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IATROGENIC RISK FACTORS FOR ALZHEIMER'S DISEASE: SURGERY AND ANESTHESIA

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Abstract

Increasing evidence indicates that patients develop post-operative cognitive decline (POCD) following surgery, with risk factors including increasing age, diabetes and low education. POCD is characterized by a bimodal incidence. Initially, there is a transient short-term decline in cognitive ability evident in the early post-operative period. This initial decline predicts a delayed cognitive decline associated with dementia 3 to 5 years post-surgery, with conversion rates up to 70% in patients who are 65 years or older. The factors responsible for this emergence of dementia are unclear and might differ for the acute post-operative emergence of cognitive decline and the subsequent delayed emergence of dementia. Clinical studies investigating the prevalence of POCD and dementia following surgery do not show an association with the type of anesthesia or duration of surgery. However, animal studies suggest that prolonged exposure to some volatile-inhalational anesthetics increase production of A β and vulnerability to neurodegeneration. Other factors might include the initiation of an inflammatory response, related to the use of indwelling devices such as the cardio-pulmonary bypass machine or initiated by intrinsic factors such as blood loss, as well as the effects of a maladaptive stress response. Identifying the factors occurring during surgery that predispose subjects to POCD and dementia and subsequent ways to provide prophylaxis against this represent important avenues of research for the health care community. Equally important, the field needs to adopt a more rigorous approach to codifying the frequency and extent of early and delayed post-operative cognitive decline.

Keywords

Alzheimer's disease; amyloid beta-protein; dementia; coronary artery bypass operation; surgery; anesthetics

I. Introduction

This review focuses on a group of risk factors that are a byproduct of medical advances in healthcare technology: surgery, anesthesia, and increased longevity and their possible interdependent role in the emergence of dementia. Worldwide, 200 million patients undergo surgery with anesthesia each year, and this number is only expected to grow with increasing lifespan and growing populations. While major surgical procedures, such as coronary artery

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bypass grafts (CABG), offer tremendous health benefits for the population, our understanding of the side effects of these procedures continues to evolve. Increasing lifespan has also lead to increasing rates of dementia. The causes of dementia are multi-factorial, and reducing rates of dementia in the elderly might require correspondingly multi-faceted interventions. Prevention by identifying risk factors and adapting lifestyles to reduce these risk factors is a very promising approach for reducing rates of dementia. Major surgery has been recently proposed as a potential risk factor for dementia and, like Alzheimer's disease (AD), may share a common denominator, such as A β , as an inciting factor. Clarifying the linkage between surgical factors and cognitive decline is critical to optimizing long-term outcomes from major surgery and reducing the risk of dementia.

II. Post-operative Cognitive Decline (POCD)

Accumulating evidence suggests that major surgical procedures are associated with acute and chronic consequences for the brain. Multiple studies document the acute occurrence of post-operative cognitive decline (POCD), which is a transient cognitive impairment that is typically manifest in the immediate post-operative period and usually resolves by one year after surgery. POCD is characterized neuropsychologically by impairments in memory, concentration, language comprehension, and social integration. Using biochemical and imaging modalities, the brain injury can be clearly documented through the use of MRI, demonstrating brain edema and injury to white matter tracts by DTI as well as subsequent brain atrophy and by magnetic resonance spectroscopy (MRS), through the reduction of biomarkers such as N-acetyl aspartate (NAA), a marker of neuronal integrity as well as by other biomarkers such as S-100B [6,37,57].

The incidence of POCD in elderly patients was shown to be approximately 33% at 2-10 days post-op with gradual resolution between 3 months and 1 year [1,3,43,46,55,63,72]. The causes of POCD are poorly understood, but factors such as anesthesia, heart-lung devices, and embolism have all been suggested as potential causes. Patients undergoing major cardiac surgery have the highest risk of POCD, and this risk increases with age. The association between POCD and CABG surgery was originally thought to be attributable to the cardiopulmonary bypass machine (CPB); however, POCD can occur in patients undergoing cardiac surgery as well as in non-cardiac surgery patients [55]. Although POCD largely resolves within a year of surgery, these major surgical procedures also appear to accelerate cognitive decline following a delay of several years after the operation, with an increased incidence of dementia.

Alzheimer's disease (AD) and Dementia

This article will present an overview of past and current research that has been done on POCD, anesthesia, and its implications on the development of dementia. We will generally use the terms dementia rather than AD throughout this review because the clinical studies generally lack sufficient diagnostic specificity to distinguish between dementia due to AD and dementia due to other causes. The two most common causes of dementia are vascular dementia and AD, although most cases of dementia have both types of pathology. Risk factors for vascular dementia are similar to those of other vascular diseases and are discussed below. The pathophysiology of vascular dementia is not explicitly reviewed in this manuscript, but is reviewed by Kalaria [33]. The pathophysiology, etiology and risk factors for AD are described below.

Dementia is the most common disorder of the brain as we age. By age 65, 13% of people suffer from some form of dementia (<http://www.alz.org>). By age 85, the incidence of dementia is nearly 50%. The most frequently diagnosed dementia is Alzheimer's disease (AD), characterized by progressive cognitive decline and specific pathological changes in

the brain, including extracellular neuritic plaques composed of amyloid- β (A β) as perhaps the earliest event, intracellular neurofibrillary tangles of hyperphosphorylated tau, astrocytic gliosis, reactive microglia and inflammation, and neuronal and synaptic loss [7,60,61]. The accumulation of aggregated β -amyloid is thought to lead to neurodegeneration and the associated accumulation of aggregated tau protein. The major risk factor for AD is the Apolipoprotein E epsilon 4 genotype (APOE ϵ 4), which is associated with an odds ratio for AD emergence of about 3.7. The APOE gene is located on chromosome 19, possession of the epsilon 4 allele was identified as a risk factor for late onset AD in 1993 [69]. Approximately 15% of the population carries this allele, the consequence of which is most prominently the enhanced accumulation of A β in the brain [53]. All other genetic risk factors identified to date exert only minor effects in comparison (odds ratios of 1.2-1.3). Genetic risk factors for AD are reviewed and updated at the web site: www.alzgene.org. Another set of factors that appear to impact the risk of AD are those commonly associated with vascular disease generally encompassed by the term metabolic syndrome (obesity, high triglycerides, low HDL hypertension and abnormal fasting blood sugar). Interestingly, hypertension and cholesterol need to be present well before the disease, such as midlife, to exert influence on the incidence of AD. Subjects with midlife hypertension, hypercholesterolemia, or midlife obesity exhibit roughly a 50% increase in the risk of AD in later life, while none of these factors are associated with AD when examined in the year preceding disease incidence. The temporal disconnect between vascular damage and dementia emphasizes the importance of studying risk factors over an extended longitudinal range, rather than focusing on relatively acute effects occurring within one year of the documented risk factor.

Brain Reserve Might Modify Identification of POCD

AD onset and progression are initiated decades prior to the manifestation of the clinical symptoms of dementia, a point that now has strong support and which speaks to the concept of cognitive or 'brain reserve'. This internal resilience of the brain is also thought to modify POCD, as well as the delayed dementia occurring after POCD. Brain reserve originally referred to differences in brain size or neuronal count contributing to resilience of the brain to trauma or degenerative insults [35]. Brain reserve is thought to modify the appearance of AD because approximately 25% of elderly patients show no cognitive decline prior to death, yet meet the full pathogenic criteria for AD upon examination of brain pathologies [27]. Education and social networking appear to increase brain reserve, presumably because they increase synaptic density, the loss of which is associated with the onset of AD. Conversely, subjects from a low educational background are more susceptible to POCD, possibly because of lower cognitive reserve, which would provide less buffer from brain insults before falling below the threshold of cognitive loss used to define POCD [3,43,46,56]. Quantifying brain reserve might ultimately facilitate prediction of POCD or dementia after CABG surgery, although such measurements are currently not technically feasible.

POCD Risk Factors—Many of the risk factors for POCD are also risk factors for AD. These factors include: age, low education, diabetes, and severity of atherosclerotic disease. Although elderly patients are most susceptible to POCD, in a study of middle-aged patients (40 to 60 years), 19% were found to have POCD at 7 days after surgery (95% CI, 15.7-23.1), compared with a rate of cognitive impairment of only 4% (95% CI, 1.6-8.0, $P < 0.001$) in age-matched control subjects [32]. These results emphasize that POCD might be a general problem for the population, although those over age 60 are at increased risk. Individuals with higher levels of education have a greater cognitive reserve, and clinical studies indicate a high proportion of patients that develop POCD come from a lower educational background [3,43,46,56]. Iatrogenic factors such as intra-operative cerebral hypoxia, hypocapnia, hypoperfusion with loss of autoregulation, cerebral emboli and an

increased brain amyloid burden (risk factors not mutually exclusive) may accelerate AD pathogenesis associated with POCD. However, a the surprising aspects of POCD is the absence of a relationship to the APOE $\epsilon 4$ genotype, which is associated with increased risk of AD. A 2004 study done by Abildstrom and colleagues found that the presence of the APOE $\epsilon 4$ allele was not a risk factor for POCD at 1 week ($p = 0.33$) or 3 months ($p = 0.57$) postoperatively [2]. Studies described below show that dementia associated with major surgery requires years (>3) to become apparent. Since the APOE $\epsilon 4$ allele is specifically associated with dementia, the lack of association of APOE $\epsilon 4$ with POCD raises the possibility that the pathophysiology of POCD and dementia occur through differing mechanisms, although both may be the result of the same upstream event of surgical intervention.

Anesthesia is another risk factor that has been examined closely. Although animal models present clear evidence that some forms of anesthesia increase vulnerability to neurodegeneration, the clinical evidence is ambiguous. For instance, Rasmussen et al. completed a study involving 364 elderly patients undergoing major surgery with either general or regional anesthesia. They found no clinical evidence of differences in the prevalence of POCD in patients with regional versus patients with general anesthesia, suggesting that type of anesthesia is not a risk factor [55]. There was also no correlation between the depth of anesthesia and the incidence of POCD one week following surgery [68].

Another potential risk factor for POCD and subsequent dementia is CPB. Use of CPB increases the risk of micro-emboli and also activates systemic inflammatory pathways, including the complement cascade. However, studies comparing coronary artery bypass graft surgeries with and without CPB, have yet to identify a statistically significant difference in POCD related to use of CPB. For instance, in a study by van Dijk et al, the rates of POCD at 3 months were 21% for patients in the off-pump group and 29% in the on-pump group (95% CI, 0.36-1.16; $P = 0.15$) [72]. At 1 year, cognitive decline occurred in 31% of patients in the off-pump group and 34% in the on-pump group (95% CI, 0.52-1.49; $P = 0.69$) [72]. A reassessment of eligible patients 5 years post-surgery indicated that 50% of the patients in each group had cognitive decline (absolute difference, 0%; 95% CI, -12.7% to 12.6%; $P > .99$) [73]. These studies suggest that there might be a small advantage to off-pump surgery in the first months post-op, although the lack of a role for CPB in the pathogenesis of POCD remains to be proven. In support of this claim is a study done in the Chinese population, where the use of CPB increased the number of cerebral micro-emboli, but it did not increase the incidence of POCD at either 1 week or 3 months after CABG surgery compared with the off-pump group. Thus, neither CPB nor cerebral micro-emboli were associated with an increased risk of POCD [40].

Clinical evidence of POCD—A summary of studies investigating POCD is presented in Table 1. The methodologies (e.g., specific tests used, number of tests used, frequency and duration of testing and the criteria for declaring cognitive decline) and results obtained in the studies vary greatly. Early studies used the Mini-Mental State Examination (MMSE), which some argue is not sufficiently sensitive to capture all cases of POCD; scoring systems such as the AD-8 or that recently described by Inzitari to detect subtle neurologic abnormalities [28,54,64,71]. Recently, studies involving both cardiac and non-cardiac patients have begun to overcome the flaws in previous methodology by applying more accurate methods for defining the incidence of POCD [4,65]. Studies also vary in other aspects related to their ability to assess subjects' baseline (pre-operative) status, the use of control groups and the learning effects of repeated testing. There is a clear need for a strict definition of POCD and the use of sensitive, standardized methods of measurement.

A possible relationship between neurodegenerative disorders, anesthesia, and surgery was first revealed in a study conducted by Savageau in 1982 examining 227 men and women, aged 25 - 69 years, before and after major cardiac surgery to determine the incidence of POCD. A decline in cognition of at least 1 SD was found in each of four test areas in 11% -17% of the patients [59]. However, 70% of patients showed no significant decline in all four areas, although this figure might reflect the wide age range of the cohort, which included young, middle-aged, and elderly participants [59]. In a related study Savageau studied 245 men and women, aged 25 - 69 years undergoing CABG surgery and found that 28% of patients showed deterioration in at least one test score 9 days post-operatively. The decline was transient, with 80% of the patients returning to a normal range by 6 months post-surgery. After 6 months, 19% had a significant decrease in at least one area, but the majority of these patients acquired this cognitive deficit after the first set of tests, which were taken post-surgery. Only 5% of patients showed consistent decline at both 9 days and 6 months [58], suggesting that POCD is reversible.

The international study of post-operative cognitive dysfunction international (ISPOCD), organized by Moller, was a large-scale study to investigate the prevalence and risk factors associated with POCD. The study involved 1218 patients over age 60 whose cognitive function was monitored before, and 1 week and 3 months after major surgery. The study concluded that POCD was present, and that age was a major risk factor. Other POCD risk factors were duration of anesthesia and poor education [43]. In a retrospective study two years later, 336 patients from the original ISPOCD study were examined for the incidence of cognitive decline 1-2 years post-surgery. 10.4% (95% CI: 7.2-13.7%) showed decline, but this fraction was not statistically significant when compared to a control group of subjects who had not had surgery. This percentage was consistent with the values observed at 3 months by Moller in the original study, indicating POCD is transient, and patients tend to recover within the first few months [1].

POCD is most commonly studied following major surgeries, specifically CABG surgery, where the incidence is especially high. The average incidence rates across studies was 53% at discharge, 28.7% at 6 weeks, 24% at 6 months, 32.3% at 1-2 years, and 39.1% at 5 years, where an early decline predicts a late decline [46,72-74]. The POCD observed is transient and reversible, with there being no significant difference between the performance of the control and surgical groups at both 3 months and 1 year postoperatively [63]. The presence of POCD might be associated with underlying damage or fragility because patients with POCD at hospital discharge are more likely to die within the first 3 months after surgery ($P=0.02$), and patients with POCD at both hospital discharge and 3 months are more likely to die in the first year after surgery ($P=0.02$), which may skew the percentage of patients with cognitive decline over time due to increased mortality rates [44]. The increased vulnerability of subjects with POCD might be a harbinger of future vulnerability to AD or dementia.

III. Does POCD precipitate AD?

Studies focusing on CABG surgery

Studies of POCD consistently document a temporary decline in cognition present 1 week postoperatively, but also indicate that patients recover by 3 – 12 months post-surgery. The acute changes associated with POCD, both neuropsychologically as well as structurally (cerebral edema, reduced NAA, reduced anisotropy by diffusion tensor imaging) and biochemically (S-100b) might also predispose to chronic changes associated with dementia and its structural MRI correlates (brain atrophy, amyloid burden). Repetitive brain insults, such as occurs with boxers, subjects with significant cerebrovascular disease, those with repetitive head injury or given whole brain irradiation may result in dementia.. ([30]). The

temporary cognitive decline classified as POCD suggests that major operations, such as those associated with CABG surgery, put tremendous stress on the brain. A small but increasing number of studies suggests that this stress increases the risk of delayed cognitive decline occurring years after the primary insult as any remaining cognitive reserve is lost. Selnes and colleagues performed long term follow up on subjects exposed to major operations. They observed a pattern of POCD similar to that found by others, documenting the initial occurrence of POCD followed by recovery by 1-year after surgery. However, as they extended the observations out to 5 years, they observed significant decline across all cognitive domains, with the exceptions of attention and executive function [62]. This pattern was also observed by Newman and colleagues, who found a 42% incidence of cognitive decline in subjects exposed to CABG surgery 5 years earlier [46]. These studies indicate a bimodal pattern of cognitive decline, where an initial early decline with improvement to 1 year predicts a late period of decline in all cognitive domains between 1 and 5 years

The relationship between cognitive decline and dementia is graded rather than binary. Increasing evidence indicates that dementia (particularly AD) presents gradually, with most patients experiencing mild cognitive impairment before the overt onset of dementia (Reviewed in [50]). Indeed, there is now mounting evidence that Alzheimer's disease can be detected decades before the emergence of significant clinical symptoms. One example is the use of amyloid imaging agents to study brain amyloid burden in life. Using this PET technology, studies consistently demonstrate an amyloid burden consistent with the distribution of AD brain pathology post-mortem that may be best characterized as a "rule of thirds": approximately 1/3 of healthy elderly subjects, 2/3 of those with mild cognitive impairment (MCI) and essentially all AD subjects had a significant amyloid burden [10,29].

This suggests that the pathophysiology of AD begins long before the clinical manifestations of dementia are evident. It also supports the notion that brain amyloid accumulation is the earliest pathophysiological event in AD, making it an appealing, tractable target for therapeutic advances. With the onset of additional brain insults capable of reducing neuronal reserve, the emergence of AD/dementia may occur at times earlier than would have previously occurred. Given this gradual path to dementia, and the likely relationship between dementia and brain trauma, we hypothesized that the POCD associated with CABG surgery might predispose to dementia. To investigate this issue we (Wolozin and colleagues) used the Decision Support System of the Veterans Affairs Health System, which follows all subjects in the Veterans Affairs Health System longitudinally. Our results showed a striking relationship between CABG surgery and subsequent dementia. The study followed 9170 patients, and compared the emergence of AD after CABG surgery under general anesthesia, and non-surgical percutaneous transluminal coronary angioplasty (PTCA) under mild sedation. The PTCA group was selected because they exhibited health co-morbidities that were similar to subjects having CABG surgery. We observed an odds ratio of 1.71 (95% CI, 1.02 to 2.87; $p = 0.04$) for the development of AD subsequent among patients having CABG surgery compared to patients having PTCA [39]. This data suggest that some aspect of the CABG surgery procedure leads to a delayed increase in the risk of dementia.

Analysis of hernia and prostate procedures: A study of brief exposure to anesthesia

Whether the increased risk resulted from the stress of the CABG surgery itself, an inflammatory event, the prolonged exposure to anesthesia or other factors (not mutually exclusive) was not addressed in our study, and has become an important question in the field. We have performed additional studies to provide insight related to this question. We examined risk of AD or dementia among subjects undergoing hernia operations (98% male) under general ($N = 2,658$) or local ($N = 1,111$) anesthesia, as well as subjects undergoing prostate operations under general ($N = 2,820$) or local ($N = 3,691$) anesthesia. Surprisingly, the data demonstrated that subjects exposed to anesthesia showed a lower risk of AD and

dementia using either an unadjusted model or after adjusting for age, length of stay, number of procedures, and number of diagnoses during the index hospitalization. The differential risk is difficult to ascribe to bias in patient selection or co-morbidities because the anesthesia groups showed slightly higher rates of chronic illness (judged by the Charlson index[18]), although they were slightly younger. The data is described below.

Hernia Study—Over 98% of the patients in the Hernia study were male, and all of the subjects in the prostate study were male. There were 3769 patients included in the Hernia Cohort, of which 2658 (70.5%) were exposed to general anesthesia and 1111 (29.5%) were exposed in the non-general anesthesia group. Patients exposed to general anesthesia were younger than patients in the non-general anesthetic cohort (68.5 yrs vs. 70.9 yrs, $p<0.001$). The general anesthesia group had longer lengths of stay (8.4 days vs. 6.7 days, $p<0.001$) due to longer stays following the procedure (6.5 days vs. 4.5 days, $p<0.001$). Also, the patients in the general anesthesia cohort had more diagnoses at their index hospitalization and higher Charlson Index scores.

The follow-up time was slightly longer in the patients exposed to general anesthesia (1685.5 days vs. 1628.6 days, $p=0.011$). The proportion of patients that died during the follow-up period was similar between the groups (General = 30.6% vs. Non-general = 32.8%, $p=0.190$). The proportion of patients experiencing an event was higher in the non-general group than in the general group for both the dementia or AD diagnosis and the AD-only diagnosis.

The incidence rate of either a senile dementia or AD diagnosis was 10.4 per 1000 person-years in the general anesthesia group and 18.2 per 1000 person-years in the non-general anesthesia group. The adjusted Hazard Ratios comparing the risk of events in the general anesthesia group compared to the non-general anesthesia group after adjusting for age, length of stay, number of procedures, and number of diagnoses during the index hospitalization show that patients exposed to general anesthesia were at lower risk for events than those exposed to non-general anesthetics. The risk when the events were dementia or AD was 0.65 (95% CI, 0.49 to 0.85) and when only AD was considered was 0.65 (95% CI, 0.43 to 0.98).

Prostate Study—A total of 6511 patients were included in the Prostate Cohort with 2820 (43.3%) exposed to general anesthesia and 3691 (56.7%) exposed to non-general anesthetics. Because of the cohort, all of the patients were male. Patients exposed to general anesthesia were younger than patients exposed to non-general anesthesia (67.6 yrs vs. 70.8 yrs, $p<0.001$). The general anesthesia group had shorter lengths of stay (7.5 days vs. 8.3 days, $p=0.013$) due to shorter lengths of stay prior to their procedures (1.5 days vs. 2.3 days, $p<0.001$). Also, the patients in the general anesthesia cohort had fewer diagnoses at their index hospitalization but slightly higher Charlson Index scores.

The unadjusted rate ratio comparing the general anesthesia prostate group to the non-general anesthesia prostate group was 0.52 (95% CI, 0.36 to 0.76). The adjusted Hazard Ratio for developing either dementia or AD after prostate surgery was 0.65 (95% CI, 0.51 to 0.83) when comparing those exposed to general anesthesia to the non-general anesthesia group. In the AD-specific analysis the adjusted ratio was 0.71 with a confidence interval that includes one (95% CI, 0.49 to 1.04).

Interpreting these data are difficult because they might reflect an unanticipated bias in the patient selection, or in the subsequent diagnosis of AD or dementia. However, these data support a hypothesis that short-term exposure to general anesthesia does not predispose to

AD. This conclusion is supported in recent work by Steinmetz, discussed above, which does also not show any relationship between depth of anesthesia and POCD [68].

Genetics—This observation of an increased emergence of post-surgical AD is reason to re-examine the issue of genetics, specifically, the Apo $\epsilon 4$ genotype. This genotype has not been shown to increase the risk for POCD at 1 week, 3 months, 6 months, or 1 year post-operatively [2,66]. A possible explanation for this involves the observation made by Hsiung that the APOE $\epsilon 4$ genotype significantly increases the risk of developing AD in the already cognitively impaired, however the possession of the APOE $\epsilon 4$ genotype was not associated with increased risk of developing cognitive impairment [26]. On a mechanistic level, the APOE4 protein likely increases the tendency of A β to aggregate. Although AD is associated with aggregation of A β , there is no clinical evidence linking POCD with the accumulation of aggregated A β , although there is animal data suggesting that some anesthetics can increase production of A β (see below). If POCD is not associated with A β aggregation (it may relate to cerebral edema, neuronal/synaptic drop-out with temporary compensation), then one might not expect any linkage with the APOE $\epsilon 4$ genotype. On the other hand, the importance of the APOE $\epsilon 4$ genotype to the incidence of AD suggests the possibility that subjects carrying one or two APOE $\epsilon 4$ alleles will have increased risk and earlier onset of AD following POCD.

IV. Animal Models

Although the current clinical data does not provide a strong link between anesthesia and AD, animal models suggest that anesthetics can increase A β plaque formation, increase tau hyperphosphorylation, and impair memory. The amount of A β accumulation is dependent upon the balance of generation and clearance. Accumulation of A β can trigger synaptic loss and neuronal dysfunction, a hallmark of AD.

It is also known that intra-cerebroventricular administration of A β into WT mouse brains results in neuronal injury, brain atrophy and memory impairment (Nakamura, 2001) as well as reduced cerebral blood flow. Similarly, anesthetics appear capable of increasing AD pathology in the brain, although the effect is specific to particular anesthetics and cannot be generalized to all anesthetics [8,19,49,80]. For instance, isoflurane exposure causes significant memory impairment in the elderly rodent that leads to a long-term deficit in learning and memory in rats in an already-learned spatial memory task [16]. In wild type (WT) mice, sevoflurane was found to induce apoptosis, and elevated levels of β -site amyloid- β precursor protein (A β PP; BACE; β -secretase) cleaving enzyme and A β [19]. With halothane, Bianchi et al. found an increased A β plaque formation in the Tg2576 mouse model of APP over-expression, one week after exposure [8]. On the other hand, the effects of the anesthetic propofol are more complex. Propofol inhibits A β oligomerization at clinical concentrations, but enhances oligomerization at high concentration, suggesting the possibility of a neuroprotective effect with respect to AD pathogenesis [20]. Further studies have shown that neither thiopental nor propofol interfere with A β PP metabolism, and do not facilitate A β toxicity, which supports the hypothesis that these anesthetics might not promote A β pathology [48].

The microtubule associated protein tau, is also an important mediator in the pathogenesis of AD. In the wild type (WT) mouse brain, regardless of the inhalational anesthetic used, anesthesia induced rapid increases in hyperphosphorylation of tau via the inhibition of the serine/threonine protein phosphatase 2A (PP2A) [51]. In a more recent study, clinically relevant doses of isoflurane increased short and long-lasting tau hyperphosphorylation, produced long-lasting detachment of tau from microtubules, and the accumulation of insoluble tau in JNPL3 tau mice [36]. These findings have provided researchers with a link

between anesthesia and AD pathogenesis. There is a strong evidence indicating that inhalational anesthetics, especially isoflurane can increase A β plaques and tau hyperphosphorylation in WT models [16,19,51,80], this effect is exacerbated in transgenic models [8,49,52]. The two key caveats are that anesthetic damage to the brain may be multi-faceted [49] and whether these studies on transgenic mice point can be reasonably extrapolated to the human condition.

The association of stress with a relative loss of immunocompetency and with a decline in hippocampal neuronal plasticity (both neurogenesis and neuronal projections) is well characterized in both animal models and in human aging. It is now well known that neurogenesis and synaptogenesis occur throughout life, albeit at lower levels with aging. While activities such as exercise are known to increase neurogenesis stress, mediated at least in part through increases in glucocorticoids, and inactivity reduce neurogenesis and hence neuronal and synaptic reserve. Surgical procedures also trigger immune and inflammatory responses, which can interfere with brain processes [78]. Inflammation will activate a stress response and glucocorticoid release, which points to bidirectional communication between the immune and neuroendocrine system.

V. Mechanisms

The use of the CPB machine is strong candidate contributing to the risk of POCD, because the CPB machine can cause embolization with micro-emboli and macro-emboli, as well as activate systemic inflammatory pathways [23]. Although this increased risk has not been correlated to cerebral micro-emboli. A study done in the Chinese population shows that although CPB increased the number of cerebral micro-emboli, it did not increase the incidence of POCD compared with the off-pump group [40], suggesting another etiology for cognitive decline, perhaps by the activation of inflammatory pathways.

Pro-inflammatory cytokines that are released in response to surgery include TNF- α and IL-1 β , which can then induce the production and release of other pro-inflammatory cytokines, including IL-6 [9], Reviewed in [13]. It is known that neuroinflammation is associated with AD pathology, and that the inflammatory response is in close vicinity of A β plaques. IL-1, IL-6, TNF- α , and TGF- β are involved in this process of inflammation. The presence of A β induces the expression of cytokines, but the cytokines can also promote the accumulation of A β into plaques [12].

Another potential surgical risk is ischemia-hypoxia, which has been associated with cognitive decline and AD. A population-based study has shown that a history of ischemic stroke increases the risk of AD, and there is increased AD pathology in patients who have suffered from prolonged hypoxia or ischemia [45,67]. Elevated levels of A β PP and A β have been found in both human AD brain, and animal models subjected to mild to severe ischemia [31,34,77]. These debilitating effects are due to enhanced A β induced apoptosis [21,47].

The aged brain is different than the young brain in many ways including size, distribution and type of neurotransmitters, capacity for plasticity, which may make it more susceptible to POCD due to the inability to compensate for the physiological stressors associated with surgery and anesthesia. The surgical risks associated with the development of cognitive decline are mainly associated with inflammation pathways and ischemia-hypoxia. Systemic inflammation exacerbates cognitive symptoms of neurological diseases and accelerates the disease progression [17]. Given the neuronal toxicity of A β , its effect on neurogenesis and neuronal plasticity and its involvement in dementia, most especially dementia of the Alzheimer's type, confirmation of this finding might lead to the study of amyloid-specific interventions to prevent these long term post-surgical effects.

Progress in Prevention: Next Generation Anesthesia

Although a definite mechanism for the surgical and anesthetic induced pathogenesis of POCD is not fully known, there have been various observations and ideas that may be able to reduce the incidence of POCD by targeting certain pathways associated with anesthesia or surgery. Several drug and chemical based interventions have been proposed, as well procedures such as vagal stimulation. Barbiturates can be given for their neuroprotective effects because they act as competitive antagonists of muscarinic acetylcholine receptors [22,81]. Xenon has been shown to be neuroprotective due to its antagonism of the NMDA receptor [42]. Increased glutamate levels in brain microdialysate are associated with cognitive decline in preclinical models of circulatory arrest. Actracurium and its metabolite laudanosine activate $\alpha 4\beta 2$ nicotinic acetylcholine receptors to levels of normal function in the CNS perioperatively and several hours post- operatively, yielding neuroprotective effects [5,70].

One of the more promising avenues of research lies in development of anesthetics that do not increase A β or otherwise injure the brain. Development of improved general anesthetics with the potential to improve postoperative neurological function or at least have intrinsic properties that are detrimental to the brain, has evolved in three directions during the last decade. One group has focused on xenon as an anesthetic agent that also may have unique neuroprotective activity. In both cellular and animal models, xenon attenuates hypoxia-induced damage, such as that may occur with traumatic brain injury, during CABG or cerebrovascular surgery, or when systemic ventilation or perfusion are otherwise impaired [41,79]. A variety of molecular mechanisms have been invoked to explain xenon neuroprotection, but, at the concentrations used clinically (up to 0.6 atm), this small molecule can inhabit many protein pockets and potentially affect many molecular signaling pathways. Clinical trials to assess xenon's potential value in preventing POCD are underway. One such trial has reported negative results [14,25]. Other trials are investigating xenon neuroprotection in CABG surgery and in neonatal asphyxia.

Most of the data implicating anesthetics as neurotoxic agents have focused on the role of volatile inhaled anesthetics, which are small amphiphilic molecules that affect many biological systems. Intravenous agents such as propofol and etomidate are known to act primarily by enhancing the activity of GABA_A receptors, and their potential for toxic side-effects is less than that of volatile anesthetics. Etomidate in particular shows significant specificity for a subgroup of GABA_A receptors containing $\beta 2$ and $\beta 3$ subunits [24], and it produces less cardiovascular and ventilatory depression than other general anesthetic drugs. However, etomidate is infrequently used, and is only used for anesthetic induction, because, as the only anesthetic imidazole, it also produces a unique toxic side-effect: inhibition of adrenal corticosteroid synthesis [76]. Recently, two structural analogs of etomidate have been reported that appear to retain anesthetic potency and safety, while minimizing adrenal suppression. Methoxycarbonyl-etomidate [15] is a "soft analog" of etomidate, designed for rapid metabolism by non-specific esterase enzymes in blood and other tissues. It produces short-lived anesthesia after bolus administration, and can be infused for maintenance of anesthesia. Because its metabolism is about 100-fold faster than that of etomidate, any adrenal suppression that it produces is expected to reverse soon after termination of its administration. A second derivative, carboetomidate [15], replaces the imidazole ring of etomidate with an isosteric pyrazole that lacks the ability to interact with the heme-based adrenal enzymes that synthesize corticosteroids. Carboetomidate has anesthetic potency near that of etomidate, produces minimal cardiovascular and respiratory depression, yet adrenal suppression is minimal in both cellular and animal models. Neither of these drugs have been tested in models of anesthetic neurotoxicity or POCD.

Looking further into the realm of possibility, a third research group has combined a surrogate molecular binding target for anesthetics that act at GABAA receptors [75] with a fluorescent anesthetic ligand [11], to create a high-throughput screening method to identify novel classes of anesthetics [38]. This early phase work holds the promise of discovering new classes of general anesthetics that may prove to have fewer neurotoxic effects than current drugs.

VI. Conclusion

Brain injury following non-cerebral surgery has been clearly documented. The brain injury that is seen following surgery may have multiple contributory factors: inflammation, activation of NMDA receptors, manipulation of brain A β (reduced clearance, increased synthesis, facilitate amyloid aggregation/shunt away from soluble amyloid monomers), increased tau and tau hyperphosphorylation, reduced immunocompetence, as well as maladaptive stress responses.

It is clear that both neuronal changes due to the results of aging, genetic factors, and cellular stress due to surgery or injury can lead to functional decline, diagnosed as POCD. The clinical evidence supporting the existence of POCD is clear and cogent. POCD is typically transient with resolution between 3 months and 1 year post-operatively. Despite the resolution of POCD after CABG surgery, subjects undergoing this surgical procedure appear to be at risk for delayed cognitive decline 3 to 5 years after the operation, where patients are at increased risk for developing AD or dementia. We hypothesize that the acute effects of the surgical procedure lead to POCD. This is associated with neuronal drop-out that results in an earlier loss of neuronal reserve, which, in turn, predisposes patients to delayed, chronic changes associated with dementia.

The relationship between CABG surgery, POCD, and subsequent dementia is only beginning to be investigated. Major risk factors for the development of POCD include: increasing age, low education and diabetes [mmb2]. These are also known risk factors for AD and dementia. If POCD reflects stress on the brain, then the presence of POCD might be a risk factor for subsequent dementia, much as subjects who experience brain trauma are at increased risk of dementia. In general, any insult that results in neuronal dropout or a reduction in synaptic density will encourage the emergence of dementia by virtue of reducing the brain reserve. Surprisingly, the APOE e4 genotype is not a risk for POCD despite being the major risk factor for AD. However, this might simply reflect the difference between the relatively acute time frame for incident POCD versus the delayed time frame for incident dementia. It is possible that the APOE e4 genotype might amplify the risk of subsequent AD among subjects who experienced POCD.

The data concerning the relationship between exposure to anesthesia and risk of AD are currently ambiguous. Studies using animal models demonstrate that some forms of anesthesia increase production of A β and susceptibility to neurodegeneration, but a clear mechanism of how volatile inhalational anesthetics affect the brain in a way that outlives their course of action is not yet clear. However, current clinical studies do not provide clear evidence that exposure to anesthesia is associated with an elevated risk of AD. The clinical studies investigating the effects of short-term anesthesia associated with minor surgeries indicate that short-term anesthetic exposure does not predispose to AD, nor do clinical studies demonstrate a relationship between depth of anesthesia and POCD. The discordance between animal and clinical studies might reflect differences between the pathophysiological processes (or stressors) driving the animal models and the clinical disease.

There are at least two strong rationales for the development of neuroprotective therapeutics for POCD. The first is that this brain injury is one of the few brain insults that can be treated prophylactically in that it is, to a great extent, iatrogenic. It is somewhat analogous to using pre-operative antibiotics for individuals who undergo surgery. This is particularly important as most acute brain injuries (e.g., TBI and stroke), even with short time windows post insult, have yet to see even one therapeutic approved for acute neuroprotection when administered following the insult.

The second is the serious, life-threatening nature of the disease. AD and dementia in general is reaching epidemic proportions world-wide. The advancing age of the population along with the increasing need for surgical intervention suggests that an iatrogenically-induced increase in the prevalence of POCD and, ultimately, AD/dementia may be a consequence.

Although the mechanism(s) are not clear at this time, that need not translate into an inability to consider neuroprotective agents as a prophylactic therapeutic, nor should the lack of approved stroke neuroprotective therapeutics in the 15 years since the approval of t-PA delay the search for or clinical trials with a therapeutic that will demonstrate both safety and efficacy when given prophylactically. This goal of developing a prophylactic neuroprotective agent will be greatly aided by a consistent and rigorous approach to POCD. This includes standardized testing done at standardized times pre and post surgery. This also implies that POCD may be used as a surrogate to predict later AD/dementia. The selection of subjects may be aided by a risk stratification which includes age, cardiovascular risk factors, ApoE genotype and a structural evaluation of the brain to assess for evidence of significant vascular disease as well as amyloid burden, each of which may be a harbinger for future cognitive decline to a state of dementia, as is being seen in several of the longitudinal, natural history AD imaging trials.

With increasing lifespan, surgical interventions will become increasingly common in older patients. Understanding the effects of surgery and anesthesia on cognitive function, and preventing deleterious effects of surgery and/or anesthesia on subsequent cognitive function is clearly a major public health issue and should be a major focus of research efforts in the future. In 2011, the first baby boomers in the United States will reach age 65. This group, totaling an estimated 70 million people, will have a significant impact on the U.S. healthcare system. The interaction between surgical intervention, cognitive decline and AD could be problematic for our society. Further research is necessary to protect patients during surgery, and to decrease the risk of POCD and the potential the earlier emergence of dementia.

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Table 1

Summary of clinical studies done investigating the incidence of POCD from 1 week to 5 years post-surgery

Study	Year	Type of Surgery	Total # Patients	1 week (% with POCD)	3 months (% with POCD)	6 months (% with POCD)	1-2 years (% with POCD)	5 years (% with POCD)	Conclusions
Abildstrom <i>et al.</i>	2000	Major Noncardiac	336 General Control				10.4 10.6		POCD is reversible, there is no statistical difference in cognitive decline between surgical and control patients 1-2 years after surgery. Statistics: Surgery: 95%CI: 7.2-13.7% Control: 95%CI: 1.8-19.4% [1]
Ancelin <i>et al.</i>	2001	Major Noncardiac	140	71	56				Found an alarmingly high incidence of POCD at both 1 week and 3 months post-surgery, perhaps due to their testing standards[3]
Moller <i>et al.</i>	1998	Major Noncardiac	Surgical Control	25.8 3.4	9.9 2.8				POCD is transient with almost complete recovery by 3 months post-surgery. Statistics: Surgical: 1wk: 95% CI 23.1-28.5, p<0.0001 3 months: 95% CI: 8.1-12.0, p=0.0037 [43]
Rasmussen <i>et al.</i>	2003	Major Noncardiac	438 General Regional	19.7 12.5	14.3 13.9				No statistical difference 3 months post-operatively. Greater risk for short term POCD with general than regional, but not statistically significant. Statistics: General: 1 week 95%CI: [14.3-26.1%] 3 months 95%: [9.5-20.4%] Regional: 1 week 95%CI: [8.0-18.3%] P=0.06 3 months 95% CI: [9.0-20.2%] P=0.93 [55]
van Dijk <i>et al.</i>	2008	CABG	281 Surgical Control					34.2 16.2	After statistical adjustments CABG patients were 1.37 times more likely to have cognitive decline after 5 years. (95% CI, 0.65 to 2.92) [74]
van Dijk <i>et al.</i>	2002/2007	CABG	281 On Pump Off Pump	29 21			33.6 30.8	50.4 50.4	The use of CPB is not a risk factor in long-term POCD. Patients who received their first CABG surgery without CPB had improved cognitive outcomes 3 months after the procedure, but the effects became negligible at 12 months. Statistics: 3 months Relative Risk = 0.65 (95% CI, 0.36-1.16; p =0.15) 12 months RR =0.88 (95% CI, 0.52-1.49; p =0.69) 5 years: absolute difference = 0% (95% CI, -13.7% to 10.3%; p = 0.79) [73]
Newman <i>et al.</i>	2001	CABG	281	53	36	24		42	Indicates bimodal pattern of cognitive decline [46]
Lee <i>et al.</i>	2005	Cardiac CABG PTCA	9170					1.5 [*] 1.0 [*]	Patients undergoing CABG surgery are 1.71 times more likely to have an AD diagnosis at 5 years post-operation (95% CI, 1.02-2.87, p=0.04) [39]

Studies using animal models to investigate the AD-like pathogenesis due to major surgery and anesthesia

Table 2

Author	Year	Animal	Transgenic	Anesthesia	Dose	Time (min)	Results
Bianchi <i>et al.</i>	2008	Mouse	Tg2576 Tg2576	Isoflurane Halothane	Clinical Clinical	120 (x5 days) 120 (x5 days)	Halothane enhances A β plaque deposition in Tg, while isoflurane does not [8]
Bianchi <i>et al.</i>	2008	Mouse	WT WT	Isoflurane Halothane	Clinical Clinical	120 (x5 days) 120 (x5 days)	Isoflurane causes a decrease in cognitive performance in WT, halothane does not [8]
Culley <i>et al.</i>	2004	Rat	WT	Isoflurane	Clinical	120	Long-term impaired memory and learning on radial arm maze task [16]
Dong <i>et al.</i>	2009	Mouse	WT	Sevoflurane	Clinical	120	Induced apoptosis and elevated levels of β -site A β PP-cleaving enzyme and A β [19]
Perucho <i>et al.</i>	2010	Mouse	APP (swe)	Isoflurane	Clinical	2x/week, 3 months	Compared to WT, the APP mice had increased mortality, less responsiveness, increased A β aggregates, & abnormal chaperone responses [49]
Planel <i>et al.</i>	2007	Mouse	WT	Isoflurane	Clinical	60	Increases hyperphosphorylation of tau [51]
Planel <i>et al.</i>	2009	Mouse	JNPL3: mut. TauP301L	Isoflurane	Clinical	240	Increase in tau hyperphosphorylation [52]
Xie <i>et al.</i>	2008	Mouse	WT	Isoflurane	Clinical	120	Time-dependent cascade of caspase activation, elevated BACE levels and increased A β levels [80]