REVIEW ARTICLE

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Neurologic Injury and Protection in Adult Cardiac and Aortic Surgery

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NEUROLOGIC INJURY can be defined as any temporary or permanent injury to the central and peripheral nervous system, including the brain, spinal cord, and peripheral nerves. This is a major perioperative complication of cardiac and aortic surgery, which can manifest as short-term coma or a state of confusion and long-term decline in cognitive function, behavioral changes, or physical dysfunction. Stroke occurs in approximately 2% to 3% of adult cardiac surgery patients. The rate of postoperative cognitive decline is less clear, due to heterogenous testing methods, but is reported in 50% to 70% of patients at 1 week, 30% to 50% at 6 weeks, and 20% to 40% at 1 year.[1,2] This review evaluates the current rationale and evidence for proposed surgical and nonsurgical techniques for the reduction of neurologic injury.

A variety of mechanisms can result in perioperative neurologic injury during cardiac and aortic surgery (Table 1), and many patients have a combination of these mechanisms. This review discusses these etiologic factors in relation to the techniques proposed to reduce them. Accurate assessment techniques to determine the etiology of neurologic injury, adequacy of cerebral perfusion, and quantification of the extent of injury are essential to assess the efficacy of potential neuroprotective measures. These techniques include intraoperative near-infrared spectroscopy and transcranial Doppler; neurologic, psychological, and cognitive examination; imaging of the nervous system; and biomarkers in cerebrospinal fluid and serum. Discussion of these methods are outside the scope of this review; however, it is important to appreciate that all methods have limitations in sensitivity and/or specificity when interpreting the results of experimental and clinical studies.[3] A recent consensus statement aimed to unify definitions and classifications of neurologic injury after aortic arch surgery.[4]

CARDIOPULMONARY BYPASS

Circuit Design

Modern cardiopulmonary bypass (CPB) circuits are designed to reduce emboli and trauma to blood components, while providing physiologic blood flow. Soft-shell venous reservoirs minimize the blood-air interface and risk of air emboli.[5] Membrane oxygenators have almost completely replaced bubble oxygenators, because they produce fewer particulate and gaseous emboli and do less damage to components of blood.[6] Filters effectively prevent both particulate and gaseous macro- and microemboli from entering the inflow stream, especially the debris that results from cardiotomy suction.[7] Although centrifugal pumps produce a pulseless flow with less negative pressure and fewer gaseous microemboli than roller pumps,[8] they have not been shown to improve neurologic outcome. The theoretical benefits of pulsatile CPB flow include increased capillary patency, decreased venous sludging, attenuation of the inflammatory response, and increased cerebral blood flow after hypothermic circulatory arrest.[9] Pulsatile CPB flow has been shown to decrease the duration of cerebral desaturation, but improved short- or long-term postoperative cognitive function has not been reported.[10,11]

Systemic Inflammatory Response

CPB contributes to the systemic inflammatory response that occurs after cardiac surgery. An early phase is triggered by blood contact with the foreign surfaces of the bypass circuit and a later phase by ischemia-reperfusion, which causes complement activation, release of pro-inflammatory cytokines, and the activation of leukocytes and endothelial cells.[12,13] In some patients, this may precipitate a systemic inflammatory response syndrome, producing pyrexia, low systemic vascular resistance, high cardiac output, and hypotension. This inflammatory response to CPB has been shown to be associated with neurologic injury, and potential mechanisms include endothelial dysfunction,[14] upregulation of neurotoxic molecules,[14] and blood-brain barrier dysfunction.[15,16] However, whether this relationship is causal is unclear. Westaby et al found no significant relationship between systemic inflammatory markers and neuropsychologic testing at 5 days and 3 months after coronary artery bypass grafting (CABG).[17] Leukocyte-depleting filters in the CPB circuit have been trialed to limit the inflammatory response, with variable

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Table 1. Potential Mechanisms of Neurologic Injury in Cardiac and Aortic Surgery

- Micro- and macroembolization of atheromatous plaque, air, debris, or clot originating from the heart, aorta, or cardiopulmonary bypass circuit
- Hypoperfusion
- Hyperperfusion
- Systemic inflammatory responses and cytotoxic-mediated damage
- Hyperthermia
- Iatrogenic interruption of blood flow

success.[18] Trials of the complement inhibitor pexelizumab found no benefit in reducing the risk of stroke and minimal effects on global measures of cognition, but did find a small reduction in visuo-spatial dysfunction.[19,20] The Dexamethasone for Cardiac Surgery trial of intraoperative high-dose dexamethasone in cardiac surgery with CPB did not significantly reduce the risk of stroke (relative risk [RR] 0.91, 95% confidence interval [CI]: 0.55-1.50).[21] It may be that the inflammatory response is a contributory factor or exacerbates injury caused by emboli or other mechanisms.

Pre-cannulation Assessment of Aortic Atherosclerosis

The arterial cannula of the CPB circuit usually is placed in the ascending aorta or proximal arch. However, atherosclerotic plaques may be dislodged by clamping, cannulation, or manipulation of the aorta and embolize to the brain. Goto et al found that patients with atherosclerosis of the ascending aorta had higher rates of postoperative neuropsychologic dysfunction and intraoperative stroke than controls;[22] in severe aortic disease, these rates were as high as 26.5% and 10.5%, respectively. The incidence of this risk factor is significant, because moderate-to-severe atheroma in the region of direct aortic manipulation occurs in 29% of patients aged 70 to 79 years and in 34% of patients aged >80 years undergoing cardiac surgery.[23] If aortic atherosclerosis is detected, then it is possible to establish CPB by cannulation of the femoral or axillary arteries instead, or perform the procedure without CPB in appropriate cases. The axillary artery is the preferred alternative, because concomitant atherosclerotic disease commonly is present in the femoral and iliac arteries, although it takes longer to set up than femoral inflow. Routine preoperative assessment of the aorta, therefore, should be performed, which is possible by manual palpation by the surgeon, transesophageal echocardiography, or epiaortic ultrasound.

Manual palpation of the aorta is the traditional method for atheroma detection but fails to detect approximately 50% of lesions even when performed by an experienced surgeon.[24,25] This is because only severe cases of atherosclerosis offer resistance to the surgeon's fingers, and the softer noncalcified lesions (which may be more likely to embolize) are often not palpable. Transesophageal echocardiography (TEE) can be used to grade atherosclerotic disease as normal/nonsignificant (plaque <2 mm), moderate (plaque or intimal thickening of 2-5 mm), or severe (plaque >5 mm or mobile atheroma). A meta-analysis of TEE for the assessment of ascending aortic atherosclerosis found a sensitivity of 21% (95% CI: 13%-32%) and specificity of 99% (95% CI: 96%-99%).[26] TEE has a low sensitivity because the right main bronchus lies between the esophagus and the distal ascending aorta/proximal aortic arch, thereby preventing ultrasound transmission and creating a blind spot. This can be overcome by placing a handheld probe directly on this part of the aorta, referred to as epiaortic ultrasound (EAU), which greatly increases the sensitivity. Suvarna et al found that EAU detected atheromas in 53%, TEE in 20%, and manual palpation in 12% of the same group of patients.[24] Royse et al also found that TEE correctly detected fewer than 30% of moderate-to-severe atheromas identified by EAU, and manual palpation detected only 50% of the atheromas identified by EAU.[25] Other studies have examined the impact EAU has had in reducing the number of embolic events. Djaiani et al found that although EAU led to modification of the surgical technique in approximately one-third of patients undergoing CABG, it did not reduce the number of transcranial doppler-detected cerebral emboli.[27] In contrast, Rosenberger et al found that EAU altered surgical technique in 4% of 6,051 patients and reduced the overall stroke rate when compared with all patients undergoing cardiac surgery.[28] Others have experienced similarly positive results.[29]

CORONARY ARTERY BYPASS GRAFTING

In standard on-pump CABG, the incidence of stroke is approximately 2%.[30] The incidence of neurocognitive decline is less clear, ranging from 0% to 80%.[1,31] Off-pump CABG (OPCAB), which avoids the use of CPB and thus cross-clamping the potentially atherosclerotic ascending aorta, has been proposed to reduce the rate of neurologic injury. In this technique, the distal graft anastomoses (to the coronary arteries) are performed with the heart beating, and the immediate area around the anastomosis is stabilized using a device, for example the Medtronic Octopus (Medtronic Inc., Minneapolis, MN). However, some observational and randomized trials of OPCAB *v* on-pump CABG, including the GOPCABE, CORONARY, and ROOBY trials, have failed to show any improvement in neurologic outcome between the 2 groups.[32–34] In these trials, an aortic side-clamp was used for performing proximal graft anastomoses in some or all of the patients, which may mitigate the potential neuroprotective benefits of OPCAB.

Alternatively, an "anaortic" or "no-touch" OPCAB technique can be used, which avoids clamping, sewing, or any manipulation of the aorta. Arterial or venous grafts are used either in situ (eg, single or bilateral internal mammary arteries) or with a free graft (eg, radial artery or saphenous vein) anastomosed to the mobilized internal mammary artery in either a Y-formation or as an end-to-end extension. In an updated 2012 meta-analysis, Edelman et al compared anaortic OPCAB (n = 4,813) to OPCAB with a side-clamp (n = 5,581), finding that the anaortic technique had a significantly lower stroke rate (0.29% *v* 1.34%, RR 0.35, 95% CI: 0.19-0.64, p = 0.006).[35,36] Further evidence implicating the deleterious role of the aortic side-clamp comes from a recent case-controlled study of on-pump CABG:[37] Double-clamping the aorta (using both a cross-clamp and side-clamp) significantly increased the risk of postoperative stoke compared with a single clamp (cross-clamp) technique (odds ratio [OR] 2.60, 95% CI: 1.03-6.67, p = 0.044).