pH-stat vs alpha-stat Management During DHCA

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Despite a half century of research and the implementation of various risk-reduction strategies among clinicians and basic scientists, patients continue to experience strokes and cognitive dysfunction related to the use of deep hypothermic circulatory arrest (DHCA) during cardiopulmonary bypass (CPB) for cardiac surgery. The debate over optimal blood gas management during DHCA continues. Most clinicians agree on fundamental differences with respect to pH-stat and alpha-stat management strategies between the pediatric/neonatal and adult cardiac surgery. Differences in brain neuroplasticity and ability to brain repair, presence of atheromatous aorta in elderly adult patients, cerebral embolic load, and presence of multiple co-morbidities may all impact the decision making with respect to pH-stat and alpha-stat management strategies in these two distinct patient populations.

Basics of pH-stat and alpha-stat management

The pH-stat and alpha-stat refers to the acid-base management strategies at different body temperatures during CPB. The solubility of CO$_2$ in blood increases as the body temperature decreases and vice versa (the coca-cola effect). The decrease in PaCO$_2$ results in alkaline pH yet the total CO$_2$ content remains the same. In order to maintain normal pH either the gas flow is reduced or the CO$_2$ is added to the CPB circuit, i.e. pH is corrected to 7.4 and PaCO$_2$ at 40mmHg according to patient’s body temperature. This is the basis of pH-stat management strategy. On the contrary, the alpha-stat management strategy does not correct for pH and CO$_2$ changes induced by hypothermia resulting in hypocarbia and alkalemia. These two management strategies result in different effects on cerebral blood flow (CBF), changes in oxygen dissociation curve shifts, altered intracellular enzyme and protein activity, and modulation in cerebral metabolic rate.

Temperature management and CPB

Temperature plays a significant role in cerebral physiology and physiopathology during CPB and DHCA. The human central nervous system (CNS) receives about 15% of the resting cardiac output and consumes about 20% of the oxygen required by the body at rest. The brain, which accounts for 2% of the total body weight, has an oxygen consumption of about 3.5 mL$^{-1}.100$ g$^{-1}.min^{-1}$. This high metabolic rate mandates a high CBF that is normally under metabolic, neural, myogenic, and chemical control. Maintaining steady body temperature preserves the cerebral metabolic rate of oxygen (CMRO$_2$) and coupling with CBF. It is known that for every 1°C decrease in body temperature, CMRO$_2$ decreases by 7%. The Q10 (the ratio of CMRO$_2$ at a given temperature divided by the CMRO$_2$ at a temperature 10°C lower) in the physiologic range of 27°C to 37°C is between 2 and 3. At temperatures less than 27°C, Q10 increases to approximately 4.5, reflecting suppression of neuronal function that occurs between 17°C and 27°C.

Hypothermia has been shown to be neuroprotective in different brain injury models. Cerebral ischemia is associated with less cytotoxic injury if brain is rendered hypothermic even after the initial insult. Hypothermia induced reduction in PaCO$_2$ acts as a direct cerebral vasoconstrictor reducing cerebral blood flow and intracranial pressure. This is associated with reduced vascular permeability, reduced leukocyte migration in the ischemic brain, and less cerebral edema. Some of the other mechanisms of action aiding
to better understanding of the therapeutic effects of hypothermia include reduced oxygen and glucose utilization, reduced glutamate and free radical formation, membrane stabilization, and reduced release of inflammatory cytokines. Furthermore, inhibition of apoptosis has also been suggested to contribute to neuroprotective effects of induced hypothermia.

With mild to moderate hypothermia, the coupling of flow to metabolism and vascular responses to PaCO2 and PaO2 are preserved. However, cerebral autoregulation may be impaired, even under hypothermic conditions, if the CO2 content of the blood is allowed to rise, which happens when the pH-stat method of blood gas management is used. Changes in CBF are most apparent in the cerebral and cerebellar cortex but are not significant in the hypothalamus and brainstem.

Intraoperative hypothermia is used to varying degrees in surgical procedures requiring circulatory arrest or CPB. With the use of CPB, CBF has been shown to decrease by up to 55% at the lowest measured temperature of 26°C correlating with a 56% reduction in CMRO2. At progressively lower temperatures, CBF continues to decrease to the point that the electroencephalogram tracing becomes isoelectric, which, in animal studies, has been found to be at approximately 18°C. During profound hypothermia (18°C-20°C), CBF is disproportionately maintained and is determined more by arterial blood pressure and systemic vascular resistance than by pump flow rates. When hypothermia is combined with doses of thiopental that produce EEG suppression, the synergistic effects further reduce the CMRO2, leading to an additional decrease in CBF. Although inhaled volatile anesthetic agents also have similar effects on CMRO2, they do not cause the additional drop in CBF. Hypothermia also attenuates cytokine release during cardiac surgery.

Martin et al randomized 1001 patients to ‘warm’ (≥ 35°C) and ‘cold’ (≤ 28°C) CPB groups. Authors reported on a three-fold increase in stroke rate in the ‘warm’ CPB group (4.5% vs. 1.4%). In contrast, the WHCS trial of 1732 patients randomized to either normothermic (n = 860) or hypothermic (n = 872) CPB techniques rendered no difference in stroke rates between the two respective groups (1.6% vs. 1.5%). More recent evidence supports the latter study suggesting that ‘cold’ CPB has little to offer in terms of better preservation of cerebral oxygenation when compared to ‘warm’ CPB management. Lack of benefit is likely related to mistiming of ischemic insult resulting in cerebral injury and application of hypothermia. Furthermore, accelerated rewarming strategies may worsen neurological outcomes as measured by cognitive dysfunction.

Controversy continues regarding benefits of hypothermia in preserving cognitive function after cardiac surgery. Regragui et al showed better cognitive outcomes with ‘tepid’ CPB (T = 32°C) versus ‘warm’ CPB (T = 37°C), and no additional benefit with ‘cold’ CPB (28°C). The majority of studies, however, have shown no benefit of hypothermic CPB with respect to cognitive dysfunction after cardiac surgery. A recent landmark study by Nathan et al provided further evidence of a neuroprotective effect of mild hypothermia in the perioperative setting. Patients who were separated from CPB at 34°C versus 37°C performed better on neurocognitive testing 1 week and 3 months after CABG surgery. However, a more recent study by the same group of investigators showed that in the absence of rewarming and cerebral hyperthermia, sustained mild hypothermia did not improve cognitive outcome.
Deep Hypothermic Circulatory Arrest

Although the actual mechanism by which DHCA protects the brain has not been definitively elucidated, it is thought to be multimodal. The most clearly demonstrated factor is temperature-induced cerebral metabolic suppression: a cerebral metabolic coefficient ($Q_{10}$) of 2.3 has been shown to occur during cooling to temperatures as low as 15°C. In addition, mild to moderate hypothermia reduces glutamate and dopamine release during ischemia and influences plasma glycine concentrations, thereby affecting the activation of NMDA receptors and reducing intracellular calcium accumulation.

DHCA has been used since the 1950s as a neuroprotective measure in cardiac surgery and is currently the most commonly used method to provide cerebral protection when surgeons repair the distal ascending aorta, transverse arch, or proximal descending aorta. DHCA is also used during procedures that require CBF to be completely interrupted.

Adequate and homogeneous hypothermia must be achieved before circulatory arrest is instituted. Some authors have recommended inducing truly profound hypothermia before circulatory arrest to achieve maximal metabolic suppression, particularly if DHCA time is anticipated to last 30 minutes or longer, in which case it has been recommended to cool the patient to 10°C to 11°C. A variety of factors are crucial in achieving optimum outcome with DHCA: 2 key components are cooling the head and maintaining CBF during the cooling phase.

Because hypothermia decreases blood viscosity, thereby decreasing CBF, hemodilution is essential in maintaining adequate CBF during cooling. Given the sensitivity of the cerebral vasculature to carbon-dioxide levels in the blood, managing pH levels, which can be optimally achieved with a combination of the _-stat or the pH-stat method, is also important. The _-stat method—in which temperature is not corrected and the oxygenator gas mixture and flows are adjusted to maintain a normothermic pH of 7.4 and a $P_{CO_2}$ of 40 mm Hg—was previously the preferred method of pH management during DHCA. An animal study using piglets has more recently shown that, during the cooling phase of CPB, a significant suppression of CMRO$_2$ occurs with the pH-stat method, in which a natural hypothermic-induced alkaline shift is corrected by addition of CO$_2$. However, the beneficial effect of using the pH-stat management is counteracted by a significant reduction in cerebral metabolic recovery during the rewarming phase of CPB. Therefore, Skaryak et al recommended that the pH stat method be used only during initial cooling and the _-stat strategy be used during the late cooling and rewarming periods of CPB.

Other studies using piglet models, have reported that the pH-stat strategy could be superior to the traditional _-stat method during both the cooling and rewarming phases of CPB. The underlying mechanism behind these findings is thought to be related to the vasodilatory effect of hypercarbia, which induces loss of cerebral autoregulation, resulting in improved cerebral cooling and tissue oxygenation before the institution of circulatory arrest and brain ischemia.
The results of another study investigating the determinants of a safe duration of DHCA agree with the latest reports favoring the pH-stat method. The authors found that using the pH-stat strategy, lower temperatures, higher hematocrit levels, and shorter duration of DHCA protect the brain more effectively and allow a safer and longer duration of DHCA.

**Adjuvant techniques during DHCA**

Two adjuvant neuroprotective surgical techniques, selective antegrade cerebral perfusion (SACP) and retrograde cerebral perfusion, have frequently been used in conjunction with DHCA to improve the safety zone of circulatory arrest and cerebral ischemic time.

With SACP, selective neuroprotection is achieved with cold antegrade intermittent blood perfusate while the rest of the body receives either DHCA or moderate hypothermic circulatory arrest. Even though there have been concerns related to the possibility of cerebral emboli originating from the cannulation site, as well as uneven distribution of CBF, there is a strong body of evidence supporting the successful use of this technique. More recently, several authors have demonstrated that SACP at 20°C provides better neurologic outcomes than does moderate hypothermic (30°C) or deep hypothermic (10°C) SACP. A recent shift toward the use of moderate hypothermic circulatory arrest with cold SACP has been shown to have superior outcomes, as compared with DHCA.

Retrograde cerebral perfusion, provides the advantage of preventing emboli by removing the air and debris from cerebral vessels and providing adequate oxygen delivery and nutrition support. However, some authors have expressed concern that the retrograde cerebral perfusion technique could lead to cerebral edema and an inadequate supply of CBF during hypothermic circulatory arrest. These concerns have been supported by Okita et al, who found a significantly higher incidence of transient brain dysfunction in a group of patients treated with retrograde cerebral perfusion, as compared with a group treated with than SACP. The results of more-recently published studies have not supported these findings, showing instead that the use of cold retrograde cerebral perfusion is an effective neuroprotective technique. These results have been sustained by Svensson et al, who found no difference in S100ß protein levels, a marker of neurologic insult, when the use of retrograde cerebral perfusion was compared with that of SACP.

**Pharmacological Neuroprotection during DHCA**

Many neuroprotective drugs that have appeared to work in animals have failed when tested in humans. It has even been suggested that with the failure of so many clinical trials, the future of neuroprotective drug development is in jeopardy. Furthermore, the pharmaceutical companies are unwilling to go through extremely costly trials even in the presence of very encouraging phase I and phase II studies.

One of the recently most studied drugs with respect to different models of neuroprotection in both animal models and humans, is erythropoietin. Although primary mechanism of neuroprotection involves an anti-apoptotic effect of erythropoietin, the other CNS protective modalities include neurotrophic, antioxidant, angiogenic, and anti-inflammatory effects of this drug.
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Ten adult dogs were randomized to receive either intravenous recombinant human erythropoietin 5000 U/kg or placebo (normal saline). CPB was initiated and 120 minutes of DHCA (18 degrees C) employed. The level of tau proteins in the cerebrospinal fluid was significantly lower in the erythropoietin-treated group than in the untreated group at 6 hours and 12 hours after DHCA. The total Neurologic Deficit Score was 59±31 (0, normal; 500, brain death) in the erythropoietin-treated group, compared with 376±30 in the placebo group, p = .01). Histopathologic examination revealed that ischemic neuronal changes and apoptosis in the hippocampus CA1 were significantly lower in the erythropoietin-treated group. This study showed that erythropoietin protected the central nervous system during prolonged DHCA, partly by preventing both necrosis (ischemic neuronal changes) and apoptosis.

Although the early animal studies are very encouraging the human data of erythropoietin application in the DHCA setting is currently lacking. Future studies will likely address this lack of data.

Conclusions

Current body of evidence is leaning towards the pH-stat based CPB management technique with employment of DHCA strategy. Monitoring of nasopharyngeal and arterial inflow temperatures are the minimum requirements. Slow rewarming rates are encouraged to avoid ‘overshooting’ and cerebral hyperthermia. The use of adjuvant techniques such as selective antegrade cerebral perfusion and retrograde cerebral perfusion may better preserve brain from ischemic insult. Further studies are required to establish current consensus nationally and internationally of best clinical practice in the management of patients undergoing cardiac surgery with CPB and DHCA.

References:

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