Chapter 54
Postoperative Cognitive Dysfunction After Cardiac Surgery and Neuroprotection

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Abstract Postoperative cognitive dysfunction (POCD) after cardiac surgery is growing in importance as the aging of the population advances. Highly sensitive neuropsychological testing is required to detect POCD, and a well-matched control group is useful in analyzing and interpreting the results. Pathophysiology studies of cognitive change after cardiac surgery focused on the role of cardiopulmonary bypass, intraoperative microemboli, hypoperfusion, and inflammatory response as possible causes of POCD. Long-term, follow-up studies that compared patients who underwent on- or off-pump coronary artery bypass surgery failed to demonstrate a significant reduction in the incidence of POCD. Therefore, the focus of research is shifting from cardiopulmonary bypass to patient-related risk factors. There is growing evidence that patient-related risk factors such as the extent of preexisting cerebrovascular disease play an important role in the pathogenesis of both short- and long-term POCD. Establishing the degree of functionally significant vascular disease in the brain preoperatively should be an essential part of patient evaluation.

Keywords Postoperative cognitive dysfunction • Cardiac surgery • Cardiopulmonary bypass • Cerebrovascular disease

54.1 Introduction

Advances in surgical techniques, perfusion systems, and perioperative management have reduced the mortality associated with cardiac surgery. However, postoperative cognitive dysfunction (POCD) remains a common outcome with potential to adversely impact quality of life. The mechanisms underlying POCD may include microemboli, hypoperfusion, and inflammatory response. Complications involving the brain are increasing substantially because older patients with advanced atherosclerotic vascular disease now undergo surgery. The objectives of this chapter are to

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review the manifestations and mechanisms of POCD after cardiac surgery and suggest an approach to neuroprotection during surgery.

54.2 Assessment of Cognitive Dysfunction

The rising number of patients of advanced age who are undergoing cardiac surgery and who have comorbid medical conditions underscores the importance of complications in overall patient outcomes. Anesthetists and surgeons have suspected for many years that some elderly patients suffer a decline in cognitive function after surgery, the so-called POCD. As noted by Shaw and colleagues in 1987, it manifests far more commonly than stroke, with 79 % of patients experiencing cognitive decline in the early period after cardiac surgery [1]. Due to the subtle nature of POCD, many physicians fail to notice when a patient's cognition declines after surgery. In many cases, it is not detected until the patient's relatives discover difficulties with normal activities at home or at work [2]. This condition is characterized by a decline in cognitive functions such as memory, ability to concentrate, and information processing. These changes can be detected in neuropsychological tests and present clinically as deficits in cognition and memory representing a significant change from the patient's previous level of functioning [3].

A consensus meeting held in 1994 encouraged a more standardized and comparable methodology of assessing POCD [4]. It was recommended that neurological and neuropsychological state be tested before surgery to provide accurate baseline information. A second important recommendation was that analyses should be based on the change in performance in an individual from baseline to a specific time after surgery. The recommended core neuropsychological battery should include: (1) the Rey Auditory Verbal Learning Test to assess memory, in which patients are asked to recall as many words as possible immediately upon viewing a list of 15 words and again after 15–25 min; (2) the Trail-Making Tests A and B, in which participants connect numbered and then alternately numbered and lettered dots in order under timed conditions to assess attention and mental flexibility; and (3) the Grooved Pegboard Test, which involves inserting notched pegs into specific holes in a shallow box to test fine motor dexterity.

It is essential to consider the many pitfalls associated with repeated neuropsychological testing of surgical patients such as the practice, floor (i.e., poor initial performance that cannot decline any further), and ceiling (i.e., excellent initial performance which cannot improve) effects [5]. Other important challenges arise with obtaining a reliable assessment of preoperative performance and defining deficits in meaningful statistical analysis. Analytic criteria used commonly are percentage change from the baseline for a defined number of tests and absolute decline from baseline scores greater than a defined proportion of the standard deviation of two or more tests [6]. These statistical methods, however, do not relate cognitive decline with data from age-matched healthy controls and thus fail to account for practice effects, normal variability, and the cognitive decline that

occurs in a healthy population. Therefore, contemporary studies have included control groups such as patients who have undergone percutaneous coronary intervention [7], off-pump surgery [8], and noncardiac surgery [9]. However, no generally agreed diagnostic criteria have been published, and several quite different definitions of POCD are found in the literature.

54.3 Preoperative Cognitive Status

From clinical psychiatry it is known well that depression is associated with cognitive deterioration. Depression is not unusual before surgery, but no clear association has been established between depression and POCD [10]. However, there is evidence that a considerable proportion of cardiac surgery patients may have significantly lower cognitive performance before surgery [11–13]. As is commonly known, aging is associated with structural cerebral changes, including vascular disease of the brain and impaired cognition [14]. In a study from Japan by Goto and colleagues in which cerebral magnetic resonance images (MRI) were obtained before cardiac artery bypass graft (CABG) in 421 patients, 30 % had small cerebral infarcts and 20 % had multiple cerebral infarcts (Table 54.1) [15]. Thus, one-half of this cohort had evidence of ischemic brain abnormalities before surgery.

Chronic cerebral infarcts, and even new deficits on diffusion-weighted MRI, have been identified in 4.5 % of patients, probably due to recent cardiac catheterization (Fig. 54.1) [16]. In addition, patients with such existing abnormalities had lower baseline cognitive performance and showed a worse postoperative neuropsychological test performance than those with normal preoperative findings. These limitations should be taken into account in choosing methods of analyzing and interpreting results.

54.4 Short-Term Cognitive Changes

While short-term cognitive change after cardiac surgery typically refers to changes observed in cognitive performance, cognitive decline in the immediate perioperative period could be related to adverse effects of anesthetic drugs, narcotics for pain control, and other clinical issues. Therefore, some investigators have chosen to defer follow-up testing until at least 3–4 weeks after surgery. The incidences reported, however, have varied enormously. In the brief period after cardiac surgery, the incidence of POCD varied from 22 to 79 % among different studies, depending on how the deficit was defined, the test methods applied, the composition of the target population, and study design [1, 17]. There are also reports of POCD after noncardiac surgery performed while the patient was under general anesthesia, suggesting that even if short-term cognitive change does occur after cardiac surgery, it is not specific to the use of cardiopulmonary bypass [8].

Table 54.1 MRI of the brain and POCD in patients undergoing coronary artery bypass grafting

	Overall ($n = 421$)	Small infarctions ($n = 126$; 30 %)	Multiple infarctions ($n = 83$; 20 %)
Age (years)	70.0 ± 5.4	70.3 ± 5.2	70.9 ± 5.9
Carotid arteries stenosis (>75 %)	28 (7 %)	8 (6 %)	12 (15 %)
Cerebral arteries stenosis (occluded)	14 (3 %)	3 (2 %)	9 (11 %)
Aortic atheroma (≥3 mm)	73 (17 %)	23 (18 %)	19 (23 %)
POCD	49 (12 %)	17 (13 %)	17 (20 %)

Source: Adapted from Goto et al. [15] with permission

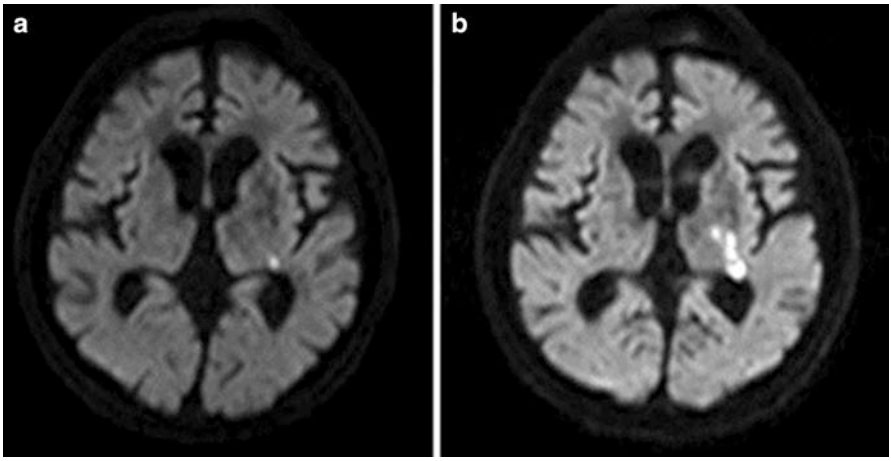

Fig. 54.1 Diffusion-weighted MRI of a 67-year-old man with no demonstrable neurologic deficits before off-pump CABG. (**a**) Preoperative MRI scan revealed small diffusion abnormality on the left posterior limb of the internal capsule. (**b**) Another scan performed 5 days after surgery demonstrated that size of diffusion restriction lesion had increased; the patient had dysarthria and right hemiparesis

54.4.1 Microemboli

The pathophysiology of short-term cognitive change after cardiac surgery remains poorly understood. The focus of most investigations has been on neurological injury secondary to microemboli, hypoperfusion, and systemic inflammatory response. The cardiopulmonary bypass circuit and the surgical field in cardiac surgery are sources of a variety of embolic particles such as thrombi, fat, and gas bubbles. In addition, emboli can be generated from disrupted aortic atherosclerotic plaques by aortic manipulation and cannulation. Some earlier studies have reported an association between embolic count and short-term cognitive outcome [18, 19], but other contemporary studies have not replicated these findings [20,

21]. Application of diffusion-weighted MRI indicates that about 50 % of patients who undergo cardiac surgery develop new discrete lesions suggestive of microembolic infarcts [22]. A number of studies have found associations between short-term cognitive change and new ischemic lesions on diffusion-weighted MRI [23, 24]. In contrast, no such correlation has been found by other studies in patients after cardiac surgery [25]. It has been hypothesized that the cognitive manifestations of microemboli may depend as much on patient-related risk factors such as the degree of preexisting cerebrovascular disease as on the quantity and size of the embolic load.

54.4.2 Hypoperfusion

Elderly patients and those with comorbid disease such as hypertension and diabetes may be vulnerable to the effects of hypoperfusion because they have altered autoregulation of cerebral blood flow. Certain regions of the brain, including the hippocampus, periventricular white matter areas, and watershed areas, may be particularly susceptible to the effects of hypoperfusion. However, the evidence that deranged cerebral hemodynamics are associated with neurological injury is weak and sometimes conflicting. Some evidence suggests that maintaining perfusion pressure at more physiological levels during cardiopulmonary bypass (80–90 mmHg) is associated with lower short-term POCD [26]. However, a study using single-photon positron-emission computed tomography failed to show a significant association between neuropsychological test performance and postoperative global or regional blood flow [27]. As discussed above, emboli and hypoperfusion may act synergistically, in that decreased flow during surgery may fail to wash out embolic materials from the brain, particularly in the watershed areas [28].

54.4.3 Systemic Inflammatory Response

Cardiac surgery is associated with a profound systemic inflammatory response, especially when cardiopulmonary bypass is used. It is known that a severe systemic inflammatory response can break down the blood–brain barrier, leading to a range of clinical consequences, including delirium and sepsis-mediated encephalopathy, with symptoms ranging from subtle cognitive deficit to coma. However, there are sparse data to support the inflammatory response alone as the causative factor. Several groups have measured biomarkers of neuronal injury such as neuron-specific enolase and S100β after cardiac surgery with cardiopulmonary bypass and have found elevated plasma levels but with varying correlations between these markers and cognitive function [29, 30]. Preclinical studies suggest that S100β may be involved in neuronal and glial growth, proliferation, and activation, thus facilitating its role as a marker to study inflammation and brain injury.

Unfortunately, it is important to note that serum S100β concentrations appear to be influenced by age, sex, on-pump or off-pump surgery, the use of cardiotomy suction or a cell saver, and the assay used [31–33]. Therefore, it is currently not possible to link these findings with pathophysiological processes.

54.5 Anesthesia

A number of studies have reported that clinically available opioids can be neurotoxic in rats [34, 35]. Fentanyl is associated with delirium [36], but there seems to be no clear relationship between dosage and the incidence of POCD at 3 or 12 months after CABG surgery [37]. Animal studies suggest that exposure to some halogenated anesthetics increases the production of the Alzheimer's amyloid peptide and vulnerability to neurodegeneration [38, 39], but these results are not always supported by clinical data [40]. Inflammation and stress responses might also contribute to cognitive decline induced by anesthesia [41]. Animal research and clinical trials are needed to establish whether anesthetic agents cause cognitive changes or if they affect aging-related cognitive decline.

54.6 Long-Term Cognitive Changes

Several studies suggest that, in addition to the immediate effects of POCD, long-term cognitive outcomes also are affected. A study by Newman and colleagues published in 2001 found that 5 years after on-pump CABG 42 % of patients available for follow-up had cognitive performance lower than at baseline [42]. This high percentage of patients with decline suggests that cardiopulmonary bypass accelerates cerebral aging and that the harmful effects of cardiopulmonary bypass become more apparent in the long term. In contrast, a 5-year follow-up by van Dijk et al. published in 2007 failed to show a difference in the frequency of POCD between patients who underwent surgery with or without cardiopulmonary bypass [43]. Interestingly, approximately 50 % of patients in both groups suffered cognitive decline, suggesting that late cognitive changes are related to factors other than cardiopulmonary bypass. Interpreting this study of cognitive outcomes after CABG has been difficult because of the lack of comparison groups, either with or without coronary artery disease. In 2009, Selnes and colleagues reported that, compared to those with no vascular disease risk factors, patients with coronary artery disease had lower baseline cognitive performance and greater decline during 6 years of follow-up [44]. Thus, vascular disease may impact cognitive performance.

Other possible causes of late cognitive decline in elderly patients include progression of subcortical small vessel disease, development of silent cerebral infarcts, and Alzheimer's disease during the follow-up period. There is evidence

from several epidemiological studies that cerebrovascular disease may be associated with accelerated cognitive decline, even without cardiac surgery. In a recent systematic review of 105 studies, silent cerebral infarcts defined on MRI were detected in 20 % of healthy elderly people [14]. Silent infarcts are associated with subtle deficits in physical and cognitive function. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia. Given that many candidates for CABG have MRI evidence of cerebral infarct even before surgery [15], it is likely that the late cognitive decline reported previously in the literature is related to the progression of underlying cerebrovascular disease.

54.7 Cognitive Recovery After Surgery

Although several previous observations are of empirical importance to the phenomenon of cognitive decline, the studies that provided them did not identify which factors influenced recovery from POCD after cardiac surgery. A 2013 study by Fontes and colleagues reported that 45 % of patients undergoing cardiac surgery who experienced cognitive decline at 6 weeks returned to baseline cognitive function by 1 year [45]. The authors suggested that heightened instrumental activities of daily living performance at 6 weeks after surgery is associated with likelihood of cognitive recovery at 1 year. One hypothesis is that interventions that encourage better performance on instrumental activities immediately after surgery improve cognitive performance.

54.8 Neuroprotective Strategies

Because adverse neurological events after cardiac surgery represent a wide range of injuries, differentiating the individual causes of types of injuries becomes difficult (e.g., stroke, delirium, and POCD). Additionally, there is growing evidence that patient-related risk factors such as the extent of preexisting cerebrovascular disease have a greater impact on both short- and long-term cognitive declines than do procedural variables. Therefore, it is important to assess those risk factors that indicate a predisposition toward POCD such as cerebrovascular disease and then adapt the surgical approach to high-risk patients (Table 54.2). It will become more important to reduce late cognitive decline by controlling modifiable patient-related risk factors such as hypertension, diabetes, hyperlipidemia, and smoking.

Table 54.2 Neuroprotective strategies used in cardiac surgery

Timing	Issue	Intervention
Before surgery	Establish risk factors	Use neuropsychological testing to identify preoperative cognitive impairment
		Use MRI to identify preexisting cerebrovascular disease
During surgery	Aortic atheroma	Use epiaortic/TEE ultrasound to identify ascending and aortic arch disease [46, 47]
		Modify surgical procedures: avoid repeated aortic clamping, choose no-touch aortic techniques for high-grade atheroma, choose site, and assess risk of cannulation
	Hypoperfusion	Use higher blood pressures during cardiopulmonary bypass
		Use alpha-stat pH management (for adults) [48]
	Brain hyperthermia	Avoid rapid/excessive rewarming [49]
	Hyperglycemia	Avoid or treat hyperglycemia [50]
	Microemboli	Minimize cardiotomy suction and dissection of mediastinal fat [51]
After surgery	Diagnosis and identification of ischemic brain lesions	Perform diffusion-weighted MRI

TEE = transesophageal echocardiography

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