Temperature and pH Management Strategies for Circulatory Arrest

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Although surgical repair of the ascending aorta and the aortic arch employing cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) allows for lifesaving therapy, 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 [1-3] inflammatory, hemostatic and oxidative stress pathways, all of which have been implicated in the pathogenesis of cerebral injury. Significant adverse cerebral outcomes can occur after major cardiovascular surgery. Despite advances in surgical, anesthetic, and neuroprotective strategies, the incidence of perioperative stroke after thoracic aortic surgery remains at 4-15%, while temporary neurological dysfunction (TND) and long-term 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 or 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. Both temperature and pH management strategies have been implicated as factors available to mitigate cerebral injury.

Without question, hypothermia has allowed for the conduct of lifesaving 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. In addition, in the pediatric population, DHCA, although used increasingly in place of low flow CPB is frequently used for the repair of life-threatening congenital cardiac abnormalities. Although the use of these low temperatures can clearly serve to preserve organ function (most notably the brain), the actual target temperature at arrest, as well as the strategies used to obtain that temperature and rewarm from it, have undergone considerable revision in recent decades. Furthermore, modifications in the choice of cannulation sites and perfusion technique, (most notably, selective cerebral perfusion), has again allowed for the modification of these hypothermic strategies.

Fundamental in the consideration of hypothermia for CPB is its putative, though far from definitively proven, global organ protective effects. 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 pathways. Moderate hypothermia has multimodal effects in the ischemic brain including blocking the release of 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 neuroprotection from hypothermia. Although experimental demonstrations of the neuroprotective benefits of hypothermia are abundant, definitive clinical examples, until the recent demonstrations of its efficacy following cardiac arrest, have been few. [18-21] Outside the DHCA setting, the optimal temperature strategy for cardiac surgery has been debated for decades. Some of the most illustrative data outlining the pros and cons of various temperature strategies during CPB have come within the past 15-20 years. In the late 1980’s and early 1990’s, warm CPB (along with continuous warm cardioplegia) was revisited because of its putative myocardial salvaging effects.[22-25] Possible cerebral effects of this warmer CPB were investigated as there was a concern that cerebral outcome could be compromised. Several large studies have been undertaken examining the effects of temperature management on cerebral outcome after cardiac surgery. The Warm Heart Investigators group, performed a trial at Emory University,[26] and a later trial at Duke University.[27] although demonstrating important methodological differences, had very similar neurocognitive outcome results,[28,29] but remarkably different results pertaining to stroke.[22] None of the studies demonstrated any neuroprotective benefit from hypothermia on neurocognitive outcome. A more recent trial by Nathan et al also failed to show any benefit to hypothermia.[30] The Warm Heart Investigators trial and the Duke trial similarly showed no difference with respect to stroke. This was in contrast to the Emory trial that demonstrated an apparent injurious effect (higher stroke incidence) of what was most likely mild degrees of hyperthermia during CPB. These divergent results could partly be explained by differences in how temperature was monitored (i.e., nasopharyngeal vs. bladder), what the peak and nadir temperatures were, and how normothermia was maintained (actively warmed vs. allowing the patient’s temperature to passively drift). Most relevant to the issue of stroke was that in the Emory trial, patients were actively warmed, which in itself is not injurious if it is precisely carried out. Furthermore, they did not measure nasopharyngeal temperature, making it highly likely that they exposed the brain to hyperthermic temperatures. These data suggest that active warming to maintain temperatures at (or greater) than 37°C may pose an unnecessary risk of stroke. 

Fundamental to the issue of temperature management is how to accurately measure temperature in situations where the brain is at risk. Whereas measuring temperature within the brain itself cannot practically be done, when this is not directly possible, a surrogate of brain temperature should be chosen. These include nasopharyngeal 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.[31] 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[32]), that these temperature gradients are maximal making a non-cerebral brain temperature site particularly prone to misrepresenting brain temperature. 

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 referred to previously [22,26,27] demonstrated no neuroprotective effects, a potential explanation for this lack of effect may be related to the obligate 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 thereby avoids the negative effects of cerebral hyperthermia. Supporting the concept that limiting rewarming may be neuroprotective was a study by Nathan et al.[35] that demonstrated a neurocognitive benefit for patients who had limited rewarming and were maintained between 34 and 36º for a prolonged (12 hours) period post-operatively. 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.

The post-operative period may be equally important with respect to temperature management and cerebral injury in cardiac surgery patients. Grocott et al. demonstrated a direct relationship between postoperative hyperthermia and cognitive loss at six weeks after surgery.[36] It is unclear, however, whether this hyperthermia is directly responsible for the cognitive decline, or the hypothermia is secondary to the cerebral injury itself, such as injury to hypothalamic theroregulatory areas. 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]

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.,[37] 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.[38] 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. [39] Larger scale randomized trials with long-term neurological follow-up are still required to properly address the issue.

References


