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Neurocognitive Function after Cardiac Surgery

From Phenotypes to Mechanisms

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ABSTRACT

For half a century, it has been known that some patients experience neurocognitive dysfunction after cardiac surgery; however, defining its incidence, course, and causes remains challenging and controversial. Various terms have been used to describe neurocognitive dysfunction at different times after cardiac surgery, ranging from “postoperative delirium” to “postoperative cognitive dysfunction or decline.” Delirium is a clinical diagnosis included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Postoperative cognitive dysfunction is not included in the DSM-5 and has been heterogeneously defined, though a recent international nomenclature effort has proposed standardized definitions for it. Here, the authors discuss pathophysiologic mechanisms that may underlie these complications, review the literature on methods to prevent them, and discuss novel approaches to understand their etiology that may lead to novel treatment strategies. Future studies should measure both delirium and postoperative cognitive dysfunction to help clarify the relationship between these important postoperative complications. (**ANESTHESIOLOGY 2018; 129:829-51**)

WE have known for more than 50 yr that many older adults have neurocognitive dysfunction after cardiac surgery,¹⁻⁵ yet precisely describing this phenomenon has remained elusive. Terms used to describe this condition have ranged from “encephalopathy”^{6,7} and “pump-head”⁸ to “post-cardiotomy/postoperative delirium,”^{1,9} and “postoperative cognitive dysfunction/decline.”¹⁰ Although these disorders also occur after noncardiac surgery,¹¹⁻²¹ they are a particular concern after cardiac surgery due to perturbations such as cardiopulmonary bypass, median sternotomy, embolic load, and long surgical/anesthetic duration (see table 1).²¹⁻³¹ Here, we discuss the definitions of delirium and postoperative cognitive dysfunction, similarities between them (including in their causes), interventions and novel approaches to study, prevent, and treat these important complications after cardiac surgery.

Delirium after Cardiac Surgery

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines delirium as a fluctuating disturbance in attention and awareness that represents an acute change from baseline, accompanied by disturbed cognition or perception, and not due to a preexisting neurocognitive disorder or occurring in context of a severely reduced arousal level (such as coma).³² The

DSM-5 refers to three delirium subtypes (hyperactive, hypoactive, and mixed); hypoactive is the most common subtype after cardiac surgery.^{33,34} Post-cardiac surgery delirium rates range from 14%³⁵ to greater than or equal to 50%,³⁶ perhaps reflecting differing levels of delirium risk factors (*e.g.*, older *vs.* younger patients, and others) in these study populations and the varied assessment tools utilized.^{37,38} Many administrative databases significantly underreport delirium rates, likely due to underdiagnosis of delirium in routine clinical care.³⁹ The most official form of delirium diagnosis is a formal psychiatric interview according to DSM-5 criteria. Additionally, many delirium assessment tools have been studied⁴⁰, and some are more appropriate for detecting delirium in intubated patients (such as the Confusion Assessment Method for the ICU [CAM-ICU]⁴¹) while some are more appropriate (*i.e.*, sensitive and specific) for detecting delirium in nonintubated patients (such as the 3-Minute Diagnostic Interview for Confusion Assessment Method [3D-CAM]⁴²).^{43,44} Many of these tools are more sensitive than chart review alone,⁴⁴ though chart review can help improve the accuracy of single assessments such as the CAM-ICU (or 3D-CAM), which can miss delirium due to its fluctuating course.⁴⁴ Thus when considering post-cardiac surgery delirium rates, it is important to consider the methods used and whether they were used in intubated or nonintubated patients.

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Table 1. Modifiable, Partly Modifiable, and Nonmodifiable Factors That May Contribute to Postoperative Delirium and/or Postoperative Cognitive Dysfunction after Cardiac Surgery*

	Pre-/Postoperative	Intraoperative
Modifiable	<ol style="list-style-type: none"> 1. Preoperative blood pressure control²³ 2. Preoperative glycemic control^{23,76} 3. Sleep disruption²⁵/sleep apnea²⁴ 4. Alcohol abuse^{21,22} 5. Postoperative sedation, analgesia and delirium management^{306–308} 	<ol style="list-style-type: none"> 1. Use of cardiopulmonary bypass^{232–235} 2. Temperature management^{212–217,219,220} 3. Surgery duration⁷⁶ 4. Arterial pressure management^{191,192,194} 5. Glycemic control^{226,228,230,231} 6. Hemodilution⁷³
Partly modifiable	<ol style="list-style-type: none"> 1. Patient frailty²⁸ 2. Preoperative cognitive function^{29,47} 3. Preoperative neurocognitive reserve^{26,27} 4. Depression^{72,76,77} 	<ol style="list-style-type: none"> 1. Surgical approach (<i>i.e.</i>, median sternotomy vs. lateral thoracotomy),^{130–134} On vs. Off CPB^{75,232–235} 2. Anesthetic dosage^{30,31} and EEG responses^{278,279}
Nonmodifiable	<ol style="list-style-type: none"> 1. Patient chronologic age^{47,48} 	<ol style="list-style-type: none"> 1. Direct myocardial injury^{134,135}

*The degree to which these factors can be modified in a real-world setting is beyond this article's scope. Selected references are listed in table 1; please see the body of the article for additional references and discussion.

Postoperative Cognitive Dysfunction after Cardiac Surgery

Many studies have used pre- and postoperative neuropsychologic testing to assess neurocognitive dysfunction after cardiac surgery, with varying testing deficit thresholds used to define postoperative cognitive dysfunction. Postoperative cognitive dysfunction incidence at one to three months after cardiac surgery ranged from ~10 to 16% (for a drop of 2 reliable change index units)^{13,45} to 40% (for a 1 SD drop in test scores).^{46,47} Most studies show postoperative cognitive dysfunction rates decrease over time from three months to one yr after surgery.^{13,47} Five issues are important for interpreting these studies. First, for most individuals, scores improve with repeat testing during short intervals. Several methods can account for this learning effect and intrinsic test-retest variability.⁴⁸ These issues can be partly mitigated by including multiple individual tests to assess each cognitive domain, and by using methods such as factor analysis to create overall cognitive domain scores that have higher test-retest reliability than single tests.^{10,47} Second, some tests have floor or ceiling effects that reduce sensitivity to detect cognitive change in patients with high or low baseline cognitive function.⁴⁹ This issue may be minimized by choosing appropriate tests for the baseline cognitive status of patients under study. For example, the Trail Making Test (part B) has high sensitivity for detecting cognitive impairment in patients with high baseline cognition, but has floor effects that reduce sensitivity for detecting postoperative cognitive change in patients with severe preoperative cognitive impairment. In contrast, the Mini-Mental Status Examination⁵⁰ has a ceiling effect in cognitively healthy individuals, but is sensitive to cognitive change in patients with mild cognitive impairment or mild dementia.⁵¹ Thus, an optimal cognitive test battery includes assessments that span different cognitive domains and cognitive ability ranges.⁵² Third, postoperative cognitive changes in older adults occur superimposed on normal age-related neurocognitive/neurophysiologic changes,^{53,54} including preexisting neurodegenerative pathology. Since Alzheimer disease-associated pathology begins decades prior to observable cognitive deficits (such as memory impairment),^{55,56}

many older cardiac surgery patients may have undetected, clinically silent Alzheimer disease-associated neuropathology; these patients are at increased risk for postoperative delirium⁵⁷ and postoperative cognitive dysfunction.^{58,59} Thus, it is important to compare postoperative cognitive changes to those seen over the cognate time interval in nonsurgical controls matched on cognitive decline risk factors (such as preclinical Alzheimer disease-associated pathology and/or genetic risk factors, age, vascular disease, and educational level), or by adjusting results based on normative test data.⁶⁰ Fourth, many statistical thresholds have been used to define cognitive dysfunction after cardiac surgery. Some incorporate changes in one⁶¹ or two⁶² tests, some rely on changes in larger cognitive domains, such as attention and verbal memory⁴⁷, and others measure global change across an entire cognitive test battery.⁶³ Depending on the statistical thresholds and rules used to define it, postoperative cognitive dysfunction may represent either a single or multidomain deficit, in particular memory, executive function or both may be affected. It is unclear how long-term cognitive trajectories differ in more detailed domain specific (memory *vs.* executive function) analysis—this is a key question for future study (table 2). Fifth, the timing of pre- and postoperative testing is important to consider. Cognitive dysfunction early after cardiac surgery is likely influenced by postoperative pain, medications like opioids, and acute postoperative recovery.⁶⁴ Thus, current guidelines consider postoperative cognitive dysfunction assessments to be free from these confounds starting 30 days after surgery.⁶⁴

For clinical practice, the international postoperative cognitive dysfunction nomenclature recommendations defines mild postoperative cognitive dysfunction (*i.e.*, postoperative mild neurocognitive disorder—postoperative cognitive dysfunction) as a 1-SD drop in test performance and major postoperative cognitive dysfunction (*i.e.*, postoperative major neurocognitive disorder—postoperative cognitive dysfunction) as a 2-SD drop in test performance, occurring between 30 days to 1 yr after surgery.⁶⁴ These recommendations help provide clarity on when postoperative cognitive dysfunction occurs, and what magnitude of deficits should

Table 2. Key Questions for Future Research on Delirium and Cognitive Dysfunction after Cardiac Surgery

1. Are there subtypes of POCD/delirium characterized by deficits in specific cognitive processes or neural networks? If so, are these subtypes caused by distinct pathophysiologic mechanisms, and do they have different long term trajectories?
2. What changes in functional brain connectivity are present in patients with delirium and/or POCD after cardiac surgery?
3. To what extent are POCD and delirium associated with similar vs. differing brain network connectivity changes?
4. What is the long term cognitive trajectory of neuroanatomic functional connectivity changes after cardiac surgery?
5. Would reversing the brain network connectivity changes seen in delirium and/or POCD by neural stimulation methods³⁰⁴ or brain training approaches³⁰¹ improve these disorders?
6. Are delirium or POCD after cardiac surgery associated with a postoperative acceleration of AD pathology, and/or with an increased long term risk of developing AD or related dementias?
7. What specific neuroinflammatory processes are present in human delirium and POCD?
8. Would blocking or resolving specific neuroinflammatory processes improve cognitive function after cardiac surgery?
9. How do neuroinflammation, preexisting AD or other neuropathology neurocognitive reserve, intraoperative cerebral microembolic load interact with each other and the intraoperative variables listed in table 1 in increasing the risk of delirium and POCD?
10. Is there an intraoperative management “bundle” to optimize multiple intraoperative physiologic variables (temperature, hemodynamics, anesthetic dosage and brain responses, glycemic control) that would result in a greater reduction in POCD/delirium than single interventions?

AD, Alzheimer disease; POCD, postoperative cognitive dysfunction.

be considered mild *versus* major postoperative cognitive dysfunction. However, these recommendations do not specify which cognitive tests should be used or whether deficit thresholds should be applied to individual tests, multiple test scores grouped by factor analysis, or to all tests within a battery. Further, these 1- and 2-SD statistical thresholds do not imply that patients who don't meet these thresholds don't have significant cognitive dysfunction that may impair their quality of life. Global cognitive dysfunction one year after coronary artery bypass graft (CABG), for example, was directly correlated with worsened quality of life measures, and both global cognitive dysfunction and worsened quality of life one year after CABG were associated with increased self-reported depressive symptoms (but not increased anxiety symptoms).⁶⁵ A continuous correlation between overall cognitive dysfunction magnitude and declining quality of life was also seen more than 5 yr after cardiac surgery, with a similar association between both measures and self-reported depressive symptoms.⁶⁶ This correlation between postoperative cognitive dysfunction severity and quality of life impairments was present across the full range of cognitive dysfunction severity at 1 and 5 yr after surgery;^{65,66} even relatively minor postoperative cognitive deficits were associated with reduced quality of life. Thus, from a patient-centric perspective, we believe postoperative cognitive

dysfunction should be conceptualized as a syndrome with a continuous severity distribution rather than as a simple dichotomous trait, and considered in terms of the degree to which it subjectively affects individual patients.^{48,67} Although the lack of a specific diagnostic threshold may seem vague, it is consistent with the notion in psychiatry and from the recent International Nomenclature recommendations for perioperative neurocognitive disorders⁶⁴ that neurocognitive disorders should be evaluated in terms of both objective signs and subjective symptoms. Further, the idea that “subthreshold” postoperative cognitive deficits may be significant for patients is consistent with the emerging view in medicine that many disease processes represent a continuous spectrum rather than dichotomous traits. For example, in cardiovascular medicine current recommendations support suppressing cardiovascular risk factors to ever lower levels,^{68–71} rather than believing that there are specific low-density lipoprotein or blood pressure thresholds below which these processes do not contribute to stroke or myocardial infarction risk.

Similarities in Risks for and Mechanisms of Postoperative Delirium and Postoperative Cognitive Dysfunction

Although postoperative delirium and postoperative cognitive dysfunction are distinct disorders measured with different instruments at differing times, similarities in their likely mechanisms, risk factors, and long-term sequelae suggest they may be part of an underlying neurobiologic continuum. We refer to both delirium and postoperative cognitive dysfunction as types of “neurocognitive dysfunction” because the recent International Code of Nomenclature recommendations⁶⁴ refers to both delirium and postoperative cognitive dysfunction as “perioperative neurocognitive disorders,” and because of the similarities between them. For example, many studies have identified increased age,^{47,72–76} depression,^{72,76,77} and altered baseline neurocognitive function^{10,36,46,47} as risk factors for both delirium and cognitive dysfunction after cardiac surgery. Overall, the risk for each disorder is associated more closely with baseline patient characteristics (such as those mentioned in table 1) than procedural factors,^{78,79} though intraoperative management can lower the risks of both postoperative cognitive dysfunction and delirium.⁸⁰ Both disorders are also thought to be caused by similar mechanisms such as neuroinflammation,^{48,79,81} and both delirium and postoperative cognitive dysfunction are associated with decreased quality of life,^{65,66,82,83} increased mortality,^{12,84} increased economic costs,^{85,86} long-term cognitive decline,^{47,87–89} and a possible increased risk for developing dementia such as Alzheimer disease (discussed at length in subsequent sections).^{88,90–92} Many patients with postoperative delirium also develop postoperative cognitive dysfunction,^{93–98} although the magnitude of this overlap varies between studies. Indeed, several investigators have proposed that delirium and postoperative cognitive dysfunction primarily differ in when

they occur, and that both are part of the same spectrum of postoperative central nervous system dysfunction (fig. 1).⁹⁹ Based on this idea, and because of the overall similarities in likely mechanisms of, risk factors for, and long-term sequelae of postoperative delirium and cognitive dysfunction, and the fact that many patients develop both disorders, here we discuss potential pathophysiologic mechanisms of and possible prevention strategies for both disorders together. Future studies should measure both delirium and postoperative cognitive dysfunction using well-defined instruments to further clarify the extent to which their pathology overlaps *versus* the extent to which distinct mechanisms are involved in each disorder. Clarifying this question is an important challenge for the field, and should help determine whether interventions could potentially help prevent or treat both disorders.

Current Understanding of the Pathophysiology of Neurocognitive Dysfunction after Cardiac Surgery

In general, risk factors and mechanisms that contribute to postoperative delirium and postoperative cognitive dysfunction can be categorized in two ways. First, they can be defined by processes present before or after surgery (such as patient factors), *versus* those present during surgery (such as cardiopulmonary bypass or anesthetic dosage; see table 1). These temporal divisions are useful because they clarify which processes can be targeted at a given time during perioperative care. It is also important to recognize that some proposed risk factors and mechanisms may be modifiable (such as smoking), some may be partially modifiable (such as frailty), and some such as chronologic age may be non-modifiable (table 1). Further, the inaccuracies of existing risk prediction models^{36,46} suggest that much remains to be discovered about the mechanisms and etiology of postoperative delirium⁷⁹ and postoperative cognitive dysfunction.⁴⁸

A second way to categorize etiology is by potential pathophysiologic processes, such as inflammation, neuronal damage, vascular damage/embolism, cerebral autoregulation and

oxygen delivery, neurodegenerative disease pathology, and brain network dysfunction, though these processes likely overlap. Here, we discuss the potential role of these processes in postoperative delirium and postoperative cognitive dysfunction.

Inflammation

Systemic inflammation and the ensuing neuroinflammatory response following peripheral surgical trauma are thought to play a causal role in delirium^{100,101} and postoperative cognitive dysfunction¹⁰²⁻¹⁰⁷ (reviewed in Berger *et al.*⁴⁸ and Terrando *et al.*¹⁰⁸). Sterile tissue injury and trauma during cardiac surgery lead to the release of damage-associated molecular patterns, chemokines and cytokines.^{109,110} These soluble mediators result in a systemic inflammatory response *via* activation of pattern recognition receptors, which leads to further release of interleukins IL-1 and IL-6, tumor necrosis factor (TNF)- α , and damage-associated molecular pattern molecules such as high mobility group box-1, and S100 calcium binding proteins (fig. 2).¹¹¹ Systemic inflammatory mediators may then be able to enter the brain due to post-surgical breakdown of the blood-brain barrier.^{103,106,112-115} Blood-brain barrier dysfunction is frequently seen in older adults (even in the absence of surgery),¹¹⁶ and has been seen in ~50% of patients after cardiac surgery.¹¹⁷ Further, the magnitude of postoperative blood-brain barrier breakdown correlates with the degree of cognitive dysfunction after cardiac surgery.¹¹⁸ Inflammatory cytokines may also be produced within the brain itself after surgery, due to peripheral-to-central signaling *via* both humoral and neural pathways.¹¹⁹ In either case, neuroinflammation has detrimental effects on the brain, is sufficient to cause deficits in cognition, memory, and behavior and overall “sickness behavior,”¹²⁰ and has been implicated in conditions ranging from mood disorders to neurodegenerative disease and postoperative cognitive dysfunction.^{48,121,122} Further, blocking neuroinflammation improves cognition in patients with autoimmune encephalitis, suggesting that neuroinflammation can be sufficient to cause cognitive dysfunction, and conversely, that blocking neuroinflammation can improve cognition.¹²³

Further support for the role of neuroinflammation in postoperative cognitive dysfunction comes from studies that have demonstrated that genetic polymorphisms that modulate inflammation (*e.g.*, in the genes *CRP*, *SELP*, *GPIIIA*, and *iNOS*) are associated with postoperative cognitive dysfunction risk.¹²⁴⁻¹²⁶ Additionally, inflammatory processes during cardiac surgery may be augmented by four factors during cardiopulmonary bypass (CPB). First, blood contact with foreign surfaces of the CPB circuit causes significant peripheral inflammation, including multiple-fold elevations of the proinflammatory cytokines interleukins 6 and 8 (IL-6, IL-8).¹²⁷ This effect can be reduced by using CPB pumps with biocompatible materials and miniaturized circuits, which reduce leukocyte aggregation, complement and coagulation cascade activation, and proinflammatory

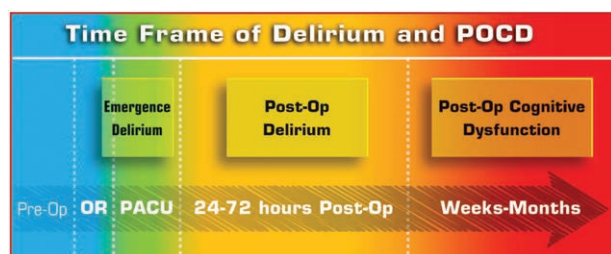


Fig. 1. One of the principal distinctions between postoperative (Post-Op) delirium and postoperative cognitive dysfunction (POCD) is the time frame in which they are found. Emergence delirium occurs in the operating room (OR) or immediately after in the post-anesthesia care unit (PACU). Postoperative delirium occurs 24 to 72h after surgery. POCD is measured at weeks to months after surgery and anesthesia. Pre-Op, preoperative. Reproduced with permission from Silverstein *et al.*⁹⁹

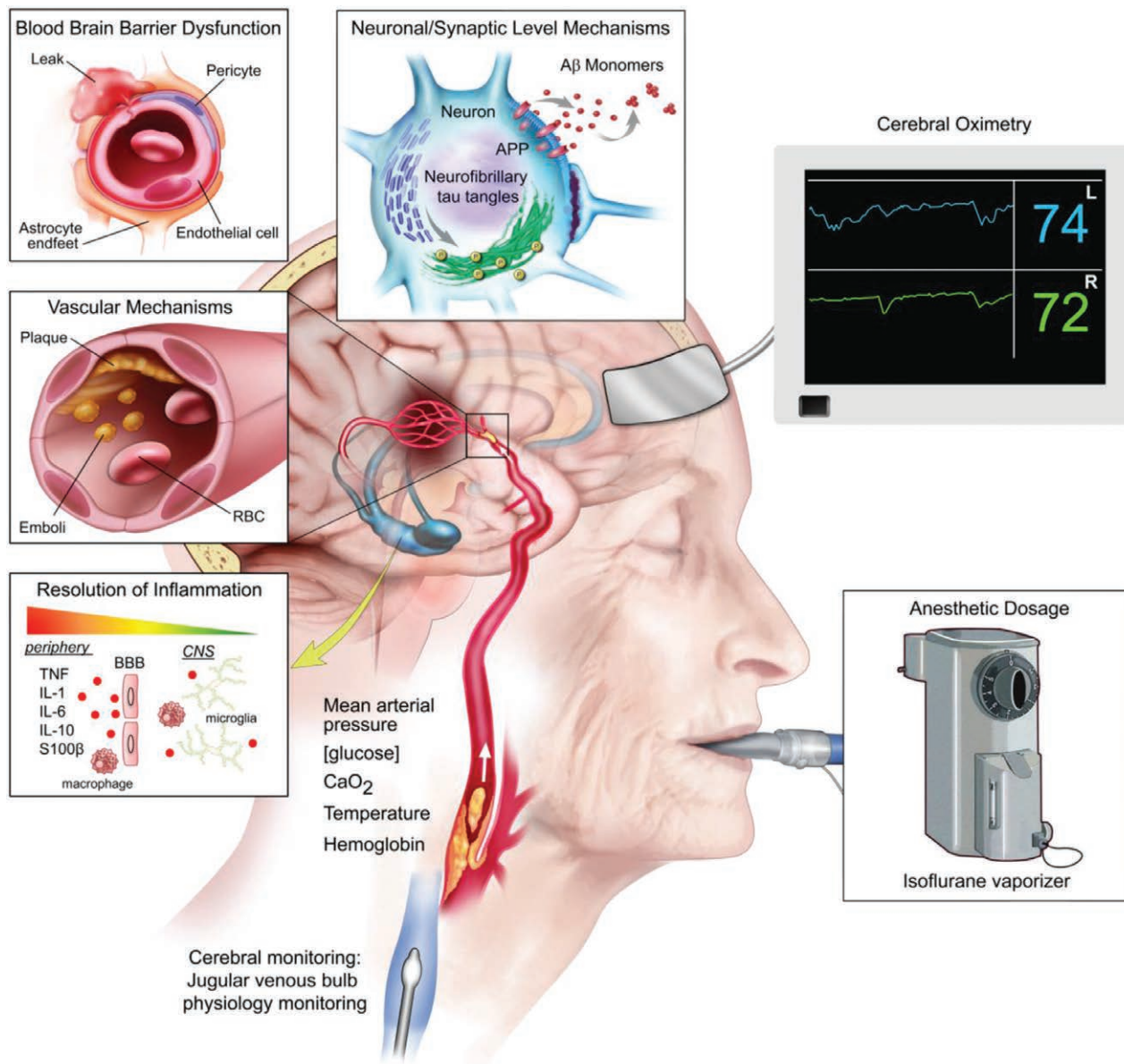


Fig. 2. Pathophysiologic mechanisms that may play a role in postoperative cognitive dysfunction (POCD) and/or delirium. Starting from the top, in clockwise order, the pullout boxes represent cellular/molecular and synaptic mechanisms (such as Alzheimer disease-related pathology), cerebral oximetry monitoring, anesthetic dosage, resolution of inflammation, vascular mechanisms (such as emboli), and blood-brain barrier dysfunction, which may be involved in POCD and delirium. APP, amyloid precursor protein; BBB, blood-brain barrier; IL, interleukin; RBC, red blood cell; TNF, tumor necrosis factor.

cytokine production (reviewed in Shann *et al.*¹²⁸). The classical complement cascade can also be activated by heparin-protamine complexes after CPB.¹²⁹ Second, median sternotomy (as opposed to smaller lateral thoracotomy approaches) increases proinflammatory cytokine levels in rats,¹³⁰ and possibly in humans,^{131,132} although some studies have not replicated these findings.^{133,134} Third, cardiac ischemia/reperfusion injury is also accompanied by significant increases in serum inflammatory cytokine/chemokine levels, and in recruitment and activation of neutrophils, monocytes, and other leukocytes.¹³⁵ Fourth, anesthetic drugs

themselves can modulate inflammation. Inhaled anesthetics have proinflammatory effects on microglia *in vitro*¹³⁶ and on the mouse brain *in vivo*,¹³⁷ and opioids and heparin can also modulate inflammation and monocyte function *in vitro*.¹³⁸ The drugs given during cardiac surgery may thus have significant effects on the overall balance of pro- and antiinflammatory cytokine levels, and on patient outcomes.¹³⁹ Taken together, these findings suggest that exposure to anesthetics and other drugs during cardiac surgery, together with the effects of the bypass circuit, median sternotomy and tissue damage, and ischemia reperfusion injury, may contribute to

neuroinflammation and ensuing postoperative delirium and postoperative cognitive dysfunction. As a whole these factors may also explain why serum IL-6 and other proinflammatory cytokine levels are higher after cardiac *versus* peripheral surgery,^{133,140} although underlying differences between these patient cohorts could also play a role.

In rodent models, cardiac surgery causes more prolonged neuroinflammation and a wider spectrum of behavioral impairments than abdominal surgery,¹⁴¹ though both surgery types reduced hippocampal neurogenesis rates and neurotrophic factor levels (such as brain derived neurotrophic factor).¹⁴² Terrando *et al.* have also found similar behavioral impairments and neuroinflammation after orthopedic surgery in mice,¹⁴² suggesting that common mechanisms involving decreased hippocampal neurogenesis, spinal pain signaling, and central neuroinflammation may lead to memory dysfunction after both orthopedic and cardiac surgery. Further, mouse orthopedic surgery studies suggest that increased brain monocyte chemoattractant protein 1 levels recruit peripheral monocyte-derived macrophages into the central nervous system, which play a role in postoperative explicit memory deficits.^{103,105,143} Blocking neuroinflammation¹⁰⁴ and microglial activation¹⁴⁴ reduced postoperative memory deficits in mouse models, though these interventions have yet to be tested in humans. Human studies have found postoperative cerebrospinal fluid (CSF) increases in monocyte chemoattractant protein 1¹⁴⁵ and other inflammatory cytokines^{146,147} after orthopedic surgery, and CSF IL-6 and IL-8 increases have been observed after cardiac surgery,¹¹⁵ though it is unclear whether CSF monocyte chemoattractant protein 1 levels increase after cardiac surgery.¹¹⁴ To our knowledge, no study has ever examined whether monocytes or macrophages enter the human central nervous system after cardiac surgery, or whether such monocyte/macrophage influx plays a role in cognitive dysfunction or delirium after cardiac surgery (or other types of surgery); these are important questions for future research.

Several antiinflammatory drug trials have failed to prevent delirium or cognitive dysfunction after cardiac surgery, including lidocaine,¹⁰ magnesium,⁴⁶ complement cascade inhibitors,¹⁴⁸ and postoperative acetylcholinesterase treatment^{149,150} (which may increase vagal antiinflammatory pathways in addition to boosting brain acetylcholine levels). However, lidocaine or magnesium may have cognitive benefits in specific patient subgroups,^{10,46} and acetylcholinesterase treatment improved postoperative memory.¹⁴⁹ Intraoperative high dose steroids were also ineffective,^{35,45,151,152} perhaps because steroids can also cause delirium and hallucinations¹⁵³ that may counterbalance their theorized cognitive-improving antineuroinflammatory effects. Intraoperative ketamine treatment reduced delirium¹⁵⁴ and cognitive dysfunction¹⁵⁵ after cardiac surgery in small pilot studies, but did not reduce delirium in a large multicenter randomized trial (which included approximately one third cardiac surgery patients).¹⁵⁶ Dexmedetomidine also had no effect

on delirium incidence after cardiac¹⁵⁷ surgery in a recent multicenter randomized trial, though it had mixed effects on delirium after noncardiac surgery^{158,159}; these divergent results may be due to differing dexmedetomidine infusion rates and durations between these studies.^{157–159}

These generally negative study findings may reflect the pathophysiologic complexity of delirium and postoperative cognitive dysfunction, which may also underlie the relatively greater success of multimodal interventions.¹⁶⁰ Alternative strategies to more specifically modulate postoperative inflammation may better help prevent postoperative delirium and postoperative cognitive dysfunction. For example, resolution of inflammation is an active process orchestrated by specialized proresolving mediators,¹⁶¹ including omega-3 fatty acid-derived lipid mediators (*i.e.*, resolvins) that have potent postoperative antiinflammatory and proresolving effects.^{162–164} Administration of the omega-3 derived resolvins D1 reduced memory impairments after orthopedic surgery in mice.¹⁶⁴ Other resolution agonists, including annexin A1 peptide mimetics, also reduced neuroinflammation and improved cognitive outcomes after CPB and deep hypothermic circulatory arrest in a rat cardiac surgery model.¹⁶⁵ Proresolving mediators can also reduce inflammatory pain,¹⁶⁶ lower antibiotic requirements,¹⁶⁷ and reduce mortality from microbial sepsis.¹⁶⁸ Thus, understanding the role of resolvins and other antiinflammatory lipids in cognitive function after cardiac surgery, and whether manipulating them can improve it, are important future research goals.

Embolus Load and Clinically Covert Stroke

Embolus load may also play a role in neurocognitive dysfunction after cardiac surgery. The direct manipulation of the aorta during cardiac surgery often disrupts atheromatous plaques. Aortic atheroma burden can be measured intraoperatively by epiaortic ultrasound, and increased intraoperative atheroma burden has been seen in patients with postoperative cognitive dysfunction (*vs.* those without postoperative cognitive dysfunction) at 1 week, but not at 3 or 12 weeks, after cardiac surgery.⁶² Current guidelines recommend epiaortic ultrasound evaluation of aortic plaque in patients with increased stroke risk, including those with a vascular disease history, and those with other evidence of aortic atherosclerosis or calcification.¹⁶⁹

Aortic plaque disruption can liberate microemboli that can travel to the brain. These microemboli can be detected by transcranial Doppler ultrasound,¹⁷⁰ although the majority of transcranial Doppler signals actually represent small gas emboli.¹⁷¹ Gaseous microemboli occur frequently in open chamber cardiac valve cases, which has led many centers to flood the open cardiac chamber with carbon dioxide, since carbon dioxide is more soluble than air and thus promotes the resorption of gas emboli (potentially before they enter the cerebral vasculature).¹⁷² However, a randomized trial found that field flooding with carbon dioxide *versus* medical air had no effect on cognitive function 6 weeks after

surgery.¹⁷³ Rather than intracardiac gas volume, the main predictor of cognitive decline in this study was atheromatous vascular disease.¹⁷³

Microemboli can also be detected by postoperative diffusion-weighted magnetic resonance imaging (MRI)¹⁷⁴ though preoperative MRI scans are needed to differentiate new microemboli from prior lesions. The percentage of cardiac surgery patients with detectable microemboli vastly outnumber the percentage with clear postoperative stroke(s). Many experts refer to these emboli and diffusion-weighted MRI abnormalities as “clinically covert strokes,”⁷⁸ because they are not associated with neurologic abnormalities detectable in routine clinical examination. Although it seems intuitive that embolic load to the brain and resulting T2-weighted MRI white matter hyperintensities would have detrimental neurocognitive effects, correlations between embolic load and postoperative cognitive changes have been inconsistent (particularly after open chamber valve cases).^{174–177} This is a paradox, because large observational studies have found these “clinically covert strokes” are associated with future risk of stroke, cognitive decline, and Alzheimer disease.^{178–181} One explanation may be that the location at which microembolic “covert strokes” occur may matter in addition to their total volume, since neurovascular coupling and neuronal circuitry can be disrupted beyond injury site(s) themselves,¹⁸² and small lesions at critical node locations can thus cause wider brain network dysfunction and impair neurocognitive processing.¹⁸² Future studies should examine this idea, and evaluate interactions between embolic load, central neuroinflammation, preexisting neurodegenerative disease pathology, and other variables that may interact in synergistic ways to produce postoperative neurocognitive dysfunction.

Cerebral Blood Flow, Autoregulation, and Oxygen Delivery and Utilization

Many cardiac surgery patients have hypertension, which can shift the normal autoregulatory range of cerebral blood flow (classically thought to be 60 to 160 mmHg). Thus, the actual autoregulation range for any given patient is unknown, and the lower limit of autoregulation during CPB may vary from 45 to 80 mmHg.¹⁸³ Newman *et al.* found significant cerebral autoregulation impairments in 215 patients during cardiac surgery, but no correlation with postoperative cognitive dysfunction.^{74,184} Similarly, Ono *et al.* found that up to 20% of cardiac surgery patients have impaired autoregulation, and these patients with “pressure passive” cerebral blood flow¹⁸⁵ had increased perioperative stroke rates.¹⁸⁶ Further, intraoperative cerebral autoregulation can dynamically change in response to intraoperative physiologic changes,^{187,188} suggesting the need for real-time cerebral autoregulation measurement. Hori *et al.* found that ultrasound-tagged near infrared spectroscopy can identify cerebral autoregulation limits, and showed (in a secondary analysis) that patients with delirium had higher blood pressure excursions above this range.¹⁸⁹ Thus, an ongoing study is investigating whether cerebral

oximetry-guided blood pressure management can decrease postoperative delirium after cardiac surgery.¹⁹⁰

These findings then led to studies examining the relationship between mean arterial pressure (MAP) management and postoperative cognitive changes. For example, maintaining intraoperative MAP within 80 to 90 mmHg, rather than 60 to 70 mmHg, was associated with less postoperative delirium and a smaller postoperative decrease in mini mental status exam scores.¹⁹¹ Gold *et al.* found that higher MAP targets (*i.e.*, 80 to 100 mmHg *vs.* 50 to 60 mmHg) were associated with lower cardiac and neurologic complication rates (*i.e.*, stroke),¹⁹² though they found no difference in postoperative cognition between groups. Postoperative MAP values below the lower limit of autoregulation have also been associated with increased levels of the glial injury biomarker glial fibrillary acidic protein, emphasizing the importance of maintaining MAP within the autoregulatory range after as well as during cardiac surgery.¹⁹³ However, observational studies have found that maintaining blood pressure above the upper limit of cerebral autoregulation is associated with increased postoperative delirium rates,^{189,194} suggesting that it may be important to avoid MAPs above, as well as below, each patient’s autoregulatory range.

One major caveat to the interventional MAP management studies discussed above is that many of these studies^{191,192} did not measure cerebral autoregulation limits in individual patients. The cerebral autoregulation range varies substantially among patients,¹⁹⁵ especially during cardiopulmonary bypass.¹⁹⁶ Thus, it is possible that the higher MAP targets in these studies^{191,192} may have been outside the cerebral autoregulation limits in some patients, particularly in patients with hypertension.¹⁹⁵ Future studies should thus measure individualized cerebral autoregulation limits and study MAP management algorithms based on them.

Maintaining blood pressure within each individual’s cerebral autoregulation range may help ensure adequate brain oxygen delivery. Lower MAP values are associated with cerebral venous oxygen desaturations, which are themselves associated with postoperative cognitive dysfunction.¹⁹⁷ In other words, inadequate mean arterial pressure management during cardiac surgery may cause postoperative cognitive dysfunction by impairing cerebral oxygen delivery, which can be detected as a cerebral venous oxygen desaturation.¹⁹⁷ Brain oxygen delivery and usage can be inferred from cerebral oximetry, which can help guide real-time intraoperative blood pressure management. Cardiac surgery patients who have intraoperative cerebral oxygen desaturations are more likely to develop postoperative delirium¹⁹⁸ and postoperative cognitive dysfunction (measured 1 week^{199,200} and 1 month²⁰⁰ after surgery). This is consistent with the finding that cerebral venous oxygen desaturations are associated with postoperative cognitive dysfunction at hospital discharge.¹⁹⁷ However, at least two other studies did not find a correlation between intraoperative cerebral oxygen desaturations and postoperative cognitive dysfunction.^{201,202} These

divergent findings could reflect differences in postoperative cognitive assessment methods and/or different patient characteristics.^{199–202} Indeed, the de Tournay-Jette *et al.*²⁰⁰ study patients were ~10 to 20 yr older and had more comorbid disease processes than patients in the Reents *et al.*²⁰¹ and Hong *et al.*²⁰² studies, suggesting cerebral oximetry may be better able to identify postoperative cognitive dysfunction and delirium risk in older/sicker patients. Additionally, hyperoxia has been associated with postoperative delirium,²⁰³ although we found no association between hyperoxia during CPB and postoperative cognitive dysfunction.²⁰⁴ A multimodal perioperative management intervention, including cerebral oximetry, reduced delirium after cardiac surgery¹⁶⁰ and postoperative cognitive dysfunction after noncardiac surgery,²⁰⁵ raising the possibility that similar interventions may help improve cognition after cardiac surgery.

These intraoperative cerebral oximetry monitoring studies are also consistent with the effect of intraoperative hemodilution on cognitive dysfunction after cardiac surgery. In a randomized trial of extreme (hematocrit of 15 to 18) versus moderate (hematocrit of 27), there was a statistically significant interaction between age and extreme hemodilution: older patients who underwent extreme hemodilution had higher postoperative cognitive dysfunction rates.⁷³ Taken together, these data suggest that ensuring adequate cerebral oxygen delivery may help reduce postoperative cognitive dysfunction.

Temperature Management during Cardiac Surgery

The cerebral metabolic rate of oxygen utilization is closely regulated by temperature, which led to the idea that lowering cerebral metabolic rate of oxygen utilization by inducing hypothermia could reduce brain oxygen deprivation and neurocognitive injury during reduced oxygen delivery periods (*e.g.*, during CPB). Indeed, hypothermia reduces neurologic injury in animal models of focal cerebral ischemia and cardiopulmonary resuscitation.^{206,207} Conversely, hyperthermia increases cerebral metabolic rate of oxygen utilization and is associated with worse neurocognitive outcomes and increased mortality risk in numerous clinical situations.^{208–210} Thus, studies have examined whether lowering cerebral metabolic rate of oxygen utilization by inducing hypothermia during CPB would improve postoperative neurocognitive function. Early work showed that patients who underwent normothermic (*i.e.*, “warm” or greater than 35°C) CPB had a threefold higher stroke incidence than those who underwent hypothermic (*i.e.*, “cold” or less than 28°C) CPB.²¹¹ Yet, one randomized trial found no benefit of hypothermia (*i.e.*, 28 to 30°C) versus normothermia (35.5 to 36.5°C) during CPB on cognitive change from before to 6 weeks after cardiac surgery.²¹² Nonetheless, the maximum postoperative temperature after cardiac surgery was associated with cognitive dysfunction severity 6 weeks after surgery,²¹³ emphasizing the importance of avoiding postoperative hyperthermia.

This concept may help explain data showing that rewarming to a lower temperature (34 *vs.* 37°C) was associated with lower cognitive dysfunction rates 1 week after surgery and improved performance on the grooved pegboard test (a manual dexterity and visuomotor processing speed task) at 3 months after surgery,²¹⁴ although there was no overall cognitive benefit at 3 months after surgery.²¹⁵ In essence, the early cognitive benefits of rewarming to a slightly lower target in this trial²¹⁴ may have been due to the prevention of postoperative hyperthermia. This group also found no neurocognitive difference among CABG patients randomized to undergo normothermic (37°C) CPB or hypothermic (34°C) CPB without operating room rewarming in either group; thus, avoiding central hyperthermia during rewarming may help optimize postoperative cognitive function.²¹⁵ Similarly, another recent randomized trial found that achieving a lower core body temperature (*via* external head cooling) during CPB was associated with less cognitive dysfunction 10 days after cardiac surgery.²¹⁶ Nonetheless, despite numerous studies (reviewed in Grigore *et al.*²¹⁷ and Hogan *et al.*²¹⁸), there is still debate about temperature management during cardiac surgery.^{219,220} Current clinical recommendations simply call for avoiding hyperthermia (arterial outlet blood temperature greater than or equal to 37°C) during cardiac surgery, and for a rewarming rate less than or equal to 0.5°C/min once temperature exceeds 30°C.²²¹ Slow rewarming may help avoid cerebral ischemia, since rapid rewarming has been shown to cause cerebral metabolic rate of oxygen utilization increases prior to corresponding increases in CBF.²²²

Glucose Homeostasis during Cardiac Surgery

Aside from oxygen delivery and perfusion pressure, neurocognitive function is also influenced by serum glucose levels (discussed in Berger *et al.*³⁷). Similar to cerebral blood flow autoregulation, neurocognitive function is typically unaltered by glucose changes within normal physiologic limits.^{223–225} Since many cardiac surgery patients have diabetes, and the surgical stress response can decrease peripheral insulin sensitivity and cause hyperglycemia, studies have investigated the relationship between intraoperative glucose management and postoperative neurocognitive outcomes. One retrospective study found that intraoperative hyperglycemia (*i.e.*, glucose levels greater than 200 mg/dL) was associated with worsened postoperative cognitive function in nondiabetic patients, but not in diabetic patients.²²⁶ This is not surprising because diabetic patients are often exposed to hyperglycemia, which causes physiologic compensatory responses (such as glucose transporter downregulation on brain capillaries) to reduce excessive glucose influx into the brain.²²⁷ This adaptation helps explain why intraoperative hyperglycemia may be more detrimental to the brains of nondiabetic patients. However, this interpretation is challenged by the results of Butterworth *et al.*,²²⁸ who found in a large randomized trial (N = 381) that intraoperative

insulin infusion (up to 4 U/h) in nondiabetic patients did not improve neurocognitive outcomes. This lack of effect may have been due to residual hyperglycemia secondary to insufficient insulin administration (possibly due to hypothermia-induced insulin resistance²²⁹) in the insulin treatment arm, though, as the authors discussed.²²⁸

The idea that hyperglycemia is detrimental to the brain led to additional interventional studies examining whether tighter glucose control (*i.e.*, to avoid hyperglycemia) would improve postoperative cognition. Yet, tight intraoperative glucose control with a hyperinsulinemic-normoglycemic clamp (glucose target 80 to 110 mg/dL) *versus* standard therapy (glucose target less than 150 mg/dL) during cardiac surgery was associated with increased delirium rates,²³⁰ perhaps due to the increased hypoglycemia in the intensive glucose control arm of this study.³⁷ However, this study did not assess delirium before surgery,²³⁰ so it is unclear how many of these cases of postoperative delirium might have reflected preexisting cognitive deficits or delirium before surgery.³⁷ Another recent pilot study found that the use of glucose and insulin infusions to maintain serum glucose at ~64 to 110 mg/dL preserved auditory learning and executive function after cardiac surgery,²³¹ suggesting that avoiding hyperglycemia may result in improved postoperative cognitive function. Thus, as with oxygen delivery and cerebral perfusion management (discussed in aforementioned section, “Cerebral Blood Flow, Autoregulation, and Oxygen Delivery and Utilization”), these data suggest that it may be equally important to avoid hypoglycemia and hyperglycemia in order to avoid postoperative delirium and postoperative cognitive dysfunction. Further, the physiologic adaptations to chronic hyperglycemia in diabetic patients suggests that, as in the case of cerebral autoregulation and intraoperative blood pressure management, intraoperative glycemic control may need to be individualized for particular patients.

Effects of On-pump *versus* Off-pump Cardiac Surgery, and Medical *versus* Surgical Management for Coronary Artery Disease, on Delirium and Postoperative Cognitive Dysfunction Rates

Given the concern that cardiopulmonary bypass alone may contribute to postoperative delirium and postoperative cognitive dysfunction, several studies have examined delirium and cognitive dysfunction rates after on-pump *versus* off-pump cardiac surgery. A recent retrospective analysis found that patients who underwent off-pump cardiac surgery had significantly lower delirium rates compared to on-pump patients,⁷⁵ although residual confounding could explain these observational findings. In the Octopus study, patients who underwent off-pump cardiac surgery, as opposed to those who underwent on-pump cardiac surgery, had a trend toward less cognitive dysfunction 3 months after surgery, but this small difference disappeared by 1 yr after surgery.²³² The Randomized On/Off Bypass (ROOBY) trial found no

difference in overall cognitive outcomes between on- *versus* off-pump cardiac surgery, although they did detect a significantly greater postoperative cognitive improvement in the clock drawing test in patients who underwent off-pump *versus* on-pump cardiac surgery.²³³ Since this difference was seen only in one of eleven tests within a larger cognitive test battery, it is difficult to ascertain whether this difference represents a true neurocognitive improvement effect of off-pump CABG *versus* a false positive due to performance of multiple tests. Similarly, Kok *et al.* found that patients who underwent off-pump cardiac surgery, as compared to those who underwent on-pump cardiac surgery, had similar cognitive dysfunction rates at 4 days after surgery but had lower cognitive dysfunction rates 1 month after surgery.²³⁴ Finally, Selnes *et al.* found no difference in 6-yr cognitive outcomes between patients with coronary artery disease who were managed medically, and patients who underwent on-pump or off-pump coronary artery bypass grafting. However, the Selnes study was not randomized; thus, residual confounding could explain the lack of differences between patients who underwent CABG *versus* medical management, and between those who underwent on- *versus* off-pump CABG.²³⁵ Further, the Selnes study used group averaged data, which may have obscured more severe long term cognitive decline in individual cardiac surgery patients.²¹⁸

These findings are compatible with two different interpretations. The first, and perhaps simplest, interpretation is that cardiopulmonary bypass does not contribute to postoperative delirium or cognitive dysfunction.²³⁶ The second interpretation is that other aspects of off-pump cardiac surgery, such as steep Trendelenburg positioning,²³⁷ which results in cerebral venous engorgement and possible cerebral oxygen desaturation,²³⁸ may be equally detrimental to postoperative cognition as cardiopulmonary bypass. Additionally, surgical manipulation of the heart in off-pump cases (*i.e.*, to expose the circumflex and right coronary arteries) may cause both increased central venous pressure and arterial hypotension, thus reducing cerebral perfusion pressure and possibly also worsening postoperative brain function. According to this interpretation, there is no advantage to avoiding cardiopulmonary bypass during cardiac surgery if current “off-pump” cardiac surgery techniques are used, but this does not mean that cardiopulmonary bypass is cognitively benign, and suggests that further advances in bypass technology may improve postoperative cognitive outcomes. Nonetheless, in other studies, off-pump cardiac surgery has been associated with worsened 1 yr composite outcomes (including mortality),²³³ so there is currently little enthusiasm for performing off-pump cardiac surgery.

Studies have also examined the relative cognitive effects of cardiac surgery *versus* medical or percutaneous therapy for patients with cardiac disease. As discussed, Selnes *et al.* found no difference in long-term cognitive outcomes between medical and surgical management for coronary artery disease.²³⁵ Similar to the discussion of cardiopulmonary bypass, these data can be interpreted in at least three

ways. The first, and simplest, interpretation is that cardiac surgery has no long-term detrimental effect on cognition. A second interpretation, which is also compatible with the data, is that operative management (CABG or valve surgery) and medical management have similar cognitive effects in patients with cardiac disease, who often have cerebrovascular disease processes that predispose them to long-term detrimental cognitive effects. For example, the detrimental cognitive effects of cardiac surgery (including anesthesia, possible cardiopulmonary bypass, postoperative pain, and sleep disruption, among others), may be counterbalanced by the beneficial cognitive effects of coronary revascularization (such as improved overall cardiovascular and physical function). These mixed cognitive effects of cardiac surgery may roughly approximate the overall mixture of beneficial and adverse effects of medical management for cardiac disease. For example, medical management for cardiac disease may help patients avoid the detrimental cognitive effects of operative management (as discussed at the beginning of this section), but would also likely deprive patients of the potential cognitive benefits of successful revascularization, and may leave patients with residual angina and related physical limitations. A third interpretation is that since postoperative cognitive dysfunction is associated with increased postoperative mortality, a long-term comparison of cognitive outcomes after surgical *versus* medical management may underestimate the long-term detrimental cognitive effects of cardiac surgery, since an increased fraction of the most cognitively impaired surgical patients may have died and not been included in longer-term assessments.²³⁵

Cardiac Surgery, Neurotoxicity, and Alzheimer Disease Pathology

Up to 30% of patients may develop dementia within 7.5 yr after cardiac surgery,⁸⁷ which has raised concern that both surgical stress and excessive exposure to volatile anesthetics and/or propofol may contribute to neurocognitive dysfunction. This would not be surprising since both volatile anesthetics and propofol increase GABA-A receptor function, and GABA-A agonist usage has been associated with increased risk of delirium,²³⁹ cognitive dysfunction²⁴⁰ and dementia²⁴¹ outside perioperative care. Mechanism(s) that could underlie a detrimental effect of anesthetic drugs on postoperative cognition could include: (a) GABAergic anesthetic-induced acceleration of Alzheimer disease processes such as amyloid- β and tau pathology,^{90,243}; (b) anesthetic-induced disruption of gamma oscillation patterns involved in amyloid beta clearance^{244–247}; (c) direct neuronal or glial cell damage (reviewed in Zheng *et al.*²⁴⁸ and Vutskits and Xie²⁴⁹); or (d) anesthetic-induced increases in neuroinflammation.^{136,137,250,251} Further, neuroinflammation can increase neuronal sensitivity to anesthetic drugs;²⁵² thus, anesthetic-induced neuroinflammation could potentially promote a positive feedback loop that further amplifies initial neuroinflammatory responses to anesthesia and surgery.

The notion that postoperative cognitive dysfunction and delirium may involve mechanisms similar to those involved in Alzheimer disease (reviewed in Palop *et al.*²⁵³ and Jack and Holtzman²⁵⁴) has led to studies of whether Alzheimer disease-associated genetic polymorphisms, such as *ApoE4*, also increase risk for postoperative delirium or postoperative cognitive dysfunction. However, the interpretation of these studies is complex, because aside from its association with Alzheimer disease risk, *ApoE4* has pleiotropic neurologic effects (including cerebrovascular dysfunction and decreased cerebral blood flow).²⁵⁵ These studies have found conflicting results; overall it appears that *ApoE4* carriers are not more likely to develop early postoperative delirium or postoperative cognitive dysfunction, but do have worse long-term cognitive trajectories after cardiac surgery.^{88,256–260} This finding could be related to the known long term detrimental effects of the *ApoE4* allele on cognition,⁸⁸ and/or to the increased aortic arch atheroma burden seen in *ApoE4* carriers²⁶¹ and thus a possible increase in cerebral microemboli during cardiac surgery. Several other genetic polymorphisms have recently been found that are associated with Alzheimer disease risk,^{262–266} and it will be important to examine whether these Alzheimer disease risk polymorphisms are also associated with postoperative cognitive dysfunction or delirium risk after cardiac surgery.

Changes in Alzheimer disease biomarkers (such as changes in CSF amyloid- β and tau levels) occur after cardiac surgery in humans,^{114,243} and both mouse model and *in vitro* data suggest that isoflurane may accelerate Alzheimer disease pathology to a greater extent than propofol.^{267,268} However, there is no human data demonstrating that any particular anesthetic agent is associated with greater (or smaller) CSF Alzheimer disease biomarker changes after cardiac surgery. A recent randomized trial in neurosurgery patients showed that propofol and isoflurane treatment were each associated with similar increases in CSF tau levels, and minimal changes in amyloid- β or phospho-tau.²⁶⁹ Thus, there is currently no human evidence to favor one anesthetic type *versus* another for avoiding changes in CSF Alzheimer disease biomarkers or Alzheimer disease pathogenesis.

Further, it is unclear whether postoperative CSF Alzheimer disease biomarker changes are associated with or play a cause role in delirium or postoperative cognitive dysfunction after cardiac surgery, or whether they merely represent an acute-phase response to cardiac surgery. To clarify these issues, future studies will need to: (1) examine whether there is a correlation between the magnitude of these pathologic processes and the magnitude of cognitive dysfunction after cardiac surgery; (2) determine whether these pathologic processes advance to a greater extent after cardiac surgery than after the same period in matched nonsurgical controls with similar comorbidities that predispose to neurocognitive dysfunction (*i.e.*, neurovascular and Alzheimer disease risk factors, among others); and (3) determine whether blocking postoperative changes in these pathways abrogates delirium or postoperative cognitive dysfunction after cardiac surgery.

Anesthetic Dosage and Potential Neurotoxicity

Several lines of evidence suggest that anesthetic administration during cardiac surgery may modulate postoperative neurocognitive function *via* effects on the Alzheimer's disease pathways discussed above or by modulating inflammation or synaptic function (reviewed in Berger *et al.*⁹⁰ and Vutskits and Xie²⁴⁹). General anesthesia is a drug-induced coma²⁷⁰; and observational studies have found both direct²⁷¹⁻²⁷³ and inverse²⁷⁴ associations between the duration of electroencephalogram (EEG) burst suppression, and postoperative delirium and/or postoperative cognitive dysfunction. Further, several interventional studies in noncardiac surgery have shown that bispectral index (BIS)-titrated anesthetic administration results in lower levels of postoperative delirium.^{80,275,276} In the Cognitive Dysfunction after Anesthesia (CODA) trial, a ~30% decrease in mean end-tidal inhaled anesthetic was associated with a 40% reduced incidence of cognitive dysfunction 3 months after surgery.⁸⁰ However, this reduction in postoperative cognitive dysfunction due to BIS-guided anesthetic administration was not observed by Radtke and colleagues, likely because BIS monitor usage was not associated with a significant reduction in anesthetic dosage in their study.²⁷⁵ Similarly, a secondary analysis of cardiac surgery patients in the BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) study showed that BIS-titrated anesthetic administration was associated with a trend (which narrowly missed statistical significance) toward lower postoperative delirium rates.²⁷⁷ This lack of significance may also partly be due to the use of the CAM-ICU instrument for all delirium assessments in this study,²⁷⁷ an instrument with limited sensitivity in nonintubated patients.⁴³

Based on these data, we and others have called for appropriately powered prospective studies to definitively determine whether EEG-guided anesthetic delivery during cardiac surgery lowers postoperative delirium rates.^{277,278} An important challenge for these future studies will be to determine whether using raw EEG measures instead of or in addition to the BIS (or other proprietary processed EEG anesthetic depth indices) reduces delirium or postoperative cognitive dysfunction rates. Although a simple anesthetic depth index is easy to use, the BIS index has a nonlinear relationship with inhaled anesthetic dose.²⁷⁹ Both theoretical work²⁸⁰ and retrospective analyses²⁸¹ demonstrate that the BIS index may be unreliable in older adults, perhaps because it does not account for age-dependent changes in the EEG spectrogram and total EEG power.²⁸⁰ Nonetheless, the findings described above suggest that processed EEG-guided anesthetic titration can lower postoperative cognitive dysfunction rates if it results in reduced anesthetic dosage. Similar to pulmonary artery catheter use in cardiac surgery (in which outcomes likely depend not on whether a pulmonary artery catheter was placed, but rather on how the information from it was used to manage patients²⁸²), patient outcomes are likely impacted not by *whether* an EEG monitor was used,

but rather by *how* the data from it was used (*i.e.*, to titrate anesthetic dosage). Thus, differences between how clinicians used EEG monitor data to make anesthetic titration decisions may explain some of the outcome differences between the studies discussed above.^{80,275} Ongoing observational²⁸³ and interventional^{240,284} studies are examining these issues in more detail to determine whether raw or processed EEG-titrated anesthetic administration protocols can reduce the incidence of postoperative delirium and postoperative cognitive dysfunction and even reduce postoperative mortality.²⁸⁵

Systems/Cognitive Neuroscience-level Mechanisms of Post-cardiac Surgery Cognitive Dysfunction

Significant neuroimaging advances have been made over the past 20 yr, and several studies have used structural and functional neuroimaging to examine the neuroanatomic basis of cognitive dysfunction after cardiac surgery. For example, cardiac surgery patients with structural MRI evidence of increased ventricular size (a likely neural correlate of cortical atrophy), have an increased odds of developing postoperative delirium.⁹

Functional MRI can also measure activity within specific brain regions *via* the blood oxygen level dependent signal, a hemodynamic correlate of neuronal activity, and can be used to measure postoperative brain activity changes. For example, Abu Omar *et al.*²⁸⁶ performed blood oxygen level dependent functional MRI scans before and 4 weeks after surgery in 12 on-pump and 13 off-pump cardiac surgery patients, while they completed a working memory task (*i.e.*, the N-back task, in which subjects see a series of letters or numbers and are asked to press a button whenever the letter or number was seen N times beforehand⁴⁸). Patients who underwent on-pump, but not those who underwent off-pump, cardiac surgery showed a postoperative decrease in prefrontal cortex activation during the most demanding attention task, the 3-back condition.²⁸⁶ Interestingly, the postoperative decrease in prefrontal cortex activation during 3-back task performance in on-pump cardiac surgery patients correlated with transcranial Doppler-detected intraoperative emboli number, though no differences in N-back task performance were observed in on-pump *versus* off-pump groups, or before *versus* after surgery.²⁸⁶ These data suggest that intraoperative embolic load may be associated with altered brain activity during cognitive task performance, although these changes may not be sufficient to impede task performance/accuracy. Future studies will be necessary to determine whether these changes in prefrontal cortex activity are associated with subjective cognitive complaints after on-pump cardiac surgery.

In addition to measuring activity within specific brain regions, functional MRI can also measure correlated activity patterns between brain regions, known as functional connectivity, even in regions that are not directly anatomically connected. Multiple "functionally connected" human brain networks play important roles in specific cognitive processes (fig. 3).²⁸⁷ Recent studies have begun

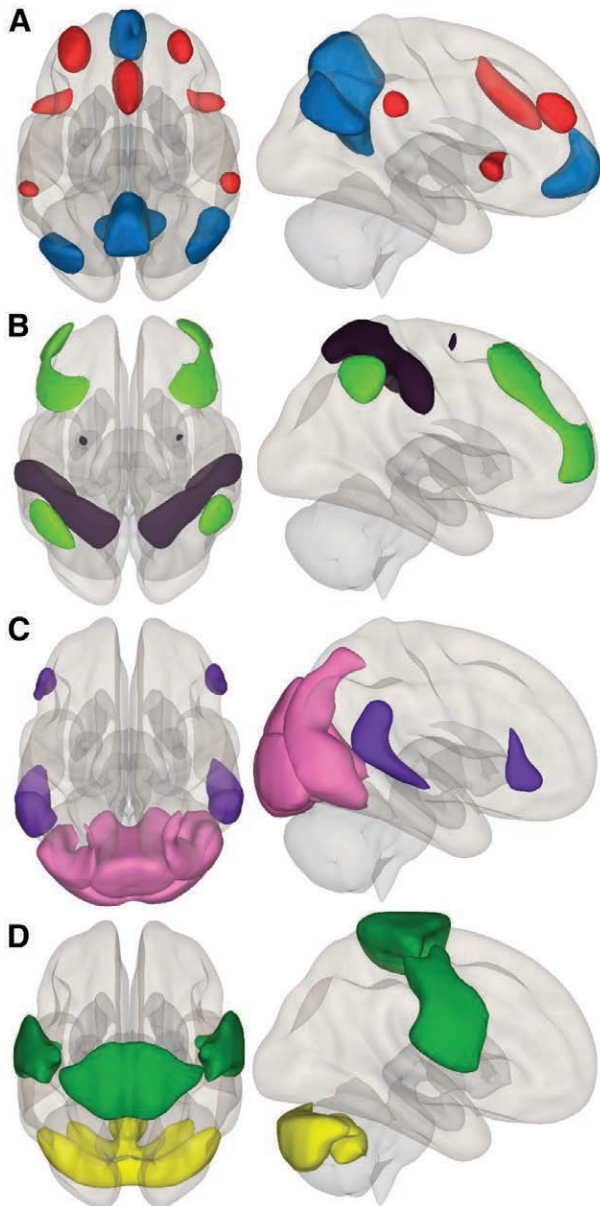


Fig. 3. Functionally connected networks in the human brain. These functional brain network region of interest maps were derived from independent components analysis of low-frequency blood oxygen dependent signal functional magnetic resonance imaging data from the Human Connectome Project dataset (N = 497).²⁸⁷ (A) default mode network regions of interest (blue), salience network regions of interest (red); (B) dorsal attention network regions of interest (black), frontoparietal network regions of interest (light green); (C) language network regions of interest (purple), visual network regions of interest (pink); and (D) cerebellar network regions of interest (yellow), sensorimotor network regions of interest (green).

to examine the function of these networks in patients before and after cardiac surgery. For example, Brown-dyke *et al.* recently examined cognitive and functional connectivity changes in 12 patients before and 6 weeks after cardiac surgery, and over the same time interval, in

12 nonsurgical “controls” with cardiac disease.⁶³ There was a larger drop in cognition after cardiac surgery than over the same interval in nonsurgical controls. Further, in cardiac surgery patients, the degree of postoperative global cognitive dysfunction correlated with the magnitude of decreased functional connectivity in the posterior cingulate cortex and the right superior frontal gyrus,⁶³ two key regions of the brain’s default mode network.^{288,289} Similarly, Huang *et al.* also recently observed decreased default mode network functional connectivity in older adults after orthopedic surgery.²⁹⁰ The default mode network is a set of brain regions that show temporally correlated blood oxygen level dependent signal activation patterns while subjects are at rest and not performing cognitive tasks^{288,289} and thus, could be viewed as an “idling state network” that is not important for cognition. Yet, these findings support the emerging view that default mode network functional connectivity is important for cognition,²⁹¹ and suggest that resting-state default mode network dysfunction may be a correlate of post–cardiac surgery cognitive dysfunction. Similar altered connectivity between the posterior cingulate (a default mode network hub region) and the prefrontal cortex has been observed in patients with delirium,²⁹² which raises the possibility that default mode network functional connectivity disruptions may underlie both postoperative delirium and postoperative cognitive dysfunction.

Studies have also used EEG recordings to identify changes in underlying brain connectivity patterns that may be associated with postoperative delirium and/or postoperative cognitive dysfunction. For example, post-cardiac surgery patients with delirium, as compared to those without delirium, had decreased postoperative EEG alpha band (8 to 13 Hz) power and connectivity.²⁹³ These findings are interesting because alpha band power under general anesthesia significantly decreases in patients older than age 65,²⁸⁰ who are at increased risk for postoperative delirium and cognitive dysfunction. Low intraoperative alpha band power has also been correlated with lower preoperative baseline cognitive function,²⁹⁴ which is a risk factor for postoperative delirium and postoperative cognitive dysfunction. Together, these findings suggest that low intra- and postoperative alpha band power and connectivity may be EEG correlates of delirium, and raise the possibility that deficits in the thalamocortical circuitry thought to produce alpha band power²⁹⁵ may play a role in postoperative delirium. These findings also support Sanders’ hypothesis that delirium represents an acute breakdown in brain network connectivity.²⁹⁶ Future studies combining multi-electrode EEG recordings with resting-state and task-based functional MRI and other modern cognitive neuroscience techniques²⁹⁷ should help clarify functional connectivity and activity changes that may underlie delirium and postoperative cognitive dysfunction after cardiac surgery.

Future Interventions to Prevent or Treat Postoperative Cognitive Dysfunction and/or Delirium

A number of novel approaches have been developed or proposed to improve neurocognitive function in older adults, ranging from video game-based brain training²⁹⁸ to vagal nerve stimulation²⁹⁹ to noninvasive transcranial magnetic^{300,301} and electrical³⁰² brain stimulation to diet interventions,³⁰³ physical exercise,^{304,305} and early postoperative ambulation.^{306–308} Many of these approaches share the common theme that they target entire brain regions and/or networks (or multiorgan systems, as in the case of vagal nerve stimulation), rather than single neurotransmitters or neuronal subtypes. Further, many of these approaches can be targeted and/or titrated in response to specific pathophysiologic brain activity patterns and/or cognitive deficits present in individual patients. Similarly, many of the best established nonpharmacologic delirium prevention interventions (such as the Hospital Elder Life Program) involve interdisciplinary, multicomponent approaches that likely target multiple underlying brain mechanisms involved in delirium.³⁰⁹ To the best of our knowledge, though, none of the novel approaches discussed above have been used to prevent or treat postoperative cognitive dysfunction or delirium in cardiac surgical patients; thus, such studies will be important to conduct in the future.

Conclusions

The brain is widely viewed as the most complex organ in the human body, and there are significant anatomical and functional differences between the brains of individual cardiac surgery patients.^{9,63} Thus, optimizing post-cardiac surgery neurocognitive function will likely require an individualized, patient-centered approach to managing multiple determinants of brain function ranging from oxygen and glucose delivery, to cerebral perfusion pressure management, to the careful pharmacologic modulation of neural network activity, the surgical stress response, and the ensuing inflammatory response (fig. 2). This suggests that improving cognitive function after cardiac surgery will be complex and challenging. An additional challenge for future interventional studies will be to track each of the variables discussed above that may influence postoperative cognitive function and/or delirium (table 1), because interventions designed to reduce postoperative cognitive dysfunction or delirium by targeting a single risk factor may have counterbalancing effects if they distract from other intraoperative tasks (*i.e.*, a fixation error³¹⁰). Thus, an important goal will be to develop “bundle” protocols designed to simultaneously and practically optimize multiple intra- and postoperative variables to promote postoperative cognitive function for older patients. The significant ongoing progress in these areas and the potential of modern cognitive neuroscience approaches to study⁶³ and to treat^{298,300,301} these problems provides optimism that we will succeed in improving neurocognitive outcomes for future older cardiac surgery patients, an important American Society of Anesthesiologists Brain Health Initiative goal.³¹¹

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Competing Interests

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