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Postoperative Cognitive Dysfunction (POCD)

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A few decades ago, surgical procedures performed under anesthesia were considered very dangerous events due to the very high mortality and morbidity that followed. Today, perioperative mortality due to anesthesia has almost disappeared and, when it does occur, it is front-page news. Although we may not die from anesthesia anymore, the question remains whether there could be short- and long-term effects from both anesthesia and surgical procedures on organ function, particularly, on neurological function. Certainly, brain dysfunction following cardiac surgery was rapidly recognized after the introduction of cardiopulmonary bypass (CPB) techniques. Although prolonged postoperative cognitive dysfunction (POCD) is reported to occur frequently after cardiac surgery, it is rarely assessed in routine clinical practice. The cerebral consequences of CPB have been measured clinically, but the resulting molecular and pathological events within the brain are only starting to be investigated. This issue of *Anesthesiology Rounds* examines the role of surgery, anesthesia, stress response, and inflammation in the pathogenesis of POCD.

It is commonly accepted that, following cardiac surgery, 3 types of neurological complications may occur:

- Some patients suffer from a stroke due to the obstruction of a cerebral vessel by an embolus of arteriosclerotic plaque arising from the aortic root, or vegetative or fibrotic tissue emanating from a diseased valve or a platelet clot.
- Other patients suffer from acute major cognitive dysfunction (eg, delirium), but this usually improves after a few days. Delirium is characterized by prominent disturbances in attention and a reduced clarity in awareness of the environment. It has an acute onset, develops within hours to days, and tends to fluctuate during the course of the day. Postoperative delirium tends to be observed between postoperative days 1 and 3, and usually resolves within hours to days, although symptoms may persist for weeks to months.[1]
- Finally, some patients suffer from long-term irreversible and progressive cognitive dysfunction that might lead to more severe diseases such as Alzheimer's disease (AD) and vascular dementia.

Postoperative cognitive dysfunction (POCD) is an impairment of recent memory, concentration, language comprehension, and social integration. It is described as a deterioration of cognition associated with surgery. Cognition is defined as the mental processing of perception, memory, and information that allows an individual to acquire knowledge, solve problems, and plan for the future. It comprises functions required for everyday living and should not be confused with intelligence.[2] Compared with delirium, where pathognomonic behavior must be detected, the characterization and determination of the severity of POCD depends on valid assessments of preoperative and postoperative cognitive functions. A neuropsychological examination measures the information processing abilities of the brain through a battery of tests.[3] As a result, it is often important to ask whether POCD actually exists or if it is a consequence of inadequate or misinterpreted neuropsychological tests. Some researchers have suggested that POCD reflects preoperative dementia that is unmasked by surgery. Although POCD is most frequently found after cardiac surgery, the prevalence of POCD after noncardiac surgery in older patients is now well-accepted and also very significant (25% at 1 week, 10% at 3 months after surgery).[4] Nevertheless, the reported incidence varies and variations between institutions and studies may be due to:

- nonstandardization of the tests used in the diagnosis of POCD
- a lack of well-established control groups
- timing of the testing
- differences in the levels of significance accepted between studies
- a "learning effect" following repeated applications of the test.

Many studies have failed to use a control group to allow for practice effects. Others have adopted tests with low sensitivity or with floor and ceiling effects, or tests without validated parallel versions. An example of a test that has been commonly misused in this situation is the Mini-Mental State Examination (MMSE) that was designed as a screening tool in the clinical examination of patients with dementia. Thus far, there is no agreement about which tests are significant and useful for patients.

In many publications, the diagnosis of POCD was made immediately after, or 1 or 2 days following surgery, clearly, at a time when patients were still under the influence of anesthetic or analgesic medication. The earliest test point should be about 2 weeks after surgery, when the central acting analgesics are no longer required and any active metabolites have been eliminated.

Anesthetic drugs clearly influence cognition, at least temporarily, since the patient is made unconscious, unaware, and amnesic for the duration of the surgery and briefly thereafter. The target organ for anesthetic drugs is the brain. For many years, it was assumed that drug effects did not outlast their pharmacological action and that the target organ was restored to its previous state once the agent was eliminated. There is growing evidence, however, that long-term and, possibly, permanent neuronal and neurological changes can follow the administration of anesthetic drugs. Despite the fact that patients wake up more rapidly after the use of new volatile and intravenous anesthetics with shorter duration, there is still the question: Can these anesthesia medications also have long-term effects on brain function?

THE EFFECTS OF ANESTHETIC DRUGS ON POCD

In humans, it is difficult to separate the effect of anesthetic drugs from the effects of disease and the diagnostic or the therapeutic procedures, since patients are not given anesthesia without surgery. Animal studies and *in vitro* experiments have revealed direct long-lasting effects on neurological function and neuronal cells from anesthetic drugs.

The cholinergic system is one of the most important modulatory neurotransmitter systems in the brain. It controls activities related to selective attention that are essential components of conscious awareness. Acetylcholine (Ach) regulates high-cognitive functions such as memory, learning, dendrite arborization, and neuronal development and differentiation. The sensitivity of the cholinergic receptors (Rs) to anesthetic drugs plays a pivotal role in determining the various stages of narcosis (amnesia, inattentiveness, hypnosis).[5] Most drugs administered during anesthesia interact with both nicotinic (n) and muscarinic (m) receptors and volatile anesthetics bind to both the "n" and "m" receptors. Barbiturates are strong competitive antagonists of the mAChRs and propofol acts on the mAChRs and nAChRs at high concentrations; morphine and fentanyl may block mAChRs and nAChRs.[6]

Ketamine is an N-methyl d-aspartate (NMDA) glutamate-receptor blocker that can be used during anesthesia as anesthetic and as a pain medication in the postoperative period, or in chronic pain management. It has a well-known acute effect on cognitive function; however, the long-term effect of ketamine on brain function is a matter of debate.

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. Therefore, animal models may provide some insights into potential mechanisms through which anesthesia may lead to POCD.

Genetic evidence, confirmed by neuropathological and biochemical studies, indicates that excessive beta-amyloid protein generated from amyloidogenic processing of the beta-amyloid precursor protein plays a fundamental role in the neuropathogenesis of AD. As a result, more studies to assess the potential relationship between anesthesia/surgery and AD dementia are urgently needed.

Changes in tau (a microtubule-associated protein) phosphorylation during anesthesia play a significant role in the development of POCD and AD. Recent studies in animal models suggest that changes in tau phosphorylation during anesthesia are not a result of anesthesia *per se*, but a consequence of anesthesia-induced hypothermia, leading to the inhibition of phosphatase activity and subsequent hyperphosphorylation of tau. These findings call for careful monitoring of core temperature during anesthesia in laboratory animals to avoid artifactual elevation of protein phosphorylation.

The use of CPB appears to induce transcription of pro- and anti-apoptotic genes in the rat brain. Elucidating the molecular biological sequelae of CPB may aid in understanding the pathophysiology of cardiac surgery-associated cerebral injury and may be useful in identifying potential therapeutic targets for pharmacologic neuroprotection.

RISK FACTORS FOR POCD

Neonatal and old age are critical periods for POCD development, since brain reserve is diminished. There are several risk factors directly related to surgery and anesthesia that may be involved in the pathogenesis of POCD. Surgery is associated with the stress response and with increased secretions of cortisol and catecholamines. Persistently high levels of stress may inhibit memory and interfere with hippocampal function. Surgery alone activates specific homeostatic responses, triggering immune mechanisms and the inflammatory cascade through the release of various inflammatory mediators. Intraoperative hypotension, hypoxia, embolization, medications, and postoperative infections have all been described as risk factors for POCD. Because the incidence of POCD appears to be influenced only partially by the type of anesthesia (ie*,* 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 for POCD. Epidural analgesia with local anesthetics and/or opioids may be better than parenteral opioids for the control of postoperative pain and the prevention of early POCD. Furthermore, patients who are prescribed postoperative oral analgesics experience less POCD compared with those receiving parenteral medication.[7]

In general, stress, surgery, anesthesia, and inflammation are considered insult factors for the brain and the question is: What can we do to decrease this insult or to increase brain reserve?

INFLAMMATION AND POCD PATHOGENESIS

Our group at the Centre Hospitalier de l'Université de Montréal (CHUM), along with other investigators, believes that inflammatory processes play a key role in the pathogenesis of POCD.[8] The cells involved in brain inflammation are a mix of structural and inflammatory cells. In the brain, supporting cells of the glial family (microglial cells) act as scavengers in much the same fashion as macrophages. The presence of activated microglial cells is an indicator of chronic inflammation. Astrocytes and/or microglia secrete most of the cytokines in the brain, such as interleukin-1β (IL-1β), IL-6, and tumour necrosis factor-α (TNFα), which circulate in the blood and communicate with neurons.

Inflammatory responses develop within the brain under a variety of pathological conditions. Cytokines are hardly detectable in the central nervous system (CNS) under physiological conditions, but they become rapidly upregulated by pathological events (eg, ischemia, excitotoxicity, lipopolysaccharide injection, and bacterial or viral infection). Glial activation and the consequent release of proinflammatory cytokines within the hippocampus interfere with cognitive function, as evidenced by abnormal memory and learning and/or the inability to develop long-term potentiation in hippocampal slice preparation. There is evidence that under certain conditions, neurons also produce cytokines. Cerebral endothelial cells can actively engage in processes of microvascular stasis and leukocyte infiltration by evoking a plethora of bio-active inflammatory cytokines and chemokines.[9]

Cytokines originating from the periphery, such as IL-1β, can act on the CNS in a wide variety of ways, provoking increases in slow-wave sleep, modulation of long-term potentiation, changes in monoamine release and turnover, and more global effects on mood and cognition. Cytokines exert effects within the CNS through both direct and indirect means. It has been demonstrated that both IL-1β and TNFα gain direct entry into the CNS through the relatively permeable blood-brain barrier in the periventricular regions. Further, IL-1β can also directly bind to its cognate receptors on endothelial cells within the brain microvasculature, thus causing a central inflammatory response. Indirectly, cytokines can induce changes within the CNS through vagal afferent nerves.

Several studies also suggest that the marked and sustained expression of inflammation-related enzymes such as cyclooxygenase-2 (COX-2) play 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. Reports suggest that COX-2 is significantly induced in astrocyte and microglial cultures by radiation injury and it has been demonstrated that COX-2 inhibitors protect the brain against amyloid beta-induced memory disturbances in mice.[10]

Matrix metalloproteinases (MMPs) have been implicated in the early breakdown of the blood-brain barrier in neuroinflammatory diseases. The MMPs comprise a group of proteolytic enzymes that act as mediators of brain injury in a wide variety of disease processes, including multiple sclerosis, AD, strokes, tumour invasion, and other inflammatory brain disorders.[11] Interruption of the MMP proteolytic cascade may be a therapeutic approach to prevent secondary progression of damage after brain injury.

Considerable evidence gained over the past decade supports the conclusion that neuroinflammation is associated with AD pathology.[12] A variety of chemokines are also expressed in human brain tissues in conjunction with dementia. It has been demonstrated that IL-8 is a key mediator of neuroinflammation in severe traumatic brain injuries and is constitutively expressed in the brain.

These inflammatory mediators should be investigated and considered as targets in the inflammatory processes associated with POCD, especially after CPB use. Sparks et al found evidence of AD-like lesions in the brains of nondemented individuals with mitral valve prolapse.[13] They suggest that POCD occurring after CPB with coronary artery grafting or valve repair/replacement is a functional sequela of AD-like neuropathology. In cardiac surgery, nonpulsatile flow generated by CPB could lower shear stress on endothelial cells, reduce nitric oxide (NO) release, and induce nonhomogeneous blood flow distribution in ischemic areas, causing reperfusion injury after weaning from CPB. Deficient NO production affects the inflammatory cascade, allowing vascular adhesion of inflammatory cells primed by contact with the extracorporeal circuit.[14]

Some researchers have suggested that 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 may somehow confer genetic susceptibility to AD.[15]

POCD AND ANIMAL MODELS

Some researchers have investigated the important role of cytokine-mediated inflammation within the CNS in a rodent model of cognitive dysfunction development. To elucidate the effect of surgery on learning and memory, Wan et al conducted the Y-maze test, which is used widely to evaluate spatial learning and memory in rodents. They demonstrated the correlation between an inflammatory response in the hippocampus and the development of POCD and found that, after surgery (splenectomy), rats displayed an impaired memory that was associated with glial activation and proinflammatory cytokine expression in the hippocampus.[16] Neurons in the hippocampus of splenectomized rats increased the expression of anti- and proapoptotic substances such that their ratio favoured apoptosis. Therefore, POCD could be the result of abnormal interactions between neurons and glial cells in the hippocampus.

Interleukin-1β is a cytokine produced by a number of peripheral cell types and it plays many roles in immune and inflammatory responses. For example, it has been consistently detected in the CNS after injury to the brain or with peripheral immune activation. Nathan et al demonstrated that systemic lipopolysaccharide (LPS) or IL-1β may affect performance in various learning tasks in mice, including the Morris water maze (MWM). Specifically, LPS stimulates Toll-like receptors and induces the expression of pro-inflammatory cytokines IL-1β, IL-6, and TNFα, primarily from macrophages.[17]

The MWM, a hippocampus-dependent task, is a useful tool for investigating the behavioral effects of immunological stimuli. Oitzl et al compared the influence of two proinflammatory cytokines on MWM learning by infusing IL-1β or IL-6 intracerebroventricularly, either 1-hour (h) before or immediately prior to testing. Animals treated with IL-1β 1-h prior to testing had significantly longer latencies and distances in spatial navigation compared with controls and animals who received IL-1β immediately before testing. The IL-6-treated animals did not differ from controls.[18]

POCD AND AGING

Peripheral inflammatory responses to immune-activating agents, as well as brain cytokine responses to stimulation, are altered with normal aging. Saito et al reported that blood levels of IL-6 produced by cecal ligation and puncture, as well as by LPS, were more elevated in aged than in young mice.[19] Within the brain, IL-1β and TNFα responses to peripheral LPS administration appear to increase with aging. It has also been demonstrated that a peripheral injection of *Escherichia coli* produces both anterograde and retrograde amnesia in 24-month-old, but not 3-month-old rats. These findings suggest that age is a vulnerability factor, increasing the likelihood for an immune challenge to produce a cognitive impairment. This cognitive vulnerability may be mediated by age-related changes in the glial environment that result in an exaggerated brain proinflammatory response to infection.

Some studies have demonstrated lasting impairment on spatial memory tasks in rats after a single, 2-h isoflurane (ISO)-nitrous oxide (N_2O) anesthetic in a radial arm maze (RAM).[20] The RAM task test assesses the integrity of the frontal cortex, entorhinal cortex, and hippocampus, and can detect subtle differences in learning caused by aging, sedatives, and anesthetics.

CONCLUSION AND FUTURE DIRECTIONS

Many questions remain unanswered, such as:

Why do we have POCD following surgery? What is its real prevalence? What is the role of surgery, of anesthesia and analgesia, or of the disease itself in POCD? Do the different medications and techniques used during anesthesia and in treating postoperative pain have the same effects on cognitive function? Who is at risk for POCD? How should it be diagnosed? Can we prevent or treat it?

The pathophysiology of POCD is poorly understood and multi-component interventions targeting well-documented risk factors are needed. A better understanding of the time course and consequences of neuroinflammation may help reduce its harmful effects.

Since POCD is more prevalent in patients with diminished brain reserve, such as neonates, the elderly, alcoholics, and patients with previous cognitive impairment, the therapeutic goal could be to increase brain reserves before surgery, while decreasing brain insult in the perioperative period. Different hippocampus enhancement techniques such as physical exercise, intellectual exercise, nutrition intervention, and medications have demonstrated efficiency in animals. Reducing the inflammatory response by physical conditioning, specific nutrients, or medications could be one of the means to decrease brain insult and cognitive impairment; these elements could be part of perioperative preparation for surgery.

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References

1. Gilman S. Cerebral disorders after open-heart operations. *N Engl J Med* 1965;272:489-498.
2. Rasmussen LS. Defining postoperative cognitive dysfunction. *Eur J Anaesthesiol* 1998;15(6):761-764.
3. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*, 4th edition. New York: Oxford University Press; 2004.
4. Moller JT. Cerebral dysfunction after anesthesia. *Acta Anaesthesiol Scand Suppl* 1997;110:13-16.
5. Yamashita M, Mori T, Nagata K, Yeh JZ, Narahashi T. Isoflurane modulation of neuronal nicotinic acetylcholine receptors expressed in human embryonic kidney cells. *Anesthesiology* 2005;102(1):76-84.
6. Fodale V, Santamaria LB. Drugs of anesthesia, central nicotinic receptors and post-operative cognitive dysfunction. *Acta Anaesthesiol Scand* 2003;47(9):1180.
7. Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM. The effects of postoperative pain and its management on postoperative cognitive dysfunction. *Am J Geriatr Psychiatry* 2007;15(1):50-59.
8. Gao L, Taha R, Gauvin D, Othmen LB, Wang Y, Blaise G. Postoperative cognitive dysfunction after cardiac surgery. *Chest* 2005;128(5):3664-3670.
9. Matsumura K, Kobayashi S. Signaling the brain in inflammation: the role of endothelial cells. *Front Biosci* 2004;9: 2819-2826.
10. Cakala M, Malik AR, Strosznajder JB. Inhibitor of cyclooxygenase-2 protects against amyloid beta peptide-evoked memory impairment in mice. *Pharmacol Rep* 2007;59(2): 164-172.
11. Anthony DC, Ferguson B, Matyzak MK, et al. Differential matrix metalloproteinase expression in cases of multiple sclerosis and stroke. *Neuropathol Appl Neurobiol* 1997;23: 406-415.
12. Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. *Int J Biochem Cell Biol* 2005;37(2): 289-305.
13. Sparks DL, Gross DR, Hunsaker JC. Neuropathology of mitral valve prolapse in man and cardiopulmonary bypass (CPB) surgery in adolescent Yorkshire pigs. *Neurobiol Aging* 2000; 21(2):363-372.
14. Wan S, LeClerc JL, Vincent JL. Cytokine responses to cardiopulmonary bypass: lessons learned from cardiac transplantation. *Ann Thorac Surg* 1997;63(1):269-276.
15. Abildstrom H, Christiansen M, Siersma VD, et al. ISPOCD2 Investigators: Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. *Anesthesiology* 2004; 101(4):855-861.
16. 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(3):436-443.
17. Sparkman NL, Martin LA, Calvert WS, Boehm GW. Effects of intra-peritoneal lipopolysaccharide on Morris maze performance in year-old and 2-month-old female C57BL/6J mice. *Behav Brain Res* 2005;159: 145-151.
18. Oitzl MS, van Oers H, Schobitz B, de Kloet ER. Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. *Brain Res* 1993;613(1):160-163.
19. Saito H, Sherwood ER, Varma TK, Evers BM. Effects of aging on mortality, hypothermia, and cytokine induction in mice with endotoxemia or sepsis. *Mech Aging Dev* 2003;124 (10-12):1047-1058.
20. Culley DJ, Baxter MG, Yukhananov R, Crosby G. Long-term impairment of acquisition of a spatial memory task following isoflurane-nitrous oxide anesthesia in rats. *Anesthesiology* 2004;100(2):309-314.

Abstracts of Interest

Postoperative cognitive dysfunction in patients with preoperative cognitive impairment: which domains are most vulnerable?

SILVERSTEIN JH, STEINMETZ J, REICHENBERG A, HARVEY PD, RASMUSSEN LS. NEW YORK, NEW YORK.

BACKGROUND: The authors explored the database of the first International Study of Postoperative Cognitive Dysfunction study to specify the domains of cognitive function that were most vulnerable and to determine the pattern of deterioration in patients with preoperative cognitive impairment.

METHODS: One thousand two hundred eighteen patients were included in the first International Study of Postoperative Cognitive Dysfunction, where neuropsychological testing was performed at entry to the study, at 1 week, and at 3 months after surgery. The authors' analyses determined the extent to which seven neuropsychological measures changed after surgery with focus on the relation with preoperative cognitive impairment, defined as a preoperative score 1.5 SD below healthy controls in the memory test.

RESULTS: Preoperative cognitive impairment was found in 74 patients at baseline. At 1 week, cognitive deterioration was seen in all tests, but in particular in the Letter Digit Coding and the time of the Stroop interference test, with 14% and 16% of the total sample (n = 1,016) exceeding 2 SD, respectively. At 3 months, deterioration was more uniform. Significantly fewer in the preoperative cognitive impairment group had deterioration in the memory test, both at 1 week and at 3 months, with no patient displaying a deterioration exceeding 2 SD.

CONCLUSIONS: Postoperative cognitive deterioration was seen in all tests, although most commonly in attention and cognitive speed at 1 week. Deterioration in memory was difficult to detect after surgery in patients with preoperative cognitive impairment.

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The effects of postoperative pain and its management on postoperative cognitive dysfunction

WANG Y, SANDS LP, VAURIO L, MULLEN EA, LEUNG JM. WEST LAFAYETTE, INDIANA

To determine risks for postoperative cognitive dysfunction (POCD), the authors conducted a prospective cohort study of 225 patients > or = 65 years of age undergoing noncardiac surgery. Cognitive testing using the Word List, Verbal Fluency, and Digit Symbol tests was conducted for each patient preoperatively and 1 and 2 days postoperatively in patients without postoperative delirium. POCD was defined as meeting statistical criteria for decline from the patient's preoperative performance levels on at least two of the three cognitive tests. Multivariate logistic regression analysis determined the association between pain and postoperative analgesia with POCD after controlling for demographics, comorbidities, preoperative level of cognitive and daily functioning, preoperative medications, duration and type of anesthesia, and adverse events. Patients were on average 72 years old and 13% of patients experienced POCD on day 1, 7% on day 2, and 15% had POCD on either day 1 or day 2 after the surgery. Multivariate regression analyses revealed that only postoperative analgesia was associated with the development of POCD. Compared with those receiving postoperative analgesia through a patient-controlled analgesia device that administered opioids intravenously, those who received postoperative analgesia orally were at significantly lower risk for the development of POCD (odds ratio: 0.22; 95% confidence interval: 0.06-0.80; Wald chi-square = 5.36, df = 1, p = 0.02). Older patients undergoing noncardiac surgery who are not delirious can experience significant declines in cognitive functioning postoperatively. Those at least risk of experiencing POCD were those who received postoperative analgesia orally.

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