Review Article

Neurological Dysfunction after Cardiac Surgery and Cardiac Intensive Care Admission: A Narrative Review Part 1: The Problem; Nomenclature; Delirium and Postoperative Neurocognitive Disorder; and the Role of Cardiac Surgery and Anesthesia

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Abstract

The association with cardiac surgery with cognitive decline was first reported in the 1960s after the introduction of coronary artery surgery. The incidence in cognitive decline was thought to be more after cardiac surgery, especially with the use of the cardiopulmonary bypass. Anesthesia and surgery are both associated with cognitive decline but many other factors appear to contribute its genesis. On-pump surgery, microembolization during manipulation of the heart and great vessels, temperature changes, pH changes, and altered cerebral perfusion, during cardiac surgery, have all been blamed for this. Postoperative cognitive decline is associated with poor clinical outcomes and higher mortality. Several studies have been conducted in the last decade to determine the genesis of this malady. Current evidence is absolving cardiac surgery and anesthesia to be the primary causes *per se* of cognitive dysfunction.

Keywords: *Cardiac surgery and anesthesia, cognitive decline, neuroinflammation and oxidative stress, perioperative neurological disorder, postoperative cognitive dysfunction*

Cognitive change after anesthesia and surgery was first described over a century back. George Savage possibly made the first presentation on the subject in 1887 and titled it as "Insanity following the use of Anesthetics in Operations" (55th Annual Meeting of the British Medical Association at Dublin).[1] There were sporadic mentions of cognitive decline in the literature in the following decades. Its association with cardiac surgery was first reported in the 1960s, after the introduction of coronary artery surgery.[2,3] The incidence in cognitive decline was later reported to be more after cardiac surgery, especially with the use of the cardiopulmonary bypass (CPB), vis-a-vis general surgery.[4] The first report on perioperative cerebral effects was by Bedford in 1955,[5] and by the year 2015, there were more than 200 publications every year on postoperative cognitive dysfunction (POCD).[6]

Delirium is an acute state of confusion and inattention, which may be accompanied by an altered level of consciousness and disorganized thinking.[7] Deliriumis common in patients after cardiac surgery, with an incidence >50%.[8,9] Cognitive decline after cardiac surgery has been systematically described over the past few decades and is reported to have an incidence of 24% at 6 months and 42% at 5 years after cardiac surgery.[10] Postoperative delirium delays convalescence, delays return to preoperative functional state, lengthens hospital stay, imposes an additional financial burden, may permanently impairs cognition, and increases morbidity and mortality.

Cognitive decline, based on a change in neuropsychological test results, is generally referred to as POCD. Several definitions have been used for POCD. It is a decline from the preoperative baseline cognition status after exposure to surgery and anesthesia. It affects one or more cognitive realms such as attentiveness, behavior, memory, intellect, visual dimensions, motor dexterity, and management function. Although anesthesia and surgery are both associated with POCD, many other factors appear to contribute its genesis. Stroke and POCD are the most common neurological

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ailments after cardiac surgery. A high incidence of POCD, in the short-term, after both major noncardiac and cardiac surgery has been reported by many studies.[11,12] Adverse neurological outcomes are important causes of morbidity and mortality after cardiac surgery.

Postoperative Delirium

Rapid onset of short episodes of distraction, disorganized thoughts, and altered consciousness are characteristic of postoperative delirium.[13] The components of delirium described in the Diagnostic and Statistical Manual, 5th edition (DSM-5) are attention and awareness disturbance, acute distress with rapid onset, cognition disturbance, and disturbances not elucidated by another mental disorder with no evidence to suggest its causation by a medical condition, drug effects, or withdrawal.[14]

Delirium is associated with poor outcomes including a tenfold higher mortality risk, fivefold higher risk of nosocomial complications, unsatisfactory functional recovery after 1 year, increased length of hospital stay, increased costs, and POCD.[15-18] Perioperative use of antipsychotics, statins, corticosteroids, H2 receptor antagonists, anticholinergics, phenothiazine, antihypertensives, anticholinergics, antidepressants, benzodiazepines, ketamine, and opioids are all said to trigger delirium.[19,20]

Patients with delirium are prone for falls, have longer length of hospital stay, need assisted care after discharge, need prolonged physical therapy, have to pay more for healthcare, and their families incur excessive burdens of time and money.[21,22] Most importantly, they may lose their independent status at an age when its needed the most, making them dependent on potentially not so willing progeny/family.

Incidence

The DSM-5 states that delirium occurs in 15–53% of older individuals after the intervention and in 70–87% of those admitted in intensive care.[14] Surgery is the precipitating event in approximately one-third of individuals aged >65 years. In a review, Krenk *et al*. found that POCD can arise at any age, but tends to last longer and is more severe in patients ≥60 years.[23]

The incidence of POCD reported after cardiac surgery is very varied in different studies. A report from 2006 suggests a POCD incidence of 11–13% at 3 months and 1 year, using one standard deviation (SD) of activities of daily living (ADLs) from norms.[24] Monk *et al*., however, reported an incidence of 41.4% in patients aged ≥60 years on discharge from hospital.[12]

Nomenclature and Classification

It was difficult to classify neurological dysfunction in the absence of an international consensus. A recently formed multinational, multidisciplinary, and multispeciality expert group (The Nomenclature Consensus Working Group) recommended that cognitive impairment identified in the perioperative period be called "perioperative neurocognitive disorders" (PND) [Table 1].[25] The use of the term "PND" was recommended to encompass all neurological changes in the preoperative or postoperative period and to include preexisting cognitive impairment before surgery/intervention; any acute event such as delirium and/or cognitive decline diagnosed up to 30 days after the surgery/intervention; and up to 12 months after surgery.

Neurocognitive disorder (NCD), identified in the preintervention period, is termed as "preexisting NCD." "Postoperative delirium" has been defined as delirium, which meets DSM-5 diagnostic criteria, and occurs within a week of the surgery/intervention or until hospital discharge. Known coexisting factors contributing to neurological dysfunction (such as physiological disturbances, drug effects, lucid interval, preexisting disorders), however, must be ruled out before the diagnosis.

Delirium or cognitive dysfunction occurring within 30 days of anesthesia and surgery is termed as "delayed neurocognitive recovery," as the change is considered transitory. The suffix "postoperative" is added if delirium is new and persists after surgery. The use of the term "postoperative" is not related to the etiology but is used primarily to specify the time of its occurrence. Cognitive dysfunction present after 30 days and up to 1 year of surgery is termed as NCD postoperative (POCD), while that present a year after surgery is termed as just NCD.

All NCD are subclassified into mild and major. If the impairments of ADLs are 1 to 2 SD below norms or

Table 1: Nomenclature of perioperative neurocognitive disorders recommended by "The Nomenclature Consensus Working Group"

Perioperative period	Delirium	Neurocognitive disorder	
		Mild	Major
Emergence from anesthesia	Emergence excitation or delirium		
Immediately postoperative with expected recovery within 30 days	Delirium (postoperative) or Delayed neurocognitive recovery	Delayed neurocognitive recovery	Delayed neurocognitive recovery
Expected recovery within 30 days and 12 months		Mild Neurocognitive Disorder postoperative (POCD)	Major Neurocognitive Disorder postoperative (POCD)
Expected recovery beyond 12 months		Mild Neurocognitive Disorder	Major Neurocognitive Disorder

controls, the PND is considered to be mild; while if ADLs are more than 2 SD below norms or controls, the NCD is termed major.

This nomenclature is valid for new neurological dysfunction, up to 12 months after surgery, provided there is no other associated medical condition. After 12 months, the "postoperative" suffix is no longer attached for newly diagnosed cognitive dysfunction, as the etiology will not be considered to be linked to the surgery/anesthesia.

The American College of Cardiology and the American Heart Association have classified neurological outcomes as Types 1 and 2. Type 1 is neurological injury leading to brain death, stroke, and new transient ischemic attack, while Type 2 injuries include delirium and POCD.

Diagnosis

The Nomenclature Consensus Working Group recommends the presence of the following criteria for a diagnosis of PND:

- Subjective symptoms: Symptoms must be described by the participant, informant, or the treating clinician
- Objective impairment/change of ADLs (basic ADLs are eating, bathing, dressing, toileting, mobility, and grooming): If impairment is 1 to 2 SD below norms or controls, the PND would be considered to be mild; and if ADLs are more than 2 SD below norms or controls, the PND is considered to be major. The impairment must in assessed in terms of z-scores derived using norms or controls
- Instrumental ADLs (more complex tasks of unassisted living such as being able to do housework and prepare meals): for major NCD/dementia, a decline in function is required.

The Nomenclature Consensus Working Group has partly met the need for a definition of PND. No universal neuropsychological testing method, however, has yet been recommended by the group. At present, multiple tests are advocated for diagnosis of PND. The tests and the criteria taken by different studies were thus diverse and chosen arbitrarily. The Working Group has also not defined the cognitive domains (such as memory, attention, visual-spatial construction, verbal fluency, motor function, processing speed) to be considered for the neuropsychological test.

Neuropsychological Diagnostic Tests

The patient and investigator can take about half an hour to complete the neuropsychological tests. With no defined gold standard diagnostic test, the choice of the tests is possibly compromised due to time constraints.[26-28] The commonly used diagnostic tests for grading dementia and POCD are listed in Table 2.

Postoperative delirium and cognitive dysfunction—same disease or different?

Postoperative delirium and POCD share risk factors and may coexist. It is, however, not well established whether they are different manifestation of the same disease spectrum. Disparate diagnostic methods, inadequate assessment, and short follow ups are possibly responsible for inability to define the relationship between delirium and cognitive decline.[9] Hudetz *et al*. reported that 89% patients experiencing delirium after cardiac surgery on CPB developed POCD as compared with 37% nonsurgical patients. They reported that odds of developing POCD after delirium to be 14 times greater than those who did not have delirium.[29]

Composite cognitive Z score at 1 month have been reported to fall considerably in patients with delirium, particularly in the visual-construction and processing speed domains.[9] The decline in processing speed persists in these patients even after a year. However, a recent evaluation of the Successful Aging after Elective Surgery (SAGES) data for cognition after major noncardiac surgery found a significantly high relative risk of POCD in patients with a history of postoperative delirium at 1 month, but not at 2 or 6 months.[30] SAGES participants underwent neuropsychologic tests up to 3 years postsurgery and this long-term follow-up found POCD to be somewhat more common among patients without delirium, indicating that delirium and POCD are probably distinct expressions of PND[31] and not the same disease.[32]

Perioperative Risk Factors

Several risk factors for postoperative delirium have been suggested based on evidence and consensus statements of the European Society of Anesthesiology guidelines[33] and

Table 2: Commonly used diagnostic tests for grading dementia and postoperative cognitive dysfunction

Diagnostic tests for grading dementia	Diagnostic tests for grading Postoperative Cognitive Dysfunction
Informant Questionnaire for Cognitive Decline in the Elderly	Trial making test: for visual attentiveness and task change
Recall component of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-Auditory Verbal Learning Test	Letter-digit coding test: to analyze speed of data processing.
Mini-Mental State Examination (MMSE)	Boston naming test: word finding capacity.
Instrumental Activities of Daily Living Questionnaire	Stroop-Word interference test: assesses interference responsiveness
The Geriatric Depression Score	Four boxes test: to assess psychomotor speed.
Nursing Delirium Screen Scale (Nu-DESC)	Paper and pencil memory scanning test: assess sensorimotor speed.
Confusion Assessment Method (CAM) or CAM-ICU	CERAD word list memory test.
Cognitive Failure Questionnaire (CFQ)	Visual verbal learning test: to test memory.

other studies. The perioperative risk factors contributing to postoperative delirium are listed in Table 3.

Role of Cardiac Surgery

The initial publications on POCD were all from cardiac surgery, leading to a belief that only cardiac surgery leads to POCD. In 1987, Shaw *et al*. reported that 79% of patients had POCD 7 days after cardiac surgery.[4] Several publications on POCD following noncardiac surgery, in the last few years, have negated the belief. Surgery has been implicated in causing long-term cognitive decline by some studies and absolved of the crime by others.[34-36] The analysis of MIND-ICU study demonstrated that surgery or anesthesia *per se* did not contribute to the risk for long-term cognitive impairment.[37] A recent meta-analysis too failed to show an association between anesthesia/surgery and the subsequent dementia. It recommended conduct of more better-designed prospective studies to establish the association.[38]

On-pump CABG was reported to be associated with a higher risk of postoperative stroke while the incidence of stroke was reported as low in OPCAB patients with no-touch techniques for a proximal anastomosis.[39] Studies on both On-pump and OPCAB patients have consistently shown no difference in stroke rates, neurocognitive outcomes, composite outcome, or mortality. However, to reduce the incidence of atheroembolism during aortic cannulation, routine epiaortic ultrasound scanning is currently a Class IIa (Level of evidence B) recommendation to detect the presence, location, and severity of atherosclerotic plaque.[40]

In cardiac surgery, surgical stress evokes a significant inflammatory response, and the processes of neuroinflammation seem to be its logical course. Multiple factors associated with cardiac surgery were thought to initiate PND. Coronary artery bypass graft (CABG) surgery elicits a complex prothrombotic and proinflammatory response that peaks within a time frame spanning from the end of CPB to the early hours after that. The tissue damage and inflammatory response to surgery are thought to impair the blood–brain barrier (BBB) causing neuroinflammation and consequent neuronal dysfunction and POCD. These molecular changes may persist for days or weeks after CABG.[41]

CPB activates systemic inflammatory response by "contact activation" of the immune mediators by exposure of blood to the foreign surfaces; ischemia-reperfusion injury to vital organs; and endotoxemia following gut translocation of endotoxin.[42] CPB induces leukocyte/platelet activation, thrombin/plasmin-mediated procoagulant and fibrinolytic effects, resulting in a multifold rise proinflammatory mediators levels.[43]

OPCAB surgery was thought to trigger a lesser inflammatory response than on-pump CABG.[44] Studies evaluating proinflammatory cytokines release after OPCAB and on-pump CABG have, however, reported contradictory results.[45] There is insubstantial evidence of reduction of the postoperative systemic inflammatory reaction and platelet activation after OPCAB.[46] The Randomized On/Off Bypass (ROOBY) trial of 2203 patients, comparing Off-pump and On-pump CABG, found no significant reduction in the incidence of POCD on shunning CPB.[47] Other studies, too, have validated the above results.[48]

Over the years, CPB use in cardiac surgery has been considered as the major risk factor for POCD. Besides, arteriosclerotic plaques can embolize at cannulation and on the application of aortic cross-clamp. Micro- and macroembolic material may originate from CPB or aorticlesions. For long, microembolization was implicated to be the main contributor to PND. Functional MRI was used to compute postoperative brain activity changes by measurement of blood oxygen level signals in OPCAB patients. Intraoperative emboli number detected by transcranial Doppler correlated with the Functional

Table 3: Perioperative risk factors contributing to postoperative delirium

Preoperative factors	Intra- and postoperative factors
Age ≥65 years	Site of surgery (abdominal and cardiothoracic)
Multimorbidities (e.g. cerebrovascular including stroke, cardiovascular, peripheral vascular diseases, diabetes, anemia, Parkinson's disease, depression, chronic pain, and anxiety disorders)	Intraoperative bleeding (blood transfusion of >3 units)
Sensory impairment (hearing/visual loss)	Long duration of surgery
Higher American Society of Anesthesiologists' physical status classification system or the Charlson Comorbidity Index (CCI) or the Clinical Impairment Assessment Score (CIAS) before surgery	Excessive pain
Frailty (malnutrition, hypoalbuminemia, hypercholesterolemia, high levels of inflammation, muscular atrophy, etc.)	Emergency surgery
Prolonged preoperative fluid fasting and dehydration	Postoperative complications
Hyponatremia/hypernatremia	Hyperthermia/Hypothermia
Anticholinergics	
Alcohol-related disorders/alcohol use disorders/substance abuse	
Cognitive impairment	

MRI findings showing a postoperative decrease in prefrontal cortex activation.[49]

Processing blood with a cell saver during CPB has been tried to restrict microembolization, but no statistical difference in the incidence of POCD could be demonstrated with its use. Small gaseous or lipid emboli during CPB are considered culprits in microembolization. Routine use of 40-micron arterial-line filters and membrane oxygenators is thus recommended to prevent PND.[50]

Similarly, no difference in the incidence of POCD has been demonstrated between pulsatile vs nonpulsatile flow use in CPB. Aykut *et al*. compared pulsatile and nonpulsatile flow on cognitive functions of patients undergoing CABG and observed an overall POCD rate of 17.3% in pulsatile and 35.6% in nonpulsatile flow group.[51] Pulsatile flow maintains the microcirculation, unlike nonpulsatile flow of conventional CPB. Nonpulsatile flow alters the microcirculatory flow, activates leukocytes, causes endothelial dysfunction, and is associated with increased vascular resistance.[52] Lower systemic vascular resistance in pulsatile flow should enhance cerebral blood flow and oxygen delivery. A later study, however, did not find the pulsatile flow to be superior to nonpulsatile flow, in context of early POCD. Two biomarkers of PND, S100 calcium-binding protein β(S100β) and neuron-specific enolase (NSE) were noted to be unaffected by the type of flow in this study.[53]

The optimal mean arterial pressure (MAP) during CPB is not defined. During CPB, MAP is usually maintained at >60 mm Hg, which is an arbitrary figure and may not cater to the patient's age, preoperative blood pressure, and medical history. An investigation in patients for cardiac surgery found deviations of cerebral perfusion above the upper limit of autoregulation is associated with delirium.[54] A recent study suggested that physiological cerebral perfusion pressure on CPB was associated with less early PND, but the evidence is not significant.[55] The addition of carbondioxide to the CPB circuit, in pH-stat-based hypothermic CPB, leads to loss of autoregulation by causing cerebral vasodilation above metabolic demands and is thought to promote POCD.[56]

Role of Anesthesia

Inhalational anesthetics have been accused of being neurotoxic and of contributing to POCD.[57] Inhaled anesthetic agents are said to increase amyloid β-oligomerization, tau phosphorylation, and its aggregation, thereby accelerating Alzheimer's neuropathology.[58] Molecular structure of halogenated inhalational anesthetics is similar to that of organic solvents. Thus, they can be presumed to dissolve the fat in the brain tissue.[59] Isoflurane has been shown to impair hippocampal learning and modulate synaptic plasticity in the postanesthetic period inducing long-lasting cognitive and learning deficits.[60] Sevoflurane-induced apoptosis and elevated levels of B-site amyloid precursor protein-cleaving enzyme have been reported.[61]

Even though Xenon anesthesia ensures immediate awakening and no residue of the agent remains in the body, Xenon anesthetic too has been reported to be associated with POCD, indicating that neural tissue absorption of inhalation agents may not be the main culprit.[62,63]

There is varied evidence regarding the depth of anesthesia and POCD. High concentrations of inhaled anesthetics are thought to increase BBB permeability. In the Cognitive Dysfunction after Anesthesia (CODA) trial Bi-spectral index (BIS) guided anesthetic was administered titrating BIS between 40 and 60. They reported the BIS titrated 30% decrease in inhaled anesthetic delivery was associated with a 40% lower three-month postoperative incidence of PND.[64] However, other studies have reported just the contrary that deep planes of anesthesia protect against delirium and POCD.[65,66]

Despite contrary views about the role of anesthetic depth, the consensus statement of the 2016 Perioperative Neurotoxicity Working group states that Anesthesiologists should monitor age-adjusted end-tidal concentrations of inhalation anesthetics, maintain optimal cerebral perfusion pressures, and monitor brain function using EEG-based devices in older adults.[20] Increasing the concentration of inhaled anesthetics to treat hypertension should thus be avoided. Depth of anesthesia monitoring may be made mandatory in the coming times to reduce anesthetic use and improve outcomes.

It was initially thought that POCD was only associated with the use of general anesthetic and this promoted the use of regional anesthetic in the elderly. Most studies found a statistically similar risk of delirium or POCD after both general and regional anesthesia,[67-69] but these results were possibly confounded by high doses of intravenous sedatives administered in most of these studies.[20] A review and analysis of the Swedish Dementia Quality Registry medical records found that exposure to both inhalational and regional anesthesia was associated with increased risk of dementia. The authors, however, felt that the risk of dementia after regional anesthesia might have been overestimated as patients chosen for regional anesthesia were probably more fragile, with cognitive involvement, older, post-orthopedic trauma and with more comorbidity.[70]

The data of three research projects on periprocedural cognitive dysfunction was evaluated and compared with data from nonoperative controls.[71] The projects taken were from three different interventional domains, i.e., nonsurgical intervention (coronary angiography under sedation—the CISCO study); major noncardiac surgery under general anesthesia (total hip joint replacement—the ACE study); and cardiac surgery (coronary artery bypass graft surgery under

general anesthesia with CPB—the ANTIPODES trial). The incidence of POCD was significantly higher after CABG as compared to hip replacement surgery on day 7. However, at 3 months, the incidence of POCD for all groups was statistically similar, indicating that the incidence of POCD was independent of the nature/type of procedure or anesthetic given. Patients needing coronary artery revascularization usually have atherosclerosis in other vasculature too, which makes them prone to embolization and thereby PND. Nonspecific factors such as procedure stress or patient characteristics may also play an essential role in the causation of POCD, or it may be related to residual effects of drugs used perioperatively.[71]

Desflurane has been reported to be associated with a lower incidence of early POCD in comparison to propofol.[72] This neuroprotection is thought to be due to the ischemic preconditioning property of inhaled agents, which prevents ischemia-reperfusion injury.[73] This protective effect of anesthetics is linked to the suppression of neuronal excitation and augmentation of gamma-amino-butyric acid (GABA) type A receptor function.[74]

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Conflicts of interest

There are no conflicts of interest.

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