

# Infective endocarditis with cerebrovascular complications: timing of surgical intervention

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## Abstract

Management of infective endocarditis (IE) with cerebrovascular complications is difficult due to absence of concrete evidence. These patients usually have multiple neurological deficits and the optimal timing for cardiac operation remains controversial. The aims of this study were to present cases and discuss the treatment options for IE with cerebrovascular complications. From 1998 to 2010, 51 patients underwent operations for IE at our institution. From a review of medical records, 10 patients (19.6%) with preoperative neurological complications were identified. Data on these 10 patients were analysed. Cerebrovascular complications included cerebral infarction ( $n = 4$ , 40.0%), mycotic aneurysm ( $n = 1$ , 10.0%), mycotic aneurysm plus cerebral infarction ( $n = 3$ , 30.0%), meningitis ( $n = 1$ , 10.0%) and mycotic aneurysm with cerebral haemorrhage plus meningitis ( $n = 1$ , 10.0%). Of 5 patients having mycotic aneurysms, 3 underwent clipping before cardiac operations. The mean interval from craniotomy to cardiac operations was  $26.7 \pm 21.8$  days. A cardiac operation was performed initially on seven patients. The mean interval from the onset of neurological deficit to cardiac operation was  $7.4 \pm 9.8$  days. The mortality rate was 10.0%. Postoperative deterioration was not observed. Management of IE with cerebrovascular complications should be based on case-by-case multidisciplinary assessment of potential risks and benefits of intracranial and cardiac operations.

**Keywords:** Infective endocarditis • Cerebrovascular complications • Surgical intervention

## INTRODUCTION

Cerebrovascular complications occur in 12–40% of patients during the active course of infective endocarditis (IE) [1]. The timing of cardiac surgery of IE patients with neurological complications is controversial. Cardiopulmonary bypass (CPB) may exacerbate neurological deficits [2]. Systemic heparinization may extend brain haemorrhage and convert brain infarction to haemorrhagic infarction [2]. Hypotension during CPB may aggravate pre-existing ischaemic neurological injury, and CPB may potentiate cerebral oedema in areas of blood-brain barrier disruption [2].

Previous studies have suggested a management algorithm for IE patients with cerebrovascular complications, but these patients frequently have multiple lesions and complicated cardiovascular condition; so in reality, the suggested management plan is difficult to be applied on them.

The objective of this study was to evaluate the results of perioperative management of IE patients with neurological complications retrospectively.

## MATERIAL AND METHODS

We reviewed the medical records of IE patients who underwent valve operations at Hirosaki University Hospital from 1998 to

2010. During this period, 51 patients had cardiac operations for IE. Of these 51 patients, preoperative neurological evaluation was routinely performed including brain computed tomography (CT) or magnetic resonance (MR) imaging. In patients with neurological symptoms, MR angiography or digital subtraction angiography was performed to evaluate mycotic aneurysm. Ten patients had one or more of the following preoperative neurological events: cerebral infarction, mycotic aneurysms, cerebral bleeding or meningitis.

Data collected on the 10 patients included age, sex, stage, valve involved, pathogen, neurological deficit, interval between neurological event and cardiac operation, type of operation, operative outcome and postoperative neurological status (Table 1). A management plan for patients who had neurological complication was decided through interactive discussion between cardiologists, cardiovascular surgeons and neurosurgeons. The following factors were considered prior to emergent cardiac operation: haemodynamics of patients with congestive heart failure unresponsive to inotropes and diuretics, flail vegetation with or without peripheral arterial embolism and severe destruction of valve.

## RESULTS

In the study group of 10 patients, the mean age was  $30.1 \pm 15.0$  years (range 1–59 years). There were six men and four women.

**Table 1:** Summary of IE patients with neurological complication

No.	Age	Sex	Stage	Valve involved	Pathogen	Neurological deficit	Interval between neurological event and cardiac operation (days)	First operative procedure	Second operative procedure	Outcome	Postoperative neurological status
1	38	M	AIIE	Aortic valve	Staphylococcus	Cerebral infarction	0	AVR	None	Alive	Improved
2	40	F	AIIE	Mitral valve	Streptococcus	Cerebral infarction	24	MVR	None	Alive	Improved
3	35	M	AIIE	Mitral valve	Streptococcus	Meningitis	4	AVR	None	Alive	Improved
4	25	M	AIIE	Aortic valve	MSSA	Mycotic aneurysm cerebral infarction	8	AVR	None	Aneurysm rupture (POD 10) Dead (POD 61)	Improved
5	23	M	HIE	Mitral valve	Streptococcus	Mycotic aneurysm cerebral infarction	N/A	Aneurysm clipping	MVP (after 20 days)	Alive	Improved
6	1	M	AIIE	Mitral valve	Unknown	Mycotic aneurysm SAH meningitis	N/A	Aneurysm clipping	MVR (after 9 days)	Alive	Improved
7	22	F	HIE	Mitral valve	Streptococcus	Mycotic aneurysm cerebral infarction	Unknown	Aneurysm clipping	MVR (after 51 days)	Alive	Improved
8	26	F	AIIE	Mitral valve	Streptococcus viridans	Cerebral infarction	1	MVR	None	Alive	Improved
9	32	F	AIIE	Mitral valve	Streptococcus viridans	Cerebral infarction	Unknown	MVR	None	Alive	Improved
10	59	M	AIIE	Mitral valve	Unknown	Mycotic aneurysm	Unknown	MVR, AVR	Aneurysm clipping	Alive	Improved

IE, infective endocarditis; AIIE, active infective endocarditis; HIE, healed infective endocarditis; SAH, subarachnoid haemorrhage; AVR, aortic valve replacement; MVR, mitral valve replacement; POD, postoperative day.

Eight had active native valve endocarditis and 2 had healed native valve endocarditis. Affected valves were the aortic valve in 2 patients, mitral valve in 7 patients and aortic and mitral valves in 1 patient. Causative microorganisms were as follows: *streptococcus*—five (50.0%), *Staphylococcus*—one (10.0%), methicillin-sensitive *Staphylococcus aureus* (MSSA)—one (10.0%) and unknown—three (30.0%).

Neurological complications included the following: cerebral infarction in four (40.0%), mycotic aneurysm in one (10.0%), mycotic aneurysm plus cerebral infarction in three (30.0%), meningitis in one (10.0%) and mycotic aneurysm with cerebral haemorrhage plus meningitis in one (10.0%).

All patients received intravenous administration of antibiotics once the diagnosis of endocarditis was established. Among 5 patients having mycotic aneurysm, 3 patients underwent clipping of the aneurysm before cardiac operation. Of these 3 patients, 2 had mycotic aneurysm that had not resolved by antibiotics but were haemodynamically stable (Patients 5 and 7). The other patient had cerebral haemorrhage owing to ruptured aneurysm (Patient 6). The mean interval from craniotomy to cardiac operation was  $26.7 \pm 21.8$  days (9–51 days). Cardiac surgery was performed first in 2 patients with mycotic aneurysm for unstable haemodynamics due to severe AR (Patient 4) and severe MR plus mild AR (Patient 10). In Case 4, craniotomy was planned on postoperative day (POD) 11; however, the mycotic aneurysm ruptured the day before the scheduled operation and the patient died of brain damage 2 months later. Of those 7 patients who received cardiac surgery initially, the interval from the onset of neurological dysfunction to cardiac operation was  $7.4 \pm 9.8$  days (range, 0–24 days), and the median interval was 4 days. In 1 patient, cardiac operation was performed on the day following the onset of cerebral infarction but the patient recovered without neurological complications (Patient 1).

There was 1 death. It occurred in the patient mentioned earlier who required urgent valve operation before aneurysm clipping (Patient 4). At 1 year follow-up, all patients survived, had no recurrent endocarditis and had normal neurological status.

## Case review

The following representative cases are shown:

- (1) Clipping of the aneurysm was performed as the first operative procedure.
- (2) Intracranial aneurysm ruptured while waiting for the scheduled clipping.
- (3) Cardiac operation was performed first due to haemodynamic instability.

Patients 5 and 6 (Table 1) were reported in the General Thoracic and CardioVascular Surgery [3, 4].

**Case 1.** A 22-year old woman with a diagnosis of IE was transferred to our unit for cardiac operation (Table 1, Patient 7). She had an episode of headache, aphasia and right hand numbness 2 months before admission. CT revealed cerebral infarction in the left parietal lobe. Echocardiography showed severe mitral regurgitation. *Staphylococcus viridans* was detected from the blood culture. MR angiography revealed aneurysm of the left middle cerebral artery (MCA) (Fig. 1). After 32 days following the onset of cerebral infarction, aneurysm clipping and

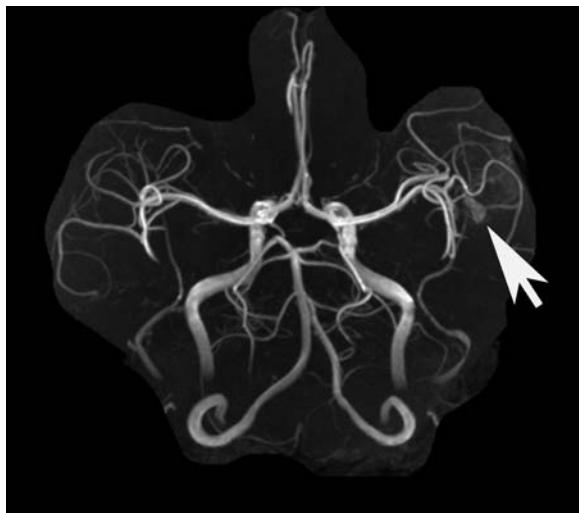


Figure 1: MR angiography showed aneurysm of the left MCA.



Figure 2: Enhanced cranial CT revealed 3 mm mycotic aneurysm in the left MCA.

MCA-superficial temporal artery anastomosis was performed. She underwent mitral valve plasty 51 days after craniotomy. She had uneventful postoperative course and had no subsequent neurological deficit.

**Case 2.** A 25-year old man with active IE was referred to our hospital (Table 1, Patient 4). Paresis of the left arm occurred 7 days before admission. MSSA was detected from the blood sample and enhanced cranial CT revealed 3 mm mycotic aneurysm in the left MCA (Fig. 2). Echocardiography showed the enlargement of vegetation attached to the aortic valve and aortic regurgitation was moderate. Emergency cardiac operation was performed. Operative findings showed

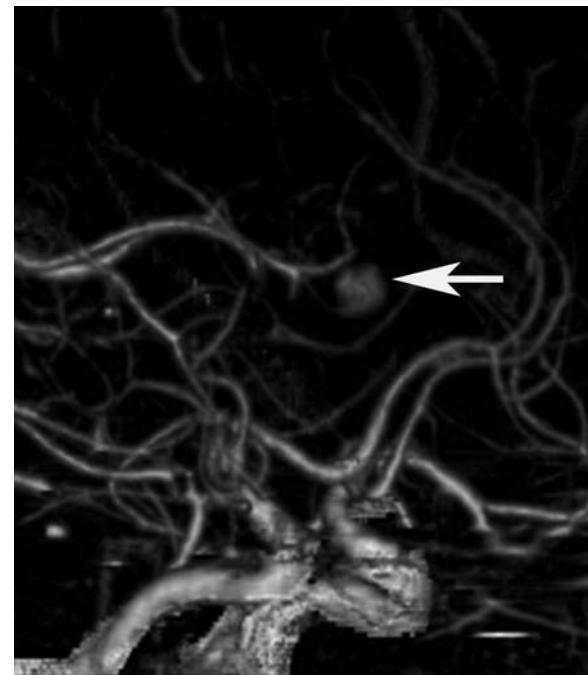


Figure 3: Cranial CT after cardiac surgery revealed enlargement of the mycotic aneurysm.

vegetation attached to the bicuspid aortic valve and extended into the ventricular septum. Debridement of the root abscess revealed destruction of the intraventricular septum and a communication between the left ventricle (LV) and right ventricle (RV). The LV-RV communication was closed with bovine pericardium and aortic valve replacement (AVR) was performed with a mechanical prosthesis (St. Jude Medical Regent, 19 mm). Since the postoperative cranial CT revealed enlargement of the mycotic cerebral aneurysm (Fig. 3), urgent clipping of the aneurysm was planned on POD 11. Unfortunately, the aneurysm ruptured the night before the operation and the patient died on POD 61.

**Case 3.** A 38-year old woman with a diagnosis of IE, who had been receiving antibiotics for 3 days, was referred to us because of pulmonary oedema and aphasia (Table 1, Patient 1). At the time of presentation, she had right hemiplegia. The head CT showed infarction in the left frontal lobe, right posterior limb of internal capsule and left occipital lobe. The echocardiography revealed large mobile vegetations on the aortic valve obstructing LV outflow and aortic root abscess. Cardiac operation was performed immediately due to uncontrollable infection and lung oedema. An abscess was found in the membranous part of the ventricular septum and it invaded into the ventriculo-atrial septum and perforating into the right atrium (RA). After complete resection of the abscess, LV-RA communication was closed with bovine pericardium. Then AVR was performed using 19 mm St. Jude Medical® regent valve (St. Jude Medical, St. Paul, MN, USA). Tracheal tube was extubated on POD 2. Fortunately, the patient recovered completely without neurological complication. Antibiotic therapy was continued for 6 weeks.

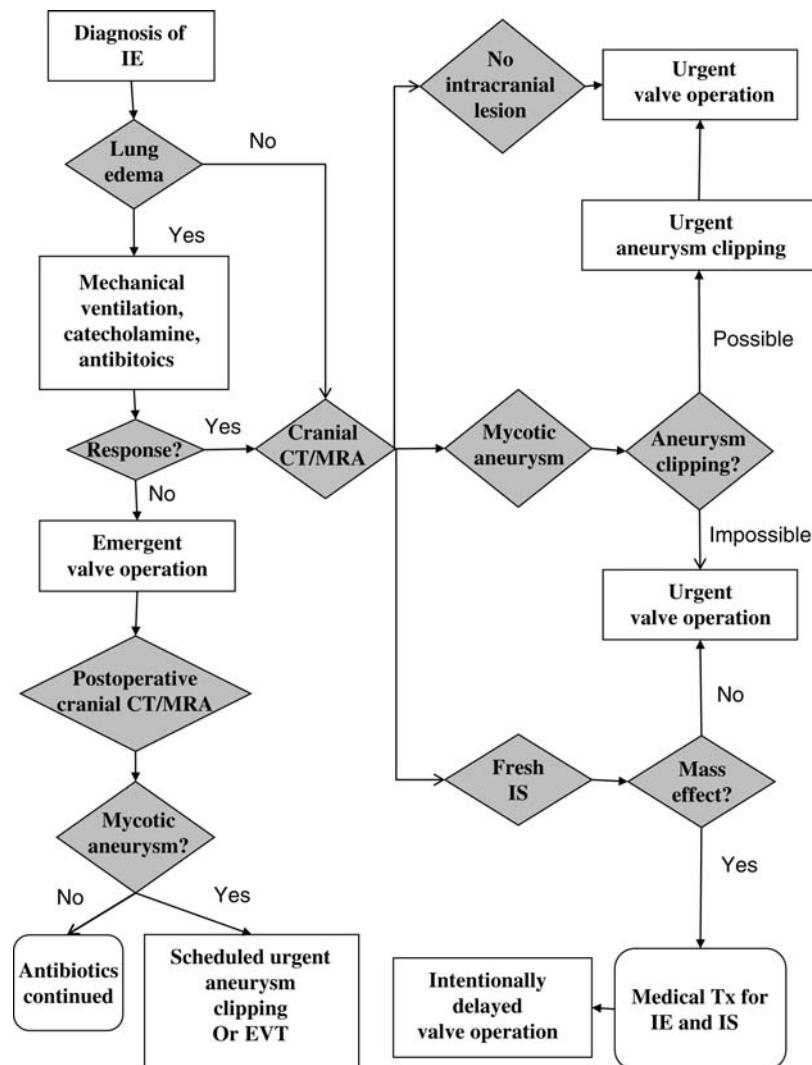


Figure 4: Algorithm for the management of IE patients. IE, infective endocarditis; EVT, endovascular therapy; IS, ischaemic stroke.

## DISCUSSION

Neurological complications of IE tend to occur early in the course of infection and are associated with increased mortality rates [5]. Cerebral infarction and mycotic intracranial aneurysms are the major concern of cardiac surgery because CPB may potentially worsen brain injuries.

Cerebral infarction, the most common of the neurological complications associated with IE, complicates the outcome of left-sided IE in 20–40% [5]. The safety period between the event of cerebral infarction and the cardiac surgery is largely debated because of lack of controlled studies. Eishi and associates [6] reported the mortality rate of 66.3% if the cardiac operation was performed within 24 h after the onset of cerebral infarction. Gillinov et al. [2] recommended a delay of 2–3 weeks in performing cardiac surgery for patients with non-haemorrhagic embolic cerebrovascular accident. The risk of neurological deterioration after the valve replacement was calculated by Angstwurm et al. [1] and they found that after brain infarction, the risk was 35% on Day 1, 15% on Days 2 and 3, 20–50% from Day 4 to Day 14, lower than 10% after 14 days and 0.4% after 4 weeks. Piper et al. [7] found the risk of deterioration to be low when cardiac surgery was performed within 72 h (when the blood-brain

barrier is not yet altered). Hosono et al. [8] determined the relationship between the size of the cerebral infarction and the timing of surgical intervention in active IE patients with recent cerebrovascular events, and they concluded that IE patients with a small, non-haemorrhagic cerebral infarction can safely undergo cardiac surgery, even within 2 weeks after onset of the cerebrovascular event.

In our series, 1 patient (Case 3) underwent valve replacement in the acute phase of cerebral infarction but postoperative neurological exacerbation was not observed. Based on the published studies, cardiac surgery performed after 4 weeks of brain infarction is associated with a low risk. However, if there is an urgent need for valve replacement due to severe heart failure, we suggest performing cardiac surgery within 72 h after the brain infarction because the mortality with severe heart failure is 80% in patients treated only medically [1].

Haemorrhagic conversion of the ischaemic infarct due to septic emboli is the most frequent mechanism followed by the rupture of pyogenic arteries and mycotic aneurysms [9]. The incidence of intracranial mycotic aneurysm is 2–4% of IE cases [10]. The mortality rate of unruptured aneurysms is 30% but the mortality rate approaches 80% when rupture occurs [11]. Treatment of intracranial mycotic aneurysms is

controversial and the answer to the question 'which operation should be performed first? Cardiac surgery or craniotomy?' is difficult.

Cardiac surgery is not usually recommended in the setting of an acute aneurysmal rupture [10]. Gillinov *et al.* [2] suggested that a ruptured aneurysm should be surgically treated, and cardiac surgery should follow 2–3 weeks later. The exception to this would be if heart failure were to develop as a consequence of IE. Endovascular treatment for cerebral mycotic aneurysm is a recent and evolving modality [12]. Endovascular techniques for embolizing unruptured/ruptured mycotic aneurysms have been described [12, 13]. Asai *et al.* [13] reported a case of mycotic intracranial aneurysm that was successfully treated by endovascular embolization 2 weeks before cardiac surgery. They stated that a patient with ruptured aneurysm who had suffered haemodynamic deterioration or large vegetations can undergo cardiac surgery after a shorter waiting period [13].

The management of unruptured mycotic aneurysm is complex. Several institutions have recommended antimicrobial therapy as the first line of treatment for intracranial aneurysms [11]. Mycotic aneurysms may resolve or decrease in size with appropriate antibiotics; however, it is impossible to predict the responses of these aneurysms to therapy. Bohmfalk *et al.* [14] reported a high mortality (44%) in patients treated with antibiotics alone, and lower mortality (23%) in patients who were treated with antibiotics and elective surgery. Kanno *et al.* [11] had also experienced higher mortality for the medically treated group although the difference was not statistically significant. Although there is no evidence that CPB or heparin treatment predisposes aneurysms to rupture, we have experienced a case of unruptured intracranial mycotic aneurysm rupturing after cardiac surgery (Case 2). Once the diagnosis is made for mycotic intracranial aneurysms, we recommend aggressive treatment in order to prevent serious complications.

In meningitis, we do not see a contraindication or benefit from a delay in cardiac operation. We have performed valve replacement in such circumstance successfully (Table 1, Patient 3).

Management of IE with cerebral complication is challenging because there are no randomized controlled trials and these patients usually present with multiple neurological deficits. We have developed an algorithm for the management of IE patients (Fig. 4). With cerebral infarction in the presence of heart failure, we recommend performing cardiac surgery within 72 h after the infarction. With unruptured mitotic aneurysms,

our policy is to initially treat the aneurysms before cardiac surgery. The optimal timing for cardiac surgery must be based on the type of neurological complications and the assessment of individual patients.

**Conflict of interest:** none declared.

## REFERENCES

- [1] Angstwurm K, Borges AC, Halle E, Schielke E, Einhäupl KM, Weber JR. Timing the valve replacement in infective endocarditis involving the brain. *J Neurol* 2004;251:1220–26.
- [2] Gillinov AM, Shah RV, Curtis WE, Stuart S, Cameron DE, Baumgartner WA *et al.* Valve replacement in patients with endocarditis and acute neurologic deficit. *Ann Thorac Surg* 1996;61:1125–30.
- [3] Suzuki Y, Minakawa M, Itaya H, Kuga T, Fukui K, Fukuda I. Mitral valve repair in a child with infective endocarditis followed by meningitis. *Jpn J Thorac CardioVasc Surg* 2004;52:429–31.
- [4] Fujita W, Daitoku K, Taniguchi S, Fukuda I. Infective endocarditis with cerebral mycotic aneurysm: treatment dilemma. *Gen Thorac CardioVasc Surg* 2010;58:622–5.
- [5] Sontineni SP, Mooss AN, Andukuri VG, Schima SM, Esterbrooks D. Effectiveness of thrombolytic therapy in acute embolic stroke due to infective endocarditis. *Stroke Res Treat* 2010;2010:841797.
- [6] Eishi K, Kawazoe K, Kuriyama Y, Kitoh Y, Kawashima Y, Omae T. Surgical management of infective endocarditis associated with cerebral complications: multi-center retrospective study in Japan. *J Thorac CardioVasc Surg* 1995;110:1745–55.
- [7] Piper C, Wiemer M, Schulte HD, Horstkotte D. Stroke is not a contraindication for urgent valve replacement in acute infective endocarditis. *J Heart Valve Dis* 2001;10:703–11.
- [8] Hosono M, Sasaki Y, Hirai H, Sakaguchi M, Makahara A, Seo H *et al.* Considerations in timing of surgical intervention for infective endocarditis with cerebrovascular complications. *J Heart Valve Dis* 2010;19: 321–5.
- [9] Hart RG, Foster JW, Luther MF, Kanter MC. Stroke in infective endocarditis. *Stroke* 1990;21:695–700.
- [10] Peters P, Harison T, Lennox JL. A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis. *Lancet Infect Dis* 2006;6:742–8.
- [11] Kanno S, Iyer R, Thomas SV, Furtado SV, Rajesh B, Kesavadas C *et al.* Intracranial infections aneurysm: presentation, management and outcome. *J Neurol Sci* 2007;256:3–9.
- [12] Dhomne S, Rao C, Shrivastava M, Sidhartha W, Limaye U. Endovascular management of ruptured cerebral mycotic aneurysms. *Br J Neurosurg* 2008;22:46–52.
- [13] Asai T, Usui A, Miyachi S, Ueda Y. Endovascular treatment for intracranial mycotic aneurysms prior to cardiac surgery. *Eur J Cardiothorac Surg* 2002;21:948–50.
- [14] Bohmfalk GL, Story JL, Wissinger JP. Bacterial intracranial aneurysms. *J Neurosurg* 1978;48:369–82.