is limited due to its retrospective nature. There might be inhomogeneity between groups, and propensity score matching analysis to establish the comparable groups would be ideal, however, it was difficult because of small sample size of this study. Second, the severity score is based on our surgical experience and outcomes, meaning a degree of subjectivity may be inevitable, and validation is required.

Nevertheless, the score is reproducible and useful in predicting successful MV repair in IE patients. Third, operative day does not precisely reflect the timing of the active stage. The precise day of development of IE is difficult and unclear: although some of our patients could identify which day was the first day of high fever, most could not say what day it occurred on. We defined operative day as the day of initiation of antibiotics administration for treatment of IE according to blood culture. In our series, causative microorganisms were identified in 48/49 patients, and an appropriate antibiotic therapy should have been given. Lastly, we did not demonstrate the long-term follow-up data, which would be our future theme.

Conclusions

The feasibility of MV repair was not associated with the timing of operation, with the percentage of MV repair remaining at 50%–60% in the urgent, acute, and subacute phases. Patients who required urgent operation within 48 hours of onset showed high rates of major complications and in-hospital mortality.

Disclosure Statement

We have nothing to declare for this study.

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