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INVITED REVIEW ARTICLE

Cerebral dysfunction after coronary artery bypass surgery

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Abstract Cerebral dysfunction after cardiac surgery remains a devastating complication and is growing in importance with our aging populations. Neurological complications following cardiac surgery can be classified broadly as stroke, encephalopathy (including delirium), or postoperative cognitive dysfunction (POCD). These etiologies are caused primary by cerebral emboli, hypoperfusion, or inflammation that has largely been attributed to the use of cardiopulmonary bypass. Preventative operative strategies, such as off-pump coronary artery bypass grafting (CABG), can potentially reduce the incidence of postoperative neurological complications by avoiding manipulation of the ascending aorta. Although off-pump CABG is associated with reduced risk of stroke, there are no convincing differences in POCD between off-pump and on-pump CABG. Recently, the focus of postoperative neurological research has shifted from managing cardiopulmonary bypass to patient-related factors. Identifying changes in brains of aged individuals undergoing cardiac surgery may improve strategies for preventing cerebral dysfunction. Advanced age is associated with more undiagnosed cerebrovascular disease and is a major risk factor for stroke and POCD following cardiac surgery. Preoperative cerebrovascular evaluation and adaptation of surgical strategies will provide preventative approaches for cerebral dysfunction after CABG. This review focuses on recent findings of the relationship between perioperative stress and underlying fragility of the brain in cardiac surgical patients.

Keywords Stroke · Cognitive dysfunction · Coronary artery bypass grafting · Cardiopulmonary bypass · Aged brain

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Introduction

Cerebral dysfunction after cardiac surgery has been consistently associated with poor outcomes and is growing in importance in the aging populations. The incidence of postoperative cerebral dysfunction increases with age and is associated with greater mortality and morbidity and longer hospital stays [1–3]. Cerebral dysfunctions following cardiac surgery appear as stroke, encephalopathy (including delirium), or postoperative cognitive dysfunction (POCD, postoperative deterioration in memory, attention, and speed of information processing, corroborated by neuropsychological testing). The mechanisms of cardiac surgery-related neurological complication are believed to arise primarily from cerebral emboli, hypoperfusion, or inflammation related to the use of cardiopulmonary bypass (CPB) [4]. Coronary artery bypass grafting (CABG) performed without CPB ("off-pump") could reduce the incidence of postoperative neurological complications by avoiding manipulation of the ascending aorta. Off-pump CABG has been associated with reduced risk of stroke, whereas there were no confirmed differences in POCD between off-pump and on-pump CABG [5, 6]. In addition, the long-term cognitive dysfunction at 6 years of follow-up after CABG was attributed to the progression of underlying cerebrovascular disease or changes related to age rather than to a history of cardiac surgery [7]. Recently, the focus of POCD research is shifting to the

patient and away from factors related to surgery, such as CPB management [8, 9].

There is growing interest in the association between perioperative stress and the underlying fragility of the brain in cardiac surgical patients [10]. By better understanding of pathophysiological changes of the brain that may be induced by cardiac surgery, perioperative strategies may protect against cerebral dysfunction and attendant ischemic cascade in the brain after cardiac surgery. This review describes recent findings on the association of stroke and cognitive dysfunction with CABG in aged brains.

Aged brain

Aging is associated with a general decline in brain volume and function [11–13]. Studies in aged rats have revealed a marked increase in expression of proinflammatory cytokines [14]. Inflammation is known to predispose toward more deleterious responses to injury [15, 16]. The aged brain can exhibit enhanced central response to operative stress leading to elevated cytokines levels and to induced cognitive decline with age [17, 18]. Recent studies have shown that activated microglia have a beneficial role of phagocyte cells in inflammation in the nervous system [19]. In contrast, oxidative stress may cause degeneration of microglia and other degenerative diseases in the aging brain [14]. Hypoperfusion with chronic hypoxia opens the blood–brain barrier, which contributes to the cognitive decline seen with lacunar infarctions and white matter injury in subcortical ischemic vascular disease [20]. In addition, neuroinflammation may aggravate existing cerebral ischemia and disturb the blood–brain barrier [21]. Several studies have demonstrated that undiagnosed ischemic cerebrovascular disease is common and is associated with impaired cognition in elderly patients [22, 23].

Inhalational anesthetics appear to be neurotoxic to the aged brain [24]. Studies in model animals suggest that general anesthetics induce neural degeneration and apoptosis, which then lead to memory decline such as in Alzheimer's disease [25, 26]. However, there is no proven association between exposure to general anesthetics and risk of Alzheimer's disease in retrospective and systematic review studies [27, 28].

Stroke

Stroke following cardiac surgery is a devastating and disabling complication that occurs in 1.4 % to 3.8 % of patients who undergo CABG and 8.7 % of patients after aortic repair [29]. Advanced age, particularly older than 70 years, is a primary factor associated with stroke, encephalopathy (including delirium), and cognitive dysfunction after CABG [1]. Age alone does not appear to predict the risk of postoperative stroke; rather, it is a marker of reduced brain reserve and underlying disease. A recent study found that the factors predicting risk of stroke within 30 days after CABG were age, prior stroke, diabetes, hypertension, peripheral vascular disease, and renal failure [30].

Tarakji and colleagues [31] studied timing of strokes after CABG and found that more than half of strokes occurred postoperatively, rather than intraoperatively. A multicenter study in Japan also demonstrated that more than half of strokes occurred postoperatively [32]. Intraoperative stroke is caused primarily by cerebral emboli, thrombosis, or hypoperfusion, whereas postoperative strokes may be more associated with hypercoagulation and/or atrial fibrillation [32, 33]. Risk factors for intraoperative and postoperative stroke with CABG are older age, preoperative stroke, preoperative atrial fibrillation, on-pump CABG, and hypothermic circulatory arrest. Although hypothermic circulatory arrest reduces the risk of stroke when a heavily diseased ascending aorta is replaced, octogenarians still have higher risk [34]. Currently, patients with severe atherosclerosis of the ascending aorta are managed with off-pump CABG or non-touch methods.

Embolism

Atherosclerosis of the ascending aorta is an important risk factor for cerebral embolism and stroke after CABG [35, 36]. Previous studies have revealed that clamp- or cannulation-induced new lesions of the ascending aorta could be attributed to intraoperative stroke [37, 38]. Non-touch methods applied to the diseased ascending aorta and off-pump bypass without side clamping help to eliminate one cause of cerebral dysfunction after CABG [5, 39].

A recent meta-analysis found that the incidence of postoperative stroke was significantly 30 % lower for off-pump CABG (1.4 %) compared to stroke after on-pump CABG (2.1 %) [40]. In addition, off-pump CABG carried a significantly lower risk of early postoperative stroke than on-pump CABG (0.1 % versus 1.1 %), whereas the incidence of postoperative delayed strokes did not differ significantly between the two groups [32]. A reported multicenter trial also demonstrated that surgery performed off-pump was associated with a significantly lower postoperative rate of stroke compared to on-pump CABG, including for older and higher-risk patients [41]. However, in this same study, intraoperative conversion from off-pump to on-pump increased the incidence of postoperative stroke. These data suggest that intraoperative surgical strategies are important in neurological outcomes after CABG in patients at high risk for stroke.

Hypoperfusion

Embolism and hypoperfusion often coexist during and after cardiac surgery. Hypoperfusion impairs the washout and clearance of microemboli that have entered the reduced cerebral blood flow subsequent to surgery [42]. In addition, hypoperfusion is a cause of bilateral watershed infarcts after cardiac surgery [43]. Maintaining higher perfusion pressure during CPB protects against stroke and attenuates the ischemic cascades in the brain [44].

Carotid stenosis is a significant risk factor for intraoperative stroke [45]. Managing patients during CABG who have existing carotid stenosis remains controversial [46, 47]. A review of carotid stenting followed by staged CABG found that the combined incidence of stroke and death within 30 days remained elevated at different levels: minor stroke 2.9 %; major stroke 3.2 %; mortality 7.6 %; and combined death and stroke 12.3 % [48]. However, prophylactic interventions, such as carotid angioplasty with stenting or carotid endarterectomy, may be appropriate in CABG patients with a prior history of stroke and transient ischemic attack (TIA).

POCD

Postoperative cognitive dysfunction is the most common complication of cardiac surgery. It occurs in 30 % to 80 % of patients at discharge and 20 % to 40 % after 6 months to 1 year [49, 50]. Several recent studies have found that POCD is transient, with no association with long-term cognitive decline [8, 51]. Evered and colleagues [51] reported that patients who underwent CABG had a significantly higher incidence of POCD (43 %) than patients who had a total hip joint replacement under general anesthetic (17 %) at 1 week. However, there was no statistically significant difference in POCD between the two types after 3 months.

Preoperative risks for POCD include age, genetic predisposition, and level of education [52]. The mechanisms for POCD are multifactorial and a complex of cerebral microemboli, hypoperfusion, or inflammation associated with CPB. POCD also has associations with surgical maneuvers such as manipulation of the atherosclerotic ascending aorta, prolonged CPB time, and cerebral hyperthermia [36, 53, 54]. A more recent study that applied multivariate analysis found that aortic atherosclerosis was associated with POCD at 1 week and was selected as a strong predictor for early POCD [55].

Postoperative cognitive dysfunction occurs frequently in the elderly after cardiac surgery. However, predictors of cognitive recovery from cognitive decline after cardiac surgery have not been examined thoroughly. Fontes and colleagues [56] reported that 45 % of patients who experienced cognitive decline 6 weeks after CABG and/or valve surgery returned to baseline cognitive function by 1 year. In their study, ability to perform more activities of daily living at 6 weeks was a significant predictor of cognitive recovery. In addition, aerobic exercise helps to prevent or even reverse cognitive decline and brain decay in the elderly [57]. These findings suggest that stimulation of the brain after cardiac surgery reduces the impact of cognitive decline and improves atherosclerosis, such as by controlling modifiable risk factors of hypertension, diabetes mellitus, and hyperlipidemia.

Microemboli

Microemboli are found in autopsies of patients who died after cardiac surgery or aortography [58]. The particles probably consist of lipid, atheromatous debris, and platelet–fibrin thrombi. These emboli generally pass through the brain in a few hours to a few days, while some remain impacted for weeks or longer [59]. Microvasculature occluded by these emboli may be a major cause of encephalopathy or POCD. Universal use of a cell saver does reduce the incidence of POCD after cardiac surgery [60]. Cerebral emboli can be detected as a high-intensity transient signal (HITS) by transcranial Doppler. However, no association has been found between the counts by HITS during CPB and POCD at 1 week and 3 months [61, 62]. A patient's tolerance of cerebral microemboli may depend on the degree of underlying cerebrovascular reserve and disease.

Diffusion-weighted magnetic resonance (MR) images (DWI-MRI) are useful to detect acute cerebral ischemic regions related to microemboli [63]. Previous studies have shown that postoperative DW-MRI finds new ischemic lesions in about 50 % of patients undergoing cardiac surgery, and that there is a correlation between new lesions and cognitive decline [64, 65]. In contrast, no such correlation was found with cardiac surgery in another study [66]. A review also compiled evidence that the association of silent new cerebral injury and cognitive decline was not convincing [67]. However, patients with existing cerebral injury may be more vulnerable to adverse effects during CABG. A previous study demonstrated that abnormalities before surgery were found by DWI-MRI in 4.4 % of elective cardiac surgery patients [68]. Preoperative DWI abnormalities are associated with preoperative cognitive impairment [69]. Neuropsychological assessment during the preoperative period is important to identify patients at risk for cerebral ischemia.

Inflammation

Systemic inflammation worsens cognitive status and accelerates progression of disease [70]. Nonsteroidal anti-inflammatory drugs are associated with protective effects on volume loss in the brain related to age and brain differences, including decreased number of activated microglia [71]. Antiinflammatory therapy with parecoxib was shown in a recent study to mitigate impaired spatial memory induced in aged rats by sevoflurane anesthesia [72]. Hudetz and colleagues [73] have reported that elevated concentration of interleukin-6 and C-reactive protein after surgery was associated with short- and medium-term cognitive dysfunction after CABG. However, these studies do not demonstrate that antiinflammatory therapy is ready for immediate clinical translation [74]. Further study is needed on the relationships between neuroinflammation, oxidative stress, and POCD in elderly patients undergoing cardiac surgery.

Neuroprotection and perioperative strategies

Although pharmacological neuroprotection has been applied in cardiac surgery, no agents have proven sufficiently effective in clinical application [75]. Perioperative evaluation can identify patients at higher risk for stroke and POCD [76]. Perioperative strategies for preventing cerebral ischemia during cardiac surgery are compiled in Table 1.

Most patients with multiple small infarctions are asymptomatic without a history of cerebrovascular accidents and have a history of association with preoperative cognitive impairment [77]. Therefore, several investigators recommend routine preoperative cognitive evaluation to detect underlying cerebral ischemia in elderly patients [78–80]. Cervical ultrasonography is common before cardiac surgery [81]. Currently, cerebral magnetic resonance angiography (MRA) gives the most definitive information about vascular anatomy, including the state of collateral circulation through the circle of Willis.

Intraoperative strategies and neurological monitor

Neurological monitoring is important to detect cerebral ischemia during CPB or off-pump CABG. Murkin and colleagues [82] reported that prolonged cerebral hypoperfusion (detected by regional cerebral oxygen saturation) was associated with increased morbidity but had no relationship with cerebral injury. Therefore, controversy continues to surround the reliability of each technique or combination to predict cerebral ischemia during cardiac surgery [83]. Operative strategies that prevent emboli and maintain higher perfusion pressure during CPB improve neurological outcomes for patients with atherosclerosis of the aorta [84]. In addition, CPB management with slow rewarming to prevent hyperthermia, avoiding hyperglycemia, and using alpha-stat pH management protects against cerebral ischemia [54, 85, 86].

Postoperative management

Patients should be monitored closely after surgery for early signs of neurological dysfunction. The treatment for cerebral infarction caused by emboli is immediate pharmacological therapy by a free radical scavenger. The scavenger

Table 1 Neuroprotective strategies used in coronary artery bypass surgery

Timing	Issue	Intervention
Before surgery	Establish risk factors	Neuropsychological testing to identify preoperative cognitive impairment [77, 78]
		Carotid ultrasonography to identify carotid artery stenosis [81]
		MRI and MRA to identify preexisting cerebrovascular disease [22]
During surgery	Aortic atheroma	Epiaortic/TEE ultrasound to identify ascending and arch aortic disease [35, 37],
		Modify surgical procedures: avoid repeated aortic clamping, choose non-touch aortic techniques for high-grade atheroma, choose the site and risk of cannulation [39]
	Hypoperfusion	Higher perfusion pressure during cardiopulmonary bypass [44]
		Alpha-stat pH management [86]
	Brain hyperthermia	Avoid rapid/excessive rewarming [54]
	Hyperglycemia	Avoid or treat hyperglycemia [85]
	Microemboli	Minimize cardiotomy suction and dissection of mediastinal fat [60]
After surgery	Diagnosis and identification of ischemic brain lesions	Perform CT or diffusion-weighted MRI

MRI magnetic resonance imaging, *MRA* magnetic resonance angiography, *TEE* transesophageal echocardiography, *CT* computed tomography

edaravone has been found to useful for acute ischemic stroke [87].

Preoperative antiplatelet therapy decreases the incidence of postoperative major cardiovascular complications in high-risk patients [88]. Recently, Bouchard and colleagues [89] reported, from a 10-year case–control study, that administering statin and beta-blockers preoperatively decreased the risk of stroke after CABG. These data suggest that the combination of beta-blockers and statin has adrenergic antagonist effects, effects of antiinflammation, antioxidants, and inhibition of apoptosis. Dexmedetomidine given during and after surgery was found to significantly reduce postoperative mortality and major adverse cardiocerebral events in patients undergoing CABG and/or valvular surgery [90]. Further studies are needed to assess whether the perioperative use of dexmedetomidine actually decreases the incidence of cerebral dysfunction after cardiac surgery in the elderly.

Conclusions

Cerebral dysfunction after CABG is linked to multiple risk factors and complex interactions of emboli, hypoperfusion, inflammation, and underlying cerebrovascular disease. Operative strategies such as the non-touch method of ascending aorta and off-pump CABG improve outcomes in patients at higher risk for stroke by minimizing aortic manipulation and limiting some deleterious effects of CPB. The association between perioperative stress and POCD must be addressed aggressively as more elderly patients undergo cardiac surgery and suffer cognitive impairment. Preoperative cerebrovascular evaluation and adaptation of surgical strategies provide the best available approaches to limit or prevent cerebral dysfunction after CABG.

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References

1. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C. Adverse cerebral outcomes after coronary bypass surgery. Multicenter study of perioperative ischemia research group and the ischemia research and education foundation investigators. N Engl J Med. 1996;335:1857–63.
2. McKhann GM, Goldsborough MA, Borowicz LM Jr, Mellits ED, Brookmeyer R, Quaskey SA, Baumgartner WA, Cameron DE, Stuart RS, Gardner TJ. Predictors of stroke risk in coronary artery bypass patients. Ann Thorac Surg. 1997;63:516–21.
3. Stamou SC, Hill PC, Dangas G, Pfister AJ, Boyce SW, Dullum MK, Bafi AS, Corso PJ. Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. Stroke. 2001;32:1508–13.
4. Hogue CW Jr, Palin CA, Arrowsmith JE. Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices. Anesth Analg. 2006;103:21–37.
5. Misfeld M, Brereton RJ, Sweetman EA, Doig GS. Neurologic complications after off-pump coronary artery bypass grafting with and without aortic manipulation: meta-analysis of 11,398 cases from 8 studies. J Thorac Cardiovasc Surg. 2011;142:e11–7.
6. Marasco SF, Sharwood LN, Abramson MJ. No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularization: a meta-analysis. Eur J Cardiothorac Surg. 2008;33:961–70.
7. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM. Cognition 6 years after surgical or medical therapy for coronary artery disease. Ann Neurol. 2008;63:581–90.
8. Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, McKhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. N Engl J Med. 2012;366:250–7.
9. van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anesthesia. Anaesthesia. 2012;67:280–93.
10. Avidan MS, Benzinger TL. Surgery and the plastic brain. Anesthesiology. 2012;116:510–2.
11. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci. 2003;23:3295–301.
12. Peters R. Ageing and the brain. Postgrad Med. 2006;82:84–8.
13. Simen AA, Bordner KA, Martin MP, Moy LA, Barry LC. Cognitive dysfunction with aging and the role of inflammation. Ther Adv Chronic Dis. 2011;2:175–95.
14. Sparkman ML, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation. 2008;15:323–30.
15. Buchanan JB, Sparkman NL, Chen J, Johnson RW. Cognitive and neuroinflammatory consequences of mild repeated stress are exacerbated in aged mice. Psychoneuroendocrinology. 2008;33:755–65.
16. Terrando N, Rei Fidalgo A, Vizcaychipi M, Cibelli M, Ma D, Monaco C, Feldmann M, Maze M. The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction. Crit Care. 2010;14:R88.
17. Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G. Postoperative cognitive dysfunction after cardiac surgery. Chest. 2005;128:3664–70.
18. Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M. Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology. 2007;106:436–43.
19. del Zoppo GJ. Inflammation and the neurovascular unit in the setting of focal cerebral ischemia. Neuroscience. 2009;158:972–82.
20. Yang Y, Rosenberg GA. Blood–brain barrier breakdown in acute and chronic cerebrovascular disease. Stroke. 2011;42:3323–8.
21. Banks WA, Farr SA, Morley JE. Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation. 2002–2003; 10:319−327.
22. Goto T, Baba T, Honma K, Shibata Y, Arai Y, Uozumi H, Okuda T. Magnetic resonance imaging findings and postoperative neurologic dysfunction in elderly patients undergoing coronary artery bypass grafting. Ann Thorac Surg. 2001;72:137–42.
23. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol. 2007;6:611–9.
24. Tang JX, Eckenhoff MF, Echenhoff RG. Anesthetic modulation of neuroinflammation in Alzheimer's disease. Curr Opin Anaesthesiol. 2011;24:389–94.

25. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, Frosch MP, Crosby G, Tanzi RE. The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid beta-protein level in vivo. Ann Neurol. 2008;6:618–27.
26. Bittner EA, Yue Y, Xie Z. Brief review: anesthetic neurotoxicity in the elderly, cognitive dysfunction and Alzheimer's disease. Can J Anaesth. 2011;58:216–23.
27. Seitz DP, Shah PS, Herrmann N, Beyene J, Siddiqui N. Exposure to general anesthesia and risk of Alzheimer's disease: a systemic review and meta-analysis. BMC Geriatr. 2011;11:83.
28. Avidan MS, Searleman AC, Storandt M, Barnett K, Vannucci A, Saager L, Xiong C, Grant EA, Kaiser D, Morris JC, Evers AS. Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness. Anesthesiology. 2009;111:964–70.
29. Selim M. Perioperative stroke. N Engl J Med. 2007;356:706–13.
30. Mérie C, Køber L, Olsen PS, Andersson C, Jensen JS, Torp-Pedersen C. Risk of stroke after coronary artery bypass grafting: effect of age and comorbidities. Stroke. 2012;43:38–43.
31. Tarakji KG, Sabik JF 3rd, Bhudia SK, Batizy LH, Blackstone EH. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. JAMA. 2011; 305:381–90.
32. Nishiyama K, Horiguchi M, Shizuta S, Doi T, Ehara N, Tanuguchi R, Haruna Y, Nakagawa Y, Fukukawa Y, Fukushima M, Kita T, Kimura T. Temporal pattern of strokes after on-pump and off-pump coronary artery bypass graft surgery. Ann Thorac Surg. 2009;87:1839–44.
33. Likosky DS, Marrin CA, Caplan LR, Baribeau YR, Morton JR, Weintraub RM, Hartman GS, Hernandez F Jr, Braff SP, Charlesworth DC, Malenka DJ, Ross CS, O'Connor GT, Northern New England Cardiovascular Disease Study Group. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. Stroke. 2003;34:2830–4.
34. Liddicoat JR, Redmond JM, Vassileva CM, Baumgartner WA, Cameron DE. Hypothermic circulatory arrest in octogenarians: risk of stroke and mortality. Ann Thorac Surg. 2000;69:1048–51.
35. Dávila-Román VG, Barzilai B, Wareing TH, Murphy SF, Schechtman KB, Kouchoukos NT. Atherosclerosis of the ascending aorta. Prevalence and role as an independent predictor of cerebrovascular events in cardiac patients. Stroke. 1994; 25:2010–6.
36. Goto T, Baba T, Matsuyama K, Honma K, Ura M, Koshiji T. Aortic atherosclerosis and postoperative neurological dysfunction in elderly coronary surgical patients. Ann Thorac Surg. 2003; 75:1912–8.
37. Ura M, Sakata R, Nakayama Y, Goto T. Ultrasonographic demonstration of manipulation-related aortic injuries after cardiac surgery. J Am Coll Cardiol. 2000;35:1303–10.
38. Kapetanakis EI, Stamou SC, Dullum MK, Hill PC, Haile E, Boyce SW, Bafi AS, Petro KR, Corso PJ. The impact of aortic manipulation on neurologic outcomes after coronary artery bypass surgery: a risk-adjusted study. Ann Thorac Surg. 2004;78:1564–71.
39. Rosenberger P, Shernan SK, Löffler M, Shekar PS, Fox JA, Tuli JK, Nowak M, Eltschig HK. The influence of epiaortic ultrasonography on intraoperative surgical management in 6051 cardiac surgical patients. Ann Thorac Surg. 2008;85:548–53.
40. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updates meta-analysis and meta-regression of randomized trials. Eur Heart J. 2012;33:1257–67.
41. Li Z, Denton T, Yeo KK, Parker JP, White R, Young JN, Amsterdam EA. Off-pump bypass surgery and postoperative stroke: California coronary bypass outcomes reporting program. Ann Thorac Surg. 2010;90:753–9.
42. Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol. 1998;11:1475–82.
43. Gottesman RF, Sherman PM, Grega MA, Yousem DM, Borowicz LM Jr, Selnes OA, Baumgartner WA, McKhann GM. Watershed strokes after cardiac surgery: diagnosis, etiology, and outcome. Stroke. 2006;37:2306–11.
44. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. J Thorac Cardiovasc Surg. 1995;110: 1302–11.
45. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. Eur J Vasc Endovasc Surg. 2002;23:283–94.
46. Li Y, Walicki D, Mathiesen C, Jenny D, Li Q, Isayev Y, Reed JF 3rd, Castaldo JE. Strokes after cardiac surgery and relationship to carotid stenosis. Arch Neurol. 2009;66:1091–6.
47. Naylor AR. Does the risk of post-CABG stroke merit staged or synchronous reconstruction in patients with symptomatic or asymptomatic carotid disease? J Cardiovasc Surg (Torino). 2009;50:71–81.
48. Guzman LA, Costa MA, Angiolillo DJ, Zenni M, Wludyka P, Silliman S, Bass TA. A systematic review of outcomes in patients with staged carotid artery stenting and coronary artery bypass graft surgery. Stroke. 2008;39:361–5.
49. van Dijk D, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R. Neurocognitive dysfunction after coronary artery bypass surgery: a systemic review. J Thorac Cardiovasc Surg. 2000;120: 632–9.
50. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001;344:395–402.
51. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg. 2011;112:1179–85.
52. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levisky S, Marcantonio ER. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systemic review. Acta Anaesthesiol Scand. 2010;54:663–77.
53. Ho PM, Arciniegas DB, Grigsby J, McCarthy M Jr, McDonald GO, Moritz TE, Shroyer AL, Sethi GK, Henderson WG, London MJ, VillaNueva CB, Grover FL, Hammermeister KE. Predictors of cognitive decline following coronary artery bypass graft surgery. Ann Thorac Surg. 2004;77:597–603.
54. Grigore AM, Grocott HP, Mathew JP, Phillips-Bute B, Stanley TO, Butler A, Landolfo KP, Reves JG, Blumenthal JA, Newman MF, Neurologic Outcome Research Group of the Duke Heart Center. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. Anesth Analg. 2002;94:4–10.
55. Evered LA, Slibert BS, Scott DA. Postoperative cognitive dysfunction and aortic atheroma. Ann Thorac Surg. 2010;89:1091–7.
56. Fontes MT, Swift RC, Phillips-Bute B, Podgoreanu MV, Stafford-Smith M, Newman MF, Mathew JP, Neurologic Outcome Research Group of the Duke Heart Center. Predictors of cognitive recovery after cardiac surgery. Anesth Analg. 2013;116:435–42.
57. Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. Br J Sports Med. 2009;43:22–4.
58. Moody DM, Bell MA, Challa VR, Johnston WE, Prough DS. Brain microemboli during cardiac surgery or aortography. Ann Neurol. 1990;28:477–86.

59. Brown WR, Thore CR. Review: cerebral microvascular pathology in ageing and neurodegeneration. Neuropathol Appl Neurobiol. 2011;37:56–74.
60. Djaiani G, Fedorko L, Borger MA, Green R, Carroll J, Marcon M, Karski J. Continuous-flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. Circulation. 2007;116:1888–95.
61. Rodriguez RA, Rubens FD, Wozny D, Nathan HJ. Cerebral emboli detected by transcranial Doppler during cardiopulmonary bypass are not correlated with postoperative cognitive deficits. Stroke. 2010;41:2229–35.
62. Liu YH, Wang DX, Li LH, Wu XM, Shan GJ, Su Y, Li J, Yu QJ, Shi CX, Huang YN, Sun W. The effects of cardiopulmonary bypass on the number of cerebral microemboli and the incidence of cognitive dysfunction after coronary artery bypass graft surgery. Anesth Analg. 2009;109:1013–22.
63. Bendszus M, Reents W, Franke D, Müllges W, Babin-Ebell J, Koltzenburg M, Warmuth-Metz M, Solymosi L. Brain damage after coronary artery bypass grafting. Arch Neurol. 2002; 59:1090–5.
64. Knipp SC, Matatko N, Wilhelm H, Schlamann M, Thielmann M, Lösch C, Diener HC, Jakob H. Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. Ann Thorac Surg. 2008;85:872–9.
65. Restrepo L, Wityk RJ, Grega MA, Borowicz L Jr, Barker PB, Jacobs MA, Beauchamp NJ, Hillis AE, McKhann GM. Diffusion- and perfusion-weighted magnetic resonance imaging of the brain before and after coronary artery bypass grafting surgery. Stroke. 2002;33:2909–15.
66. Cook DJ, Huston J 3rd, Trenerry MR, Brown RD Jr, Zehr KJ, Sundt TM 3rd. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. Ann Thorac Surg. 2007;83:1389–95.
67. Sun X, Lindsay J, Monsein LH, Hill PC, Corso PJ. Silent brain injury after cardiac surgery: a review: cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. J Am Coll Cardiol. 2012;60:791–7.
68. Maekawa K, Goto T, Baba T, Yoshitake A, Morishita S, Koshiji T. Abnormalities in the brain before elective cardiac surgery detected by diffusion-weighted magnetic resonance imaging. Ann Thorac Surg. 2008;86:1563–9.
69. Maekawa K, Goto T, Baba T, Yoshitake A, Katahira K, Yamamoto T. Impaired cognition preceding cardiac surgery is related to cerebral ischemic lesions. J Anesth. 2011;25:330–6.
70. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010;140:918–34.
71. Bendlin BB, Newman LM, Ries ML, Puglielli L, Carlsson CM, Sager MA, Rowley HA, Gallagher CL, Willette AA, Alexander AL, Asthana S, Johnson SC. NSAIDs may protect against age-related brain atrophy. Front Aging Neurosci 2010;2:35.
72. Gong M, Chen G, Zhang XM, Xu LH, Wang HM, Yan M. Parecoxib mitigates spatial memory impairment induced by sevoflurane anesthesia in aged rats. Acta Anaesthesiol Scand. 2012;56:601–7.
73. Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS. Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. J Anesth. 2011;25:1–9.
74. Sanders RD, Avidan MS. Postoperative cognitive trajectories in adults. The role of inflammatory processes. Anesthesiology. 2013;118:484–6.
75. Kellermann K, Jungwirth B. Avoiding stroke during cardiac surgery. Semin Cardiothorac Vasc Anesth. 2010;14:95–101.
76. Nakamura M, Okamoto F, Nakanishi K, Maruyama R, Yamada A, Ushikoshi S, Terasaka S, Kuroda S, Sakai K, Higami T. Does intensive management of cerebral hemodynamics and atheromatous aorta reduce stroke after coronary artery surgery? Ann Thorac Surg. 2008;85:513–9.
77. Ito A, Goto T, Maekawa K, Baba T, Mishima Y, Ushijima K. Postoperative neurological complications and risk factors for preexisting silent brain infarction in elderly patients undergoing coronary artery bypass grafting. J Anesth. 2012;26:405–11.
78. Silbert BS, Scott DA, Evered LA, Lewis MS, Maruff PT. Preexisting cognitive impairment in patients scheduled for elective coronary artery bypass graft surgery. Anesth Analg. 2007;104: 1023–8.
79. Stroobant N, Vingehoers G. Pre-existing cognitive impairment in candidates for cardiac surgery: an overview. Heart. 2009;95: 1820–5.
80. Crosby G, Culley DJ, Hyman BT. Preoperative cognitive assessment of the elderly surgical patients: a call for action. Anesthesiology. 2011;114:1265–8.
81. D'Agostino RS, Svensson LG, Neumann DJ, Balkhy HH, Willamson WA, Shahian DM. Screening carotid ultrasonography and risk factors for stroke in coronary artery surgery patients. Ann Thorac Surg. 1996;62:1714–23.
82. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg. 2007;104:51–8.
83. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. Anesth Analg. 2013;116:663–76.
84. Gold JP, Torres KE, Maldarelli W, Zhuravlev I, Condit D, Wasnick J. Improving outcomes in coronary surgery: the impact of echo-directed aortic cannulation and perioperative hemodynamic management in 500 patients. Ann Thorac Surg. 2004; 78:1579–85.
85. Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar-Yosef S. Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg. 2007;84:1467–73.
86. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. J Thorac Cardiovasc Surg. 1995;110:349–62.
87. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. Cerebrovasc Dis. 2003;15:222–9.
88. Cao L, Young N, Liu H, Silvestry S, Sun W, Zhao N, Diehl J, Sun J. Preoperative aspirin use and outcomes in cardiac surgery patients. Ann Surg. 2012;255:399–404.
89. Bouchard D, Carrier M, Demers P, Cartier R, Pellerin M, Perrault LP, Lambert J. Statin in combination with β-blocker therapy reduces postoperative stroke after coronary artery bypass graft surgery. Ann Thorac Surg. 2011;91:654–9.
90. Ji F, Li Z, Nguyen H, Young N, Shi P, Fleming N, Liu H. Perioperative dexmedetomidine improves outcomes of cardiac surgery. Circulation. 2013;127:1576–84.