Cerebral protection: inflammation, endothelial dysfunction, and postoperative cognitive dysfunction

Bernhard Riedel, Kimberley Browne, and Brendan Silbert

Purpose of review
Postoperative cognitive dysfunction (POCD) is a well recognized perioperative syndrome, with approximately 15% of patients over the age of 60 years displaying objectively measured decrease in cognitive function as a consequence of anesthesia and surgery. The exact cause, however, remains unknown. This review aims to update anesthesiologists on the recent advancements in the understanding of the pathophysiology of POCD.

Recent findings
Recent evidence suggests that the observed predilection to POCD is likely mediated by a neuro-inflammatory response – with surgery being a major contributing factor. The blood–brain barrier, a highly specialized endothelial layer, is exquisitely sensitive to an inflammatory insult and implicated in the cause of other neurocognitive syndromes also characterized by neuro-inflammation such as cerebral malaria. Inflammatory changes may disrupt the blood–brain barrier and facilitate migration of macrophages into the brain, damaging synapses and neurones and ultimately lead to POCD. This review explores the important question of causality – the potential relationship between inflammation, endothelial dysfunction, and postoperative cognitive decline.

Summary
Recent research points to a central role of a neuro-inflammatory cascade in POCD, with endothelial dysfunction potentially aggravating the insult. Investigating the genomic and molecular mechanisms that underlie the intervarition in the inflammatory response to surgery, improving the identification of appropriate endothelial and inflammatory biomarkers, and developing endothelial modulatory and anti-inflammatory (prevention and resolution) strategies are key areas of future translational research. This is important as the elderly, who show increased susceptibility to this and other perioperative illness syndromes, represent an ever-increasing proportion of patients presenting for surgery.

Keywords
endothelial dysfunction, postoperative cognitive dysfunction, neuro-inflammation

INTRODUCTION
Although postoperative cognitive dysfunction (POCD) is a well recognized perioperative syndrome, a consequence of anesthesia and surgery, the exact cause remains unknown. Approximately 15% of patients over the age of 60 years will display objectively measured decreases in cognitive function after anesthesia and surgery and that, in common with cognitive decline in community studies, the incidence increases with age and is somewhat protected by higher intelligence and education [1]. We also know that POCD not only follows cardiac surgery, but also persists after noncardiac surgery [2], and may even be the consequence of minor noninvasive procedures under sedation.

These observations have altered our thinking regarding the cause of POCD. Thus, cardiopulmonary bypass (CPB), long held to be an important element of POCD, can no longer be held
accountable. This was highlighted by van Dijk et al. [3] who demonstrated that the incidence of POCD was the same for off-pump as for on-pump surgery, these findings have since been confirmed by others [4]. A review on the aspects of CPB on neurological dysfunction by Hogue et al. [5] failed to implicate any particular component of CPB in POCD. In particular, microemboli now appear to be highly unlikely candidates as a cause of POCD [6,7].

It is important that we address the cause of POCD, especially since the elderly, who show increased susceptibility to this and other perioperative syndromes, represent an ever-increasing proportion of patients who present for surgery. Although anesthesia is often implicated as a major contributor to POCD, it is relevant to realize that in the clinical situation, surgery or at least some invasive procedure usually accompanies anesthesia. Even for clinical research purposes, it is difficult to administer one without the other. Thus, although anesthesia is often implicated on the basis of circumstantial evidence, the contribution of surgery itself cannot be discounted.

To separate the contribution of anesthesia and surgery toward POCD development, researchers have turned to animal models. Although there is experimental animal evidence that anesthetic agents may contribute to cognitive decline, there are also animal studies that implicate surgery as a major mechanism in the cause of POCD. Cibelli et al. [8], measuring memory function in mice, compared fear conditioning in three groups: surgery and anesthesia combined (tibial fracture of the hind-paw and open intramedullary fixation under general anesthesia), anesthesia alone, and control animals. The surgery group displayed memory impairment that was not evident in either the anesthesia alone or control animal groups.

**MECHANISMS OF POSTOPERATIVE NEUROCOGNITIVE DYSFUNCTION: THE ROLE OF SYSTEMIC INFLAMMATION**

The mechanism for the observed predilection to POCD in the surgical mouse model appears to be mediated by the inflammatory response. In the aforementioned study, Cibelli et al. [8] reported that plasma proinflammatory cytokines, interleukin (IL)-1β and IL-6, peak at 6 h after surgery, increasing by seven-fold and 20-fold, respectively, compared with the baseline levels and remained elevated 24-h postoperatively. The anesthesia alone and control animal groups showed no change in cytokine levels at any time point. Preoperative administration of minocycline (an antibiotic with anti-inflammatory properties) reduced cytokine levels to presurgery levels with consequent abolition of memory impairment. Similar reversal of memory impairment after surgery was also evident after treatment with interleukin antagonists.

Eckenhoff and Laudansky [9] proposed that anesthesia and surgery exert an effect on the central nervous system (CNS) via a burst of inflammatory mediators (typically TNF-α, IL-1β, and IL-6, and muted anti-inflammatory responses from IL-4, IL-10, and TGFβ), which communicate with the CNS by vagal afferents and by crossing the blood–brain barrier (Fig. 1). The result is an exaggerated and detrimental neuro-inflammatory response which may damage synapses and neurones, and ultimately lead to POCD [9]. Terrando et al. [10] highlighted this mechanism of neuroinflammation as a consequence of the systemic inflammatory response, demonstrating that peripheral surgery disrupts the blood–brain barrier via release of TNF-α. This facilitates the migration of macrophages into the hippocampus. Further studies have shown that TNF-α initiates a peripheral cytokine cascade resulting in NF-κB-mediated cognitive decline and that prophylaxis with antitumor necrosis factor (TNF) antibody attenuates these inflammatory pathways [11].

These animal experiments also support observations on the microglial priming hypothesis [12], which maintains that microglia in the diseased or aged brain are ‘primed’ by chronic, smouldering subclinical neurodegeneration and switch their phenotype to produce neurotoxic molecules in response to systemic inflammatory signals [13]. In the diseased brain, systemic inflammation thus leads to an exaggerated inflammatory response, resulting in increased neurodegeneration through...
expression and transcription of inflammatory factors by brain microglia. Lipopolysaccharide (LPS), a bacterial endotoxin, produces exaggerated behavioral responses and increased CNS cytokines in a neurodegenerative mouse model compared with controls [14]. Brain microglia are activated by LPS-induced peripheral inflammation to produce chronically elevated inflammatory factors, with TNF-α playing a key role in the transmission [15]. In these mouse models, LPS challenges initiate increased cytokine transcription [16], exacerbate CNS inflammation, and increase tau phosphorylation [17]. Eckenhoff and Laudansky [9] has likened this to a mine which has been fused and is lying in wait. The trigger for this ‘mine’ is the occurrence of an acute inflammatory episode that follows infection, major illness, or anesthesia and surgery. Further research is required as to how chronic low-grade inflammatory disease, harbored by many elderly and manifesting as diabetes, atherosclerosis, hypertension, etc., may relate to this priming hypothesis and fuel POCD. Another clinical example is seen in cirrhotic liver disease, in which patients with hepatic encephalopathy (compared with patients without encephalopathy) exhibit an altered intestinal microbiome, endotoxemia, and increased inflammation [18].

Proinflammatory cytokines, traditionally thought of as signaling molecules of the inflammatory immune system, are interestingly also endogenously produced in the brain and might interact with the growth factors, thereby influencing the neuronal and synaptic growth as well as neural plasticity.

Spurred by the limited success achieved with pharmacological strategies aimed at altering the monoamine availability, researchers are now exploring a possible role for proinflammatory cytokines and growth factors in major depression [19]. Such cytokines and growth factors might be useful biomarkers for individualized treatments of depressive illnesses, POCD and other perioperative syndromes including acute kidney injury, in which great interindividual variability in the inflammatory response and subsequent oxidative stress occur in response to surgical insult.

**MEASUREMENT OF PERIOPERATIVE SYSTEMIC INFLAMMATION**

Research on the stress response to surgery has typically focused on the hormonal response (growth hormone and thyroid hormones, pituitary-adrenal axis, vasopressin, and prolactin) [20]. This research has been concerned with metabolism, gluconeogenesis, protein synthesis, catabolism, and regional blood flow and less on the immunologic consequences of inflammation. The emerging role of inflammatory mediators as a key instigator of POCD indicates that this avenue of investigation may improve our understanding of the cause, prevention, and treatment of POCD.

The anesthesia-surgical process is an acute, predictable initiator of inflammation; yet, descriptions
of the changes in levels of peripheral inflammatory markers after surgery are fragmented. Reports of changes in IL-6 after surgery appeared as early as 1992, with an increase in IL-6 levels associated with poor postoperative outcome [21,22]. In cardiac surgery, Parolari et al. [23] compared the inflammatory response between on-pump and off-pump surgery. They reported that TNF-\(\alpha\) and IL-6 increased in both groups from protamine administration up to 8 days following surgery, whereas C-reactive protein (CRP) and fibrinogen did not rise until after surgery but then remained elevated for 8 days. In orthopedic surgery, IL-6 and CRP have been shown to increase after surgery [24], with these increases occurring regardless of whether spinal anesthesia or general anesthesia is administered [25], thereby abrogating the part played by general anesthesia in the inflammatory response.

The magnitude of the inflammatory response may be an important factor in POCD. A study investigating the relationship between early postoperative serum CRP levels, as a marker of systemic inflammatory response, and 2-year neurodevelopment-associated outcomes among survivors undergoing the Norwood procedure reported that both cognitive and language scores significantly and negatively correlated only with peak CRP level [26]. This underpins the impact of magnitude of systemic inflammatory response on postoperative cognitive function in susceptible brains. As such, future studies on postoperative organ dysfunction are required to delineate the impact of interindividual differences (high versus low inflammatory phenotype) and consequent magnitude of the oxidative stress in response to surgery.

Although the inflammatory process resulting from surgery and anesthesia can be tracked over time by serial measurements of inflammatory mediators, this requires serial blood sampling and analysis for many different proteins that play an interrelated part in inflammation and innate immunity. A practical alternative is to use endothelial function as a proxy for the inflammatory cascade.

### PERIOPERATIVE ENDOTHELIAL (DYS)FUNCTION AND POSTOPERATIVE NEUROCOGNITIVE DYSFUNCTION

Interestingly, risk factors are similar for cardiovascular disease and neurocognitive dysfunction. Both disease states are underpinned by an inflammatory process, with endothelial dysfunction likely playing a central role in the pathogenesis of each.

The endothelium, a delicate monolayer of cells lining all the blood vessels, is a highly responsive sensor-effector organ. Through the secretion of a multitude of mediators, the endothelium controls vascular tone, interacts with the inflammatory-coagulation cascades, promotes antiaggregation, regulates immune cellular trafficking, and is crucial to angiogenesis [27\(*\)]. In brief, the endothelium is a major determinant of vascular homeostasis. It is easily damaged by intrinsic and extrinsic factors, and given its low proliferative potential and limited capacity for self-repair, is dependent on circulating bone-marrow-derived endothelial progenitor cells for regeneration [27\(*\)].

Endothelial dysfunction has been implicated as a central pathophysiological feature in a number of disease states. It is one of the earliest events in the pathophysiological process leading to atherosclerotic vascular disease, is identified as a central component in the pathogenesis of disease states such as diabetes mellitus and sepsis [28,29], and is increasingly associated with postoperative morbidity [30,31\(*\)].

Endothelial cell functions are sensitive to noxious stimuli [32], many of which are common to the perioperative period, including hypoxia (e.g., ischemia–reperfusion injury), exposure to endotoxins, inflammatory cytokines, various microparticles, and through direct injury from surgical manipulation or hemodynamic shear stress (Fig. 2). Injury alters the endothelial phenotype (with loss of the ability to synthesize and release mediators, e.g., nitric oxide), tipping the balance of endothelial-derived factors to disrupt barrier function, enhance vasoconstriction, coagulation and leukocyte adhesion, and promote smooth muscle cell proliferation. These responses to injury are likely to exist as protective mechanisms. However, if the underlying basal endothelial reserve is limited, the injury severe or persistent, or the host response exaggerated, then the altered phenotype may result in barrier disruption. This results in a loss of circulatory homeostasis, reduced tissue oxygen supply and end-organ dysfunction, and culminates in an increased risk of perioperative illness syndromes, including POCD.

The endothelium acts as the selective barrier between the vessel lumen and the interstitial space. In the brain specifically, structural and functional alterations of blood–brain barrier endothelial cells have been associated with increased microvascular permeability and impaired microcirculation in inflammatory and infectious disease states. Terrando et al. [10] highlighted that neuroinflammation as a consequence of the systemic inflammatory response (e.g., after peripheral surgery) disrupts the blood–brain barrier to facilitate the migration of macrophages into the CNS.
In the recent research conducted in the critically ill patient population, Hughes et al. [33] reported a negative association between systemic endothelial function and intensive care associated delirium. This prospective study of 140 critically ill patients reported that those with lower vascular reactivity [as measured by peripheral artery tonometry (PAT)], and indicative of worse systemic endothelial function, had increased duration of acute brain dysfunction. These findings may result directly from altered microvascular vasomotor function, with altered blood–brain barrier permeability. This reduced blood flow and increased permeability may increase neuronal inflammation and tissue damage, modulating the synthesis of neurotransmitters and altering the expression of neurotransmitter receptors.

The aforementioned study raises the important question of causality – the potential relationship between inflammation, endothelial dysfunction, and postoperative cognitive decline. Pre-existing (basal) endothelial dysfunction may predispose or ‘prime’ the blood–brain barrier to greater insult from the inflammatory cascade. Alternatively, deterioration in endothelial function may be an epiphenomenon of the inflammatory and innate immune process, similar to that which is seen in sepsis (which represents the archetypical inflammatory stimulus and also leads to endothelial dysfunction) [34]. It is not entirely clear whether endothelial dysfunction in the perioperative setting is ‘cause and effect’ from the circulating inflammatory insult or from a pre-existing inflammatory state attributed to comorbidities such as obstructive sleep apnea [35], diabetes mellitus [29] or cardiovascular disease [36], or a combination.

Extrapolation of these findings in critically ill patients to the perioperative inflammatory insult suggests that the ability to measure systemic endothelial function may provide indirect information on blood–brain barrier function and the magnitude of the deleterious perioperative inflammatory
process. Both these processes have the potential to produce downstream effects on cerebral function.

Elucidation of this answer proposes that the measurement of endothelial function in the perioperative period may prove to be a useful resource in both predicting those patients who may be susceptible to cognitive decline after surgery and in tracking the endothelial changes in this period. Although a single preoperative measurement may be predictive, serial measurements may likely be more useful in tracking acute endothelial decline, especially in high-risk patients such as those with diabetes or cardiovascular disease. Hu et al. [37] prospectively evaluated 106 patients undergoing abdominal surgery under general anesthesia and measured endothelial function longitudinally over the course of the perioperative period. Endothelial function was significantly lower postoperatively, with recovery to baseline values only occurring by day 7 postoperatively. Patients undergoing laparoscopic surgery had less impairment than those undergoing laparotomy, consistent with reduced inflammatory response, and potential cardiovascular and neurocognitive benefit.

### Measurement of Perioperative Endothelial Function

The complexity of the endothelium’s multitude of activities is reflected in the relative difficulty to track and monitor its function. Research on perioperative endothelial biomarkers (e.g., endothelial microparticles) is in its infancy and is complicated by the large number of extrinsic and intrinsic factors contributing to measured levels of these biomarkers. No one single blood measurement exists to reflect endothelial function alone. Hence, indirect assessment of endothelial function through examination of endothelial vasodilator influences in response to hyperemia-induced shear stress is commonly used [38]. Options for measuring reactive hyperemia include PAT, brachial artery reactivity testing (BART), and digital thermal monitoring (DTM). None of these tests is perfect in its ability to measure endothelial function and the logistical applicability from the research setting to the perioperative environment often proves less than ideal.

The EndoPAT (Itamar Medical Ltd, Franklin, Massachusetts, USA) device as used by Hughes et al. [33] in their ICU study of delirium has the advantages of being portable and less operator dependent than BART that requires a vascular ultrasound laboratory and expertise to measure flow-mediated dilatation (FMD). The EndoPAT technique, based on a system of inflatable latex air cuffs placed on the middle finger, measures hyperemia-induced peripheral vasodilator response using fingertip pulse amplitude tonometry for noninvasive assessment of microvascular function [39]. Impairment of pulse amplitude hyperemic response has been demonstrated among patients with coronary artery endothelial dysfunction [40] and those with multiple traditional metabolic risk factors [41]. Although its validity varies in different clinical settings, it holds promising potential use in the perioperative period. It remains contentious whether predominantly microvascular hyperemic responses, as measured at the fingertip by DTM or EndoPAT techniques, correlate with the gold standard of BART FMD, a macrovascular measure. One study investigated pulse waveform analysis and refuted the claims that large (macrovascular) and small (microvascular) arterial stiffness are substitute measures for sonographic assessments of brachial FMD [42]. Moreover, large clinical trials are yet to investigate whether either of these noninvasive techniques are a useful clinical tool – to refine preoperative patient risk assessment and care.

### Potential Perioperative Strategies

If indeed POCD results from the inflammatory process and associated endothelial dysfunction, then the magnitude and incidence may vary depending on both the extent of the inflammatory process and the susceptibility of each patient. These are impacted upon by factors such as the degree of surgical insult, the magnitude of inflammatory response, genetic polymorphisms [43], underlying (basal) endothelial function, and microglial priming.

The relationship between endothelial dysfunction and postoperative morbidity has been established, with measures of endothelial dysfunction improving risk prediction for adverse postoperative events after vascular surgery [30] and thoracic [31] surgery. To our knowledge, data describing such a relationship between systemic endothelial dysfunction and POCD is lacking, but is supported by the recent findings in critically ill patients.

Currently, there is limited human data on the relationship between the levels of inflammatory mediators and POCD. Increases in IL-6, IL-10, and CRP were higher in patients undergoing open colonic resection compared with laparoscopic resection [44]. Similar results implicating the degree of surgical stress were also observed when unilateral knee arthroplasty showed a smaller rise in IL-6 than bilateral knee arthroplasty [45]. Hudetz et al. [46] measured IL-6 and CRP during coronary artery bypass grafting surgery and found that cognitive decline was associated with increased levels of these mediators. Susceptibility to POCD may vary with...
age and the intrinsic state of microglia. For example, Alzheimer’s disease, even in the preclinical form, may be associated with an ongoing inflammatory process in the microglia, which would lead to cognitive vulnerability [47]. In contrast, some patients may already have an ongoing inflammatory process in the periphery (e.g., metabolic syndrome and atherosclerosis), which are known to be associated with elevated inflammatory mediators, likely contributing to POCD through the microglial priming hypothesis.

Given the mounting evidence that inflammatory mediators have a central action in POCD, it behoves us as anesthesiologists to understand the inflammatory processes in our patients, how it may change in response to surgery, what molecular mechanisms lead to cognitive dysfunction, and what strategies can be used to reduce the inflammatory response. The importance of understanding the surgical inflammatory response is further highlighted in the developing field of oncoanesthesiology, in which anesthesia technique and perioperative strategies, potentially including anti-inflammatory strategies, may impact early risk of recurrence during the first two postoperative years after cancer surgery [48–51]. Inflammatory mediators [including prostan-95aldins (PGEs) and growth factors], involved in tissue injury and postoperative wound healing, may mediate lymphovascular angiogenesis and lympathic dilation, and thereby potentially mediate metastatic progression [52–55].

This bidirectional communication between the brain and immune system following surgery identifies pivotal molecular mechanisms that can be targeted to prevent and resolve postoperative neuroinflammation and cognitive decline. Broad strategies may include reducing the inflammatory response after surgery by optimizing fluid replacement [56] or administration of anti-inflammatory adjuncts such as statins [57]. More targeted strategies in the future may pursue three key areas: blocking the inflammatory response, promoting resolution of the inflammatory response, or stabilization of the endothelial blood–brain barrier.

**Blocking the inflammatory response**

Using a mouse model of surgery-induced cognitive decline, Vacas et al. [58**] clearly demonstrated the importance of the following therapeutic targets: tissue trauma, damage-related signaling (alarmins), cytokine cascade, chemoattractant neural signaling, and bone-marrow-derived mobilization of phagocytes. They reported that alarmins (a group of damage-related proteins), especially high-mobility group box 1 protein (HMGB1), an ubiquitous nucleosomal protein, are released by surgical trauma into the circulation and independently activate the inflammatory response, promoting cytokine expression and chemoattractant (CMP-1) expression in the hippocampus of the brain. The latter promotes neuroinflammation through activation and trafficking of circulating bone-marrow-derived macrophages to the brain. They reported that therapeutic strategies targeting HMGB1 (antibodies) and depletion of bone-marrow-derived macrophages reduced the magnitude of cognitive decline in this surgical mouse model.

**Resolving the inflammatory response**

Resolvins are potent endogenous lipid mediators biosynthesized during the resolution phase of acute inflammation that displays immunoresolvent actions. Using a mouse model of surgery-induced cognitive decline, Terrando et al. [59*] demonstrated that systemic prophylaxis with aspirin-triggered resolvin D1 modulated a proinflammatory milieu, with abolished signs of synaptic dysfunction and improved memory decline following surgery. Delayed therapy, 24 h after surgery, also attenuated the signs of neuronal dysfunction postoperatively.

**Stabilizing the endothelial blood–brain barrier**

In a mouse model of cerebral malaria, postcapillary venules (but not capillaries or arterioles) exhibited platelet marginalization, extravascular fibrin deposition, CD14 expression, and extensive vascular leakage [60**]. Blockage of LFA-1-mediated cellular interactions prevented leukocyte adhesion, vascular leakage, neurological signs, and death from cerebral malaria. Endothelial barrier-stabilizing mediators (Imatinib and FTY720) inhibited vascular leakage and neurological signs, and prolonged survival to cerebral malaria. Thus, it appears that neurological signs and coma in cerebral malaria are due to regulated opening of paracellular–junctional and transcellular–vesicular fluid transport pathways at the neuroimmunological blood–brain barrier. This study highlights the importance of endothelial stabilization and blood–brain barrier integrity in preventing inflammation/infection induced brain injury.

**CONCLUSION**

In the perioperative setting, assessment of endothelial dysfunction may not only be an indirect measure of systemic inflammation, but also has the potential to indicate susceptibility of brain dysfunction, including POCD and even delirium. Further translational research into the genomic and molecular mechanisms that underlie the
intervention in the inflammatory response to surgery, the pathogenesis of POCD as a perioperative syndrome, improved identification of appropriate endothelial and inflammatory biomarkers, and the development of endothelial modulatory and anti-inflammatory strategies represent the future fields of investigation.

Acknowledgements
B.R. was a past recipient of an International Anesthesia Research Society – Clinical Scholar Research Award to study the ‘Perioperative Endothelial Kinetics – An Outcome Predictor Following Major Surgery’.

Conflicts of interest
B.R. serves on the Scientific Advisory Board, Critical Care, Edwards Life Sciences Inc. For the remaining authors, none were declared.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest


A review of the perioperative implications of endothelial dysfunction.

This study demonstrates that poor baseline endothelial function associates with increased risk for postoperative complications after noncardiac surgery.

This study demonstrates an association between endothelial dysfunction and acute brain dysfunction after critical illness.

This longitudinal study of endothelial function during the perioperative period demonstrates the delayed recovery of endothelial function after surgery.


57. Animal experiments, which demonstrate that alarmins (damage-associated molecules) independently trigger neuro-inflammation, promote chemokine expression by brain tissue, and macrophage infiltration into the brain tissue. This research identifies potential therapeutic targets to prevent neuro-inflammation.

58. Animal experiments that implicate the potential role for resolution of the inflammatory process in preventing cognitive dysfunction after surgery.

59. Animal experiments that implicate endothelial dysfunction in cerebral malaria and draw attention to the potential therapeutic role of endothelial-stabilizing strategies.