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Neurocognitive Function after Cardiac Surgery: From Phenotypes to Mechanisms

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Abstract

For half a century, we have known that some patients experience neurocognitive dysfunction after cardiac surgery, yet 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-V). Postoperative cognitive dysfunction is not included in the DSM-V and has been heterogeneously defined, though a recent international nomenclature effort has proposed standardized definitions for it. Here, we 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.

We have known for over 50 years 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]

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to post-cardiotomy/post-operative delirium,[1,9] and postoperative cognitive dysfunction/decline (POCD).[10] Although these disorders also occur after non-cardiac surgery,[11-20] 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 POCD, similarities between them (including in their causes), interventions to prevent them, and novel approaches to study, prevent and treat these important complications after cardiac surgery.

Delirium after cardiac surgery

The 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 pre-existing 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 ≥ 50%,[36] perhaps reflecting differing levels of delirium risk factors (e.g. older vs younger patients, etc.) in these study populations and the varied assessment tools utilized.[37,38] Many administrative databases significantly underreport delirium rates, likely due to under-diagnosis 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 studied (reviewed in[40]), and some are more appropriate for detecting delirium in intubated patients (such as the CAM-ICU[41]) while some are more appropriate (i.e. sensitive and specific) for detecting delirium in non-intubated patients (such as the 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 non-intubated patients.

POCD after cardiac surgery

Many studies have used pre- and postoperative neuropsychological testing to assess neurocognitive dysfunction after cardiac surgery, with varying testing deficit thresholds used to define POCD. POCD incidence at 1–3 months after cardiac surgery ranged from ~10-16% (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 POCD rates decrease over time from 3 months to 1 year after surgery.[13,47] Five issues are important for interpreting these studies. First, for most individuals, scores improve with repeat testing over 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 do 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 Examination[50] 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 pre-existing neurodegenerative pathology. Since Alzheimer's Disease (AD)-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 AD-associated neuropathology; these patients are at increased risk for postoperative delirium[57] and POCD.[58,59] Thus, it is important to compare postoperative cognitive changes to those seen over the cognate time interval in non-surgical controls matched on cognitive decline risk factors (such as preclinical AD-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 one[61] or two[62] tests; others rely on changes in larger cognitive domains, such as attention and verbal memory[47]; and others measure global change across an entire cognitive test battery.[63] Depending on the statistical thresholds and rules used to define it, POCD may represent either a single or multi-domain 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 post-operative 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 POCD assessments to be free from these confounds starting 30 days after surgery.[64]

For clinical practice, the international POCD nomenclature recommendations defines mild POCD (i.e. neurocognitive disorder, or mild NCD-postoperative) as a 1-SD drop in test performance and major POCD (i.e. major NCD-postoperative) as a 2-SD drop in test performance, occurring between 30 days to 1 year after surgery.[64] These recommendations help provide clarity on when POCD occurs, and what magnitude of deficits should be considered mild vs major POCD. 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 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 over 5 years after cardiac surgery, with a similar association between both measures and self-

reported depressive symptoms.[66] This correlation between POCD severity and quality of life impairments was present across the full range of cognitive dysfunction severity at 1 and 5 years 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 POCD should be conceptualized as a syndrome with a continuous severity distribution rather than as a simple dichotomous trait, and considered in terms of how much 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 disorders[64] that neurocognitive disorders should be evaluated in terms of both objective signs and subjective symptoms. Further, the idea that "sub-threshold" 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 LDL or blood pressure thresholds below which these processes do not contribute to stroke or MI risk.

Similarities in risks for and mechanisms of postoperative delirium and POCD

Although postoperative delirium and POCD 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 neurobiological continuum. We refer to both delirium and POCD as types of "neurocognitive dysfunction" because the recent International Nomenclature Recommendations[64] refers to both delirium and POCD 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 above) than procedural factors,[78,79] though intraoperative management can lower the risks of both POCD and delirium.[80] Both disorders are also thought to be caused by similar mechanisms such as neuroinflammation,[48,79,81] and both delirium and POCD are associated with decreased quality of life,[65,66,82,83] increased mortality,[12,84] increased economic costs,[85,86] long-term cognitive decline,[87-90] and a possible increased risk for developing dementia such as Alzheimer's disease (AD, discussed at length in subsequent sections).[91-94] Many patients with postoperative delirium also develop POCD,[95-100] although the magnitude of this overlap varies between studies. Indeed, several investigators have proposed that delirium and POCD primarily differ in when they occur, and that both are part of the same spectrum of postoperative central nervous system dysfunction (Figure 1).[101] 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 POCD 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 POCD can be categorized in two ways. First, they can be defined by processes present before or after surgery (such as patient factors), vs 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 chronological 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 delirium[79] and POCD.[48]

A second way to categorize etiology is by potential pathophysiological 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 POCD.

Inflammation

Systemic inflammation and the ensuing neuroinflammatory response following peripheral surgical trauma are thought to play a causal role in delirium[102,103] and POCD[104-109] (reviewed in[48,110]). Sterile tissue injury and trauma during cardiac surgery lead to the release of damage-associated molecular patterns (DAMPs), chemokines and cytokines.[111,112] 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 DAMP molecules such as high mobility group box-1 (HMGB1), and S100 calcium binding proteins (Figure 2).[113] Systemic inflammatory mediators may then be able to enter the brain due to post-surgical breakdown of the blood-brain barrier.[105,108,114-117] Blood brain barrier dysfunction is frequently seen in older adults (even in the absence of surgery),[118] and has been seen in ~50% of patients after cardiac surgery.[119] Further, the magnitude of postoperative blood-brain barrier breakdown correlates with the degree of cognitive dysfunction after cardiac surgery.[120] Inflammatory cytokines may also be produced within the brain itself after surgery, due to peripheral-to-central signaling via both humoral and neural pathways.[121] In either case, neuroinflammation has detrimental effects on the brain, is sufficient to cause deficits in cognition, memory, and behavior and overall “sickness behavior,”[122] and has been implicated in conditions ranging from mood disorders to neurodegenerative disease and POCD.[48,123,124] 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.[125]

Further support for the role of neuroinflammation in POCD comes from studies that have demonstrated that genetic polymorphisms that modulate inflammation (i.e. in the genes *CRP*, *SELP*, *GPIIIA*, and *iNOS*) are associated with POCD risk.[126-128] Additionally, inflammatory processes during cardiac surgery may be augmented by 4 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 pro-inflammatory cytokines interleukins 6 and 8 (IL-6, IL-8).[129] 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 pro-inflammatory cytokine production (reviewed in[130]). The classical complement cascade can also be activated by heparin-protamine complexes after CPB.[131] Second, median sternotomy (as opposed to smaller lateral thoracotomy approaches) increases pro-inflammatory cytokine levels in rats,[132] and possibly in humans,[133,134] although some studies have not replicated these findings.[135,136] 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.[137] Fourth, anesthetic drugs themselves can modulate inflammation. Inhaled anesthetics have pro-inflammatory effects on microglia *in vitro*,[138] and on the mouse brain *in vivo*,[139] and opioids and heparin can also modulate inflammation and monocyte function *in vitro*.[140] The drugs given during cardiac surgery may thus have significant effects on the overall balance of pro- and anti-inflammatory cytokine levels, and on patient outcomes (reviewed in[141]). 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 re-perfusion injury, may contribute to neuroinflammation and ensuing postoperative delirium and POCD. As a whole these factors may also explain why serum IL-6 and other pro-inflammatory cytokine levels are higher after cardiac vs peripheral surgery,[135,142] 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, though both surgery types reduced hippocampal neurogenesis rates and neurotrophic factor levels (such as brain derived neurotrophic factor).[143] Terrando et al. have also found similar behavioral impairments and neuroinflammation after orthopedic surgery in mice,[144] 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 (MCP-1) levels recruit peripheral monocyte-derived macrophages into the CNS, which play a role in postoperative explicit memory deficits.[105,107,145] Blocking neuroinflammation[106] and microglial activation[146] reduced postoperative memory deficits in mouse models, though these interventions have yet to be tested in humans. Human studies have found postoperative CSF increases in MCP-1[147] and other inflammatory cytokines[148,149] after orthopedic surgery and CSF IL-6 and IL-8

increases have been observed after cardiac surgery,[117] though it is unclear whether CSF MCP-1 levels increase after cardiac surgery.[116] 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 anti-inflammatory drug trials have failed to prevent delirium or cognitive dysfunction after cardiac surgery, including lidocaine,[10] magnesium,[46] complement cascade inhibitors,[150] and postoperative acetylcholinesterase treatment[151,152] (which may increase vagal anti-inflammatory 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.[151] Intraoperative high dose steroids were also ineffective,[35,45,153,154] perhaps because steroids can also cause delirium and hallucinations[155] that may counter-balance their theorized cognitive-improving anti-neuroinflammatory effects. Intraoperative ketamine treatment reduced delirium[156] and cognitive dysfunction[157] after cardiac surgery in small pilot studies, but did not reduce delirium in a large multi-center randomized trial (which included ~1/3 cardiac surgery patients).[158] Dexmedetomidine also had no effect on delirium incidence after cardiac[159] surgery in a recent multicenter randomized trial, though it had mixed effects on delirium after non-cardiac surgery;[160,161] these divergent results may be due to differing dexmedetomidine infusion rates and durations between these studies.[159-161]

These generally negative study findings may reflect the pathophysiologic complexity of delirium and POCD, which may also underlie the relatively greater success of multi-modal interventions.[162] Alternative strategies to more specifically modulate postoperative inflammation may better help prevent postoperative delirium and POCD. For example, resolution of inflammation is an active process orchestrated by specialized pro-resolving mediators,[163] including omega-3 fatty acid-derived lipid mediators (i.e. resolvins) that have potent postoperative anti-inflammatory and pro-resolving effects.[164-166] Administration of the omega-3 derived resolvin D1 reduced memory impairments after orthopedic surgery in mice.[166] 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.[167] Pro-resolving mediators can also reduce inflammatory pain,[168] lower antibiotic requirements,[169] and reduce mortality from microbial sepsis.[170] Thus, understanding the role of resolvins and other anti-inflammatory lipids in cognitive function after cardiac surgery, and whether manipulating them can improve it, are important future research goals.

Embolic load and clinically covert stroke

Embolic 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 POCD (vs those without POCD) 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.[171]

Aortic plaque disruption can liberate micro-emboli that can travel to the brain. These micro-emboli can be detected by transcranial Doppler (TCD) ultrasound,[172] although the majority of TCD signals actually represent small gas emboli.[173] Gaseous micro-emboli occur frequently in open chamber cardiac valve cases, which has led many centers to flood the open cardiac chamber with CO_2, since CO_2 is more soluble than air and thus promotes the resorption of gas emboli (potentially before they enter the cerebral vasculature).[174] However, a randomized trial found that field flooding with CO_2 versus medical air had no effect on cognitive function six weeks after surgery.[175] Rather than intracardiac gas volume, the main predictor of cognitive decline in this study was atheromatous vascular disease.[175]

Micro-emboli can also be detected by postoperative diffusion-weighted MRI[176] though preoperative MRI scans are needed to differentiate new micro-emboli from prior lesions. The percentage of cardiac surgery patients with detectable micro-emboli 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 hyper-intensities would have detrimental neurocognitive effects, correlations between embolic load and postoperative cognitive changes have been inconsistent (particularly after open chamber valve cases).[176-179] This is a paradox, because large observational studies have found these “clinically covert strokes” are associated with future risk of stroke, cognitive decline and AD.[180-183] One explanation may be that the location at which micro-embolic “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,[184] and small lesions at critical node locations can thus cause wider brain network dysfunction and impair neurocognitive processing.[184] Future studies should examine this idea, and evaluate interactions between embolic load, central neuroinflammation, pre-existing 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 60–160 mHg). Thus, the actual autoregulation range for any given patient is unknown, and the lower limit of autoregulation during CPB may vary from 45–80 mm Hg.[185] Newman et al. found significant cerebral autoregulation impairments in 215 patients during cardiac surgery, but no correlation with POCD.[74,186] Similarly, Ono et al. found that up to 20% of cardiac surgery patients have impaired autoregulation, and these patients with “pressure passive” cerebral blood flow[187] had increased perioperative stroke rates.[188] Further, intraoperative cerebral autoregulation can dynamically change in response to intraoperative physiologic changes,[189,190] 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.[191] Thus, an ongoing study is investigating whether cerebral oximetry-guided blood pressure management can decrease postoperative delirium after cardiac surgery.[192]

These findings then led to studies examining the relationship between MAP management and postoperative cognitive changes. For example, maintaining intraoperative MAP within 80–90 mm Hg, rather than 60–70 mm Hg, was associated with less postoperative delirium and a smaller postoperative decrease in mini mental status exam scores.[193] Gold *et al* found that higher MAP targets (i.e., 80–100 mm Hg vs 50–60 mm Hg) were associated with lower cardiac and neurologic complication rates (i.e. stroke),[194] 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 (GFAP), emphasizing the importance of maintaining MAP within the autoregulatory range after as well as during cardiac surgery.[195] However, observational studies have found that maintaining blood pressure above the upper limit of cerebral autoregulation is associated with increased postoperative delirium rates,[191,196] 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[193,194] did not measure cerebral autoregulation limits in individual patients. The cerebral autoregulation range varies substantially among patients,[197] especially during cardiopulmonary bypass.[198] Thus, it is possible that the higher MAP targets in these studies[119,120] may have been outside the cerebral autoregulation limits in some patients, particularly in patients with hypertension.[197] 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 POCD.[199] In other words, inadequate mean arterial pressure management during cardiac surgery may cause POCD by impairing cerebral oxygen delivery, which can be detected as a cerebral venous oxygen desaturation.[199] 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 delirium[200] and POCD (measured one week[201,202] and one month[202] after surgery). This is consistent with the finding that cerebral venous oxygen desaturations are associated with POCD at hospital discharge.[199] However, at least 2 other studies did not find a correlation between intraoperative cerebral oxygen desaturations and POCD.[203,204] These divergent findings could reflect differences in postoperative cognitive assessment methods and/or different patient characteristics.[201-204] Indeed, the de Tournay-Jette[202] study patients were ~10-20 years older and had more co-morbid disease processes than patients in the Reents[203] and Hong[204] studies, suggesting cerebral oximetry may be better able to identify POCD and delirium risk in older/sicker patients. Additionally,

hyperoxia has been associated with postoperative delirium,[205] although we found no association between hyperoxia during CPB and POCD.[206] A multi-modal perioperative management intervention including cerebral oximetry reduced delirium after cardiac surgery[162] and POCD after non-cardiac surgery,[207] 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 15-18) versus moderate (hematocrit of 27), there was a statistically significant interaction between age and extreme hemodilution: older patients who underwent extreme hemodilution had higher POCD rates.[73] Taken together, these data suggest that ensuring adequate cerebral oxygen delivery may help reduce POCD.

Temperature Management During Cardiac Surgery

The cerebral metabolic rate of oxygen utilization ($CMRO_2$) is closely regulated by temperature, which led the idea that lowering $CMRO_2$ by inducing hypothermia could reduce brain oxygen deprivation and neurocognitive injury during reduced oxygen delivery periods (i.e. such as during CPB). Indeed, hypothermia reduces neurologic injury in animal models of focal cerebral ischemia and cardiopulmonary resuscitation.[208,209] Conversely, hyperthermia increases $CMRO_2$ and is associated with worse neurocognitive outcomes and increased mortality risk in numerous clinical situations.[210-212] Thus, studies have examined whether lowering $CMRO_2$ by inducing hypothermia during CPB would improve postoperative neurocognitive function. Early work showed that patients who underwent normothermic (i.e. “warm” or >35 deg C) CPB had a three-fold higher stroke incidence than those who underwent hypothermic (i.e. cold or <28 deg C) CPB.[213] Yet, one randomized trial found no benefit of hypothermia (i.e. 28–30 deg C) vs normothermia (35.5-36.5 deg C) during CPB on cognitive change from before to 6 weeks after cardiac surgery.[214] Nonetheless, the maximum postoperative temperature after cardiac surgery was associated with cognitive dysfunction severity six weeks after surgery,[215] emphasizing the importance of avoiding postoperative hyperthermia. This concept may help explain data showing that rewarming to a lower temperature (34 vs 37 deg 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,[216] although there was no overall cognitive benefit at 3 months after surgery.[217] In essence, the early cognitive benefits of rewarming to a slightly lower target in this trial[216] 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 deg C) CPB or hypothermic (34 deg C) CPB without OR rewarming in either group; thus, avoiding central hyperthermia during rewarming may help optimize postoperative cognitive function.[217] 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.[218] Nonetheless, despite numerous studies (reviewed in[219,220]), there is still debate about temperature management during cardiac surgery.[221,222] Current clinical recommendations simply call for avoiding hyperthermia (arterial outlet blood temperature ≥37 deg C) during cardiac surgery, and for a rewarming

rate ≤0.5 deg C/min once temperature exceeds 30 deg C.[223] Slow rewarming may help avoid cerebral ischemia, since rapid rewarming has been shown to cause CMRO2 increases prior to corresponding increases in CBF.[224]

Glucose Homeostasis During Cardiac Surgery

Aside from oxygen delivery and perfusion pressure, neurocognitive function is also influenced by serum glucose levels (discussed in[37]). Similar to cerebral blood flow autoregulation, neurocognitive function is typically unaltered by glucose changes within normal physiologic limits.[225-227] 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 >200 mg/dL) was associated with worsened postoperative cognitive function in non-diabetic patients, but not in diabetic patients.[228] 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.[229] This adaptation helps explain why intraoperative hyperglycemia may be more detrimental to the brains of non-diabetic patients. However, this interpretation is challenged by the results of Butterworth *et al*,[230] who found in a large randomized trial (N=381) that intraoperative insulin infusion (up to 4 U/hour) in non-diabetic 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 resistance[231]) in the insulin treatment arm, though, as the authors discussed.[230]

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 80–110 mg/dL) vs standard therapy (glucose target <150 mg/dL) during cardiac surgery was associated with increased delirium rates,[232] 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,[232] so it is unclear how many of these cases of postoperative delirium might have reflected pre-existing 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 ~64-110 mg/dL preserved auditory learning and executive function after cardiac surgery,[233] suggesting that avoiding hyperglycemia may result in improved postoperative cognitive function. Thus, as with oxygen delivery and cerebral perfusion management (discussed above), these data suggest that it may be equally important to avoid hypoglycemia and hyperglycemia in order to avoid postoperative delirium and POCD. Further, the physiologic adaptions 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 vs off-pump cardiac surgery, and medical vs surgical management for CAD, on delirium and POCD rates

Given the concern that cardiopulmonary bypass alone may contribute to postoperative delirium and POCD, several studies have examined delirium and cognitive dysfunction rates after on-pump vs 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 towards less cognitive dysfunction 3 months after surgery, but this small difference disappeared by 1 year after surgery.[234] The ROOBY trial found no difference in overall cognitive outcomes between on- vs 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 vs on-pump cardiac surgery.[235] 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 vs a false positive due to performance of multiple tests. Similarly, Kok and colleagues 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.[236] Finally, Selnes and colleagues found no difference in 6-year 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 vs medical management, and between those who underwent on- vs off-pump CABG. [237] Further, the Selnes study used group averaged data, which may have obscured more severe long term cognitive decline in individual cardiac surgery patients.[220]

These findings are compatible with 2 different interpretations. The first, and perhaps simplest, interpretation is that cardiopulmonary bypass does not contribute to postoperative delirium or cognitive dysfunction.[238] The second interpretation is that other aspects of off-pump cardiac surgery, such as steep Trendelenberg positioning,[239] which results in cerebral venous engorgement and possible cerebral oxygen desaturation,[240] 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 year composite outcomes (including mortality),[235] so there is currently little enthusiasm for performing off-pump cardiac surgery.

Studies have also examined the relative cognitive effects of cardiac surgery vs medical or percutaneous therapy for patients with cardiac disease. As discussed above, Selnes *et al* found no difference in long-term cognitive outcomes between medical and surgical management for coronary artery disease.[237] 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, etc), 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 above), 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 POCD is associated with increased postoperative mortality, a long-term comparison of cognitive outcomes after surgical vs 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.[237]

Cardiac Surgery, Neurotoxicity and Alzheimer's disease (AD) pathology

Up to 30% of patients may develop dementia within 7.5 years after cardiac surgery,[88] 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,[241] cognitive dysfunction[242] and dementia[243] outside perioperative care. Mechanism(s) that could underlie a detrimental effect of anesthetic drugs on postoperative cognition could include *a*) GABA-ergic anesthetic-induced acceleration of AD processes such as amyloid beta and tau pathology,[91,244,245] *b*) anesthetic-induced disruption of gamma oscillation patterns involved in amyloid beta clearance,[246-249] *c*) direct neuronal or glial cell damage (reviewed in[250,251]), or *d*) anesthetic-induced increases in neuroinflammation,[138,139,252,253] Further, neuroinflammation can increase neuronal sensitivity to anesthetic drugs;[254] thus, anesthetic-induced neuroinflammation could potentially promote a positive feedback loop that further amplifies initial neuroinflammatory responses to anesthesia and surgery.

The notion that POCD and delirium may involve mechanisms similar to those involved in AD (reviewed in[255,256]) has led to studies of whether AD-associated genetic polymorphisms, such as *ApoE4*, also increase risk for postoperative delirium or POCD. However, the interpretation of these studies is complex, because aside from its association

with AD risk, ApoE4 has pleiotropic neurologic effects (including cerebrovascular dysfunction and decreased cerebral blood flow).[257] These studies have found conflicting results; overall it appears that *ApoE4* carriers are not more likely to develop early postoperative delirium or POCD, but do have worse long-term cognitive trajectories after cardiac surgery.[258-263] This finding could be related to the known long term detrimental effects of the *ApoE4* allele on cognition,[259] and/or to the increased aortic arch atheroma burden seen in *ApoE4* carriers[264] and thus a possible increase in cerebral microemboli during cardiac surgery. Several other genetic polymorphisms have recently been found that are associated with AD risk,[265-269] and it will be important to examine whether these AD risk polymorphisms are also associated with POCD or delirium risk after cardiac surgery.

Changes in AD biomarkers (such as changes in CSF amyloid beta and tau levels) occur after cardiac surgery in humans,[117,245] and both mouse model and *in vitro* data suggest that isoflurane may accelerate AD pathology to a greater extent than propofol.[270,271] However, there is no human data demonstrating that any particular anesthetic agent is associated with greater (or smaller) CSF AD 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 beta or phospho-tau.[272] Thus, there is currently no human evidence to favor one anesthetic type versus another for avoiding changes in CSF AD biomarkers or AD pathogenesis.

Further, it is unclear whether postoperative CSF AD biomarker changes are associated with or play a cause role in delirium or POCD 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 non-surgical controls with similar comorbidities that predispose to neurocognitive dysfunction (i.e. neurovascular and AD risk factors, etc), and *3)* determine whether blocking postoperative changes in these pathways abrogates delirium or POCD 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[91,251]). General anesthesia is a drug-induced coma[273]; and observational studies have found both direct[274-276] and inverse[277] associations between the duration of electroencephalogram (EEG) burst suppression, and postoperative delirium and/or POCD. Further, several interventional studies in non-cardiac surgery have shown that BIS-titrated anesthetic administration results in lower levels of postoperative delirium.[80,278,279] In the 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 POCD 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.[278] Similarly, a secondary analysis of cardiac surgery patients in the BAG-RECALL study showed that BIS-titrated anesthetic administration was associated with a trend (which narrowly missed statistical significance) toward lower postoperative delirium rates.[280] This lack of significance may also partly be due to the use of the CAM-ICU instrument for all delirium assessments in this study,[280] an instrument with limited sensitivity in non-intubated 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.[280,281] 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 POCD rates. Although a simple anesthetic depth index is easy to use, the BIS index has a non-linear relationship with inhaled anesthetic dose.[282] Both theoretical work[283] and retrospective analyses[284] 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.[283] Nonetheless, the findings described above suggest that processed EEG-guided anesthetic titration can lower POCD rates if it results in reduced anesthetic dosage. Similar to pulmonary artery (PA) catheter use in cardiac surgery (in which outcomes likely depend not on whether a PA catheter was placed, but rather on how the information from it was used to manage patients[285]), 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.[80,278] Ongoing observational[286] and interventional[244,287] 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 POCD and even reduce postoperative mortality.[288]

Systems/cognitive neuroscience-level mechanisms of post-cardiac surgery cognitive dysfunction

Significant neuroimaging advances have been made over the past 20 years, 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 (fMRI) can also measure activity within specific brain regions via the blood oxygen level dependent (BOLD) signal, a hemodynamic correlate of neuronal activity, and can be used to measure postoperative brain activity changes. For example, Abu Omar *et al*[289] performed BOLD fMRI 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 beforehand[48]). 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.[289] 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 vs off-pump groups, or before vs after surgery.[289] 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 (Figure 3).[290] Recent studies have begun to examine the function of these networks in patients before and after cardiac surgery. For example, Browndyke *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 non-surgical "controls" with cardiac disease.[63] There was a larger drop in cognition after cardiac surgery than over the same interval in non-surgical 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] 2 key regions of the brain's default mode network (DMN).[291,292] Similarly, Huang et al also recently observed decreased DMN functional connectivity in older adults after orthopedic surgery.[293] The DMN is a set of brain regions that show temporally correlated BOLD signal activation patterns while subjects are at rest and not performing cognitive tasks[291,292] and thus, could be viewed as an "idling state network" that is not important for cognition. Yet, these findings support the emerging view that DMN functional connectivity is important for cognition,[294] and suggest that resting-state DMN dysfunction may be a correlate of post-cardiac surgery cognitive dysfunction. Similar altered connectivity between the posterior cingulate (a DMN hub region) and the prefrontal cortex has been observed in patients with delirium,[295] which raises the possibility that DMN functional connectivity disruptions may underlie both postoperative delirium and POCD.

Studies have also used EEG recordings to identify changes in underlying brain connectivity patterns that may be associated with postoperative delirium and/or POCD. For example, post-cardiac surgery patients with delirium, as compared to those without delirium, had decreased postoperative EEG alpha band (8-13 Hz) power and connectivity.[296] These findings are interesting because alpha band power under general anesthesia significantly decreases in patients over age 65,[283] 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,[297] which is a risk factor for postoperative delirium and POCD. Together, these findings suggest that low intra- and post-operative alpha band power and connectivity may be EEG correlates of delirium, and raise the

possibility that deficits in the thalamo-cortical circuitry thought to produce alpha band power[298] may play a role in postoperative delirium. These findings also support Sanders' hypothesis that delirium represents an acute breakdown in brain network connectivity.[299] Future studies combining multi-electrode EEG recordings with resting-state and task-based functional MRI and other modern cognitive neuroscience techniques[300] should help clarify functional connectivity and activity changes that may underlie delirium and POCD after cardiac surgery.

Future Interventions to Prevent or Treat POCD 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 training[301] to vagal nerve stimulation[302] to non-invasive transcranial magnetic[303,304] and electrical[305] brain stimulation to diet interventions,[306] physical exercise,[307,308] and early postoperative ambulation.[309-311] Many of these approaches share the common theme that they target entire brain regions and/or networks (or multi-organ 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 pathophysiological brain activity patterns and/or cognitive deficits present in individual patients. Similarly, many of the best-established non-pharmacological delirium prevention interventions (such as the HELP program) involve interdisciplinary, multi-component approaches that likely target multiple underlying brain mechanisms involved in delirium.[312] To the best of our knowledge, though, none of the novel approaches discussed above have been used to prevent or treat POCD 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 (Figure 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 POCD or delirium by targeting a single risk factor may have counterbalancing effects if they distract from other intraoperative tasks (i.e. a fixation error[313]). Thus, an important goal will be to develop "bundle" protocols designed to simultaneously and practically optimize multiple intra- and post-operative 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 study[63] and to treat[301,303,304] these problems provides optimism

that we will succeed in improving neurocognitive outcomes for future older cardiac surgery patients, an important ASA Brain Health Initiative goal.[314]

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References

1. Blachy PH, Starr A. Post-Cardiotomy Delirum. Am J Psychiatry. 1964; 121:371–5. [PubMed: 14211412]
2. Blachly PH, Kloster FE. Relation of cardiac output to post-cardiotomy delirium. J Thorac Cardiovasc Surg. 1966; 52:422–7. [PubMed: 5919394]
3. Sachdev NS, Carter CC, Swank RL, Blachly PH. Relationship between post-cardiotomy delirium, clinical neurological changes, and EEG abnormalities. J Thorac Cardiovasc Surg. 1967; 54:557–63. [PubMed: 6051444]
4. Egerton N, Kay JH. Psychological Disturbances Associated with Open Heart Surgery. Br J Psychiatry. 1964; 110:433–9. [PubMed: 14142537]
5. Silverstein A, Krieger HP. Neurologic complications of cardiac surgery. Trans Am Neurol Assoc. 1960; 85:151–4. [PubMed: 13912948]
6. McKhann GM, Grega MA, Borowicz LM Jr, Bechamps M, Selnes OA, Baumgartner WA, Royall RM. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. Arch Neurol. 2002; 59:1422–8. [PubMed: 12223028]
7. Mullges W, Berg D, Schmidtke A, Weinacker B, Toyka KV. Early natural course of transient encephalopathy after coronary artery bypass grafting. Crit Care Med. 2000; 28:1808–11. [PubMed: 10890624]
8. Stutz B. Pumphead. Sci Am. 2003; 289:76–81.
9. Brown CHtFaigle R, Klinker L, Bahouth M, Max L, LaFlam A, Neufeld KJ, Mandal K, Gottesman RF, Hogue CW, Jr. The Association of Brain MRI Characteristics and Postoperative Delirium in Cardiac Surgery Patients. Clin Ther. 2015
10. Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, Blumenthal JA, Newman MF. Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke. 2009; 40:880–7. [PubMed: 19164788]
11. McDonagh DL, Mathew JP, White WD, Phillips-Bute B, Laskowitz DT, Podgoreanu MV, Newman MF, Neurologic Outcome Research G. Cognitive function after major noncardiac surgery, apolipoprotein E4 genotype, and biomarkers of brain injury. Anesthesiology. 2010; 112:852–9. [PubMed: 20216394]
12. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008; 108:18–30. [PubMed: 18156878]

13. Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg. 2011; 112:1179–85. [PubMed: 21474666]
14. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998; 351:857–61. [PubMed: 9525362]
15. Jurga J, Tornvall P, Dey L, van der Linden J, Sarkar N, von Euler M. Does Coronary Angiography and Percutaneous Coronary Intervention Affect Cognitive Function? Am J Cardiol. 2016; 118:1437–1441. [PubMed: 27634030]
16. Auffret V, Campelo-Parada F, Regueiro A, Del Trigo M, Chiche O, Chamandi C, Allende R, Cordoba-Soriano JG, Paradis JM, De Larochelliere R, Doyle D, Dumont E, Mohammadi S, Cote M, Marrero A, Puri R, Rodes-Cabau J. Serial Changes in Cognitive Function Following Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016; 68:2129–2141. [PubMed: 27692728]
17. Mokin M, Zivadinov R, Dwyer MG, Lazar RM, Hopkins LN, Siddiqui AH. Transcatheter aortic valve replacement: perioperative stroke and beyond. Expert Rev Neurother. 2016:1–8.
18. Schoenenberger AW, Zuber C, Moser A, Zwahlen M, Wenaweser P, Windecker S, Carrel T, Stuck AE, Stortecky S. Evolution of Cognitive Function After Transcatheter Aortic Valve Implantation. Circ Cardiovasc Interv. 2016; 9
19. Haussig S, Mangner N, Dwyer MG, Lehmkuhl L, Lucke C, Woitek F, Holzhey DM, Mohr FW, Gutberlet M, Zivadinov R, Schuler G, Linke A. Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial. JAMA. 2016; 316:592–601. [PubMed: 27532914]
20. Paredes S, Cortinez L, Contreras V, Silbert B. Post-operative cognitive dysfunction at 3 months in adults after non-cardiac surgery: a qualitative systematic review. Acta Anaesthesiol Scand. 2016; 60:1043–58. [PubMed: 27027720]
21. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Hyde TF, Reddy DM, Hudetz AG, Warltier DC. Postoperative cognitive dysfunction in older patients with a history of alcohol abuse. Anesthesiology. 2007; 106:423–30. [PubMed: 17325499]
22. Hudetz JA, Patterson KM, Byrne AJ, Iqbal Z, Gandhi SD, Warltier DC, Pagel PS. A history of alcohol dependence increases the incidence and severity of postoperative cognitive dysfunction in cardiac surgical patients. Int J Environ Res Public Health. 2009; 6:2725–39. [PubMed: 20049218]
23. Krzych LJ, Wybraniec MT, Krupka-Matuszczyk I, Skrzypek M, Bochenek AA. Delirium Screening in Cardiac Surgery (DESCARD): a useful tool for nonpsychiatrists. Can J Cardiol. 2014; 30:932–9. [PubMed: 24996371]
24. Roggenbach J, Klamann M, von Haken R, Bruckner T, Karck M, Hofer S. Sleep-disordered breathing is a risk factor for delirium after cardiac surgery: a prospective cohort study. Crit Care. 2014; 18:477. [PubMed: 25189637]
25. Todd OM, Gelrich L, MacLullich AM, Driessen M, Thomas C, Kreisel SH. Sleep Disruption at Home As an Independent Risk Factor for Postoperative Delirium. J Am Geriatr Soc. 2017
26. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn Sci. 2013; 17:502–9. [PubMed: 24018144]
27. Braskie MN, Thompson PM. Understanding cognitive deficits in Alzheimer's disease based on neuroimaging findings. Trends Cogn Sci. 2013; 17:510–6. [PubMed: 24029445]
28. Brown CHtMax L, LaFlam A, Kirk L, Gross A, Arora R, Neufeld K, Hogue CW, Walston J, Pustavoitau A. The Association Between Preoperative Frailty and Postoperative Delirium After Cardiac Surgery. Anesth Analg. 2016; 123:430–5. [PubMed: 27096563]
29. Robinson TN, Wu DS, Pointer LF, Dunn CL, Moss M. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg. 2012; 215:12–7. discussion 17-8. [PubMed: 22626912]
30. Burkhart CS, Dell-Kuster S, Gamberini M, Moeckli A, Grapow M, Filipovic M, Seeberger MD, Monsch AU, Strebel SP, Steiner LA. Modifiable and nonmodifiable risk factors for postoperative

delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2010; 24:555–9. [PubMed: 20227891]

31. Silbert BS, Scott DA, Evered LA, Lewis MS, Kalpokas M, Maruff P, Myles PS, Jamrozik K. A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. Anesthesiology. 2006; 104:1137–45. [PubMed: 16732083]
32. Association AP. Diagnostic and Statistical Manual of Mental Disorders. 5th. Washington, DC: American Psychiatric Association; 2013.
33. Kumar AK, Jayant A, Arya VK, Magoon R, Sharma R. Delirium after cardiac surgery: A pilot study from a single tertiary referral center. Ann Card Anaesth. 2017; 20:76–82. [PubMed: 28074801]
34. McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, Burns KM, Thompson JL, Shintani AK, Ely EW, Pandharipande PP. Delirium in the cardiovascular ICU: exploring modifiable risk factors. Crit Care Med. 2013; 41:405–13. [PubMed: 23263581]
35. Sauer AM, Slooter AJ, Veldhuijzen DS, van Eijk MM, Devlin JW, van Dijk D. Intraoperative dexamethasone and delirium after cardiac surgery: a randomized clinical trial. Anesth Analg. 2014; 119:1046–52. [PubMed: 24810262]
36. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, Khuri SF, Lipsitz LA, Ramlawi B, Levitsky S, Marcantonio ER. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation. 2009; 119:229–36. [PubMed: 19118253]
37. Berger M, Browndyke J, Mathew JP. Intraoperative Glycemic Control to Prevent Delirium after Cardiac Surgery: Steering a Course between Scylla and Charybdis. Anesthesiology. 2015; 122:1186–8. [PubMed: 25844843]
38. Brown CHtNeufeld KJ, Needham DM. Delirium, steroids, and cardiac surgery. Anesth Analg. 2014; 119:1011–3. [PubMed: 25329015]
39. McCoy TH Jr, Snapper L, Stern TA, Perlis RH. Underreporting of Delirium in Statewide Claims Data: Implications for Clinical Care and Predictive Modeling. Psychosomatics. 2016; 57:480–8. [PubMed: 27480944]
40. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. JAMA. 2017; 318:1161–1174. [PubMed: 28973626]
41. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001; 286:2703–10. [PubMed: 11730446]
42. Marcantonio ER, Ngo LH, O'Connor M, Jones RN, Crane PK, Metzger ED, Inouye SK. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med. 2014; 161:554–61. [PubMed: 25329203]
43. Kuczmarska A, Ngo LH, Guess J, O'Connor MA, Branford-White L, Palihnich K, Gallagher J, Marcantonio ER. Detection of Delirium in Hospitalized Older General Medicine Patients: A Comparison of the 3D-CAM and CAM-ICU. J Gen Intern Med. 2016; 31:297–303. [PubMed: 26443577]
44. Pisani MA, Araujo KL, Van Ness PH, Zhang Y, Ely EW, Inouye SK. A research algorithm to improve detection of delirium in the intensive care unit. Crit Care. 2006; 10:R121. [PubMed: 16919169]
45. Ottens TH, Dieleman JM, Sauer AM, Peelen LM, Nierich AP, de Groot WJ, Nathoe HM, Buijsrogge MP, Kalkman CJ, van Dijk D, Group DEfCSS. Effects of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. Anesthesiology. 2014; 121:492–500. [PubMed: 25225745]
46. Mathew JP, White WD, Schinderle DB, Podgoreanu MV, Berger M, Milano CA, Laskowitz DT, Stafford-Smith M, Blumenthal JA, Newman MF, Neurologic Outcome Research Group of The Duke Heart C. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. Stroke. 2013; 44:3407–13. [PubMed: 24105697]

47. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001; 344:395–402. [PubMed: 11172175]
48. Berger M, Nadler JW, Browndyke J, Terrando N, Ponnusamy V, Cohen HJ, Whitson HE, Mathew JP. Postoperative Cognitive Dysfunction: Minding the Gaps in Our Knowledge of a Common Postoperative Complication in the Elderly. Anesthesiol Clin. 2015; 33:517–50. [PubMed: 26315636]
49. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. Dysfunction IgTISoPC: The assessment of postoperative cognitive function. Acta Anaesthesiol Scand. 2001; 45:275–89. [PubMed: 11207462]
50. Folstein MF, Folstein SE, McHugh PR, Dysfunction IgTISoPC. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–98. [PubMed: 1202204]
51. Galvin JE, Sadowsky CH, Nincds A. Practical guidelines for the recognition and diagnosis of dementia. J Am Board Fam Med. 2012; 25:367–82. [PubMed: 22570400]
52. Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg. 1995; 59:1289–95. [PubMed: 7733754]
53. Cabeza R. Cognitive neuroscience of aging: contributions of functional neuroimaging. Scand J Psychol. 2001; 42:277–86. [PubMed: 11501741]
54. Wang WC, Dew IT, Cabeza R. Age-related differences in medial temporal lobe involvement during conceptual fluency. Brain Res. 2015; 1612:48–58. [PubMed: 25305568]
55. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013; 12:207–16. [PubMed: 23332364]
56. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012; 367:795–804. [PubMed: 22784036]
57. Xie Z, Swain CA, Ward SA, Zheng H, Dong Y, Sunder N, Burke DW, Escobar D, Zhang Y, Marcantonio ER. Preoperative cerebrospinal fluid beta-Amyloid/Tau ratio and postoperative delirium. Ann Clin Transl Neurol. 2014; 1:319–328. [PubMed: 24860840]
58. Xie Z, McAuliffe S, Swain CA, Ward SA, Crosby CA, Zheng H, Sherman J, Dong Y, Zhang Y, Sunder N, Burke D, Washicosky KJ, Tanzi RE, Marcantonio ER. Cerebrospinal fluid abeta to tau ratio and postoperative cognitive change. Ann Surg. 2013; 258:364–9. [PubMed: 23732272]
59. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction. Anesthesiology. 2016; 124:353–61. [PubMed: 26580833]
60. Culley DJ, Crosby G. Dementia after Cardiac Surgery: Is It the Procedure or the Patient? Anesthesiology. 2016; 125:14–6. [PubMed: 27127918]
61. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. Br J Anaesth. 2012; 108:623–9. [PubMed: 22311364]
62. Evered LA, Silbert BS, Scott DA. Postoperative cognitive dysfunction and aortic atheroma. Ann Thorac Surg. 2010; 89:1091–7. [PubMed: 20338312]
63. Browndyke JN, Berger M, Harshbarger TB, Smith PJ, White W, Bisanar TL, Alexander JH, Gaca JG, Welsh-Bohmer K, Newman MF, Mathew JP. Resting-State Functional Connectivity and Cognition After Major Cardiac Surgery in Older Adults without Preoperative Cognitive Impairment: Preliminary Findings. J Am Geriatr Soc. 2017; 65:e6–e12. [PubMed: 27858963]
64. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, Oh ES, Crosby G, Berger M, Eckenhoff RG. Recommendations for the nomenclature of cognitive change associated with anesthesia and surgery. Anesthesiology. 2017 In Press.

65. Phillips-Bute B, Mathew JP, Blumenthal JA, Grocott HP, Laskowitz DT, Jones RH, Mark DB, Newman MF. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med. 2006; 68:369–75. [PubMed: 16738066]

66. Newman MF, Grocott HP, Mathew JP, White WD, Landolfo K, Reves JG, Laskowitz DT, Mark DB, Blumenthal JA, Neurologic Outcome Research G, the Cardiothoracic Anesthesia Research Endeavors Investigators of the Duke Heart C. Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. Stroke. 2001; 32:2874–81. [PubMed: 11739990]

67. Terrando N, Eriksson LI, Eckenhoff RG. Perioperative neurotoxicity in the elderly: summary of the 4th International Workshop. Anesth Analg. 2015; 120:649–52. [PubMed: 25695580]

68. Sherbet DP, Garg P, Brilakis ES, Banerjee S. Low-density lipoprotein cholesterol: how low can we go? Am J Cardiovasc Drugs. 2013; 13:225–32. [PubMed: 23609530]

69. Verdecchia P, Angeli F, Reboldi G. How Low Should We Go With Blood Pressure? Circ Res. 2017; 120:27–29. [PubMed: 28057786]

70. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Committee FS, Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017

71. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129:S1–45. [PubMed: 24222016]

72. Kadoi Y, Kawauchi C, Ide M, Kuroda M, Takahashi K, Saito S, Fujita N, Mizutani A. Preoperative depression is a risk factor for postoperative short-term and long-term cognitive dysfunction in patients with diabetes mellitus. J Anesth. 2011; 25:10–7. [PubMed: 21161290]

73. Mathew JP, Mackensen GB, Phillips-Bute B, Stafford-Smith M, Podgoreanu MV, Grocott HP, Hill SE, Smith PK, Blumenthal JA, Reves JG, Newman MF, Neurologic Outcome Research Group of the Duke Heart C. Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. Anesthesiology. 2007; 107:577–84. [PubMed: 17893453]

74. Newman MF, Croughwell ND, Blumenthal JA, White WD, Lewis JB, Smith LR, Frasco P, Towner EA, Schell RM, Hurwitz BJ, Reves JG. Effect of aging on cerebral autoregulation during cardiopulmonary bypass. Association with postoperative cognitive dysfunction. Circulation. 1994; 90:II243–9. [PubMed: 7955260]

75. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, Schmitt DV, Mohr FW. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg. 2004; 127:57–64. [PubMed: 14752413]

76. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg. 2012; 27:481–92. [PubMed: 22784203]

77. Humphreys JM, Denson LA, Baker RA, Tully PJ. The importance of depression and alcohol use in coronary artery bypass graft surgery patients: risk factors for delirium and poorer quality of life. J Geriatr Cardiol. 2016; 13:51–7. [PubMed: 26918013]

78. McDonagh DL, Berger M, Mathew JP, Graffagnino C, Milano CA, Newman MF. Neurological complications of cardiac surgery. Lancet Neurol. 2014; 13:490–502. [PubMed: 24703207]

79. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014; 383:911–22. [PubMed: 23992774]

80. Chan MT, Cheng BC, Lee TM, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol. 2013; 25:33–42. [PubMed: 23027226]

81. Culley DJ, Snayd M, Baxter MG, Xie Z, Lee IH, Rudolph J, Inouye SK, Marcantonio ER, Crosby G. Systemic inflammation impairs attention and cognitive flexibility but not associative learning in

aged rats: possible implications for delirium. Front Aging Neurosci. 2014; 6:107. [PubMed: 24959140]

82. Basinski JR, Alfano CM, Katon WJ, Syrjala KL, Fann JR. Impact of delirium on distress, health-related quality of life, and cognition 6 months and 1 year after hematopoietic cell transplant. Biol Blood Marrow Transplant. 2010; 16:824–31. [PubMed: 20100587]
83. Naidech AM, Beaumont JL, Rosenberg NF, Maas MB, Kosteva AR, Ault ML, Cella D, Ely EW. Intracerebral hemorrhage and delirium symptoms. Length of stay, function, and quality of life in a 114-patient cohort. Am J Respir Crit Care Med. 2013; 188:1331–7. [PubMed: 24102675]
84. Loponen P, Luther M, Wistbacka JO, Nissinen J, Sintonen H, Huhtala H, Tarkka MR. Postoperative delirium and health related quality of life after coronary artery bypass grafting. Scand Cardiovasc J. 2008; 42:337–44. [PubMed: 18609064]
85. Leslie DL, Inouye SK. The importance of delirium: economic and societal costs. J Am Geriatr Soc. 2011; 59(Suppl 2):S241–3. [PubMed: 22091567]
86. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, Group I. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology. 2009; 110:548–55. [PubMed: 19225398]
87. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA, Neurological Outcome Research G, the Cardiothoracic Anesthesiology Research Endeavors I. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001; 344:395–402. [PubMed: 11172175]
88. Evered LA, Silbert BS, Scott DA, Maruff P, Ames D. Prevalence of Dementia 7.5 Years after Coronary Artery Bypass Graft Surgery. Anesthesiology. 2016; 125:62–71. [PubMed: 27127919]
89. Schenning KJ, Murchison CF, Mattek NC, Silbert LC, Kaye JA, Quinn JF. Surgery is associated with ventricular enlargement as well as cognitive and functional decline. Alzheimers Dement. 2015
90. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Travison TG, Saczynski JS, Ngo LH, Alsop DC, Jones RN. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. Alzheimers Dement. 2016
91. Berger M, Burke J, Eckenhoff R, Mathew J. Alzheimer's disease, anesthesia, and surgery: a clinically focused review. J Cardiothorac Vasc Anesth. 2014; 28:1609–23. [PubMed: 25267693]
92. Steinmetz J, Siersma V, Kessing LV, Rasmussen LS, Group I. Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study. Br J Anaesth. 2013; 110(Suppl 1):i92–7. [PubMed: 23274780]
93. Evered LA, Silbert BS, Scott DA, Maruff P, Ames D. Prevalence of Dementia 75 Years after Coronary Artery Bypass Graft Surgery. Anesthesiology. 2016
94. Lundstrom M, Edlund A, Bucht G, Karlsson S, Gustafson Y. Dementia after delirium in patients with femoral neck fractures. J Am Geriatr Soc. 2003; 51:1002–6. [PubMed: 12834522]
95. Hudetz JA, Patterson KM, Byrne AJ, Pagel PS, Warltier DC. Postoperative delirium is associated with postoperative cognitive dysfunction at one week after cardiac surgery with cardiopulmonary bypass. Psychol Rep. 2009; 105:921–32. [PubMed: 20099555]
96. Youngblom E, DePalma G, Sands L, Leung J. The temporal relationship between early postoperative delirium and postoperative cognitive dysfunction in older patients: a prospective cohort study. Can J Anaesth. 2014; 61:1084–92. [PubMed: 25287962]
97. Franck M, Nerlich K, Neuner B, Schlattmann P, Brockhaus WR, Spies CD, Radtke FM. No convincing association between post-operative delirium and post-operative cognitive dysfunction: a secondary analysis. Acta Anaesthesiol Scand. 2016; 60:1404–1414. [PubMed: 27578364]
98. Fong TG, Hshieh TT, Wong B, Tommet D, Jones RN, Schmitt EM, Puelle MR, Saczynski JS, Marcantonio ER, Inouye SK. Neuropsychological profiles of an elderly cohort undergoing elective surgery and the relationship between cognitive performance and delirium. J Am Geriatr Soc. 2015; 63:977–82. [PubMed: 25944109]
99. Mu DL, Wang DX, Li LH, Shan GJ, Su Y, Yu QJ, Shi CX. Postoperative delirium is associated with cognitive dysfunction one week after coronary artery bypass grafting surgery. Beijing Da Xue Xue Bao. 2011; 43:242–9. [PubMed: 21503120]

100. Rudolph JL, Marcantonio ER, Culley DJ, Silverstein JH, Rasmussen LS, Crosby GJ, Inouye SK. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia. 2008; 63:941–7. [PubMed: 18547292]
101. Silverstein JH, Timberger M, Reich DL, Uysal S. Central nervous system dysfunction after noncardiac surgery and anesthesia in the elderly. Anesthesiology. 2007; 106:622–8. [PubMed: 17325520]
102. Vasunilashorn SM, Ngo L, Inouye SK, Libermann TA, Jones RN, Alsop DC, Guess J, Jastrzebski S, McElhaney JE, Kuchel GA, Marcantonio ER. Cytokines and Postoperative Delirium in Older Patients Undergoing Major Elective Surgery. J Gerontol A Biol Sci Med Sci. 2015; 70:1289–95. [PubMed: 26215633]
103. Liu P, Li YW, Wang XS, Zou X, Zhang DZ, Wang DX, Li SZ. High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study. Chin Med J (Engl). 2013; 126:3621–7. [PubMed: 24112153]
104. Hovens IB, van Leeuwen BL, Nyakas C, Heineman E, van der Zee EA, Schoemaker RG. Prior infection exacerbates postoperative cognitive dysfunction in aged rats. Am J Physiol Regul Integr Comp Physiol. 2015; 309:R148–59. [PubMed: 25972458]
105. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, Jonsson Fagerlund M, Charo IF, Akassoglou K, Maze M. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol. 2011; 70:986–95. [PubMed: 22190370]
106. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci U S A. 2010; 107:20518–22. [PubMed: 21041647]
107. Degos V, Vacas S, Han Z, van Rooijen N, Gressens P, Su H, Young WL, Maze M. Depletion of bone marrow-derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology. 2013; 118:527–36. [PubMed: 23426204]
108. He HJ, Wang Y, Le Y, Duan KM, Yan XB, Liao Q, Liao Y, Tong JB, Terrando N, Ouyang W. Surgery upregulates high mobility group box-1 and disrupts the blood-brain barrier causing cognitive dysfunction in aged rats. CNS Neurosci Ther. 2012; 18:994–1002. [PubMed: 23078219]
109. Lu SM, Yu CJ, Liu YH, Dong HQ, Zhang X, Zhang SS, Hu LQ, Zhang F, Qian YN, Gui B. S100A8 contributes to postoperative cognitive dysfunction in mice undergoing tibial fracture surgery by activating the TLR4/MyD88 pathway. Brain Behav Immun. 2015; 44:221–34. [PubMed: 25449673]
110. Terrando N, Brzezinski M, Degos V, Eriksson LI, Kramer JH, Leung JM, Miller BL, Seeley WW, Vacas S, Weiner MW, Yaffe K, Young WL, Xie Z, Maze M. Perioperative cognitive decline in the aging population. Mayo Clin Proc. 2011; 86:885–93. [PubMed: 21878601]
111. Haque A, Kunimoto F, Narahara H, Okawa M, Hinohara H, Kurabayashi M, Saito S. High mobility group box 1 levels in on and off-pump cardiac surgery patients. Int Heart J. 2011; 52:170–4. [PubMed: 21646740]
112. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010; 464:104–7. [PubMed: 20203610]
113. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubes P, Lilford RJ. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014; 384:1455–65. [PubMed: 25390327]
114. Terrando N, Yang T, Wang X, Fang J, Cao M, Andersson U, Erlandsson HH, Ouyang W, Tong J. Systemic HMGB1 Neutralization Prevents Postoperative Neurocognitive Dysfunction in Aged Rats. Front Immunol. 2016; 7:441. [PubMed: 27822212]
115. Bartels K, Ma Q, Venkatraman TN, Campos CR, Smith L, Cannon RE, Podgoreanu MV, Lascola CD, Miller DS, Mathew JP. Effects of deep hypothermic circulatory arrest on the blood brain barrier in a cardiopulmonary bypass model–a pilot study. Heart Lung Circ. 2014; 23:981–4. [PubMed: 24931068]

116. Reis HJ, Teixeira AL, Kalman J, Bogats G, Babik B, Janka Z, Teixeira MM, Palotas A. Different inflammatory biomarker patterns in the cerebro-spinal fluid following heart surgery and major non-cardiac operations. Curr Drug Metab. 2007; 8:639–42. [PubMed: 17691923]

117. Reinsfelt B, Ricksten SE, Zetterberg H, Blennow K, Freden-Lindqvist J, Westerlind A. Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery. Ann Thorac Surg. 2012; 94:549–55. [PubMed: 22698770]

118. Hainsworth AH, Minett T, Andoh J, Forster G, Bhide I, Barrick TR, Elderfield K, Jeevahan J, Markus HS, Bridges LR. Neuropathology of White Matter Lesions, Blood-Brain Barrier Dysfunction, and Dementia. Stroke. 2017; 48:2799–2804. [PubMed: 28855392]

119. Merino JG, Latour LL, Tso A, Lee KY, Kang DW, Davis LA, Lazar RM, Horvath KA, Corso PJ, Warach S. Blood-brain barrier disruption after cardiac surgery. AJNR Am J Neuroradiol. 2013; 34:518–23. [PubMed: 22918429]

120. Abrahamov D, Levran O, Naparstek S, Refaeli Y, Kaptson S, Abu Salah M, Ishai Y, Sahar G. Blood-Brain Barrier Disruption After Cardiopulmonary Bypass: Diagnosis and Correlation to Cognition. Ann Thorac Surg. 2017

121. Steinberg BE, Sundman E, Terrando N, Eriksson LI, Olofsson PS. Neural Control of Inflammation: Implications for Perioperative and Critical Care. Anesthesiology. 2016; 124:1174–89. [PubMed: 26982508]

122. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther. 2011; 130:226–38. [PubMed: 21334376]

123. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. J Neuroinflammation. 2013; 10:43. [PubMed: 23547920]

124. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015; 14:388–405. [PubMed: 25792098]

125. Mittal MK, Rabinstein AA, Hocker SE, Pittock SJ, Wijdicks EF, McKeon A. Autoimmune Encephalitis in the ICU: Analysis of Phenotypes, Serologic Findings, and Outcomes. Neurocrit Care. 2016; 24:240–50. [PubMed: 26319044]

126. Mathew JP, Podgoreanu MV, Grocott HP, White WD, Morris RW, Stafford-Smith M, Mackensen GB, Rinder CS, Blumenthal JA, Schwinn DA, Newman MF, Team PI. Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. J Am Coll Cardiol. 2007; 49:1934–42. [PubMed: 17498578]

127. Mathew JP, Rinder CS, Howe JG, Fontes M, Crouch J, Newman MF, Phillips-Bute B, Smith BR. Platelet PlA2 polymorphism enhances risk of neurocognitive decline after cardiopulmonary bypass. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Ann Thorac Surg. 2001; 71:663–6. [PubMed: 11235724]

128. Yocum GT, Gaudet JG, Lee SS, Stern Y, Teverbaugh LA, Sciacca RR, Emala CW, Quest DO, McCormick PC, McKinsey JF, Morrissey NJ, Solomon RA, Connolly ES Jr, Heyer EJ. Inducible nitric oxide synthase promoter polymorphism affords protection against cognitive dysfunction after carotid endarterectomy. Stroke. 2009; 40:1597–603. [PubMed: 19286578]

129. Steinberg BM, Grossi EA, Schwartz DS, McLoughlin DE, Aguinaga M, Bizekis C, Greenwald J, Flisser A, Spencer FC, Galloway AC, Colvin SB. Heparin bonding of bypass circuits reduces cytokine release during cardiopulmonary bypass. Ann Thorac Surg. 1995; 60:525–9. [PubMed: 7677475]

130. Shann KG, Likosky DS, Murkin JM, Baker RA, Baribeau YR, DeFoe GR, Dickinson TA, Gardner TJ, Grocott HP, O'Connor GT, Rosinski DJ, Sellke FW, Willcox TW. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. J Thorac Cardiovasc Surg. 2006; 132:283–90. [PubMed: 16872951]

131. Bruins P, te Velthuis H, Eerenberg-Belmer AJ, Yazdanbakhsh AP, de Beaumont EM, Eijsman L, Trouwborst A, Hack CE. Heparin-protamine complexes and C-reactive protein induce activation

of the classical complement pathway: studies in patients undergoing cardiac surgery and in vitro. Thromb Haemost. 2000; 84:237–43. [PubMed: 10959695]

132. Hayashi Y, Sawa Y, Nishimura M, Satoh H, Ohtake S, Matsuda H. Avoidance of full-sternotomy: effect on inflammatory cytokine production during cardiopulmonary bypass in rats. J Card Surg. 2003; 18:390–5. [PubMed: 12974923]
133. Gu YJ, Mariani MA, Boonstra PW, Grandjean JG, van Oeveren W. Complement activation in coronary artery bypass grafting patients without cardiopulmonary bypass: the role of tissue injury by surgical incision. Chest. 1999; 116:892–8. [PubMed: 10531149]
134. Friscia ME, Zhu J, Kolff JW, Chen Z, Kaiser LR, Deutschman CS, Shrager JB. Cytokine response is lower after lung volume reduction through bilateral thoracoscopy versus sternotomy. Ann Thorac Surg. 2007; 83:252–6. [PubMed: 17184673]
135. Diegeler A, Doll N, Rauch T, Haberer D, Walther T, Falk V, Gummert J, Autschbach R, Mohr FW. Humoral immune response during coronary artery bypass grafting: A comparison of limited approach, “off-pump” technique, and conventional cardiopulmonary bypass. Circulation. 2000; 102:III95–100. [PubMed: 11082370]
136. Gulielmos V, Menschikowski M, Dill H, Eller M, Thiele S, Tugtekin SM, Jaross W, Schueler S. Interleukin-1, interleukin-6 and myocardial enzyme response after coronary artery bypass grafting - a prospective randomized comparison of the conventional and three minimally invasive surgical techniques. Eur J Cardiothorac Surg. 2000; 18:594–601. [PubMed: 11053823]
137. Liu J, Wang H, Li J. Inflammation and Inflammatory Cells in Myocardial Infarction and Reperfusion Injury: A Double-Edged Sword. Clin Med Insights Cardiol. 2016; 10:79–84. [PubMed: 27279755]
138. Ye X, Lian Q, Eckenhoff MF, Eckenhoff RG, Pan JZ. Differential general anesthetic effects on microglial cytokine expression. PLoS One. 2013; 8:e52887. [PubMed: 23382826]
139. Wu X, Lu Y, Dong Y, Zhang G, Zhang Y, Xu Z, Culley DJ, Crosby G, Marcantonio ER, Tanzi RE, Xie Z. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF-alpha, IL-6, and IL-1beta. Neurobiol Aging. 2012; 33:1364–78. [PubMed: 21190757]
140. McBride WT, Armstrong MA, McMurray TJ. An investigation of the effects of heparin, low molecular weight heparin, protamine, and fentanyl on the balance of pro- and anti-inflammatory cytokines in in-vitro monocyte cultures. Anaesthesia. 1996; 51:634–40. [PubMed: 8758154]
141. McBride WT, McBride SJ. The balance of pro- and anti-inflammatory cytokines in cardiac surgery. Curr Opin Anaesthesiol. 1998; 11:15–22. [PubMed: 17013200]
142. Wirtz DC, Heller KD, Miltner O, Zilkens KW, Wolff JM. Interleukin-6: a potential inflammatory marker after total joint replacement. Int Orthop. 2000; 24:194–6. [PubMed: 11081839]
143. Hovens IB, van Leeuwen BL, Mariani MA, Kraneveld AD, Schoemaker RG. Postoperative cognitive dysfunction and neuroinflammation; Cardiac surgery and abdominal surgery are not the same. Brain Behav Immun. 2016; 54:178–93. [PubMed: 26867718]
144. Zhang MD, Barde S, Yang T, Lei B, Eriksson LI, Mathew JP, Andreska T, Akassoglou K, Harkany T, Hokfelt TG, Terrando N. Orthopedic surgery modulates neuropeptides and BDNF expression at the spinal and hippocampal levels. Proc Natl Acad Sci U S A. 2016; 113:E6686–E6695. [PubMed: 27791037]
145. Vacas S, Degos V, Tracey KJ, Maze M. High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. Anesthesiology. 2014; 120:1160–7. [PubMed: 24162463]
146. Feng X, Valdearcos M, Uchida Y, Lutrin D, Maze M, Koliwad SK. Microglia mediate postoperative hippocampal inflammation and cognitive decline in mice. JCI Insight. 2017; 2:e91229. [PubMed: 28405620]
147. Hirsch J, Vacas S, Terrando N, Yuan M, Sands LP, Kramer J, Bozic K, Maze MM, Leung JM. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016; 13:211. [PubMed: 27577265]
148. Buvanendran A, Kroin JS, Berger RA, Hallab NJ, Saha C, Negrescu C, Moric M, Caicedo MS, Tuman KJ. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. Anesthesiology. 2006; 104:403–10. [PubMed: 16508385]

149. Yeager MP, Lunt P, Arruda J, Whalen K, Rose R, DeLeo JA. Cerebrospinal fluid cytokine levels after surgery with spinal or general anesthesia. Reg Anesth Pain Med. 1999; 24:557–62. [PubMed: 10588562]

150. Mathew JP, Shernan SK, White WD, Fitch JC, Chen JC, Bell L, Newman MF. Preliminary report of the effects of complement suppression with pexelizumab on neurocognitive decline after coronary artery bypass graft surgery. Stroke. 2004; 35:2335–9. [PubMed: 15331798]

151. Doraiswamy PM, Babyak MA, Hennig T, Trivedi R, White WD, Mathew JP, Newman MF, Blumenthal JA. Donepezil for cognitive decline following coronary artery bypass surgery: a pilot randomized controlled trial. Psychopharmacol Bull. 2007; 40:54–62. [PubMed: 17514186]

152. Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A, Filipovic M, Seeberger MD, Pargger H, Siegemund M, Carrel T, Seiler WO, Berres M, Strebel SP, Monsch AU, Steiner LA. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery–a randomized controlled trial. Crit Care Med. 2009; 37:1762–8. [PubMed: 19325490]

153. Royse CF, Saager L, Whitlock R, Ou-Young J, Royse A, Vincent J, Devereaux PJ, Kurz A, Awais A, Panjasawatwong K, Sessler DI. Impact of Methylprednisolone on Postoperative Quality of Recovery and Delirium in the Steroids in Cardiac Surgery Trial: A Randomized, Double-blind, Placebo-controlled Substudy. Anesthesiology. 2017; 126:223–233. [PubMed: 27775998]

154. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum A, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S, Investigators S. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 386:1243–53. [PubMed: 26460660]

155. Kenna HA, Poon AW, de los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. Psychiatry Clin Neurosci. 2011; 65:549–60. [PubMed: 22003987]

156. Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, Warltier DC, Pagel PS. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2009; 23:651–7. [PubMed: 19231245]

157. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Hudetz AG, Pagel PS, Warltier DC. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand. 2009; 53:864–72. [PubMed: 19422355]

158. Avidan MS, Maybrier HR, Abdallah AB, Jacobsohn E, Vlisides PE, Pryor KO, Veselis RA, Grocott HP, Emmert DA, Rogers EM, Downey RJ, Yulico H, Noh GJ, Lee YH, Waszynski CM, Arya VK, Pagel PS, Hudetz JA, Muench MR, Fritz BA, Waberski W, Inouye SK, Mashour GA, Group PR. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet. 2017; 390:267–275. [PubMed: 28576285]

159. Li X, Yang J, Nie XL, Zhang Y, Li XY, Li LH, Wang DX, Ma D. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. PLoS One. 2017; 12:e0170757. [PubMed: 28182690]

160. Deiner S, Luo X, Lin HM, Sessler DI, Saager L, Sieber FE, Lee HB, Sano M, the Dexlirium Writing G. Jankowski C, Bergese SD, Candiotti K, Flaherty JH, Arora H, Shander A, Rock P. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. JAMA Surg. 2017; 152:e171505. [PubMed: 28593326]

161. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016; 388:1893–1902. [PubMed: 27542303]

162. Palmbergen WA, van Sonderen A, Keyhan-Falsafi AM, Keunen RW, Wolterbeek R. Improved perioperative neurological monitoring of coronary artery bypass graft patients reduces the incidence of postoperative delirium: the Haga Brain Care Strategy. Interact Cardiovasc Thorac Surg. 2012; 15:671–7. [PubMed: 22778141]

163. Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. FASEB J. 2017; 31:1273–1288. [PubMed: 28087575]
164. Orr SK, Butler KL, Hayden D, Tompkins RG, Serhan CN, Irimia D. Gene Expression of Proresolving Lipid Mediator Pathways Is Associated With Clinical Outcomes in Trauma Patients. Crit Care Med. 2015; 43:2642–50. [PubMed: 26488221]
165. Su X, Feng X, Terrando N, Yan Y, Chawla A, Koch LG, Britton SL, Matthay MA, Maze M. Dysfunction of inflammation-resolving pathways is associated with exaggerated postoperative cognitive decline in a rat model of the metabolic syndrome. Mol Med. 2013; 18:1481–90. [PubMed: 23296426]
166. Terrando N, Gomez-Galan M, Yang T, Carlstrom M, Gustavsson D, Harding RE, Lindskog M, Eriksson LI. Aspirin-triggered resolvin D1 prevents surgery-induced cognitive decline. FASEB J. 2013; 27:3564–71. [PubMed: 23709617]
167. Zhang Z, Ma Q, Shah B, Mackensen GB, Lo DC, Mathew JP, Podgoreanu MV, Terrando N. Neuroprotective Effects of Annexin A1 Tripeptide after Deep Hypothermic Circulatory Arrest in Rats. Front Immunol. 2017; 8:1050. [PubMed: 28912778]
168. Xu ZZ, Zhang L, Liu T, Park JY, Berta T, Yang R, Serhan CN, Ji RR. Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. Nat Med. 2010; 16:592–7. 1p following 597. [PubMed: 20383154]
169. Chiang N, Fredman G, Backhed F, Oh SF, Vickery T, Schmidt BA, Serhan CN. Infection regulates pro-resolving mediators that lower antibiotic requirements. Nature. 2012; 484:524–8. [PubMed: 22538616]
170. Spite M, Norling LV, Summers L, Yang R, Cooper D, Petasis NA, Flower RJ, Perretti M, Serhan CN. Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. Nature. 2009; 461:1287–91. [PubMed: 19865173]
171. Glas KE, Swaminathan M, Reeves ST, Shanewise JS, Rubenson D, Smith PK, Mathew JP, Shernan SK. Guidelines for the performance of a comprehensive intraoperative epiaortic ultrasonographic examination: recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists; endorsed by the Society of Thoracic Surgeons. Anesth Analg. 2008; 106:1376–84. [PubMed: 18420847]
172. Doblar DD. Intraoperative transcranial ultrasonic monitoring for cardiac and vascular surgery. Semin Cardiothorac Vasc Anesth. 2004; 8:127–45. [PubMed: 15247999]
173. Guerrieri Wolf L, Choudhary BP, Abu-Omar Y, Taggart DP. Solid and gaseous cerebral microembolization after biologic and mechanical aortic valve replacement: investigation with multirange and multifrequency transcranial Doppler ultrasound. J Thorac Cardiovasc Surg. 2008; 135:512–20. [PubMed: 18329462]
174. Chaudhuri K, Marasco SF. The effect of carbon dioxide insufflation on cognitive function during cardiac surgery. J Card Surg. 2011; 26:189–96. [PubMed: 21395683]
175. Chaudhuri K, Storey E, Lee GA, Bailey M, Chan J, Rosenfeldt FL, Pick A, Negri J, Gooi J, Zimmet A, Esmore D, Merry C, Rowland M, Lin E, Marasco SF. Carbon dioxide insufflation in open-chamber cardiac surgery: a double-blind, randomized clinical trial of neurocognitive effects. J Thorac Cardiovasc Surg. 2012; 144:646–653 e1. [PubMed: 22578685]
176. Mirow N, Zittermann A, Korperich H, Borgermann J, Koertke H, Knobl H, Gieseke J, Ostertun B, Coskun T, Kleesiek K, Burchert W, Gummert JF. Diffusion-weighted magnetic resonance imaging for the detection of ischemic brain lesions in coronary artery bypass graft surgery: relation to extracorporeal circulation and heparinization. J Cardiovasc Surg (Torino). 2011; 52:117–26.
177. Cook DJ, Huston J 3rd, Trenerry MR, Brown RD Jr, Zehr KJ, Sundt TM 3rd. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. Ann Thorac Surg. 2007; 83:1389–95. [PubMed: 17383345]
178. Knipp SC, Matatko N, Wilhelm H, Schlamann M, Massoudy P, Forsting M, Diener HC, Jakob H. Evaluation of brain injury after coronary artery bypass grafting. A prospective study using neuropsychological assessment and diffusion-weighted magnetic resonance imaging. Eur J Cardiothorac Surg. 2004; 25:791–800. [PubMed: 15082284]

179. Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, Blackman DJ, Plein S, Greenwood JP. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. Heart. 2012; 98:18–23. [PubMed: 21737581]

180. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, Price T, Cardiovascular Health Study Collaborative Reseach G. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. Neurology. 2001; 57:1222–9. [PubMed: 11591840]

181. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM, Rotterdam Scan S. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003; 34:1126–9. [PubMed: 12690219]

182. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003; 348:1215–22. [PubMed: 12660385]

183. Hassell ME, Nijveldt R, Roos YB, Majoie CB, Hamon M, Piek JJ, Delewi R. Silent cerebral infarcts associated with cardiac disease and procedures. Nat Rev Cardiol. 2013; 10:696–706. [PubMed: 24165909]

184. Summers PM, Hartmann DA, Hui ES, Nie X, Deardorff RL, McKinnon ET, Helpern JA, Jensen JH, Shih AY. Functional deficits induced by cortical microinfarcts. J Cereb Blood Flow Metab. 2017; 37:3599–3614. [PubMed: 28090802]

185. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke. 2010; 41:1951–6. [PubMed: 20651274]

186. Newman MF, Croughwell ND, White WD, Lowry E, Baldwin BI, Clements FM, Davis RD Jr, Jones RH, Amory DW, Reves JG. Effect of perfusion pressure on cerebral blood flow during normothermic cardiopulmonary bypass. Circulation. 1996; 94:II353–7. [PubMed: 8901774]

187. Joshi B, Brady K, Lee J, Easley B, Panigrahi R, Smielewski P, Czosnyka M, Hogue CW Jr. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. Anesth Analg. 2010; 110:321–8. [PubMed: 20008083]

188. Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, Baumgartner W, Hogue CW. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. Br J Anaesth. 2012; 109:391–8. [PubMed: 22661748]

189. Severdija EE, Gommer ED, Weerwind PW, Reulen JP, Mess WH, Maessen JG. Assessment of dynamic cerebral autoregulation and cerebral carbon dioxide reactivity during normothermic cardiopulmonary bypass. Med Biol Eng Comput. 2015; 53:195–203. [PubMed: 25412609]

190. Severdija EE, Vranken NP, Simons AP, Gommer ED, Heijmans JH, Maessen JG, Weerwind PW. Hemodilution Combined With Hypercapnia Impairs Cerebral Autoregulation During Normothermic Cardiopulmonary Bypass. J Cardiothorac Vasc Anesth. 2015; 29:1194–9. [PubMed: 26146135]

191. Hori D, Max L, Laflam A, Brown C, Neufeld KJ, Adachi H, Sciortino C, Conte JV, Cameron DE, Hogue CW Jr, Mandal K. Blood Pressure Deviations From Optimal Mean Arterial Pressure During Cardiac Surgery Measured With a Novel Monitor of Cerebral Blood Flow and Risk for Perioperative Delirium: A Pilot Study. J Cardiothorac Vasc Anesth. 2016; 30:606–12. [PubMed: 27321787]

192. Hogue CW. Cerebral Autoregulation Monitoring During Cardiac Surgery. 2009. clinicaltrials.gov, clinicaltrials.gov

193. Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, Beyersdorf F. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. Eur J Cardiothorac Surg. 2011; 40:200–7. [PubMed: 21168339]

194. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, Hartman GS, Yao FS, Hollenberg JP, Barbut D, Hayes JG, Thomas SJ, Purcell MH, Mattis S, Gorkin L, Post M, Krieger KH, Isom OW. Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. J Thorac Cardiovasc Surg. 1995; 110:1302–11. discussion 1311-4. [PubMed: 7475182]

195. Hori D, Ono M, Rappold TE, Conte JV, Shah AS, Cameron DE, Adachi H, Everett AD, Hogue CW. Hypotension After Cardiac Operations Based on Autoregulation Monitoring Leads to Brain Cellular Injury. Ann Thorac Surg. 2015; 100:487–93. [PubMed: 26089226]

196. Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, Neufeld KJ, Gottesman R, Adachi H, Hogue CW. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. Br J Anaesth. 2014; 113:1009–17. [PubMed: 25256545]

197. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation. 1976; 53:720–7. [PubMed: 815061]

198. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg. 2012; 114:503–10. [PubMed: 22104067]

199. Croughwell ND, Newman MF, Blumenthal JA, White WD, Lewis JB, Frasco PE, Smith LR, Thyrum EA, Hurwitz BJ, Leone BJ. Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. Ann Thorac Surg. 1994; 58:1702–8. [PubMed: 7979740]

200. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger KU. Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. Crit Care. 2011; 15:R218. [PubMed: 21929765]

201. Slater JP, Guarino T, Stack J, Vinod K, Bustami RT, Brown JM 3rd, Rodriguez AL, Magovern CJ, Zaubler T, Freundlich K, Parr GV. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg. 2009; 87:36–44. discussion 44-5. [PubMed: 19101265]

202. de Tournay-Jette E, Dupuis G, Bherer L, Deschamps A, Cartier R, Denault A. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2011; 25:95–104. [PubMed: 20650659]

203. Reents W, Muellges W, Franke D, Babin-Ebell J, Elert O. Cerebral oxygen saturation assessed by near-infrared spectroscopy during coronary artery bypass grafting and early postoperative cognitive function. Ann Thorac Surg. 2002; 74:109–14. [PubMed: 12118739]

204. Hong SW, Shim JK, Choi YS, Kim DH, Chang BC, Kwak YL. Prediction of cognitive dysfunction and patients' outcome following valvular heart surgery and the role of cerebral oximetry. Eur J Cardiothorac Surg. 2008; 33:560–5. [PubMed: 18272385]

205. Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, Shaw AD, Roberts LJ 2nd, Billings FTt. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med. 2017; 103:192–198. [PubMed: 28039082]

206. Fontes MT, McDonagh DL, Phillips-Bute B, Welsby IJ, Podgoreanu MV, Fontes ML, Stafford-Smith M, Newman MF, Mathew JP, Neurologic Outcome Research Group of the Duke Heart C. Arterial hyperoxia during cardiopulmonary bypass and postoperative cognitive dysfunction. J Cardiothorac Vasc Anesth. 2014; 28:462–6. [PubMed: 23972739]

207. Ballard C, Jones E, Gauge N, Aarsland D, Nilsen OB, Saxby BK, Lowery D, Corbett A, Wesnes K, Katsaiti E, Arden J, Amoako D, Prophet N, Purushothaman B, Green D. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. PLoS One. 2012; 7:e37410. [PubMed: 22719840]

208. Choi KE, Hall CL, Sun JM, Wei L, Mohamad O, Dix TA, Yu SP. A novel stroke therapy of pharmacologically induced hypothermia after focal cerebral ischemia in mice. FASEB J. 2012; 26:2799–810. [PubMed: 22459147]

209. Nozari A, Safar P, Stezoski SW, Wu X, Kostelnik S, Radovsky A, Tisherman S, Kochanek PM. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. Circulation. 2006; 113:2690–6. [PubMed: 16769925]

210. Grossestreuer AV, Gaieski DF, Donnino MW, Wiebe DJ, Abella BS. Magnitude of temperature elevation is associated with neurologic and survival outcomes in resuscitated cardiac arrest patients with postrewarming pyrexia. J Crit Care. 2017; 38:78–83. [PubMed: 27866109]

211. Meier K, Lee K. Neurogenic Fever. J Intensive Care Med. 2017; 32:124–129. [PubMed: 26772198]

212. Kasdorf E, Perlman JM. Hyperthermia, inflammation, and perinatal brain injury. Pediatr Neurol. 2013; 49:8–14. [PubMed: 23683657]

213. Martin TD, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT, Guyton RA. Prospective, randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurologic threat. Ann Thorac Surg. 1994; 57:298–302. discussion 302-4. [PubMed: 8311588]

214. Grigore AM, Mathew J, Grocott HP, Reves JG, Blumenthal JA, White WD, Smith PK, Jones RH, Kirchner JL, Mark DB, Newman MF, Neurological Outcome Research G, Endeavors CIotDHCCAR. Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery. Anesthesiology. 2001; 95:1110–9. [PubMed: 11684979]

215. Grocott HP, Mackensen GB, Grigore AM, Mathew J, Reves JG, Phillips-Bute B, Smith PK, Newman MF, Neurologic Outcome Research G, Cardiothoracic Anesthesiology Research Endeavors Investigators' of the Duke Heart C. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. Stroke. 2002; 33:537–41. [PubMed: 11823666]

216. Nathan HJ, Wells GA, Munson JL, Wozny D. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. Circulation. 2001; 104:I85–91. [PubMed: 11568036]

217. Boodhwani M, Rubens F, Wozny D, Rodriguez R, Nathan HJ. Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study. J Thorac Cardiovasc Surg. 2007; 134:1443–50. discussion 1451-2. [PubMed: 18023662]

218. Sirvinskas E, Usas E, Mankute A, Raliene L, Jakuska P, Lenkutis T, Benetis R. Effects of intraoperative external head cooling on short-term cognitive function in patients after coronary artery bypass graft surgery. Perfusion. 2014; 29:124–9. [PubMed: 23878011]

219. Grigore AM, Murray CF, Ramakrishna H, Djaiani G. A core review of temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg. 2009; 109:1741–51. [PubMed: 19923500]

220. Hogan AM, Shipolini A, Brown MM, Hurley R, Cormack F. Fixing hearts and protecting minds: a review of the multiple, interacting factors influencing cognitive function after coronary artery bypass graft surgery. Circulation. 2013; 128:162–71. [PubMed: 23836829]

221. Cook DJ. CON: Temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg. 2009; 109:1733–7. [PubMed: 19923498]

222. Grocott HP. PRO: Temperature regimens and neuroprotection during cardiopulmonary bypass: does rewarming rate matter? Anesth Analg. 2009; 109:1738–40. [PubMed: 19923499]

223. Engelman R, Baker RA, Likosky DS, Grigore A, Dickinson TA, Shore-Lesserson L, Hammon JW. The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical Practice Guidelines for Cardiopulmonary Bypass–Temperature Management during Cardiopulmonary Bypass. J Extra Corpor Technol. 2015; 47:145–54. [PubMed: 26543248]

224. Enomoto S, Hindman BJ, Dexter F, Smith T, Cutkomp J. Rapid rewarming causes an increase in the cerebral metabolic rate for oxygen that is temporarily unmatched by cerebral blood flow. A study during cardiopulmonary bypass in rabbits. Anesthesiology. 1996; 84:1392–400. [PubMed: 8669681]

225. Lindgren M, Eckert B, Stenberg G, Agardh CD. Restitution of neurophysiological functions, performance, and subjective symptoms after moderate insulin-induced hypoglycaemia in non-diabetic men. Diabet Med. 1996; 13:218–25. [PubMed: 8689841]

226. Schafer RJ, Page KA, Arora J, Sherwin R, Constable RT. BOLD response to semantic and syntactic processing during hypoglycemia is load-dependent. Brain Lang. 2012; 120:1–14. [PubMed: 22000597]

227. Davis EA, Soong SA, Byrne GC, Jones TW. Acute hyperglycaemia impairs cognitive function in children with IDDM. J Pediatr Endocrinol Metab. 1996; 9:455–61. [PubMed: 8910814]

228. Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar-Yosef S. Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg. 2007; 84:1467–73. [PubMed: 17954047]

229. Cornford EM, Hyman S, Cornford ME, Clare-Salzler M. Down-regulation of blood-brain glucose transport in the hyperglycemic nonobese diabetic mouse. Neurochem Res. 1995; 20:869–73. [PubMed: 7477681]

230. Butterworth J, Wagenknecht LE, Legault C, Zaccaro DJ, Kon ND, Hammon JW Jr, Rogers AT, Troost BT, Stump DA, Furberg CD, Coker LH. Attempted control of hyperglycemia during cardiopulmonary bypass fails to improve neurologic or neurobehavioral outcomes in patients without diabetes mellitus undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2005; 130:1319. [PubMed: 16256784]

231. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med. 2009; 37:S186–202. [PubMed: 19535947]

232. Saager L, Duncan AE, Yared JP, Hesler BD, You J, Deogaonkar A, Sessler DI, Kurz A. Intraoperative tight glucose control using hyperinsulinemic normoglycemia increases delirium after cardiac surgery. Anesthesiology. 2015; 122:1214–23. [PubMed: 25992877]

233. Schricker T, Sato H, Beaudry T, Codere T, Hatzakorzian R, Pruessner JC. Intraoperative maintenance of normoglycemia with insulin and glucose preserves verbal learning after cardiac surgery. PLoS One. 2014; 9:e99661. [PubMed: 24941010]

234. Van Dijk D, Jansen EW, Hijman R, Nierich AP, Diephuis JC, Moons KG, Lahpor JR, Borst C, Keizer AM, Nathoe HM, Grobbee DE, De Jaegere PP, Kalkman CJ. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA. 2002; 287:1405–12. [PubMed: 11903027]

235. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D, Veterans Affairs Randomized On/Off Bypass Study G. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med. 2009; 361:1827–37. [PubMed: 19890125]

236. Kok WF, van Harten AE, Koene BM, Mariani MA, Koerts J, Tucha O, Absalom AR, Scheeren TW. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass*. Anaesthesia. 2014; 69:613–22. [PubMed: 24750013]

237. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM. Do management strategies for coronary artery disease influence 6-year cognitive outcomes? Ann Thorac Surg. 2009; 88:445–454. [PubMed: 19632391]

238. Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, McKhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. N Engl J Med. 2012; 366:250–7. [PubMed: 22256807]

239. Calafiore AM, Di Giammarco G, Teodori G, Mazzei V, Vitolla G. Recent advances in multivessel coronary grafting without cardiopulmonary bypass. Heart Surg Forum. 1998; 1:20–5. [PubMed: 11276435]

240. Miura N, Yoshitani K, Kawaguchi M, Shinzawa M, Irie T, Uchida O, Ohnishi Y, Mackensen GB. Jugular bulb desaturation during off-pump coronary artery bypass surgery. J Anesth. 2009; 23:477–82. [PubMed: 19921353]

241. Rothberg MB, Herzig SJ, Pekow PS, Avrunin J, Lagu T, Lindenauer PK. Association between sedating medications and delirium in older inpatients. J Am Geriatr Soc. 2013; 61:923–30. [PubMed: 23631415]

242. Airagnes G, Pelissolo A, Lavallee M, Flament M, Limosin F. Benzodiazepine Misuse in the Elderly: Risk Factors, Consequences, and Management. Curr Psychiatry Rep. 2016; 18:89. [PubMed: 27549604]

243. Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Begaud B. Benzodiazepine use and risk of Alzheimer's disease: case-control study. BMJ. 2014; 349:g5205. [PubMed: 25208536]

244. Berger M. DREAMER study. 2016. clinicaltrials.gov

245. Palotas A, Reis HJ, Bogats G, Babik B, Racsmany M, Engvau L, Kecskemeti E, Juhasz A, Vieira LB, Teixeira AL, Mukhamedyarovi MA, Rizvanov AA, Yalvac ME, Guimaraes MM, Ferreira

CN, Zefirov AL, Kiyasov AP, Wang L, Janka Z, Kalman J. Coronary artery bypass surgery provokes Alzheimer's disease-like changes in the cerebrospinal fluid. J Alzheimers Dis. 2010; 21:1153–64. [PubMed: 21504113]

246. Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, Mathys H, Seo J, Kritskiy O, Abdurrob F, Adaikkan C, Canter RG, Rueda R, Brown EN, Boyden ES, Tsai LH. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature. 2016; 540:230–235. [PubMed: 27929004]
247. Plourde G, Reed SJ, Chapman CA. Attenuation of High-Frequency (50-200 Hz) Thalamocortical EEG Rhythms by Isoflurane in Rats is More Pronounced for the Thalamus than for the Cortex. Anesthesia & Analgesia. 2015 TBD: ___ to __.
248. Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN. Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proc Natl Acad Sci U S A. 2013; 110:E1142–51. [PubMed: 23487781]
249. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical Electroencephalography for Anesthesiologists: Part I: Background and Basic Signatures. Anesthesiology. 2015; 123:937–60. [PubMed: 26275092]
250. Zheng L, Fan QM, Wei ZY. Serum S-100beta and NSE levels after off-pump versus on-pump coronary artery bypass graft surgery. BMC Cardiovasc Disord. 2015; 15:70. [PubMed: 26179379]
251. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. Nat Rev Neurosci. 2016; 17:705–717. [PubMed: 27752068]
252. Shen X, Dong Y, Xu Z, Wang H, Miao C, Soriano SG, Sun D, Baxter MG, Zhang Y, Xie Z. Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. Anesthesiology. 2013; 118:502–15. [PubMed: 23314110]
253. Zhang L, Zhang J, Yang L, Dong Y, Zhang Y, Xie Z. Isoflurane and sevoflurane increase interleukin-6 levels through the nuclear factor-kappa B pathway in neuroglioma cells. Br J Anaesth. 2013; 110(Suppl 1):i82–91. [PubMed: 23604542]
254. Avramescu S, Wang DS, Lecker I, To WT, Penna A, Whissell PD, Mesbah-Oskui L, Horner RL, Orser BA. Inflammation Increases Neuronal Sensitivity to General Anesthetics. Anesthesiology. 2016; 124:417–27. [PubMed: 26566283]
255. Palop JJ, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. Nat Rev Neurosci. 2016; 17:777–792. [PubMed: 27829687]
256. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron. 2013; 80:1347–58. [PubMed: 24360540]
257. Tai LM, Thomas R, Marottoli FM, Koster KP, Kanekiyo T, Morris AW, Bu G. The role of APOE in cerebrovascular dysfunction. Acta Neuropathol. 2016; 131:709–23. [PubMed: 26884068]
258. Tagarakis GI, Tsolaki-Tagaraki F, Tsolaki M, Diegeler A, Tsilimingas NB, Papassotiropoulos A. The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations. Am J Alzheimers Dis Other Demen. 2007; 22:223–8. [PubMed: 17606532]
259. Schenning KJ, Murchison CF, Mattek NC, Silbert LC, Kaye JA, Quinn JF. Surgery is associated with ventricular enlargement as well as cognitive and functional decline. Alzheimers Dement. 2016; 12:590–7. [PubMed: 26610898]
260. Askar FZ, Cetin HY, Kumral E, Cetin O, Acarer A, Kosova B, Yagdi T. Apolipoprotein E epsilon4 allele and neurobehavioral status after on-pump coronary artery bypass grafting. J Card Surg. 2005; 20:501–5. [PubMed: 16153291]
261. Silbert BS, Evered LA, Scott DA, Cowie TF. The apolipoprotein E epsilon4 allele is not associated with cognitive dysfunction in cardiac surgery. Ann Thorac Surg. 2008; 86:841–7. [PubMed: 18721571]
262. Abelha FJ, Fernandes V, Botelho M, Santos P, Santos A, Machado JC, Barros H. Apolipoprotein E e4 allele does not increase the risk of early postoperative delirium after major surgery. J Anesth. 2012

263. Leung JM, Sands LP, Wang Y, Poon A, Kwok PY, Kane JP, Pullinger CR. Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. Anesthesiology. 2007; 107:406–11. [PubMed: 17721242]

264. Ti LK, Mackensen GB, Grocott HP, Laskowitz DT, Phillips-Bute BG, Milano CA, Hilton AK, Newman MF, Mathew JP. Apolipoprotein E4 increases aortic atheroma burden in cardiac surgical patients. J Thorac Cardiovasc Surg. 2003; 125:211–3. [PubMed: 12539012]

265. Benitez BA, Jin SC, Guerreiro R, Graham R, Lord J, Harold D, Sims R, Lambert JC, Gibbs JR, Bras J, Sassi C, Harari O, Bertelsen S, Lupton MK, Powell J, Bellenguez C, Brown K, Medway C, Haddick PC, van der Brug MP, Bhangale T, Ortmann W, Behrens T, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD, Haines JL, Turton J, Braae A, Barber I, Fagan AM, Holtzman DM, Morris JC, Group CS, consortium E, Alzheimer's Disease Genetic C, Alzheimer's Disease Neuroimaging I, Consortium G. Williams J, Kauwe JS, Amouyel P, Morgan K, Singleton A, Hardy J, Goate AM, Cruchaga C. Missense variant in TREML2 protects against Alzheimer's disease. Neurobiol Aging. 2014; 35:1510 e19–26.

266. Carrasquillo MM, Belbin O, Hunter TA, Ma L, Bisceglio GD, Zou F, Crook JE, Pankratz VS, Dickson DW, Graff-Radford NR, Petersen RC, Morgan K, Younkin SG. Replication of CLU, CR1, and PICALM associations with alzheimer disease. Arch Neurol. 2010; 67:961–4. [PubMed: 20554627]

267. Chen LH, Kao PY, Fan YH, Ho DT, Chan CS, Yik PY, Ha JC, Chu LW, Song YQ. Polymorphisms of CR1, CLU and PICALM confer susceptibility of Alzheimer's disease in a southern Chinese population. Neurobiol Aging. 2012; 33:210 e1–7.

268. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, European Alzheimer's Disease Initiative I. de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanche H, Dartigues JF, Tzourio C, Gut I, Van Broeckhoven C, Alperovitch A, Lathrop M, Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009; 41:1094–9. [PubMed: 19734903]

269. Luo J, Li S, Qin X, Song L, Peng Q, Chen S, Xie Y, Xie L, Li T, He Y, Deng Y, Wang J, Zeng Z. Meta-analysis of the association between CR1 polymorphisms and risk of late-onset Alzheimer's disease. Neurosci Lett. 2014; 578:165–70. [PubMed: 24996192]

270. Zhang Y, Zhen Y, Dong Y, Xu Z, Yue Y, Golde TE, Tanzi RE, Moir RD, Xie Z. Anesthetic propofol attenuates the isoflurane-induced caspase-3 activation and Abeta oligomerization. PLoS One. 2011; 6:e27019. [PubMed: 22069482]

271. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, Pidikiti R, Keller JM, Eckenhoff MF. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology. 2004; 101:703–9. [PubMed: 15329595]

272. Berger M, Nadler JW, Friedman A, McDonagh DL, Bennett ER, Cooter M, Qi W, Laskowitz DT, Ponnusamy V, Newman MF, Shaw LM, Warner DS, Mathew JP, James ML, team M-Pt. The Effect of Propofol Versus Isoflurane Anesthesia on Human Cerebrospinal Fluid Markers of Alzheimer's Disease: Results of a Randomized Trial. J Alzheimers Dis. 2016; 52:1299–310. [PubMed: 27079717]

273. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med. 2010; 363:2638–50. [PubMed: 21190458]

274. Fritz BA, Kalarickal PL, Maybrier HR, Muench MR, Dearth D, Chen Y, Escallier KE, Ben Abdallah A, Lin N, Avidan MS. Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium. Anesth Analg. 2016; 122:234–42. [PubMed: 26418126]

275. Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. BMC Anesthesiol. 2015; 15:61. [PubMed: 25928189]

276. Muhlhofer WG, Zak R, Kamal T, Rizvi B, Sands LP, Yuan M, Zhang X, Leung JM. Burst-suppression ratio underestimates absolute duration of electroencephalogram suppression

compared with visual analysis of intraoperative electroencephalogram. Br J Anaesth. 2017; 118:755–761. [PubMed: 28486575]

277. Deiner S, Luo X, Silverstein JH, Sano M. Can Intraoperative Processed EEG Predict Postoperative Cognitive Dysfunction in the Elderly? Clin Ther. 2015; 37:2700–5. [PubMed: 26621628]
278. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth. 2013; 110(Suppl 1):i98–105. [PubMed: 23539235]
279. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, Mears SC. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc. 2010; 85:18–26. [PubMed: 20042557]
280. Whitlock EL, Torres BA, Lin N, Helsten DL, Nadelson MR, Mashour GA, Avidan MS. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. Anesth Analg. 2014; 118:809–17. [PubMed: 24413548]
281. Berger M, Nadler J, Mathew JP. Preventing delirium after cardiothoracic surgery: provocative but preliminary evidence for bispectral index monitoring. Anesth Analg. 2014; 118:706–7. [PubMed: 24651223]
282. Whitlock EL, Villafranca AJ, Lin N, Palanca BJ, Jacobsohn E, Finkel KJ, Zhang L, Burnside BA, Kaiser HA, Evers AS, Avidan MS. Relationship between bispectral index values and volatile anesthetic concentrations during the maintenance phase of anesthesia in the B-Unaware trial. Anesthesiology. 2011; 115:1209–18. [PubMed: 22037642]
283. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, Zhou DW, Solt K, Brown EN. The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth. 2015; 115(Suppl 1):i46–i57. [PubMed: 26174300]
284. Ni K, Cooter M, Gupta DK, Sbahi F, Thomas J, Hopkins TJ, Miller T, James ML, Kertai MD, Berger M. A Paradox of Age: Older Patients receive higher age adjusted MAC values, yet display higher average BIS values. Anesthesiology. 2017 submitted.
285. Lee M, Curley GF, Mustard M, Mazer CD. The Swan-Ganz Catheter Remains a Critically Important Component of Monitoring in Cardiovascular Critical Care. Can J Cardiol. 2017; 33:142–147. [PubMed: 28024552]
286. Deiner SG. Optimizing Postoperative Cognition the Elderly. 2017. Clinicaltrials.gov, clinicaltrials.gov
287. Avidan M. ENGAGES study. 2015. clinicaltrials.gov
288. Short TG, Leslie K, Chan MT, Campbell D, Frampton C, Myles P. Rationale and Design of the Balanced Anesthesia Study: A Prospective Randomized Clinical Trial of Two Levels of Anesthetic Depth on Patient Outcome After Major Surgery. Anesth Analg. 2015; 121:357–65. [PubMed: 25993386]
289. Abu-Omar Y, Cader S, Guerrieri Wolf L, Pigott D, Matthews PM, Taggart DP. Short-term changes in cerebral activity in on-pump and off-pump cardiac surgery defined by functional magnetic resonance imaging and their relationship to microembolization. J Thorac Cardiovasc Surg. 2006; 132:1119–25. [PubMed: 17059932]
290. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, Consortium WU-MH. The WU-Minn Human Connectome Project: an overview. Neuroimage. 2013; 80:62–79. [PubMed: 23684880]
291. Raichle ME. The brain's default mode network. Annu Rev Neurosci. 2015; 38:433–47. [PubMed: 25938726]
292. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98:676–82. [PubMed: 11209064]
293. Huang H, Tanner J, Parvataneni H, Rice M, Horgas A, Ding M, Price C. Impact of Total Knee Arthroplasty with General Anesthesia on Brain Networks: Cognitive Efficiency and Ventricular Volume Predict Functional Connectivity Decline in Older Adults. J Alzheimers Dis. 2018; 62:319–333. [PubMed: 29439328]

294. Spreng RN. The fallacy of a “task-negative” network. Front Psychol. 2012; 3:145. [PubMed: 22593750]

295. Choi SH, Lee H, Chung TS, Park KM, Jung YC, Kim SI, Kim JJ. Neural network functional connectivity during and after an episode of delirium. Am J Psychiatry. 2012; 169:498–507. [PubMed: 22549209]

296. van Dellen E, van der Kooi AW, Numan T, Koek HL, Klijn FA, Buijsrogge MP, Stam CJ, Slooter AJ. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. Anesthesiology. 2014; 121:328–35. [PubMed: 24901239]

297. Giattino CM, Gardner JE, Sbahi FM, Roberts KC, Cooter M, Moretti E, Browndyke J, Mathew JP, Woldorff M, Berger M. Intraoperative Frontal Alpha-Band Power Correlates with Preoperative Neurocognitive Function in Older Adults. Frontiers in Cognitive Neuroscience. 2017 Under Review.

298. Vijayan S, Ching S, Purdon PL, Brown EN, Kopell NJ. Thalamocortical mechanisms for the anteriorization of alpha rhythms during propofol-induced unconsciousness. J Neurosci. 2013; 33:11070–5. [PubMed: 23825412]

299. Sanders RD. Hypothesis for the pathophysiology of delirium: role of baseline brain network connectivity and changes in inhibitory tone. Med Hypotheses. 2011; 77:140–3. [PubMed: 21498007]

300. Shafi MM, Santarnecchi E, Fong TG, Jones RN, Marcantonio ER, Pascual-Leone A, Inouye SK. Advancing the Neurophysiological Understanding of Delirium. J Am Geriatr Soc. 2017

301. Anguera JA, Boccanfuso J, Rintoul JL, Al-Hashimi O, Faraji F, Janowich J, Kong E, Larraburo Y, Rolle C, Johnston E, Gazzaley A. Video game training enhances cognitive control in older adults. Nature. 2013; 501:97–101. [PubMed: 24005416]

302. Vonck K, Raedt R, Naulaerts J, De Vogelaere F, Thiery E, Van Roost D, Aldenkamp B, Miatton M, Boon P. Vagus nerve stimulation… 25 years later! What do we know about the effects on cognition? Neurosci Biobehav Rev. 2014; 45:63–71. [PubMed: 24858008]

303. Nilakantan AS, Bridge DJ, Gagnon EP, VanHaerents SA, Voss JL. Stimulation of the Posterior Cortical-Hippocampal Network Enhances Precision of Memory Recollection. Curr Biol. 2017; 27:465–470. [PubMed: 28111154]

304. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, Hermiller MS, Voss JL. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science. 2014; 345:1054–7. [PubMed: 25170153]

305. Stephens JA, Berryhill ME. Older Adults Improve on Everyday Tasks after Working Memory Training and Neurostimulation. Brain Stimul. 2016; 9:553–9. [PubMed: 27178247]

306. Masana MF, Koyanagi A, Haro JM, Tyrovolas S. n-3 Fatty acids, Mediterranean diet and cognitive function in normal aging: A systematic review. Exp Gerontol. 2017; 91:39–50. [PubMed: 28213052]

307. Culley DJ, Crosby G. Prehabilitation for Prevention of Postoperative Cognitive Dysfunction? Anesthesiology. 2015; 123:7–9. [PubMed: 26001030]

308. Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M. Impact of Preoperative Environmental Enrichment on Prevention of Development of Cognitive Impairment following Abdominal Surgery in a Rat Model. Anesthesiology. 2015; 123:160–70. [PubMed: 26001032]

309. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, Cherubini A, Jones C, Kehlet H, MacLullich A, Radtke F, Riese F, Slooter AJ, Veyckemans F, Kramer S, Neuner B, Weiss B, Spies CD. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017; 34:192–214. [PubMed: 28187050]

310. Ely EW. The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. Crit Care Med. 2017; 45:321–330. [PubMed: 28098628]

311. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, Longrois D, Strom T, Conti G, Funk GC, Badenes R, Mantz J, Spies C, Takala J. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med. 2016; 42:962–71. [PubMed: 27075762]

312. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM Jr. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999; 340:669–76. [PubMed: 10053175]

313. Stiegler MP, Tung A. Cognitive processes in anesthesiology decision making. Anesthesiology. 2014; 120:204–17. [PubMed: 24212195]

314. Fleisher LA. Brain Health Iniative: A New ASA Patient Safety Initiative. ASA Monitor. 2016; 80:10–11.

Summary Statement

Postoperative delirium and cognitive dysfunction occur frequently after cardiac surgery, and are associated with decreased quality of life and increased mortality risk. This review discusses the potential mechanisms that may underlie these complications, and questions for future study.

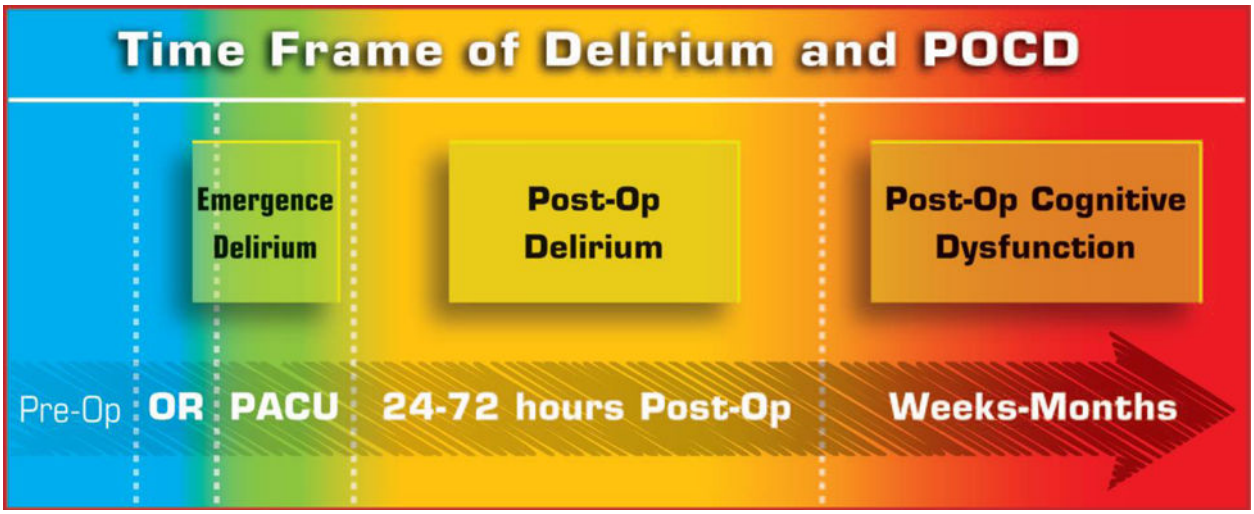

Figure 1.

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 24–72 h after surgery. POCD is measured at weeks to months after surgery and anesthesia. Pre-Op= preoperative. Reproduced from Silverstein J *et al.*[101]

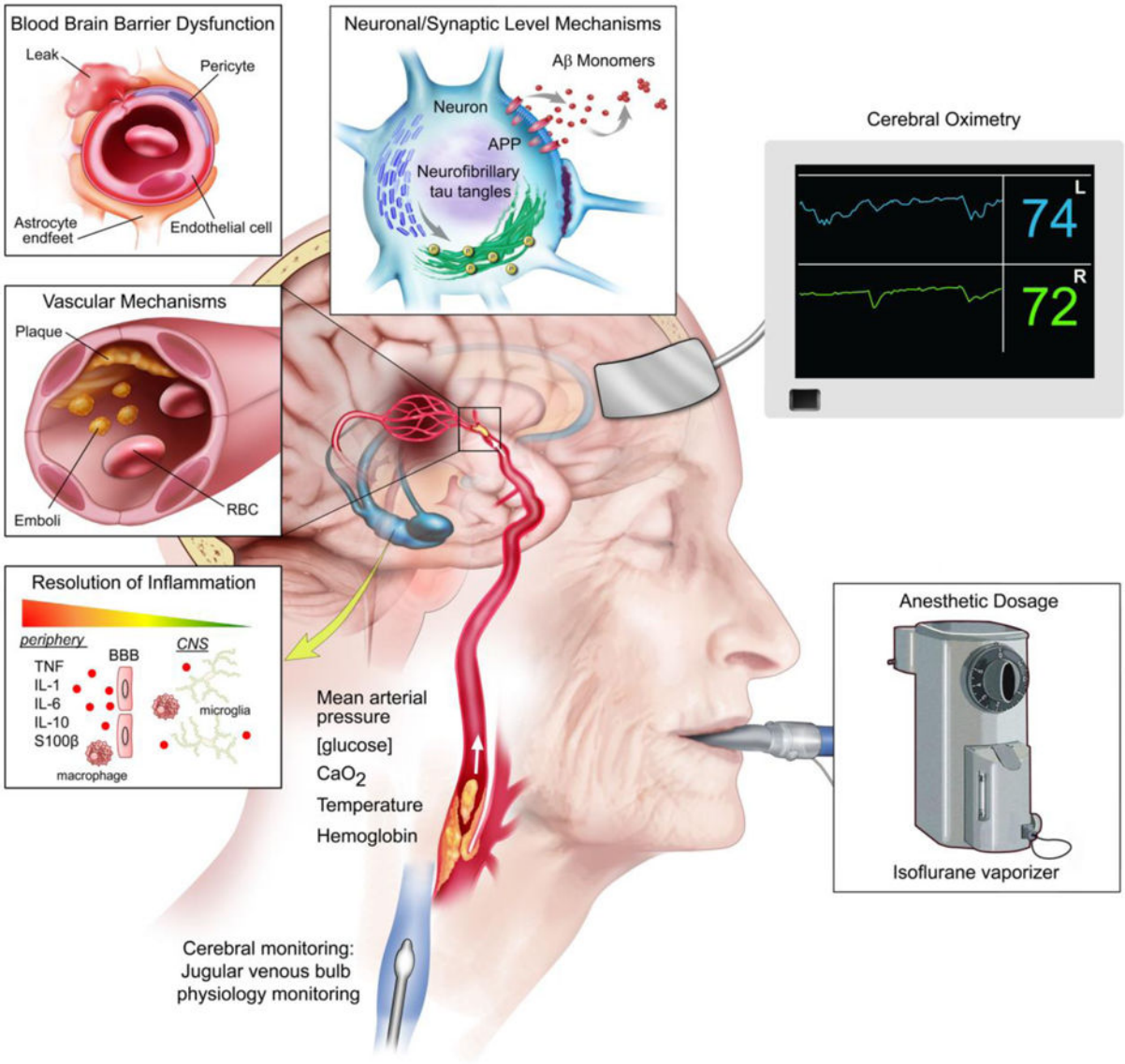

Figure 2.

Pathophysiologic Mechanisms That May Play a Role in Postoperative Cognitive Dysfunction and/or Delirium. Starting from the top, in clockwise order the pullout boxes represent cellular/molecular and synaptic mechanisms (such as AD-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. Additional physiologic variables that may be involved in POCD and delirium are listed in free text.

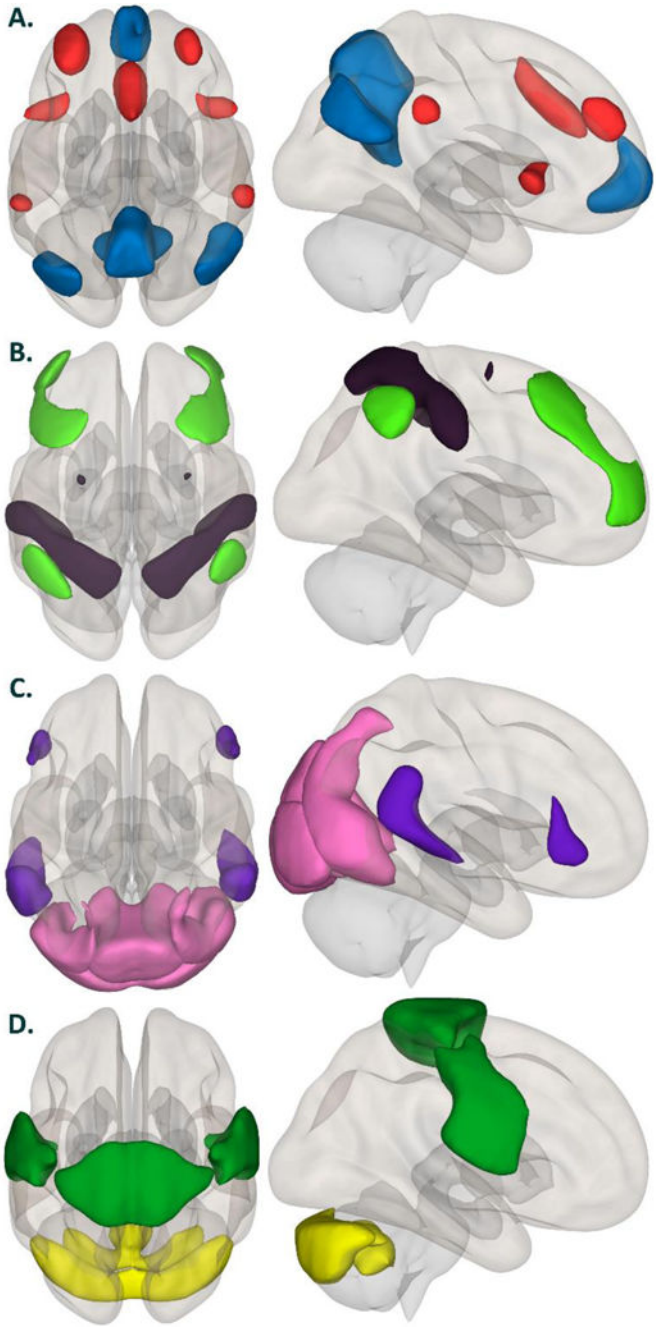

Figure 3.

Functionally Connected Networks in the Human Brain. These functional brain network region of interest (ROI) maps were derived from independent components analysis (ICA) of low-frequency BOLD fMRI data from the Human Connectome Project dataset (n = 497).[290] ***A)*** default mode network ROIs (blue), salience network ROIs (red); ***B)*** Dorsal attention network ROIs (black), frontoparietal network ROIs (light green); ***C)*** Language network ROIs (purple), visual network ROIs (pink); and ***D)*** Cerebellar network ROIs (yellow),

sensorimotor network ROIs (green). Abbreviations: ROIs = Regions of Interest, BOLD = Blood Oxygen Dependent Signal, fMRI = functional magnetic resonance imaging.

Table 1

Modifiable, partly modifiable, and non-modifiable factors that may contribute to postoperative delirium and/or POCD after cardiac surgery. The degree to which these factors can be modified in a real-world setting is beyond this article's scope. Selected references are listed below, please see the body of the article for additional references and discussion.

	Pre-/Post-operative	**Intraoperative**
Modifiable	1. Preoperative blood pressure control[23] 2. Preoperative glycemic control[23,76] 3. Sleep disruption[25]/sleep apnea[24] 4. Alcohol Abuse[21,22] 5. Postoperative sedation, analgesia and delirium management[309-311]	1. Use of cardiopulmonary bypass[234-237] 2. Temperature management[214-219,221,222] 3. Surgery duration[76] 4. Arterial pressure management[193,194,196] 5. Glycemic control[228,230,232,233] 6. Hemodilution[73]
Partly modifiable	1. Patient frailty[28] 2. Preoperative cognitive function[29,47] 3. Preoperative neurocognitive reserve[26,27] 4. Depression[72,76,77]	1. Surgical approach (i.e. median sternotomy vs lateral thoracotomy)[132-136], On vs Off CPB[75,234-237] 2. Anesthetic dosage[30,31] and EEG responses[280,281]
Non-modifiable	1. Patient chronological age[47,48]	1. Direct myocardial injury[136,137]

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 methods[304] or brain training approaches[301] improve these disorders?
6. Are delirium or POCD after cardiac surgery associated with a postoperative acceleration of Alzheimer's disease 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, pre-existing 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, etc) that would result in a greater reduction in POCD/delirium than single interventions?