Cerebral protection during CPB

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At the conclusion of this lecture, the participant should be able to:

1. Learn practice strategies on CPB to minimize cerebral injury
2. Review some of the pharmacologic agents with a possible role in cerebral protection

Despite advances in surgical, anesthetic, and neuroprotective strategies, cerebral injury after cardiac surgery remains a significant source of post-operative morbidity and is responsible for an increasing proportion of peri-operative deaths. Technological advancements have allowed cardiac surgery to be performed on a progressively older and sicker population who, in turn, are at increased risk for the associated cerebral injury. The underlying mechanism of the associated cerebral injury is incompletely understood. While considered multifactorial, the most importantly cited etiologic factors are cerebral macro- and microembolism and hypoperfusion, exacerbated by ischemia/reperfusion injury. Extensive research has been undertaken in an attempt to minimize the incidence of peri-operative cerebral injury, and both pharmacological and non-pharmacological strategies have been investigated. Although many agents showed promise in pre-clinical studies, there is currently insufficient evidence from clinical trials to recommend the routine administration of any pharmacological agents for neuroprotection during cardiac surgery. Non-pharmacological strategies that can be recommended on the basis of evidence include TEE and epiaortic ultrasound guided assessment of the atheromatous ascending aorta with appropriate modification of cannulation, clamping or anastomotic technique and optimal temperature management. Large-scale randomized controlled trials are still required to further address the issues of optimal pH management, glycemic control, blood pressure management, and hematocrit during CPB.

The spectrum of cerebral injury ranges from cognitive dysfunction to overt stroke, and the quoted incidence varies with both the type of injury and the risk factor profile of the patient. The overall stroke rate after cardiac surgery in the analysis of large cohorts is approximately 1-3%. Cognitive dysfunction, which occurs far more commonly than stroke, also has a variable incidence, depending upon when and how it is assessed. It is characterized by a persistent decline in cognitive function following surgery and anesthesia and includes impairment of attention, concentration, short-term memory and fine motor function. Cognitive dysfunction is identified by pre and post-operative cognitive testing and reported incidences range as high as 50-60% in the early postoperative period, 25% at three months after surgery, and 15% at one year. Longitudinal studies have demonstrated that cognitive dysfunction after cardiac surgery is not transient but rather persists up to five years and longer where the reported incidence is as high as 40%. While cognitive dysfunction is less devastating than stroke, the twenty-fold greater incidence imparts on it far more significance in terms of impact on quality of life and overall health-care resources utilization.

The exact etiology of cardiac surgery-associated cerebral injury remains incompletely understood. Cerebral embolism and hypoperfusion exacerbated by ischemia/reperfusion injury are likely to be the primary underlying causes. Inflammation (both cerebral and systemic), cerebral edema, blood brain barrier dysfunction, hyperthermia, and a genetic susceptibility to injury or genetically defined inability to repair following injury have all been implicated. Embolization of particulate and gaseous material into the cerebral microvasculature resulting in focal areas of
cerebral ischemia has been well studied \cite{7,8}, but evidence showing a direct association between cerebral microembolic load and post-operative cognitive dysfunction is conflicting \cite{8,9}. It may be that quality rather than quantity of cerebral emboli plays a more important role in the pathogenesis of cerebral injury. Global cerebral hypoperfusion may result from the non-pulsatile nature of CPB \cite{10}, and cerebral edema has been demonstrated by MRI in the post-operative period \cite{11}. Cerebral and systemic inflammatory pathways can be activated during CPB leading to direct and indirect injury of brain cells. Neuronal cell death in the context of ischemia-reperfusion injury is thought to occur by two distinct mechanisms, apoptosis and necrosis. Both are closely linked to the inflammatory cascade. While necrosis occurs as a result of prolonged ischemia, apoptosis occurs despite adequate cellular energetics due to the activation of specific genes and receptors leading to the generation of a family of serine proteases called caspases, which mediate cell death. Although further characterization is required, these pathways of ischemia-reperfusion induced cerebral injury are potentially important targets for pharmacologic and gene therapy.

**Neuroprotective strategies**

**Temperature management:** Despite the convention of inducing mild hypothermia during CPB, evidence that supports efficacy has been difficult to produce and replicate. Human research focused on this question with at least 8 prospective randomized trials and 1 large retrospective analysis reported. Techniques for measuring neurocognitive and neurologic outcome varied amongst studies as did target temperature for the hypothermic intervention and rewarming strategies yielding difficulty in comparing the studies respective findings. The preponderance of these large clinical trials has failed to demonstrate any benefits of hypothermia for the prevention of postoperative neurologic and neurocognitive deficits. These discouraging results raise not only the question regarding appropriateness of cooling and target temperature during CPB, but also the question as to why hypothermia is not robustly efficacious given the known focal and global ischemic insults presented by CPB and cardiac/aortic surgery.

One potential source of injury is rewarming from hypothermic CPB. This involves perfusion with warmed blood, the temperature of which, in part defines that rate by which rewarming occurs. Another factor dictating the speed of rewarming is the actual temperature gradient between body temperature (e.g., nasopharyngeal) and CPB perfusate temperature. Of practical necessity, rapid rewarming within 10-15 min was long favored to complete the procedure. Work in animals has shown that even negligible hyperthermia markedly exacerbates ischemic brain insults \cite{12,13}, and this is just as true if hyperthermia is delayed \cite{14}. Work in humans has shown that hypertemic overshoots occur during rewarming \cite{15}. Later work associated post-bypass hyperthermia with worsened neurocognitive outcome \cite{16}. The influence of hyperthermia on rewarming has likely confounded clinical trials assessing efficacy of intraoperative hypothermic protection.

Major progress has occurred over the past decade in preclinical CPB models. Of particular importance has been invention of systems allowing CPB to be studied in rats \cite{17,18}. This permits standardization of CPB procedures and long-term neurologic/neurocognitive outcome to be assessed in association with study of cellular responses to CPB. Such models produce various levels of injury, most likely related to CPB conduct. Injury can be amplified by tandem middle cerebral artery occlusion \cite{19}, injection of standardized embolic loads \cite{20} or addition of periods of deep hypothermic circulatory arrest (DHCA). \cite{21}

de Lange et al. \cite{22} provided evidence for the potential value of these models in discriminating effects of CPB conduct. Rats exposed to normothermic CPB had deficits in Morris water maze testing 3-9 days later. In rats where hypothermia was induced either only during CPB with rapid rewarming, or where hypothermia was induced only after CPB, Morris water maze performance was not improved. In contrast, when hypothermia was instituted during CPB, and combined with slow rewarming to 35 °C during CPB, post-CPB neurocognitive deficits were decreased.
This laboratory work complements human trials within the timeframe the outcome analysis was conducted. Nathan et al. 23 cooled 233 CABG patients to 32 °C as a neuroprotective strategy during CABG and then randomized them to either rewarming target temperatures of 37 °C or 34 °C while on CPB. Patients rewarmed to the lower temperature had fewer post-operative neurocognitive deficits when examined 1 week postoperatively. By 3 months, benefit from hypothermia remained but was less robust. Grigore et al. 16, in a corroborative study, also found fewer neurocognitive deficits with slow rewarming compared to warming in a conventional manner when assessed 6 weeks post-operatively.

However, the impact of delayed rewarming (and thus hypothermia itself) on long-term outcome from CPB has been questioned. Boodhwani et al. 24 performed a randomized double-blind trial in 262 patients to examine the effects of sustained mild hypothermia (34 °C) versus normothermia (37 °C) on postoperative neurocognitive function after CABG surgery. This study obviated rewarming and cerebral hyperthermia as confounding variables and found that mild intraoperative hypothermia still did not decrease the incidence of neurocognitive deficits as measured 3 months post-operatively. This was supported by the recent report of a 5-year follow-up on the study by Nathan et al. who found benefit from delayed rewarming as late as 3 months 23. After 5 years efforts to identify benefit were inconclusive 25.

Collectively, these studies indicate an adverse effect from rapid rewarming and the probably cerebral hyperthermia. In contrast, when hyperthermia is prevented, hypothermia itself fails to provide benefit. Slow rewarming constitutes a change in practice for many clinicians who seek both rapid and complete rewarming during CPB, but its use is reflected in a decreased incidence of post-operative hyperthermia. Given available evidence, however, it must be questioned why hypothermia should be induced in this patient population.

While laboratory evidence for a sustained neuroprotective effect of mild hypothermia after ischemia/reperfusion is irrefutable, absence of persistent benefit in humans brings to question whether ischemia/reperfusion injury is the principal cause of cognitive decline after cardiac surgery. It remains plausible that with further bench research to guide design of human trials, CPB methods will be devised to allow demonstration of efficacy from mild hypothermia during CPB for either valvular or CABG surgery. The high prevalence of post-CBP neurologic/neurocognitive morbidity and its associated economic burden calls for an urgent pursuit of a better understanding of the underlying pathomechanisms, thus allowing optimization of CPB conduct in humans.

Pharmacologic Neuroprotection

**Thiopentone** was one of the earliest agents used for neuroprotection in cardiac surgery following a study by Nussmeier et al. who, in a group of patients undergoing open ventricle procedures requiring CPB, showed less neuropsychiatric dysfunction on day 10 post-operatively in the group who received thiopentone to maintain EEG silence during the bypass period (p=0.025). 26 However, a later study of 300 coronary artery bypass graft (CABG) patients failed to corroborate these neuroprotective findings and showed several disadvantages in the thiopentone group, including longer time to awakening and tracheal extubation and increased vasoconstrictor requirements. 27 As of January 2011, the manufacturer of thiopental in the US has discontinued its production.

N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity has received much attention in the field of neuroprotection. While human trials of NMDA antagonists in stroke have been limited by psychomimetic side effects, there is a wealth of animal data, including data from CPB models, which suggests that these agents are effective neuroprotective agents. 19,28,29 NMDA receptor antagonists which have been evaluated to date for neuroprotective properties in cardiac surgery patients include remacemide, magnesium, xenon, and ketamine. 30

**Xenon** gas is also thought to be related to antagonism at the excitatory NMDA receptor and has recently been found to possess neuroprotective properties. 31 This has been demonstrated both in the setting of cerebral ischemia, but most importantly, in the setting of animal models of
CPB-associated cognitive decline.\textsuperscript{29} These positive experimental results have led to early phase clinical trials ultimately aimed at protecting the brain during cardiac surgery.\textsuperscript{32} However, more recent work by Jungwirth et al.\textsuperscript{33,34} in a rat model of combined cerebral emboli and CPB showed that perioperative administration of Xenon resulted in impaired neurologic and cognitive outcome and also resulted in higher cerebral infarct volumes. Potential neuroprotective properties of Xenon may have been outweighed by Xenon’s effect on cerebral air embolism as it is known to expand gaseous bubbles.

Intravenous \textit{lidocaine} has been investigated as a neuroprotective agent in several cardiac surgical trials which show varied results. Its mechanism of action is thought to be via blockade of sodium channels in addition to potential anti-inflammatory effects. In the first study of 55 patients undergoing valvular surgery, a lidocaine infusion (in an anti-arrhythmic dose of 1 mg/min) was begun pre-induction and maintained for 48 hours following surgery.\textsuperscript{35} Neurocognitive testing was performed preoperatively and again eight days, two and six months post-operatively. Compared to placebo, neurocognitive outcome eight days after surgery was significantly better in the lidocaine group (p = 0.025). A second trial by Wang et al.\textsuperscript{36} in 118 patients undergoing elective CABG with CPB, who received a lidocaine bolus and then infusion of 4mg/min or placebo, also demonstrated a short-term benefit of lidocaine in preventing post-operative cognitive dysfunction. However, a much larger double-blind randomized trial in cardiac surgery failed to replicate these findings.\textsuperscript{37} As a result, lidocaine cannot be recommended as a clinical neuroprotective agent in cardiac surgery.

The use of \textit{beta-blockers} is widespread in patients with coronary artery disease. While primarily directed towards the prevention of adverse myocardial events, a recent study of neurologic outcomes following cardiac surgery demonstrated an association between beta-blocker therapy and an improvement in neurologic outcome.\textsuperscript{38} 

\textit{Aprotinin} is a non-specific serine protease inhibitor that was first used in the 1950s for the treatment of pancreatitis, long before its cardiac surgical applications. Its primary indication in cardiac surgery was for the reduction of blood loss and peri-operative transfusion. However, in a large multi-center trial of aprotinin in primary or redo CABG and valvular surgery, the group receiving high-dose aprotinin was noted to have a lower stroke rate (p = 0.032).\textsuperscript{36,40} This was supported in a study by Frumento et al. who retrospectively examined patients who were at high risk for stroke due to the presence of significant aortic atheroma. Similarly, the subgroup who received aprotinin had a significantly lower stroke rate. When studying the effect of aprotinin on cognitive deficits following CABG surgery in a small, prospective randomized trial in 36 patients, the incidence of cognitive deficit was also reduced in the aprotinin group (58%, aprotinin vs. 94% placebo; p = 0.001). Importantly, the extrapolation of these results to the broader population is cautioned due to the high rate of cognitive deficit in the placebo group, the small size of the study, and some methodological concerns.

Considerable discussion and investigation as to the mechanism underlying the potentially neuroprotective effects of aprotinin has remained inconclusive. Initially, the focus was on the potential of its anti-inflammatory effects to prevent some of the adverse inflammatory sequelae of cerebral ischemia. However, animal investigations in the setting of both focal and global cerebral ischemia failed to show any direct benefit on either functional or neurohistological outcome.\textsuperscript{41} The explanation for the divergent results in animal and human studies is unclear, but suggests the beneficial effects of aprotinin are independent of any direct neuroprotective effect. An indirect neuroprotective mechanism that has been postulated is the modulation of cerebral emboli. The cardiotomy suction has been identified as a major source of cerebral emboli during CPB.\textsuperscript{42} One could extrapolate that if a drug reduces the amount of particulate-containing blood returning from the operative field to the cardiotomy reservoir (by decreasing overall blood loss), then cerebral emboli and their adverse consequences might also be decreased.

More recently, the aprotinin question has been readdressed by Mangano et al. in a retrospective study of 4374 patients, who reported a 181% increase in the risk of stroke or encephalopathy in those receiving aprotinin.\textsuperscript{43} However, this was a retrospective study with
significant methodological concerns, and in the absence of a properly conducted and powered prospective randomized trial, the question as to the true effect of aprotinin on cardiac surgery-related neurologic injury remains unanswered. There was hope that the BART study -- Blood Conservation using Antifibrinolytics: A Randomized Trial in High-Risk Cardiac Surgery Patients -- a multi-institutional, blinded, randomized controlled trial to compare the efficacy and safety of the use of aprotinin, aminocaproic acid and tranexamic acid in approximately 3000 high-risk cardiac surgical patients would also address this question. However, patient enrollment was prematurely halted by the studies data safety and monitoring board late in 2007 due to increased risk of death in the aprotinin arm of the trial. This led to the subsequent removal of aprotinin from the market by the U.S. Food and Drug Administration (FDA).

**Corticosteroids** have long been considered as potential neuroprotective agents due to their ability to reduce the inflammatory response, which is considered an important factor in propagating ischemia-mediated brain injury.\(^{44,45}\) However, with the exception of the setting of spinal cord injury,\(^{46}\) they have never been demonstrated to possess any significant clinical neuroprotective properties. Furthermore, in the CRASH trial, a study of 10,008 patients with clinically significant head injury, administration of intravenous corticosteroids actually worsened cerebral outcome. This trial showed an increased relative risk of death from all causes (OR 1.18 [95% CI, 1.09 – 1.27], p=0.0001) in those receiving high dose steroids within 8 hours of injury. This adverse effect may be explained in part by the hyperglycemia that generally follows the administration of steroids,\(^{47}\) which, in animal models and several human studies of cerebral injury, has been associated with worsened neurological outcome.\(^{48,49}\) A review of prospective, randomized, double-blind placebo-controlled investigations involving methylprednisolone and patients undergoing cardiac surgery with CPB concluded that, while methylprednisolone suppresses the systemic inflammatory response associated with CPB, it was associated with delay in extubation and increased blood glucose levels.\(^{50}\)

The realization that the efficacy of methylprednisolone in reducing secondary neurological injury in animal models was due to inhibition of lipid peroxidation of neuronal membranes and independent of its glucocorticoid activity led to the development of a group of steroid analogues, the lazaroids (21-aminosteroids). These are potent antioxidants which specifically inhibit lipid peroxidation without any glucocorticoid or mineralocorticoid activity, thereby avoiding the hyperglycemic and other side effects. Evidence from animal models of head injury and stroke\(^{51}\) indicates that tirilazad, a lazaroid, reduces secondary brain injury, promotes recovery, and improves neurological outcomes. However, evidence from Phase 3 clinical trials remains inconclusive.

Of note, there is a multicenter, randomized, double-blind trial, comparing clinical outcomes after the administration of high-dose [dexamethasone](https://www.drugs.com/dexamethasone.html) versus placebo in patients undergoing heart surgery with the use of cardiopulmonary bypass. The primary endpoint is the occurrence of major complications (including all-cause mortality, myocardial infarction, stroke, renal failure, and prolonged mechanical ventilation) in the first 30 days after surgery. However, with the current body of evidence, the administration of steroids with the intent of conferring some degree of neuroprotection during cardiac surgery cannot be recommended.

Other inhibitors of the inflammatory cascade including **complement inhibitors** have also been investigated.\(^{52}\) The activation of complement is an essential step in the CPB-associated inflammatory response. Mathew et al. studied pexelizumab, a humanized antibody directed against the C5 complement component, in a 914-patient study aimed at evaluating its effect on both myocardial outcome and mortality.\(^{53}\) One of the secondary endpoints was neurocognitive outcome, and, while pexelizumab had no effect on overall cognition, it reduced dysfunction in the visuospatial domain (p=0.003 on post-operative day 4, p=0.016 on post-operative day 30).

**Glypromate®**, another compound that at least made it to a Phase III clinical trial aiming to reduce the incidence of cognitive decline after CABG surgery, was developed due to convincing neuroprotective effects of the N-terminal tripeptide of insulin-like growth factor-1, glycine-proline-
glutamate (GPE) in a variety of animal models of cerebral injury. While favorable results from a Phase IIa trial were reported in regards to Glypromate’s® pharmacokinetic and safety data, the Phase III trial was determined unsucessful.

Another recent clinical trial looking at the effect of acesadine, a purine nucleoside on reducing cardiovascular and cerebrovascular adverse events in CAGB surgery was terminated in 2010. This decision was made based upon the DSMB's review of a pre-specified interim futility analysis which showed a low probability of the trial meeting its primary efficacy endpoint.

References: