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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

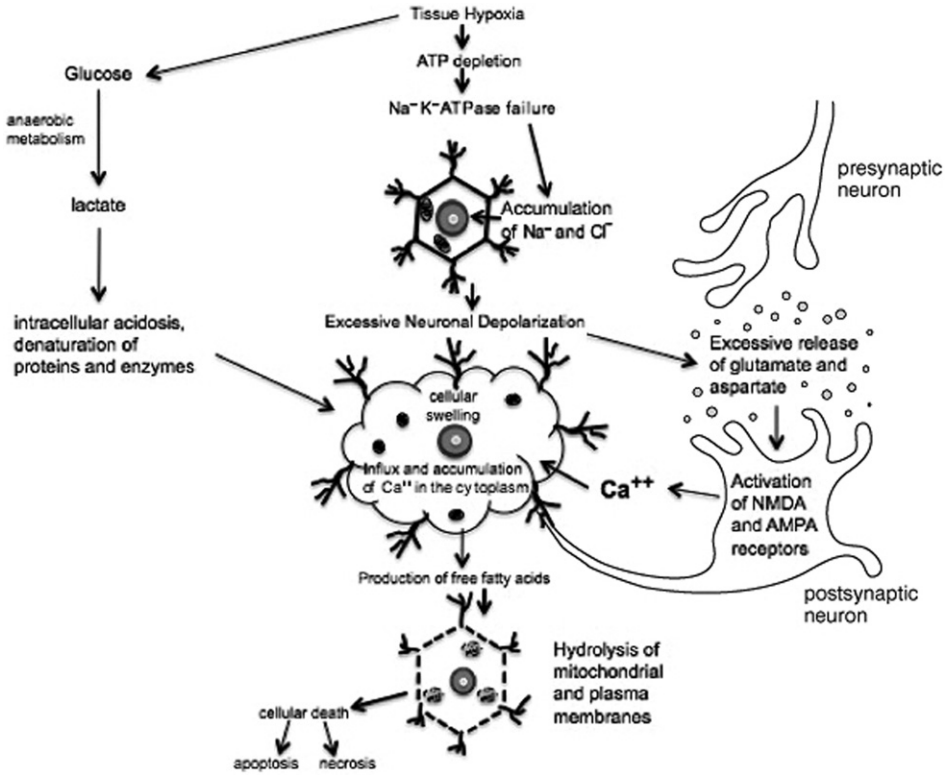

Fig 1. Pathophysiologic events during ischemic injury from circulatory arrest.

relative contribution of endothelium-derived relaxing and contracting factors (such as endothelin-I, angiotensin, and oxidant radicals), which leads to an increase in vascular resistance.[16] On the other hand, overproduction and accumulation of NO after hypothermic arrest has been shown to be neurotoxic.[17]

The aggregation of both platelets and neutrophils lead to the release of inflammatory mediators and the initiation of the whole-body inflammatory response. Proinflammatory endothelial cell changes promote widespread leukosequestration, cytokines release, an increasing level of tumor necrosis factor, interleukins, oxygen-derived free radicals, and adherence molecules (E-selectin, P-selectin, and intracellular adhesion molecule) throughout the body. This further slows the circulation, leading to a cascade of worsening ischemia and cell injury. In animal studies, leukocyte infiltration and cytokine-depleting filtration seemed to mitigate reperfusion injury in the brain.[18]

Innate immunity now is emerging as an important mechanism in the inflammatory cascade of IR injury. Necrotic or apoptotic cell death produces neoepitopes that are recognized by immunoglobulin M as pathologic.[19] This recognition leads to activation of the complement system, release of inflammatory cytokines, and recruitment of inflammatory cells that amplify the injury beyond that caused by the intracellular process alone (Fig 3).

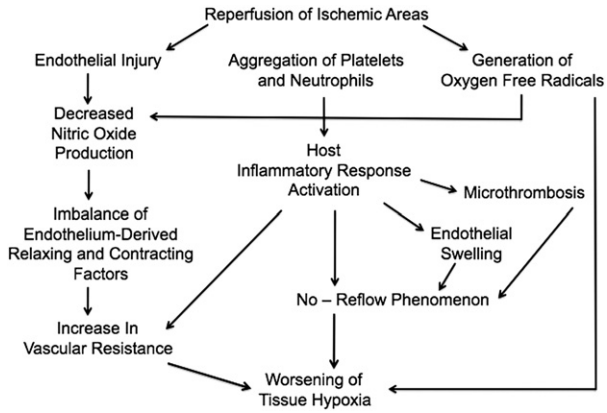

Fig 2. Ischemia-reperfusion injury.

METHODS OF END-ORGAN PROTECTION DURING DHCA

Hypothermia

Hypothermia acts by reducing the metabolic rate of the brain and improving the balance between energy supply and demand. Hypothermia reduces cerebral blood flow (CBF) in a linear manner, but the decrease in cerebral metabolic rate of oxygen ($CMRO_2$) is not exactly linear. On average, the reduction in $CMRO_2$ is about 7%/1°C. Between 37°C and 22°C, $CMRO_2$ is reduced by about 5%/1°C, and then the reduction accelerates when $CMRO_2$ reaches 20% at 20°C and 17% at 18°C, at which point about 60% of patients achieve electrical silence on electroencephalography (EEG) (Fig 4).[20]

However, animal models of global cerebral ischemia have shown a protective effect (no injury after 20 minutes of ischemia)

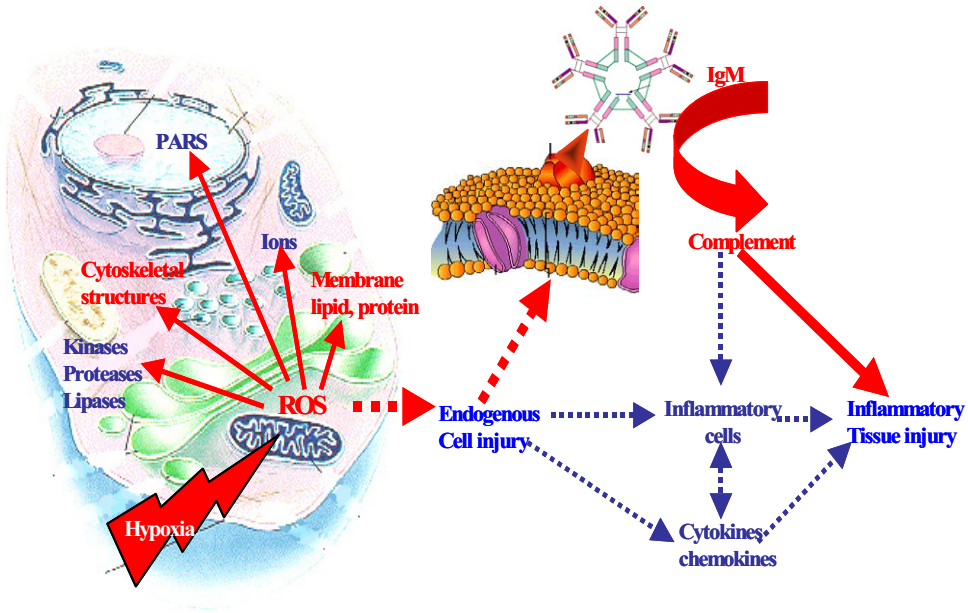

Fig 3. Inflammatory cascade of ischemia-reperfusion injury. (Color version of figure is available online.)

during the use of mild (33°C) hypothermia.[21] It could be due to additional mechanisms including halting the ischemic injurious cascade, reducing glutamate excitotoxicity, suppressing intracellular calcium influx, decreasing formation of oxygen free radicals, and increasing gamma-aminobutyric acid release.[22]

Pharmacologic Protection

Many pharmacologic interventions have been proposed for organ protection during DHCA. Animal studies have suggested a beneficial effect of barbiturates, steroids, anticonvulsants, lidocaine, calcium channel blockers (nimodipine), and antagonists to the glutamate receptor subtypes. However, there is little conclusive evidence of benefits through prospective, randomized, controlled clinical trials. As a result, clinical practice varies widely in regard to agents, doses, and timing of administration. A postal survey was sent to members of the Association of Cardiothoracic Anesthetists (UK) to ascertain current practice in the use of pharmacologic agents because cerebral protective agents during DHCA showed that

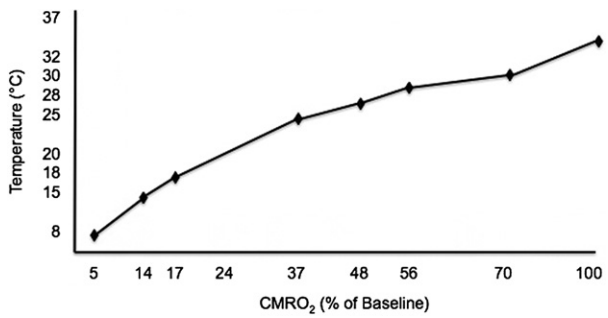

Fig 4. The effect of temperature on $CMRO_2$.

83% of respondents used some form of pharmacologic agent for cerebral protection; 59% of respondents used thiopental, 29% used propofol, and 48% used a variety of other agents, the most common of which were steroids.[23]

Barbiturates act by reducing $CMRO_2$, CBF, free fatty acids, free radicals, cerebral edema, and seizure activity. Barbiturates have been studied extensively in animal models of focal ischemia with varying degree of success. Nussmeier et al[24] were among the first to report beneficial effects of thiopental in the prevention of neuropsychiatric complications after cardiac surgery, but a similar study by Zaidan et al[25] could not substantiate these findings. Trials of barbiturates as protective agents in global ischemia failed to show an improvement in outcome.[26]

It has even been suggested that barbiturates may jeopardize the energy state of the brain in DHCA patients.[23] Despite the lack of conclusive evidence of neuroprotection, barbiturates still are used for that purpose in clinical practice during DHCA. Barbiturates have been shown to be protective in incomplete focal ischemia because of multiple emboli such as those seen during CPB.[23] In addition, they may be helpful in brain protection during rewarming after DHCA, particularly in the early phase, when jugular venous oxygen desaturation indicates decreased oxygen delivery. Disadvantages of large doses of barbiturates include delayed awakening and myocardial depression.[27]

Steroids, in particular dexamethasone and methylprednisolone, counteract the systemic inflammatory response during and after CPB by decreasing proinflammatory cytokines, which are thought to play a role in brain ischemic injury as well as myocardial depression and β-adrenergic desensitization. Steroids previously have been shown to improve neurologic outcome in DHCA patients.[28] However, high-dose steroids might lead to an increased risk of sepsis and an alteration in glucose metabolism. Glucose control (110-180 mg/dL) should be used

for patients receiving glucocorticoids to avoid postoperative hyperglycemia.

Mannitol is an osmotic diuretic that protects the kidney by lowering renal vascular resistance, preserving tubular integrity, and reducing endothelial cell edema. It also reduces cerebral edema and scavenges free radicals, thus reducing tissue damage.[29] Furosemide blocks renal reabsorbtion of sodium and increases renal blood flow, probably mediated by prostaglandins. The combination of furosemide and mannitol has been shown to preserve renal function in ischemic conditions.[30]

Hyperglycemia might worsen neurologic injury by increasing tissue lactic acidosis. Insulin has been shown to have a neuroprotective effect against such injury.[31] A retrospective analysis of patients undergoing aortic arch surgery revealed that hyperglycemia more than 250 mg/dL was associated with an adverse neurologic outcome.[32] The Society of Thoracic Surgeons (US) have laid down guidelines for intraoperative control of blood glucose during adult cardiac surgery because higher glucose levels during surgery were found to be an independent predictor of mortality in patients with and without diabetes mellitus.[33] As per Society of Thoracic Surgeons guidelines, a glucose level of >180 mg/dL in diabetic patients should be treated with single or intermittent doses of intravenous insulin. However, if the level is persistently more than 180 mg/dL, a continuous insulin infusion should be started. If an insulin infusion is started in the preoperative period, it should be continued in the intraoperative and early postoperative periods to keep the level below 180 mg/dL. The blood glucose level should be monitored every 30 to 60 minutes during insulin infusion with more intense monitoring (every 15 minutes) during the administration of cardioplegia, cooling, and rewarming. In patients with no history of diabetes, blood glucose levels higher than 180 mg/dL should be treated similarly with single or intermittent doses of intravenous insulin. In such patients, when insulin infusions are used intraoperatively, caution should be exercised regarding the possibility of hypoglycemia in the postoperative period, and an endocrinology consult should be obtained.[33]

Because Ca++ ions play a major role in the ischemic cascade, several studies have examined the role of calcium antagonists as neuroprotective agents.[34] Nimodipine, which is used for vasospasm prophylaxis after subarachnoid hemorrhage, has been shown to have some efficacy in improving cognitive outcome after CPB but was associated with increased complication rates (hypotension) in patients undergoing valve replacement, requiring termination of the trial.[35]

Magnesium, another Ca++ channel blocker, showed evidence of protection against hypoxia in the rat hippocampus.[36] This can be explained by magnesium-induced blockade of both voltage-sensitive and NMDA-activated neuronal Ca++ channels, whereas nimodipine only blocks voltage-sensitive channels.[36]

Lidocaine selectively blocks Na+ channels in neuronal membranes. In a dog model, high doses of lidocaine induced isoelectric EEG, indicating a pronounced reduction in $CMRO_2$.[37] In this respect, it mimics the effect of hypothermia. Unlike barbiturates, lidocaine can reduce $CMRO_2$ by an additional 15% to 20%. In this dog model, lidocaine at doses of 4 mg/kg before DHCA and 2 mg/kg at the start of reperfusion improved neurologic deficit scores in the treatment group in comparison to placebo.[37] In a human study, a continuous infusion of lidocaine (4 mg/min) during and after CPB resulted in better short-term cognitive outcome.[38] However, a more recent clinical trial of lidocaine in cardiac surgery patients found variable effects depending on study population. In diabetic patients, there was an association between higher total dose (35 mg/kg) of lidocaine and increased postoperative neurocognitive decline. In nondiabetic patients, lidocaine doses of <42.6 mg/kg were associated with an improvement in cognitive outcome 1 year after surgery. Lidocaine did not decrease perioperative cytokine response. These findings suggest that the protective effects of lidocaine need to be evaluated further.[39]

Dexmedetomidine, a selective α_2-adrenoreceptor agonist, has been shown in rats to be neuroprotective in both focal and global ischemia.[40] The inhibition of ischemia-induced norepinephrine release might be associated with these effects, particularly in the hippocampus. Acadesine, an adenosine-regulating agent, has been shown to mitigate the effect of reperfusion injury and decrease stroke rates after coronary artery bypass graft surgery.[41] Remacemide, a glutamate antagonist, has been shown to have neuroprotective effects during coronary artery bypass graft surgery.[42] However, there is no sufficient current evidence to support the clinical use of this drug for neuroprotection during DHCA[42] (Table 1).

Adjunctive Nonpharmacologic Protection

Recent research has focused on adjunctive methods of cerebral protection, which may augment the safety of DHCA.[43] To

Table 1. Proposed Mechanisms of Action of Potentially Neuroprotective Pharmacologic Agents

Pharmacologic Agent	Proposed Mechanism
Barbiturates	Reducing $CMRO_2$, CBF, free fatty acids, free radicals, and cerebral edema. Protective in focal ischemia.
Steroids	Decreasing proinflammatory response
Mannitol	Reducing cerebral edema, scavenging free radicals, protecting the kidneys by lowering renal vascular resistance, preserving tubular integrity, and reducing endothelial cell edema
Furosemide	Blocking renal reabsorption of sodium and increasing renal blood flow
Insulin	Controlling hyperglycemia, preventing intracellular acidosis
Calcium channel blockers	Blockade of voltage-sensitive and NMDA-activated neuronal Ca^{2+} channels, decreasing calcium influx into cytoplasm
Lidocaine	Selective blockade of Na+ channels in neuronal membranes, reducing $CMRO_2$
Dexmedetomidine	Inhibition of ischemia-induced norepinephrine release, protective in both focal and global ischemia
Remacemide	Glutamate antagonist
Acadesine	Mitigates the effects of reperfusion injury
β-Blockers	Decreasing inflammatory response

diminish cerebral ischemia time, selective perfusion of the brain during deep hypothermia has been implemented in the form of both RCP or antegrade cerebral perfusion (ACP). ACP has been thought to be superior to RCP for cerebral protection because it achieves near-physiologic brain perfusion with homogenous distribution of blood and may extend the safe time of circulatory arrest.[43] RCP, on the other hand, offers only a trivial amount (10%-20% of normal perfusion volume) of blood through brain capillaries, which is thought to meet the metabolic demands during deep hypothermic conditions, enhances cerebral hypothermia, and might decrease neural intracellular acidosis.[44-46]

ACP could be hemispheric (through the right axillary, subclavian, or innominate artery) or bihemispheric (by adding the left common carotid artery). There is no consensus regarding appropriate levels of pressure and flow. A flow of 10 to 20 mL/kg/min is used in a majority of institutions and adjusted to maintain the pressure between 40 and 70 mmHg in the right radial artery or 60 to 70 mmHg in the carotid arteries.[47,48] Higher-pressure ACP, although theoretically appealing, is associated with increased CBF, elevated intracranial pressure, high post bypass $CMRO_2$, and poorer neurobehavioral recovery.[49]

Advantages of ACP include a better ability to meet the demands of brain metabolism, flushing brain metabolic waste during ischemia, and better control of brain temperature. ACP may obviate the need for deep hypothermia, thus reducing pump time and complications related to deep hypothermia.[13] Drawbacks of ACP include the risks of arterial wall dissection, malperfusion, embolism of atheromatous plaque or air, the cluttered operative field, and the cumbersome procedure.

RCP is achieved by cannulating the superior vena cava and instituting flow rates of 300 to 500 mL/min to maintain a mean pressure of 25 to 35 mmHg. Occlusion of the inferior vena cava or snaring of the superior vena cava often is done to prevent preferential flow of blood to the inferior vena cava. RCP allows for deep and homogenous cooling of the brain and helps in flushing solid particles, air bubbles, and metabolites from the arteries, thus reducing embolic phenomena and delaying onset of acidosis in the ischemic brain. RCP is more efficacious in the absence of atherosclerotic disease.[50] RCP has been reported to reduce mortality rates from 14.8% to 7.9% and stroke rates from 6.5% to 2.4% during DHCA.[51] Other investigators reported similar findings in reducing stroke rates from 9% to 3% through the use of RCP during DHCA.[52]

Cerebral hypothermia during RCP is achieved through arteriovenous shunts to overcome any deficiencies in transcapillary perfusion. Studies have found that most RCP blood is shunted away from capillaries even during normothermia, and this shunting is increased during deep hypothermia as arteriovenous and venovenous shunts open.[53] The partial perfusion provided by RCP is insufficient to sustain cerebral metabolism, which might be impaired further with RCP-induced cerebral edema.[54] Some investigators suggested that a combination of circulatory arrest under moderate systemic hypothermia and cold RCP might provide adequate cerebral protection for up to 30 minutes.[55] Others have suggested the following strategies on the basis of the expected operative procedure and circulatory arrest time: (1) for limited arch replacement with short circulatory arrest time (30-40 minutes), DHCA alone would be sufficient; (2) for more extensive repairs that require prolonged circulatory arrest times, DHCA plus ACP is recommended; and (3) for operations with high embolic risk, DHCA plus RCP is recommended[56,57] (Table 2).

MONITORING DURING DHCA

Monitoring for adult patients undergoing DHCA includes all noninvasive monitoring according to the standards of the American Society of Anesthesiologists, invasive hemodynamic monitoring including an arterial catheter and pulmonary artery catheter, transesophageal echocardiography (TEE), and neurophysiologic monitoring.

TEE is extremely useful in monitoring many aspects of cardiovascular function including assessing cardiac function before and after DHCA, examining the entire aorta, confirming proper cannula placement, assessing volume status, detecting intracardiac air, and evaluating the adequacy of surgical repair. Temperature monitoring is standard during general anesthesia and is essential during hypothermic techniques. Sites of measuring core body temperature include the tympanic membrane, nasopharynx, esophagus, urinary bladder, rectum, pulmonary artery, and jugular venous bulb. It is preferred to use more than 1 site for core body temperature monitoring to detect differences in circulatory distribution. Common sites include the pulmonary artery and the urinary bladder. The esophageal site seldom is used in conjunction with transesophageal echocardiographic monitoring for safety and efficacy concerns. Temperature monitoring at the tympanic membrane might provide the closest assessment of brain temperature.[58] When used, jugular venous temperature monitoring would be particularly useful during rewarming to ascertain the lack of cerebral hyperthermia because jugular venous bulb temperature is consistently greater than that of any other sites including the brain.[59] The CPB outflow temperature is the best indicator of the jugular venous blood temperature. When DHCA is intended, circulatory arrest usually is initiated when the core body temperature has reached around 12° to 15°C. During rewarming, the perfusate temperature is kept at a maximum of 10°C above core body temperature and never above 36°C. A urinary bladder temperature of about 34°C is used as an indicator of adequate rewarming. Rewarming to greater temperatures is avoided to prevent dangerous rebound hyperthermia after CPB.[60]

Table 2. Comparative Characteristics of ACP and RCP as Adjunctive Methods of Cerebral Protection

Characteristics	ACP	RCP
Simplicity and ease of application	−−	+
Adequacy to support cerebral metabolism	++	−
Reduced pump time	+	−−
Limited manipulation of arch branches	−−	++
Reduced embolic load	−−	++
Risk of arterial wall dissection, malperfusion, embolism	++	−−
Interstitial edema, cerebral edema	−	++

NOTE. + and − indicate degree of presence or absence, respectively.

Neurophysiologic monitoring might include EEG, somatosensory-evoked potentials, oxygen saturation of the jugular venous bulb (SjO_2), and near-infrared spectroscopy (NIRS).

NIRS is a noninvasive monitoring technique that measures regional cerebral oxygen saturation (rSO_2) and detects changes in cerebral oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome aa3 concentration in brain tissue. In brain tissue, the vascular compartment is predominantly venous (70%-80% *v* 20%-30% arterial). Oxygen saturation of cerebral venous blood is about 60% versus 98% to 100% in the arterial blood. Based on these assumptions, the average rSO_2 is 60% to 70%. During cardiovascular surgery, decreasing rSO_2 trends seem to reliably reflect decreasing cerebral oxyhemoglobin saturation. Levels of rSO_2 of <55% are indicative of neurologic compromise and have been associated with adverse clinical outcome including postoperative cognitive dysfunction.[61] During aortic arch surgery under DHCA and ACP, decreases in rSO_2 to <55%, particularly when longer than 5 minutes, were associated with the occurrence of postoperative neurologic adverse events.[62] Some authors have suggested maximizing rSO_2 values before instituting DHCA; however, the role of such a method in improving outcome has yet to be shown.[63]

The earliest NIRS devices to receive Food and Drug Administration approval (mid 1990s) and, thus, the most studied are INVOS (Somanetics Corporation, Troy, MI) and NIRO (Hamamatsu Photonics KH, Hamamatsu City, Japan). A recent review stated that a majority of high-volume aortic arch surgery centers are using cerebral NIRS on a routine basis.[64] Previously, the same author suggested an algorithm of managing signs of decreased cerebral oxygenation as detected by NIRS. The proposed factors to be addressed and their order of management is as follows: the position of aortic and superior vena cava cannulae including head and neck position, cerebral perfusion pressure including mean arterial pressure, arterial oxygen content, partial pressure of carbon dioxide, hemoglobin level, cardiac output, and $CMRO_2$.[65]

NIRS has several limitations that need to be considered (Table 3). It provides information on rSO_2 in only a limited region of the brain (part of the frontal lobes) and cannot monitor the entire brain. Therefore, rSO_2 might fail at detecting ischemia at sites different from monitored ones. The use of electrocautery may interfere with the NIRS monitoring. The contribution of external carotid blood flow and variations in the ratio of cerebral arterial/venous blood flow (contaminants) might result in inaccurate rSO_2 values. NIRS cannot differentiate between the different causes of declining rSO_2 (embolus and malperfusion). It can be affected by excessive bilirubin and different forms of hemoglobin. NIRS can produce a normal rSO_2 reading when positioned over an area in which cerebral perfusion is absent and the brain tissue is presumably dead. The interpretation of absolute rSO_2 values may be confounded by hypothermia, alkalosis, or hypocapnia. Therefore, it is essential to follow trends in oxygen saturation changes rather than absolute values.[66]

Table 3. Basic Advantages and Disadvantages of NIRS

Advantages	Disadvantages
Noninvasive	Cannot monitor entire brain
Continuous	Electrocautery interference
Real time	Can be affected by variation of cerebral blood flow
Inexpensive	Can not differentiate between causes of declining rSO_2 values
Portable, readily available	Can be affected by different forms of hemoglobin, excessive bilirubin
Safe	Can produce normal rSO_2 over an area with dead brain tissue
Easy to interpret	Interpretation may be confounded by hypothermia, alkalosis, or hypocapnia

Oxygen saturation of the jugular venous bulb (SjO_2) has been advocated as a marker of global cerebral oxygenation.[67] Decreased values of SjO_2 indicate a decreased oxygen supply relative to demand. Values of <50% during rewarming have been associated with postoperative cognitive decline.[67] Increased values of SjO_2 indicate decreased oxygen extraction relative to supply. Increased values might be caused by a hypothermic decrease in $CMRO_2$, pharmacologic suppression of $CMRO_2$, or severe brain injury to the point of reduced oxygen extraction.[67]

Electroencephalographic monitoring provides continuous detection of brain electrical activity. EEG can be used before initiating DHCA and during DHCA to document electrical silence, which reduces $CMRO_2$ by about 50%. It is a nonspecific monitor of global ischemia, which could be caused by malperfusion, hypotension, or CPB. It is more specific for the detection of epileptiform activity, which might be seen at temperatures of 30°C or caused by pathologic causes including ischemia. EEG is used to detect burst suppression, which can be induced at temperatures of 24°C or by pharmacologic agents such as barbiturates or etomidate. Burst suppression provides evidence of suppression of metabolic brain activity. EEG is used to detect electrical silence, which is achieved at about 17°C and which provides ultimate suppression of metabolic and electric brain activity. Circulatory arrest can be instituted once electrical silence has been present for 3 minutes. Limitations of electroencephalographic monitoring include its inability to reflect the activity of deeper brain structures, such as hippocampus and basal nuclei, which are very vulnerable to ischemia that affects neurocognitive function.[68] Although EEG is likely to reflect changes in energy expenditure necessary for electrical neuronal transmission, it is unlikely to reflect changes in energy consumption necessary for the maintenance of cellular integrity. Therefore, EEG is insufficient as an isolated method for ascertaining adequacy of cerebral protection. Somatosensory-evoked potentials are generally easier to implement than EEG because it is less prone to external electric noise, less influenced by anesthetic drugs, and remains detectable as long as cortical activity is present.[69]

ACID-BASE MANAGEMENT DURING HYPOTHERMIA

Hypothermia alters the results of analysis of arterial blood gases by increasing the solubility of CO_2 and O_2 in plasma. The increase in CO_2 solubility decreases the concentration of the insoluble portion and, thus, the partial pressure. However, the total content of CO_2 in the blood remains the same. During hypothermia, if a blood sample is taken and warmed to 37°C in the blood gas analyzer, the CO_2 initially dissolved will now

contribute to the partial pressure of CO_2 (PCO_2) and the PCO_2 will be within the normal normothermic range. If, on the other hand, the value is estimated at the patient's actual temperature, the PCO_2 will be reduced despite similar arterial CO_2 content. In addition to its effect on gas solubility, hypothermia decreases the metabolic rate and CO_2 production.

Maintaining the PCO_2 within the normal range in rewarmed 37°C blood is called "alpha-stat." If the PCO_2 is corrected to the patient's actual temperature and that value is kept within the normal range, the management is called "pH-stat."

Alpha-stat management is aimed at maintaining autoregulation of the brain and cellular enzymatic activity. It does so by maintaining normal acid and blood gas values in the rewarmed blood. At hypothermic temperatures, the blood remains alkalemic, and this, in addition to hypothermia, increases the affinity of hemoglobin to oxygen. Alpha-stat management would cause relative hypocarbia, which would produce cerebral vasoconstriction and reduce CBF. This would make this approach advantageous in decreasing embolic load and preventing overperfusion and subsequent cerebral edema.

The pH-stat method aims at maintaining normal values in vivo by adding CO_2, and when rewarmed the blood becomes acidemic and hypercarbic. The resulting hypercarbia causes cerebral vasodilation, increased CBF, and a loss of autoregulation. Increased CBF in conjunction with reduced $CMRO_2$ allow quick and homogenous cooling of the brain and increased oxygen delivery.

The pediatric literature generally supports the use of pH-stat management during DHCA for providing both cerebral and myocardial protection.[70] Clinical studies suggest that pH-stat is particularly beneficial in cyanotic neonates and infants because it shifts more CPB flow away from the aortopulmonary collateral circulation toward the cerebral circulation, improving cerebral cooling and oxygen supply.[71]

Because it maintains a physiologic coupling between CBF and $CMRO_2$, the alpha-stat strategy appears advantageous in adults in whom the risk of under- or overperfusion within the brain is substantial. Cerebral edema, which can be a consequence of cerebral overperfusion, is less likely to occur with alpha-stat strategy. However, the preservation of cerebral autoregulation may attenuate the uneven distribution of blood, which might occur in patients with an underlying vasculopathy like atherosclerosis, hypertension, or diabetes.[72]

Studies favoring pH-stat revealed significantly fewer episodes of jugular venous desaturation upon rewarming and reductions in cerebral arteriovenous glucose and oxygen gradients in comparison to alpha-stat.[73,74] Prior studies have shown worse neurologic outcomes using pH-stat during hypothermic CPB.[75] Theoretically, pH-stat management might provide the benefit of excessive cerebral blood flow but with an increased risk of macro- or microcerebral embolization.[76] Empirically, in an animal (pig) model of controlled microembolic load during DHCA, pH-stat was associated with improved outcomes when compared with alpha-stat.[77]

In the absence of definitive data favoring one strategy over the other, it might be prudent to use a combined strategy in which pH-stat is used while cooling, thus using the benefits of cerebral vasodilatation to enhance the rate and homogeneity of brain cooling; followed by the alpha-stat strategy from the interval immediately before cessation of circulation to the time of rewarming, thus minimizing extracellular acidosis and aiming for the preservation of CBF-$CMRO_2$ coupling during reperfusion and rewarming.[78]

TEMPERATURE MANAGEMENT

Cooling

The cooling phase should be gradual, thorough, and long enough to achieve homogenous allocation of blood to various organs and to prevent a gradual updrift of temperature during DHCA.[79] To achieve a final core body temperature (bladder and esophageal) of 10° to 13°C, cooling should last at least 30 minutes.[80] Rapid cooling might create imbalance between oxygen delivery and demand, and it might decrease oxygen availability to the tissues by increasing the affinity of hemoglobin to oxygen. This increased affinity combined with extreme hemodilution from the priming solution for CPB might lead to cellular acidosis before DHCA.

Moderate hemodilution leads to improved microcirculation, but extreme hemodilution might lead to tissue hypoxia. Studies have shown that intracellular acidosis was not present with a hematocrit (Hct) level of 30%, mild with an Hct of 20%, and severe with an Hct of 10%.[81,82] These studies showed that the cerebral capillary flow was maintained with an Hct of 30% despite increased blood viscosity during deep hypothermia.[82,83] Appropriate levels of Hct during pre- and post-DHCA would range from 22% to 28%, with proportional relationship to the core temperature.

Topical (Head) Cooling

A delay in temperature equilibrium may occur because of occlusive vascular disease that reduces cerebral perfusion. Ice packing of the skull enhances cerebral hypothermia via conduction across the skull.[84] Ice packing the head, in addition to keeping body temperature around 10° to 13°C, also might help in preventing an undesirable rewarming of the brain during DHCA. An animal (pig) study showed improved behavioral outcome with head ice packing during DHCA.[85] Another animal study showed improved recovery of metabolic function by >50% in piglets who had their heads packed in ice in comparison to those who did not.[86] Systems of continuous cooling of the head during DHCA recently have been developed. They consist of a cooling cap with an incorporated circuit of continuously circulated water at a desirable temperature.[87]

Rewarming

Rewarming increases CBF and the risk of embolization, cerebral edema, and hyperthermic brain injury. During rewarming, extracranial sites of temperature monitoring underestimate brain temperature by about 5° to 7°C; therefore, caution is required to avoid hyperthermic arterial inflow, which may result in brain hyperthermia.[88] During rewarming, it is recommended that the perfusate temperature not exceed core body temperature by more than 10°C; to stop rewarming when core body temperature is 36°C (esophageal) or 34°C (urinary bladder); and for perfusate temperature not to exceed 36°C.[60]

Relative hypothermia (36°C, esophageal; 34°C, urinary bladder) might be beneficial to prevent cerebral electrical hyperactivity.[89] When available, EEG should be monitored during rewarming to detect electrical hyperactivity, and when detected it should

be treated promptly with deepening the level of anesthesia and lowering the temperature. Initial reperfusion with relatively cold blood at low pressures allows washout of accumulated metabolites and free radicals and provides substrates for high-energy molecules. A period of initial hypothermic perfusion has been shown to improve neurologic outcome.[90]

DURATION OF DHCA

A number of biochemical and cellular structural changes take place as the duration of circulatory arrest lengthens. After 15 minutes of ischemia at 18°C, the recovery of oxygen consumption is impaired, and after 20 minutes, cerebral lactate is detected in the effluent blood. The safe duration of circulatory arrest at 15°C was predicted to be about 29 minutes and at 10°C about 40 minutes.[91] If ischemic tolerance is considered 5 minutes at normothermia, the calculated safe period of circulatory arrest at 18°C would be 15 minutes[91] (Fig 5). Clinical studies have shown a persistent loss of cognitive function (lasting more than 6 weeks) and deterioration in postoperative cognitive scoring/testing in patients who underwent aortic arch surgery by using DHCA for more than 25 minutes at 10°C.[92]

Intermittent DHCA with low-flow ("trickle") CPB has been used to extend the safe duration of DHCA. Intermittent perfusion is associated with higher oxygen saturation and lower lactate levels in the sagittal sinus, indicating a better supply of energy demands. Metabolic hemostasis is better maintained when intermittent perfusion is used every 20 minutes at 18°C.[92]

An experimental study using a combination of head ice packing and low-flow ("trickle") CPB during DHCA showed (1) that DHCA caused an impairment of cerebral metabolism, directly proportional to its duration; (2) a better recovery of metabolic function (improving >50%) in the group with head ice packing; (3) a "trickle" of a CPB of only 5 to 10 mL/kg/min during DHCA is superior to a DHCA only application at the same temperature; and (4) despite achieving a core body temperature of 18°C for 30 minutes, the brain requirement for O_2 may persist according to a higher level of temperature because the brain temperature tends to be higher than core body temperature.[86]

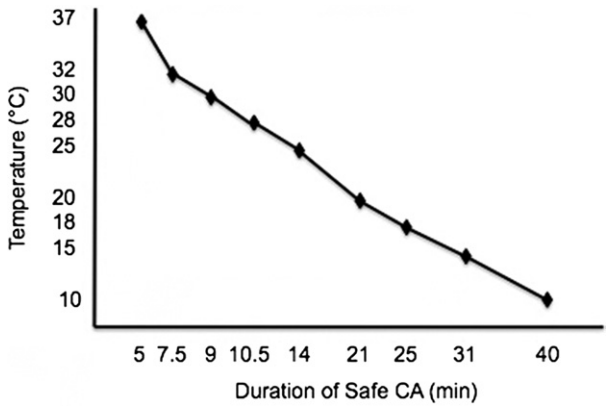

Fig 5. The relationship between the degree of hypothermia and safe duration of circulation arrest (CA).

Pulsatile flow maintains patent microcirculation at lower mean perfusion pressures than nonpulsatile flow, which allows the use of lower flow rates. Peak pressures developed during pulsatile flow helps to overcome the critical opening pressure of the capillaries. Pulsatile flow is associated with reduced cerebral vascular resistance and improved recovery of $CMRO_2$.[93] It also might be advantageous in improving the balance between myocardial oxygen supply and demand, especially during rewarming.[94]

NEUROLOGIC INJURY CAUSED BY DHCA

Neurologic injury is the most troublesome adverse effect of DHCA and CPB, presenting either as transient neurologic deficit (5.9%-28.1%) or irreversible neurologic injury (1.8%-13.6%). Early postoperative mortality markedly is increased (18.2%) in patients with neurologic injury, and long-term cognitive disability is common among survivors.[95] A focal deficit is usually an embolic phenomenon, whereas a prolonged poor perfusion of the brain may produce necrosis in watershed zones. Age, atherosclerosis, and manipulation of the aorta are risk factors for both. Global cerebral ischemia leads to diffuse neurologic deficit, which may be benign and reversible or more debilitating (seizures, Parkinsonism, and coma). Risk factors include increased duration of circulatory arrest and CPB, diabetes mellitus, and hypertension. Transient neurologic dysfunction appears to be a marker of long-term cerebral injury.[96] Deficits of memory and fine-motor function may persist after hospital discharge. Reductions in $CMRO_2$ and the duration of DHCA reduce the risk of neurologic injury.[32] The length of time on CPB might be a better predictor of postoperative death and stroke than the duration of DHCA time.[97] Microembolization during prolonged CPB is likely to be a greater risk factor for stroke than cerebrovascular ischemic time.[43]

In the pediatric population, evidence of overt brain injury might be found in up to 10% of patients exposed to DHCA, whereas subtle but detectable neuropsychiatric defects might be found in up to 50%.[98] In infants undergoing heart surgery, DHCA, compared with low-flow CPB, was associated with a greater degree of central nervous system perturbation (clinical and electroencephalographic seizures and a longer time to the recovery of normal brain activities as assessed by EEG) and a higher level of BB isoenzyme of creatine kinase during the early postoperative period, but at the time of hospital discharge both groups had similar overall incidence of abnormalities on neurologic examination and EEG.[99]

Measures that clearly have been documented to provide brain protection include the following: (1) systemic cooling and localized ice packing, (2) electroencephalographic silence, and (3) continuous or intermittent ACP. Measures that possibly have a role in brain protection include the following: (1) continuous RCP and (2) pharmacologic blockade of neurotransmitters. Hypothetical measures include pharmacologic blockade of reperfusion injuries.

CONCLUSION

DHCA is an established technique that is used during surgical repair of the aortic arch and other major vessels including the thoracoabdominal aorta, cerebral vessels, and

inferior vena cava. Circulatory arrest provides the convenience of a bloodless surgical field, whereas deep hypothermia provides significant protection to the brain and other major organs against circulatory arrest. Alternatives for DHCA include lesser degrees of hypothermia, to the point of normothermia, and lesser degrees of circulatory arrest through the use of various forms of intermittent or continuous perfusion techniques of the brain and other organs. There are both theoretic and experimental evidence of benefits and risks of DHCA and each of its alternatives. Although there is no conclusive evidence of the superiority of DHCA or any of its alternatives in affecting overall or specific outcomes in indicated procedures, there is sufficient reason to base the use of DHCA and/or any of its adjuncts and alternatives on the complexity of the vascular lesion, the expected duration of surgical repair, and the expertise of the operative team. Regardless of the degree of hypothermia or circulatory arrest that is being used, advances in monitoring cerebral and other organ functions and in pharmacologic and nonpharmacologic therapeutic interventions continue to provide tools for improving the outcome of care of patients with complex vascular lesions. Enhanced understanding of ischemic injury and IR injury provide further targets for intervention to improve outcome.

REFERENCES

1. Polderman KH: Application of therapeutic hypothermia in the ICU: Opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. Intensive Care Med 30:556-575, 2004

2. Fay T: Observations on generalized refrigeration in cases of severe cerebral trauma. Assoc Res Nerv Ment Dis Proc 24:611-619, 1943.

3. Bigelow WG, Lindsay WK, Greenwood WF: Hypothermia; its possible role in cardiac surgery: An investigation of factors governing survival in dogs at low body temperatures. Ann Surg 132:849-866, 1950

4. Drew CE, Keen G, Benazon DB: Profound hypothermia. Lancet 1:745-748, 1959

5. Griepp RB, Stinson EB, Hollingsworth JF, et al: Prosthetic replacement of the aortic arch. J Thorac Cardiovasc Surg 70:1051-1063, 1975

6. Gega A, Rizzo JA, Johnson MH, et al: Straight deep hypothermic arrest: Experience in 394 patients supports its effectiveness as a sole means of brain preservation. Ann Thorac Surg 84:759-766, 2007

7. Pieter J, van der Starre A: Deep Hypothermia and Circulatory Arrest in Thoracic Aortic Diseases. Berlin, Germany, Springer, 2006, pp 101-108

8. Haverich A, Hagl C: Organ protection during hypothermic circulatory arrest. J Thorac Cardiovasc Surg 125:460-462, 2003

9. Moon MR, Miller DC: Aortic arch replacement for dissection. Op Tech Thorac Cardiovasc Surg 4:33-57, 1999

10. Touati GD, Marticho P, Farag M, et al: Totally normothermic aortic arch replacement without circulatory arrest. Eur J Cardiothorac Surg 32:263-268, 2007

11. Kunihara T, Grun T, Aicher D, et al: Hypothermic circulatory arrest is not a risk factor for neurologic morbidity in aortic surgery: A propensity score analysis. J Thorac Cardiovasc Surg 130:712-718, 2005

12. Toyama M, Matsumura Y, Tamenishi A, et al: Safety of mild hypothermic circulatory arrest with selective cerebral perfusion. Asian Cardiovasc Thorac Ann 17:500-504, 1999

13. Kaneda T, Saga T, Onoe M, et al: Antegrade selective cerebral perfusion with mild hypothermic systemic circulatory arrest during thoracic aortic surgery. Scand Cardiovasc J 39:87-90, 2005

14. Klein JJ, Ergin A: Principles of cerebral protection during operations on the thoracic aorta, in Franco KL, Verrier ED (eds): Advanced Therapy in Cardiac Surgery. Hamilton, London, BC Decker Inc, 2003, pp 291-303

15. Boyle EM, Pohlman T, Cornejo C, et al: Endothelial cell injury in cardiovascular surgery: Ischemia-reperfusion. Ann Thorac Surg 62: 1858-1875, 1996

16. Verma S, Anderson TJ: Fundamentals of endothelial function for the clinical cardiologist. Circulation 105:546-549, 2002

17. Tseng RR, Brock MV, Lange MS, et al: Neuronal nitric oxide synthase inhibition reduces neuronal apoptosis after hypothermic circulatory arrest. Ann Thorac Surg 64:1639-1647, 1997

18. Rimpilainen J, Pokela M, Kiviluoma K, et al: Leukocyte filtration improves brain protection after a prolonged period of hypothermic circulatory arrest: A study in a chronic porcine model. J Thorac Cardiovasc Surg 120:1131-1141, 2000

19. Zhang M, Carroll MC: Natural Ig M-mediated innate autoimmunity: A new target for early intervention of ischemia-reperfusion injury. Expert Opin Biol Ther 7:1575-1582, 2007

20. Kimura T, Muraoka R, Chiba Y, et al: Effect of intermittent deep hypothermic circulatory arrest on brain metabolism. J Thorac Cardiovasc Surg 108:658-663, 1994

21. Busto R, Dietrich WD, Globus MY, et al: Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7:729-738, 1987

22. Dorotta I, Kimball-Jones P, Applegate R: Deep hypothermia and circulatory arrest in adults. Semin Cardiothorac Vasc Anesth 11:66-76, 2007

23. Dewhurst AT, Moore SJ, Liban JB: Pharmacological agents as cerebral protectants during deep hypothermic circulatory arrest in adult thoracic aortic surgery. A survey of current practice. Anaesthesia 57:1016-1021, 2002

24. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 64:165-170, 1986

25. Zaidan JR, Klochany A, Martin WM, et al: Effect of thiopental on neurologic outcome following coronary artery bypass grafting. Anesthesiology 74:406-411, 1991

26. Brain Resuscitation Clinical Trial 1 Study Group: A randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 314:397-403, 1986

27. Hirotani T, Kameda T, Kumamoto T, et al: Aortic arch repair using hypothermic circulatory arrest technique associated with pharmacological brain protection. Eur J Cardiothorac Surg 18:545-549, 2000

28. Shum-Tim D, Tchervenkov CI, Jamal AM, et al: Systemic steroid pretreatment improves cerebral protection after circulatory arrest. Ann Thorac Surg 72:1465-1471, 2001

29. Yang MW, Lin CY, Hung HL, et al: [Mannitol reduces plasma hydrogen peroxide free radical in patients undergoing coronary artery bypass graft surgery]. Ma Zui Xue Za Zhi 30:65-70, 1992

30. Hanley MJ, Davidson K: Prior mannitol and furosemide infusion in a model of ischemic acute renal failure. Am J Physiol 241: F556-F564, 1981

31. Strong AJ, Fairfield JE, Monteiro E, et al: Insulin protects cognitive function in experimental stroke. J Neurol Neurosurg Psychiatry 53:847-853, 1990

32. Ceriana P, Barzaghi N, Locatelli A, et al: Aortic arch surgery: Retrospective analysis of outcome and neuroprotective strategies. J Cardiovasc Surg (Torino) 39:337-342, 1998

33. Lazar HL, McDonnell M, Chipkin SR, et al: Society of Thoracic Surgeons Blood Glucose Guideline Task Force. The Society of Thoracic Surgeons practice guideline series: Blood glucose management during adult cardiac surgery. Report from the STS workforce on evidence based surgery. Ann Thorac Surg 87:663-669, 2009

34. Hadani M, Young W, Flamm ES: Nicardipine reduces calcium accumulation and electrolyte derangement in regional cerebral ischemia in rats. Stroke 19:1125-1132, 1998

35. Legault C, Furberg CD, Wagenknecht LE, et al: Nimodipine neuroprotection in cardiac valve replacement: Report of an early terminated trial. Stroke 27:593-598, 1996

36. Kass IS, Cottrell JE, Chambers G: Magnesium and cobalt, not nimodipine, protect neurons against anoxic damage in the rat hippocampal slice. Anesthesiology 69:710-715, 1988

37. Zhou Y, Wang D, Du M, et al: Lidocaine prolongs the safe duration of circulatory arrest during deep hypothermia in dogs. Can J Anaesth 45:692-698, 1998

38. Wang D, Wu X, Li J, et al: The effect of lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery. Anesth Analg 95:1134-1141, 2002

39. Mathew JP, Mackensen GB, Phillips-Bute B, et al: Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. Stroke 40:880-888, 2009

40. Jolkkonen J, Puurunen K, Koistinaho J, et al: Neuroprotection by the alpha2-adrenoceptor agonist, dexmedetomidine, in rat focal cerebral ischemia. Eur J Pharmacol 372:31-36, 1999

41. Effects of acadesine on the incidence of myocardial infarction and adverse cardiac outcomes after coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Anesthesiology 83:658-673, 1995

42. Arrowsmith JE, Harrison MJG, Newman SP, et al: Neuroprotection of the brain during cardiopulmonary bypass. A randomized trial of remacemide during coronary artery bypass in 171 patients. Stroke 29:2357-2562, 1998

43. Chong SY, Chow MY, Kang DS, et al: Deep hypothermic circulatory arrest in adults undergoing aortic surgery: Local experience. Ann Acad Med Singapore 33:289-293, 2004

44. Pochettino A, Cheung AT: Retrograde cerebral perfusion is useful for deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 17:764-767, 2003

45. Coselli JS, Buket S, Djukanovic B: Aortic arch operation: Current treatment and results. Ann Thorac Surg 59:19-27, 1995

46. Coselli JS: Retrograde cerebral perfusion is an effective means of neural support during deep hypothermic circulatory arrest. Ann Thorac Surg 64:908-912, 1997

47. Bachet J, Guilmet D, Goudot B, et al: Antegrade cerebral perfusion with cold blood: A 13-year experience. Ann Thorac Surg 67:1874-1878, 1999

48. Di Eusanio M, Schepens MA, Morshuis WJ, et al: Brain protection using antegrade selective cerebral perfusion: A multicenter study. Ann Thorac Surg 76:1181-1189, 2003

49. Halstead JC, Chir MB, Meier M, et al: Optimizing selective cerebral perfusion: Deleterious effects of high perfusion pressures. J Thorac Cardiovasc Surg 135:784-791, 2008

50. Muller D, Fieguth H, Wimmer-Greinecker G, et al: Neurologic outcome after surgery of the aortic arch: Comparison of deep hypothermic arrest, antegrade and retrograde cerebral perfusion. IJTCVS 20:72-76, 2004

51. Coselli JS, LeMaire SA: Experience with retrograde cerebral perfusion during proximal aortic surgery in 290 patients. J Card Surg 12:322-325, 1997 (suppl)

52. Safi HJ, Letsou GV, Iliopoulos DC, et al: Impact of retrograde cerebral perfusion on ascending aortic and arch aneurysm repair. Ann Thorac Surg 63:1601-1607, 1997

53. Usui A, Oohara K, Murakami F, et al: Body temperature influences regional tissue blood flow during retrograde cerebral perfusion. J Thorac Cardiovasc Surg 114:440-447, 1997

54. Bechtel JFM, Eleftheriadis S, Sievers HH: Surgical strategies for neuroprotection during ascending aortic and arch surgery. Appl Cardiopulm Pathophysiol 13:219-223, 2009

55. Moshkovitz Y, David TE, Caleb M, et al: Circulatory arrest under moderate systemic hypothermia and cold retrograde cerebral perfusion. Ann Thorac Surg 66:1179-1184, 1998

56. Svensson LG: Antegrade perfusion during suspended animation? J Thorac Cardiovasc Surg 124:1068-1070, 2002

57. Svensson LG, Hussain A, Penney DL, et al: A prospective randomized study of neurocognitive function and S-100 protein after antegrade or retrograde brain perfusion with hypothermic arrest for aortic surgery. J Thorac Cardiovasc Surg 119:163-166, 2000

58. Camboni D, Philipp A, Schebesch KM, et al: Accuracy of core temperature measurement in deep hypothermic circulatory arrest. Interact Cardiovasc Thorac Surg 7:922-924, 2008

59. Marino MR, Cheng WP, Romagnoli A, et al: Temperature bias: Jugular bulb venous temperature versus conventional sites. Ann Thorac Surg 70:1792, 2000

60. Ergin MA: Hypothermic circulatory arrest, in Coselli JS, LeMaire SA (eds): Aortic Arch Surgery: Principles, Strategies and Outcomes. West Sussex, UK, Willey Blackwell, 2008, pp 135-151

61. Hirofumi O, Otone E, Hiroshi I, et al: The effectiveness of regional cerebral oxygen saturation monitoring using near-infrared spectroscopy in carotid endarterectomy. J Clin Neurosci 10:79-83, 2003

62. Orihashi K, Sueda T, Okada K, et al: Near-infrared spectroscopy for monitoring cerebral ischemia during selective cerebral perfusion Eur J Cardiothorac Surg 26:907-911, 2004

63. Tobias JD, Russo P, Russo J: Changes in near infrared spectroscopy during deep hypothermic circulatory arrest. Ann Card Anesth 12:17-20, 2009

64. Murkin JM: NIRS: A standard of care for CPB vs. an evolving standard for selective cerebral perfusion? J Extra Corpor Technol 41:P11-P14, 2009

65. Denault A, Deschamps A, Murkin JM: A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth 11:274-281, 2007

66. Schepens M, Waanders F: Monitoring the brain: Near-infrared spectroscopy, in Coselli JS, LeMaire SA (eds): Aortic Arch Surgery: Principles, Strategies and Outcomes. West Sussex, UK, Wiley Blackwell, 2008, pp 114-124

67. Leyvi G, Bello R, Wasnick JD, et al: Assessment of cerebral oxygen balance during deep hypothermic circulatory arrest by continuous jugular bulb venous saturation and near-infrared spectroscopy. J Cardiothorac Vasc Anesth 20:826-833, 2006

68. Kahn RA: EEG monitoring is required during hypothermic circulatory arrest. Society of Cardiovascular Anesthesiologists Newsletter, October 2001

69. Hagl C, Khaladj N, Karck M, et al: Hypothermic circulatory arrest during ascending and aortic arch surgery: The theoretical impact of different cerebral perfusion techniques and other methods of cerebral protection. Eur J Cardiothorac Surg 24:371-378, 2003

70. DePlessis AJ, Jonas RA, Wypij D, et al: Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg 114:990-1001, 1997

71. Sakamoto T, Kurosawa H, Shin'oka T, et al: The influence of pH strategy on cerebral and collateral circulation during hypothermic cardiopulmonary bypass in cyanotic patients with heart disease: Results of a randomized trial and real-time monitoring. J Thorac Cardiovasc Surg 127:12-19, 2004

72. Muzic D, Chaney M: What's new with alpha-stat versus pH-stat? Society of Cardiovascular Anesthesiologists Newsletter, December 2005

73. Shaaban-Ali M, Harmer M, Vaughan RS, et al: Changes in cerebral oxygenation during cold and warm cardiopulmonary bypass using different blood gas strategies in patients undergoing coronary artery bypass grafting surgery. Acta Anesth Scand 48:837-844, 2004

74. Kiziltan HT, Baltah M, Bilen A, et al: Comparison of α-stat and pH-stat cardiopulmonary bypass in relation to jugular venous oxygen saturation and cerebral glucose-oxygen utilization. Anesth Analg 96: 644-650, 2003

75. Murkin JM, Martzke JS, Buchan AM, et al: A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. J Thorac Cardiovasc Surg 110:349-362, 1995

76. Plochl W, Cook DJ: Quantification and distribution of cerebral emboli during cardiopulmonary bypass in the swine: The impact of $PaCO_2$. Anesthesiology 90:183-190, 1999

77. Dahlbacka S, Heikkinen J, Kaakinen T, et al: PH-stat versus alpha-stat acid-base management strategy during hypothermic circulatory arrest combined with embolic brain injury. Ann Thorac Surg 79:1316-1325, 2005

78. Murkin J: Cerebral Autoregulation: The role of CO2 in Metabolic Homeostasis. Semin Cardiothorac Vasc Anesth 11:269-273, 2007

79. Harrington DK, Fragomeni F, Bonser RS: Cerebral perfusion. Ann Thorac Surg 83:S799-S804, 2007

80. Griepp RB: Cerebral protection during aortic arch surgery. J Thorac Cardiovasc Surg 121:425-427, 2001

81. Duebener LF, Sakamoto T, Hatsuoka S, et al: Effect of hemoglobin on cerebral microcirculation and tissue oxygenation during deep hypothermic bypass. Circulation 104:I260-I264, 2001

82. Shin'oka T, Shum Tim D, Jonas RA, et al: Higher hematocrit improves cerebral outcome after deep hypothermic circulatory arrest. J Thorac Cardiovasc Surg 112:1610-1621, 1996

83. Shin'oka T, Shum Tim D, Laussen PC, et al: Effects of oncotic pressure and hematocrit on outcome after hypothermic circulatory arrest. Ann Thorac Surg 65:155-164, 1998

84. Matalanis G, Hata M, Buxton BF: A retrospective comparative study of deep hypothermic circulatory arrest, retrograde and antegrade cerebral perfusion in aortic arch surgery. Ann Thorac Cardiovasc Surg 9:174-179, 2003

85. Griepp RB, Ergin MA, Mc Cullough JN, et al: Use of hypothermic circulatory arrest for cerebral protection during aortic surgery. J Card Surg 12:312-321, 1997

86. Mault JR, Ohtake S, Klingensmith ME, et al: Cerebral metabolism and circulatory arrest: Effects of duration and strategies for protection. Ann Thorac Surg 55:57-63, 1993

87. Lighthall GK, Cartwright CR, Haddow GR: An improved method for topical cerebral cooling during deep hypothermic circulatory arrest. J Thorac Cardiovasc Surg 120:403-404, 2000

88. Kaukuntla H, Harrington D, Bilkoo I, et al: Temperature monitoring during cardiopulmonary bypass—Do we undercool or overheat the brain? Eur J Cardiothorac Surg 26:580-585, 2004

89. The Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549-556, 2002

90. Ehrlich MP, McCullough J, Wolfe D, et al: Cerebral effects of cold reperfusion after hypothermic circulatory arrest. J Thorac Cardiovasc Surg 121:923-931, 2001

91. McCullough JN, Zhang N, Reich DL, et al: Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg 67:1895-1899, 1999

92. Reich DL, Uysal S, Sliwinski M, et al: Neuropsychologic outcome after deep hypothermic circulatory arrest in adults. J Thorac Cardiovasc Surg 117:156-163, 1999

93. Watanabe T, Washio M: Pulsatile low-flow perfusion for enhanced cerebral protection. Ann Thorac Surg 56:1478-1481, 1993

94. Soeda M: Antegrade selective cerebral perfusion combined with deep hypothermic circulatory arrest on cerebral circulation: Comparison between pulsatile and nonpulsatile blood flows. Ann Thorac Cardiovasc Surg 13:93-101, 2007

95. Stier GR, Verde EW: The postoperative care of adult patients exposed to deep hypothermic circulatory arrest. Semin Cardiothorac Vasc Anesth 11:77-85, 2007

96. Ergin MA, Uysal S, Reich DL, et al: Temporary neurological dysfunction after deep hypothermic circulatory arrest: A clinical marker of long-term functional deficit. Ann Thorac Surg 67:1887-1890, 1999

97. Svensson LG, Crawford ES, Hess KR, et al: Deep hypothermia with circulatory arrest. Determinants of stroke and early mortality in 656 patients. J Thorac Cardiovasc Surg 106:19-31, 1993

98. Gandhi S, Pigula F: Strategies for aortic arch reconstruction without circulatory arrest in Franco KK, Verrier ED (eds): Advanced Therapy in Cardiac Surgery. Hamilton, London, BC Decker Inc, 2003, pp 334-346

99. Newburger JW, Jonas RA, Wernovsky G, et al: A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med 329:1057-1064, 1993