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# A NOVEL HEAD-NECK COOLING DEVICE FOR CONCUSSION INJURY IN CONTACT SPORTS

## Abstract

Emerging research on the long-term impact of concussions on athletes has allowed public recognition of the potentially devastating effects of these and other mild head injuries. Mild traumatic brain injury (mTBI) is a multifaceted disease for which management remains a clinical challenge. Recent pre-clinical and clinical data strongly suggest a destructive synergism between brain temperature elevation and mTBI; conversely, brain hypothermia, with its broader, pleiotropic effects, represents the most potent neuro-protectant in laboratory studies to date. Although well-established in selected clinical conditions, a systemic approach to accomplish regional hypothermia has failed to yield an effective treatment strategy in traumatic brain injury (TBI). Furthermore, although systemic hypothermia remains a potentially valid treatment strategy for moderate to severe TBIs, it is neither practical nor safe for mTBIs. Therefore, selective head-neck cooling may represent an ideal strategy to provide therapeutic benefits to the brain. Optimizing brain temperature management using a National Aeronautics and Space Administration (NASA) spacesuit spinoff head-neck cooling technology before and/or after mTBI in contact sports may represent a sensible, practical, and effective method to potentially enhance recover and minimize post-injury deficits. In this paper, we discuss and summarize the anatomical, physiological, preclinical, and clinical data concerning NASA spinoff head-neck cooling technology as a potential treatment for mTBIs, particularly in the context of contact sports.

## Keywords

• Head-neck cooling • Mild traumatic brain injury • Brain hypothermia • Brain temperature • Sports

## Introduction

*"No head injury is too trivial to ignore" Hippocrates 4th century BC.*

An estimated 1.6-3.8 million sports-related traumatic brain injuries (TBIs), including those not treated by a health care provider, occur in the United States annually [1]. However, 75-80% of TBIs are mild, involving only a brief alteration in consciousness or mental status [2]. The term mild traumatic brain injury (mTBI) is generally interchangeable with concussion. Clinical presentation includes loss of consciousness for less than 30 minutes, alteration of mental state for less than 24 hours, posttraumatic amnesia for less than 24 hours, and a Glasgow Coma Scale score of 13-15 [3]. However, mTBI represents not only an acute, but also a chronic process. Postconcussion syndrome is characterized by experiencing numerous cognitive, somatic, and/or affective symptoms

for longer than three months [3]. Representing as many as 5-20% of all mTBIs, postconcussion syndrome can often lead to chronic disability [4-6]. Recently, emerging research on the long-term effects of mTBI has drawn intense media attention and Congressional scrutiny of current health policy in the United States.

Repetitive head impacts add another level of complexity to the characterization of mTBI because the emergence and duration of pathogenic events can overlap. Further, the destructive effect of recurrent mTBIs is likely synergistic rather than additive; for example, chronic repetitive subconcussive head impacts, which individually may have little noticeable effect, may result in cumulative long-term deleterious effects [7-11]. Therefore, the summed effects of both concussive and subconcussive injuries may better represent the more complicated clinical landscape for mTBI.

Understanding the compounding effects of repetitive mTBI is of particular relevance to modern athletes. Common long-term health disorders associated with recurrent mTBIs include neurocognitive deficits (attention, memory, processing speed, etc.), posttraumatic stress disorder (PTSD), chronic traumatic encephalopathy, psychosocial health problems (e.g., binge drinking, major depression, impairment of social functioning and ability to work, suicide), epilepsy, pain, and other alterations in personality or behavior [9,12-14].

The pathophysiology underlying TBI likely occurs along a spectrum from mild to more severe injuries [15-19]. TBI is a multifaceted disease with prolonged secondary pathogenesis and potentially long-lasting adverse neurological sequelae. Successful clinical management of TBI is challenging because of the multiple and complex pathophysiological processes. Interventions

targeting the acute phase of TBI such as prevention of hypoxia and excitotoxicity will differ from those that affect the chronic phase of TBI. Phase III clinical trials thus far have failed to yield an effective pharmacological strategy for neuroprotection in TBI, which may be in part due to the use of drugs that target only a single pathophysiological pathway rather than the multiple mechanisms involved in secondary injury post-TBI [20]. Therefore, targeting multiple pathways that each contribute to a deleterious secondary cascade may result in more successful clinical outcomes.

In laboratory studies to date, brain hypothermia, with its broad and pleiotropic effects, represents the most potent neuroprotectant technique [21]. Brain hypothermia has well established therapeutic roles in selected clinical conditions, including anoxic brain injury due to cardiac arrest and hypoxic ischemic neonatal encephalopathy [22-25]. However, a systemic approach to accomplish regional hypothermia, i.e., whole body cooling to secondarily achieve brain hypothermia, has thus far failed to yield an effective interventional strategy in TBI. Furthermore, although systemic hypothermia remains a potentially valid treatment strategy for moderate to severe TBIs, it is neither practical nor safe for mTBIs. An alternative approach to systemic hypothermia is selective cooling, i.e. therapeutically targeting the region of interest.

Theoretically, selective head-neck cooling would avoid the systemic physiological responses and potential complications associated with whole body cooling. It may represent an ideal strategy to provide therapeutic benefits to the intended target organ: the brain. Recent animal data demonstrated that mild brain temperature elevation induced before and after mTBIs aggravated histopathological outcomes [26]. In contact sports, body temperature elevation between 38.9°C and 40°C (102°F to 104°F) is common during practices and games [27-34]. During these same time periods, the athlete has also a much greater risk for high-velocity head impacts that, over time, may result in cumulative concussive and sub-concussive injuries. Therefore, head-neck cooling may be a sensible, practical, and effective strategy to optimize brain temperature management before and/or after an mTBI to potentially enhance recovery and minimize the subsequent cognitive and/or behavioral deficits. In this paper, we discuss and summarize the anatomical, physiological, preclinical, and clinical data concerning NASA spacesuit spinoff head-neck cooling technology (Fig. 1) as a potential treatment for mTBIs, particularly in the context of contact sports.

Although the history of medicine is replete with examples of cures and effective therapies obtained years, decades, and even centuries before the elucidation of the underlying disease pathophysiology and the treatment mechanism of action, efforts to understand the fundamental aspects of brain temperature are crucial for the eventual success of developing effective and pragmatic clinical treatments for patients with mTBIs.

## Brief overview of brain temperature

Our group recently published an extensive review on brain temperature and its fundamental properties [35]. In general, deep brain temperature is higher than body temperature but correlates well with body temperature. Fluctuating in both physiological and pathological conditions, brain temperature itself largely depends on the summed effects of the following principle variables: brain metabolism, cerebral blood flow (CBF) and volume, and blood temperature [36].

Temperature changes of 1°C or less can result in functional alterations in various areas of the nervous system [37], indicating the high thermal sensitivity of the brain. The significance of thermal impacts on several principal neurophysiological properties, such as resting potential, action potential, nerve conduction velocity, synaptic transmission, etc., is well established [37].

The temperature-dependent nature of human cerebral performance has also been well-reported. For example, impairment of memory encoding starts at 36.7°C and progresses to the point that 70% of information normally retained is lost at approximately 34°C-35°C [38].

## Effects of exercise-induced hyperthermia on the brain-body thermal gradient

Physical exertion changes the physiological parameters of cerebral thermal regulation. During significant periods of intense exercise or physical activities, body temperature elevates 1-2°C [39,40]. This temperature increase is critically important to understanding the acute effects of sports-related mTBI, which typically occurs during periods of intense physical
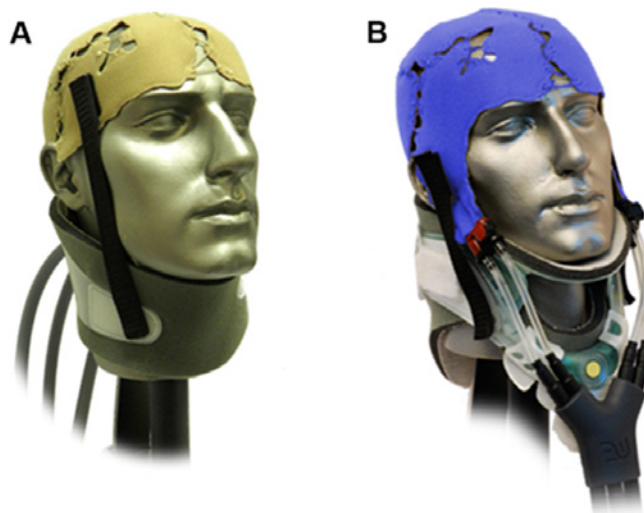


Figure 1. Two examples of head-neck cooling apparatuses. A) Depiction with a soft collar, as could be utilized during sporting events for prophylactic cooling. B) Depiction with a cervical stabilizing collar, as could be utilized after a suspected traumatic injury. Courtesy of WElkins, LLC, Chicago, IL, USA.

exertion. As the body temperature rises, a window of increased cerebral vulnerability to injury may occur (Fig. 2).

Hyperthermia during exercise is associated with hyperventilation [41,42], which reduces blood levels of carbon dioxide, and carbon dioxide is a well-known potent mediator of CBF. For example, $CO_2$ produces cerebral vasodilatation, which enhances cerebral heat clearance and narrows the brain-blood temperature gradients. Similarly, hypocapnia, induced with hyperventilation, widens the brain-blood temperature gradients [36]. In addition, cerebral $CO_2$ reactivity (i.e. the magnitude of change in CBF for a given change in $PaCO_2$) appears to increase during hyperthermia [43]. Hyperventilation-induced hypocapnia combined with increased cerebral $CO_2$ reactivity lead to significant reduction in CBF [41,44,45]. Thus, a temperature-associated reduction in $CO_2$ levels compromises cerebral heat clearance capacity when heat clearance is most needed physiologically (Fig. 2).

Intense exercise increases cerebral metabolism and oxygen utilization, which subsequently increases cerebral metabolic heat production [46-48]. The increase in cerebral metabolic heat production with the concomitant decrease in CBF leads to a significant net cerebral heat storage [40], sustaining a widened brain-body thermal gradient (Fig. 2).

At the termination of exercise, the cerebral venous to arterial temperature difference (v-a $D_{temp}$) markedly increases, indicating a thermal recovery process from the net cerebral heat storage accumulated during exercise [40]. However, the cerebral venous blood temperature decreases at a much slower rate than the drop in body temperature. Therefore, the cerebral thermal recovery response from exercise-induced hyperthermia is relatively slow (Fig. 2) [40].

In sum, intense physical exertion/exercise perturbs the thermal balance between cerebral heat production and heat removal via the cerebral circulation. Consequently, the brain-body thermal gradient widens, potentially creating a temporal window of greatly increased cerebral vulnerability to the deleterious effects from mTBIs both during

and immediately after intense exercise [26]. However, this same temporal window may represent a window of opportunity for optimal selective brain temperature management to potentially lessen the cerebral vulnerability to concomitant concussive and subconcussive injuries.

## Temperature elevation and mTBI in contact sports

### Occurrences
In contact sports, temperature elevation between 38.9°C and 40°C (102°F to 104°F) is common during practices and games [27-34]. In contact sports such as boxing and football, repeated blows to the head are inevitable. Frequent head impacts are also common in soccer, ice hockey, lacrosse, basketball, etc. For male athletes, football and hockey have the highest number of sports-related concussions (SRC) [49,50]. For female athletes, hockey, soccer, and basketball are considered to be high-risk organized sports [49,50].

### Experimental and clinical data
In the context of a single concussion, spontaneous and complete recovery is the general rule. However, the mild injury results in a temporal window of much increased cerebral vulnerability to more serious damage in the case of a second injury to produce greater damage if repeat injury occurs [51,52]. Analogously, although intense activity-induced hyperthermia (< 40°C), a common occurrence

in contact sports, does not typically lead to any deleterious effects in athletes, recent evidence suggests that it may also significantly increase the cerebral vulnerability to any further mild traumatic injury [26].

In experimental studies to date, mild elevations in brain temperature (< 40°C) have consistently been demonstrated to worsen neurological outcome in moderate to severe TBI animal models [53]. A strong clinical associative relationship between the incidence of fever and poor outcome in patients with moderate to severe brain injuries has also been well-established [54,55]. However, there has been a relative dearth of information regarding the impact of brain temperature elevations on mTBI outcome. Sakurai *et al.* recently demonstrated in a rodent model that mild brain temperature elevation induced before and after mTBI aggravated histopathological outcomes [26]. In a recent clinical analysis of 7145 patients with acute head trauma, including 4297 cases of mTBIs, Li *et al.* indicated that early post-trauma hyperthermia (< 72 hours) was closely correlated with unfavorable outcomes [56].

### Key overlapping pathological pathways
Mild hyperthermia and mTBI have overlapping effects in several key pathological pathways (Fig. 3), such as blood-brain-barrier (BBB) breakdown, mitochondria malfunction, apoptotic cell death, glutamate triggered excitotoxicity, energy demand-and-supply mismatch, cerebral autoregulation
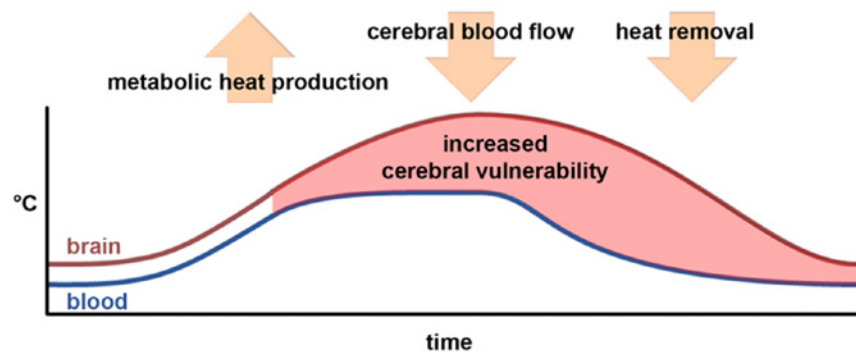


Figure 2. Intense physical exertion/exercise perturbs the thermal balance between cerebral heat production and heat removal via the cerebral circulation. Consequently, the brain-body thermal gradient widens, potentially creating a temporal window of greatly increased cerebral vulnerability to the deleterious effects of mTBIs both during and immediately after intense exercise.
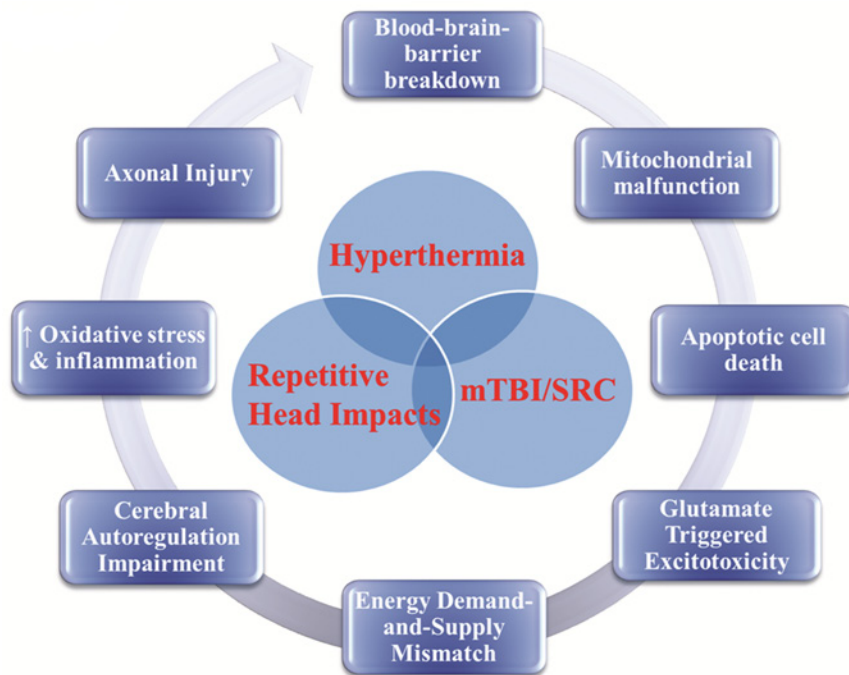
Figure 3. Mild hyperthermia and mTBIs have overlapping effects in several key pathological pathways, such as blood-brain-barrier (BBB) breakdown, mitochondria malfunction, apoptotic cell death, glutamate triggered excitotoxicity, energy demand-and-supply mismatch, cerebral autoregulation impairment, injury-induced oxidative stress and inflammation, and axonal injury. Although there does not appear to be histopathological consequences of induced mild hyperthermia by itself, the effect of combining mild hyperthermia and mTBIs (particularly recurrent concussions), is likely synergistic. mTBI/SRC = mild Traumatic Brain Injury / Sports-Related Concussion.

impairment, injury-induced oxidative stress and inflammation, and axonal injury [44,57-70]. Although there does not appear to be histopathological consequences of induced mild hyperthermia by itself [71,72], the effect of combining mild hyperthermia and mTBIs (particularly recurrent concussions), is likely synergistic. For example, arachidonic acid (AA)-induced dysfunction is one of the key destructive signaling pathways put in motion by both hyperthermia and mTBI. Hyperthermia-induced increases in cytokine concentrations, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), may persist for hours to days in athletes after strenuous exercise [73]. The binding of TNF and IL-1 to their specific membrane receptors lead to the production of phospholipid $A_2$ ($PLA_2$). $PLA_2$ then hydrolyzes membrane phospholipids, producing arachidonic acid (AA). AA is a key metabolite, leading to the production of potent inflammatory mediators and oxygen free radicals, such as prostaglandins, leukotrienes, and thromboxane $A_2$. These toxic

mediators of pro-death signaling pathways induce inflammation and capillary leakage, and damage cellular DNA [74,75]. Similar pathological changes result from mTBI, in which the concussive force destabilizes and disrupts the neuronal cell membrane [59-61]. Cell membrane disruption leads to the release of AA that rapidly induces the subsequent production of toxic prostaglandins and leukotrienes.

The intracellular calcium-dependent signaling pathway is another example of how hyperthermia may increase the cerebral vulnerability to a concomitant or subsequent mTBI. With hyperthermia, cytosolic calcium rises significantly from both increased influx of extracellular calcium and the release of calcium from intracellular stores [76]. Heat acclimation seems to blunt the heat-induced rise in calcium [77]. With mTBI, the cell membrane disruption, induced by the concussive force, leads to ion channel alterations and efflux of the excitotoxic neurotransmitter glutamate [59-61]. Excess glutamate leads to massive

influx of calcium with subsequent induction of both programmed and necrotic cell death via calcium-dependent proteases [78,79]. Furthermore, surplus intracellular calcium increases oxidative stress. Influx of excessive calcium in mitochondria increases the formation of reactive oxygen species (ROS). ROS directly damage DNA and proteins and further induce programmed cell death [78]. ROS also propagate further free radical formation by initiating the process of lipid peroxidation. Because antioxidant defense mechanisms are relatively scarce in the human central nervous system, such continued production of ROS via lipid peroxidation further depletes endogenous free radical scavengers [80].

In contact sports, both intense activity-induced hyperthermia and repeated head impacts occur commonly. During and immediately after practices and games, the physiological perturbation in cerebral metabolic heat production and removal, combined with the relatively slow cerebral thermal recovery, further widens the brain-body thermal gradient. In contact sports such as football, the situation is further exacerbated. Because these athletes are typically larger and wear heavy football equipment, they have significant physiological disadvantages to dissipate heat effectively. The resultant deleterious synergism may create a temporal window of greatly increased cerebral vulnerability to the damaging effects of mTBIs. Therefore, optimizing brain temperature management before and/or after an mTBI in contact sports may represent a sensible, practical, and effective strategy to potentially enhance recovery and minimize the subsequent behavioral deficits.

## NASA spin-off selective head-neck surface cooling technology

### Selective cerebral hypothermia
Incorporating National Aeronautics and Space Administration (NASA) spacesuit spinoff technology, Wang and colleagues demonstrated the feasibility and validity of using a specially designed head-neck surface cooling garment (Fig. 1) to accomplish rapid and substantial selective cerebral hypothermia,

as well as delayed systemic hypothermia in brain injury patients (Fig. 4A) [81]. In the described study, eight patients were randomly assigned to the study group and six to the control group. On average, 1.84°C (range: 0.9-2.4°C) of brain temperature reduction (measured at 0.8 cm below the cortical surface) was accomplished within one hour in the study group. Systemic hypothermia (< 36°C) occurred, on average, 6.67 hours (range: 1-12 hours) after initiation of brain temperature reduction. The average ΔT (brain – body temperature) calculated from 277 data hours in the study group was -1.6°C as compared with an average ΔT of +0.22°C calculated from 309 data hours in the control group (p < 0.0001). Harris et al. did not reproduce the same results in a similarly designed study [82]; however, the head-neck surface cooling garment used in their study was engineered quite differently with substantially less heat transfer efficiency and capacity [83].

## Selectivity of head-neck cooling on cerebral tissue with compromised perfusion

Cerebral tissue with compromised perfusion, a common clinical concern in patients with mTBI [84,85], is very responsive to head-neck surface cooling. Wang, et al., described a patient with a large left hemispheric stroke secondary to a combined occlusion of the left internal carotid artery and the middle cerebral artery (Fig. 4B) [86]. At baseline (48 hours after the onset of the stroke), the frontal white matter temperature (measured at 0.8 cm below the cortical surface) of the healthy hemisphere was 0.1°C above the body temperature. The infarcted hemisphere temperature (measured in the frontal white matter at 0.8 cm below the cortical surface) was approximately 1.8°C below the body temperature. After one hour of head-neck surface cooling, with body temperature maintained at approximately 35°C, the measured brain temperature in the healthy hemisphere dropped approximately 5.6°C while the brain temperature in the infarcted hemisphere dropped approximately 8°C. Over time, a brain-body temperature gradient of -6°C in the healthy hemisphere and -14°C in the infarcted hemisphere was maintained.

Thus, head-neck surface cooling is particularly effective in reducing temperatures on poorly perfused cerebral tissues.

There are alternative approaches to accomplish brain cooling. For example, inserting a temperature-controlled balloon catheter into the nasal cavity has been shown to selectively reduce the brain temperature without significant adverse effects [87]. Other methods include endovascular or body surface cooling. However, such alternative cooling methods (intranasal, endovascular, body surface cooling, etc.) are not as practical in a contact sports setting as selective head-neck cooling. Furthermore, since these mostly relying on cerebral circulation to accomplish

effective thermal exchange with various brain regions, these alternative cooling approaches may not reliably induce significant temperature reduction in injured and poorly perfused cerebral tissues. This differential cerebral tissue susceptibility to direct surface cooling due to perfusion differences represents a unique advantage of the head-neck cooling technology over other technologies.

## Proposed mechanisms of action

Head-neck cooling technology may have beneficial effects on brain temperature and outcome through several different mechanisms. There are direct temperature effects on the brain as the tissue is cooled, and there are
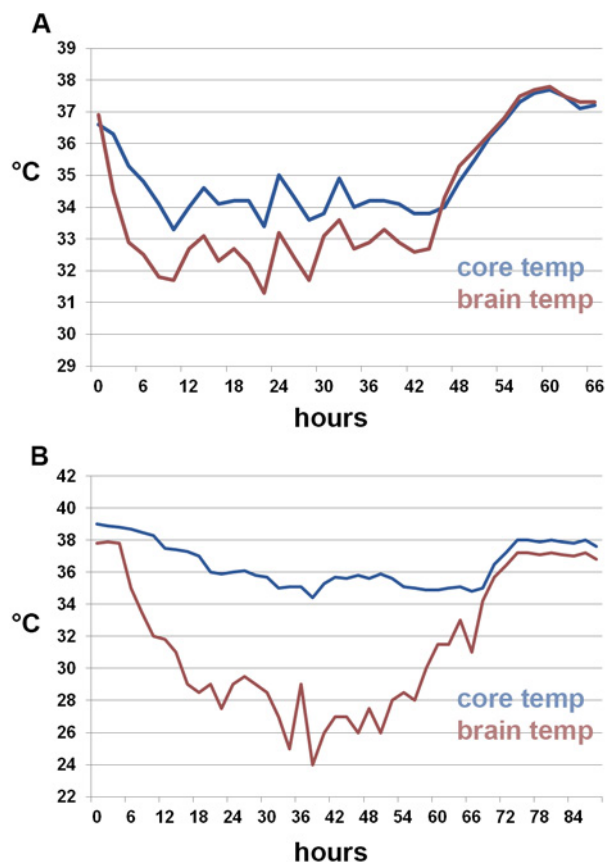


Figure 4. The head-neck cooling apparatus is effective in selectively reducing cerebral temperature. A) In head trauma patients, selective head-neck cooling resulted in an average temperature reduction of 1.84°C within one hour. Systemic hypothermia (< 36°C) occurred, on average, 6.67 hours after initiation of cooling. The average ΔT (brain – body temperature) of -1.6°C was maintained throughout the cooling phase. B) After a large left hemispheric stroke secondary to arterial occlusion, one hour exposure to selective head-neck cooling resulted in a temperature reduction of 8°C in the infarcted hemisphere (LB) versus 5.6°C in the healthy hemisphere (RB). Over time, with body temperature maintained at approximately 35°C, a ΔT of -14°C in the infarcted hemisphere (LB) versus a ΔT of -6°C in the healthy hemisphere (RB) was maintained. Figure 4B was reprinted with the permission from Wang et al., 2006 [86].

effects via stimulation of temperature-sensitive fibers in superficial tissue. The NASA spacesuit spinoff head-neck cooling technology is engineered to optimize conductive heat exchange with the brain, thereby reducing physical temperature (Fig. 5A). The integrated layers of the design consist of both a conformal liquid cooling heat exchanger and a pneumatic layer. The pneumatic layer not only provides air counter-pressure to optimize thermal contact with the cranium and neck, but also isolates the liquid cooling heat exchanger layer from the ambient environment (Fig. 5B).

In addition to the optimal thermal interactions with the brain, head-neck cooling may be particularly effective for activating temperature-sensitive skin afferents. Facial skin contains the highest concentration of the sensory receptors in the entire body [88]. More specifically, the face presents with the highest distribution density of free nerve endings with temperature sensory function [89]. Activation of temperature-sensitive fibers may have protective implications in contact sports.

The brain has a relatively slow recovery response from hyperthermia, as well as a low perfusion state early in the recovery [40,44]. Because $CO_2$ is a well-known potent mediator of CBF, $CO_2$ inhalation or voluntary hypoventilation has been proposed as a strategy for a faster restoration of CBF and dissipation of heat from the brain [40]. Such proposed strategies are not practical in contact sports. Skin cooling reduces minute ventilation and respiratory rate, a physiological response to reduce respiratory heat loss in cold environment [90,91]. Although the exact underlying mechanism remains unclear, numerous studies have demonstrated that selective facial skin cooling may increase CBF [48,92-94]. Therefore, via direct activation of temperature-sensitive skin afferents, head-neck cooling may present a practical and effective strategy in contact sports for a faster restoration of CBF and cerebral heat clearance.

Activation of temperature-sensitive fibers may also have protective neuroendocrine implications. Body temperature elevation, from either passive heating or exercise, stimulates prolactin release from the anterior pituitary [95-97]. Central serotonergic (5-HT)

and dopaminergic (DA) pathways likely play an important role in temperature homeostasis [98]. As targets of pharmacotherapies, the dysregulation and imbalance of these two monoamine neurotransmitters have also been well described in experimental and clinical settings of TBI, including mTBI [99-108]. Because 5-HT stimulates while DA inhibits prolactin release from the anterior pituitary [97], the release of prolactin has been consistently used as an indirect measure to reflect the state of thermal perturbation in humans [95-97]. Head-neck cooling is particularly effective in modulating the secretion of prolactin by direct stimulation of skin afferents without necessarily cooling the brain [109-111]. The well-observed effect on prolactin secretion by direct stimulation of head-neck skin afferents may be mediated through the modulations of central 5-HT and DA pathways. Therefore, selective head-neck cooling may have protective effects via neuroendocrine pathways.

NASA spacesuit spinoff head-neck cooling technology likely has several mechanisms of protective actions, including both effective thermal interactions with the brain as well as direct stimulation of head-neck skin afferents. Thus, NASA spacesuit spinoff head-neck cooling technology may represent a sensible, practical, and effective strategy to potentially enhance recovery and minimize the subsequent behavioral deficits commonly associated with recurrent mTBIs in contact sports.

## Clinical and practical considerations

Strategies to reduce body temperature before exercise and exertion have long been recognized and adopted by many athletes to decrease heat stress and improve performance [112]. However, pre-cooling may be impractical in some contact sports. With the development of a practical and effective brain cooling technology, there may be opportunities for active brain cooling during breaks in games such as soccer, hockey, basketball and American football. Although the breaks may be too short to accomplish a meaningful reduction of brain temperature, data collected using forearm immersion in cool (18°C) water demonstrated that about 70% of the cooling may be achieved during the first 10 minutes [113]. With MR thermometry technique, our preliminary data (study in progress) in healthy human volunteers demonstrated possibly significant brain temperature reduction within a period comparable to the half-time break.

Active brain cooling immediately after an mTBI may represent the most practical strategy in contact sports to optimize brain temperature management to potentially enhance recovery and minimize the subsequent behavioral deficits. However, further clinical studies are warranted to closely examine not only the potential therapeutic benefits but also several clinical concerns as follows:
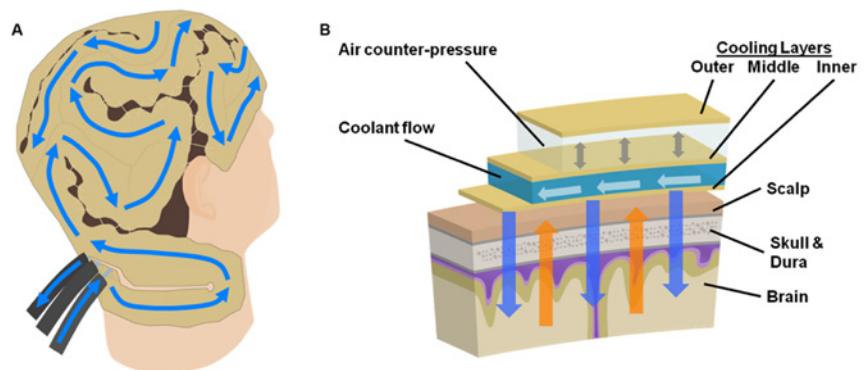


**Figure 5.** Diagram of coolant flow and the integrated layers of head-neck cooling technology. A) Depiction of overall flow of the liquid coolant heat exchange system through the cooling apparatus. Liquid coolant is provided and refreshed through an in-flow tube and removed through an out-flow tube located at the base of the apparatus. B) The cooling apparatus consists of three layers (outer, middle, inner) that create a pneumatic ("air counter-pressure") insulating space, which both insulates from the environment and improves apparatus contact with the scalp, and a fluid flow ("coolant") space. Courtesy of WElkins, LLC, Chicago, IL, USA.

## Diving reflex

In humans, breath-hold face immersion in cold water elicits the diving reflex [114]:

1. Decrease in heart rate
2. Increase in total peripheral resistance
3. Decrease in cardiac output
4. Increase in mean arterial pressure

In addition, supraventricular arrhythmias have been reported following breath-hold submersions in cold water [115]. Head-neck surface cooling has been reported to increase systolic and diastolic blood pressures by more than 15 mmHg within 120 min [116]. Thus, because cold stimulation to the head-neck region may activate both the sympathetic and parasympathetic pathways and potentially result in a competitive interaction between the two autonomic systems [117,118], safety studies are required prior to further therapeutic investigations in athletes with mTBIs.

## Brain temperature and cognition

Cognitive impairments are common after an mTBI, particularly in the domains of visual-motor reaction time and information processing, memory, and attention [119-121]. The temperature-dependent nature of human cognitive performance has also been well reported [38]. Therefore, head-neck surface cooling can theoretically affect the cognitive evaluation and performance in athletes after an mTBI. Studies to examine the interactions between head-neck surface cooling and human cognitive performance are warranted.

## Activation of cerebral representations of thermal stimuli

Integrated with homeostasis, temperature sensation can motivate behavioral changes and reflexively generate autonomic responses. Temperature sensation conveys both an exteroceptive aspect, i.e. objective recognition of the environment, and an interoceptive aspect, i.e. an interpreted perception of the physiological condition of the body itself [122]. The cerebral representations of temperature stimuli include the insular cortex, the somatosensory cortex, the orbitofrontal cortex, the cingulate cortex, and the ventral striatum [122-124]. Head-neck cooling stimulates the temperature sensory receptors and activates the representative cerebral cortices. Further studies are needed to elucidate how such activation interacts with the pathophysiology of and recovery from an mTBI during the acute, sub-acute and chronic phases.

## Conclusion and future directions

Although thousands of athletes have played contact sports for many years without obvious long-term adverse effects, emerging research and recent recognition of the potentially devastating impact in athletes with recurrent mTBIs have drawn intense media attention and even Congressional scrutiny. Recent preclinical and clinical data strongly suggest the destructive synergism between brain temperature elevation and mTBIs. Therefore, optimizing brain temperature management using a NASA spinoff head-neck cooling technology before and/or after an mTBI in contact sports may represent a sensible, practical, and effective strategy to potentially enhance recovery and minimize the subsequent behavioral deficits.

The temperature of deep cerebral structures correlates well with body temperature. Therefore, without significantly altering body temperature, it is not likely that head-neck surface cooling could induce significant thermal impact upon the deep structures. This may limit the potential therapeutic benefits of head-neck surface cooling technology. For example, traumatic axonal injury (TAI) represents one of the pathological hallmarks of mTBI [125-128]. Because the gray and white matter differ in their respective rigidity, TAI is more commonly seen at gray-white matter junctions [18,129-133]. However, it is well-established in mTBI literature that TAI also affects the corpus callosum [125-128]. As a deep cerebral structure, the corpus callosum is not likely to receive any significant thermal impact with head-neck surface cooling without concomitant body temperature reduction. Some of the potential benefits from head-neck surface cooling may be independent from the thermal interactions with brain but derived from direct cooling of the head-neck skin afferents. However, further studies are warranted to examine the therapeutic limitations of this NASA spinoff technology on concussion injuries.

The current and future research efforts on selective head-neck cooling should span across both applications and science. Feasibility and safety studies in athletes in contact sports, including high-school athletes, followed by therapeutic trials, are warranted. Further developing and refining MR thermometry would allow detailed examination of the thermal impact of this technology in different regions of the brain. Sophisticated studies to evaluate the head-neck-surface-cooling induced changes in regional brain perfusion patterns and functional connectivity are also warranted.

To lessen the risks for and detrimental outcomes of mTBIs, a multidisciplinary scientific approach is required. Active and selective brain cooling using NASA spacesuit spinoff technology merits scientific evaluation for its potential therapeutic benefits, as well as any possible drawbacks. Currently, there are focused and promising research efforts in advancing neuroimaging, developing mobile applications for injury assessment, and combining biomarkers to create a "biomarker signature". Such research efforts are crucial in achieving the much-needed objectivity and certainty in first defining and recognizing an mTBI, and then assessing and stratifying its injury severity. Athletes and patients who struggle with the often devastating impact of recurrent mTBIs greatly appreciate the recently resurrected perspective on and pursuit of higher standards of treatment for mTBIs. As stated by Hippocrates (460-377 B.C.): "No head injury is too trivial to ignore".

## Acknowledgment

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