

The Neurologic Sequelae of Cardiopulmonary Bypass-Induced Cerebral Hyperthermia and Cerebroprotective Strategies

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Abstract: Cerebral hyperthermia during the rewarming phase of cardiopulmonary bypass (CPB) is associated with adverse outcomes. Cerebral hyperthermia can exacerbate a preexisting injury prior to rewarming, and may be damaging in itself. Temperature and cerebral metabolic rate (CMRO₂) play a vital role in cerebral autoregulation. Therefore, hyperthermia can have a strong impact on cerebral oxygen transfer, and neurologic outcome. Glutamate levels can increase during cerebral hyperthermia, leading to eventual cell death. Rapid rewarming decreases jugular venous hemoglobin saturation, creating a mismatch be-

tween cerebral oxygen consumption and delivery. With these ill effects in mind, cerebral protection during CPB is imperative. Special attention should be given during rewarming to prevent these harmful outcomes. Pharmacologic agents such as sodium nitroprusside can be used to assist the rewarming process. Temperature management is the key component during the rewarming phase of CPB in the prevention of cerebral hyperthermia. **Keywords:** cardiopulmonary bypass (CPB), cerebral hyperthermia, neurologic dysfunction, cerebroprotection. *JECT. 2003; 35:317–321*

With respect to mortality, perioperative neurologic complications account for up to 20% of deaths in cardiac surgery (1,2). Although overall mortality following cardiopulmonary bypass (CPB) from cardiac causes has decreased, the incidence of identified neurologic complications has not (3). Furthermore, neuropsychologic impairment following CPB has been suggested to occur in upwards of two-thirds of all cases (4). During and after the perioperative period, cerebral ischemia is a common contributor of neurologic injury (5). The principle mechanisms of the cerebral ischemic injury are gaseous and particulate emboli and hypoperfusion caused by cerebrovascular occlusive disease or inadequate cerebral perfusion during CPB. While a fraction of all neurologic complications are the product of embolic events, the contribution of cerebral hyperthermia during the rewarming phase of CPB cannot be excluded.

Cerebral hyperthermia (perfusate temperatures greater than 38°C) during the rewarming phase of CPB is often appreciated. CPB rewarming replaces patient heat energy loss during hypothermic CPB and results in a gradual increase in patient temperature adequate for termination from CPB. Currently, cerebral hyperthermia during CPB has not been independently linked to neurologic compromise. However, during cardiac surgery with cardiopulmonary bypass, ischemic changes on electroencephalography (EEG) as a result of impaired central nervous system blood supply have been demonstrated, as well as post-

CPB neuropsychologic deficit (6–7). These studies and other data suggest that CPB-induced cerebral ischemia could represent one arm of a double insult when coupled with cerebral hyperthermia during the rewarming phase.

Many studies employing a double insult model that combines cerebral hyperthermia and cerebral ischemia have demonstrated evidence of significant neurologic dysfunction (8). Postischemic hyperthermia exacerbates neurologic injury (9) and causes a worsened recovery of cerebral hemoglobin oxygenation (10). Stroke literature demonstrates mild hyperthermia worsens neurologic outcome in cerebral ischemia independently (11), and postischemic hyperthermia aggravates neurologic injury in stroke and head injury patients (12–14). Dietrich et al. concluded hyperthermia greatly increases ischemic brain damage and mortality when compared to normothermia, transforms ischemic cell injury into infarction, and accelerates changes in appearance of ischemic brain injury where delayed neuronal necrosis is usually demonstrated (15).

Annually, there are more than 800,000 cardiac surgeries performed in the United States and abroad (16). Therefore, growing acceptance and interest in identifying and reducing adverse cerebral outcomes is paramount. With this in mind, the focus of this discussion is to review some of the current literature on cerebral hyperthermia, cerebral ischemia, and neurologic dysfunction and from this exchange derive a cerebroprotective strategy to use during the rewarming phase of CPB.

PATHOPHYSIOLOGY OF CEREBRAL HYPERTHERMIA

Cerebral hyperthermia may contribute to neurologic and neurocognitive injury, as well as encephalopathy and

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post-CPB confusion (17). Cerebral hyperthermia can exacerbate injury that occurred before rewarming. Furthermore, cerebral hyperthermia may be damaging itself, thereby removing any protective effect of hypothermia normally used during cardiac procedures with CPB support (3). Cerebral hyperthermia can occur during the rewarming phase of CPB because of the proximity of the carotid arteries to the aortic cannulation site and high cerebral blood flow fraction of cardiac output (17). Because of the relative high flow of blood to the brain, the brain rewarms quickly and could be hyperthermic during prolonged rewarming periods (3). The pathophysiology of cerebral hyperthermia, cerebral ischemia, and neurologic complication are reviewed in the following sections.

Cerebral Hyperthermia and Neurologic Outcome

As previously mentioned, cerebral hyperthermia, as a direct contributor of neurologic dysfunction is a link not yet established. However, when cerebral ischemia is added to the clinical situation, neurologic complications arise, as demonstrated in the following studies.

In a canine study of complete cerebral ischemia, Wass et al. demonstrated that small changes in temperature of 1° or 2°C beyond normal body temperature during rewarming resulted in significant alterations in cerebral histopathology and postischemic neurologic function (18). The central nervous system (CNS) has been shown to be sensitive to heat (19); therefore, an elevated temperature after hypothermia could worsen neurologic outcome.

Reith et al., while examining acute strokes at normothermia, found mortality was lower and outcome was better in those patients with mild hypothermia on admission and both were worse in patients with hyperthermia. The patients in this study were admitted to the hospital within 6 hours of the stroke event. Increases in body temperature beyond normothermia were proportionally related to mortality, lesion size, initial stroke severity, and predictive of outcome. The results of this study suggest the key to reducing mortality and improving outcome in survivors is to lower temperature after stroke. This study also found brain lesion size to increase exponentially with increasing temperature; therefore, lowering the temperature would apply, especially to hyperthermic patients (20).

Cerebral Hyperthermia on Cerebral CMRO₂

Shum-Tim et al. demonstrated in a piglet model that postischemic hyperthermia caused significantly worse recovery of cerebral hemoglobin oxygenation (10). Three groups were used in this study; the first group had cerebral temperatures of 34°C, the second had brain temperatures of 37°C, and a third group had hyperthermic temperatures of 40°C. In this study, hyperthermia was associated with deterioration of neurobehavioral outcome. Electroencephalographic (EEG) seizures were only seen in the hy-

perthermic animals, leading to significantly lower EEG amplitude in this group. The potential for severe brain edema in the hyperthermic group may be reflected by an increase in body weight and total body water content (10). Normothermic and hyperthermic brain temperatures following ischemia increases the blood-brain barrier permeability, which most likely accounts for increased cerebral edema (21).

Brain temperature also increases after cerebral ischemia, despite normal body temperature regulation (10). Cerebral metabolism, which is among the highest in the body and measured by the cerebral metabolic rate (CMRO₂), generates significant heat (22,23). A principal determinant of cerebral blood flow (CBF) during CPB is temperature (24). Similarly, increases or decreases in CMRO₂ are associated with changes in CBF, regulated by the brain responding to its oxygen demand (24). Temperature and CMRO₂ play a vital role in cerebral autoregulation (25). The message from this group of studies implies that cerebral ischemia accompanied by hyperthermia has a dramatic impact on neurologic outcome, cerebral oxygen transfer and cerebral autoregulation, emphasizing the necessity for closely monitoring temperature during the rewarming phase of CPB, as well as the venous saturation, and venous PO₂.

Cerebral Hyperthermia and Systemic Inflammatory Response

Cardiac surgery and the use of CPB results in a multifactorial activation of the systemic inflammatory response as demonstrated by the presence of leukocyte activation, elevated cytokines, complement activation, and platelet dysfunction. The downstream pathologic effects are exhibited by increases in reperfusion injury, postoperative bleeding, vasoplegia, and hyperthermia (23,26). Cerebral hyperthermia may also be caused by an increase in endogenous pyrogens (Il-1 β , Il-6, TNF- α), the surgery itself, or from the use of hypothermia and promotion of inflammatory reactions (27). Il-6, TNF- α , and Il-1 β either directly or in a co-stimulatory mechanism, circulate to the hypothalamus eliciting the release of prostaglandin E₂ (28), thereby resetting and altering the hypothalamus, as well as the systemic temperature regulation (28). The production of pyrogenic molecules leads to heat promoting mechanisms, such as vasoconstriction, increased metabolism, and shivering, to become activated (28). These mechanisms may uncouple the flow-metabolism relationship. This message highlights the importance of developing more biocompatible CPB circuit components to ameliorate this inflammatory process.

Cerebral Hyperthermia and Cerebral Oxygenation

Hyperthermia increases cerebral oxygen demand (10, 17) which may stress the ischemia-related injury cascade

(17). Hyperthermia may precipitate neuronal cell death early in the postischemic period when neurons are especially vulnerable (10). Small, hyperthermic temperature increases of 1–2°C can worsen neurologic outcome (18). Minamisawa et al. examined mild hyperthermia in rats and found neuronal necrosis following 10 minutes of ischemia. The percentage of damaged neurons increased from 15–80% as temperature climbed from 35°C to 39°C (29).

During the rewarming phase of CPB, jugular venous hemoglobin saturation decreases with rapid rewarming (30). Jugular venous desaturation (a decrease in jugular venous oxygen saturation to <50%) has been reported in 17–50% of CPB patients (17,31–33). Jugular venous saturation reflects the balance between cerebral oxygen consumption and cerebral oxygen delivery (34). Jugular venous desaturation can be caused by an increase in cerebral metabolism or by a reduction in cerebral oxygen delivery (34). Reports suggest the severity of postoperative neuropsychological deficit has been associated with the magnitude of rewarming-induced jugular venous hemoglobin desaturation (31,35). Therefore, during the rewarming phase of CPB, a mismatch between cerebral oxygen consumption and delivery can develop (30). The mismatch of flow and metabolism could be caused by the inability of the cold vasculature of the brain to respond to vasodilatory stimuli or the increased CMRO₂ is not followed by a response of the vasodilatory mediators from the cold cerebral neuronal tissue (30). Also, cerebral oxygen requirements may exceed cerebral oxygen delivery because of: the loss of cerebral autoregulation, alterations in blood flow caused by nonpulsatile bypass, and hemodilution effects (32). When rewarming slowly versus quickly, the faster rewarming group displays a greater oxygen extraction, thereby corresponding to greater levels of jugular venous desaturation (30). These studies demonstrate cerebral oxygen transfer is linked to temperature and length of the rewarming period.

Cerebral Hyperthermia and Neurotransmitter Excitotoxicity

Glutamate, the main excitatory neurotransmitter in the CNS (36), increases in concentration in focal ischemic areas in the brains of rats with cerebral hyperthermia (37). The extracellular concentration of glutamate is amplified several times during ischemia. Excessive glutamate receptor stimulation can lead to neuronal cell death attributable to large extracellular accumulation of glutamate (38,39). The action of glutamate, under normal conditions, is terminated quickly by its reuptake by astrocytes. Astrocytes prevent extracellular accumulation of glutamate, thereby preventing an excitation of neurons causing excitotoxicity (36,40). Astrocytes subjected to deep hypothermia and rewarming may experience a loss of capacity to produce a significant amount of energy through oxidative phosphorylation, thus, relying on anaerobic metabolism (41). The

reduced availability of high-energy phosphates (41), diminish cellular regulation of glutamate concentration, resulting in neuronal cell compromise.

POTENTIAL CEREBROPROTECTIVE STRATEGIES

Temperature Management during CPB

The benefits of systemic hypothermia and neurologic outcome have been well documented and appear to exist as a standard of practice in many CPB protocols. There are many benefits to slow rewarming versus aggressive or quick rewarming during CPB. An aggressive rewarming technique (H₂O temperature >40°C) can result in overheating the brain, resulting in the aforementioned detriments. Slowly rewarming produces less oxygen extraction, maintaining a normal relationship between CBF and CMRO₂. This balance aids in maintaining a greater jugular venous saturation, facilitating adequate cerebral oxygen transfer (30). Slow rewarming should begin earlier during CPB to maintain lower water temperatures, thereby reducing the risk of cerebral hyperthermia. Earlier rewarming allows heat to redistribute to the periphery while sustaining a greater time period to replenish lost heat energy to the patient (41). Rewarming rates should not exceed a gradient of 10°C between venous blood and the heat exchanger water source (42). Maintaining temperatures within this gradient will prevent the liberation of gas from solution, also decreasing the chance for neurologic complications (42). Furthermore, slow rewarming will maintain the cerebral flow/metabolism coupling, ensuring adequate oxygen delivery to the brain.

Modes of Temperature Monitoring during CPB

Monitoring of blood temperatures is an absolute imperative while rewarming patients during CPB. These temperatures usually require a nasopharyngeal temperature (NP) or esophageal temperature of 37°C, bladder or rectal at 35°C, and a site such as the great toe of 30°C (42). Studies have reported NP temperatures to underestimate cerebral temperature (11,17,43). Therefore, the possibility of inadvertent hyperthermia of the brain while monitoring NP temperature during the rewarming period of CPB exists (43). Others have reported esophageal temperatures to be 1°C less than brain temperature and rectal temperature 2°C less than brain temperature (10). Although it is apparent that NP temperatures will underestimate brain temperature, bladder and rectal temperatures change more slowly because of decreased blood flow to these peripheral sites (11). Monitoring bladder temperature alone could result in an extended period of cerebral hyperthermia because heat from the arterial blood dissipates as it reaches peripheral sites (11). NP or tympanic sites should be used during CPB to monitor patient temperature, in addition to bladder or rectal sites, because of

closer brain temperature monitoring (11). However, even these two sites can underestimate cerebral temperature (11,17,43). When greater hypothermic temperatures have been used, bladder temperature can assist in monitoring rewarming in showing uniformity of rewarming (11). Blood returning to the patient should reach a maximum of 38°C, while that of the water temperature at a maximum of 38.5°C, thereby decreasing the chances of cerebral hyperthermia (11).

Rebound hypothermia is the product of inadequate rewarming during CPB. Insufficient rewarming during CPB can result in a 2–3°C drop in temperature before arrival to the ICU. Rebound hypothermia can lead to shivering, cardiac rhythm abnormalities, increased oxygen consumption, as well as increased peripheral vascular resistance (42). When bladder temperatures fall below 35°C, shivering should be anticipated (42). Ralley et al. demonstrated in the early postoperative period after CPB that significant increases in oxygen consumption, production of carbon dioxide, heart rate (HR), cardiac output (CO), are present and increased further when patients shiver (44). Patients who shivered had significantly higher cardiac index (CI) and HR during the period of greatest muscular activity. The venous saturation decreased in those who shivered, even though CO increased significantly (44). Oxygen demands can increase up to 400–500% in those shivering attributable to hypothermia (45,46). Adequate rewarming and muscle relaxants can be used to combat shivering in the early post-operative period (42). The message from this study suggests that maintaining normothermia post-operatively can have a profound effect on patient outcome.

Modulation of Vascular Tone during CPB

Vasoconstriction occurs during hypothermia while on CPB, thereby decreasing blood flow through peripheral vascular beds. During rewarming, the periphery is slow in rewarming because of the decreased blood flow, causing the periphery to remain relatively hypothermic following termination of CPB (47). After CPB, the periphery steals heat from the core, thereby decreasing core temperature. The use of vasodilators to facilitate the rewarming phase of CPB causes the periphery to vasodilate, enhancing blood flow and, therefore, heat transfer to those tissues (48).

Sodium nitroprusside (SNP) and nitroglycerin (NTG) may be used to accentuate rewarming and decrease the risk of the post-operative hypothermia. These agents are useful because of their potency, rapid onset, and short duration of action (42). SNP, a major arterial vasodilator and venodilator, is enzymatically converted directly to nitric oxide in the plasma, hence the predominant arterial effect (42). NTG, on the other hand, undergoes intracellular bioconversion in the vascular endothelium, as a result venous effects predominate (42). Phenoxybenzamine

(PBZ) alongside SNP and NTG all produce vasodilatory effects in canines, but significantly less time is required to rewarm to 36°C as compared to NTG or SNP (49). Furthermore, PBZ produces a greater decrease in systemic vascular resistance than NTG or SNP (49). The use of nitroprusside and other mechanistically similar vasodilators can lead to the requirement for volume expansion or augmented perfusion flow to compensate for pressure fluctuations (42).

CONCLUSION

In closing, with the current amount of procedures requiring CPB support, the concerns for CPB-induced neurologic dysfunction are well founded. Therefore, temperature management during the rewarming phase of cardiopulmonary bypass is of the utmost importance. To reiterate, hyperthermia has not been directly implicated to affect neurologic outcomes. However, when hyperthermia is associated with ischemia, the following sequelae can occur: enhanced release of neurotransmitters, increased blood–brain barrier permeability, impaired recovery of cerebral metabolism, increased free radical production, worsening of cytoskeletal proteolysis, and an increase in ischemic depolarization in the penumbra (8), alteration of neuronal cells viability, increased initial stroke severity, lesion size, and worsened recovery of cerebral hemoglobin oxygenation, among others. Therefore, protective cerebral measures should include: slow rewarming, lower water temperatures; maintenance of an arterial–venous gradient less than 10°C; several foci of patient temperature monitoring, allowing for inconsistencies seen in NP, bladder, and rectal temperatures. Bladder temperature is suggested to monitor total body rewarming during CPB, and NP temperature is useful for observing trends in brain rewarming temperature, as a complement to bladder temperature (50). The use of such vasodilators as SNP and NTG can be used to facilitate rewarming with the understanding that volume expansion or increases in flow may be required for maintenance of adequate perfusion pressures. Rebound hypothermia, which may lead to patient complications, should be avoided. Jugular venous bulb oxygen saturation is a valuable tool for measuring the ability of blood flow to meet metabolic demands. The degree of desaturation may reflect the ability of the brain to extract oxygen, when inadequately supplied (32). Although CPB involves rewarming patients back to normothermic temperatures, the rewarming phase of cardiopulmonary bypass should continue to be of primary concern, as well as the focus of continued research.

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