82 Cognitive Dysfunction and Other Long-Term Complications of Surgery and Anesthesia

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KEY POINTS

- Postoperative cognitive concerns have been voiced by older patients, their families, and caregivers for over a century, and more recently documented with objective testing.
- The term postoperative cognitive dysfunction (POCD) is neither recognizable by the general medical community nor sufficiently granular to cover the spectrum of perioperative cognitive disorders. It will be replaced by a DSM-5-motivated nomenclature, which will include postoperative delirium.
- The new Perioperative Neurocognitive Disorder (PND) nomenclature will require subjective complaints in addition to objective testing and assessment of daily function.
- Objective testing can take many forms, and can be variously analyzed to establish if a decline has occurred.
- Cognitive screening in older adults should be included in preoperative consultations, and informed consent discussions should include PND.
- PND is the most common perioperative complication in older adults, and the strongest risk factors for PND are advanced age and prior cognitive disorder.
- Few intraoperative parameters or drugs are associated with PND, although some EEG metrics predict delirium and PND in a few studies.
- Many mechanisms for PND have been proposed and tested in preclinical models. Neuroinflammation induced by the surgery in the setting of a vulnerable or "primed" brain has the most support at this time.
- Other than cognitive screening, validated imaging or biofluid biomarkers are not yet available for either risk stratification or disease monitoring.

Introduction

Anesthesia and surgery have been associated with cognitive changes in older adults for more than 100 years,[1] but these observations were largely anecdotal until the International Study of Post-Operative Cognitive Dysfunction (ISPOCD) was undertaken in the late 1990s.[2] Since then, there has been intense investigation and interest in all aspects of "POCD," ranging from mechanistic to therapeutic, rodent to human. This chapter hopes to capture this breadth of investigation in a manner that informs the clinician and peaks the interest of the investigator. At the outset, we emphasize problems with the existing definitions and terminology, and present recommendations for a new nomenclature and diagnostic criteria. We will then present and discuss the details related to both subjective and objective metrics of cognitive decline. Of perhaps greatest interest to clinicians are the pre- and intraoperative risk factors associated with cognitive decline, and if the perioperative management can be adjusted to mitigate the risk. Finally, we review and discuss potential mechanisms underlying the various postoperative neurocognitive disorders (NCDs), both related to the anesthetic management as well as the surgery and associated comorbidities. The chapter is thoroughly referenced, but this field is advancing rapidly, and thus it is inevitable that some current literature is not represented.

Nomenclature, Diagnosis, and Measurement

NOMENCLATURE

The ISPOCD group coined the term postoperative cognitive dysfunction (POCD), which reflected an objectively measured decline in cognitive function that typically persists beyond the period expected for normal recovery from the physiological and pharmacological effects of anesthesia and surgery.[3] When patients presenting for anesthesia and surgery are identified with cognitive impairment at baseline, this has been referred to as preexisting cognitive impairment (PreCI).[4]

TABLE 82.1 Constructs Previously Used to Define Cognitive Change Associated with the Perioperative Period and the Recommended New Nomenclature

Time Period	Previous Nomenclature	Old Criteria	New Nomenclature	New Criteria
OVERARCHING TERM: PERIOPERATIVE NEUROCOGNITIVE DISORDERS (PND)				
Preoperative Baseline	Preexisting cognitive impairment (PreCI)	≥2 SD below norms on ≥2 tests	Mild/Major NCD	NCD criteria, DSM-5: 1 to <2 SD (mild) or ≥2SD (major) below norms or controls in ≥1 cognitive domain *Plus:* Subjective complaint, *and* IADLs (preserved for mild NCD and declined for Major NCD)
Acute postoperative	Postoperative delirium (POD)	DSM-5	Delirium (postoperative) (POD)	DSM-5
1-30 days postoperatively	Postoperative cognitive dysfunction (POCD)	≥1.96 SD below controls on ≥2 tests	Delayed neurocognitive recovery	NCD criteria, DSM-5
30 days-12 months postoperatively	Postoperative cognitive dysfunction (POCD)	≥1.96 SD below controls on ≥2 tests	Mild NCD (postoperative) Major NCD (postoperative)	NCD criteria, DSM-5
New diagnosis beyond 12 months postoperatively	Postoperative cognitive dysfunction (POCD)	≥1.96 SD below controls on ≥2 tests	Mild NCD Major NCD (unless not a new diagnosis)	NCD criteria, DSM-5

IADLs, Instrumental Activities of Daily Living; *NCD*, neurocognitive disorder.

Postoperative delirium (POD) refers to a form of acute cognitive disruption characterized by inattention, a fluctuating course, and cognitive disturbance, and is diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders, version 5 (DSM-5).[5] Delirium in the community conforms to the same definitions and criteria. In contrast to POD, which conforms to the criteria for delirium diagnosed in any situation, POCD and PreCI have been confined to the field of perioperative medicine research where they have been historically defined by objective criteria with no attention given to subjective or functional criteria. In contrast, cognitive impairment and decline diagnosed in the general community conforms to either DSM-5 definitions and criteria, and/or the National Institute of Aging-Alzheimer's Association (NIA-AA) definitions, all of which require a subjective component and an assessment of activities of daily living (ADL). The NIA-AA terms Mild Cognitive Impairment (MCI[6] and dementia[7]) are more familiar than the DSM-5 terms (mild and major NCD), but the definitions and criteria roughly map onto each other.

The NIA-AA nomenclature is more granular, making provisions for the inclusion of biomarkers (biochemical and imaging). This is currently useful for research purposes, but is likely to apply to clinical scenarios in the future. In addition to the subjective complaint and functional criteria, another important difference between DSM-5/NIA-AA and POCD/PreCI has been the objective criteria applied. Although variable, many POCD/PreCI studies require a decline of 1.96SD below controls on two or more tests from a battery of 8-10 neuropsychological tests. Mild NCD and major NCD require 1-2SD and ≥ 2SD, respectively, below controls/norms in only one cognitive domain.

These differences, combined with the variability of POCD criteria (and timing) prompted an international multidisciplinary group to consider a new nomenclature for POCD.[8] Not only would diagnostic standardization facilitate further research in the area, but it would allow effective communication between clinicians at a clinical level. This new nomenclature recommends "perioperative neurocognitive disorders" (PND) as an overarching term for cognitive impairment or change, including delirium, identified in the perioperative period. Constructs previously used to define cognitive change associated with the perioperative period are discussed below with the recommended new nomenclature (Table 82.1).

Preexisting Cognitive Impairment

PreCI was used to refer to objectively assessed cognitive impairment that is observed in patients at baseline (compared to population norms). This is a preoperative assessment of impairment and should be considered in terms of cognitive impairment that might be coincidentally identified in the community and not just in terms of impending anesthesia and surgery. Hence, it is recommended that the term PreCI be replaced by mild NCD (MCI) or major NCD (dementia).

Delirium

POD should be recognized as a specific category consistent with DSM-5 terminology if the patient is in the immediate postoperative period and other specific causes have been excluded. The reported incidence of POD in the elderly is highly dependent on how it is diagnosed and screened. The most widely used and validated tool is the Confusion Assessment Method (CAM) (Box 82.1)[81]. The term *postoperative* refers to a specific and known temporal association with anesthesia and surgery, noting that surgical procedures occur annually in approximately 30% of individuals aged 65 years or more. POD is therefore defined as delirium which occurs in hospital up to 1 week postprocedure or until discharge, and which meets DSM-5 diagnostic criteria.

Postoperative Cognitive Dysfunction

POCD has been used in research studies to describe an objectively measurable decline in cognitive function at intervals from one day to 7.5 years after surgery.[9-11]

BOX 82.1 Confusion Assessment Method

Must include both:
A. Acute onset and fluctuating course
B. Inattention
And one of either:
C. Disorganized thinking
D. Altered level of consciousness

Significant heterogeneity around the definitions, time points for assessment, and criteria for POCD has resulted in widely varying results. As stated above, POCD does not require a subjective complaint or evidence of functional impairment, while the DSM-5 requires both. Thus, the major differences between POCD and NCD are the requirement for a cognitive concern, evidence of daily function, and the requirement for an objective decline in only one cognitive domain in the latter.

Cognitive Concern

The subjective cognitive complaint could be reported by the individual, family member, caregiver, or clinician. It is unlikely in the early postoperative period that a patient or an informant would be able to make an accurate assessment of subtle cognitive decline. Therefore, while assessment for NCD after discharge but prior to full recovery may be technically possible, the clinical relevance of its attribution would be unclear. Therefore, the term "delayed neurocognitive recovery" (dNCR) is recommended for this interval. This term should be used up to 30 days after the procedure, when recovery from most surgery and hospitalization should have occurred. The diagnostic criteria for NCD may be applied, but the outcome if impaired would be dNCR. It is possible that high functioning individuals may report cognitive concerns without objective evidence of decline. Because the subjective report from the participant, informant, or clinician is an essential element of diagnosing a PND, this may still be considered dNCR, and considered in the context of each individual case for clinical interpretation.

Activities of Daily Living Assessment

Assessment of daily function is an essential element of classifying mild and major NCD. This is achieved using an appropriate tool to measure ADL, which are everyday *personal care* activities that are fundamental to caring for oneself and maintaining independence. To detect more subtle declines in function, Instrumental Activities of Daily Living (IADLs) are used, which include activities like shopping, driving, and managing finances. For mild NCD (MCI), ADLs are maintained, while for major NCD (dementia), a decline is required.

Objective Testing

According to DSM-5[5] and our recommended PND terms,[8] mild NCD (postoperative) requires a 1 to <2 SD decline in cognitive testing compared to controls or norms, and major NCD (postoperative) requires a decline of 2 or more standard deviations on one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition)[5] using an appropriate neuropsychological assessment. Neither the DSM-5 nor the NIA-AA criteria for objective testing specify individual neuropsychological tests, nor the number of tests required in a battery. It is important to note that this refers to psychometric assessments that objectively assess specific cognitive domains, *not to the use of screening tools* such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). While useful for preoperative risk assessment, these brief screening tools do not have the sensitivity to assess change in specific cognitive domains.

Thirty days after surgery, the term mild NCD (postoperative) (postoperative MCI) or major NCD (postoperative) (postoperative dementia) should be used instead of dNCR. The "postoperative" modifier should be used as long as the criteria are met, and as long as first diagnosed prior to 12 months postoperatively. If first noticed or diagnosed 12 or more months following surgery, the postoperative modifier is not used.

MEASUREMENT AND DIAGNOSIS OF PERIOPERATIVE NEUROCOGNITIVE DISORDERS

Historically, a diagnosis of POCD has relied only on an objective assessment of decline using a battery of neuropsychological tests that cover many cognitive domains (e.g., executive function, memory, attention, visuospatial, psychomotor, and language). In most studies, very conservative cut-points were applied (e.g., 1.96 standard deviations below controls on two or more tests out of a battery of 8-10). These research applications contrast sharply with the simple objective criteria required for mild NCD (postoperative) or major NCD (postoperative) as described above, and are described in detail elsewhere.[12]

Assumptions Underlying Assessment of Postoperative Cognitive Dysfunction/ Perioperative Neurocognitive Disorder

Prospective studies investigating POCD usually assessed baseline cognition at a single time point only, often within days to weeks of the procedure. This makes three important and not necessarily valid assumptions. First, it assumes normal preoperative cognitive function, because screening was performed with a tool insensitive to cognitive impairment, such as the MMSE or MoCA. Second, a single time-point assessment assumes stable cognition. The third assumption is that results are reproducible, even without an intervention. Even if we assume that patients have stable cognition, it is unlikely that two consecutive assessments would yield the same results, due to a variety of intrinsic and extrinsic factors.

Cognitive Decline Outcome Criteria

There are several criteria that studies have used to define POCD in the past. These include the 1SD rule,[13] the 20% rule,[14] and the reliable change index (RCI).[15-17] Each has advantages and limitations, but the latter has the large advantage of incorporating the changes observed in a control group over a similar time period, largely to account for practice and time effects. Because the RCI can be related to a control group or normative data, it satisfies the DSM-5 criteria for NCD (postoperative).

Sensitivity. The number of tests directly impacts the sensitivity of the measure; for example, if the definition of POCD is a decline of 2SD in 2 tests from a battery of 8 tests, the probability of identifying a decline of 2SD in 2 tests from 10 tests is doubled to 0.10.[18] For the assessment of NCD, the DSM-5 only requires decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition), but does not recommend specific neuropsychological tests or a specific number of tests. Sensitivity can be improved by considering small declines across a number of tests, or a single very large decline in what is termed, "combined z-scores."[9,17]

While seemingly esoteric, the various methods of analysis can markedly impact the diagnosis of POCD/PND, highlighted by Keizer et al., who reported a POCD incidence of 10.5%, 31%, and 7.7% using the same test results with different methods of analysis (1SD definition, 20% definition and RCI, respectively).[19] Clearly, standardization will be required to interpret results across many studies.

More recently, computerized cognitive assessment batteries have been developed that avoid practice effects, offer easier administration, are quicker and standardized, and have the potential to overcome cultural and language difficulties. To date, however, computerized test batteries have received limited attention in POCD/PND research mainly due to a lack of relevant validation studies.

GROUP CHANGE VERSUS INDIVIDUAL CHANGE. Studies investigating POCD have variously used either individual or group change. Individual change refers to a dichotomous outcome of "decline" versus "no decline," whereas group analysis considers differences between groups on a continuous scale. Clinical studies typically then use statistics to compare an *a priori* primary outcome between two groups to test whether any observed difference is due to chance. But this approach misses important individual information within each group. In particular, the individuals who decline the most may be a small fraction of the group, but arguably are the most critical to consider. Some individuals may even demonstrate cognitive improvement, due to correction of underlying pathology and improved function (e.g., reduction in pain, improved mobility, improved ADL). Statistics that simply average these groups together will miss these important individual changes (Fig. 82.1), which might be due to identifiable and perhaps correctable factors.

Issues Associated With Repeated Testing

Serial neuropsychological testing is important to reliably assess the trend over time; however, repeated testing may introduce several sources of error, such as reliability, floor/ceiling effects, and practice effects. It is unclear if practice effects can be eliminated, as such effects can be observed as far out as 2.5 years. Individual (e.g., age, sex, culture, language, education, comorbidities, baseline cognitive function) as well as perioperative factors (anxiety, medications, pain, etc.) may also modulate the effect of repeated testing. Other strategies to improve reliability include parallel test versions and the use of control groups (*vide supra*). The major concern with control groups is selecting a well-matched one. It is generally desirable to match for comorbid conditions, even including the need for surgery, to evaluate the effect of the surgery itself.

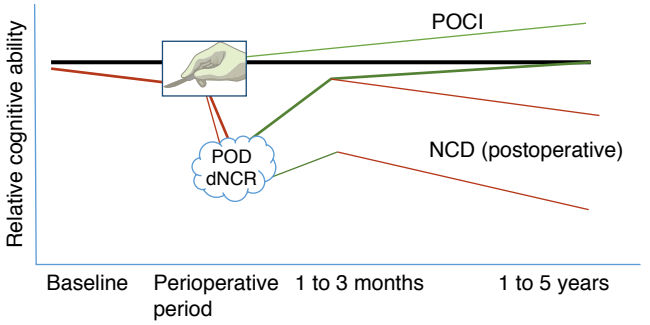

Fig. 82.1 Perioperative cognitive trajectories. Perioperative patients come into surgery having either a stable *(black)* or declining trajectory of cognition *(red)*. After surgery, the majority are unchanged *(black)*, with a small fraction showing postoperative cognitive improvement (*POCI*, *green*). Some postoperative patients have an acute decline into POD or dNCR, from which most recover *(green)*. A fraction of these will decline again later, perhaps matching their preoperative trajectory. The bottom red trajectory is meant to indicate that a very small fraction of perioperative patients never fully recover, and assume a steeper downward trajectory than if they had not had surgery. Thickness of line is intended as a rough reflection of probability of following the indicated trajectory. Other trajectories are possible. *dNCR*, Delayed neurocognitive recovery; *NCD*, neurocognitive disorder; *POD*, postoperative delirium.

Summary

Patient complaints of cognitive dysfunction after anesthesia and surgery have been reported for over a hundred years, but only recently studied systematically. These studies have included a wide variety of definitions, but all leading to the same provincial diagnosis, POCD. Recent work has standardized definitions and nomenclature for the clinical diagnosis of what are now called the PNDs, to make these consistent with that in the general population, and to recognize differences in magnitude and timing. Finally, we offer a more research-oriented framework for objective study in the future.

Risk Factors, Informed Consent, and Perioperative Management

RISK FACTORS

Multiple studies have investigated risk factors for the development of postoperative NCDs, with the most commonly cited being advanced age, a history of PreCI, and type of surgical procedure.[20,21] Other factors include a prior history of delirium, frailty, psychotropic medications, ASA physical status, number of medications, impairments in IADLs or ADL, and smoking.[22-25] PND is the likely combination of patient vulnerability along with the risks of the surgical procedure and its related complications that enhance the risk for the development of POD and potentially POCD. While many of these risk factors such as age and a prior history of delirium are not modifiable, there is growing interest

in identifying modifiable risk factors and the use of multidisciplinary teams combined with prehabilitation to decrease the risk of developing PND.[26-29] Moreover, there has been growing interest in whether genetic risk factors, specifically the apolipoprotein-Ee4 genotype, are associated with the development of either POD or PND. Studies performed to date suggest that the presence of apolipoprotein-Ee4 genotype is not associated with the development of POD, but the data are less clear for other forms of PND, with some studies suggesting that it is, or is not, a predictor for the development of both dNCR and NCD (postoperatively).[30-36]

INFORMED CONSENT

It is currently uncommon that older adults are informed of their risk of PND in the consent process, despite clear evidence that PND is more common than most complications of which patients are routinely informed. However, informed consent is difficult to obtain in older operative patients because of a high prevalence of unrecognized MCI in this population. Among community-dwelling elders, as many as 70% may have some degree of cognitive impairment,[37] although the prevalence appears to be lower for those presenting for elective surgical procedures.[4,21] Preexisting MCI confounds their ability to understand the complex anesthesia and surgical procedures and risks, but also their risk for the development of subsequent NCDs. One must also remain cognizant that there may be substantial risks of forfeiting a surgical procedure that may be of benefit. While it is beyond the scope of this discussion to describe the entirety of the informed consent process, at a minimum, all older patients consenting for anesthesia care should clearly understand and actively participate in discussions about their risks and be capable of understanding the information provided about the planned management and potential adverse outcomes, including the risks of postoperative NCDs.[38-40]

PREOPERATIVE MANAGEMENT

Older patients often have geriatric syndromes that are not considered to be a part of the routine preoperative evaluation, yet are associated with an increased risk for the development of PND. For example, the risk of developing delirium is significantly increased in patients with preoperative cognitive impairment, frailty, functional impairment, depression, and among those taking certain psychotropic medications.[41] Accordingly, the American College of Surgeons together with the American Geriatrics Society have developed guidelines for the perioperative evaluation of older surgical patients that are relevant to the development of PND, including an assessment of preoperative cognitive performance, depression, functional status, frailty, and a review of prescription and over-the-counter medications, in order to identify those associated with a risk of PND. In the presence of these risk factors, the perioperative physician should consider referral to either a primary care physician, geriatrician, or mental health specialist for optimization or prehabilitation prior to the surgical procedure.[28] Identification of patients at highest risk for the development of PND may enhance patient-centered outcomes by providing patients and their families with a better understanding of their perioperative course and allow practitioners an opportunity to deploy resources to those at highest risk.

Intraoperative Management

TYPE OF ANESTHESIA

Researchers and clinicians have widely debated whether regional anesthesia is preferable to general anesthesia in suitable surgical cases for the prevention of PND. For all forms of PND, including POD, it is intuitive that regional anesthesia will be preferable, as general anesthesia targets the CNS, and data now suggest that deep anesthesia is associated with a higher incidence of NCDs. However, most studies have been unable to show differences in the risk of either POCD or POD following surgery under either general or regional anesthesia.[42-45] There are a number of potential reasons for this lack of difference. One is that regional anesthesia is often accompanied by sedation at levels comparable with general anesthesia based on processed electroencephalogram monitoring.[46] However, even in the few studies that have limited or randomized sedation during regional anesthesia, little difference was found.[45] This is the basis for the current hypothesis that most forms of PND, including POD, are the result of the surgery itself, combined with preexisting vulnerabilities.

DEXMEDETOMIDINE

Studies have demonstrated that dexmedetomidine, as compared to benzodiazepines and/or propofol for sedation, decreased the incidence of delirium in the intensive care unit. This observation has led to investigations of dexmedetomidine as an intraoperative adjunct to either regional or general anesthesia in older patients.[47,48] The majority of these studies have found that perioperative dexmedetomidine was associated with a lower prevalence of PND as compared to propofol in both cardiac and noncardiac surgery patients.[49-52]

However, it remains unclear whether the reduction in PND is due to the pharmacologic actions of dexmedetomidine itself or simply less brain depression. There is a growing body of evidence that deep sedation or general anesthesia based upon EEG monitoring during a regional anesthetic is associated with a higher prevalence of PND as compared to lighter levels of sedation or general anesthesia.[53] In other words, it may be the state of the brain (and duration) that is responsible for a lower risk of PND, rather than any specific effect of the drugs themselves.

KETAMINE

Ketamine is rarely used as a sole anesthetic, but it is frequently administered intraoperatively to reduce postoperative pain. Most studies performed to date have not shown that intraoperative administration of ketamine, despite its ability to decrease postoperative opioid requirements, decreases the incidence of POD and some studies suggest

that it may increase it.[54-56] In addition, at least one study noted that intraoperative administration of ketamine may be associated with postoperative hallucinations and nightmares.[56]

INTRAOPERATIVE BRAIN MONITORING

There has been a growing interest in whether intraoperative management based on processed EEG or cerebral oxygen monitoring decreases the risk of either PND or POD. There is evidence to suggest that the use of the processed EEG to guide anesthetic management may reduce the risk of both, although the evidence is greater for POD.[57-59] Questions remain as to the mechanism, whether PND is a direct result of the anesthetic or its dosage, or the development of EEG burst suppression patterns. Evidence indirectly supports the latter, as the dosage of anesthetic being administered to the patients has not been rigorously correlated with the development of PND.[58,60] As there is little risk of EEG monitoring in most surgical procedures, some have recommended that EEG-based management be used to reduce the risk of PND in older surgical patients.

The evidence is less clear for the use of intraoperative cerebral oximetry to reduce the risk of PND. While some studies have suggested that higher perioperative cerebral oxygen saturation is associated with a lower risk of POD, therapeutic restoration of regional cerebral oxygen desaturation has not been shown to lower POD risk. Overall, the evidence for the use of cerebral oximetry for the prevention of POCD is greater than that for POD, although the majority of studies performed to date have been in the setting of cardiac surgery.[61,62] Taken together, the evidence makes it difficult to make a recommendation regarding the measurement of cerebral oxygenation during routine surgical procedures.

BLOOD PRESSURE CONTROL

There is currently significant interest in whether hypotension, hypertension, or blood pressure variability are associated with the development of PND, but the data are often difficult to interpret. Early studies that randomized patients to either high or low blood pressure management failed to find a difference in cognitive outcomes.[63] However, subsequent observational studies have suggested that intraoperative hypotension, hypertension, and blood pressure variability were each associated with the development of PND, as were vasopressor administration and postoperative hypertension.[64-67] While there is no clear evidence for what constitutes optimal blood pressure management in older surgical patients, maintenance of normal blood pressures without significant variability may decrease the risk of developing PND.

Postoperative Management

PAIN MANAGEMENT

The national opioid crisis has focused anesthesiologists' attention to the use of opioid-sparing techniques in the perioperative period. This is particularly relevant for older surgical patients, in that both postoperative pain and the administration of opioids have been associated with the development of POD. However, the outcomes from opioid-sparing pain management studies are often mixed.[55,68] For example, while regional analgesic techniques to manage postoperative pain are associated with decreased opioid consumption, their role for preventing the development of POD is less clear.[55,69-72]

As described above, perioperative administration of dexmedetomidine has been shown to decrease the development of POD in the majority of studies.[49] Contributing to this action may be that the α-2 adrenergic receptor agonist analgesic effects of dexmedetomidine decrease opioid requirements.[73] Interestingly, there exists little evidence on whether clonidine, another α-2 agonist, is associated with a reduction in POD risk in older surgical patients.[74] Similarly, early studies suggested that the perioperative use of gabapentin reduces the development of POD, but subsequent investigations have demonstrated that, despite decreasing opioid consumption, gabapentin administration did not reduce the development of POD, and may increase respiratory side effects.[75-78] Acetaminophen and COX2 inhibitors have also been suggested as a part of multimodal pain management strategy to reduce POD. While acetaminophen administration has been associated with a reduction in postoperative opioid utilization, it has not been associated with a reduction in POD.[79] In contrast, COX2 inhibitors have been shown to decrease pain severity, opioid utilization, and POD in patients greater than 60 years of age undergoing lower extremity joint replacement surgery. This provides hope that multimodal management of postoperative pain in elders will be associated with a decreased risk of POD, yet may be associated with increases in the costs of pain management.[68,80]

At this point, the effective strategy to reduce PND in older patients is nonpharmacologic—for example, assuring good sleep and nutritional hygiene, rapid mobilization, and early orientation to familiar aspects of their environment, such as family members. Older patients may need their glasses and hearing aids to facilitate orientation. It is also important to remove devices such as Foley catheters to avoid urinary tract infections, to avoid Beers' criteria medications, and to promote normal bowel function. One cannot know the success of these interventions without testing for POD using validated instruments like the CAM.[81] Without formal screening, many cases of delirium, especially the hypoactive type, go undetected.

If a patient is found to be delirious, the cause may be identifiable. For example, delirium might be due to unrecognized hypoxia, pneumonia, urinary tract infection, electrolyte abnormalities, urinary retention, fecal impaction, acute renal failure, hypoglycemia, and dysrhythmias. The medication record may reveal drugs associated with the development of delirium, which should be discontinued, if possible. Nonpharmacologic interventions might include a calm environment and reorientation tools such as the presence of a clock, calendar, family members and familiar items, and the removal of restraint devices. Pharmacologic interventions should be reserved for those who pose a threat to themselves or others, as these drugs may mask, rather than treat, delirium. Effective drugs include dexmedetomidine

TABLE 82.2 Summary of Pathways and Biomarkers

Mechanism	Anesthetic Effect Rank/Order	Biomarker (Type*)	Biofluid	Imaging
Amyloidopathy	Enhanced, Halo>Iso>Des>Pfl	Amyloid $\beta_{1\text{-}42}$ (1) Amyloid $\beta_{1\text{-}40}$ (1)	Plasma, CSF,	Yes, several; e.g. ^{18}F-florbetapir
Tauopathy	Enhanced, Iso>Pfl	Total Tau (1,2) Phospho-Tau (1,2)	Plasma, CSF,	Yes, several; e.g. ^{18}F-AV1451
Apoptosis, Necrosis, Lysis	Enhanced, Iso>Pfl	S100β (2) Neurofilament Light (NFL) (2) Neuron-specific enolase (NSE) (2) Total Tau (1,2)	Plasma, CSF,	MRI. Loss of cellular thickness and/or enlargement of ventricles.
Calcium Dysregulation	Enhanced. Iso>Sevo=Des>Pfl	None	None	None
Neuroinflammation	Various, Sevo/Iso enhanced or no effect. Pfl reduces.	Cytokines, (1,2) Chemokines, CRP (1,2) Prostanoids, (2) Resolvins (2)	Plasma, CSF, Urine	Yes, several; e.g. ^{11}C-PBR28

*Biomarker type; 1, risk stratification; 2, disease progression.
Halo, Halothane; *Iso*, isoflurane; *Sevo*, sevoflurane; *Pfl*, propofol; *CRP*, C-reactive Protein; *CSF*, cerebrospinal fluid; *MRI*, magnetic resonance imaging.

and haloperidol, but the adage of "start low and go slow" to avoid exacerbating the duration or severity of delirium should be adopted.

For patients who develop PND of any form, it is important to refer them to their primary care provider, geriatrician, or mental health expert, as evidence is beginning to suggest that POD and PND are predictors of subsequent cognitive decline.[82-84]

Mechanisms and Biomarkers

As reviewed above, numerous studies in patients have documented a variety of cognitive syndromes following anesthesia and surgery, most of which resolve in several weeks. These clinical studies have only identified age and preexisting cognitive disorders as consistent risk factors; other perioperative features, such as surgery duration, anesthetic management, and intraoperative physiology (e.g., hypotension, hypoxemia) have not been rigorously implicated. Because these associative studies in patients have not yet provided strong clues as to the underlying mechanism, investigators have turned to preclinical models in order to understand causation and thereby design potential interventions. We will first review these preclinical studies and the various pathways that have been implicated, and then discuss how various biomarkers can be used to test for these mechanisms in patients. It is important to point out that early in this exploration, the general anesthetic drug was implicated in a form of "neurotoxicity," and then a gradual shift occurred to view the surgery itself as the primary causation. In reality, it is likely that both, as well as other factors, are involved.

Although PND findings and complaints vary widely, there are similarities in both symptoms and risk factors with neurodegenerative disorders, such as Alzheimer disease. Thus, early studies examined the canonical disease pathways in either cellular/molecular systems and animals, both wild type and transgenic, and these studies then paved the way toward human studies. Three disease-associated pathways will be considered as contributing to PND: amyloidopathy, tauopathy, and calcium dysregulation. Finally, we will discuss neuroinflammation as the principle surgical contribution to PND, and then final common pathways to cellular death. It is essential to realize that biomarkers can be used in at least two principal ways. The first is for risk stratification if collected preoperatively and may not be directly involved in either surgery or anesthesia mechanistic pathways. The second is for detecting and following disease progression and is more likely to directly reflect surgery or anesthesia pathways. Some biomarkers can be used in both ways. These pathways and biomarkers are summarized in Table 82.2.

AMYLOIDOPATHY

The involvement of a small proteolytic fragment of the membrane protein amyloid precursor protein (APP) in neurodegeneration was strongly implicated from both pathological as well as genetic studies.[85] The pathognomonic feature of Alzheimer disease (AD), the senile plaque, contains considerable quantities of this peptide in a characteristic aggregated form, but data now suggest that plaques are a less toxic, sequestered form of the peptide; the neurotoxic forms are thought to be the more labile small (~dodecamers) oligomers of the amyloid β peptide.[85] These oligomers are produced at various rates over a period of decades prior to the onset of symptoms (Fig. 82.2), and are variously eliminated or sequestered into plaque, making a causal association with symptoms exceedingly difficult. In fact, the mechanism by which such small aggregates produce cytotoxicity is not at all clear, but may involve a detergent-like action whereby an amphiphilic peptide inserts into, and disrupts, cell membranes.[86] Despite being a pathognomonic feature of AD, imaging and cerebrospinal fluid (CSF) studies (discussed later) have demonstrated a poor relationship between amyloid β accumulation and cognitive loss.

CELL AND MOLECULAR STUDIES

Initial studies found that inhalational anesthetics like halothane enhanced the aggregation of amyloid β in the test tube, and that when combined with cells in culture, also enhanced the cytotoxicity of exogenously added

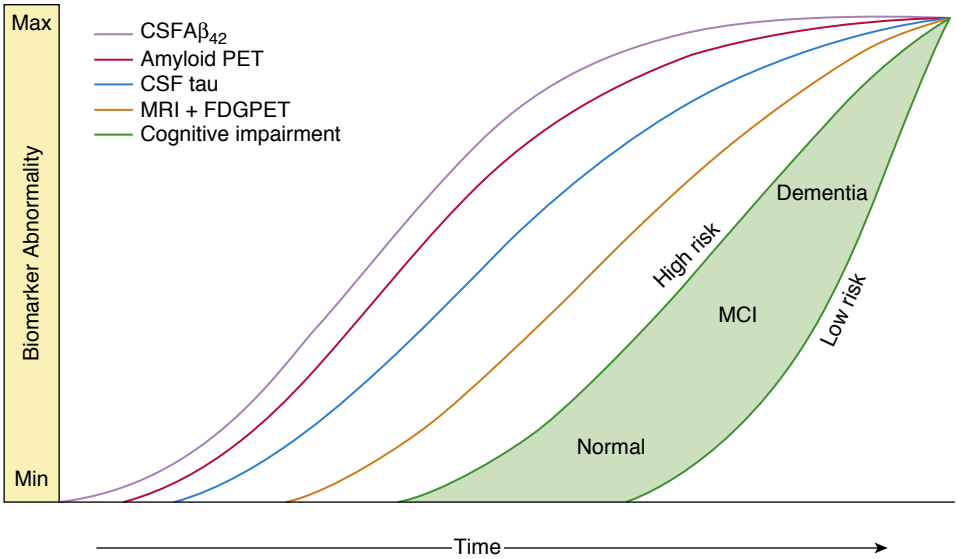

Fig. 82.2 A model of the progression of neurodegeneration and cognition. Cerebrospinal fluid *(CSF)* Aβ42 *(purple)* and deposition of amyloid on PET imaging *(red)* occur early and are then followed by elevations in CSF tau *(blue)* and probably tau aggregates on PET imaging (data not yet available). Neurodegeneration as measured by FDG PET and structural magnetic resonance imaging *(MRI, yellow)*, respectively, follow and precede functional changes such as Mild Cognitive Impairment *(MCI)* or dementia. By definition, all curves converge at the top right-hand corner, the point of maximum abnormality (not levels). The horizontal axis is time, which although highly variable, is on the order of decades. A vertical line drawn between normal and MCI approximates a large fraction of older patients presenting for surgery, which implies that many of our patients will have significant neuropathology at the time of their operation. (From Jack C, Knopman, DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 2013;12:207–216.)

amyloid β peptide.[87] Further studies found that the activity of the enzyme responsible for cleaving and releasing the amyloid β peptide, the β-acting cleavage enzyme, was enhanced by anesthetics like isoflurane, so that amyloid β *production* was also increased.[88] So even without exogenous amyloid β, this pathway was capable of causing apoptosis in cell culture systems. Moreover, isoflurane enhances the cytotoxicity of presenilin-1 mutations in cultured neurons.[89] Presenilin-1 is an important regulator of amyloid β production through effects on the γ-secretase complex, and the mutation in question upregulates this complex to amplify the production of amyloid β. Thus, it is clear that certain anesthetics intersect the amyloidopathy pathways at several points that result in exaggerated cytotoxicity.

There appeared to be variation in the degree that different anesthetics caused these effects. Halothane and isoflurane both caused substantial amyloid β production, aggregation, and cytotoxicity in cell culture.[87] On the other hand, desflurane caused less amyloid β production and apoptosis than isoflurane.[90] Perhaps most importantly, propofol at clinical concentrations (~1 uM) actually inhibited amyloid aggregation in vitro, and was without cytotoxicity in cultured cells.[87] Such rank-order effects are extremely important means of translating hypotheses to intact animals.

ANIMAL STUDIES

In early PND/POCD research, it was found that wild-type rats had impaired learning and memory after isoflurane anesthesia, and this was most apparent in older animals.[91] In addition to age, other vulnerabilities were introduced, such as human transgenes for AD, so that the amyloid mechanism could be explored in vivo. The Tg2576 animal contains the APP Swedish mutation that overproduces amyloid β and acquires cognitive deficits by 10 to 12 months of age. Several 2-hour exposures of aged animals to either halothane or isoflurane caused no further deficits in the already impaired learning or memory, but significantly increased the number and density of amyloid plaques in their brains.[92] Other rodent work, even in wild-type animals, has confirmed that anesthetic exposure (largely isoflurane) increases amyloid β levels in the brain.[93] Rank-order effects appear to be mostly retained, as halothane exposure increases amyloid plaque more than isoflurane,[92] and propofol had little effect, although this was in a different transgenic (3xTgAD) animal.[94]

HUMAN STUDIES

Amyloid β can be assayed in humans either postmortem or in the living by ELISA analysis of CSF, or PET imaging of amyloid β plaque. Low amyloid β in the CSF is consistent with AD pathology because the peptide is thought to be sequestered into plaque and less available for distribution into CSF. In addition, it might also reflect fewer active synapses, as the APP tends to be highly expressed in synaptic regions. Consistent with this, PET imaging that shows high density of amyloid-ligand binding is consistent with AD.[95] Studies have examined amyloid β preoperatively as a risk biomarker, or postoperatively as a marker of PND occurrence and progression. In the former case, it is relatively straightforward to get a sample of CSF when a spinal anesthetic is initiated. Analysis, however, is nontrivial, and should be conducted by standardized laboratories specifically established for this purpose. In one study, low CSF amyloid β predicted dNCR at 3 months postoperatively.[96] PET imaging with any of

several amyloid β ligands can also be performed preoperatively for risk assessment. In a recent study of cardiac surgical patients, amyloid imaging was performed at 6 weeks and 1 year postsurgery. At neither time point was amyloid load associated with PND, but it was noted that amyloid load increased more between the two time points than in matched nonsurgical controls.[97] This result is directly analogous to the above animal study in that the increased amyloidopathy was not reflected in worse cognitive outcomes. The reasons are suggested by the mixed role that amyloidopathy represents, both reflecting the presence of, and the sequestering, of toxic oligomers, as well as the delay between this particular proteinopathy and neurodegeneration.

In addition to its use in risk prediction, the use of amyloid β as a marker of disease progression has been studied by several investigators, but in general for very limited periods (days). For example, in patients with lumbar drains in place for the operation and up to 2 days after surgery, repetitive sampling of CSF showed no significant change in the amyloid β.[98,99] An uncontrolled study in cardiac patients showed a significant decrease in CSF amyloid β 6 months after surgery, consistent with progressive amyloidopathy.[100] Finally, one study has shown that CSF amyloid β increases acutely after anesthesia and surgery, which may be consistent with prior data showing anesthetic-induced increases in amyloid β production.[101]

AMYLOIDOPATHY SUMMARY

It is now clear that anesthetics interact directly with the amyloid β pathways, and in a differential manner. The haloalkanes, exemplified by halothane, are the most provocative, predicting acceleration, whereas propofol has little effect. The critical in vivo data confirms these in vitro studies, but they also support the growing recognition that amyloidopathy is itself not temporally associated with cognitive ability, suggesting that amyloidopathy might not underlie the most prevalent form of PND, dNCR. It may, however, contribute to later forms of PND, such as mild or major NCD (postoperative), but the separation in time makes this association difficult to establish. Amyloid β will continue to be useful as a risk biomarker, especially if amyloid imaging or CSF is available preoperatively. Assays of amyloid β in blood have not reached the stage where they are considered sensitive and specific, but this is obviously a highly desired goal.

TAUOPATHY

The other major pathognomonic feature of AD (as well as various tauopathies) is the intracellular neurofibrillary tangle (NFT), now known to consist largely of tau protein. Tau is a microtubule-associated protein (MAP) that regulates microtubule stability and dynamics, both of which are critical for neuronal structure and intracellular transport.[102] Phosphorylation of tau at several sites causes it to detach from the microtubule, which if extensive, ultimately results in loss of microtubular function. Like amyloid, high concentrations of phosphorylated tau will begin to self-assemble into ordered fibrillary structures, which either directly cause further cell stress, or serve to isolate tau from the microtubule. In either case, both neurodegeneration and cognitive loss relate better to NFT prevalence (both by imaging and CSF levels) than does amyloid β, as it is thought to be a later event reflecting cell demise (see Fig. 82.2).[102] Release of tau from damaged cells is thought to enhance tauopathy in neighboring cells in a prion-like manner.[103] Release also deposits tau into the CSF and ultimately bloodstream, making it a useful biomarker of CNS stress/injury.

CELL AND MOLECULAR STUDIES

The effect of isoflurane has been evaluated in a few cell culture studies, and in each case, isoflurane (~2%) caused tau hyperphosphorylation, perhaps by upregulation of the associated kinase, GSK-3b.[104,105] Similarly, both propofol and dexmedetomidine caused tau phosphorylation in a neuronal cell line.[106,107] The mechanism appears to center around inhibition of the associated phosphatase, PP2A, either directly by hypothermia or direct anesthetic binding, or through inhibition of the PP2A-tau complex.

ANIMAL STUDIES

Early work showed that wild-type mice exposed to isoflurane had a dramatic increase in tau phosphorylation in their brains.[108] However, it was found that this was largely due to the extreme temperature sensitivity of the PP2A phosphatase, and the fact that the animals had been allowed to cool during the anesthetic.[108] Subsequent work has determined that a degree of excessive tau phosphorylation exists for several days after the anesthetic, even when animal temperature is carefully maintained.[109] A transgenic mouse that incorporates human genes associated with both amyloid and tau pathology also found that abdominal surgery under volatile anesthesia (desflurane) increased tau deposits, and that this was associated with learning and behavioral defects.[110] Interestingly, neither enhanced tau nor cognitive deficits were observed if propofol was used for the brief surgical procedure.[94]

HUMAN STUDIES

Clinical studies to date have been limited to assays of tau in CSF before and after surgery of various types. As stated previously for amyloidopathy, these studies often take advantage of the need for a subarachnoid catheter for the surgical procedure itself, but in some cases, repeated single CSF draws have been used. Results have been remarkably consistent. Total tau, but not phosphotau, is elevated after surgery, and it continues to rise for at least a day or two, when most of the sampling is terminated.[111] Presumably, this elevation of tau reflects CNS cellular damage, but the implications in terms of future cognition are not yet clear. It is important to note that PET ligands with affinity for NFT tau are now available, yet transsurgical studies have yet to appear in the literature. Sensitive and specific blood assays for tau and other injury biomarkers (neurofilament light, S100β) are now available, and a recent study shows elevations after surgery.[112] While far more convenient than CSF, blood is likely to be contaminated by peripheral tissue sources that are almost invariably damaged during surgery.

TAUOPATHY SUMMARY

The MAP tau is gaining much attention as a more proximal biomarker of CNS injury and neurodegeneration than amyloid β. The effect of anesthesia and surgery on tau is remarkably consistent across species and models, and suggests a form of CNS stress and injury in the immediate postoperative period. The upstream mechanism may reside in surgery-induced neuroinflammation (discussed later), but animal studies suggest that direct effects on tau phosphorylation may also contribute. Postoperative tau imaging studies hold substantial promise for defining the magnitude and time course of any surgery-induced CNS injury.

CALCIUM DYSREGULATION

Intracellular calcium is a critical cell function regulator, which, if excessively elevated, also leads to cell stress, apoptosis, autophagy, and necrosis. Calcium dysregulation has therefore been considered an important link between amyloidopathy/tauopathy and cell death, and has recently been proposed as a target for mitigation of neurodegeneration in disorders like AD,[113] although no trials are underway. The primary source of elevated calcium in neurons is thought to be the endoplasmic reticulum, released via the two major channels, the ryanodine receptor (RyR) and the inositol 1,4,5-trisphosphate receptor (InsP3R). An antagonist of RyR, dantrolene, is available and well known to anesthesiologists, but has two principle drawbacks. First, it is distributed only poorly to the brain with the usual parenteral administration, and second, it has the significant side effect of causing weakness due to effects on skeletal muscle. Dantrolene has been proposed as a treatment for AD.[114]

CELL AND MOLECULAR STUDIES

Electrophysiology and cell culture studies have shown that the volatile anesthetics enhance the opening of both the RyR and InsP3R, resulting in concentrations of intracellular calcium that activate apoptosis pathways.[115,116] These effects were not apparent in cell lines devoid of the $InsP_3R$, and were completely mitigated in normal cells treated with either dantrolene or an $InsP_3R$ antagonist, xestospongin-c. It is important to note that fairly high concentrations and long durations of volatile anesthetic exposure were necessary to produce these isolated cell effects, arguing against the in vivo relevance. Also, even higher concentrations of propofol were required to induce cytotoxic calcium levels, suggesting that potentially useful rank-order effects exist among the general anesthetics.

ANIMAL AND HUMAN STUDIES

There are only a few rodent studies that have demonstrated modest efficacy of chronic dantrolene in slowing cognitive decline and neurodegeneration,[117,118] but none to date on the efficacy of acute dantrolene in preventing POD or losses in memory or cognition. Perioperative human studies have not yet been reported.

CALCIUM SUMMARY

Calcium dysregulation is probably an important upstream event in anesthesia and surgery-induced cognitive decline, and yet has remained largely unstudied. While chronic dantrolene administration to slow the progression of AD might be considered implausible, the potential for acute, intraoperative use is attractive, especially given that the various formulations of dantrolene are already clinically approved, and that muscle relaxation during surgery is typically desirable.

NEUROINFLAMMATION

The consistent observation in animals that anesthetics alone induce only modest effects on pathology and cognition, and that more robust and consistent effects are produced in both when a surgical procedure is added, have led to the hypothesis that surgery-induced inflammation due to activation of the innate immune system is the principle contributor to PND. It is well established that surgery induces a classical systemic inflammatory response, triggered by damage-associated molecular pattern molecules, and propagated systemically by a variety of cytokines and chemokines. This inflammatory response is essential for wound healing and microbial defense, but can also exaggerate ongoing inflammatory processes in some individuals. In general, an intact blood-brain barrier (BBB) isolates the brain from significant inflammatory mediators and cells. But the BBB can become "leaky" in the elderly, and in those with preexisting neuroinflammation, so that the peripheral innate immune response can be more effectively transduced into the brain. This is the probable reason that age, preexisting cognitive decline, cardiovascular disease, diabetes, and frailty[2,84,119-124] are important risk factors for PND.

CELL AND MOLECULAR STUDIES

It is not possible to simulate surgery in cell culture systems, but attempts at pro-inflammatory influences have been combined with anesthetic exposure to understand the response of a variety of cell types. For example, a cultured microglia cell line had little cytokine response to sevoflurane and isoflurane (1 and 2 MAC) or to 1 or 2 ED_{50} of propofol. However, in the presence of low-dose lipopolysaccharide (LPS), robust cytokine responses occurred, which were amplified by exposure to the volatile drugs, sevoflurane more than isoflurane. On the other hand, clinical concentrations of propofol completely ablated the cytokine response to LPS.[125] While translation of cell culture results continues to be vexing, such studies will continue to be important to define molecular pathways contributing to cytotoxicity in specific cell types.

ANIMAL STUDIES

The literature contains numerous animal studies demonstrating the contribution of the inflammatory response to PND/POCD. For example, while subtle changes in behavior can be detected after anesthesia alone (typically

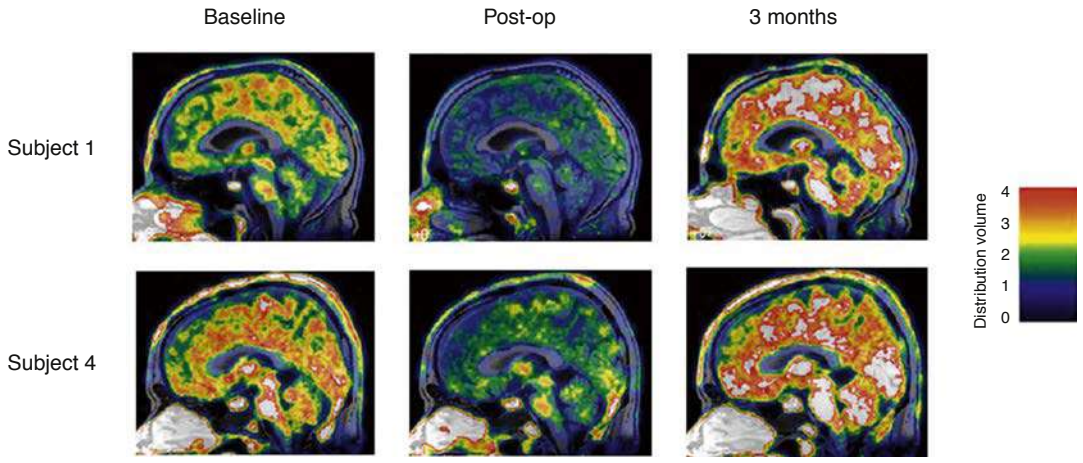

Fig. 82.3 Neuroinflammation imaging by PET after surgery. Two subjects undergoing abdominal surgery were scanned using a PET ligand that targets activated glia ([^{11}C]PBR28), generally thought to reflect the degree of immune activation in the brain. The baseline scan is before the operation and the "postop" scan, clearly showing immune suppression, is 4 days after the operation. At least in these two subjects, the "3-month" scan shows a degree of activation greater than baseline, which correlated with their cognitive assays. The suppression at 4 days may have followed an acute activation in the first day or two after surgery. (From Forsberg et al., *Ann Neurol.* 2017;81:572–582.)

isoflurane), the effects are considerably larger and longer lasting when combined with even a brief surgical procedure.[110,126,127] The effects of surgery-induced inflammation are further magnified in aged animals, metabolic syndrome animals, and in those with human disease transgenes, consistent with predictions above based on BBB disruption.[110,128-132] The cognitive effects are usually accompanied by more pronounced elevations in both peripheral and brain cytokine levels, and activation of astrocytes and microglia, disrupting the precise glia-neuron signaling axis.[133] Removal of pro-inflammatory components, either via cytokine antibodies (to IL-6 or TNFα) or antiinflammatory drugs (e.g., dexamethasone, statins), at least partially mitigates the effect of anesthesia and surgery on both behavior and pathology.[91,127,134,135] Because the pro-inflammatory effect is important for surgical recovery, some of these studies have noted that blocking these cytokines impairs wound healing. Thus, attention is shifting to modulation of inflammation via cholinergic pathways[130,136,137] or to the inflammatory resolution pathways, a complex mixture of specific cytokines (IL-4, 10) as well as small lipid mediators (resolvins). Two studies suggest efficacy of either exogenous cholinergic agonists or resolvin therapy to mitigate PND in rodents.[130,138] Finally, the bidirectional involvement of pain and analgesics in neuroinflammation is well appreciated, but the role in PND/POCD has not yet been systematically studied.

Although the evidence to date suggests that the anesthetic plays only a minor role in producing PND/POCD, the choice of drug may modulate the magnitude and duration of the neuroinflammatory response. For example, the cell culture studies suggested that propofol mitigated the effect of LPS on cultured microglia; accordingly, the use of propofol as compared to desflurane significantly reduced both the pathology and the behavioral effects of surgery in a transgenic animal.[94] In fact, one study suggested that chronic (subanesthetic) doses of propofol reduced the trajectory of decline in a model of murine AD.[139]

HUMAN STUDIES

As is becoming more the rule than the exception, the above rodent studies have only modestly translated to humans. This is undoubtedly a result of extreme variability in how patients are treated, and in the patients themselves. For example, most patients receive both propofol and a volatile agent; few receive a volatile agent alone. There is clear evidence of a peripheral pro-inflammatory effect of surgery, but of widely varying magnitude and duration.[140] Very consistent evidence for this peripheral immune response being mirrored in the CNS has also been reported. A series of studies sampled CSF before and out to 24 or 48 hours after surgery and measured several cytokines.[98,111,141,142] In each case, significant elevations in pro- and antiinflammatory cytokines were detected, which appeared to still be rising even at 48 hours. In addition, one study confirmed preclinical evidence of early changes in BBB integrity as indicated by an abrupt and transient increase in CSF/plasma albumin ratio after orthopedic surgery.[143] Interestingly, the nonrandomized study[98] found that total IV anesthesia was associated with lower CSF pro-inflammatory cytokines than inhalational anesthesia, although the larger randomized study could detect no difference between isoflurane- and propofol-based anesthetics. Again, it may be important to note that the isoflurane group also received propofol for induction in both studies, and that the dose-response relationship for antiinflammatory effects of this drug have not been established. A more recent PET imaging study noted that a marker of activated astrocyte microglia activation was significantly suppressed in patients 4 days after abdominal surgery and followed by an elevation at 3 months postsurgery that was associated with a reduction in cognitive capacity (Fig. 82.3).[144] These findings are consistent with earlier studies with the same PET probe in primates and humans, where an initial and rapid (4 hours) pro-inflammatory signal due to LPS was followed by depression at 22 hours.[145,146] Although difficult and expensive, more time points will be necessary in these biomarker studies to define the contribution of innate immunity to the cognitive outcomes.

Given an important role for inflammation, several studies have attempted mitigation with antiinflammatory medications, typically given in the immediate preoperative period or after induction of anesthesia. Two recent RCTs found dexamethasone reduced the inflammatory response and incidence of POCD[147,148] while two other clinical trials did not find a beneficial effect or even worse outcome.[134,149] A COX2 inhibitor (parecoxib) was found to reduce dNCR in elderly patients, as well as both pain and pro-inflammatory cytokines.[150,151] It is likely that optimal antiinflammatory dosages and timing have yet to be realized, or that emphasis needs to be shifted to enhancement of pro-resolution rather than blockage of pro-inflammation.

In addition, multi "omics" approaches are providing new insights into distinct immune-cellular responses after surgery that will likely inform better therapeutic strategies to prevent PND.[152]

NEUROINFLAMMATION SUMMARY

The evidence that surgery causes both peripheral and CNS inflammation is strong, but its mitigation has to date been largely unrewarding. In vitro studies suggest that the choice of general anesthetic drug might modulate the inflammatory response; however, this has yet to be borne out in patient studies. Future directions will involve deployment of appropriately timed antiinflammatory drugs or pro-resolution therapies in the perioperative setting.

Summary

The pathology and mechanisms are presented above as independent possibilities; however, it is likely that more than one, or all, are present simultaneously after surgery, especially in vulnerable individuals. For example, patients with preexisting MCI may already have both amyloidopathy and tauopathy, which has provoked a smoldering neuroinflammatory state (termed a "primed" state) prior to surgery (see Fig. 82.2). The super-imposed acute inflammatory response to surgery, together with any modulatory effects of the anesthetic, then interact with this primed state to acutely alter the effects of this pathology on synaptic, and therefore, cognitive function. This may be transient, resulting in dNCR, or might in turn accelerate the pathology itself, to result in further neurodegeneration and more durable NCD. This mechanistic work has provided the basis for biomarker development, and for a multimodal campaign on reducing the effects of anesthesia and surgery on the aging brain.

CLOSING COMMENTS

Interest in perioperative brain health issues in older adults is accelerating dramatically. Patients, their families, and caregivers, as well as perioperative providers and scientists, need to become familiar with the risk factors for, and consequences of, POCD/PND and the best practices to mitigate them. In this chapter, we have attempted to provide an up-to-date summary of most aspects related to POCD/PND, from mechanisms to therapy, but the reader desiring more detail should refer to the primary literature.

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