Reviews

Preoperative Cerebrovascular Evaluation in Patients With Infective Endocarditis

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ABSTRACT

Approximately 12% to 40% of infective endocarditis patients experience cerebrovascular complications. One of the major clinical challenges in cerebrovascular medicine is management of infective endocarditis patients with cerebrovascular complications who require valve operations. Cerebrovascular specialists are often summoned to address appropriate preoperative brain imaging, timing of surgery, and estimation of the risk of perioperative cerebral embolization and hemorrhage. This article addresses these issues based on the available evidence.

Introduction

Cerebrovascular complications (CVC) are one of many sequelae of infective endocarditis (IE) and may manifest as both ischemic and hemorrhagic forms of stroke. The estimated risk of CVC in IE is 12% to 40%, with cerebral septic embolism as the predominant pathophysiological mechanism.[1–3] Silent cerebral embolism can occur in up to 30% of these patients.[4] The rate of embolism does not seem to be different in native vs prosthetic IE, but embolism is more frequent in left-heart infections and with mitral more than the aortic valve.[5,6] *Staphylococcus aureus* is the most common organism associated with distal embolization in IE.[5] Most emboli occur within the first 2 to 4 weeks of antimicrobial therapy, but they can occur before diagnosis, during therapy, or after completion of therapy.[7] Symptomatic complications include embolic cerebral infarction (CI) with or without hemorrhagic transformation, and intracranial hemorrhage (ICH). Stroke is an independent predictor of early mortality in IE patients.[5]

One of the major clinical challenges in cerebrovascular medicine is management of IE patients with CVC who require valve operations. Neurologists are often summoned to evaluate IE patients with CVC prior to surgery. The main questions are: (1) appropriate preoperative imaging modality, (2) timing of surgery, and (3) estimation of risk of perioperative cerebral embolization and hemorrhage. This review addresses these issues based on the available evidence.

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Preoperative Cerebral Imaging

To assess the need for preoperative cerebral imaging, one must first determine if the purpose is to detect mycotic aneurysms, visualize symptomatic lesions, or uncover silent CVC. The choice of imaging must therefore be tailored to the diagnostic plan. Then, one must adjudicate how the results of the study modify subsequent management.

A noncontrasted computed tomography (CT) of the head has high accuracy for diagnosing ICH, which occurs in approximately 5% of patients with IE.[8,9] The mechanisms of ICH in IE include ruptured mycotic aneurysms, septic erosion of the arterial wall, and hemorrhagic transformation of CI.[9] Based on postmortem studies, hemorrhagic transformation of the CI due to septic emboli is the most frequent mechanism.[10] Naturally, large hemorrhages will express some degree of neurological deficit, and hence the purpose of brain imaging in this scenario is to identify and visualize the symptomatic lesion. The presence of an ICH undoubtedly influences preoperative decision-making.

Magnetic resonance imaging (MRI) of the brain has high accuracy for detecting acute CI or silent infarcts, and is at least as accurate as CT in identification of ICH.[8] Cerebral microbleeds (CMB) are also frequent in patients with IE and can be delineated via MRI.[11] The degree to which MRI results affect surgical decision-making depends upon what is actually visualized. Occult, asymptomatic CMB and ischemic lesions are frequent in IE, but whether or not these lesions play a significant role in prognosis or predict perioperative complications is unclear.[12] In a study of 40 IE patients, MRI evidence of acute brain embolization was demonstrated in 32 (80%), of which 13 had suffered clinical stroke.[13] Among 16 patients with MRI findings

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who underwent valve surgery at a median of 4 days, none suffered a new CI or symptomatic hemorrhagic transformation of a previous CI after surgery.[13] In another study of 141 IE patients, the investigators reported that surgical treatment was modified for 18 patients (13%) solely on the basis of the MRI results.[14] Surgical-plan modifications included changing the surgery date (6 postponements and 6 advancements), modifying the type of valvular prosthesis (1 patient), changing reasons for surgery (1 patient), canceling surgery (2 patients), and deciding to operate (2 patients).[14] The same group of investigators conducted a more recent study with the same objective. In this study, of the 58 patients with IE who underwent MRI, the surgical decision was modified in 7 (12%).[15] Finally, in a more recent study, MRI led to surgical-plan modifications for 6 out of 30 (20%) patients. In 3 patients, MRI results led physicians to perform valvular replacement due to the embolic nature of the vegetations revealed by MRI (multiple brain ischemic lesions and large cardiac vegetation); in the other 3, MRI led to postponement of surgery due to the discovery of hemorrhagic lesions.[16] No patients experienced postoperative neurological worsening. The results of MRI merely indicate that the incidence of CVC associated with IE is high, but these findings are of undetermined significance.[4]

With perioperative anticoagulation and potential hemodynamic fluctuations, rupture of occult mycotic aneurysms is sometimes a concern. Vascular anatomy of the brain can be visualized by various methods: digital subtraction angiography (DSA), CT angiography (CTA), or magnetic resonance angiography (MRA). Digital subtraction angiography in this case is the standard method for diagnosis.[17] For detection of mycotic aneurysms, CTA has a sensitivity of 90% and a specificity of 86% when compared with DSA.[18] In comparison with CTA, MRA has a specificity of 95% and a sensitivity of 87%.[18] For aneurysms measuring $\leq$3 mm, sensitivities of MRA and CTA fall to 38% and 61%, respectively.[18] With the currently available modalities and their respective levels of accuracy, one must gauge the necessity of aneurysm screening prior to surgery.

Cerebral mycotic aneurysms are uncommon, occurring in 2% to 3% of IE patients.[19] A recent retrospective study showed that among 168 IE patients who underwent angiography, mycotic aneurysms were detected in 15 (8.9%); 14 presented with ICH.[20] Angiography, therefore, may be more appropriate in IE patients with ICH.[21,22] Otherwise, there is no strong evidence that screening brain angiography is indicated in the preoperative assessment of IE patients. Moreover, aneurysms could shrink or disappear with antibiotic therapy or be masked by ICH after rupture. Specific guidelines for the management of mycotic aneurysms are lacking. Aside from antibiotic therapy, surgical or endovascular treatment may confer additional management options. They do, however, depend on the character and location of the aneurysm, as well as the clinical status of the patient.[23] A review of Nationwide Inpatient Survey data files in the United States from 2002 to 2009 revealed that, of the 1915 patients admitted with the diagnosis of mycotic aneurysms, 83 (4.3%) underwent endovascular embolization and 59 (3.1%) underwent surgical obliteration.[24] The low rate of interventional treatment further questions the utility of screening angiography. The American Heart Association (AHA) suggests that, in the absence of neurological signs or symptoms, routine screening imaging for mycotic aneurysms is not warranted.[25]

Based on the evidence available, it seems that the only radiological findings that would modify the timing of surgical treatment are CMB on MRI, and ICH on CT or MRI. There is currently little evidence that the presence of silent infarcts, mycotic aneurysms, or clinical stroke significantly alters surgical decision-making.

Timing of Surgery

Evidence for the optimal time interval between CVC and valve surgery is conflicting because of a lack of controlled studies. There are compelling nonneurological factors that dictate the urgency of operation: the presence and severity of heart failure, refractory sepsis, and vegetation size.[26] In patients with CVC, the decision depends on the type of CVC and the necessity and urgency of valve replacement. A prospective cohort study of 2781 adults with definite IE who were admitted to 58 hospitals in 25 countries showed that up to 50% of patients undergo surgery during the acute phase.[27] A systemic review of literature reported that timing of surgery ranged from 4 days to 4 weeks from diagnosis of CVC.[28] For native-valve IE, early surgery is associated with an in-hospital mortality benefit compared with medical therapy alone.[29] The prognosis for patients operated within 72 hours of cerebral embolism who have no evidence of hemorrhage has been shown to be significantly more favorable than for those treated medically.[30] Early surgery seems to improve outcome by effectively decreasing systemic embolism.[31] Ideally, surgery should be performed within 72 hours of cerebral embolism, when the risk of hemorrhagic transformation is relatively low.[30] The 2009 European Society of Cardiology (ESC) guidelines on the prevention, diagnosis, and treatment of IE recommend early surgery for prevention of embolic events.[32] For silent cerebral embolism and clinical CI without coma, surgery should not be delayed, but, in case of ICH, postponed for $\geq$1 month.[32]

Perioperative Stroke Risk

Indeed, the strategy for surgical intervention to avoid systemic embolization and the risk of perioperative stroke in IE is specific to the individual patient. The 2 main mechanisms for CVC during surgery are further brain embolization and ICH associated with perioperative anticoagulation. The risk of perioperative cerebral embolization increases with vegetation size (especially >10 mm), but prediction and quantification of this risk for the individual patient is very difficult.[6,33] Staphylococcal and candida IE appear to carry a high rate of embolization independent of vegetation size.[7] Patients with silent CI or transient ischemic attack (TIA) have a relatively good prognosis, whereas those with clinical stroke have significantly higher mortality, particularly those with mechanical prosthetic-valve IE or impaired consciousness.[5] This was reported in a study of 109 IE patients with CVC who underwent valve surgery at a median time of 9 days.[5] Overall, postoperative neurologic

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exacerbation was infrequent in patients with a CVC and was never observed after a silent cerebral embolism or a TIA.[5] A more recent study reported no difference in postoperative hemiparesis rates between patients with silent embolism (5%) vs symptomatic embolism (3%; $P = 0.69$).[6]

Infective endocarditis patients who suffer ICH invariably have poor outcomes. The risk of ICH with anticoagulation is a general concern in IE and not limited to the perioperative course. Most experts advise against the use of anticoagulation because of increased risk of early hemorrhagic transformation and ICH, particularly in IE caused by *S aureus*.[34] There are currently no randomized studies of anticoagulant therapy in patients with IE. A prospective cohort study reported no increased risk of ICH in *S aureus* IE patients receiving anticoagulation.[35] In fact, anticoagulation was associated with a reduced risk of cerebral embolic events before initiation of antibiotics.[35] Data and opinion with regard to anticoagulation in IE are conflicting. Fortunately, several reports have noted that patients with preoperative stroke have a relatively low risk of postoperative neurological deterioration caused by the hemorrhagic transformation of a preexisting CI.[30,36,37] Nonetheless, with presence of preexisting ICH and/or of silent CMB, it is prudent to delay surgery and anticoagulation for as long as possible.

Conclusion

Seventy percent of IE survivors who experience a cardioembolic stroke achieve full neurological recovery after cardiac surgery.[36] Although long-term survival is significantly influenced by preoperative CI, cerebral embolism does not appear to be a risk factor for early mortality.[6] Based on the evidence presented, the overall risk of perioperative or postoperative CVC seems to be low. In conclusion, performing an MRI can be very helpful in diagnosing CMB or foci of CI and hence in influencing surgical management, but screening angiography does not seem to have an equal impact. To minimize perioperative CVC, factors that need to be considered are: (1) indication and urgency of surgery, (2) duration of surgery (which translates into duration of perioperative anticoagulation), (3) imaging evidence of CMB or early hemorrhagic transformation, (4) patient's level of consciousness, and (5) infarct size.

References

1. Hart RG, Foster JW, Luther MF, et al. Stroke in infective endocarditis. *Stroke.* 1990;21:695–700.
2. Salgado AV, Furlan AJ, Keys TF, et al. Neurologic complications of endocarditis: a 12-year experience. *Neurology.* 1989;39(2 part 1):173–178.
3. Jones HR Jr, Siekert RG. Neurologic manifestations of infective endocarditis: review of clinical and therapeutic challenges. *Brain.* 1989;112(part 5):1295–1315.
4. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. *Clin Infect Dis.* 2008;47:23–30.
5. Thuny F, Avierinos JF, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. *Eur Heart J.* 2007;28:1155–1161.
6. Misfeld M, Girrbach F, Etz CD, et al. Surgery for infective endocarditis complicated by cerebral embolism: a consecutive series of 375 patients. *J Thorac Cardiovasc Surg.* 2014;147:1837–1844.
7. Vilacosta I, Graupner C, San Román JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. *J Am Coll Cardiol.* 2002;39:1489–1495.
8. Latchaw RE, Alberts MJ, Lev MH, et al; American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. *Stroke.* 2009;40:3646–3678.
9. Hart RG, Kagan-Hallet K, Joerns SE. Mechanisms of intracranial hemorrhage in infective endocarditis. *Stroke.* 1987;18:1048–1056.
10. Masuda J, Yutani C, Waki R, et al. Histopathological analysis of the mechanisms of intracranial hemorrhage complicating infective endocarditis. *Stroke.* 1992;23:843—850.
11. Klein I, Iung B, Labreuche J, et al. Cerebral microbleeds are frequent in infective endocarditis: a case–control study. *Stroke.* 2009;40:3461–3465.
12. Hess A, Klein I, Iung B, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. *AJNR Am J Neuroradiol.* 2013;34:1579–1584.
13. Cooper HA, Thompson EC, Laureno R, et al. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. *Circulation.* 2009;120:585–591.
14. Duval X, Iung B, Klein I, et al; IMAGE (Resonance Magnetic Imaging at the Acute Phase of Endocarditis) Study Group. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. *Ann Intern Med.* 2010;152:497–504.
15. Iung B, Klein I, Mourvillier B, et al. Respective effects of early cerebral and abdominal magnetic resonance imaging on clinical decisions in infective endocarditis. *Eur Heart J Cardiovasc Imaging.* 2012;13:703–710.
16. Goulenok T, Klein I, Mazighi M, et al; IMAGE Study Group. Infective endocarditis with symptomatic cerebral complications: contribution of cerebral magnetic resonance imaging. *Cerebrovasc Dis.* 2013;35:327–336.
17. Chappell ET, Moure FC, Good MC. Comparison of computed tomographic angiography with digital subtraction angiography in the diagnosis of cerebral aneurysms: a meta-analysis. *Neurosurgery.* 2003;52:624–631.
18. White PM, Wardlaw JM, Easton V. Can noninvasive imaging accurately depict intracranial aneurysms? A systematic review. *Radiology.* 2000;217:361–370.
19. Lerner PI. Neurologic complications of infective endocarditis. *Med Clin North Am.* 1985;65:385–398.
20. Hui FK, Bain M, Obuchowski NA, et al. Mycotic aneurysm detection rates with cerebral angiography in patients with infective endocarditis. *J Neurointerv Surg.* doi:10.1136/neurintsurg-2014-011124.
21. Salgado AV, Furlan AJ, Keys TF. Mycotic aneurysm, subarachnoid hemorrhage, and indications for cerebral angiography in infective endocarditis. *Stroke.* 1987;18:1057–1060.
22. Gillinov AM, Shah RV, Curtis WE, et al. Valve replacement in patients with endocarditis and acute neurologic deficit. *Ann Thorac Surg.* 1996;61:1125–1129.
23. Ducruet AF, Hickman ZL, Zacharia BE, et al. Intracranial infectious aneurysms: a comprehensive review. *Neurosurg Rev.* 2010;33:37–46.
24. Afzal M, Hassan M, Chaudhry S, et al. Outcomes of patients undergoing endovascular treatment for mycotic intracranial aneurysms. *Neurology.* 2012. doi:10.1212/WNL.78.1_MeetingAbstracts.P05.252 [abstract].
25. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and

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Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America [published corrections appear in *Circulation.* 2005;112:2373, *Circulation.* 2007;115:e408, *Circulation.* 2007;116:e547, and *Circulation.* 2008;118:e497]. *Circulation.* 2005;111:e394–e434.
26. Tornos P, Iung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lessons from the Euro Heart Survey. *Heart.* 2005;91:571–575.
27. Murdoch DR, Corey GR, Hoen B, et al; International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med.* 2009;169:463–473.
28. Rossi M, Gallo A, De Silva RJ, et al. What is the optimal timing for surgery in infective endocarditis with cerebrovascular complications? *Interact Cardiovasc Thorac Surg.* 2012;14:72–80.
29. Lalani T, Cabell CH, Benjamin DK, et al; International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. *Circulation.* 2010;121:1005–1013.
30. Piper C, Wiemer M, Schulte HD, et al. Stroke is not a contraindication for urgent valve replacement in acute infective endocarditis. *J Heart Valve Dis.* 2001;10:703–711.
31. Kim DH, Kang DH, Lee MZ, et al. Impact of early surgery on embolic events in patients with infective endocarditis. *Circulation.* 2010;122(11 suppl):S17–S22.
32. Habib G, Hoen B, Tornos P, et al; ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J.* 2009;30:2369–2413.
33. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation.* 2005;112:69–75.
34. Tornos P, Almirante B, Mirabet S, et al. Infective endocarditis due to *Staphylococcus aureus*: deleterious effect of anticoagulant therapy. *Arch Intern Med.* 1999;159:473–475.
35. Rasmussen RV, Snygg-Martin U, Olaison L, et al. Major cerebral events in *Staphylococcus aureus* infective endocarditis: is anticoagulant therapy safe? *Cardiology.* 2009;114:284–291.
36. Ruttmann E, Willeit J, Ulmer H, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. *Stroke.* 2006;37:2094–2099.
37. Yoshioka D, Sakaguchi T, Yamauchi T, et al. Impact of early surgical treatment on postoperative neurologic outcome for active infective endocarditis complicated by cerebral infarction. *Ann Thorac Surg.* 2012;94:489–496.

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