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Perioperative Management of Deep Hypothermic Circulatory Arrest

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THE GOAL OF this article is to provide a review of deep hypothermic circulatory arrest (DHCA), covering major issues including pathophysiology of ischemic injury, organ protection (both pharmacologic and nonpharmacologic), temperature control, and perfusion methods. The purpose of this review is to serve as a resource for board review or as introductory material for a cardiac anesthesia rotation. The reference list should help in directing the reader for more in-depth review of particular areas.

The use of therapeutic hypothermia dates back to the ancient Egyptians, Greeks, and Romans.[1] In modern times, the use of therapeutic hypothermia progressed from observation case reports to animal studies to clinical use in children and then adults. In 1945, Fay[2] provided observational reports of therapeutic use of hypothermia in patients with severe cerebral trauma. Subsequently, in 1950, Bigelow et al[3] reported an experimental study in dogs that suggested a therapeutic role for hypothermia for cerebral protection during cardiac surgery. In 1959, Drew et al[4] reported the use of profound hypothermia (12° C, nasopharyngeal) with circulatory arrest (up to 1 hour) in children undergoing surgical repair of the tetralogy of Fallot. In 1975, Griepp et al[5] described the use of deep hypothermic cardiopulmonary arrest (DHCA, 14-18°C) as a method for cerebral protection during the prosthetic replacement of the aortic arch.[5] Later, the use of DHCA was extended into other major vascular surgeries such as the repair of thoracoabdominal aortic lesions, clipping of giant and complex cerebral aneurysms, and resection of renal carcinoma with tumor thrombus extending into the inferior vena cava or atrium.

DHCA provides 2 clinical benefits. The circulatory arrest component provides a bloodless surgical field without the need for the use of intrusive clamps and cannulae. The deep hypothermic component significantly decreases brain metabolism and oxygen requirements and thus permits a longer period of interrupted blood perfusion to the brain. The cerebral metabolic rate is related exponentially to brain (core body) temperature, with the cerebral metabolic rate decreasing by about 50% for each 6°C drop in brain temperature.[6]

Disadvantages of DHCA include increased cardiopulmonary bypass (CPB) time, edema formation, coagulopathy, and alteration in many organ functions including the kidney, the brain, vascular smooth muscles, intestinal mucosa, alveolar epithelium, the liver, and the pancreas.[7,8] Based on reports from 8 major cardiac surgery centers in the United States, Europe, and Japan, the risk of permanent neurologic injury after aortic arch surgery using DHCA ranged from 3% to 12%, renal dysfunction from 5% to 14%, pulmonary insufficiency from 5% to 39%, and left ventricular failure or low-cardiac-output syndrome from 7% to 34%.[9]

Alternatives to the use of DHCA during aortic arch replacement are the use of normothermic CPB[10] or mild-to-moderate degrees of hypothermia. These alternatives obviously require the use of a perfusion system for the brain, separate from the rest of the body, which might increase the risk of cerebral embolization.[11] Advantages of normothermic CPB include less time restriction for the completion of surgical repair, maintenance of cerebral blood flow (CBF) autoregulation, and avoidance of many other disadvantages of DHCA.[10] Safety reports of aortic arch repair under less-than-deep degrees of hypothermia have been provided from small case series and nonrandomized comparative studies. A case series of 6 patients who underwent normothermic (36°-37°C) aortic arch replacement reported no intraoperative or postoperative mortality or neurologic deficit.[10] A larger case series of 26 patients who underwent thoracic aortic repair under mild (34°C) hypothermic circulatory arrest with antegrade selective cerebral perfusion (ASCP) at 30°C reported only 1 postoperative death caused by the rupture of residual descending thoracic aneurysm and 2 cases (7.7%) of permanent neurologic deficit.[12] A larger retrospective comparison of 68 patients who underwent aortic arch repair under 1 of 3 techniques, mild hypothermia (28°-32°C) with ASCP, moderate hypothermia (24°-28°C) with ASCP, or deep hypothermia (18°-24°C) with retrograde cerebral perfusion (RCP), reported no differences among the groups in either hospital mortality (10.3%) or permanent neurologic dysfunction (8.8%). The mild hypothermic ASCP group had the advantages of decreased transfusion volume, intubation time, and intensive care unit stay.[13]

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Pathophysiology of Ischemic Brain Injury

Circulatory arrest leads to tissue hypoxia, which affects all aerobic functions, particularly the production of the energy source, adenosine triphosphate (ATP) molecules. ATP depletion leads to the failure of energy-dependent cell functions such as the Na+-K+-ATPase pump. This failure is most detrimental in neural tissues because electrolyte disruption leads to depolarization dysfunction and, ultimately, cellular structural damage. Failure of the Na+-K+-ATPase pump leads to intracellular accumulation of Na+ and Cl^-, which leads to cellular swelling and excessive neuronal depolarization. This depolarization causes an influx of Ca+ ions, which activates phospholipases, resulting in the production of free fatty acids, particularly arachidonic acid, which leads to hydrolysis of mitochondrial and plasma membranes. During reperfusion, arachidonic acid is further metabolized to prostaglandins, thromboxane, leukotrienes, and free radicals. All these reactions result in an additional accumulation of Ca+ ions in the cytoplasm.

Excessive neuronal depolarization leads to the excessive release of neuronal excitatory amino acids such as glutamate and aspartate. These amino acids are present in excitatory presynaptic terminals throughout the brain and are essential for memory, cognition, and consciousness. Glutamate and aspartate are the primary messengers used by neurons for interneuronal communication. After release into the intercellular space, glutamate rapidly is converted to glutamine and then re-enters the neuron ready to be used for the next message. Under normal conditions, powerful neuronal and glial uptake systems rapidly remove synaptically released excitatory amino acids from the extracellular space. Any cause that interrupts conversion of glutamate to glutamine will lead to the accumulation of glutamate in the intercellular space, whereas in increasing concentration it acts as a potent neurotoxic substance. During ischemia, there is insufficient ATP available for glutamine-glutamate conversion and neuron re-entering. Excessive neurotransmitter accumulation in the interneuronal spaces may lead to neuronal injury and death.

During ischemic conditions, glucose is metabolized in an anaerobic way to lactate, which accumulates in the neurons and causes the development of intracellular acidosis, cell swelling, and denaturation of proteins and enzymes. A decrease in pH is also a potent stimulus for the release of the glutamate and aspartate. The process is accelerated in the presence of hyperglycemia, and there is ample clinical evidence to suggest that hyperglycemia compounds ischemic cerebral injury.

All events in the depolarization phase are reversible, and current clinical protective methods are aimed at delaying or preventing the sequence of these events. Hypothermia and continued antegrade perfusion are the most effective measures to maintain aerobic glycolysis in the presence of reduced flow. Hypothermia and retrograde cerebral perfusion (RCP) are effective in delaying the depletion of ATP in the zero antegrade flow state. Circulatory arrest helps to reduce anaerobic glycolysis and accompanying acidosis by eliminating continued glucose supply to fuel the pathway. The trickle flow supplied by RCP supplies substrate to maintain anaerobic glycolysis, yet at the same time may help to remove acid metabolites.[14]

The collapse of the neurotransmitter transport mechanism starts the vicious cycle that constitutes the second phase, the biochemical cascade. Excessive activation and the presynaptic release of the excitatory amino acids cause neuronal death by 2 mechanisms: immediate and delayed. In the immediate mechanism, glutamate activates postsynaptic N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors, leading to Na+ and Cl^- influx and increasing cellular edema and, ultimately, membrane lysis and death. In the delayed mechanism, the activated NMDA receptor promotes the influx of Ca, leading to the activation of phospholipases and proteases with formation of free radicals, lipid peroxidation, and cell death.

The inability to restore calcium homeostasis and the turnover of cytoskeletal proteins lead to progressive cellular dysfunction and apoptosis. Apoptosis usually occurs in zones of borderline ischemia and is an energy-requiring process, whereas necrosis occurs in conditions of complete ischemia and is not energy dependent (Fig 1).

There are some promising experimental pharmacologic approaches (neurotransmitter-antagonists, neurotransmitter-receptor blockers, and calcium channel blockers) that aim to modify or prevent the events of the biochemical cascade. Glutamate antagonists have been shown to be protective in animals after ischemic injury to the brain.[8] However, there is no practical pharmacologic remedy currently ready for clinical application for brain protection during ischemia. The search for effective inhibitors of neurotransmitter release and neurotransmitter receptor blockers continues.[14] There is experience with calcium channel blockers with mixed clinical results.[14] Amino steroids show promise in countering the toxic effects of free fatty acids, especially arachidonic acid.[14] Suppression of apoptosis offers a new venue for the prevention of delayed neuronal loss.[14]

The last phase of ischemic injury occurs during reperfusion and is known as ischemia-reperfusion (IR) injury. IR injury involves the generation of oxygen free radicals, the most important of which are superoxide radicals, which attack membranes, leading to the further disruption of intracellular organelles and cell death. A period of overperfusion (hyperperfusion) also may occur after ischemia (including that caused by hypothermic cardiac arrest), leading to a hyperperfusion injury, including cerebral edema, which can worsen the outcome of ischemic injury (Fig 2).

Recently, the endothelium has been shown to play a key role in the injury suffered after ischemia and reperfusion. When rendered hypoxic and then reoxygenated, endothelial cells become activated to express proinflammatory properties that include the induction of leukocyte-adhesion molecules, procoagulant factors, and vasoconstrictive agents.[15] Nitric oxide (NO) is the key endothelium-derived relaxing factor that plays a pivotal role in the maintenance of vascular tone and reactivity. In addition to being the main determinant of basal vascular smooth muscle tone, NO opposes the action of potent endothelium-derived contracting factors such as angiotensin-II and endothelin-I. NO inhibits platelet and leukocyte activation and maintains the vascular smooth muscle in a nonproliferative state. In addition to NO, endothelium may produce other relaxing factors, including prostacyclin, endothelium-derived hyperpolarizing factor, bradykinin, adrenomedullin, and C-natriuretic peptide. Endothelial dysfunction leads to the decreased production of or availability of NO and/or an imbalance in the