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Clinical Review

ENVIRONMENTAL HYPERTHERMIA IN PREHOSPITAL PATIENTS WITH MAJOR TRAUMATIC BRAIN INJURY

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☐ **Abstract—Background: Traumatic brain injury (TBI) results in an estimated 1.7 million emergency department visits each year in the United States. These injuries frequently occur outside, leaving injured individuals exposed to environmental temperature extremes before they are transported to a hospital. Objective: Evaluate the existing literature for evidence that exposure to high temperatures immediately after TBI could result in elevated body temperatures (EBTs), and whether or not EBTs affect patient outcomes. Discussion: It has been clear since the early 1980s that after brain injury, exposure to environmental temperatures can cause hypothermia, and that this represents a significant contributor to increased morbidity and mortality. Less is known about elevated body temperature. Early evidence from the Iraq and Afghanistan wars indicated that exposure to elevated environmental temperatures in the prehospital setting may result in significant EBTs, however, it is unclear what impact these EBTs might have on outcomes in TBI patients. In the hospital, EBT, or neurogenic fever, is thought to be due to the acute-phase reaction that follows critical injury, and these high body temperatures are associated with poor outcomes after TBI. Conclusion: Hospital data suggest that EBTs are associated with poor outcomes, and some preliminary reports suggest that early EBTs are common after TBI in the prehospital setting. However, it remains unclear whether patients with TBI have an increased risk of EBTs after exposure to high environmental temperatures, or if this very early "hyperthermia" might cause secondary injury after TBI.** © 2015 Elsevier Inc.

☐ **Keywords—hyperthermia; traumatic brain injury; fever; prehospital**

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INTRODUCTION

Every year, over 1.7 million patients are evaluated in United States (US) emergency departments (EDs) for traumatic brain injury (TBI); 275,000 of these patients require hospitalization, and 50,000 die (1,2). The lifetime cost of TBIs sustained in the year 2000 alone was estimated to be over 60 billion dollars, and more than 2% of the US population required long-term assistance with activities of daily living as a result of TBI (3–5). Secondary brain injury is a major contributor to increased morbidity and mortality from TBI. Secondary damage occurs after the injury, when blood or oxygen transport to the brain is compromised. Several factors have been identified as causing secondary brain injury in the early patient care intervals, including hypotension, hypoxia, and hyperventilation, all of which have been independently associated with increased mortality after TBI (6–9). Although these factors are known to contribute to secondary brain

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injury by decreasing central nervous system (CNS) perfusion, they also result in electrolyte shifts and initiation of cellular cascades, ultimately resulting in the induction of apoptosis in susceptible CNS cells (10).

In the Intensive Care Unit (ICU) setting, patients with severe TBI are known to develop elevated body temperatures (EBTs), or neurogenic fever, often associated with poor outcomes and increased mortality (11–14). Although poorly understood, it is thought that these neurogenic fevers are caused by a failure of the brain to appropriately regulate temperature after injury, a process known as thermodysregulation (15). This inability to properly regulate body temperature may leave the patient susceptible to wide fluctuations in body temperature, either environmentally induced *hypo*thermia or EBTs. The majority of the current literature focuses on EBTs induced by thermodysregulation, occurring hours to days after injury (the acute-phase reaction). However, less is known about whether the propensity of severe TBI patients to have dysregulation might also put them at higher risk for environmentally induced EBTs while still in the field (i.e., during the prehospital phase of their care). Given the fact that so many TBI patients have issues with thermoregulation, there is a possibility that they are "set up" to be sensitive to high environmental temperatures that may happen in the prehospital environment. Furthermore, even if this is not the case, the simple fact that such patients may have a significant environmental heat load prior to arrival at the hospital makes it possible that some of them present with passively induced higher body temperatures. Thus, even if thermodysregulation is not yet occurring, they may simply "start hotter" at the beginning of their hospital course. Thus, they may be at higher risk to be affected by subsequent dysregulation based simply upon the fact that their body temperatures were warmer when their hospital course began.

Environmental hyperthermia has long been recognized as a deadly emergency medical condition that requires rapid treatment (16–18). Hyperthermia can occur rapidly in vulnerable populations, such as in children, the elderly, undocumented immigrants, or those with genetic predisposition to heat susceptibility (19–21). Although the precise definition varies, heat stroke is a highly lethal clinical condition that involves multiorgan failure and CNS dysfunction, including thermal dysregulation, in the setting of environmental hyperthermia (11,16). Thermally stressed individuals are at significantly increased risk for heat stroke when the body's core temperature exceeds 40°C. Medical comorbidities and other conditions such as acclimatization play a significant role in an individual's susceptibility to heat stroke and death (22). Heat stroke is traditionally thought of as a disease associated with environmental heat waves. Heat waves are usually defined as 3 or more consecutive days with high temperatures that exceed 32.2°C (90°F) (11,16). Currently, little is known about whether brief exposure to environmental temperature extremes might result in significantly increased body temperatures after TBI, and whether this might cause decreased survival or compromised functional outcomes.

DISCUSSION

Traumatic Brain Injury

In individuals, body temperature is exquisitely regulated (23). Although poorly understood, temperature regulation is thought to depend on cold- and heat-sensitive neurons in the CNS that modify local heat production and blood flow to adjust for changes in the temperature of incoming blood (24–26). In the case of brain injury, these normal mechanisms of heat regulation become disrupted and cause fever, in the absence of an infectious source. This dysregulation can result in very high body temperatures, commonly exceeding 41.1°C (15).

Early care is another factor that seems to affect patient outcomes after TBI, likely because the initial insult, or "primary brain injury," is not the sole determiner of outcomes (27,28). "Secondary injury" to the CNS also increases disability and the risk of death. When this happens early in the patient's course, this potentially preventable (or perhaps even reversible) damage may become indelible, despite subsequent optimal management (8,29–38). Secondary brain injury can occur through a variety of mechanisms, most of them by decreasing nutrient delivery to the brain through decreased cerebral perfusion pressure or cerebral blood flow. Hypotension and hypoxemia are common causes of secondary CNS damage, and early hypoxia and hypotension have been associated with poor outcomes (6–8,30–35,37,39–54). Similarly, hyperventilation has been associated with secondary brain injury, acting by reducing cerebral blood flow through a variety of mechanisms including global cerebral vasoconstriction (10).

Therapeutic interventions that target secondary injury are currently the mainstay of the evidence-based guidelines for care of patients with TBI, both in and out of the hospital (30,55). Current prehospital guidelines for the care of patients with severe TBI include: administration of high-flow oxygen, administration of intravenous fluids to maintain a systolic blood pressure at or above 90 mm Hg, and, when bag-valve-mask ventilation or endotracheal intubation is necessary, maintain

an End-tidal Carbon Dioxide ($ETCO_2$) between 35 and 45 mm Hg (30). Ongoing investigations evaluate these interventions to determine if broad application of evidence-based guidelines for the care of patients with TBI will improve outcomes (38). Likely due to lack of evidence, current guidelines for the care of patients with TBI do not recommend measurement of temperature or any effort to maintain a normal body temperature in the very early prehospital setting.

Pathophysiology: Elevated Body Temperature as a Mechanism of Secondary Brain Injury

Hyperthermia causes injury in healthy individuals and is associated with a broad spectrum of injury patterns commonly recognized as heat stroke (16). Exposure to heat alone can cause direct cellular and tissue damage (56). Fortunately, the damaging effects of heat are normally mitigated by the expression of heat shock proteins enabling the brain and other vital organs to tolerate temperatures of up to 41.5°C for short periods of time with minimal damage (57). This protective "thermal threshold" seems to be dependent on the ability of the hyperthermic individual to maintain normal perfusion, dissipate heat, and successfully produce protective heat shock proteins. When unable to mount a successful response to hyperthermia (due to factors such as age, dehydration, lack of acclimatization, or genetic polymorphisms), individuals are more susceptible to heat and progress to heat stroke at lower body temperatures (16). As discussed above, primary brain injury is also likely to result in increased susceptibility to heat and body temperatures in excess of 41°C.

Heat may induce secondary brain injury through several mechanisms. In the early prehospital setting in which patients may be exposed to high ambient temperatures, both systemic and local factors have the potential to result in secondary brain injury after TBI (58). Secondary CNS injury from systemic insults such as hypotension, hypoxia, and hyperventilation have all been linked to increased mortality after TBI, as discussed above. Even relatively mild increases in body temperature may exacerbate these factors.

Several examples of how elevated temperature might cause a systemic insult and secondary injury include the following: increases oxygen utilization, resulting in or exacerbating local or systemic hypoxia; promotes peripheral vasodilatation, resulting in decreased central blood volume, thereby inducing hypotension (16,59,60). Elevated temperature induces tachypnea as a mechanism of heat dissipation (16). Although the significance of tachypnea in the absence of endotracheal intubation is unknown, the potential for tachypnea to induce hypocarbic vasoconstriction, decreased cerebral blood flow, and secondary CNS damage has been demonstrated (10).

Elevated body temperature has several local effects on the CNS that also may result in secondary damage after TBI. For example, hyperthermia is associated with disorders in coagulation and microvascular hypercoagulability. This has been demonstrated to lead to CNS damage after injury in several animal studies (60–63). Neurons also may be exposed to a greater heat burden than other organ systems. CNS temperature, although tightly regulated, is higher (by 0.39°–2.5°C) than core body temperature, potentially exposing neurons to higher temperatures than other cell types and increasing the risk of direct cellular damage (56,57,64). Hyperthermia also seems to result in neuronal excitotoxicity, leading to increased neurotransmitter release and cellular depolarization in areas surrounding CNS injury. This excited state accelerates free radical production and intercellular acidosis, contributing to additional CNS damage (65–67).

Elevated Body Temperature in Patients with TBI

Temperature regulation seems to fail after brain injury, with both EBTs and low temperatures commonly occurring (68,69). The best current information linking hyperthermia to poor outcomes after TBI come from the hospital setting. In the ICU, observational studies have demonstrated that "fever burden" (both the height of fever and duration of fever) is associated with poor outcomes after TBI, even after controlling for severity of injury. Indeed, in several studies, fever was associated with a statistically significant increase in the length of ICU stay, lower Glasgow Coma Scale score on discharge from the ICU, and lower neurologic function at 6 months after initial injury (12,13). In addition, fever measured in the first 3 days of hospitalization seems to be associated with increased mortality (14). These observations have lead to several recommendations for aggressive and strict control of temperature in the ICU (11,70).

Although these data suggest that the fever after TBI is an independent predictor of mortality, it is very unlikely that ambient temperatures contribute to this effect. In the climate-controlled environment of an ICU, hyperthermia is much more likely to be a *result* of brain injury caused by thermodysregulation and the acute-phase reaction associated with critical illness (15,71). In fact, EBTs are seen in the hospital after many types of critical illnesses, including cardiac arrest, stroke, and spinal cord injury (65).

EBT very early in a TBI patient's course is much more likely to be due to the effects of ambient environmental temperatures than to other causes. This early EBT has

been documented both in the field and on arrival at the hospital. Recent combat experience in Iraq and Afghanistan has demonstrated that when injury occurs in a hot environment, it often is associated with EBT. This may be seen in 7.4% of general trauma patients and in as many as 47% of patients with TBI (69,72,73). A report by Wade et al. suggests that EBT in the field may be associated with increased risk of death. Mortality has been reported as 2.3% in patients with a normal temperature, compared to 14% in patients with a temperature > 38°C (69). Unfortunately, the study reporting this was an unadjusted retrospective analysis of outcomes, and patients with an elevated temperature also had more serious injuries, as indicated by the significantly higher Trauma–Injury Severity Score and Injury Severity Score in the group of patients with EBT. Although these injuries occurred in a warm region, there is little evidence to directly link the elevated temperature in the field, or on arrival at the hospital, to environmental heat exposure. The only study we identified as attempting to link environmental temperatures with TBI outcomes demonstrated no association between environmental temperatures and any measured outcome after injury (74).

Treatment of Hyperthermia and TBI Outcomes

We have been unable to find any studies that specifically evaluate the effect of treating or preventing hyperthermia in TBI patients. Given the limited knowledge in this arena, it is not surprising that the most recent editions of the Brain Trauma Foundation guidelines for hospital and prehospital care of patients do not address this question (16,56). The few published recommendations regarding the management of EBT and hyperthermia after TBI recommend that, in the very controlled ICU setting, body temperature should be controlled (11). Yet, it has been widely recognized that control of hyperthermia is difficult and not without risk (e.g., hypotension, increased bleeding due to hypothermia-associated coagulopathy) (70). Perhaps the best proxy for attempting to understand the early management of EBT/hyperthermia in TBI patients is the plethora of trials evaluating the effect of mild therapeutic hypothermia on TBI.

A great deal of work has been done on therapeutic hypothermia for the treatment of severe TBI. Unfortunately, despite multiple high-quality studies being conducted, results have been inconclusive at best, with several trials demonstrating no effect on mortality or nonmortality outcomes related to control of temperature (31,75). One major problem encountered in several therapeutic hypothermia trials has been the high incidence of fever after therapeutic hypothermia. Some have suggested that these episodes of fever may be responsible for some of the negative study results (76). Despite attempts to control fever, these studies have found no improvement in outcomes (76). Two recent meta-analyses evaluating the effectiveness of therapeutic hypothermia in TBI have suggested that the procedure of cooling the brain should occur only in the setting of randomized clinical trials because there is not enough scientific evidence to support the routine use of this technique for managing TBI (77,78).

Any discussion of treating EBTs must consider that inadvertent hypothermia is a significant risk even in an ICU setting, let alone in the earlier environments of an ED or prehospital setting. In uncontrolled settings, with disrupted thermoregulation, inadvertent hypothermia is common and poses significant risks to TBI patients (68,69). This is particularly relevant because several studies indicate that early hypothermia in trauma patients results in increased mortality (79–81). Not only is hypothermia associated with a significant risk of death, but it also causes hypotension, which is known to cause secondary brain injury. Further, correction of hypothermia has been associated with improved outcomes after injury (82). Any measure taken to prevent EBT/hyperthermia must carefully consider the risk of inadvertent hypothermia and the other associated mechanisms of secondary injury.

In our literature review, we were unable to identify sufficient evidence to determine whether environmentally induced hyperthermia causes significant secondary brain injury or whether any interventions to correct or prevent hyperthermia might improve outcomes. In the controlled hospital setting, it seems that a temperature management strategy targeting normothermia may be the best option to prevent secondary brain injury. However, even this approach is based upon a weak and controversial literature.

CONCLUSION

In the hospital setting, evidence from observational studies suggests that thermodysregulation after TBI is common, and that EBTs after TBI are associated with poor functional outcomes and increased mortality. Recent observational studies suggest that EBTs occur frequently in the prehospital setting after exposure to high environmental temperatures. It remains unclear whether temperature elevation is a result of exposure to ambient environmental temperature extremes or is part of the acute phase response that is common in patients after severe injury or cardiac arrest. Furthermore, it remains unknown whether EBTs occurring soon after the injury are associated with increased mortality or worsened functional outcomes. Further study is needed to clarify the relationship between environmental heat exposure,

EBTs, bona fide hyperthermia, and outcomes after TBI. Although it is tempting to implement therapeutic interventions aimed at treating elevated body temperature in TBI patients, the unintended consequence of overcorrection, creating inadvertent hypothermia, may be more harmful than the hyperthermia itself. Further evaluation of hospital-based initiatives that target normothermia are required before any consideration should be given to the potential for trying to manage body temperature prior to arrival at the hospital.

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ARTICLE SUMMARY

1. Why is this topic important?

Traumatic brain injury (TBI) is common, and very early (prehospital) alterations in physiologic variables (hypotension, hypoxia, and hypocarbia) are associated with poor outcomes. It is unknown if elevated body temperatures (EBTs) have the same effect on outcomes.

2. What does this review attempt to show?

This review evaluates the potential for EBTs to occur after TBI in the prehospital setting, as well as the potential of early EBTs to result in secondary brain injury after TBI.

3. What are the key findings?

EBTs have the potential to cause secondary brain injury and are associated with poor outcomes when an EBT occurs in the hospital. In the prehospital setting, EBTs occur commonly; however, it remains unclear what causes early EBTs and if early EBTs have a significant impact on patient outcomes.

4. How is patient care impacted?

The current literature does not support any intervention to treat EBTs in the prehospital setting.