Surgical repair of the ascending aorta and aortic arch that employs cardiopulmonary bypass (CPB), often with the use of deep hypothermic circulatory arrest (DHCA), allows for life-saving therapy. In doing so, however, it also represents a unique injury paradigm leading to derangements in numerous homeostatic pathways. Organ injury, most notably cerebral injury, may result as a consequence of these various perturbations in inflammatory and oxidative stress pathways that have been implicated in the pathogenesis of cerebral injury. [1-3] Adverse cerebral outcomes are a major source of morbidity after major cardiovascular surgery, particularly after aortic surgery. Despite advances in surgical, anesthetic, and neuroprotective strategies, the incidence of perioperative stroke after thoracic aortic surgery remains approximately 4-15%, while temporary neurological dysfunction (TND) and cognitive decline have a documented incidence of 16-22% and up to 30%, respectively. [4-8] The incidence of adverse cerebral outcomes is particularly high in patients undergoing emergent repair / replacement of the ascending aorta or aortic arch. [7,9] Preventing or treating perioperative cerebral injury remains difficult, partly because the underlying mechanisms associated with the ischemia-reperfusion injury introduced by DHCA and CPB are incompletely understood.

Without question, hypothermia allows for the conduct of many cardiovascular procedures on the heart and aorta that would otherwise not be possible. No more dramatic an example of this are procedures requiring deep hypothermic circulatory arrest (DHCA). Completely arresting the circulation is critical for the conduct of a number of procedures, examples of which include surgery on the aortic arch and pulmonary embolectomy. Although the use of these low temperatures can clearly preserve organ function (particularly the brain), the actual target temperature at circulatory arrest, as well as the strategies used to obtain that temperature and rewarm from it, have undergone considerable revision in recent years. Furthermore, modifications in the choice of cannulation sites and perfusion techniques, (most notably, selective cerebral perfusion), has also allowed for the modification of these hypothermic strategies.

Fundamental to the consideration of hypothermia for DHCA is its putative global organ protective effects. As it pertains to the brain, hypothermia, while having a suppressing effect on cerebral metabolism (approx. 6-7% decline per °C),[10] likely has other neuroprotective effects that are mediated by non-metabolic mechanisms. Moderate hypothermia has multimodal effects on the ischemic brain including blocking the release excitotoxic amino acids (such as glutamate),[11] reducing calcium influx,[12] hastening recovery of protein synthesis,[13] diminishing membrane-bound protein kinase C activity,[14] slowing of the time to onset of depolarization,[15] reducing formation of reactive oxygen species,[16] and suppressing nitric oxide synthase activity.[17] It is likely that the additive effect of these mechanisms conveys a hypothermia-mediated neuroprotective effect. However, although the experimental demonstrations of the neuroprotective benefits of hypothermia are abundant, definitive clinical examples, until the demonstrations of its efficacy following cardiac arrest, have been few. [18-23]
Fundamental to the issue of temperature management is its accurate measurement. Whereas measuring temperature within the brain itself cannot practically be done, an appropriate surrogate of brain temperature should be chosen. These surrogates include nasopharyngeal (NP) temperature as well as tympanic membrane temperature. More invasive brain temperature surrogates have also been used including the measurement of jugular bulb temperature with a thermistor placed retrogradely from the internal jugular vein.[24] Interestingly, newer non-invasive technologies providing information on brain temperature are also emerging. It is clear from these different temperature sites that significant temperature gradients exist across the body and across the brain during bypass. It is likely that during periods of rapid flux (such as during rewarming [25]), that these temperature gradients are maximal making a non-cerebral brain temperature site particularly prone to misrepresenting brain temperature.

The risks and benefits of hypothermia need to be balanced. Lower temperatures and slower rewarming times significantly prolong CPB and all its inherent risks. In general, three techniques for temperature selection have been described for DHCA. The first is to cool all patients to a specific target temperature, usually in the 15°C-19°C range without regard to time or other monitoring targets. The second is to cool the patient to a neurophysiologic endpoint such as EEG silence, which allows clinicians to individually tailor the depth of hypothermia. However, as approximately 60% of CMRO$_2$ is utilized for neuronal function (with the remainder being required for cellular integrity), there may still be significant cerebral metabolic requirements requiring deeper hypothermia to suppress. This may in part explain why achieving EEG silence pharmacologically does not appear to offer adequate neuroprotection in cardiac surgery.[26,27] The third is to cool a patient to a specific temperature based on the predicted safe times for various degrees of hypothermia and the surgeon’s expected circulatory arrest time. [28,29]

Related to the issue of temperature and organ injury is the counter current argument related to hyperthermia. Compared to hypothermia, hyperthermia, in an opposite and disproportionate fashion, has injurious effects.[11] Although the normothermic vs. hypothermic CPB studies, which were a major focus for cardiac surgery in the 1990s [30-32], demonstrated few neuroprotective effects, a potential explanation for this lack of effect may be related to the obligatory rewarming that occurs at the end of bypass. Indeed, Grigore et al.,[33] studied the effect of different rewarming rates on neurocognitive outcome after CABG. These investigators compared conventional “fast” rewarming to slower rewarming and found a lower incidence of neurocognitive dysfunction six weeks after cardiac surgery. These slower rewarming rates were accompanied by lower peak cerebral temperatures during rewarming, consistent with past observations that rapid rewarming can lead to an overshoot in cerebral temperature resulting with the occurrence of inadvertent cerebral hyperthermia.[34] By reducing this rewarming rate, one limits (and ideally prevents), the overshoot in temperature and avoids the negative cerebral effects of hyperthermia. Indeed, the beneficial effect may actually have been mediated by the avoidance of cerebral hyperthermia during rewarming rather than the prolonged hypothermia.[35] These rewarming studies, when coupled with the post-operative temperature data suggesting that early postoperative fever is associated with worse neurocognitive decline, [36] suggests that avoiding hyperthermia may be beneficial in this population. Taken together, the postoperative period represents a potentially important time period in which to intervene with a strategy of preventing hyperthermia and associated cognitive impairment. Thus, we have no convincing evidence from clinical trials that mild hypothermia during non-DHCA CPB is neuroprotective. The likely explanation for this is that any degree of neuroprotection afforded by hypothermia is negated by the obligatory rewarming period that ensues.[33]
Once circulation to the brain has been arrested, it is no longer exposed to cold perfusate. However, concerns have been raised that the brain is at risk to passively rewarm, increasing CMRO$_2$, and thus increasing the risk for the development of cerebral ischemia. Given that the mechanism is presumed to be the transfer of heat from the immediate surrounding environment, topically cooling the patient’s head has been proposed as technique to mitigate this problem. The use of **topical cooling** as an adjunct to DHCA has recently been debated.[37,38] The experimental data is somewhat mixed. Some evidence in animal models supports that topical cooling maintains a lower cortical temperature provides superior neuroprotection and allows quicker return of normal cerebral metabolism. [39-41] However, there is contradictory evidence in other animal models where no benefits were identified and the lactate:glucose ratio was poorer in the group receiving topical cooling.[42] Opponents additionally point out that it can be logistically difficult, may interfere with the use of neurophysiologic monitoring, and likely has limited impact on heat transfer in the adult human brain. [37] Furthermore, the cranium has been studied in various models of heat transfer and it is not particularly conducive to conductive heat transfer. Furthermore, the surrounding OR temperatures are usually relatively low, making the gradient that heat must follow also very low. Given current short DHCA times, adjunct perfusion techniques (RCP and ACP), and lack of definitive evidence, it is unclear what role topical cooling has in aortic arch procedures.

Various **pharmacologic therapies** have been considered as adjuncts to hypothermia for neuroprotection in cardiac surgery and have been previously reviewed.[43-46] Conceptually, several of the mechanisms of neuroprotection are similar to those from hypothermia, including the reduction of CMRO$_2$ and cerebral energy demand or interfering with pathways involved in neuronal ischemic injury and apoptosis. Many of the processes involved in ischemic injury occur in parallel, so agents that function within a narrow range of effects may have limited value. Agents with multiple mechanisms of action, multiple agents, or both may be required to achieve optimum neuroprotection.

The neuroprotective properties of barbiturates have been studied for several years. Their protective mechanisms of action include CMRO$_2$ reduction and improved regional blood flow as well as decreasing cation fluxes (Na+, K+ and Ca2+) and scavenging free radicals. Interest in the benefits for cardiac surgery patients mounted following the results of a study where patients given thiopental until EEG silence displayed fewer postoperative neurologic complications.[47] Subsequent studies failed to duplicate this outcome and in addition to prolonged sedation, longer time to extubation and higher vasopressor requirements, these negative results led to less enthusiasm to barbiturate therapy.[26,48] Propofol, etomidate, benzodiazepines and the volatile agents are other anesthetics that have been studied and show varying potential as neuroprotectants. To date their evidence remains mixed inconclusive or requires further study.[44,46]

Excitotoxicity, with the binding of glutamate released during reperfusion to N-methyl-D-aspartate (NMDA) receptors is central to the ischemic cascade. NMDA receptors may be involved in excitotoxic neuronal injury and have been addressed in several studies. Studies of magnesium and ketamine, both NMDA antagonists, have been unconvincing in the degree of benefit. Magnesium was shown to preserve short-term memory and brainstem function following cardiac surgery, however the benefits did not persist past the first post-operative days.[49] Ketamine did not show any significant improvement in cognitive function 10 weeks after
perioperative administration.[50] This lack of benefit was reinforced by a review of trials demonstrating the futility of ketamine for neuroprotection in cardiac surgery.[51]

Corticosteroid administration is one of the most common adjuncts administered because of the evidence that it reduces the post-CPB inflammatory response. Intuitively, decreasing the inflammatory cascade should reduce neuronal injury given the prominent role its components play in the process. Current literature presents a mixed picture. In patients undergoing DHCA, steroid administration was shown to improve neurologic outcomes.[52] But in a systematic review of surgeries requiring CPB, steroids demonstrated a reduction in inflammatory markers but no difference in neurologic outcomes.[53] Furthermore, in traumatic brain injury steroid therapy was even shown to cause harm, likely in part to hyperglycemia.[54] This inconclusive evidence, as well as the possibility of immune suppression and hyperglycemia, must be taken into account when considering it as adjunctive therapy.

Cation influx of sodium and calcium play important roles in the initiation and propagation of ischemic cellular injury. The antagonism of these influxes, using sodium and calcium channel blockers, has been a therapeutic target in several studies. Lidocaine can slow the large sodium influx into ischemic neurons, reducing the degree of depolarization, preserving ATP stores, and blocking apoptotic pathways.[55-57] Its use has been shown to preserve neuronal integrity, reduce infarct size and prolong the duration of safe DHCA in various animal studies.[58,59] In humans undergoing cardiac surgery there have been small studies demonstrating improved postoperative cognitive function.[60,61] However in one larger prospective, randomly-controlled trial, lidocaine administration did not result in any improved neurological outcome and caused worse outcomes in a subset of diabetic patients. [62]

Closely linked to temperature is the issue of blood gas management. Our understanding of how to manage intraoperative pH has also evolved, particularly in the pediatric population. It was once a choice to use either pH-stat or alpha-stat, now using these two strategies in a combined, sequential manner, is now commonplace. Alpha-stat blood gas management is currently the most frequently utilized strategy in adult CPB. In contrast to pH-stat management, in alpha-stat management hypothermia-induced hypocarbia and alkalosis are not corrected, but rather a pH 7.4 and PaCO2 40mmHg is targeted and measured at 37°C (regardless of the actual patient temperature). Evidence in the literature for benefit of one strategy over the other is conflicting. In a study of 316 patients by Murkin et al.,[63] 90% of the subgroup of patients who were on CPB for 90 minutes or more showed a significant reduction in post-operative cognitive impairment with the alpha-stat method (p=0.047 versus pH-stat). Stephan et al., in a study of 65 patients, also showed a higher incidence of neurological dysfunction on day 7 post-operatively in the pH-stat group.[64] The proposed protective mechanism is the avoidance of the excessive increase in cerebral blood flow, and the associated increase in cerebral microemboli that occurs with pH-stat management. Patel et al. studied pH versus alpha-stat ABG management in 70 patients undergoing cardiac surgery, demonstrating reduced neuropsychologic impairment in the alpha-stat patients. [65] Larger scale randomized trials with long-term neurological follow-up are still required to properly address the issue.

In retrograde cerebral perfusion (RCP), once DHCA is initiated, CPB flow is reversed delivering cold perfusate in retrograde fashion into the superior vena cava (SVC) at a rate which maintains a pressure of 25-30 mmHg. It does require special attention to venous cannulation and pressure monitoring of the SVC. RCP may provide 10-30% of the baseline CBF delivering metabolic substrate, and extending safe DHCA time beyond 60 minutes.[66-68] These benefits
come at the expense of potential harm, such as increased cerebral edema. Some studies dispute the effectiveness of RCP to provide significant CBF.

Its mechanism for protection has been debated. Some have suggested that the benefit is obtained via the flushing out of emboli previously delivered on the arterial side of the circuit, RCP has been shown to reduce both mortality and stroke rates when compared to straight DHCA in large retrospective studies.[69,70] The other possible RCP-related mechanisms for these improved outcomes are related to better homogeneity of brain cooling. [71]

Selective antegrade cerebral perfusion (SACP) has been popularized over the past decade and is now used as a first-line neuroprotective technique – even in cases where DHCA times would be less than 30 minutes, particularly when higher temperatures are used. The merits of SACP compared to DHCA or RCP have been reviewed previously.[71-81] Animal models of SACP have shown preserved cerebral energy balance and metabolism, greater protection form neuronal ischemia, less cerebral edema and improved neurophysiological recovery when compared to DHCA.[82-85] There are studies that have shown improved outcome, including fewer neurologic deficits and even reduced mortality. [86-91] One proposed disadvantage of SACP is the potential for increased risk of embolic stroke secondary to additional arterial manipulation and cannulation. [92,93]

Most results, whether supportive or not of SACP, are clouded by the extensive use of retrospective analysis, significant patient and institution heterogeneity, different methods of defining and investigating outcomes, and a general paucity of prospective or randomized studies of perfusion techniques. [94] Despite the uncertainty on the superiority of any technique, the surgical community is generally in agreement that some form of SACP is required in repairs where >60 minutes of circulatory arrest is expected.[79] As the experience with SACP has grown institutions have performed aortic arch surgery using progressively warmer temperatures, even to the point of a normothermic approach.[95] The major proposed benefit of minimizing hypothermia is to avoid the previously discussed complications such as prolonged CPB times as well as hypothermia induced organ injury and coagulopathy. In an attempt to avoid the negative consequences of cooling and prolonged CPB times, various groups have begun operating with SACP and lower body circulatory arrest at mild hypothermic (28-34°C) temperatures. This trend has led several authors to question the safety of this strategy. [73,96,97] The major concern is for the potential of increased risk for spinal cord and visceral ischemia at milder temperatures. The emerging results of these studies suggest that mild hypothermia with ACP is safe and has comparable outcomes to other methods.

Cerebral monitoring is central to the management of patients undergoing DHCA. Electroencephalographic monitoring (EEG) detects the brain’s cortical neuronal electrical activity. The pattern of recorded electrical activity will change, in a step-wise fashion, as neuronal electrical function decreases. Burst suppression represents the stage where cerebral metabolism is significantly suppressed. EEG silence represents full suppression of neuronal electrical activity, though gives no information on the metabolic requirements for maintenance of cellular integrity. Burst suppression and EEG silence can result from hypothermic metabolic suppression, anesthetic agents, or the brain’s response to ischemia. [98,99] Studies have shown a wide range of temperatures and duration of hypothermia before EEG silence is achieved.[99-101] Excessive depth of hypothermia or duration of cooling can be avoided with the use of individualized cooling with EEG guidance, rather than a “one size fits all” strategy, for commencing DHCA. [102]
Near infrared spectroscopy (NIRS) may provide supplementary information on residual brain metabolism and oxygen supply/demand balance during circulatory arrest. The regional brain oxygen saturation (rSO₂) principally represents oxygenated venous blood (approximately 70%) and NIRS has previously been correlated with SJVO₂.[103,104] During DHCA the continued cerebral oxygen consumption, albeit suppressed, is theoretically detectable by a declining rSO₂ value.[105] While this may help determine the limit of cerebral protection and onset of ischemia, it may also assist in deciding between unilateral vs. bilateral antegrade perfusion or titrating the antegrade perfusion flows.[106-108] Recently, Fischer et al [109] studied a cohort of patients undergoing aortic arch surgery. They measured SpO₂ intraoperatively, relating various cerebral saturation thresholds and both cerebral and non-cerebral adverse outcomes. Although NIRS represents a significant area for advancing neuroprotection, further investigations are required before it can be confidently recommended outside the field of aortic arch surgery.

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