CHAPTER 26

The effects of surgery and anesthesia on memory and cognition

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Abstract: This chapter describes current findings from the research into postoperative cognitive dysfunction (POCD) following cardiac and non-cardiac surgery in older adults. The evidence suggests that a significant proportion of patients show POCD in the early weeks following surgery and anesthesia. Specific domains of cognition are affected, especially memory. Much less evidence supports the presence of POCD several months or years after surgery, suggesting that POCD may be transient. However, several methodological issues make it difficult to compare findings across studies. Increasing age is among the most consistently reported patient-related risk factor. Other factors more directly related to the surgery and anesthesia are likely to contribute to the pathogenesis of POCD, including inflammatory processes triggered by the surgical procedure. Animal studies have provided valuable findings otherwise not possible in human studies; these include a correlation between the inflammatory response in the hippocampus and the development of POCD in rodents.

Keywords: anesthesia; post-operative cognitive dysfunction; inflammatory cells; aging; neuropsychology

Introduction

A few decades ago, having a surgical procedure under anesthesia was a very dangerous event as the mortality and morbidity following surgery and anesthesia were very high. It was common to say that the patient did not tolerate anesthesia if perioperative mortality happened. Surgical procedures at that time had to be very short in order to survive anesthesia. Nowadays, the safety of anesthesia is so high that perioperative mortality due to anesthesia has almost disappeared, and when it happens, it makes front-page headlines. Though we no longer die from anesthesia, can anesthesia and the surgical procedure have short and long-term effects on cognitive function?

Postoperative cognitive dysfunction (POCD) was first described after cardiac surgery using cardiopulmonary bypass (CPB) technique. It is defined as a subtle dysfunction in one or more cognitive domains, of which memory is typically affected. Such cognitive changes should be distinguished from postoperative delirium defined as an acute deficit of attention and cognition with fluctuating levels of consciousness as well as disturbed sleep–wake cycles (for a review, see

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Contrary to POCD, postoperative delirium tends to occur mainly on the first days following surgery and is generally considered to be transient. On a subjective level, patients, and especially older adults, complain of forgetfulness and difficulty to concentrate after surgery and anesthesia. These can be illustrated by problems with remembering names of familiar people or what one has read in the morning paper. However, many older adults not having undergone surgery and anesthesia have similar complaints, adding to the difficulty of establishing the presence of POCD. This underlines the importance of the neuropsychological evaluation in detecting subtle cognitive changes after surgery and anesthesia. Family members also report that their relative is not the same as before the operation. Although such complaints are usually anecdotal, and studies assessing their incidence with more objective measures such as questionnaires are few (Møller et al., 1993; Dijkstra et al., 1999), they are compatible with current evidence suggesting the existence of POCD at a time which exceeds that for pharmacological action of anesthetic drugs on the brain.

How do we define POCD? Is it transient or permanent? Who are the people at risk? What are the causes of POCD? Can animal models help us understand the pathogenesis of POCD? We will try to answer these questions based on the current literature. Our focus will be on older adults given that much of the evidence suggesting POCD has been gathered in this population, and most surgeries occur later in life.

### Incidence of POCD

A large part of the evidence for POCD comes from older patients undergoing cardiac surgery (for a recent review, see Selnes and McKhann, 2005). In such cases, the incidence of POCD in the first 2 weeks post surgery ranges from 24 to 79%, and from 10 to 60%, 12 weeks postoperatively (Savageau et al., 1982b; Shaw et al., 1987; McKhann et al., 1997; Newman et al., 2001; Van Dijk et al., 2002). Factors specific to cardiac surgery, such as the use of CPB or heart–lung machine have been suggested as contributing heavily to such high incidences (e.g., Lee et al., 2003). CPB is associated with embolization, reduction of cerebral perfusion, and loss of the pulsatile component of flow which may contribute to cerebral injury (Moody et al., 1990; Anderson et al., 1999).

Although the type of surgery appears as a determinant factor, other factors are likely involved in POCD given that it is observed in older patients undergoing non-cardiac surgery (for a recent review, see Rasmussen, 2006; Newman et al., 2007). The incidence of POCD, independent of the cognitive domain, ranges from 16 to 59%, 7 days postoperatively, and from 10 to 34%, 12 weeks after surgery (Williams-Russo et al., 1995; Møller et al., 1998; Ancelin et al., 2001; Rasmussen et al., 2003; Monk and Phillips-Bute, 2004). In one of the largest multicenter studies to date (1218 patients), the International Study of Post-Operative Cognitive Dysfunction (ISPOCD1; Møller et al., 1998), cognitive status of older patients was examined the day before surgery, as well as 1 and 12 weeks after a major non-cardiac surgery (abdominal and orthopedic surgeries). Performance was compared to that of a control group (n = 176) not admitted to the hospital but assessed at similar time intervals as patients. By comparing changes in performance from baseline (preoperative assessment) to 1 week after surgery in control participants, the investigators were able to obtain an estimate for the learning effects on each test. Similar change scores were calculated for patients but the average learning effect obtained from the control group was subtracted from this score, which was then converted into a z-score for each test. Results showed that 25.8% of patients had POCD after 1 week relative to 3.4% in control participants. At 12 weeks after surgery, the investigators found POCD in 9.9% of patients compared with 2.8% in the control group. They also found a significant correlation between a decline in the activities of daily living and POCD at 12 weeks. However, no correlation was found between subjective complaints and POCD. Some evidence suggests that self-assessed measures of POCD tend to overestimate its incidence (Rödig et al., 1999; Johnson et al., 2002). Subjective feelings of cognitive...
dysfunction in some patients may reflect sudden awareness of age-related cognitive changes.

A key issue in the incidence of POCD in older adults is whether patients have pre-existing cognitive impairment. Such patients were excluded from the ISPOCD1 (Moller et al., 1998), resulting in a possible underestimation of POCD in the general population. An exception to this rule is the study by Ancelin et al. (2001). They examined the incidence of POCD after orthopedic surgery in patients over the age of 64 years, and deliberately chose not to use formal exclusion criteria so that a more representative sample of the general population would be assessed rather than a subpopulation of very healthy older adults. Pre-existing cognitive deficits in patients were assessed with an informant questionnaire (Détérioration Cognitive Observée or DéCO) that measures changes in cognitive performance over the past year (Ritchie and Fuhrer, 1995). From the 140 patients who completed baseline assessment, 15% were identified as being at risk of having early-stage dementia, a percentage that is similar to what is typically observed in the general elderly population (Canadian Study on Health and Aging or CSHA Working Group, 1994). The investigators also looked at which domains of cognition were more likely to be affected by surgery and anesthesia. Six cognitive domains were investigated preoperatively, as well as 1 and 12 weeks after surgery, using a comprehensive computerized cognitive battery (Ritchie et al., 1993). These included attention, short-term memory, episodic memory, implicit memory, visuo-spatial ability, and language. Decline in each domain was calculated by subtracting scores at 1 and 12 weeks from scores obtained preoperatively. A positive score indicated cognitive deterioration, and a negative score indicated improved performance. Results showed differences in susceptibility to POCD across cognitive domains. Depending on which aspect of cognition was measured, the incidence of POCD ranged from 0 to 25.4% after 1 week, and from 0 to 19.1% after 12 weeks. Cognitive domains most affected by surgery and anesthesia were episodic and implicit memory, visuo-spatial ability (measured by a reasoning task), and language (measured by verbal fluency). The same domains tended to be systematically affected at 1 and 12 weeks. Interestingly, no patient met criteria for dysfunction in attention tasks, and a significant deterioration in short-term memory tasks was found in less than 5% of patients after 12 weeks. Importantly, among the patients identified as being at risk of dementia, half of them withdrew before completing the neuropsychological evaluation at 12 weeks; withdrawal from study may be indicative of POCD, leading to underestimation of incidence in the general population. However, there was no control group so that POCD may have been underestimated by excluding patients that showed learning effects, albeit reduced. On the other hand, Ancelin and colleagues used a less stringent criterion than the one used in the ISPOCD1 (Moller et al., 1998). POCD was defined as a deterioration of more than 1 SD on at least one cognitive measure.

The issue of late POCD

Another important question regarding POCD is whether it is transient or permanent. Only a few studies using a longitudinal design have assessed the incidence of late POCD, that is, several months or years after surgery and anesthesia. Most of these studies concern cardiac surgery patients. The incidence of cognitive dysfunction in studies that extended follow-up to 6–12 months, ranges from 24 to 57% (Savageau et al., 1982a; Shaw et al., 1987; McKhann et al., 1997; Van Dijk et al., 2002). Newman et al. (2001) found that 42% of their patients showed decline when assessed 5 years after surgery. Selnes et al. (2001) found significant declines in visuoconstruction and psychomotor speed tests 5 years after cardiac surgery. Findings from these studies suggest a pattern defined by early decline, followed by improvement, and then later decline at 5 years. However, as with many studies, there was no control group allowing measurement of confounding factors such as aging and history of cardiovascular disease. In a more recent study, Selnes et al. (2003) compared cognitive changes in coronary artery bypass graft patients and a non-surgical control group with similar risk factor for coronary artery disease.
They found no evidence for POCD at 12 months after cardiac surgery (nor at 3 months postoperatively, similar to Jones et al., 1990, in non-cardiac patients). The investigators concluded that decline in the early postoperative period may be transient, and later cognitive changes may be associated with progressive cerebrovascular disease. However, in a retrospective study that included a total of 9170 patients, Lee et al. (2005) compared the emergence of Alzheimer’s disease following CPB surgery (n = 5216) and non-surgical percutaneous transluminal coronary angioplasty (n = 3954). After adjusting for age, length of hospitalization, comorbidity and number of procedures, results showed that CPB patients had an increased risk for emergence of Alzheimer’s disease compared to the angioplasty group.

In non-cardiac surgery patients, Williams-Russo et al. (1995) found that only 5% of patients showed a late (6 months postoperatively) deterioration in cognitive function. However, the study lacked a non-surgical control group that takes into account learning effects from repeated testing. Goldstein and Fogel (1993) found that immediate postoperative scores on the Mini Mental State Examination (MMSE; Folstein et al., 1975) predicted 10-month postoperative MMSE scores. Using a subgroup of older patients (n = 336) from the ISPOCD1 (Moller et al., 1998), Abildstrom et al. (2000) found an incidence of decline of 10.4% after 1 or 2 years postsurgery. A similar incidence of cognitive decline (10.6%) was observed in their smaller group of controls (n = 47), suggesting that early POCD is transient. However, Monk and Phillips-Bute (2004) reported an incidence of decline of 42%, 2 years after surgery, but they did not use a control group. Clearly, more studies are needed to determine whether surgery and anesthesia lead to more permanent cognitive changes. However, the evidence so far seems to indicate that POCD is transient.

Methodological issues in the study of POCD

A striking feature is the important variability in the incidences of POCD reported across studies. Many of the earlier studies were designed to compare factors such as surgical methods or type of anesthesia (general vs. regional) rather than establishing the incidence of POCD. This partly explains why some of these studies only used global scales to assess cognitive changes, such as the MMSE. The MMSE is a commonly used screening test for dementia and may be used to quantify dementia severity. However, studies have shown that the MMSE is insensitive to patients in the earlier stages of dementia, and ceiling effects have been reported in patients with mild cognitive impairment (MCI) (Tombaugh and Melaryne, 1992; Wind et al., 1997; Nasreddine et al., 2005). Similarly, the use of comprehensive batteries, such as the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997), has been found to be insensitive to the detection of subtle cognitive changes in cardiac surgery patients (Newman, 1995). Neuropsychological tests should be selected on the basis of their sensitivity to detect even small modifications in cognitive functioning (for a review, see Rasmussen et al., 2001). Test–retest validity is a crucial aspect to consider in the selection of cognitive tests, given that patients are assessed repeatedly over time. The use of validated parallel versions appears essential to minimize learning effects, although such effects cannot be completely eliminated; participants become familiar with the task structure and some of them may develop novel strategies to perform the task. Thus, studies assessing POCD should include a control group evaluated at a similar timetable as patients in order to measure learning effects. The absence or reduction of learning effects on repeated testing may be a strong indicator of subtle cognitive dysfunction.

The time at which cognitive changes are measured both before and after the operation varies greatly across studies. Many studies have assessed POCD within 1 week after the surgery while patients are still in the hospital. However, given the greater likelihood that potential confounds would also occur at that time, such as hypoactive state of delirium or severe pain, we contend that a minimum of 2 weeks might constitute better clinical practice for assessment of short-term POCD. Similarly, assessment of patients before surgery often occurs 1–2 days before surgery; factors associated with impending surgery such as stress and anxiety may negatively
affect test performance. In turn, postoperative improvement in scores may be due to stress reduction rather than recovery from POCD. Ideally, preoperative assessment should be performed a few weeks before surgery and a placebo group not receiving surgery and anesthesia, but hospitalized, should be included to allow measurement of effects associated with stress or pain, which are known to affect memory performance.

There is very little consensus in the literature on which criteria to use for defining POCD. How many cognitive tests should be used? What level of change constitutes a significant decline? In the earlier studies, cut-off scores on screening tests were often used to define POCD. The neuropsychological assessment should include different domains of cognition. However, for practical reason, the assessment should be limited in time and not go beyond 2h. In more recent studies, individual change scores comparing performance on different cognitive measures before and after surgery are typically used. Some investigators used a more lenient criterion such as deterioration in performance equal to or greater than 1 SD on at least one neuropsychological measure while others used more stringent criteria. In the ISPOCD1 (Moller et al., 1998), the investigators used a change score that was superior to 2 $z$-scores on at least two distinct cognitive measures or on a combined $z$-scores of all tests. Such criteria have the advantage of taking into consideration a decline in specific tests as well as a general deterioration in all tests.

**Patient-related factors**

POCD is likely to be multi determined and some of the factors contributing to its occurrence may be related to the patients themselves. Among patient-related risk factors, increasing age is consistently reported in the literature although most of these studies focused on older adults and did not encompass the entire age spectrum (Smith et al., 1986; Shaw et al., 1987; Moller et al., 1998; Ancelin et al., 2001; Johnson et al., 2002; Newman et al., 1994). Basic functions of organs are generally not compromised by normal aging, however, the aged brain is different from the younger brain in several important aspects, including size, distribution of neurotransmitters, and metabolic function. In turn, this leads to a diminished functional reserve which may reduce capacity to compensate for physiological stress such as surgery and anesthesia. In Ancelin et al.’s (2001) study, patients aged 75 years and older showed reduced learning effects on several cognitive tests relative to patients aged between 65 and 75 years old. Johnson et al. (2002) measured POCD in a large cohort of patients ($n = 508$) between the ages of 40 and 59 years. The investigators also included an age-matched control group not hospitalized ($n = 185$). The incidence of POCD in patients undergoing general surgery and anesthesia was 19.2%, 1 week after surgery, and dropped at 6.2%, 3 months postoperatively. In the control group, the incidence was 4.0 and 4.1%, respectively for the same time period. Thus, only the incidence 1 week postoperatively was statistically different between patients and controls, suggesting that structural and physiological changes that occur in the aging brain may be modulating the response to surgery and anesthesia. Education may also act as a protective factor against cognitive decline in older adults by increasing cognitive reserve in more educated individuals. Several studies have found that poor education constituted a significant risk factor for POCD (Moller et al., 1998; Ancelin et al., 2001).

Some studies have found a correlation between POCD and depression and/or anxiety (Ancelin et al., 2001; Newman et al., 2001). The patient’s operation could trigger symptoms of depression/anxiety which in turn may affect performance on neuropsychological test, and especially those assessing memory. It is thus important to measure psychological status of patients before surgery. Ancelin et al. (2001) found that 21% of participants meet criteria for major depressive episode before surgery and anesthesia compared with 14% in the general elderly population (Fuhrer et al., 1992). These patients showed decreased performance in episodic memory. However, the investigators found that depression status was not modified by the surgery and anesthesia.

Pre-existing cognitive impairment might constitute an important risk factor for POCD (Dijkstra...
et al., 1999; Rankin et al., 2003). Some researchers have suggested that POCD reflects a preoperative dementia unmasked by the surgery. However, as we have already mentioned, most studies have used screening tests for dementia that are not sensitive enough to identify people with pre-existing MCI or early dementia. MCI is seen as a transitional state between the cognition of normal aging and mild dementia. In such cases, there is a memory complaint, and performance on objective memory test is at least 1.5 SD below that of an age-matched control group. However, the person remains functional and does not meet formal criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994). Importantly, people with MCI have an increased risk of developing a dementia, although a sizeable portion remain stable or even improve their performance on subsequent testing (Palmer et al., 2002). Because of limited cognitive reserve to cope with the physiological stress of surgery and anesthesia, individuals with MCI may be those more susceptible to POCD; they should be identified preoperatively using a comprehensive evaluation that includes more sensitive screening tests such as the Montreal Cognitive Assessment (Nasreddine et al., 2005).

The role of surgery and anesthesia in POCD

There are several risk factors more directly related to surgery and anesthesia that may be involved in the pathogenesis of POCD (Rolfson et al., 1999). Surgery is associated with the stress response, with increasing secretion of cortisol and catecholamines. Persistently high levels of stress may inhibit memory and interfere with hippocampal function. Surgery alone also activates specific homeostatic responses, triggering immune mechanisms and the inflammatory cascade through the release of various inflammatory mediators (Westaby et al., 2001). Intraoperative hypotension, hypoxia, embolization, medications, and postoperative infections have also been described as risk factors for POCD. Because the incidence of POCD does not seem to be influenced by the type of anesthesia (i.e., general vs. regional), attention has begun to focus on the role of the surgical intervention itself in the genesis of this condition. Postoperative pain is a possible etiological factor in POCD mechanisms. Epidural analgesia with local anesthetics and/or opioids has been found to be probably better than parenteral opioids for the control of postoperative pain and the prevention of early POCD (Rasmussen and Moller, 2000; Bekker and Weeks, 2003; Cohendy et al., 2005). Furthermore, those who received postoperative analgesia orally were at least risk of experiencing POCD compared with parenteral analgesia (Bekker and Weeks, 2003; Wang et al., 2007).

Depression of central nervous system function is a part of anesthesia. This condition is expected to be perfectly reversible and transient, but several complications may arise, some of them causing serious disability. General anesthesia affects brain function at all levels, including neuronal membranes, receptors, ion channels, neurotransmitters, cerebral blood flow, and metabolism. Impairment of cognitive and psychomotor performance in the days following general anesthesia is common and typically attributed to incomplete drug clearance.

The possibility that general anesthesia contributes to cognitive deterioration has not been tested directly; partly because clinical studies have not controlled for the anesthetics used and cannot differentiate between the effects of illness, hospitalization, surgery, and anesthesia. In that respect, animal models may provide some insights into potential mechanisms by which anesthesia may lead to POCD as will be discussed below.

Inflammation and POCD pathogenesis

We and other investigators believe that inflammatory processes play a key role in the pathogenesis of POCD (Gao et al., 2005; Mathew et al., 2007). The cells involved in brain inflammation are mixtures of structural and inflammatory cells. In the brain, supporting cells of the glial family, known as microglial cells, act as scavengers, in much the same fashion as macrophages (Von Bernhardi and Ramirez, 2001; Guo et al., 2007). They engulf and eliminate dead neurons that have been damaged by injury or illness. The presence of activated microglial cells is an indicator of chronic
inflammation. Astrocytes and/or microglia secrete most cytokines in the brain, such as interleukin(IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), which circulate in the blood and communicate with neurons. As it is now well recognized, inflammatory responses develop within the brain under a variety of pathological conditions. Cytokines are hardly detectable in the central nervous system under physiological conditions, but they become rapidly upregulated by pathological events, like ischemia (Minamikawa et al., 1992; Wang and McCubrey, 1997), excitotoxicity (Minami et al., 1991), lipopolysaccharide (LPS) injection (Gabellec et al., 1995), or viral infection (Marquette et al., 1996). Glial activation and the consequent release of proinflammatory cytokines within the hippocampus interfere with cognitive function as evidenced by abnormal memory and learning in the intact organism and/or inability to develop long-term potentiation in hippocampal slice preparation (Von Bernhardi and Ramirez, 2001). There is evidence that under certain conditions, neurons can also produce cytokines (Guo et al., 2007). Cerebral endothelial cells are actively engaged in processes of microvascular stasis as well as leukocyte infiltration by evoking a plethora of bioactive inflammatory cytokines and chemokines (Matsumura and Kobayashi, 2004).

It has been suggested that proinflammatory cytokines could play a role in the development of cognitive decline that may acutely follow surgery. The peripheral IL-6 response to surgical injury has extended our understanding of the role of proinflammatory cytokine response to surgery. Within 2 h of skin incision, IL-6 levels increase, peak between 4 and 12 h, and remain elevated for up to 3 days postoperatively (Biffl et al., 1996). Extent of surgical trauma is an important factor; there was a greater degree of IL-6 elevation after abdominal aortic and colorectal procedures than after hip replacement despite similar surgical procedure times. Further, four separate studies illustrate that the increment in IL-6 is less after laparoscopic versus open cholecystectomy, despite similar surgical times. The IL-6 response is not modified by anesthetic regimen but is decreased by use of anti-inflammatory analgesic agents. Cytokines originating from the periphery, such as IL-1β, can act on the central nervous system in a wide variety of ways, including increases in slow-wave sleep, modulation of long-term potentiation, changes in monoamine release and turnover, and more global effects on mood and cognition (Von Bernhardi and Ramirez, 2001; Gao et al., 2005; Mathew et al., 2007). Cytokines exert effects within the central nervous system through both direct and indirect means. Both IL-1β and TNF-α have been shown to gain direct entry into the central nervous system through the relatively permeable blood–brain barrier in the periventricular regions. Further, IL-1β can also directly bind to its cognate receptors on the endothelial cells within the brain microvasculature where these can elaborate a central inflammatory response. Indirectly, cytokines can induce changes within the central nervous system through vagal afferent nerves. In many studies, either LPS or IL-1β, when administered peripherally, induced brainstem and hippocampal IL-1β production and central nervous system expression of IL-1β, IL-6, and TNF-α, all of which could be abolished by vagotomy (Hansen et al., 2000; Chauvet et al., 2001).

Several studies also suggest that the marked and sustained expression of inflammation-related enzymes such as cyclooxygenase-2 (COX-2) plays an important role in secondary events that amplify cerebral injury after ischemia. The contribution of COX-2 to peripheral inflammation is well documented, but little is known about its involvement in brain inflammation (Minghetti, 2004). It has been reported that COX-2 is significantly induced in astrocyte and microglial cultures by radiation injury (Kyrkanides et al., 2002). It has been shown that COX-2 inhibitor protects the brain against amyloid beta-induced memory disturbances in mice (Giovannini et al., 2003; Cakala et al., 2007).

Matrix metalloproteinases (MMPs) have been implicated in early breakdown of the blood–brain barrier in neuroinflammatory disease. MMPs comprise a group of proteolytic enzymes that act as mediators of brain injury in a wide variety of disease processes, including multiple sclerosis, Alzheimer’s disease (AD), stroke, tumor invasion, and other inflammatory brain disorders (Anthony et al., 1997; Kolb et al., 1998; Romanic et al., 1998; Yong et al., 1998). Interruption of the MMPs
proteolytic cascade may be a possible therapeutic approach to preventing the secondary progression of damage after brain injury.

Considerable evidence gained over the past decade supports the conclusion that neuroinflammation is associated with AD pathology (Cacquevel et al., 2004; Yao et al., 2004; Tuppo and Arias, 2005). Inflammatory brain cells, such as microglia and astrocytes, as well as cytokines, including IL-6, TNF-α, and transforming growth factor-beta, have clearly been implicated in this inflammatory process (Meeuwsen et al., 2003). Many varieties of chemokines, such as IL-8, monocyte chemoattractant protein, and RANTES, are also expressed in brain tissue from humans in conjunction with dementia. It has been shown that IL-8 is a key mediator of neuroinflammation in severe traumatic brain injuries, and is constitutively expressed in the brain (Kushi et al., 2003).

These inflammatory mediators should be widely investigated and considered as targets in the inflammatory process associated with POCD, and especially after CPB, given that the incidence of AD has been linked to cardiac surgery. Sparks et al. (2000) found evidence of AD-like lesions in the brains of non-demented individuals with mitral valve prolapse. They and others suggested that cognitive dysfunction occurring after CPB with coronary artery grafting or valve repair/replacement is a functional sequel of AD-like neuropathology. In cardiac surgery, non-pulsatile flow generated by the CPB machine could lower shear stress on endothelial cells, reduce nitric oxide (NO) release, and induce non-homogenous blood flow distribution in ischemic areas presenting reperfusion injury after weaning from CPB. Deficient NO production affects the inflammatory cascade, allowing the vascular adhesion of inflammatory cells primed by contact with the extracorporeal circuit. This initial deficit in endothelial NO synthase is particularly marked in older patients (Wan et al., 1997; Maffei et al., 2004).

As suggested by some researchers, genetics may play a role in the pathogenesis of POCD. This is indicated by the presence of the apolipoprotein ε4 (APO-ε4) allele in a subgroup of POCD patients. Previous data have confirmed the association between AD and APO-ε4, and support the hypothesis that the APO-ε4 allele either confers genetic susceptibility to AD or may be in linkage disequilibrium with another susceptibility locus (Abildstrom et al., 2004; Hsiung et al., 2004). Ethnic variability in the allelic frequency of APO-ε4 in the elderly warrants further investigation.

Animal models and POCD

In the past decade, although the mechanisms for POCD remain unclear, progress has been made with the help of animal models. The role of cytokine-mediated inflammation within the central nervous system in the development of cognitive dysfunction has been studied in rodents. To elucidate the effect of surgery and anesthesia on learning and memory, Wan et al. (2007) used the Y-maze test to evaluate spatial learning and memory in rodents. They found a correlation between the inflammatory response in the hippocampus and the development of POCD. They also found that after surgery (splenectomy), rats displayed impaired memory that was associated with glial activation and proinflammatory cytokine expression in the hippocampus.

Neurons in the hippocampus of splenectomized rats increased expression of both B-cell CLL/lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax). However, the ratio of Bcl-2:Bax was decreased after surgery, suggesting that neurons in the hippocampus are inclined toward apoptosis. So the cognitive dysfunction is not necessarily associated with the presence of actual cell death in hippocampus; rather, there may be abnormal interaction between neurons and glial cells in the hippocampus (Jarrard, 1995; Tanaka et al., 2006).

IL-1β has consistently been detected in central nervous system after injury to the brain or peripheral immune activation. For example, IL-1β bioactivity and immunoreactivity and mRNA have all been found to be present in brain after peripheral administration of LPS in the rat (Buttini and Boddeke, 1995). It has been demonstrated that IL-1β may lead to some “sickness behavior” which reduces food and water intake, decreases exploration, decreases social interactions, and somnogenesis (Dantzer et al., 1998),
and may produce alterations in cognitive processes, including learning and memory. Nathan et al. (2005) have shown that systematic LPS or IL-1β may affect performance in various learning tasks in mice. Specifically, LPS stimulates Toll-like receptors and induces expression of proinflammatory cytokines IL-1β, IL-6, and TNF-α, primarily from macrophages (Gibertini et al., 1995; Dantzer et al., 1998; Dantzer, 2001). Although these cytokines may exert neurobiological effects, the strongest case has been made for IL-1β (Gibertini et al., 1995; Gibertini, 1996; Bianchi et al., 1998; Dantzer et al., 1998). Furthermore, many of the physiological and behavioral effects associated with LPS administration can be removed with the administration of IL-1 receptor antagonist. In our laboratory we are currently injecting LPS intraperitoneally to induce systemic inflammation in rats, and then testing their spatial memory using the Morris water maze, a hippocampus-dependent task to examine brain inflammation by molecular biology technique to test for the level of proinflammatory cytokines.

Oitz et al. (1993) compared the influences of two proinflammatory cytokines on Morris water maze learning by infusing IL-1β or IL-6 intracerebroventricularly either 1 h before or immediately prior to the first of 2 days of testing. Results showed that animals treated with IL-1β 1 h prior to testing showed significantly longer latencies and distances on the first trial of days compared to vehicle controls and animals receiving IL-1β immediately before testing. IL-6-treated animals did not differ from controls.

In addition, peripheral inflammatory responses to immune activating agents, as well as brain cytokine responses to stimulation are altered with normal aging. For example, Saito et al. (2003) reported that the levels of IL-6 in blood produced by cecal ligation and puncture, as well as by LPS, were elevated more in aged than in young mice. Within the brain, IL-1β and TNF-α responses to peripheral LPS administration appear to increase with aging (Terao et al., 2002; Xie et al., 2003). Barrientos et al. (2006) report that a peripheral injection of Escherichia coli produces both anterograde and retrograde amnesia in 24 month old, but not 3 month old rats for memories that depend on the hippocampus, which is memory for context, contextual fear, and place learning. And it produced a masked increased in IL-1β levels in the hippocampus, but not in parietal cortex or serum. These findings manifested that age is a vulnerability factor that increases the likelihood that an immune challenge will produce a cognitive impairment. It is possible that this cognitive vulnerability is mediated by age-related changes in the glial environment that results in an exaggerated brain pro-inflammatory response to infection.

Some studies have previously demonstrated lasting impairment on a spatial memory task in rats after a single-2 h isoflurane (ISO)-nitrous oxide (N₂O) anesthetic, where rats were trained on a radial arm maze for 2 months before anesthesia and then tested for 8 weeks beginning 24 h after anesthesia. The ability of aged rats to improve their maze performance was worse than that of identically treated, unanesthetized control rats (Culley et al., 2003, 2004b). These results showed that general anesthesia affects performance for longer than would be expected based on the pharmacology of the drugs and suggested that aged rats might be more susceptible to such disruption. This radial arm maze task tests spatial working memory, assesses the integrity of the frontal cortex, entorhinal cortex, and hippocampus (Decker and Gallagher, 1987; Baxter et al., 1997), and can detect subtle differences in learning caused by aging, sedatives and anesthetics (Decker and Gallagher, 1987; Luine and Rodriguez, 1994; Borde et al., 1998; Culley et al., 2003, 2004b). Culley et al. (2004a) also demonstrated that general anesthesia produces long-lasting impairment in the ability of rats to acquire and perform a spatial memory task and the aged rats’ performance on a spatial memory task remains impaired for at least 2 weeks after general anesthesia. These results cannot be explained by the pharmacokinetics of the drugs involved.

**Conclusion**

With increasing longevity of the general population, more and more surgical interventions will be performed on older adults. As older patients must be informed about the risks associated with their
surgery, understanding the effects of surgery and anesthesia on memory and cognition has become a key issue. There is evidence for short-term POCD affecting the memory and cognition of older adults following cardiac surgery and anesthesia, and to a lesser extent that of patients having undergone non-cardiac surgery. More research is needed to determine whether POCD is permanent but the evidence so far suggests that cognitive dysfunction is reversible. Importantly, however, this research area suffers from a large number of methodological difficulties. These include the differences in surgery and participants, the diversity, number, and range of neuropsychological tests used with varying sensitivity to change and learning, and the variety of definitions used to classify individuals as having POCD. These differences make it difficult to compare results across studies. To overcome some of the methodological issues, it would be useful to recognize the arbitrariness of any definition of POCD and to consider whether it is timely to establish a consensus that specifies a limited number of tests to be used in all studies and the value of pooling data across studies to increase power in secondary analyses.

Patient-related risk factors, such as increased age, have been identified in several studies as well as factors more directly related to surgery and anesthesia. Inflammatory processes appear to play a key role in the pathogenesis of POCD. Biochemical markers and new sensitive methods are needed to detect early POCD after cardiac and non-cardiac surgery. Stable NO products represent a potential biochemical predictor of POCD. It has been demonstrated that preoperative and postoperative plasma concentrations of stable NO products (nitrate/nitrite) are associated with the early detection of POCD after cardiac surgery. Animal models provide a way to test the role of cytokine-mediated inflammation within the central nervous system in POCD. Future research should also focus on prevention of POCD. It is conceivable that therapeutic interventions aimed at attenuating the inflammatory response might result in better outcomes. A prevention program that prepares patients before surgery and anesthesia might also help alleviate complaints regarding memory and cognition and reduce stress. POCD diminishes the quality of the patient’s life and adds costs to hospitalization and out-of-hospital care. Research must be geared towards understanding POCD in older adults and identifying those at risk. Clearly, a multidisciplinary approach appears as the most fruitful means for study and management of POCD.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>APO-ε4</td>
<td>Apolipoprotein ε4</td>
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<tr>
<td>Bax</td>
<td>Bcl2-associated X protein</td>
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<td>Bcl-2</td>
<td>B-cell CLL/lymphoma 2</td>
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<td>COX-2</td>
<td>Cyclooxygenase-2</td>
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<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
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<tr>
<td>CSHA</td>
<td>Canadian Study on Health and Aging</td>
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<tr>
<td>IL-1β</td>
<td>Interleukin-1β</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>IL-8</td>
<td>Interleukin-8</td>
</tr>
<tr>
<td>ISO</td>
<td>Isoflurane</td>
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<tr>
<td>ISPOCD1</td>
<td>International Study of Postoperative Cognitive Dysfunction</td>
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<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
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<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
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<tr>
<td>MMPs</td>
<td>Matrix metalloproteinases</td>
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<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
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<tr>
<td>N2O</td>
<td>Nitrous oxide</td>
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<tr>
<td>NOCD</td>
<td>Postoperative cognitive dysfunction</td>
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<tr>
<td>RANTES</td>
<td>Regulated upon activation, normal T-cell expressed and secreted</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor-α</td>
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<tr>
<td>WAIS</td>
<td>Wechsler Adult Intelligence Scale</td>
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</table>

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**References**


