Protecting The Brain During Deep Hypothermic Circulatory Arrest

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Neurological complications after cardiac surgery are a recognized source of prolonged hospitalization, high hospital cost, altered quality of life, and mortality. Surgery involving the aortic arch is a particularly high risk procedure associated with stroke rates over four times higher than after CABG surgery (~9% vs ~2%). Although the use of selective antegrade cerebral perfusion via the brachiocephalic arteries or retrograde cerebral perfusion are advocated by some teams, deep hypothermic circulatory arrest (DHCA) remains the cornerstone of brain protection during surgery involving the aortic arch. In this lecture the relative role of pharmacologic neuroprotection during DHCA will be discussed.

Mechanisms of Brain Injury from DHCA
The brain is dependent on a constant supply of O₂ and nutrients since it has minimal energy stores yet a high metabolic rate. An estimated 60% of energy is utilized for maintaining cellular ionic gradients and 40% for maintaining cellular integrity. At normal body temperature EEG slowing occurs when cerebral blood flow (CBF) is reduced from the normal 50 ml/100 g/min to ~20 ml/100 g/min and neuronal death occurs when CBF is < 6 ml/100 g/min. These changes, though, are highly dependent on body temperature. Cerebral metabolic O₂ demand (CMRO₂) is reduced roughly 7% for each 1°C decrease in body temperature or 50% for each 10°C decrease. At body temperatures of 20°C and 15°C, CMRO₂ is reduced to ~23% and ~17% of normal, respectively. The safe duration of DHCA is not known and highly variable which may reflect incomplete regional brain cooling due to cerebral vascular disease and/or injury arising from other sources. Rates of neurological complications have been reported to be 4%, 7.5%, and 10.7% after DHCA of 30 min, 45 min, and 60 min, respectively.

Ischemic brain injury results in activation of multiple pathways (“ischemic cascade”) that determine the ultimate extent of injury and functional outcome. In a canine model (2hrs of circulatory arrest at 18°C), experiments by Baumgartner et al at Johns Hopkins have demonstrated that glutamate is released during DHCA and its activation of glutamate and AMPA receptors is an important mechanism of secondary neuronal injury and neuronal death. Further, these investigators have shown that DHCA increases production of neuronal NO and that inhibition of NO synthase reduces neuronal injury. NO and peroxynitrate lead to mitochondrial injury that in turn leads to free radical production, cellular membrane injury, and cell necrosis. Mitochondrial injury further results in release of cytochrome c that activates apoptotic cell death pathways. In this experimental model it has been demonstrated that activation of the ATP sensitive K⁺ channel on the inner mitochondrial membrane can mediate neuronal ischemic
preconditioning reducing the histopathological and functional extent of brain injury from DHCA. Triggering of inflammatory pathways by ischemia including IL-1 and TNF-α leads to induction of NO and free radical production that leads to activation of other pathways leading to cellular dysfunction, DNA damage, and mitochondrial dysfunction. Matrix metalloproteinases are released as well leading to breakdown of the blood brain barrier and other deleterious effects.

**Neuroprotection**

The aims of neuroprotection during cardiac surgery are a) to reduce primary injury from brain embolization or hypoperfusion and b) to reduce secondary injury from activation of the ischemic cascade. In addition to reducing CMRO$_2$, experimentally, hypothermia protects against ischemic brain injury by attenuating excitotoxicity and by other mechanisms. After cardiac arrest, induced hypothermia improves neurological outcomes and survival. In contrast, fever after stroke is associated with poor functional outcome, extended hospital length of stay, and mortality. Indirect cerebral hyperthermia during re-warming on CPB has been proposed to explain the ineffectiveness of moderate hypothermia for reducing the frequency of neurological complications after cardiac surgery. Cerebral hyperthermia can occur during re-warming if blood temperature is $> 37^\circ$C since the aortic cannulae are positioned at the origin of the cerebral vessels. Temperature monitoring sites (e.g., nasopharynx, esophagus) underestimate brain temperature, a phenomenon which might result in failure to detect brain hyperthermia. Thus, care must be taken to protect against cerebral hyperthermia during re-warming after DHCA.

The use of pharmacological agents to prevent primary and secondary brain injury during cardiac surgery has received considerable investigative attention. The majority of studies, though, have been performed in patients undergoing CABG and/or valve surgery. Whether these data can be extrapolated to DHCA where global ischemia is a dominant concern is not known and probably unlikely. Regardless, the results from neuroprotective studies in adults undergoing cardiac surgery with CPB have been largely disappointing. Tested compounds have included NMDA receptor antagonists, calcium channel blockers, agents that block oxidant stress, GABA receptor agonists, and others. It is likely that for such a strategy to be beneficial, agents that block multiple pathways, including apoptosis, will be necessary.

A survey in the United Kingdom found that 83% of anaesthetist/anesthesiologist administer drugs for neuroprotection during DHCA including thiopental (63% of respondents), propofol (29% of respondents) or other agents usually corticosteroids, regardless of any perceived benefit of such therapy. The mechanism of experimental brain protection from barbiturates is not completely known but is probably via mechanisms in addition to global reduction in CMRO$_2$. Several clinical studies have provided conflicting findings on whether thiopental in doses sufficient for EEG burst suppression leads to a reduced frequency of neurological complications after cardiac surgery. Nussmeier et al$^{13}$ found that thiopental reduced the incidence of neuropsychiatric complications 10 days after open-chamber surgery compared with placebo. In contrast, Zaidan et al$^{14}$ found no differences in the frequency of postoperative neurocognitive dysfunction between patients receiving thiopental versus controls during CABG surgery. These conflicting findings are explained in part by the different types of surgery, approach to temperature management, and CPB equipment (bubble versus membrane oxygenator; arterial line filtration). A downside of the use of large doses of thiopental (30-40 mg/kg) is the increased need for inotropic agents after surgery. Pharmacologic reduction in CMRO$_2$ with anesthetics has
not been shown to be a robust strategy for brain protection. There are insufficient data from well designed clinical trials adults to support the use of thiopental during DHCA.

Experimentally, corticosteroids have neuroprotective properties, although the mechanisms are not completely known. Proposed explanations include anti-oxidant effects, cytoprotective effects, reduced release of excitatory amino acids, inhibition of proinflammatory pathways activated by CPB and ischemia, and attenuation of altered CBF resulting from hypothermic arrest. There are conflicting findings, though, on any neuroprotective benefits of corticosteroids during experimental DHCA. Support for the clinical use of corticosteroids for neuroprotection during DHCA is in part based on the positive effects of large doses of methylprednisolone (30 mg/kg) after spinal cord injury, although these data are controversial. There are no data from well designed clinical studies showing any benefit or harm from high dose corticosteroids for neuroprotection for DHCA. Of concern, corticosteroid may lead to hyperglycemia. Even mild glucose elevation (i.e., >140 mg/dL) is associated with poor outcome after stroke mandating close monitoring of glucose during surgery.

Magnesium has multiple physiologic effects and, experimentally, it is neuroprotective in animal stroke models via several mechanisms. Mg$^{++}$ acts as a Ca$^{++}$ channel and NMDA receptor antagonist. Intracellular Ca$^{++}$ overload activates proteolytic enzymes, phospholipases, induces NO, endonucleases and other deleterious processes. Inhibition of Ca$^{++}$ channels by Mg$^{++}$ prevents intracellular Ca$^{++}$ accumulation as well as induces arteriolar vasodilation and reduces the risk for vasospasm. Magnesium has been investigated as a neuroprotectant in a randomized, blinded, placebo controlled trial in 350 patients undergoing cardiac surgery. In a dose that increased serum levels 1 to 2 times normal, Mg$^{++}$ use was associated with improved cognitive performance 24 to 96 hrs after surgery compared with placebo, but these benefits were not present 3 months after cardiac surgery. In a randomized trial of 2589 non-surgical patients, MgSO$_4$ given within 12hr of acute stroke (16 mmol MgSO$_4$ intravenously over 15 min and then 65 mmol over 24 h) was not found to improve the primary outcome (death and disability within 90 days) or secondary outcome (functional status and death within 90 days) compared with placebo. Planned data sub-analysis in that trial found that Mg$^{++}$ treatment did benefit patients with non-cortical or lacunar infarcts. Of note, in focal and global cerebral ischemia stroke models, MgSO$_4$ was not found to be neuroprotective unless it is combined with mild hypothermia. Whether these results apply to humans undergoing DHCA remains to be tested.

**Investigational agents**

Valproic acid is a widely used anticonvulsant drug that has been found in small and large animal experiments to possess neuroprotective properties. In a canine model of DHCA, valproic acid use led to better neurological function, less neuronal damage on histologic examination, and preserved N-acetyl-aspartate levels determined with NMR spectroscopy. Reduction in NAA is associated with neuronal loss or dysfunction. In this study, the entorhinal cortex that is associated with learning and memory, was particularly preserved with valproic acid. There are several neuroprotective mechanisms of valproic acid including reduction in lipid peroxidation and protein oxidation in the setting of oxidative stress, induction of heat shock proteins, prevention of glutamate excitatocity, protection against apoptosis, and inhibition of histone deacetylation. Deacetylated histones bind DNA leading to chromatin condensation and
reduction in transcription factor activity. Acetylation of histones release from DNA allowing transcription of enzymes that protect against oxidative stress.

There are other agents either under development or in clinical trials as neuroprotectants that are of interest (Table 1). Many of these trials involve evaluation of neuroprotectants as adjuvant with thrombolytic agents or body cooling. The use of Mg++ for neuroprotection is under investigation for stroke and after subarachnoid hemorrhage. In the Field Administration of Stroke Therapy Magnesium (FAST-MAG) trial, the administration of Mg++ in the field by paramedics to patients within 2 hrs of stroke is being evaluated versus placebo for improving long-term functional outcomes. The Magnesium in Aneurysmal Subarachnoid Hemorrhage (MASH-II) study is evaluating whether Mg++ reduces poor outcomes for patients admitted within 4 days of subarachnoid hemorrhage. The use of Mg++ to improve neurocognitive outcomes after CABG surgery is also under investigation in the POINT trial. The Albumin Therapy for Neuroprotection in Acute Ischemic Stroke (ALIAS) trial is evaluating high dose albumin (2.05 g/kg) in patients with acute stroke. There are also several trials evaluating mild hypothermia for neuroprotection after stroke including endovascular techniques (ICTuS study) and in combination with t-PA. Knowledge of the endogenous genomic and proteomic pathways activated during cerebral ischemia holds promise for future therapeutic agents. Potential strategies might include non-coding RNAs such as microRNAs or short interfering RNAs that modify transcription and translation of genes coding cell injuring proteins.

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<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Status</th>
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<tr>
<td>Enecadin</td>
<td>Blocks Na+ and Ca++ channels</td>
<td>Clinical development</td>
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<tr>
<td>Maxipost</td>
<td>K+ channel opener</td>
<td>Early data shows limited neuroprotection vs placebo</td>
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<tr>
<td>Traxoprodil</td>
<td>Selective NMDA2B antagonist</td>
<td>Clinical trials</td>
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<tr>
<td>YM872</td>
<td>AMPA receptor antagonist</td>
<td>Clinical trials</td>
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<tr>
<td>Edaravone</td>
<td>Free radical scavenger</td>
<td>Clinical trials</td>
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<tr>
<td>Citicoline</td>
<td>Endogenous phosphatidylycholine precursor (cell membrane component)</td>
<td>Clinical trials but data appear inconsistent</td>
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<tr>
<td>ONO-2506</td>
<td>Inhibits astrocyte activation during ischemic cascade protecting neurons</td>
<td>Clinical trials</td>
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Recommendations
At the present time there are no drugs with proven efficacy for preventing brain injury from DHCA. Importantly, there is a lack of well designed and conducted clinical trial in patients undergoing DHCA evaluating potential compounds. As a result, clinicians must rely on animal data and that derived from humans undergoing CABG and/or valve surgery in weighing the risk versus benefits of various drugs for this purpose. It must be remembered that neurological complications might arise not only from cerebral hypoperfusion during the period of cessation of CPB but also from cerebral emboli arising from the atherosclerotic aorta, lipid particles, entrained air, and multiple other sources. The predominance of data suggests that any benefits of hypothermia for protecting the brain might be countered by brain injury induced by re-warming. It is thus imperative to avoid hyperthermia during re-warming from DHCA. General recommendations for neuroprotection during DHCA are listed in Table 2.
Table 2. General neuroprotective strategies for DHCA.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Details</th>
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<tbody>
<tr>
<td>Use membrane oxygenator with arterial line filter</td>
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<td>Epiaortic ultrasound to guide aortic manipulations</td>
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<tr>
<td>Avoid rapid re-warming</td>
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<tr>
<td>Avoid cerebral hyperthermia</td>
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<td>α-stat pH management should be considered to maintain cerebral blood</td>
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<td>flow autoregulation</td>
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<td>Maintain serum glucose &lt; 140 mg/dl</td>
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<td>Avoid introduction of lipid particles into the systemic circulation by</td>
<td>using a cell saver</td>
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<td>Transfusion of packed red blood cells should be considered in high risk</td>
<td>hemoglobin is ≤ 7 g/dL or higher depending on other patient specific</td>
</tr>
<tr>
<td>patients when hemoglobin is ≤ 7 g/dL</td>
<td>considerations.</td>
</tr>
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References:

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