Yamazato *et al. Vessel Plus* 2023;7:2
DOI: 10.20517/2574-1209.2022.01

Vessel Plus

Mini Review

Open Access

What to do with patients with active infective endocarditis complicated by intracranial bleeding

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How to cite this article: Yamazato T, Munakata H, Okada K, Okita Y. What to do with patients with active infective endocarditis complicated by intracranial bleeding. *Vessel Plus* 2023;7:2. https://dx.doi.org/10.20517/2574-1209.2022.01

Received: 1 Jan 2022 **Accepted:** 23 Feb 2022 **Published:** 19 Jan 2023

Academic Editors: Carlos A. Mestres, Francesco Nappi **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Cerebral complications, especially intracranial hemorrhage (ICH), are critical determinants of the early outcomes of cardiac surgery for active infective endocarditis (AIE). Relevant society guidelines still recommend delaying cardiac surgery for AIE complicated by ICH for 4 weeks. Some early studies indicated that the mortality decreases when cardiac surgery for ICH is delayed. In contrast, some reported that surgical intervention should not be delayed if an early operation is indicated, even in patients with ICH. The current literature on early versus late surgery for AIE with ICH is conflicting. ICH is classified by its mechanism which includes primary intraparenchymal hemorrhage, hemorrhagic transformation of ischemic infarcts, and rupture of intracranial infectious aneurysms. Some reported that for AIE with a mycotic cerebral aneurysm, early cardiac surgery should be done after repair of the aneurysm, either surgically or endovascularly. Except for the rupture of mycotic aneurysm, primary intraparenchymal hemorrhage and hemorrhagic transformation of ischemic infarcts remain a critical and challenging dilemma. Modifying the cardiopulmonary bypass (CPB) strategy might be necessary to improve the surgical outcomes of AIE with ICH. Some studies reported that cardiac surgery using nafamostat mesylate as an alternative anticoagulant during CPB (NM-CPB) was performed successfully. The NM-CPB can be a useful option as an anticoagulant in critical situations of cardiac surgery with ICH. The timing of surgery should be decided on a case-by-case basis with multidisciplinary specialties including cardiac and neurological teams.

Keywords: Intracranial hemorrhage, early cardiac surgery, primary intraparenchymal hemorrhage, hemorrhagic transformation of ischemic infarcts, rupture of intracranial infectious aneurysms, low-dose heparin, nafamostat mesylate

INTRODUCTION

Cerebral complications are critical determinants of the in-hospital outcomes of cardiac surgery for active infective endocarditis (AIE). Intracranial hemorrhage (ICH) is a major potential risk factor for worse outcomes in patients who are undergoing open cardiac surgery for AIE. Delaying cardiac surgery for patients with ICH may exacerbate local or systemic infections. On the other hand, early cardiac surgery using normal heparin doses of systemic anticoagulation carries the risk of further bleeding and neurologic deterioration. Therefore, AIE with ICH has a critical and challenging dilemma. In this report, the current literature on cardiac surgery for patients with AIE and ICH was reviewed and discussed.

METHODS

We systematically searched MEDLINE without language restrictions for relevant studies using the following Medical Subject Headings (MeSH) terms present in either the title or abstract: "endocarditis", "cardiac surgery", "stroke", "intracranial complications", and "intracranial hemorrhages". Our search strategy was that eligible studies had to fulfill the following criteria for inclusion: (1) cohort study, either prospective or retrospective; (2) patients receive a definite diagnosis of AIE according to the modified Duke criteria[1]; (3) the study treated early surgery for AIE patients with intracranial complications, including late surgery (we defined early surgery as surgery performed within 2 weeks from the onset of the neurological event[2]); and (4) the study investigated short-term and long-term efficacy and neurological exacerbation as outcomes. After screening titles and abstracts, 183 clinical studies were found and analyzed.

Current guidelines

Current guidelines for AIE stated that cardiac surgery should be considered without any delay in patients with heart failure, uncontrolled infection, annular abscess, or persistent high-risk of systemic embolism, except for patients with coma, brain hernia, or large major central lesions[2-5][Table 1]. However, postponing the cardiac surgery for AIE with ICH for four weeks is still recommended. As for a relationship of neurological outcomes and the size of the brain lesions of stroke or ICH secondary to AIE, no study has ever been published.

Early studies

There have been many earlier studies regarding treating AIE patients with cerebral complications. In 1995, Eishi *et al.* analyzed 34 patients with ICH and reported that the risk of neurological deterioration is still significantly high 15 days and even four weeks after cerebral hemorrhage[6]. In 1996, Gillinov *et al.* reported good outcomes in 7 patients with AIE and ICH, in whom the surgery was postponed for 2 to 3 weeks[7]. In 2014, Wilbring *et al.* reported that a neurological deterioration was found in 33% of 6 patients with AIE and ICH who underwent surgery after 17 ± 24 days of diagnosis[8]. In 2006, Ruttmann *et al.* reported a mortality of 66% after an early surgery of patients with ICH[9]. In 2013, Garcia-Cabrera *et al.* reported that the mortality of patients with AIE and ICH who had surgery within 14 days was 75%, and that neurological exacerbation occurred in 50%[10]. In 2016, A multi-center registry data analyzing the AIE patients complicated with stroke or ICH by Okita *et al.* demonstrated that patients with AIE and ICH who underwent open cardiac surgery had higher mortality when the surgery was performed within seven days after AIE and ICH onset than those who underwent surgery 8-21 days after the onset[11]. These studies indicate that the mortality rate decreases when cardiac surgery for patients with ICH is delayed.

Table 1. Guidelines and indication for cardiac surgery for the patients with intracranial hemorrhage

		COR	LOE
ESC 2015[3]	Following intracranial hemorrhages, surgery should be generally postponed for > 1 month	IIb	B
AATS 2017[4]	In patients with a recent intracranial hemorrhage, a delay in operation for three or more weeks is reasonable	IIb	B
ACC/AHA 2017[2]	Delaying the valve surgery for at least four weeks may be considered for patients with IE and major ischemic stroke or intracranial hemorrhage if hemodynamically stable	IIb	B
JCS 2019[5]	Surgery should be postponed for at least four weeks when a new intracranial hemorrhage is detected Note: Except for cases involving cerebral microbleeds	IIb	B

COR: Class of recommendation; LOE: level of evidence.

Recent studies

Conversely, recent studies by Shang *et al.* reported that cardiac surgery on 16 patients with AIE and ICH within four days after admission whose ICH size was smaller than 1-2 cm was safely performed[12]. Yoshioka *et al.* analyzed 30 patients with AIE and preoperative ICH who underwent surgery[13]. Irrespective of the timing of surgery, none of these 30 patients had neurological deterioration or died from neurologic complications. They also reported that postoperative neuroimaging did not demonstrate exacerbation of hemorrhagic lesions, even in 11 patients who underwent surgery within two weeks of ICH diagnosis. Kume *et al.* compared the postoperative outcomes of 25 patients with preoperative ICH with patients without ICH and they found that there was no significant difference in mortality or incidence of ICH worsening[14]. They also found that there was no significant difference in ICH exacerbation between patients who were operated on within 14 days of ICH occurrence and those operated on after 14 days of ICH onset. A meta-analysis by Tam *et al.*, including 27 observational studies, demonstrated no significant difference in mortality after cardiac surgery regarding the timing of surgery[15]. These studies are summarized in Table 2.

Insights from neurology

ICH is classified into primary intraparenchymal hemorrhage [Figures 1 and 2], hemorrhagic transformation of ischemic infarcts [Figure 3], and rupture of intracranial infectious aneurysms [Figure 4][16]. Primary intraparenchymal hemorrhage is due to the septic erosion of the arterial wall with rupture. For non-IE primary intraparenchymal hemorrhage, several scoring systems were developed for predicting long-term outcomes. Many factors, such as lesion size, lesion location, neurologic function at presentation, age, and pre-morbid functional status may contribute to patients' outcomes. An ICH with a volume of 30 mL, measured by computerized tomography (CT) scan, and intraventricular/infratentorial ICH tend to be associated with a worse prognosis[17,18]. The hemorrhagic transformation of ischemic infarcts can be attributed to dysfunctions in the blood-brain barrier and the degradation of the extracellular matrix of the brain[19]. While mycotic aneurysm is not included in the category of ICH, these lesions are common in AIE patients. They are considered to be a potential cause of subarachnoid hemorrhage [Figure 5]. In patients with cerebral aneurysms, neuro-surgical or endovascular intervention prior to cardiac surgery should be strongly considered[20,21]. A recent study by Salaun *et al.* showed that patients with an undetermined etiology of ICH had significantly higher mortality compared to patients with ICH secondary to ruptured mycotic aneurysm or ischemic stroke[22].

Innovations in cardiopulmonary bypass (CPB) strategy

During a conventional CPB using a normal conventional dose of heparin, the coagulo-fibrinolytic system is greatly activated[23]. Modifying the CPB strategy might be necessary to improve the surgical outcomes for AIE with ICH. Some authors have reported that using low-dose heparin (100 IU/kg) during cardiac surgery resulted in reduced blood loss and transfusion requirements[24,25]. We reported the advantages of open cardiac surgery using nafamostat mesylate (NM; 6-amino-2 naphthalene-p-guanidinobenzoate dimethanesulfonate) as an alternative anticoagulant during CPB (NM-CPB) to reduce ICH exacerbation in

Table 2. Summary of the studies of cardiac surgery for infective endocarditis with preoperative ICH

Authors	Study design	No. PTs with ICH	Onset to surgery, median	Neurological exacerbtion	Mortality	Authors' comments
Eishi *et al.*[6]	Retro	ICH 34	< 24 h (*n* = 1) 5 days (*n* = 1) 15-21 days (*n* = 5) 22-28 days (*n* = 6) > 4 weeks (*n* = 210)	< 24 h:100% > 4 weeks:19% 2-28 days: 0%	< 24 h: 100% 5 days: 0% 15-21 days: 20% 22-28 days: 0% > 4 weeks: 19%	There is some risk of progression of cerebral damage 15 days and even 4 weeks after the hemorrhage, regardless of the timing of the operation. Reduced heparization in conjunction with a heparin-coated pump system would useful during cardiac operations
Ruttmann *et al.*[9]	Retro	ICH 6	4.0 days	4 Pts	66.5% (4/6)	
Garcia-Cabrer *et al.*[10]	Retro	ICH 12	< 14 days (*n* = 4) 14-21 days (*n* = 3) > 21 days (*n* = 5)	< 14 days 75% 14-21 days 66%, > 21 days 40%	58.3% (7/12)	In patients with cerebral hemorrhage, it may be advisable to postpone cardiac surgery for > 4 weeks
Okita *et al.*[11]	Retro	ICH 54	< 7 days (*n* = 13) 8-21 days (*n* = 17) > 21 days (*n* = 24)		< 7 days: 15.4% 8-21 days: 5.9% > 21 days: 0%	Very early surgery (within 7 days) should be avoided in patients with ICH
Shang et al.[12]	Retro	ICH16	4.0 days (admission to surgery)	0	0	We do not delay cardiac surgery because of ICH that does not exceed 1 or 2 cm in size
Yoshioka *et al.*[13]	Retro	ICH 30	< 7 days (*n* = 5) 8-14 days (*n* = 6) 15-28 days (*n* = 9) > 29 days (*n* = 10)	0	0	No neurologic deterioration, regardless of surgical timing
Kume *et al.*[14]	Retro	ICH 25	< 14 days (*n* = 17) > 14 days (*n* = 8)	4.0% (*n* = 1)	4.0% (*n* = 1)	No significant difference in post-operative hemorrhage between pts within or after 14 days
Tam *et al.*[15]	Retro. meta-analysis	ICH 38	< 4 weeks (*n* = 17) Median 34 days	18.8%	15.8%	The Pts with ICH might benefit from delayed surgery beyond 21 days

Retro: Retrospective; ICH: intracranial hemorrhage; PTs: patients.

AIE patients with stroke or ICH[26,27]. NM has a strong inhibitory activity on various proteases in the coagulo-fibrinolytic system. Although its exact mechanism has not been elucidated, NM has a very short half-time and has potential inhibitory effects on the coagulation, fibrinolysis, and platelet aggregation system. Our anticoagulation protocol during NM-CPB has been that NM (1.0 mg/kg) was administered intravenously to assess for any allergic reaction after induction of anesthesia. An initial dose of heparin (50 IU/kg; 25% of normal dosage) was administrated to achieve the activated clotting time of over 400 s. After initiating the CPB, the NM was infused continuously through the venous line of the pump circuit at 1.8 mg/kg/h. The activated clotting time was maintained at 350-500 s by a fine titration of the NM dose, which was added at 0.8 mg/kg/h to the cardiotomy reservoir and at 1.0 mg /kg/h in the pump circuit. The

Figure 1. 76-year-old male with mitral prosthetic valve endocarditis. Parenchymal hemorrhage.

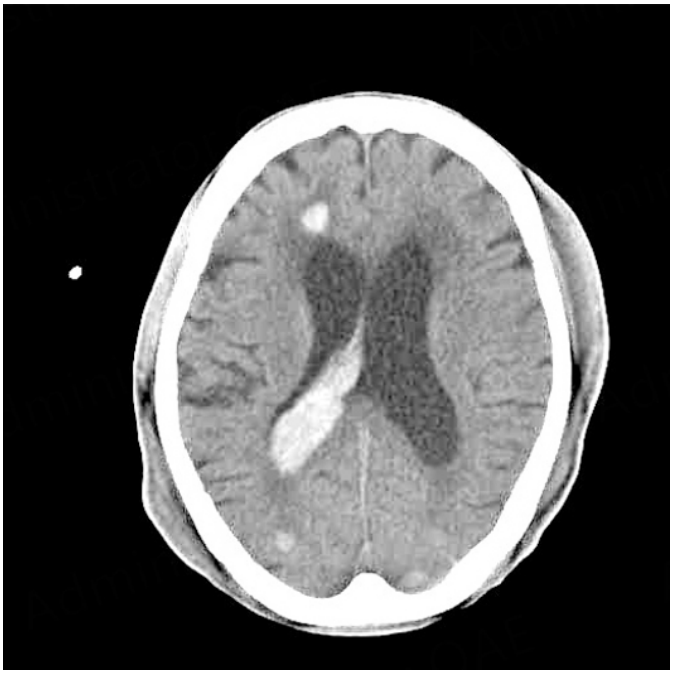

Figure 2. 68-year-old female with aortic valve infective endocarditis. Intraventricular hemorrhage.

activated clotting time was measured every 15 min. The strategy and methods of NM-CPB are shown in [Figure 6]. Sakamoto *et al.* reported that the timing of cardiac surgery in patients with AIE was 2.1 ± 1.2 days after the onset of AIE and the mortality was 33.3% with no worsening hemorrhages[26]. Ota *et al.* reported a similar outcome when the timing of cardiac surgery was within 2.1 days from the onset of

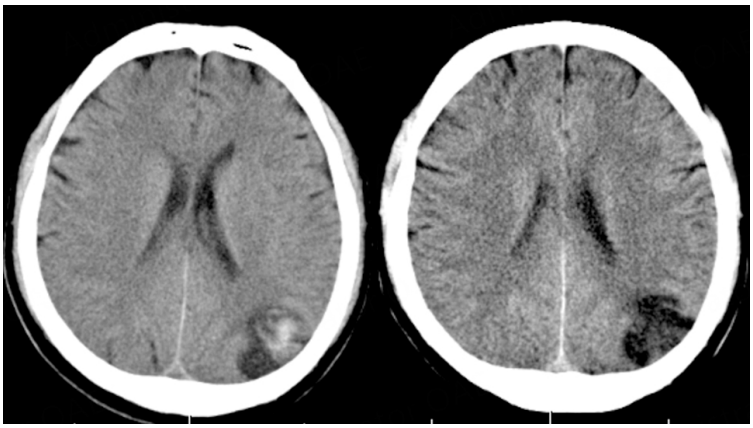

Figure 3. 66-year-old male with aortic valve infective endocarditis. Hemorrhagic transformation of stroke after surgery.

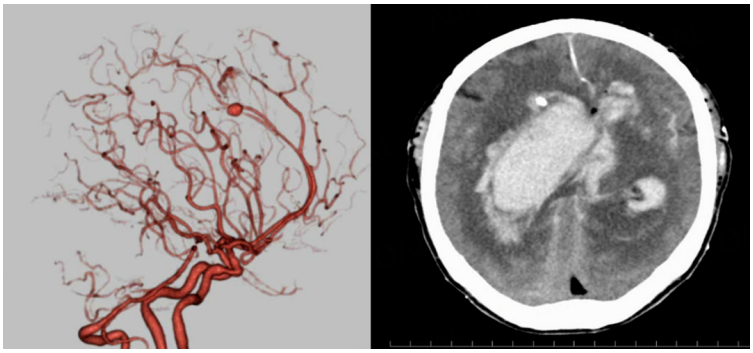

Figure 4. 74-year-old male with aortic valve infective endocarditis. Cerebral mycotic aneurysm ruptured.

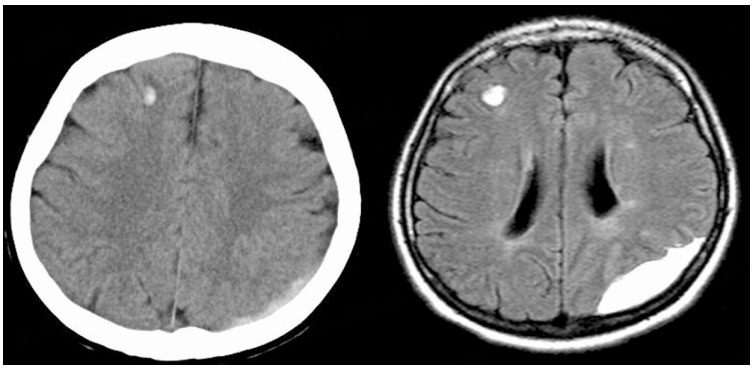

Figure 5. 37-year-old female with mitral infective endocarditis. Subarachnoid hemorrhage.

AIE[27]. In both studies, the mortality was not related to the timing of cardiac surgery. Recently, in our study dealing with four patients with AIE and ICH[28], the timing of cardiac surgery was 6.7 days after the onset of AIE and ICH, and fortunately the mortality was zero. NM can be a useful option as an anticoagulant in critical situations of cardiac surgery with bleeding tendencies involved by the CPB.

We showed the relationships between the size of infarction or hemorrhage and the timing of cardiac surgery for patients who underwent NM-CPB. Regarding acute stroke [Figure 7], in two patients who had normal

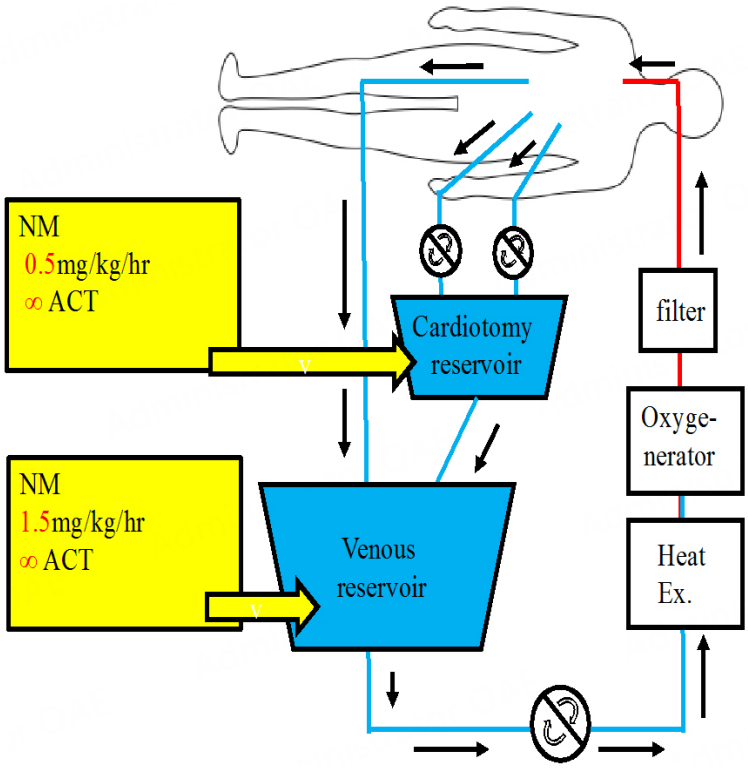

Figure 6. Methods of cardiopulmonary bypass using nafamostat mesylate (NM-CPB). Shown in the image is the pump circuit of NM-CPB. Nafamostat mesylate was infused continuously to the cardiotomy reservoir and venous reservoir at 0.8 mg/kg/h and 1.0 mg/kg/h, respectively. The rate of injection was changed according to the activated clotting time (ACT). Heparin: 50 IU/kg (25% of normal), ACT: 350-450 q 15 min, Mild hypothermia: (33 °C), Pump flow: 2.4-2.6 L/m^2/min, Systemic pressure: 50 mmHg.

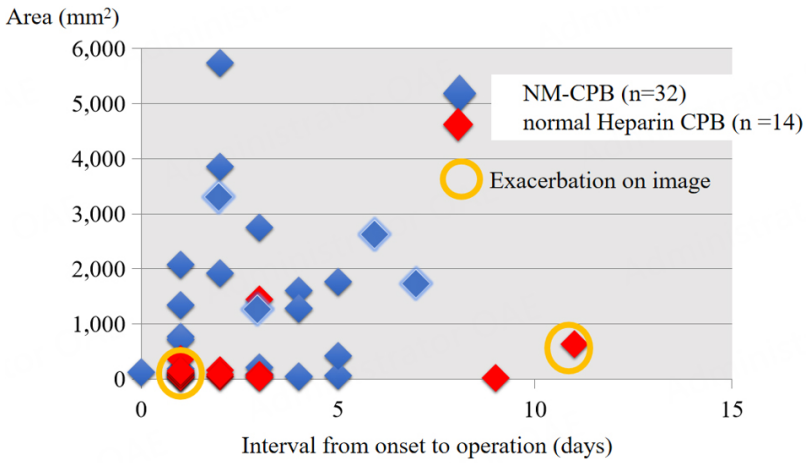

Figure 7. Relationships between the size of acute cerebral infarction and the interval from onset to operation (total *n* = 4 6, NM-CPB *n* = 32, normal CPB *n* = 14). There were two patients of exacerbation, where cardiac surgery was performed with cardiopulmonary bypass using a normal dose of heparin. Case 1: Multiple infarction and subdural hemorrhage with an area of 41 mm^2 turned to parenchymal hemorrhage from preoperative infarct lesion postoperatively. Case 2: Hemorrhagic infarction with an area of 633 mm^2 turned to ectopic subdural hematoma postoperatively. NM-CPB: Cardiopulmonary bypass using nafamostat mesylate; normal CPB: of cardiopulmonary bypass using heparin.

CPB using the conventional dose of heparin, a hemorrhagic transformation of the brain lesions occurred postoperatively. However, another patient who had a stroke over 3000 mm^2 in size, had a successful early

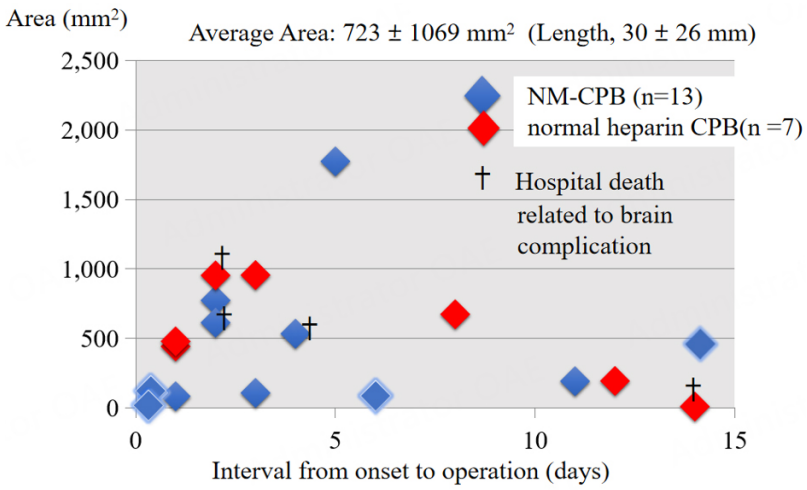

Figure 8. Relationships between the size of intracranial hemorrhage and the interval from onset to operation (total *n* = 20, NM-CPB *n* = 13, normal CPB *n* = 7). There were four hospital deaths related to brain complications, of which two underwent NM-CPB, while the other two underwent CPB using normal heparin. An early surgery within seven days from the onset was performed in 12 patients of NM-CPB and three patients of normal heparin CPB. The average size of intracranial hemorrhage was 723 ± 1069 mm. NM-CPB, cardiopulmonary bypass using nafamostat mesylate; normal CPB, of cardiopulmonary bypass using heparin.

cardiac surgery without any exacerbation of stroke. As for ICH [Figure 8], there were four hospital death related to brain complications in two with NM-CPB and two with normal heparin CPB. The hospital mortality in patients with NM-CPB, and patients with normal heparin CPB were 15.3% and 28.5%, respectively. Among patients who underwent surgeries within seven days from the onset of the AIE, mortality in patients with NM-CPB and with normal heparin CPB were 16.6% (2/12), and 33.3% (1/3), respectively. This might indicate that an early surgery for ICH could be performed more safely by NM-CPB.

CONCLUSIONS

The current guidelines still recommend delaying cardiac surgery for patients with AIE with ICH for four weeks. Understanding the spectrum of ICH with AIE based on the mechanism of hemorrhage, early cardiac surgery for the AIE with mycotic aneurysm may be safely done by preceding surgical or endovascular repair for cerebral aneurysm. NM is a useful option as an anticoagulant during the open cardiac surgery with ICH. The timing of surgery should be decided on a case-by-case basis with multidisciplinary specialties, consisting of cardiac and neurologic teams.

DECLARATIONS

Authors' contributions

Wrote the manuscript: Yamazato T
Carried out the trial and analyzed data: Okada K, Munakata H
Supervised the project: Okita Y

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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REFERENCES

1. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633-8. DOI PubMed
2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57-185. DOI PubMed
3. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J* 2015;36:3075-128. DOI PubMed
4. Pettersson GB, Coselli JS, Pettersson GB, et al. 2016 The American Association for Thoracic Surgery (AATS) consensus guidelines. *J Thorac Cardiovasc Surg* 2017;153:1241-1258.e29. DOI PubMed
5. Nakatani S, Ohara T, Ashihara K, et al. JCS 2017 guideline on prevention and treatment of infective endocarditis. *Circ J* 2019;83:1767-809. DOI PubMed
6. Eishi K, Kawazoe K, Kuriyama Y, Kitoh Y, Kawashima Y, Omae T. Surgical management of infective endocarditis associated with cerebral complications. *J Thorac Cardiovasc Surg* 1995;110:1745-55. DOI PubMed
7. Gillinov AM, Shah RV, Curtis WE, et al. Valve replacement in patients with endocarditis and acute neurologic deficit. *Ann Thorac Surg* 1996;61:1125-30. DOI PubMed
8. Wilbring M, Irmscher L, Alexiou K, Matschke K, Tugtekin SM. The impact of preoperative neurological events in patients suffering from native infective valve endocarditis. *Interact Cardiovasc Thorac Surg* 2014;18:740-7. DOI PubMed
9. Ruttmann E, Willeit J, Ulmer H, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. *Stroke* 2006;37:2094-9. DOI PubMed
10. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis. *Circulation* 2013;127:2272-84. DOI PubMed
11. Okita Y, Minakata K, Yasuno S, et al. Optimal timing of surgery for active infective endocarditis with cerebral complications: a Japanese multicentre study. *Eur J Cardiothorac Surg* 2016;50:374-82. DOI PubMed
12. Shang E, Forrest GN, Chizmar T, et al. Mitral valve infective endocarditis: benefit of early operation and aggressive use of repair. *Ann Thorac Surg* 2009;87:1728-33. DOI PubMed
13. Yoshioka D, Toda K, Sakaguchi T, et al. Valve surgery in active endocarditis patients complicated by intracranial haemorrhage. *Eur J Cardiothorac Surg* 2014;45:1082-8. DOI PubMed
14. Kume Y, Fujita T, Fukushima S, et al. Intracranial mycotic aneurysm is associated with cerebral bleeding post-valve surgery for infective endocarditis. *Interact Cardiovasc Thorac Surg* 2018;27:635-41. DOI PubMed
15. Tam DY, Yanagawa B, Verma S, et al. Early vs late surgery for patients with endocarditis and neurological injury. *Can J Cardiol* 2018;34:1185-99. DOI PubMed
16. Hart RG, Kagan-hallet K, Joerns SE. Mechanisms of intracranial hemorrhage in infective endocarditis. *Stroke* 1987;18:1048-56. DOI PubMed
17. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage. *Stroke* 2008;39:2304-9. DOI PubMed
18. Parry-Jones AR, Abid KA, Di Napoli M, et al. Accuracy and clinical usefulness of intracerebral hemorrhage grading scores: a direct comparison in a UK population. *Stroke* 2013;44:1840-5. DOI PubMed
19. Lakhan SE, Kirchgessner A, Tepper D, Leonard A. Matrix metalloproteinases and blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 2013;4:32. DOI PubMed PMC
20. 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. PubMed
21. Maruyama R, Yamada A, Sugiyama T, et al. Mitral valve repair for endocarditis can be performed 3 days after repair of a bleeding mycotic brain aneurysm. *J Thorac Cardiovasc Surg* 2016;151:e59-61. DOI PubMed

22. Salaun E, Touil A, Hubert S, et al. Intracranial haemorrhage in infective endocarditis. *Arch Cardiovasc Dis* 2018;111:712-21. DOI PubMed
23. Tanaka K, Morimoto T, Yada I, Kusagawa M, Deguchi K. Physiologic role of enhanced fibrinolytic activity during cardiopulmonary bypass in open heart surgery. *ASAIO Trans* 1987;33:505-9. PubMed
24. Segesser LK, Weiss BM, Pasic M, Garcia E, Turina MI. Risk and benefit of low systemic heparinization during open heart operations. *Ann Thorac Surg* 1994;58:391-8. DOI PubMed
25. Øvrum E, Brosstad F, Aˆm Holen E, Tangen G, Abdelnoor M. Effects on coagulation and fibrinolysis with reduced versus full systemic heparinization and heparin-coated cardiopulmonary bypass. *Circulation* 1995;92:2579-84. DOI PubMed
26. Sakamoto T, Kano H, Miyahara S, et al. Efficacy of nafamostat mesilate as anticoagulation during cardiopulmonary bypass for early surgery in patients with active infective endocarditis complicated by stroke. *J Heart Valve Dis* 2014;23:744-51. PubMed
27. Ota T, Okada K, Kano H, Okita Y. Cardiopulmonary bypass using nafamostat mesilate for patients with infective endocarditis and recent intracranial hemorrhage. *Interact Cardiovasc Thorac Surg* 2007;6:270-3. DOI PubMed
28. Yamazato T, Oyama N, Fujii T, et al. Aggressive early surgical strategy in patients with intracranial hemorrhage: a new cardiopulmonary bypass option. *Gen Thorac Cardiovasc Surg* 2022;70:602-10. DOI PubMed