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Emboli, Inflammation, and CNS Impairment: An Overview

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ABSTRACT

Perioperative stroke occurs in 2-3% of adult cardiac surgery patients, and significant cognitive dysfunction is experienced by 40-60% of patients in the first postoperative week. Perioperative neurocognitive abnormalities are associated with a greatly increased risk of perioperative mortality, lengthy intensive care and hospital stay, and more intensive rehabilitative care. Long-term cognitive dysfunction, ranging from months to years, occurs in 25-40% of adult cardiac surgery patients, resulting in a decreased quality of life.

Cerebral emboli are an important cause of perioperative neurocognitive abnormalities. Aortic cannulation, clamping, and manipulation during surgery may dislodge atheromatous materials into the cerebral circulation, leading to perioperative or postoperative stroke. Nevertheless, acute and chronic neurocognitive dysfunction frequently occurs in non-cardiac surgery patients as well, suggesting that some element of surgery and/or anesthesia *itself* causes or contributes to this phenomenon.

One possible cause may be central nervous system (CNS) responses to peripheral tissue injury or inflammation. The CNS is sensitive to systemic pro-inflammatory mediators such as endotoxin and the cytokines interleukin-6 and interleukin-8, which are activated by surgical trauma. This article discusses the behavior and effects of these inflammatory agents and their intensification in combination with postoperative hyperthermia. The potential beneficial role of pharmacological agents such as heparin, lidocaine, and aprotinin is also examined.

BACKGROUND

Perioperative stroke occurs in 2-3% of adult cardiac surgery patients [Almassi 1999, Hogue 1999, John 2000]. In addition, 40-60% of patients experience significant cognitive dysfunction in the first postoperative week [Neville 2001, Newman 2001b]. Perioperative neurocognitive abnormalities are associated with a five- to ten-fold increase in perioperative mortality, a three- to four-fold increase in intensive care and/or hospital stay, and a four- to five-fold increase in rehabilitative care [Roach 1996, Almassi 1999, Hogue 1999, John 2000]. Long-term cognitive dysfunction, ranging from months to years, occurs in 25-40% of adult cardiac surgery patients [van Dijk 2000, Newman 2001b] and is associated with a decreased quality of life [Newman 2001a].

DISCUSSION

Cerebral emboli are an important cause of perioperative neurocognitive abnormalities. Transcranial Doppler studies demonstrate that hundreds of cerebral emboli can occur during cardiac surgery [Barbut 1994, Pugsley 1994, Neville 2001]. Greater numbers of cerebral emboli are associated with a greater incidence of postoperative neurocognitive abnormalities [Barbut 1994, Pugsley 1994, Hammon 1997, Sylivris 1998, Diegeler 2000]. At least three types of cerebral emboli occur during cardiac surgery: atheroma [Blauth 1992], gas or air [Pugsley 1994, Borger 2001], and lipid [Brooker 1998, Brown 1999, Brown 2000]. Atherosclerosis of the ascending aorta/arch is one of the most significant risk factors for perioperative stroke [Roach 1996, Hogue 1999, John 2000]. With aortic cannulation and clamping, atheromatous debris can be dislodged into the systemic and cerebral circulations [Barbut 1996]. Aortic manipulations also contribute to postoperative stroke [Ura 2000]. Although not established by randomized trials, techniques that decrease disruption of aortic atheroma (epiaortic scanning, alternative clamp and graft sites) appear to decrease perioperative neurocognitive abnormalities [Duda 1995, Hammon 1997, Royse 2000]. The nature and severity of neurologic injuries from other types of emboli are less well characterized. Although microscopic gas emboli can contribute to postoperative cognitive dysfunction [Pugsley 1994, Borger 2001], in some studies they appear to have minimal adverse effect [Grocott 1998, Sylivris 1998, Neville 2001]. The apparent tolerance to microscopic gas emboli may be due, in part, to the fact that heparin is protective in air embolism models [Ryu 1996]. Lipid emboli, originating from cardiotomy blood [Brooker 1998], cause formation of small capillary and arteriolar dilations (SCADs) [Brooker 1998, Brown 1999, Brown 2000]. Although pathologic studies do not show extensive brain injury to be associated with SCADs [Brown 1999], animal models indicate that fat emboli result in acute blood-brain barrier dysfunction [Drew 1998]. Gas and lipid microemboli almost certainly contribute to neurocognitive dysfunction associated with cardiac surgery.

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Nevertheless, emboli are probably not the whole story. Techniques that decrease cerebral blood flow during cardiopulmonary bypass (CPB) would be expected to decrease brain embolic burden and to consistently improve neurocognitive outcomes. They do not. In patients undergoing valve replacement, propofol-induced electroencephalographic burst suppression did not improve acute or chronic neurocognitive outcomes [Roach 1999]. Likewise, in patients undergoing coronary artery bypass (CAB), neurocognitive outcomes did not differ between hypothermic and normothermic CPB [Grigore 2001]. Even avoiding CPB altogether, which should virtually eliminate both gas and lipid microemboli, does not significantly decrease chronic cognitive dysfunction when compared to a CPB-based technique [van Dijk 2002]. There must be something in addition to emboli that contributes to postoperative cognitive dysfunction. In fact, cognitive dysfunction also occurs after *non*-cardiac surgery. In 1,218 patients undergoing thoracic, abdominal, or orthopedic surgery, 26% had cognitive dysfunction one week after surgery and 10% had cognitive dysfunction three months later [Moller 1998]. Perioperative hypotension and hypoxemia were not risk factors. Heyer *et al*. [Heyer 1995] and Murkin *et al*. [Murkin 1995] both observed that cardiac surgery patients had greater rates of neurocognitive abnormalities in the first week after surgery compared to non-cardiac surgery patients. However, when observed one to two months later, cardiac and non-cardiac surgery patients had equivalent rates of cognitive dysfunction. Thus, there is some element of surgery and/or anesthesia *itself* that results in, or contributes to, acute and chronic postoperative cognitive dysfunction—an element that is not unique to cardiac surgery.

One possibility may relate to central nervous system (CNS) responses to peripheral tissue injury and/or inflammation. Cardiac surgery and CPB are associated with complement and neutrophil activation, increased systemic concentrations of pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-8, and frequently endotoxemia [Hall 1997, Hill 1998]. Concentrations of these pro-inflammatory mediators vary greatly among individuals, probably on a genetic basis (*e.g*., E4 allele [Drabe 2001] or IL-6 gene variants [Burzotta 2001]). Although usually of lesser magnitude, many of these same systemic inflammatory mediators increase with non-cardiac surgery as well. IL-6 increases after all types of non-cardiac surgery [Reber 1998, Wiezer 1999, Bölke 2001] and appears to be a significant determinant of postoperative recovery [Hall 2001]. IL-8 increases after major intra-abdominal surgery [Wiezer 1999], and endotoxemia likewise commonly occurs during and after intra-abdominal surgery [Bölke 2001, Buttenschoen 2001]. Finally, complement activation occurs in response to surgical trauma in the absence of CPB [Gu 1999, Ascione 2000]. The CNS is sensitive to these systemic pro-inflammatory mediators.

In animals, systemic inflammatory mediators trigger extensive changes in CNS inflammatory gene expression, neurochemistry, neuroendocrine status, thermoregulation, behavior, and cognition [Dantzer 1998, Linthorst 1998, Brebner 2000]. For example, systemic inflammatory mediators trigger expression of IL-1([Wong 1996, Turrin 2001], IL-6 [Vallières 1999], tumor necrosis factor-alpha (TNFα) [Turrin 2001], complement components [Nadeau 2001], inducible cyclooxygenase (COX-2) [Lacroix 1998], and inducible nitric oxide synthase (iNOS) [Wong 1996] in the brain parenchyma, cerebral vasculature, and/or perivascular microglia. Notably, the glial response to injury increases with age, resulting in increased brain expression of all of these inflammatory genes [Kyrkanides 2001]. Acutely, expression of brain inflammatory genes and microglial activation results in increased blood-brain barrier permeability [Mayhan 1998, Tsao 1999], adrenocorticotropic hormone (ACTH), and cortisol secretion, and the induction of fever [Rivest 2000]. The link between CPB and brain inflammatory gene induction was recently demonstrated. Compared with surgical controls, brain COX-2 mRNA expression was increased in rats four hours after CPB and was proportional to increased post-CPB systemic IL-6 concentrations [Hindman 2001]. Hence, CNS responses to systemic inflammatory mediators rapidly alter CNS gene expression and functional status, and, by their nature, are likely to augment CNS injury from any coexisting perioperative neurologic insults [Allan 2001]. Furthermore, CNS inflammatory gene induction and microglial activation may have long-term consequences. Recent work suggests that these processes participate in the pathogenesis of several neurodegenerative diseases, including Alzheimer's, multiple sclerosis, and AIDS dementia complex [González-Scarano 1999, Gahtan 1999]. Hence, chronic CNS responses to systemic inflammatory mediators may result in delayed and/or long-term postoperative CNS dysfunction.

The simultaneous presence of endotoxin and other pro-inflammatory mediators may be important in determining the extent of CNS responses to peripheral tissue injury/inflammation. Extremely minute quantities of endotoxin have direct effects upon the vasculature (*e.g*., increasing adhesion molecule expression) and also are able to greatly increase the production of inflammatory cytokines and the brain's response to them [Vallières 1999]. Three human studies have shown that low preoperative titers of anti-endotoxin antibodies are associated with a greater systemic inflammatory response [Rothenburger 2001] and poorer cardiopulmonary outcomes following cardiac surgery [Bennet-Guerrero 1997, Hamilton-Davies 1997, Rothenburger 2001]. A recent report likewise indicates that cognitive dysfunction six weeks after CAB is also related to low preoperative anti-endotoxin titers [Mathew 2002a].

If the CNS response to systemic inflammatory stimuli were nothing more than fever, that *alone* might be sufficient to significantly worsen neurologic outcomes. Both animal [Dietrich 1996] and human [Azzimondi 1995] data indicate that hyperthermia markedly worsens outcomes following a neurologic insult. Recently, Grocott *et al.* reported maximum postoperative temperature following CAB was a significant independent determinant of cognitive dysfunction six weeks after surgery [Grocott 2002]. Following *non*-cardiac surgery, factors independently related to long-term cognitive dysfunction were patient age, early postoperative cognitive impairment, and postoperative infection [Abildstrom 2000]. Postoperative infection almost certainly is associated with increased systemic inflammatory mediators, endotoxemia, and/or fever.

Especially provocative is the interaction between endotoxin exposure and fever. In cell culture, induction of heat shock proteins (by fever) *prior* to endotoxin exposure is protective. In contrast, endotoxin exposure *followed* by fever results in apoptosis [Xu 1996]. Therefore, perioperative induction of CNS inflammatory genes combined with subsequent fever might, in certain individuals [Tardiff 1997] or circumstances, initiate apoptosis and/or subacute neurodegeneration. Support for this hypothesis comes from a rat model of CPB, where significant up-regulation of apoptotic genes was observed [Sato 2001]. Simply preventing postoperative fever may have tremendous neurologic benefits.

Other interventions that decrease systemic and/or CNS inflammatory responses have the potential to decrease the incidence and severity of postoperative neurocognitive dysfunction. A recent study observed no relationship between the systemic inflammatory response and postoperative cognitive dysfunction after CAB [Westaby 2001]. However, this study did not measure endotoxin concentrations and likely missed peak IL-6 and IL-8 concentrations, which occur four to six hours after surgery. In contrast, Heyer *et al.* found that heparin-coated CPB circuits appeared to decrease peak systemic IL-6 and TNF(levels (20-25%) and significantly improved cognitive status five days after surgery [Heyer 2002]. Lidocaine also has recently been recognized as having anti-inflammatory properties [Hollmann 2000] and has been found to significantly decrease neurologic injury in an animal stroke model [Lei 2001]. In one randomized clinical trial, lidocaine improved neurocognitive outcomes after cardiac surgery [Mitchell 1999]. Aprotinin also has multiple anti-inflammatory properties [Hill 1995, Hill 1997, Asimakopoulos 2000, Asimakopoulos 2001]. In contrast to lidocaine, in non-CPB animal models of transient cerebral ischemia, aprotinin did not improve neurologic outcome [Grocott 1999]. However, in a setting conducive to heightened systemic inflammatory mediators (*e.g.*, cardiac surgery and CPB), the anti-inflammatory properties of aprotinin may have greater potential to improve CNS outcomes. A randomized clinical trial studying aprotinin's effect on cognitive outcomes has recently been completed. Other approaches to attenuating systemic and/or brain inflammatory responses are being explored. These include anti-complement antibodies [Mathew 2002b], gene-based therapy [Ueno 2001], and cytokine inhibitors [Beech 2001]. The future prospects for addressing this problem are fascinating and promising.

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