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Expert Reviews

Cardiac Surgery, the Brain, and Inflammation

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Abstract: Cognitive deterioration can reliably be measured after procedures requiring anesthesia and surgery. Cardiac surgery has had the spotlight because of the high reported incidence of postoperative cognitive dysfunction in early studies, but such effects occur after other surgical procedures as well. "Early" postoperative cognitive dysfunction should be considered as a different phenomenon, relating to acute pharmacological, physiological, and stress-related recovery. The focus should be on what is affecting patients at 3 months, 12 months, and 5 years later. Like with many other aspects of perioperative risk, a significant element is the patient's preoperative cognitive status. We now know that up to one-third of overtly "normal" elective cardiac surgical patients enter surgery with some degree of pre-existing cognitive impairment or, when applying psychogeriatric measures, mild cognitive impairment. The latter is a known prodrome or early stage of the amyloid associated Alzheimer's disease dementia. Inflammatory responses during cardiac surgery have been recognized for years, but our understanding of the complexity of systemic inflammatory response has grown significantly with the ability to assay neurohumoral markers such as interleukins. The blood–brain barrier is made vulnerable by both pre-existing disorders (mild cognitive impairment/amyloid; vascular disease) and by the inflammatory response to surgery and cardiopulmonary bypass. Inflammation affecting the brain at this time may set in motion accelerated neurological and hence cognitive decline that, despite an initial recovery and even functional improvement, may proceed to further long-term decline at an accelerated rate in susceptible individuals. Clinical data are emerging from longer-term studies to support this concern, but evidence for effective preventive or therapeutic strategies is limited. **Keywords:** neurocognitive deficits, surgery, complications, cardiopulmonary bypass, brain. *JECT. 2014;46:15–22*

Surgery is always undertaken with the anticipation of improving an individual's condition. This improvement extends over a wide range of health issues such as cosmetic procedures, providing a diagnosis for directing therapy, improving quality of life like in hip joint replacement surgery, or even prolonging or saving life like in cancer resection or cardiac surgery. Any factors that adversely affect outcomes may potentially negate the purpose of the surgery and should therefore be aggressively identified and managed. After reductions in perioperative mortality in most areas of surgery, the complications that most significantly affect outcome and quality of life are those that affect the brain. The brain is well protected from external threats anatomically by a rigid skull, behaviorally by high-level strategies to avoid physical injury, and physiologically by homeostatic mechanisms to maintain perfusion and ensure oxygenation. Unfortunately, internal threats are less well defended, including exposure to drugs and alcohol. The brain is particularly susceptible to metabolic and pharmacologic interference, a susceptibility that is exploited when administering general anesthesia which uses volatile or intravenous drugs to induce a deep coma, often misdescribed as "sleep."

Over 100 years ago Savage (1) reported that some individuals did not return to their preanesthetic cognitive state after surgery and anesthesia but despite reports in the 1950s and 1960s (2,3), it was the description of cognitive decline after cardiac surgery that attracted major attention (4). Even then, cognitive decline was viewed a minor

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complication because the major focus in cardiac surgery was to improve survival. In the first two decades of open heart surgery, the main cerebral events of concern were stroke and acute confusional states ("pump brain").

Postoperative cognitive dysfunction (POCD) after surgery began to be measured consistently throughout the 1980s. Unfortunately, there was much confusion regarding testing procedures and diagnostic criteria. Many investigators included delirium in the POCD category, and testing time points after surgery ranged from days to months. A consensus statement emerged, providing some clarity regarding the selection of neuropsychological tests to be used (5); however, the "diagnosis" of POCD remained open to interpretation, usually relying on a change in a patient's test performance of a specified magnitude in a specified number of cognitive tests. In an effort to improve consistency, most investigators now use a form of Reliable Change Index (RCI) (6) to compare patients with a comparable control group. POCD is not a clinical syndrome, is not defined in the "bible" of neuropsychological diagnoses, the *Diagnostic and Statistical Manual of Mental Disorders*, and remains a diagnosis based solely on neuropsychological test performance. This has led some investigators to question its validity as a construct, but weight of evidence supports its existence, including the consistency of POCD "detection" by multiple investigators and the adverse association of POCD with outcomes such as length of hospital stay, quality of life, and mortality (7).

There remain many unanswered questions: why does POCD develop, who is susceptible, is it reversible, and how does it relate to other neurodegenerative conditions? The answers to these questions are likely to be interrelated and include recognition of pre-existing vulnerabilities, a better understanding of POCD at different stages of the patient's recovery, and quite possibly the overarching role of inflammation in the process. This review explores aspects of the current status of these concepts and also relates them to emerging concerns regarding long-term cognitive impairment and, in particular, dementia.

POSTOPERATIVE COGNITIVE DYSFUNCTION AND CARDIAC SURGERY

POCD follows both cardiac and noncardiac surgery. When patients are tested at hospital discharge or at 1 week after the procedure, the incidence of POCD is higher after cardiac surgery than noncardiac surgery (Table 1). Up to 43% of patients have POCD at 7 days after coronary artery bypass graft surgery (8). By 3 months and 12 months after the procedure, however, there is no significant difference in the incidence of POCD regardless of the type of surgery or anesthesia. In a prospective investigation using RCI to diagnose POCD in three patient populations (one group undergoing elective CABG with cardiopulmonary bypass [CPB] under general anesthesia [GA], one group having total hip joint replacement with spinal anesthesia and GA and the third having coronary angiography with sedation), the incidence of POCD at 3 months was 16%, 17%, and 21%, respectively (8). Despite the great variation in the magnitude of surgery and type of anesthesia, any difference in the incidence of POCD at 3 and 12 months was indistinguishable. When viewed in comparison with the incidence of POCD after 1 week in the cardiac group, this suggests that testing at 1 week after surgery may be identifying a phenomenon arising from a different mechanism. Thus, the likelihood is that "early" POCD is largely a different entity to later POCD.

Table 1. Prevalence of postoperative cognitive dysfunction after coronary artery bypass graft (CABG) surgery, total hip joint replacement (THJR), and coronary angiography (CA).

Time after Surgery	Control (n = 34)	CABG (n = 312)	THJR (n = 161)	CA (n = 167)
7 days	6%	43%	17%	
3 months	0%	16%	16%	21%

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Within the realm of cardiac surgery, it was long held that the physical or physiological "insult" of CPB was the cause of postoperative delirium and POCD. It seemed highly plausible that the presence of microemboli, hypotension or the abnormal perfusion of CPB were contributing to the etiology of POCD. With the advent of off-pump surgery, it finally became possible to compare cognitive outcomes in patients having similar operative procedures and anesthetics with or without the heart–lung machine. The initial studies of van Dijk (9) in 281 patients surprisingly showed an incidence at 3 months of 27% on-pump versus 21% off-pump ($p = .15$) and these outcomes have been confirmed by others (10,11). This demonstrates that the process of CPB is not the primary factor in POCD. Others have investigated cerebral microembolic load using transcranial Doppler and found no association (12–14), although some have reported a link between elevations in the astrocytic protein S100beta, cognitive outcomes, and microembolic load (15,16). Overall, however, these findings further dissociate the heart–lung machine from POCD.

The identification of POCD with cardiac surgery remains important. Despite it being a nonclinical diagnosis, the presence of POCD has been associated with an average of 1.2 days longer hospital stay (mean [standard deviation] for no POCD 7.1 [3.4] days versus POCD 8.3 [4.1] days; $p = .02$) (17). Quality-of-life scores were found to be lower at 12 months in those with POCD (18), and 1-year mortality was higher (7). Patients with cognitive impairment

before and 6 months after cardiac surgery had a higher 11-year mortality risk than those with no cognitive impairment (hazard ratio, 1.83; 95% confidence interval, 1.08–3.10, $p = .03$) (19). Finally, the identification of cognitive decline 5 years postcardiac surgery was associated with POCD at 7 days (20).

Risk factors for development of POCD are consistently identified as increasing age and lower IQ (or education levels) (17–21). These may both relate to the degree of "cognitive reserve" that an individual has. Baseline cognitive test performance has also been analyzed to indicate the presence of pre-existing cognitive impairment (PreCI) or a more formal diagnosis of mild cognitive impairment (MCI), which is a precursor to Alzheimer's disease dementia (AD) (22). The latter requires specific information, which is not part of the "routine" test batteries for POCD, in particular both subjective and objective reports of memory impairment. MCI is an important consideration because of the association with neuronal injury and its possible exacerbation by anesthetic agents or the inflammatory processes associated with surgery.

DELIRIUM AND CARDIAC SURGERY

Delirium after cardiac surgery is independently associated with mortality up to 10 years postoperatively (23). Delirium is an acute neuropsychiatric syndrome characterized by decline in attention, fluctuating conscious levels, and disorganized thinking. It is of particular concern because of its high incidence, clinical and social consequences, and because it is associated with physical precipitants. In the perioperative period, delirium occurs with a high incidence in surgical patients and patients in critical care environments. After cardiac surgery, the incidence is reported at up to 52% (24,25) and in intensive care at up to 90% (26). In cardiac surgery, many triggers are present such as a need for many days of hospitalization, including time spent in a high-dependency environment where circadian cues are absent. Further triggers include exposure to multiple drugs, general anesthesia for many hours, postoperative sedation, analgesics for pain management, and indwelling urinary catheters.

Delirium has significant short- and long-term consequences affecting quality of life, social needs, and clinical morbidity and mortality (24,27,28), yet its diagnosis is frequently missed (29), in part because the common hypoactive presentation may be undiagnosed. Clinical studies relying on a retrospective diagnosis of delirium as an indicator of cognitive outcomes are often flawed for this reason. The exact cause(s) of delirium is unknown but it is associated with a combination of predisposing and precipitating factors (30). There is some likelihood that delirium is associated with increasing age (as for POCD) and pre-existing cognitive impairment or dementia (31). The final common pathway of many of the insults associated with delirium is likely to be some degree of challenge, which erodes the individual's cognitive reserve (e.g., changed environment, pain, and stress), alters inhibitory and cognitive pathways (e.g., medications), and activates the inflammatory cascade (32). In patients undergoing cardiac surgery, it is not possible to modify many of the factors that have been identified as triggers for delirium. Therefore, in these patients, despite the best of physical and psychological clinical care, there is a need to seek protective strategies for the brain, especially during the initiation period of peak neurochemical disruption, i.e., during anesthesia, surgery, and CPB.

Although an association between postoperative delirium and pre-existing dementia has been made, to date the contribution of postoperative delirium to long-term cognitive impairment or to subsequent dementia is less clear (33).

PREOPERATIVE COGNITION, MILD COGNITIVE IMPAIRMENT, AND DEMENTIA

The population of patients presenting for all forms of surgery is aging as the population ages. Cognitive decline is highly associated with increased age. For example, the prevalence of MCI identified by subtle cognitive changes increases with age. At present, approximately 16% of patients older than 70 years of age will have MCI and over 17% will progress to dementia every year (34,35). This is a huge problem where currently 32% of anesthetics are administered to those aged older than 65 years, which is projected to rise to 48% by 2051 (36). In elderly patients (mean [standard deviation] age, 69.8 [6.3] years) presenting for elective total hip joint replacement surgery, PreCI was identified in 20% and amnestic MCI in 22% (22). This figure for nonamnestic or mixed MCI is even higher in patients presenting for coronary artery surgery (37% and 33%, respectively) (19). The relevance of this is that cognitive impairment may predispose to postoperative delirium and that the processes underlying some forms of cognitive impairment may be exacerbated, accelerating clinical deterioration (37).

Subtle cognitive impairment (either MCI or PreCI) is believed to represent early stages of AD (38). The neuronal degeneration and neuroinflammation of AD is associated with amyloid protein deposition (A-β 40, A-β 42) causing amyloid plaques and τ proteinopathy resulting in neurofibrillary tangles (39). These processes progress over time at different rates in affected individuals. The rate of cognitive decline is seldom assessed in studies of cognition and thus the effect of cardiac surgery and CPB on the trajectory of decline is unknown. There is a debate at the moment on the impact of anesthesia on dementia (37)

with conflicting epidemiological data (40–42). However, laboratory data suggest that anesthetic agents, especially volatile agents, may have some effect on the underlying processes of AD (43). The key to understanding these effects, especially in cardiac surgery, may lie in the underlying inflammatory processes (32–44).

INFLAMMATION

It is well known that cardiac surgery and CPB are associated with a systemic inflammatory response. Triggering factors include tissue injury and organ ischemia, the neurohumoral stress response, and of course the process of CPB with the extensive foreign surface exposure and physical trauma to blood elements (45,46). The inflammatory responses to CPB include activation of clotting factors, platelets and fibrinolysis, elevation of a vast range of inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor-α, and activation of endothelial and leukocyte responses (46).

Genetics may affect the inflammatory response or vulnerability to inflammation. Specific genetic polymorphisms affecting IL-6 and C-reactive protein have been identified and associated with an increased risk of stroke after cardiac surgery (47). Apolipoprotein E (APOE) affects central nervous system (CNS) acetylcholine synthesis, and individuals with the epsilon-4 subtype (APOE-e4) are at increased risk of both vascular dementia and vascular disease. An association with the APOE-e4 genotype and AD is well established, but it has not been associated with POCD in cardiac surgery (48,49).

Systemic inflammation is common to the numerous medical and surgical conditions associated with cognitive change and delirium (32–50). The inflammatory response provides a common process that unites the multitude of precipitating factors in vulnerable patients, and it has been implicated in dementia (32). One mechanism by which inflammation may contribute to cognitive change is by proinflammatory cytokines produced by macrophages and monocytes increasing permeability of the blood–brain barrier and altering neurotransmission (51).

Cardiac surgery thus provides a "tetrad" of circumstances that may set the scene for initiating or accelerating cognitive decline. These are: 1) pre-existing cognitive impairment (PreCI, MCI, or dementia) with its associated diminished cognitive reserve; 2) pre-existing inflammatory states such as vascular disease or AD; 3) the triggering of widespread systemic inflammation; and 4) alteration in the blood–brain barrier increasing exposure of CNS neurons to toxic or inflammatory effects. In addition, microembolism, regional or global hypoperfusion, or hypoxia may increase vulnerability. Items 1) through 3 are present to a greater or lesser extent in many procedural situations.

PREVENTIVE STRATEGIES

In many physiologic and pathologic processes, preventive interventions are more effective than treatments. For example, prevention of the triggering event is most effective in relation to coagulation, immunologic, inflammatory, or neuroexcitatory responses (such as in acute nociceptive responses). There are many studies investigating pharmacological and physical strategies to modify or prevent cognitive decline after cardiac surgery. Many of these studied only small numbers of patients and it should also be noted that cognitive assessments and the criteria for the determination of cognitive change vary considerably between individual studies. Benefits, when identified, are often small, which makes combining or comparing outcomes between investigations difficult.

Pharmacological

Steroids: Steroids would seem an obvious choice to modify inflammatory responses, although few studies have been designed to investigate their efficacy in improving cognitive outcomes. Blunting of the normal diurnal variation in cortisol levels was significantly related to POCD at 1 week after cardiac surgery. A meta-analysis of perioperative steroids in cardiac surgery did not assess POCD but showed no advantage in stroke (52). A study in 4494 cardiac surgical patients compared high-dose dexamethasone (1 mg/kg) with placebo and found dexamethasone use to be associated with reductions in postoperative infection, duration of postoperative mechanical ventilation, and duration of intensive care unit and hospital stays. It was not associated with a reduction in the incidence of major adverse events, including stroke at 30 days, compared with placebo (53).

Nonsteroidal anti-inflammatory drugs: Limited animal data suggest that inhibition of microglial proliferation by meloxicam was associated with improved short-term memory function in rodents (54).

Ketamine: Ketamine is a phencyclidine anesthetic and antihyperalgesic agent with a range of pharmacological effects that are potentially neuroprotective (55). As an N-methyl D-aspartate receptor antagonist, ketamine reduces glutamate induced calcium ion influx, which has been shown to trigger neural injury and cell death (56). In vivo studies using ketamine protection against glutamate-induced or ischemic neural injury resulted in less neuronal damage. In addition, ketamine possesses anti-inflammatory effects, which are demonstrable in vitro (57), are protective after head trauma in rats (58) and attenuate human inflammatory responses postsurgery (59). In subanesthetic doses, ketamine appears to have a role in out-of-hospital emergency medicine to treat excited delirium (60). As a preventive strategy, in a small study of cardiac surgical patients, ketamine

administration immediately before the procedure has been shown to reduce the incidence of postoperative delirium (61). If this is borne out in a more rigorous investigation, then important short- and long-term effects such as progression to dementia may also be evaluated.

Specific drugs: Etanercept is a tumor necrosis factor-α antagonist that has been used in some trials to modify the inflammatory response (62). Its effect on cognition has not yet been explored. It is unlikely, on its own, to be effective at brain "protection" because it is a highly specific antagonist and there are a great many inflammatory mediators at work. Side effects include an increased risk of infectious complications. It may be useful as part of a larger integrated strategy.

Lignocaine has pharmacologic properties (neuronal stabilization, anti-inflammatory effects) and laboratory data (63), which have led some investigators to explore its efficacy but with equivocal clinical results (64). A double-blinded randomized controlled trial in cardiac patients (65) used 48-hour exposure to lignocaine in 241 patients and showed no differences in cognitive measures at 6 weeks and 1 year postoperatively. The investigation of lignocaine is difficult in cardiac surgery because it is frequently administered either as a component of cardioplegic solutions or in the treatment of dysrhythmias. Thiopentone is another agent that has long been used as a cerebral protective agent in a range of situations but for which evidence for efficacy in cardiac surgery is lacking (64).

Cognitive

The brain is an incredibly adaptive organ, and strategies to exploit neuroplasticity to buffer cognitive insults and increase cognitive reserve offer the most practical postoperative intervention opportunities at present. In the acute phase, avoiding cognitive disruption by improving postoperative sleep patterns has been advocated as part of a multifaceted approach to perioperative care (66). In the medium to longer term, cognitive enrichment including improved social engagement is likely to be beneficial and has been demonstrated in human and animal investigations (67–70). This is supported by a retrospective analysis of predictors of recovery from cognitive change after cardiac surgery, which identified greater activities of daily living at 6 weeks as a significant predictor of recovery (odds ratio, .891 [.810–.981]) along with baseline education level and baseline cognition (21).

Procedural

Avoiding conditions that stress the metabolism of the brain may also be beneficial in improving cognitive outcomes. Intraoperative hyperglycemia (>11 mmol/L) has been associated with increased POCD in nondiabetic patients ($p = .035$) (71). Rewarming hyperthermia (>37°C nasopharyngeal temperature) may create a hypermetabolic state and in one small study was linked to a higher incidence of POCD at 6 weeks ($p = .05$) (72). The temperature gradient between the CPB arterial line and the brain may be a factor. One study identified less cognitive impairment with a 2°C gradient compared with a 4–6°C gradient when rewarming patients from 28–32°C (73).

Hypotension and hypoxemia might be expected to have an association with cognitive decline, and this is clearly the case for prolonged or extreme episodes where global cerebral insults occur. However, in the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) study, in elderly noncardiac surgery patients, neither factor was associated with POCD (74). It is likely that these events are more pronounced in cardiac surgery and strategies to optimize cerebral perfusion and oxygenation may lead to improved outcomes. The use of near infrared spectroscopy to continually monitor cerebral oxygenation (cerebral oximetry) may lead to more effective maintenance of global cerebral state (75,76). There are little data on electroencephalography-based depth of anesthesia monitoring and cognitive outcomes, although this is an emerging field. One study in noncardiac surgical patients found no association between a depth of anesthesia index and POCD at 1 week (77).

Minimizing macroembolism would clearly reduce focal ischemia and stroke but the situation is less clear for microembolic load and POCD. Washing cardiotomy blood to remove contaminants before reinfusion was not associated with improved cognitive outcomes (78). The incidence of cognitive dysfunction has not been consistently shown to be associated with microembolic load as detected by transcranial Doppler after cardiac surgery (79,80), possibly because the majority are gaseous (81). The introduction of routine 40-μm arterial line filtration has probably removed much of the impact of CPB-generated microemboli on subtle cognitive impairment (82). Nonetheless, it seems prudent to avoid exposure of the brain to unnecessary microembolism.

Other aspects of CPB circuit design may influence inflammatory responses or microembolic load. The use of centrifugal pumps has not been shown to improve cognitive outcomes (83). The inflammatory response to CPB is reduced by the use of biocompatible circuits (84), and a few small studies have shown beneficial cognitive outcomes (85,86). Larger, definitive studies in these areas may be difficult to perform because the use of biocompatible circuits has become routine. Reduction in the surface area and volume of CPB circuits using miniaturized circuits has shown benefits in a number of areas, but the impact on cognitive outcomes is unconvincing. A meta-analysis was unable to demonstrate a benefit for miniaturized circuits in neurocognitive events except in one of four subgroup analyses (87).

CONCLUSION

The cardiac patient is vulnerable to cognitive impairment as a result of a tetrad of circumstances: 1) pre-existing cognitive impairment; 2) pre-existing inflammatory states; 3) the triggering of widespread systemic inflammation; and 4) alteration in the blood–brain barrier. This is in addition to physical and physiological insults. In concert with well-established cognitive support strategies, the use of neuroprotective drugs during exposure to anesthesia and surgical stress may in the future offer clinical benefits to the incidence of delirium, POCD, and possibly dementia. For preventive strategies to be most effective, with minimal side effects, they need to be targeted at those who are identified as most at risk. This requires attention to preoperative identification of vulnerable patients with mild or even subclinical cognitive impairment and possibly in the future identifying relevant biomarkers or even genotypes. Care does not end at discharge and ongoing treatments, including cognitive enrichment strategies, should be considered well into the postoperative period to maximize outcomes.

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