POSTOPERATIVE COGNITIVE IMPAIRMENT AND POSTOPERATIVE DELIRIUM: RISK FACTORS, PATHOPHYSIOLOGY AND MANAGEMENT

*Soilemezi Eleni MD, #Konstantinidis A. Panagiotis MD, §Georgiadou Theodora MD

ABSTRACT

Postoperative cognitive impairment and postoperative delirium: risk factors, pathophysiology and management

Soilemezi E, Konstantinidis P, Georgiadou Th.

A significant number of patients exhibit impairment in cognitive function immediately following surgery or later; the impact of this postoperative cognitive dysfunction on the recovery and quality of life of the patient but also on the necessity for supportive and rehabilitation care is important. Risk factors for postoperative cognitive impairment and postoperative delirium have been described and it is these groups of patients that require early identification and careful follow up to avoid complications in postoperative care. Central nervous system complications continue to be major causes of morbidity and mortality especially after cardiac surgery, and there is a growing interest in literature in the evaluation of the effects of on pump and off pump coronary artery bypass grafting surgery on postoperative cognitive impairment. Despite several recent attempts, no gold standard treatment has been devised for postoperative cognitive impairment; however, the potential beneficial role of some pharmacological agents is currently examined. There is also fascinating research evolving with regard to the pathophysiologic mechanisms of cognitive dysfunction; it seems possible that the central nervous system responsiveness to systemic inflammatory mediators augments injury from perioperative neurological insults.

Recent improvements in surgery and anesthetic care have allowed surgery in patients who previously would not have been considered eligible. Among this population lies a subgroup of patients expected to manifest postoperative cognitive impairment (PCI) or postoperative delirium (PD).

PCI describes deterioration in cognition associated with surgery; its severity is characterized by the use of neuropsychological testing which measures the information processing abilities of the brain, such as attention, perception, verbal abilities, learning and memory and abstract thinking[1]. Postoperative cognitive dysfunction is frequently seen in most batteries of neuropsychological testing, although it most commonly involves attention and cognitive speed tasks at one week[2].
Patients suffering from PD show a change in mental status characterized by a prominent disturbance of attention and reduced clarity of awareness of the environment; it has an acute onset and tends to fluctuate during the course of the day[1]. It is often accompanied by other cognitive symptoms, such as disorientation and/or perceptual disturbances, such as illusions or hallucinations[2]. Delirium increases morbidity, mortality and length of hospitalization for both medical and surgical patients, is associated with decline in functional status after discharge and has a substantial social and economic impact[3,4].

RISK FACTORS ASSOCIATED WITH POSTOPERATIVE COGNITIVE IMPAIRMENT AND POSTOPERATIVE DELIRIUM

Primary prevention rather than treatment of established cases of PCI or PD would seem more effective, particularly if focused on high risk patients. Literature, indeed, suggests that risk factor reduction contributes at least in part to the effectiveness of any intervention strategy[4]. Among an impressive load of studies identifying risk factors for PCI or PD in various subspecialty surgical populations, Minden et al described preoperative depressive symptoms, alcohol use and pre-existing cognitive impairment as predictors of PD in patients undergoing surgical repair of abdominal aortic aneurysm[5]. Previous delirium, age≥70 years and pre-existing cognitive impairment were risk factors for PD in patients undergoing various elective surgical procedures[6,7], whereas Galanakis et al recognized higher age, prior cognitive impairment as measured by Mini-Mental State Examination, depression, low educational level and preoperative abnormal sodium as risk factors for acute confusional state among elderly hip surgery patients[8]. Indeed, delirium is the most common complication after hip fracture, but these patients have a high incidence of delirium also preoperatively[1].

In medical elderly patients predisposing factors for PD include vision impairment, severe illness, cognitive impairment and serum urea nitrogen/creatinine ratio of 18 or greater[1]. Precipitating factors include use of physical restraints, malnutrition, more than three medications added 24-48 hrs before the onset of delirium, use of urinary catheter, and abnormal biochemistry or pathology such as infections[1]. Several other studies have identified possible risk factors for PD and rather than referring to each study one by one, one can simply refer to a review article of 80 studies of PD by Dyer et al, where it was concluded that age was a risk factor along with preoperative dementia and depression[9]; in addition the use of anticholinergics appeared to be a risk factor.

Most of the recent literature recognizes as the most frequent etiologies of PD the following: drug toxicity (56%), acute cardiovascular disease (48%) and acute metabolic and endocrine disease (43%)[10].

ANESTHESIA AS RISK FACTOR FOR POSTOPERATIVE COGNITIVE IMPAIRMENT

To date, the etiology of PCI remains unclear; cerebrovascular disease, cerebral hypoperfusion, genetic susceptibility, alteration in neurotransmitter function, neurohumoral stress and CNS inflammatory responses are all possible contributing factors, but the principal suspect has been anesthesia[1]. The role of anesthesia as a causative factor for PCI was already being discussed in the 1950’s; Bedford emphasizes that among 4250 elderly anesthetized patients, 9.6% developed serious behavioral problems, with 2.8% of this latter population never returning to the previous level of functioning and 0.6% eventually receiving a pure diagnosis of dementia[11]. It wasn’t long after that, though, that in the literature appeared papers discussing that such undesired postoperative cognitive effects could not be attributed solely to anesthesia; Simpson et al clarified that at least some of the patients in Bedford’s study underwent emergency procedures, therefore one could assume that there was concomitant patho-
In the following years, the role of anesthesia in PCI and PD was better defined and a fair comment would be most probably to state that postoperative cognitive impairment may largely be attributed to factors other than anesthesia: the health of the subject at the time of surgery, complications due to extracorporeal circulation, low perfusion pressure, cerebral blood flow changes, hypoxia, microemboli, the use of opioids, benzodiazepines and anticholinergic drugs postoperatively, posture, stress, depression, recall of surgical procedures, and sleep deprivation are all possible contributing factors.[13]

Still discussing the role of anesthesia in PCI, it is interesting to mention the impressive come-back of regional techniques in the preservation of neurocognitive functioning perioperatively. Papaioannou et al found a significant neurocognitive decline in the first three post-operative days in patients who received general anesthesia compared to those who received regional anesthesia for various surgical procedures.[14] The lower incidence of pulmonary complications such as pneumonia, atelectasis and hypoxaemia in patients at risk for pulmonary complications is well established following regional anaesthesia with postoperative neuraxial analgesia.[15], and the subsequent improvement in oxygenation is most probably the key factor that justifies the neurocognitive improvement in the regional anesthesia group. That is also in agreement with the observation by Rosenberg et al, that there is significant relationship between mental dysfunction on the 3d postoperative day and mean SpO2 on the 2nd postoperative night.[16] Interestingly, reviewed randomized trials did not find a significant difference between epidural and general analgesia with respect to PD or cognitive decline.[17]

A lot of discussion also takes places regarding the possibility of different influences of various anesthetic agents in neurocognitive function. Comparing patients who received desflurane or sevoflurane anesthesia, Chen et al did not find any difference in postoperative recovery of neurocognitive functioning[18], whereas Larsen et al did not find any differences in neurocognitive functioning 90 minutes after the end of anesthesia in patients who received either intravenous anesthesia with remifentanil-propofol or inhalational anesthesia with desflurane or isoflurane[19].

POSTOPERATIVE COGNITIVE IMPAIRMENT AND POSTOPERATIVE DELIRIUM IN CARDIOTHORACIC PATIENTS

It is estimated that 40-60% of the patients who undergo cardiothoracic procedures develop some degree of neurocognitive dysfunction during the first postoperative week, whereas in 25-40% of this population, such neurocognitive abnormalities persist long term.[20] The significance of perioperative neurocognitive dysfunction is extremely important as it bears important sequel; in particular, it is associated with increased perioperative mortality, increase in length of ICU stay, and increased need for rehabilitation care.[20]

The neurocognitive status of the cardiothoracic patient and the associated functions at the time of discharge from the hospital are of great interest, since they are, along with the respective parameters in 6 months postoperatively, predictive of the neurocognitive functioning of the patient 5 years after the procedure.[21]

All the above are extremely important matters to consider and guidelines published by the American College of Cardiology and the American Heart Association suggest that “improvements in quality of life, and not just survival, should be accounted for when offering coronary artery bypass grafting (CABG) surgery as an option to a patient with coronary artery disease”[22].

There is rich literature that describes risk factors for PCI or PD following cardiothoracic procedures, and it is of special interest the observation that, despite the fact that atheromatic ulcerations of the ascending aorta are a well known risk factor for the occurrence of postoperative stroke, they are not associated with...
neurocognitive adverse effects postoperatively[23,24].

**ON PUMP VS OFF PUMP CABG WITH RESPECT TO NEUROCOGNITIVE PRESERVATION**

What is also of great interest is whether there is a difference in neurocognitive outcome in patients who undergo CABG surgery on pump or off pump. A quick look at the literature suggests that, despite the theoretical advantages of the off pump procedure, there is no significant difference between the two; moreover, CABG surgery is a high risk surgical procedure regarding adverse neurological effects. Indeed, MRI scanning following GABG, either on pump or off pump, reveals new focal brain lesions in 21-45% of operated patients[25], with no difference in neurocognitive functioning or MRI scans observed between the two groups at 3 and 12 months postoperatively[26].

Cognitive dysfunction after CABG surgery has a multifactorial pathophysiology including cerebral embolism, systemic inflammation, body temperature and cerebral hemodynamics[27]. These pathophysiologic factors are, however, of different importance for off pump and on pump surgery. Off pump surgery is associated with reduced intraoperative cerebral embolization and systemic inflammatory responses. On the other hand, hypothermia during on pump procedures may play a neuroprotective role. Cerebral blood flow is pulsatile during off pump surgery, which may subsequently lead to a reduction in cerebral perfusion pressure and neuronal ischemia[26].

Some very interesting results regarding all the above come from the study of Stroobant et al, who studied the relationship between neurocognitive impairment, embolic load and cerebrovascular reactivity in both on pump and off pump CABG patients using ultrasound[28]. These researchers studied blood flow velocity using transcranial Doppler both preoperatively and postoperatively (indeed, blood flow velocity may serve as a surrogate measurement of cerebral blood flow, even when cerebral autoregulation is disturbed[29]), and also measured HITS (High Intensity Transient Signals), again via transcranial Doppler, as a reflection measurement of embolic load during both procedures. Standardized neuropsychological tests were also given pre- and postoperatively. The results were as following: a higher embolic load (represented by a greater number of HITS) was found in the on-pump group; in the on pump group aortic cannulation was the most important HITS-prone surgical maneuver, although that constituted only a small percentage of the total number of HITS observed; the vast majority of HITS (86%) occurred when no specific surgical manipulation was identified. Also of great interest is the fact that despite its theoretical significance, there was no correlation between the number of HITS (greater in the on pump group) and early or late postoperative neuropsychological impairment. Also, no main effect of surgery (of either type) was found for neuropsychological performance and blood flow velocity.

**WHY AREN’T THE THEORETICAL ADVANTAGES OF OFF-PUMP SURGERY ASSOCIATED WITH CLINICALLY BETTER NEUROCOGNITIVE OUTCOME FOR PATIENTS?**

One suggestion is that the composition and size of HITS might be more important for the development of neurocognitive decline than is the absolute number of HITS. Emboli can be particulate, air or gaseous in nature. Obviously, large particulate emboli and massive air embolism will cause more injury than minor embolic events[28]; but, until very recently, it has been impossible for transcranial Doppler to determine the nature of the HITS recorded.

In addition, although specific cardiopulmonary bypass components may be associated with increased risk of brain injury, it must be noted that non-cardiopulmonary bypass patients are also susceptible to perioperative neuropsychological deficits. It might be that other factors independent of cardiopulmonary bypass impart a greater independent risk than cardiopulmonary
bypass alone, such as hospitalization, sleep deprivation, and potential adverse effects of anesthesia[30].

Also, the fact that the vast majority of HITS occurred when no specific surgical manipulation could be identified, suggests that there are possibly two separate major sources of emboli: 1) those secondary to surgical and manual manipulation of the heart and arteries, and 2) emboli from a non obvious source[28].

EMBOLI ARE NOT THE WHOLE STORY…

Therefore, emboli alone can not explain the pathophysiology of perioperative neurocognitive impairment. Techniques that decrease cerebral blood flow during cardiopulmonary bypass, such as EEG burst suppression induced by propofol[31] and hypothermic cardiopulmonary bypass[32], would be expected to decrease brain embolic burden; however, they were not associated with improved neurocognitive outcome in cardiothoracic patients.

It is obvious, therefore, from all the above that there must be something in addition to emboli that results in postoperative cognitive dysfunction. That explains why cognitive dysfunction frequently occurs after non-cardiac surgery too; Moller et al described cognitive dysfunction one week postoperatively in 26% and three months later in 10% of 1218 patients who underwent thoracic, abdominal or orthopedic surgery without perioperative hypoxemia or hypotension being risk factors[33]. Thus, as Hindman elegantly summarizes, “there is some element of surgery and/or anesthesia itself that results in, or contributes to, acute and chronic postoperative cognitive dysfunction - an element that is not unique to cardiac surgery”[20].

CNS RESPONSIVENESS TO INFLAMMATORY MEDIATORS

Another possible explanation may involve the CNS responses to peripheral tissue injury or inflammation[20]. The CNS is sensitive to inflammatory mediators such as endotoxin, interleukin-6 and interleukin-8, all of which are activated by surgical trauma[20]. Cardiothoracic procedures and cardiopulmonary bypass circuit are also associated with complement and neutrophil activation. In fact, it seems likely that CNS responses to systemic inflammatory mediators may alter CNS gene expression and functional status and augment CNS injury from any coexisting perioperative neurologic insults[34]. These processes may actually participate in the pathogenesis of neurodegenerative diseases, such as Alzheimer’s, multiple sclerosis and AIDS dementia complex[35,36]. Hence, chronic CNS responses to systemic inflammatory mediators may result in delayed and/or long term postoperative CNS dysfunction[20].

Even a seemingly simple response to systemic inflammatory stimuli such as fever, may prove sufficient to significantly worsen neurologic outcomes[20,37,38] and in the study by Grocott et al maximum postoperative temperature following CABG was a significant independent determinant of cognitive dysfunction six weeks after surgery[39].

PREVENTION AND TREATMENT OF POSTOPERATIVE COGNITIVE DYSFUNCTION

Despite several recent attempts, no gold standard treatment has been devised for postoperative cognitive impairment. Szalma et al investigated the effectiveness of piracetam to treat the cognitive impairment after CABG[40]; the drug was administered from the day before surgery to six days after surgery and cognitive function was assessed both before surgery and six weeks after surgery using a battery of neuropsychological tests. Six weeks after surgery the investigators found a statistically significant treatment effect in the treated population. The mechanisms of action of piracetam are not fully understood; numerous studies have shown piracetam-induced neuronal protection against brain insults through several neuronal and hemodynamic effects. Piracetam improves erythrocytes deformability and de-
creases blood viscosity and platelet hyperaggregation, resulting in a probable decreased incidence of microemboli[40].

A lot of discussion in the relevant literature also involves the role of heparin-bonded cardiopulmonary bypass (HB-CPB) circuits in reducing the incidence of cerebral dysfunction in cardiothoracic patients[41,42]. The use of HB-CPB is one of the techniques which can be utilized to reduce the embolic load associated with CPB; other measures include the use of arterial catheter filters, CABG procedures performed off pump, reduced manipulation of an atheromatus aorta, meticulous removal of residual air and debris from the heart after open chamber procedures; the first results seem rather encouraging.

Many other drugs have been studied as neuroprotective during cardiac surgery, including thiopental[43], remacemide[44], clomethiazole[45], prostacyclin[46] and GM1 ganglioside[47]; nevertheless, no study results have provided sufficient evidence to induce a change in everyday clinical practice. On the other hand, lidocaine, an inexpensive and widely available local anesthetic and class Ib antiarrhythmic agent, is frequently met in the literature regarding neuroprotection and cardiac surgery. Possible mechanisms for cerebral protection by lidocaine include deceleration of ischemic transmembrane ion shifts [48], reduction in cerebral metabolic rate[49], modulation of leukocyte activity[50], and reduction of ischemic excitotoxin release[51]. There is, though, evidence coming from recent trials, that lidocaine may have a neuroprotective effect in patients undergoing cardiac surgery with cardiopulmonary bypass [52,53].

Regardless of the new and promising prophylaxis against PCI/PD, haloperidol remains the gold standard in the treatment of delirium independent of the clinical presentation; it is usually used in doses that do not exceed 20 mg in a 24-hr-period[54], frequently in combination with a benzodiazepine in cases of refractory agitation. Olanzepine or risperidone can be used as alternatives.

SOME MORE CONSIDERATIONS…

There is some controversy in the literature regarding what would be the appropriate way to look at the results of the neuropsychometric tests mentioned in various trials[55]; for instance, one could compare the incidence of deficits or the group mean scores on individual tests. What is also not precisely known is the optimum time to perform these neuropsychometric tests; performance in tests which are done soon after surgery inevitably takes into consideration residual effects of perioperatively given drugs, whereas tests performed longer than six months postoperatively may take into consideration events not related to surgery.

Another complicating issue involves the different tests performed in clinical trials to detect and measure cognitive dysfunction. Cognitive function consists of a variety of mental capabilities which include memory, attention, language, organization and concentration. Unfortunately, there is no single test to reliably measure all these variables at the same time; on the contrary, single tests focus on individual abilities. Just to mention some of the tests frequently used in studies, Story Memory measures the ability to learn and recall a narrative story in two trials immediately and after a brief delay[56]. List learning assesses the ability to learn and remember a list of ten unrelated words[56]. Semantic fluency involves executive functions related to speech[56]. All the above are sensitive markers of early dementia. Digit span measures attention span, concentration and working memory[56]. Concept shifting test, part C, is considered a measure of cognitive flexibility[2]. Stroop test, part 3, is considered a measure of interference susceptibility[2]. Letter Digit Coding Test assesses speed of information processing[2]. There are numerous more tests that measure different aspects of cognitive function and which are often supplemented with neurological examination and/or questionnaires that involve symptoms of related disorders such as depression.

It is worth mentioning at this point that the Mini Mental State Examination (MMSE) is very often used among the neuropsychometric tests used for the assessment of cognitive function,
and, it has proven very easy to conduct and not tiring for elderly patients[14]. It has a good test-retest and inter-observer reliability, can be used to monitor changes in cognitive function and it can be repeated postoperatively to detect early changes of cognitive function[57].

CONCLUSIONS

Central nervous system complications continue to be major causes of mortality and morbidity in the postoperative period. Risk factors for PCI and PD have been identified and patient populations that comprise these characteristics deserve careful follow up throughout the perioperative period to avoid appearance of neurological complications which lengthen hospital stay with costly consequences. Common risk factors for PD include old age, preoperative cognitive dysfunction or depression and drug toxicity, whereas the pathophysiology of PCI is equally complex and involves cerebrovascular disease, cerebral hypoperfusion, abnormal biochemistry, CNS responsiveness to inflammatory mediators and also the impact of anesthesia. Patients undergoing cardiothoracic procedures are amongst these high risk populations. Recently, there is fascinating information coming to light both regarding possible therapeutic interventions, and also with respect to the complex pathophysiology of central nervous system injury during the perioperative period.

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Address for correspondence:
Soilemezi Eleni, ICU Department, Papageorgiou Hospital of Thessaloniki, GR-564 03
Tel: 2310-693369
E-mail: elenisoil@hotmail.com

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