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Research Article

Post-Operative Cognitive Dysfunction in the Elderly: Talking Points and Treatment Suggestions for Clinicians

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Abstract

The phenomenon of Postoperative Cognitive Dysfunction (POCD) is complex, multifactorial and poorly understood in clinical settings aside from anesthesiology. Although there is ongoing POCD research and discussion about POCD by the anesthesiologists, the clinical pearls from their research are not being widely reported in the geriatric, internal medicine and primary care literature. POCD may have life altering consequences including decreased quality of life, decreased functional capacity, loss of independence and increased morbidity. Among the patient-related risk factors for POCD are advanced age, genetic predisposition, pre-existing cognitive impairment, duration of surgery, type of anesthesia, pre- and postoperative delirium, pain management, inflamation and infection. This review article discusses some of the multifactorial origins of POCD syndrome to assist in the dissemination of several important understandings of this clinical phenomenon gleaned from the anesthesiology literature. Becoming better informed about POCD will benefit both physicians and patients, with the goal of reducing POCD morbidity and mortality.

Keywords: Adverse effects; Aging; Anesthesia; Apolipoproteins E; Attention; Blood-brain barrier; Cognition; Genetics; Leaky gut; Memory; Neuropsychological tests; Physiology; Post-operative cognitive dysfunction; Postoperative complications.

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Abbreviations

POCD: Postoperative Cognitive Dysfunction
GA: General Anesthesia
RA: Regional Anesthesia
PCA: Patient-Controlled Analgesia
AD: Alzheimer's Disease
MMA: Multimodal Analgesia
CNS: Central Nervous System
MCI: Mild Cognitive Impairment
CSF: Cerebral Spinal Fluid
CRP: C-Reactive Protein
Aβ: Amyloid Beta Protein
APP: Amyloid Precursor Protein
IL-1b: Interleukin 1b
IL-6: Interleukin-6
IL-2: Interleukin-2
Tau: Tau protein
pTau: Phosphorylated-Tau
pTau/Ab 1–42: Alzheimer's disease biomarker
MDA: Malonaldehyde
BBB: Blood-Brain Barrier
Qalb: cerebrospinal fluid/plasma albumin ratio
CPB: Cardio-Pulmonary Bypass
MISTLIF: Minimally Invasive Transforaminal Lumbar Interbody Fusion
PreCI: Pre-Existing Cognitive Impairment
BDNF: Brain-Derived Neurotrophic Factor
DOA: Depth of Anesthesia
S100B: protein S-100 Beta
ReCODE: Reversal of Cognitive Decline
TRAIL: Tumor Related Apoptosis Inducing Ligand

Introduction

Approximately 234 million persons worldwide and 20 million persons in the USA undergo surgical procedures. Postoperative Cognitive Dysfunction (POCD) affects both the young, middle aged and elderly that undergo major surgery [1,2]. POCD generally presents with fluctuating symptoms of impaired memory, learning, sensory

and language processing, concentration, social integration and sleep-wake cycles for varying lengths of time post-operatively. It is characterized by a slowing of brain processing speed, deficits in memory and executive function, in addition to other neuropsychological domains [1,3-5]. Even though POCD is a common finding after surgery with General Anesthesia (GA) and Regional Anesthesia (RA), there are currently no ICD -10 or DSM V codes for this syndrome [6]. Yet, POCD may have significant implications in terms of length of hospital stay, postsurgical level of independence, quality of life, utilization of social financial assistance and mortality [7-10].

While POCD can be present in the young (36.6%), middle aged (30.4%) and elderly (41.4%) patients following surgery, only the elderly have significantly higher rates of POCD at three months compared to controls [7]. In addition, the elderly often have permanent damage that impacts their quality of life. As the world population ages, the POCD burden will increase for patients, family members and health care systems. POCD is extensively described in the anesthesiology literature and it is essential that this syndrome becomes more widely understood for geriatric clinicians, internists and primary care providers. We present selected findings drawn from the anesthesia literature that may be instructive in increasing the working knowledge of POCD for clinicians managing geriatric patients undergoing surgery.

Historical Studies on POCD

The problem of POCD following anesthesia has been reported in the literature for several centuries. Postoperative delirium was described in the 16th century and first documented in 1819 [11]. In 1955, Bedford reported that of 1,193 elderly patients who had surgery under GA, approximately 10 percent developed cognitive problems. Bedford hypothesized that a combination of the anesthetic agents and intraoperative hypotension contributed to the POCD and dementia symptoms, suggesting that nonessential general surgery for the elderly presented a significant risk for POCD [12]. In the 1980's, POCD was thought to be primarily associated with cardiac surgery sequalae [13,14]. Age, duration of anesthesia, low education level, prior surgeries, postoperative infections, in hospital versus clinic surgery, and respiratory complications were thought to be the primary risk factors for early POCD in 25.8 percent of patients seven days following surgery and in 9.9 percent of patients three months post intervention [15,16]. However, only age was thought to be a risk factor for long-term POCD. Hypoxemia and hypotension were not considered significant risk factors at either seven days or three months post-surgery [15].

More recently, POCD has been observed to be associated with major cardiac and non-cardiac surgery as well as non-invasive procedures such as coronary angiography [17,18]. Studies exploring the question of whether anesthetic agents may directly cause permanent POCD [19,20] have been superseded as continuing research suggests that the pathogenesis of POCD is multifactorial, not related merely to the types of surgery and/or anesthesia [18,21,22].

POCD in the elderly

A study of 8,632,679 surgical cases of patients aged 18 to older than 90 years, compiled in the Anesthesia Quality Institute's National Anesthesia Clinical Outcomes Registry (NACOR), found that 34.1 percent of all surgeries were performed on the elderly (65 years old and older), with seniors being 35.3 percent of the population experiencing inpatient procedures [23]. Deiner and colleagues emphasized that the medical care of older surgical patients is "complex and multifactorial", and they suggest a collaborative process working across disciplines and partnering with community hospitals. Geriatric patients run a higher risk of mortality and other complications. Among these complications, POCD is a frequent post-surgical sequalae in the elderly in some studies [7,18,23-26]. POCD may initiate a permanent and possibly a progressive cognition decline [27], or it may recede with time following surgery [28,29]. A few studies have recorded that the surgery with anesthesia does not generally precipitate POCD for more than one week or more following surgery [30,31].

Multiple intraoperative procedures and mechanisms may contribute to POCD. In a prospective study of 70 cardio-pulmonary bypass (CPB) surgeries, more than 200 emboli were recorded in 40 patients during aortic clamping and release, at bypass initiation and during defibrillation. These emboli were associated with increased memory loss; however, the memory loss in the CPB patients receded after 2 months [32]. The intraoperative use of lidocaine versus placebo has been found to decrease the incidence of POCD in the early post-operative period [33]. Diurnal variations in cortisol production during surgery have been reported to contribute to POCD [34]. The role of brain inflammation post-surgically has been investigated using cerebral spinal fluid and blood biomarkers. Seven days postsurgical patients undergoing hip replacement surgeries had increased IL-1b, Tau/Ab 1-42, pTau/Ab 1-42 and increased plasma MDA, in addition to decreased Cerebral Spinal Fluid (CSF) Ab 1-42 when compared with the Non-POCD group [35]. Li et al., reported that prophylactic dexamethasone had no advantage in diminishing POCD 30 days post-surgery compared to a placebo [36]. Intraoperative blood pressure regulation has been a point of interest in the search for contributing factors of POCD [7,12]. Langer et al., investigated the association of personalized intraoperative blood pressure target and mean arterial pressure (MAP, greater than 90% of preoperative values, Target Group) versus more liberal intraoperative blood pressure management (No-Target Group) on POCD. They reported that there was no correlation between intraoperative hypotension and POCD [37] [Table 1].

Authors	Age Yrs	No. Subjects	Study Type	Study Questions and Evaluations	Results
Moller [15]	≥60	1218 non-cardiac surgeries; 176 controls, age-matched non-surgical volunteers.	P	Incidence of POCD post-surgery. Neuropsychological tests at: pre surgery; 1 week; and 3 months post-surgery.	POCD observed at1 week: exp. 25.8%; control 9.9% ($p < 0.0001$); At 3 months: exp. 3.4%; control 2.8% ($p < 0.0037$).
Abildstrom [28]	>60	336 non-cardiac surgeries; 47 controls, age-matched non-surgical volunteers.	P	Incidence of POCD post-surgery. 7 neuropsychological tests at: base line; postoperatively at days 7; 98; and 532.	Cognitive dysfunction 1-2 years post-surgery: Surgery patients 10.4% (35/336) and controls 10.6% (5/47). Age, early POCD and post-surgical infection were identified as risk factors for long-term POCD.

Newman [24]	61.9 ± 10	261CPB surgeries.	P	Incidence of cognitive decline post-surgery. Neuropsychological tests at: pre surgical baseline; before discharge; 6 weeks; 6 months; and 5 years.	Cognitive decline occurred in: 53% discharge; 36% 6 weeks; 24% 6 months; 42% 5 years post-surgery.
Fearn [32]	Mean 60; range 43-77	70 CPB surgeries; 19 controls, urology surgery without cardiopulmonary bypass.	P	Influence of cerebral perfusion and embolization during CPB on cognitive function and recovery. Computerized battery of tests: pre surgery; 1 week; 2 months; and 6 months post-surgery.	More than 200 emboli were detected in 40 bypass patients and were associated with memory loss ($r = 0.3$, $P < .02$, Spearman). Initial greater cognitive dysfunction occurred in cardio patients vs urology controls, but equivalent after 2 months.
Wang [33]	≥70	88 CPB surgeries: 43 lidocaine vs 45 placebo controls	P	Lidocaine influence on post-operatively POCD: evaluations 10 min before CPB and 10, 30, and 60 min after CPB; neuropsychological tests administered before and 9 days after surgery.	Lidocaine use had a significant correlation with the reduced occurrence of POCD: 18.6% lidocaine group vs 40.0% control ($P = 0.028$).
Rasmussen [38]	>60	non-cardiac surgery: 188 general anesthesia (GA); 176 regional anesthesia (RA).	P	Test variability effect on measurements of POCD. Neuropsychological tests: pre surgery; 7 days post; and 3 months post-surgery.	30-48% of patients that had POCD at 7 days also showed POCD at 3 months. Neuropsychological test variability did not explain POCD incidence post-surgery.
Rasmussen [39]	>40	4 published studies with 2536 surgery patients and 359 healthy controls.	R	Does test variability differentiate true POCD vs random test variation. Evaluation 4 neuropsychological tests: pre surgery; 7 days; and 3 months post-surgery.	30-48% of patients that had POCD at 7 days also had POCD at 3 months. Neuropsychological test variability did not explain POCD incidence post-surgery.
Wu [40]	≥60	24 trials: 19 randomized; 4 observational; 1combination of randomized + observational data.	R	RA (neuraxialspinal, epidural) vs. GA. Neurocognitive test evaluation.	23/24 of all trials and 18/19 of randomized trials demonstrated no difference between RA and GA in POCD occurrence.
Rasmussen [34]	>60	187 non-cardiac surgery patients.	P	Peri-operative cortisol secretion relationship to POCD. Cortisol measured at 8h and 16h pre-operatively; 7 days; and 3 months post-operatively. Neuropsychology tests for POCD.	The persistent flattening in am/pm cortisol ratios was significantly related to POCD at 1 week (18.8%) and 3 months (15.2%).
Monk [7]	>18	1064 non cardiac surgery patents; 210 age matched controls (primarily family members of patients in the study).	P	Incidence of POCD. Neuropsychological tests before surgery, at hospital discharge, and 3 months after surgery. Three age groups: young, 18-39; middle-aged, 40-59; and elderly> 60.	There was a significant difference in POCD between all 3 surgical groups and the age-matched control subjects ($P < 0.001$). POCD at discharge: young (36.6%); middle-aged (30.4%), and elderly 138 (41.4%). POCD at 3 months after surgery: young 5.7%; middle-aged 5.6%; elderly 12.7%. Only elderly (≥60) are at significant risk for long-term POCD post-surgery.
Guay [29]	Of 26 studies, 22 had patients >60	1169 RA and 1196 GA. 12 RCTs assessor blinded to anesthetic technique: 393 RA; 405 GA.	M	Risk of POCD after single non-cardiac surgery: RA vs. GA. Standardized difference in means (SDM) for the tests of POCD.	SDM for 26 RCTs= -0.08 ($P = 0.094$); SDM for 12 RCT blinded to anesthetic technique or RA vs GA for POCD cognitive tests = 0.05 ($p= 0.51$). A single exposure of GA in adults did not significantly contribute to permanent POCD after non-cardiac surgery.
Osman [41]	18-60	60 open cholecystectomies randomly divided into: Propofol group; Isoflurane group; Sevoflurane group	P	Measurement of in vivo effects of 3 anesthesias on apoptosis. Blood levels as apoptotic markers: caspase-3; serum tumor necrosis factor related apoptosis inducing ligand (TRAIL); hemoglobin; hematocrit; creatinine; liver enzymes levels. Blood samples measured: preoperatively; immediately postoperative; and after 24 hours.	No significant difference in hematological markers and serum creatinine. Propofol group: significant ↑TRAIL and caspase-3 immediately post-surgery; both ↓ 24 hour ($p < 0.05$). Isoflurane group; significant ↑ TRAIL, post-surgery; ↓ 24 hour ($p < 0.05$). Sevoflurane group: significant ↑ TRAIL, caspase-3 levels immediately post-surgery and 24 hours. Significant ↑ 24 hour TRAIL vs Isoflurane and Propofol groups. Protection against apoptosis: isoflurane > propofol > sevoflurane
Ji [35]	≥65	61 total hip replacement surgeries	P	Association of post-surgery POCD with ↑ biomarkers of brain injury and inflammation. Analysis of CSF and blood samples plus neurocognitive tests pre surgery and 7 days post-surgery.	No difference in preoperative CSF Tau, IL-6, pTau or plasma IL-1b, IL-6, BDNF and CRP levels between POCD and Non-POCD groups ($P = 0.05$). POCD patients had: ↑ IL-1b; ↑ Tau/Ab 1-42; ↑pTau/Ab1-42; ↓ CSF Ab 1-42 ($P = 0.05$) in CFS and ↑ plasma MDA ($P = 0.05$) compared with the Non-POCD group at 7 days post-surgery.
Zywiel [31]	Avg, approx. 69; range 25-95	Total joint arthroplasties: 28 studies: 21 randomized; 2 prospective; 2 case control; 1 retrospective	R	Development of POCD: GA vs. RA; optimization of depth of general anesthesia; multimodal anesthetic techniques; different postoperative pain management regimens (avoiding morphine and limiting narcotics to oral formulations).	POCD manifested: no difference between RA and GA after 7 days; equivocal evidence for optimization of depth of general anesthesia; no evidence supporting use of multimodal anesthetic techniques; reduced POCD with non opioid postoperative pain management techniques.

Silbert [42]	≥60	300 hip replacement patients; 51 non-surgical controls	P	Association between preoperative cognitive impairment (PreCl) and POCD. Eight neuropsychological tests: pre-surgery; 7 days; 3 months; and 12 months.	PreCI was identified in 96 of 300 patients (32%), and these had a significantly increased incidence of POCD at 7 days and 3 months and cognitive decline at 12 months.
Li [43]	>60	laparoscopic cholecystectomy; 100 patients randomized: Dexmedetomidine (DEX) group; \placebo (P) saline group	P	Association of dexmedetomidine with POCD and cytokine levels. Cognitive function (MMSE) was assessed: 1 day prior to surgery; 6 hours, 1 day, 2 days post- surgery. Interleukin (IL) -1β, IL-6 and C-Reactive Protein (CRP) levels were also measured at these times.	POCD day 1: DEX 20%; P 42%. 6 hours: IL−1β, IL−6, CRP significant ↑ (P<0.01) compared with DEX and P baseline levels. DEX vs P 6 hours and 1 day: IL−1β, IL−6 and CRP levels significant ↓ (P < 0.01).
Valantine [44]	60-87	140; double blind, randomized; Exp group dexamethasone 8 mg before general anesthesia under Bispectral Index (BIS) between 35-45 or 46-55; Control no dexamethasone	P	Association of dexamethasone on POCD, neuroprotection. Neuropsychological tests: pre-operatively; 3rd, 7th, 21st, 90th and 180th days post-surgery. Comparison with normative data. S100β was evaluated before and 12 hours after anesthesia induction.	POCD day 3: Exp 25.2% BIS 35-45; 15.3% BIS 46-55. POCD Control: 68.2% BIS 35-45; 27.2% BIS 46-55. S100β no difference from baseline in Exp group; significant ↑ from baseline in control group (p<0.05).
Li [36]	≥18	3 studies with 855 dexamethasone patients and 538 placebo controls; 2 studies with 410 dexamethasone patients and 420 placebo controls	M	Examination of the effect of dexamethasone as a POCD prophylaxis vs no dexamethasone (placebo) for adults receiving GA.	Low quality of the evidence of post-operative incidence of POCD was found. No significant difference (p = 1.00) was observed between dexamethasone and placebo groups 30 days post-surgery.
Shoair [26]	≥65	69 non cardiac surgery patients; 54 non-surgical older adults as controls	P	Assessment of POCD in elderly surgery patients using computerized neurocognitive battery pre surgery and 3 months post-surgery. Assessment of POCD risk factors collected before, during, and after surgery, including patient medications and surgery risk factors.	15.9% post-surgical patients had POCD 3 months post-surgery. POCD risk factors included: APOE4 genotype; anticholinergic or sedative-hypnotic drugs prior to surgery; receiving sevoflurane for anesthesia.
Daiello [25]	≥70	560 non cardiac surgeries	P	Associations between delirium and POCD examined at 1, 2, and 6 months.	Delirium: 24% of 560 patients. POCD: 47% at 1 month; 23% at 2 months; 16% at 6 months. Increased relative risk POCD for delirium patients at 1 month (Relative Risk [RR] 1.34); however, not increased at 2 months (RR 1.08) or at 6 months (RR 1.21).
Langer [37]	≥75	101 non cardiac surgery patients under GA ; 33 age matched healthy control interventions	R	Effect of personalized intraoperative blood pressure target and mean arterial pressure (MAP≥ 90% of preoperative values) for Target Group and more liberal intraoperative blood pressure management (No-Target Group) on POCD. Neurocognitive tests preoperatively and 3 months post-surgery	Target Group spent a higher percentage of intraoperative time with MAP ≥90% of preoperative values vs No-Target Group (65 ± 25% vs. 49 ± 28%, p < 0.01). No correlation between intraoperative hypotension and POCD was found (p = 0.75).
Salem [45]	55 ± 16.6	254: 127 Kuwaiti patients (Group A); 127 Egyptian patients (Group B)	R	Association of the preoperative vitamin D level and POCD risk. ELISA estimation of serum 25OHD (Vitamin D levels): sufficient (≥75nmol/L); insufficient (50-75nmol/L); deficient (<50nmol/L). Cognitive function assessed: preoperatively, 48-hr; 1-week; and 2-weekspost-surgery.	Group A had insufficient serum 25OHD level compared to Group B (p = .00002). Old age, high BMI, duration and severity of surgery are co-factors for POCD. Preoperative low serum 25OHD is a significant independent specific predictor for POCD.

Table 1: Selected studies of post-operative cognitive dysfunction.

Study Type: P = Prospective; PM = Randomized prospective; R = Review; M = Meta-analysis.

The debate about whether GA or RA are more effective in reducing POCD is ongoing [29,31,38]. In a large review of 24 trial studies Wu et al., found no difference between RA and GA in contributing to POCD [40]. In a meta-analysis of 26 Randomized Controlled Trials (RCT) and 12 RCT (with assessor blinded to the type of anesthesia) of single non-cardiac surgeries, there was no increased risk of POCD using either GA or RA [29]. Zywiel et al., examined 28 case series of joint arthroplasties and reported that, except for one series, there was no difference between GA or RA one week following surgery regarding POCD incidence [31] [Table 1].

Numerous anesthesiology studies have focused on the association of surgery with anesthesia with POCD in the very young [2,46] young, middle aged [7] and elderly patients [7,47-50]. Monk et al., reported that POCD is present at hospital discharge following major non-cardiac surgery in all 3 adult patient groups studied (young 18-39 yr, middle-aged 40-59 yr, elderly >60 yr). However, only the elderly had a significant risk for long-term cognitive problems. Three months post-surgery, independent risk factors for non-cardiac surgery POCD included increased age, lower educational level, a history of previous cerebral vascular accidents with no residual impairment and POCD

at hospital discharge [7]. POCD sequelae range from a reduction of Independent Activities of Daily Living (IADL) in patients living independently to the development of disabling dementia. Regarding mortality, Monk et al., found that patients with POCD at hospital discharge were more likely to die during the first-year post-surgery [51]. Several studies have examined cognitive function before and after surgery [7,15,22,24,25,28,38,42]. The results of studies examining POCD post-surgery have yielded differing results. Perhaps the most consistent finding is that POCD is very frequent among the elderly seven days post-intervention [15,31,34,38,39,42] and less often after three months [7,15,26,34,38,39,42]. Compared to older patients without POCD three months after surgery, patients with POCD had increased rates of mortality and fewer returned to cognitive function when compared to controls [7,10,38,47]. Of note, patients with POCD at one week after surgery had an increased risk of leaving the labor market prematurely and had a higher prevalence of time receiving the equivalent of US Social Security Disability [22].

Despite the voluminous anesthesia research about POCD, this syndrome remains an incompletely understood and a complicated maze of interacting variables which have produced conflicting findings [52]. The number of surgeries for an individual may be a factor. A meta-analysis concluded that a single non cardiac surgery with GA would not significantly contribute to permanent POCD [29]. Some randomized controlled studies suggest the method of anesthesia is a major variable associated with prolonged cognitive impairment [10,15,24,28,39]. Rasmussen et al., found no significant difference in cognitive dysfunction three months postoperatively, while Shoair et al., reported 15.9 percent POCD in elderly postoperative patients [26,38]. The early findings of Moller et al. [15] that hypotension was not a significant risk factors seven days or three months post-surgery was confirmed by randomized cohort studies demonstrating no correlation between intraoperative hypotension and POCD [45]. Given the conflicting evidence of effective vitamin D levels for patients, especially for the elderly (unpublished data), the finding that preoperative low serum vitamin D levels are a significant independent specific predictor for POCD needs further investigation [45] [Table 1].

The number of variables that confound POCD understanding are numerous and include, but are not limited to the following: method of anesthesia administration (GA vs RA) [24,34,38,38,40,42]; pre-existing cognitive impairment [27,42,53]; perioperative pain management [31,33,54]; low sensitivity of neurocognitive test batteries for surgical patients [10]; pre-, intra- and post-surgery comorbidities (e.g., cerebral emboli history of cerebral vascular accidents) [7,32,55]; role of biomarkers [18,35]; prophylaxis potential of dexamethasone to decrease POCD risk [36]; perioperative neuroprotection [21,56]; genetic disposition [26]; neuroinflammation, potentially neurotoxic drugs [27]; duration of anesthesia, low educational level, a second operation, postoperative infections and respiratory complications [15]. The discussion of these and other POCD variables for geriatric patients are discussed below.

Variables Related to POCD

Chronic pain

Chronic pain has been associated with changes in global and regional brain morphology in addition to brain volume loss with decreases in connectivity between brain regions [57]. Structural brain changes in the middle corpus callosum, middle cingulate, white matter and the grey matter of the posterior parietal cortex can be associated with chronic pain which diminishes attention and mental flexibility as measured by neuropsychological tests [58]. Pain can result in brain atrophy and white matter lesions that have been shown to be associated with increased risk of delirium which is associated with and may contribute to the POCD prodrome [6,30,42,58].

Elderly patients often receive pre-surgery opioids for their comorbid medical conditions including chronic pain conditions (e.g., low back pain, chronic tension-type headache, fibromyalgia), which complicate both post-surgery recovery and the return to presurgical cognitive and functional levels [24,59]. Closely supervised pain management, minimal surgical incisions for total hip and total knee arthroplasties and physical therapy protocols improved outcomes compared to the same surgical interventions with standard procedures [60]. Singh et al., compared three postoperative pain management interventions following minimally invasive Transforaminal Lumbar Interbody Fusion (MIS TLIF): Patient-Controlled Analgesia (PCA); narcotic consumption; and, Multimodal Analgesia (MMA). The study revealed both PCA and MMA resulted in similar analgesia for patients during the inpatient stay, although MMA patients had reduced inpatient nausea/vomiting and shorter hospital stays [61]. Conscientious anesthesiologists and surgeons have cooperated to modulate perioperative pain and opioid use to decrease post-operative complications including POCD [48,58,60,61].

Prior medications

Improved anesthesia outcomes are more challenging in the geriatric population that commonly has a larger number of prescribed medications [55,62]. Aging is usually accompanied by physiologic changes such as reduced renal clearance with prolongation of medication elimination half-life and elevation in medication steady-state concentrations contributing to the increased risk of toxicity. Both the number of concurrent medications that older individuals routinely use, in addition to physiologic changes in these patients, render them more susceptible to developing cognitive toxicity [63]. Medications that can result in cognitive impairment during and after surgery include, but are not limited to: narcotics (e.g., tramadol, meperidine); sedative hypnotics (avoid benzodiazepines, prefer short acting remifentanil, dexmedetomidine); anticholinergics; sedative-hypnotics; corticosteroids; digoxin and diuretics [31,63]. Additional POCD risk factors include the autonomic neuropathy of diabetes mellitus that reduces gastrointestinal motility and hepatic functions, consequently increasing the risk of opioid and anesthesia drug side effects [31,55].

Inflammation

Elderly patients are particularly predisposed to POCD secondary to a variety of variables such as the negative sequelae of reduced anatomical and cognitive reserve associated with comorbid medical and psychiatric problems [3-5,64]. Inflammation and infection prior to surgery may contribute to diminished brain reserve [65] and increased risk of POCD [55]. Microglia, astrocytes and CNS-associated macrophages in the brain may respond to inflammatory signals from the peripheral nervous system. Peripheral inflammation can result in compromised anti-inflammatory feedback and decreased brain function [66]. This inflammation plays an important role in POCD related disruption of the Blood-Brain Barrier (BBB) permeability with subsequent leakage of inflammatory blood products into the brain. Compromise of the BBB function permits peripheral immune system products to invade the Central Nervous System (CNS) immune

system, initiating a damaging immune response in the brain [67]. Aging may also be associated with increased BBB permeability [68] due to reductions in microvascular density, capillary lumen size and number of mitochondria per endothelial cell [69]. Inflammation in the brain may initiate from a variety of sources. AD associated inflammation may include pathogens from mouth bacteria (Fusobacterium nucleatum, Prevotella intermedia), viruses (Herpes simplex) and *Borrelia* from Lyme disease identified at autopsy [70]. Risk factors accelerating these changes include hypertension, hyperlipidemia, diabetes mellitus and adverse drug reactions. Subsequent inflammatory processes contribute to the pathogenesis of white matter disease and alter the response to ischemia permitting entry of blood derived products and pathogens into the brain, resulting in chronic inflammation with increased risk for cognitive decline and POCD [70-71]. For example, when there is amplified BBB permeability in the hippocampus, CA1 and dentate gyrus subdivisions, there may be an accelerated cognitive decline [70-72].

One of the major contributing factors to POCD is gastrointestinal integrity. The connection between intestinal microbes and the brain is known as the gut-brain axis [73]. The gastrointestinal epithelium creates an anatomic/physiologic protective barrier [74] in addition to an immunological barrier that in turn protects the circulatory system from infection, inflammation and toxinstoxins (70,75). Gastrointestinal tight junctions are designed to allow absorption of essential molecules from the digestive track contents to be transported into the cells lining the gastrointestinal tract and to exclude inflammatory and/or toxic gastric contents from entering the circulatory system [70,76]. The integrity of the gastrointestinal epithelium can be compromised by inflammation secondary to surgical interventions and trauma, resulting in a post-operative or post-traumatic systemic inflammatory response syndrome, sepsis and multiple organ failure [70,77]. Neuroinflammation and microglia activation are regulated by the gastrointestinal microbiota [78,79]. Notably, amyloid, the protein forming AD extrasellar plaques, is produced during inflammation [70]. Abnormal disturbances of the tight junctions of the gastrointestinal tract are referred to as "leaky gut". Intestinal permeability may be assessed using oral ingestion of small to large-sized probe molecules (e.g., lactulose and mannitol) and measured in the urine to quantitatively assess the degree of leaky gut damage [70,80].

Genetic predisposition and modern Western eating habits also are thought to contribute to POCD. Studies suggest that a diet low in fiber, high in sugar and saturated fats, combined with stress and heavy alcohol use are key players in the leaky gut syndrome [81]. Fragments of bacteria, yeast and other substances, such as pesticides, may enter the blood stream and are identified by the immune system as foreign invaders which may precipitate autoimmune reactions. This response may perpetuate a low-level inflammation or a frank autoimmune response such as multiple sclerosis, rheumatoid arthritis, lupus erythematosus, diabetes mellitus type 1, chronic fatigue syndrome, fibromyalgia, HIV-associated dementia and cerebral ischemic disease or Alzheimer's dementia [70,81,82]. Other factors that can damage gastrointestinal permeability include gluten, environmental chemicals, sugar, dairy products, processed foods, preservatives, carbonated beverages, yeast, fungi, parasites, inflammation products and medications (e.g., aspirin, acetaminophen) [70,81]. The body responds to inflammation by producing amyloid both systemically, such as in amyloid A amyloidosis, or in the brain as illustrated by the amyloid plaques of AD [83]. The inflammatory agents and toxins that enter the blood stream via the leaky gut may cross the BBB to create inflammatory and infective processes in the brain resulting in neurodegenerative disorders [70]. Compromised BBB permeability, as measured by the cerebrospinal fluid/plasma albumin ratio (Qalb) has been demonstrated to be elevated in patients with AD, Lewy body dementia, Parkinson's disease dementia, subcortical vascular dementia and frontotemporal dementia when compared with controls [84]. Thus, alterations in the gastrointestinal integrity from leaky gut may be responsible for susceptibility to and continuation of POCD.

Type of Surgery and Trauma

The incidence of POCD varies among surgical studies. The type of surgery such as cardiac surgery, orthopedic surgery (e.g., joint replacement) and non-cardiac/orthopedic surgeries is important in the discussion of POCD [28,32,85,86]. The impressive study of NACOR by Denier et al identified the ten most frequent surgeries by age groups. Orthopedic surgeries were among the top three for ages 60 to 90 or older, usually consisting of hip or knee replacements, arthroplasty and fractures or dislocations. Lens and cataract procedures were also high on the list. The invasive procedure of coronary artery bypass grafting (CABG) was the eighth most common procedure for patients 65 to 69 [25]. When comparing mortality rates for hip replacement surgery versus CPB at 30 days (0.30% vs 2.44% respectively) and at one year (21.2% vs 6.25% respectively), hip replacement surgery mortality was markedly less than CPB at 30 days, but markedly more than CPB at one year [87-89].

In other research, the incidence of POCD has been observed to be approximately 25-50 percent following orthopedic procedures [90] and 20-50 percent following cardiac surgery [24]. Additional studies found an incidence of POCD of 6.6 percent in elderly patients three months following minor surgery under GA, and 10.4 percent demonstrated cognitive dysfunction two years following major surgery [16,28]. For minimally-invasive procedures such as cataract removal, POCD has been estimated to occur in one to three percent of cases [24,40,91]. These discrepancies in findings may be due to different indices used to assess POCD [39,92].

During CPB, hypoperfusion and embolic factors have been found to be associated with parieto-occipital watershed area injury contributing to neurocognitive deficits [93]. Studies have demonstrated that microemboli from ascending aortic atheromas are independent and significant risk factors for stroke and neurocognitive deficits post operatively [32,94-97]. Patients with a higher microembolic load during the pre-incision phase of CPB have an increased risk of post-surgery neuropsychological deficits such as POCD compared to patients with a lower pre-incision microembolic load [98]. The influence of cerebral perfusion and embolization during CPB on cognitive function was compared with post-operative cognition in a control group undergoing urologic surgery. While cognitive function deteriorated more in patients having CPB than in the urinary surgery control patients, recovery was similar in most tests by two months. In the CPB group, premorbid cerebrovascular disease was more severe than expected and predisposed to attention difficulties, whereas emboli caused increased memory deficits [32].

Type of Anesthesia

There are numerous risk variables involved in the use of GA, particularly in patients 60 years or older. Stabilizing cardiovascular and respiratory system comorbidities prior to surgery improves outcome [55]. Compromised respiratory function impairs regulatory sensitivity to hypoxia and hypercapnia thus increasing risk of postoperative respiratory complications [99]. A meta-analysis of non-cardiac surgeries, including 26 randomized controlled trials with 1169 adults receiving RA and 1196 adults receiving GA, concluded that one exposure to GA does not result in permanent POCD [29]. Anesthesia risk factors include the duration of anesthesia and the use of agents causing neuroinflammation, neurotoxicity or low intraoperative cerebral oxygenation [21,26,27,84,100]. However, it has been demonstrated that in the outpatient setting, both propofol and volatile anesthesias may be used for GA, and the complications of POCD are not as frequent as with equivalent inpatient surgical procedures that involve the added stress of hospitalization [42].

Some of the most frequently employed volatile anesthesias in the USA include the halogenated hydrocarbons isoflurane, sevoflurane and desflurane [21]. Three advantages of volatile anesthetics are that they quickly induce adequate anesthesia, anesthesia concentrations can be accurately monitored and the majority of patients recover quickly without post-surgical difficulties [21]. Data suggest that specific volatile anesthetics, such as desflurane, may have a less harmful neurotoxic profile compared to others in the pre-clinical and clinical settings [20]. Research suggests that sevoflurane and isoflurane alter mitochondrial membrane permeability and thus induce apoptosis in human T lymphocytes [101]. *In vivo* studies demonstrated the effects of propofol, isoflurane and sevoflurane on apoptosis by measuring caspase-3 and TRAIL blood levels preoperatively, immediately postoperative and 24 hours post-surgery. Based on caspase-3 and Tumor Related Apoptosis Inducing Ligand (TRAIL) blood levels, isoflurane provided the best protection against apoptosis, while sevoflurane provided the least. The authors opined that the results did not definitively characterize propofol as an anesthesia associated with induced apoptosis [41].

The choice of using RA versus GA is multifactorial for geriatric patients. These anesthesias might include general, spinal, epidural anesthesia or peripheral nerve blocks. As above, the question of whether RA reduces the risk of POCD has not definitively been answered. Some of the advantages of RA compared to GA include: reduced blood loss and need for transfusion; reduced deep vein thrombosis and pulmonary embolism; improved postoperative pain control and decreased procedural and hospital costs [55,102,103]. One disadvantage is the risk of some geriatric patients developing anxiety during RA. The operating room can be very alienating for persons unfamiliar with the advanced technology common to most hospital surgical theaters. If the patient is not educated about the relative details of their surgical procedure using RA prior to the intervention, they may have anxiety reactions in the operating room related to such factors as the impersonality of the gowned surgical team members, anesthetic induced paralysis or numbness of a limb, or the variety of operating room equipment sounds [55]. Also, when the patient is awake during RA, increased anxiety during surgery may lead to restlessness, interfere with patient cooperation and compromise the outcome [104].

What can be done to reduce anxiety during RA? Discussion with the patient of what to expect during the surgery while obtaining the informed consent procedure is important. Having the team be on the same page will decrease the possibility of something being said by one team member that may alarm the patient. A survey of 111 anesthesiologists documented their most commonly employed management strategies to reduce anxiety are: communication with the patient and providing reassurance (95%); sedation (82%); distraction techniques (e.g., listening to music) (54%); partner attendance or watching the operation through a camera in the operating theatre (15%-20%) [105]. When these anxiety management methods are ineffective or the patients insist on GA, GA is preferable for this subpopulation of geriatric patients [55].

Prior Neurocognitive Deficits

Studies suggest that early signs of AD, extracellular Aβ deposits and intracellular neuronal tangles associated with predominantly synaptoclastic brain activity, may increase POCD risk. Early AD neuropathology without clinical symptoms may anticipate POCD susceptibility following surgery with anesthesia. Evered et al., concluded that low CSF Aβ could predict POCD at three months post-surgery [106]. Cellular death secondary to anesthesia toxicity appears to be related in part to microRNA-125b accelerating neuronal death. In AD, over-expression of miR-125b in primary neurons causes tau hyper phosphorylation which increases accumulation of extracellular Aβ deposits and intracellular neuronal tangles [107].

POCD CSF Biomarkers as Future Clinical Tools

Biomarkers can be utilized as indices of inflammation in the peripheral and CNS [35,108]. For example, C-Reactive Protein (CRP) is a biomarker of inflammation in general, and malondialdehyde levels may indicate the degree of oxidative stress in keratoconus, bullous keratopathy and osteoarthritic joint disease [35]. Researchers have investigated biomarkers that indicate the possibility of POCD in the CSF pre- and post-surgery. One biomarker is the cytokine IL-2, a type of cytokine signaling molecule in the immune system. It is a protein that regulates the activities of white blood cells (leukocytes, often lymphocytes) that are responsible for immunity. IL-2 and other biomarkers such as total Tau protein, phosphorylated-tau (pTau), CSF tau phosphorylated at threonine-181, Ab 1-42, Interleukin 1β, other interleukins and Brain-Derived Neurotrophic Factor (BDNF) may also serve as POCD biomarkers [35,108].

Ji et al., investigated the changes in plasma and cerebrospinal fluid biomarkers in aged patients exhibiting early POCD following total hip-replacement surgery [35]. They hypothesized that elderly patients (>65 years old) that experienced POCD following total hip-replacement with spinal anesthesia would have different patterns of injury and inflammation brain biomarkers compared to a control group without POCD. Of the sixty-one patients that completed the CSF, blood sample collections and the neurocognitive tests, 24.6 percent of the surgery patients demonstrated POCD seven days post- surgery. Compared to the non-POCD patient group, the POCD patient group had significantly higher IL-1b, Tau/Ab 1-42, pTau/Ab 1-42, higher plasma levels of MDA and a lower CSF levels of Ab 1-42 [35].

Prevention of POCD

In general, anesthesiologists focus on minimizing cardiovascular and pulmonary risks intraoperatively in addition to minimizing nausea, vomiting and pain postoperatively. A Swedish study sent

questionnaires to greater than 2500 Swedish anesthesiologists and nurse anesthetists. The survey revealed that often postoperative neurocognitive deficits were considered to be of minimal importance in the anesthesia protocol. Anesthesiologists have historically not focused on the reversible and irreversible postoperative cognitive loss occurring principally in the elderly [9]. Some studies suggest the use of electroencephalography-based depth of anesthesia (DOA) monitoring to ascertain the best anesthetic delivery to reduce post-operative cognitive deficits [109]. DOA monitors allow individualization of anesthesia by permitting accurate drug administration to better measure the patients' state of arousal. Monitoring DOA reduces the risk of excessive anesthetic depth that may contribute to POCD [109].

There is considerable variability in detecting cognitive changes pre- and post-surgically as some studies utilize test batteries with low sensitivity in surgical patients [10]. Neuropsychological testing for POCD has included a variety of test batteries depending on the psychological domains chosen as indices of memory disturbance. For example, testing instruments often cited to assess POCD include the Logical Memory Test, the CERAD word list memory, the Boston Naming test, Category Fluency test, Digit Span Test, Trail making test and Digit symbol substitution test to name a few [23]. Lloyd et al., 2012 delineated specific pre-surgery and peri-surgical parameters to reduce the risk of POCD [110]. The presence of POCD 12 months or more following surgery is a strong predictor of permanent cognitive loss [42].

Most geriatric clinicians encounter complaints of POCD after their patients have undergone their surgical procedures. Studies show that self-reports of cognitive status post surgically is poorly correlated with objective testing results. Objective diagnosis of POCD requires baseline presurgical neuropsychological testing followed by post-surgical testing with the patient being their own control [23]. The pre- and post-surgery neuropsychological tests utilized to assess POCD have varied widely among studies.

Surgery often exposes pre-existing cognitive impairment (PreCI) that has not been previously identified. Studies in the anesthesiology literature have established an association between PreCl and POCD [23,39]. PreCI is defined as "a decline of at least 2 SD on two or more of seven neuropsychological tests compared to population norms" [42]. It has been suggested that cognitive impairment be defined as a z-score of 2 or more tests [110].

Presurgery cognitive capacity is an important independent risk factor for POCD. In one study of 300 patients with PreCI, hip joint replacement surgical patients were compared with 61 non-surgical controls. The PreCl group had increased POCD at seven days (25.3% vs 13.3%) and 30 days (14.9% vs 7.1%). Twelve months post-surgery, the PreCl group demonstrated increased cognitive decline compared to the control group (9.4% vs 1.1%) [42,48].

Pre-Surgical, Intra-Operative and Post-Surgical Treatment

Studies regarding the treatment of POCD are beginning to appear in the literature. One of the many probable contributing factors involved in POCD is inflammation. Li et al., employed intravenous dexmedetomidine during surgery to investigate its effect in suppressing surgical inflammation following surgery. On day one, 20 percent of the dexmedetomidine group demonstrated signs of POCD versus 42 percent of the control group as measured by the Mini-Mental State Examination. Also, concentrations of IL-1β, IL-6 and CRP were significantly lower in the dexmedetomidine group than found in the control group [43]. Another study investigated the role of perioperative inflammatory and protein S-100β concentrations with POCD in elderly patients after total hip-replacement surgery. The authors found that patients with POCD one day after surgery had significantly higher serum levels of IL-6 six hours post-surgery and also significantly elevated S-100β one hour after surgery. These results suggest that both IL-6 and S-100β may serve as predictive biomarkers for POCD [111]. An additional study specifically explored the biomarker S-100β. Valentin et al., administered a low dose of dexamethasone (anti-inflammatory drug) immediately before surgery and used a lighter depth of anesthesia during the surgery. In their prospective phase III, double blind, randomized study, 140 elderly patients undergoing non-cardiac and non-neurologic surgery, the experimental group received 8mg of IV dexamethasone before general anesthesia and the control group did not. The dexamethasone group had less POCD and lower levels of protein S100B compared to the non-dexamethasone group three days postoperatively [44]. Delirium is another surgical dilemma often coexisting with POCD. Delirium has been shown to have an increased relative risk with POCD in 560 non-cardiac surgeries with an incidence of POCD of 47 percent at one month, 23 percent at two months and 16 percent at 6 months [25]. Once the patient is out of the hospital and demonstrates memory problems either subjectively or objectively (comparison of preoperative baseline with postoperative neurocognitive testing), lingering post discharge delirium should be ruled out [10].

Occasionally, elderly patients have had cognitive screenings to assess dementia risk prior to their surgery. While the cognitive screens may be quite fundamental compared to research neurocognitive batteries, they may provide a presurgical index to assess POCD risk. Some clinicians go through a differential diagnosis including ongoing post-surgical delirium associated with comorbid infection, inflammation, metabolic irregularities (e.g., Vitamin B12, folate, vitamin D, thyroid function) in addition to medical, psychiatric, pharmacy and substance abuse problems. This replicates the clinical approach often employed by geriatricians for persons presenting to the outpatient clinic with memory disorders from subjective cognitive impairment, Mild Cognitive Impairment (MCI) and the Dementias (AD, vascular dementia, LBD, PD, frontotemporal dementia, etc.,) [45].

Preserving Cognitive Function

In the past several years, a group of researchers at the University of California, Los Angeles (UCLA) School of Medicine and the Buck Institute Buck Institute for Research on Aging at the University of California, San Francisco, have developed a treatment protocol to improve cognition and reverse the cognitive decline of AD. Dr. Dale Bredesen and colleagues at the UCLA School of Medicine and the Buck Institute Buck Institute have identified 150 known factors that contribute to AD. To assist in the differential diagnosis of AD and other dementias, Dr. Bredesen has recommended that everyone over the age of 45 have a cognoscopy, regardless of their cognitive condition. A cognoscopy involves a series of screening tests which provide indices of the cognitive state of anyone whether they are asymptomatic or have signs of cognitive deficits such as POCD [69,112], Dr. Bredesen has published a 36-point program called ReCODE (Reversal of Cognitive Decline) involving metabolic enhancement [113] which

has successfully reversed AD even for persons with two copies of the ApoE4 allele. This treatment protocol has been supported by over 200 peer reviewed publications [69]. While the ReCODE protocol was not intended for the treatment of POCD, it addresses most of the complex factors that may be contributing to the memory deficits of POCD: insulin resistance; inflammation and infections; hormone, nutrient and trophic factor optimization; toxins (biological, chemical, physical); and restoration and protection of damaged synapses [69]. The protocol includes changes in lifestyle, diet, sleep patterns, exercise and mediation to reverse cognitive decline. Outcomes are measured by cognitive scales, homocysteine levels, hippocampal volume changes and other biomedical markers. Hence, it may be hypothesized that the ReCODE protocol will provide treatment benefits for some elderly with POCD.

The ReCODE protocol is designed to restore mitochondrial function by creating a state of cyclical ketosis in patients with memory disorders. Protocol screening tests include many that are used in geriatric clinical practice: Ferritin; GGT; 25 hydroxy vitamin D; fasting insulin; high sensitivity CRP; TSH; free T3; reverse T3; and free T4. The ReCODE protocol screening tests that are not commonly used in geriatric clinics include: ApoE4; blood levels of vitamin E, glutathione and serum selenium; serum copper and zinc ratio; TNF alpha; and omega-3 index; and, omega 6:3 ratio. Optimizing metabolic balance decreases mitochondrial free radical formation thus reducing mitochondrial DNA alterations that contribute to cognitive decline [45,69,114].

ReCODE establishes the need to address nutritional ketosis. The protocol encourages patients to get ketone meters to help them maintain a mildly ketogenic state of 0.5-4.0 beta hydroxylate millimolar beta-hydroxybutyrate. Dr. Bredesen recommends maintaining a mild ketosis with a principally plant-based diet. He also suggests daily fasting of 12 hours between dinner and breakfast. To reduce inflammation, the protocol includes methods to reduce leaky gut syndrome and pathogenic microbes in the nose, nasal sinuses and oral cavity (e.g., *P. gingivalis*, and Herpes simplex virus-1). The protocol recommends exercise to increased BDNF in addition to optimizing sleep. Important animal-based nutrients include omega-3, magnesium, vitamin D and fiber. Extensive information is available on line at numerous sites referencing Dr. Dale Bredesen, the Recode Report from "MPI Cognition" [115] and his book The End of Alzheimer's with the Bredesen Protocol-ReCODE [70].

Important Considerations for Surgeons and Supportive Medical Staff

Understanding the patient's presurgical status to establish baseline cognitive function is an essential component of assessing and treating POCD [110,116]. An important point regarding PreCl and POCD is that the prodromal stages of many dementias are often difficult to identify pre-surgically. The most frequent dementia in the United States is AD. It is a progressive syndrome which may be identified in its various prodromal states such as MCI. Cognitive impairment such as MCI may already exist in many elderly patients who undergo surgery, thus increasing risk for POCD following surgery [17]. MCI may be preceded by 80 months of degenerative cognitive capacities prior to diagnosis. Following the cognitive decline to MCI, the diagnosis of AD may be preceded by five to six years of global cognitive decline, semantic memory and/or working memory [117].

Cognition Screening and Preexisting Cognitive Impairment in POCD

It is important that patients at-risk for POCD receive pre-surgical workups for reversible cognitive deficits such as vitamin deficiencies, endocrine problems and polypharmacy. In addition, the clinician responsible for the patient's care must become an active participant in determining the best anesthesia route (e.g., general, regional, local) and introduction of anesthesia (e.g., inhalation, intravenous, intramuscular, or subcutaneous, oral, etc.,). The specific anesthetic agent needs to be selected as diligently as possible to minimize POCD risk.

Education and Cooperation of Medical Staff Prior to Surgery

The foundation of understanding POCD and improving post-surgery outcomes begins with the education of all persons working in clinical medicine and anesthesiology. The phenomenology of POCD should be a mandatory component for students in nursing, physician assistant, nurse practitioner, medical school, clinical residencies and medical fellowship programs. POCD should be a core subject in clinician geriatric programs [1]. Such preparation will encourage the staff to educate patients at risk for POCD before surgery regarding measures available if POCD is part of the surgical outcome. It has been suggested that anesthesiologists could play an active role in assessing cognitive function in older adults before surgery just as they currently screen for heart disease risk factors [110]. Usually, the geriatrician, internist, primary care physician and anesthesiologists are the clinicians that see the elderly patient prior to surgery and have the best opportunity to instruct the patient about POCD risk and treatment. Following patient education, if there is a risk of POCD based on clinical presentation or on the patient's medical history, a presurgical brief cognitive screen should be performed to serve as a presurgical baseline and an index for possible postsurgical POCD problems [115]. Successively, the clinical and anesthesia teams should meet to discuss the risks and benefits of surgery and POCD. Finally, the type of anesthesia should be chosen that minimizes POCD on a case by case basis. Following surgery, the treatment team needs to minimize pain and inflammation with medications least likely to contribute to POCD. The goals of the treatment teams should include not only the survival of high-risk patients during and after major surgery, but also the minimization of short- and long-term cognitive disability [110].

Conclusion

POCD is more common than perceived by most clinicians. Advanced age, complex surgery, prolonged surgical duration, postoperative delirium and infection have been recognized for several decades as risk factors. Increased clinical awareness and education about POCD are needed for all clinicians seeing elderly patients. While research is ongoing in anesthesiology, new research understandings need to be communicated to the geriatricians, internists and primary care physicians that routinely see elderly patients that are considering or scheduled for surgery. Recent studies have identified the importance of neuroinflammation, neurotoxic drugs and volatile gas chemical characteristics as confounding POCD variables. POCD pathophysiology is related to numerous variables requiring a multifactorial presurgical assessment and postsurgical treatment program such as the ReCode protocol. Future research is needed for formulating a

consensus understanding of POCD etiologies and treatment protocols to reduce morbidity and mortality. POCD is an under-appreciated problem mainly for the geriatric population that needs to come out of the shadows. Quality care for the elderly patients requires attention to the possibility of POCD prior to, during and after surgery. Clinicians are strongly encouraged to address this issue with their patients.

Conflict of Interest

The authors report no conflict of interest. The report findings do not represent the views of the Department of Veterans Affairs or the United States Government. This material is the result of work supported with resources and the use of facilities at the Veterans Affairs Medical Center, Salem, Virginia.

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