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THE EFFECT OF SELECTIVE HEAD-NECK COOLING ON PHYSIOLOGICAL AND COGNITIVE FUNCTIONS IN HEALTHY VOLUNTEERS

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Abstract

In general, brain temperatures are elevated during physical sporting activities; therefore, reducing brain temperature shortly after a sports-related concussion (SRC) could be a promising intervention technique. The main objective of this study was to examine the effects of head and neck cooling on physiological and cognitive function in normal healthy volunteers. Twelve healthy volunteers underwent two different sessions of combined head and neck cooling, one session with a cold pack and one session with a room temperature pack. Physiological measurements included: systolic/diastolic blood pressure, pulse oximetry, heart rate, and sublingual and tympanic temperature. Cognitive assessment included: processing speed, executive function, and working memory tasks. Physiological measurements were taken pre-, mid- and post-cooling, while cognitive assessments were done before and after cooling. The order of the sessions was randomized. There was a significant decrease in tympanic temperature across both sessions; however more cooling occurred when the cold pack was in the device. There was no significant decrease in sublingual temperature across either session. The observed heart rates, pulse oximetry, systolic and diastolic blood pressure during the sessions were all within range of a normal healthy adult. Cognitive assessment remained stable across each session for both pre- and post-cooling.
We propose that optimizing brain temperature management after brain injury using head and neck cooling technology may represent a sensible, practical, and effective strategy to potentially enhance recovery and perhaps minimize the subsequent short and long term consequences from SRC.

Introduction

Traumatic brain injury (TBI) has increasingly become a significant public health problem over the past decade worldwide [1]. Each year, traumatic brain injuries contribute to a substantial number of deaths and cases of permanent disability. In sports, mild traumatic brain injuries (mTBI), or concussions, have been a growing concern from youth to professional levels, mainly due to evidence of short- and long-term consequences from suffering a concussion [2-7].

An estimated 1.6-3.8 million sports-related TBIs, including those that never get treated by a health professional, occur in the United States annually [8]. However, the majority of TBIs are mild, involving only a brief alteration in consciousness or mental status [9]. TBI is a multifaceted disease with prolonged secondary pathogenesis and potentially long-

lasting adverse neurological sequelae [2, 3, 5, 7, 10].

In 2004, our group 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 patients with severe brain injuries [11]. In that study, subjects had an average brain temperature reduction of 1.84°C (range: 0.9 - 2.4°C), which was accomplished within one hour of cooling.

The head-neck cooling technology may have beneficial effects on brain temperature in the athletic world when body temperature, and presumably brain temperature, are elevated and even more so when the athlete is at an elevated risk for a TBI [12, 13]. In athletics, especially in contact sports like American football, it is commonly reported that the body temperature elevates to 102° - 104°F (38.9 -

40°C) [9, 14-17]. Elevated body temperature and repetitive head impacts during the same time frame may result in cumulatively worse concussive and subconcussive brain injuries [8, 18-23]. Consistent with this idea, animal data have shown that mild brain temperature elevation induced before and after mTBI results in worsened histopathological outcomes [24], whereas mild hypothermia in animals after repetitive mTBI has beneficial effects [25]. Miyauchi and colleagues subjected rats to repetitive mTBI by impact acceleration injury followed by four different interventional treatment groups: control, mild hypothermia, superoxide dismutase, and Tempol, a nitroxide antioxidant [26]. Cerebral function and axonal damage were analyzed 3-4 hours post-injury. The results showed that mild hypothermia provides axonal and microvascular protection when administered immediately after repetitive mTBI. Furthermore, Sakurai et al and

Titus et al., demonstrated, in a rat model, that inducing cooling immediately after mTBI back to normothermia could alleviate long-term cognitive deficits caused by hyperthermia [24, 27]. Thus, research examining the effect of selective head and neck cooling methods in athletes after repetitive mTBI is needed. The long term goal of our research is to develop a simple, non-invasive method of selective head-neck cooling for athletics in which brain/core temperatures can be reduced back to normothermia quickly following mTBI.

This study was designed to assess the safety and tolerability of selective head and neck cooling by measuring associated physiological and cognitive changes to establish its feasibility and to determine the degree to which cooling occurs in healthy adults. The results from this study show that head-neck cooling could lower body temperature without interfering with other physiological and cognitive measures.

Methods

This study was approved by the Institutional Review Board of the University of Illinois, Urbana -Champaign.

Participants

Written consent was obtained from twelve participants (mean age 27 ± 11 years; range 18 to 57 years). Seven participants were female (58%) and 5 males (42%). All were considered healthy with no health issues. Exclusion criteria were: no history of central nervous system disease or prior brain injuries, use of medication to regulate blood pressure, anemia or heart complications.

Cooling device

The WElkins EMT Temperature Management System (Fig. 1) (Welkinsmed, Downers Grove, IL, USA) is a portable thermoregulatory device that reduces and/or maintains subject's body temperature within a range of 86°F (30°C) to 98.6°F (37°C) [11]. The head-neck cooling technology is engineered to optimize conductive heat exchange with the brain, thereby reducing brain and body temperatures. The integrated layers of the design consist of both a conformal liquid cooling heat exchanger

Figure 1. The WElkins EMT unit and Headliner. The cooling helmet has an outer pneumatic liner pressurized to allow close contact with the cranium and neck. The device also is adjustable to fit a significant range of head sizes.

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 (see [11] for detailed description of cooling system).

Temperature and other physiological and cognitive measurements

Temperature measurements: To measure approximate changes in brain temperature, tympanic and sublingual temperatures were recorded. Tympanic temperature was measured with an electronic infrared thermometer (Genius 2 tympanic thermometer, Tyco Healthcare Group, Mansfield, MA, USA). Sublingual temperature was measured by SureTemp Plus 692 (Welch Allyn, Skaneateles Falls, NY, USA).

Other physiological measurements: To monitor participant safety and the impact of cooling on other physiological measures, systolic and diastolic blood pressure, peripheral oxygen saturation, and heart rate were also recorded. Systolic and diastolic blood pressure was measured with an Omron 10 series upper arm Blood Pressure monitor (Omron Healthcare Inc., Lake Forest, IL, USA). Peripheral oxygen saturation and heart rate were measured with

a pulse oximeter (NONIN GO2 9570 finger Pulse oximeter, NONIN Medical Inc., Plymouth, MN, USA).

Cognitive Measurements: To measure impact of cooling on participant's cognitive abilities, performance on three tasks was assessed using *BrainBaseline*, a digital application developed by Digital Artefacts LLC (Iowa City, IA, USA), on an iPad (Apple Inc., Cupertino, CA, USA). The cognitive assessment consisted of three tasks that are known to be sensitive to cortical function, especially prefrontal cortical areas. The tasks included: *Speed* - to measure processing speed [28], *Stroop* - to measure inhibition and executive function [29], and *N-back* (1-back and 2-back) - to measure working memory [30]. The same tasks were always administered in the same order: Speed, Stroop, N-Back, and took approximately 10 min to complete.

Once consent was signed, height and weight were taken for each participant for BMI calculation. Participants were allowed to sit and relax for 15 min in order to acclimate to the environment. All baseline levels for temperature and other physiological and cognitive measurements were then recorded. For the session referred to here as "Cold Day," the WElkins EMT unit was set to maximum cool

and a frozen ice pack (4°C) was placed into the unit. For the session referred to here as "Room Temp Day," the EMT unit was set to bypass mode and a room temperature water pack (72 - 77°C) was placed into the unit. Participants wore the headliner for 60 min on both "Cold Day" and "Room Temperature Day" sessions. The order of the sessions was counterbalanced between participants.

Throughout each session, temperature (tympanic and sublingual), peripheral oxygen saturation and heart rate were recorded every ten min with the last recording at 90 min (except at 70 min when participants were engaged in the post cooling cognitive assessment). Systolic and diastolic blood pressure was recorded every 30 min with the last recording at 90 min. The cognitive assessment was also completed after the EMT unit was turned off at 60 min and at 90 min.

Results

Twelve subjects (M_{age} = 27 ± 11 years; range 18 to 57 years) were enrolled. We collected full data sets from eleven subjects (Table 1) and present their data below. Analyses were conducted using a commercially available statistical program (SPSS, SPSS Inc., Chicago, IL, USA).

Temperature measurements

To determine whether a significant and reliable amount of cooling occurred while wearing the helmet with the frozen ice pack and the room temperature water pack, we performed a two-way repeated measures analysis of variances (ANOVA) on tympanic temperatures with pack type and time-point as factors. The ANOVA revealed a main effect of time-point, $F_{8,80}$ = 8.062, p < 0.0001, reflecting a decrease in temperature across the duration of both sessions. There was a pack-by-time-point interaction, $F_{8,80}$ = 2.77, p = 0.052, further revealing that more cooling occurred over the duration of the session when the frozen ice pack was used. The decrease in tympanic temperature when the frozen ice pack was used was -0.036 (± 0.40) at the end of 60 min of wearing the cooling device and -0.028 (± 0.33) at 90 min the end of the session. The decrease in tympanic temperature when
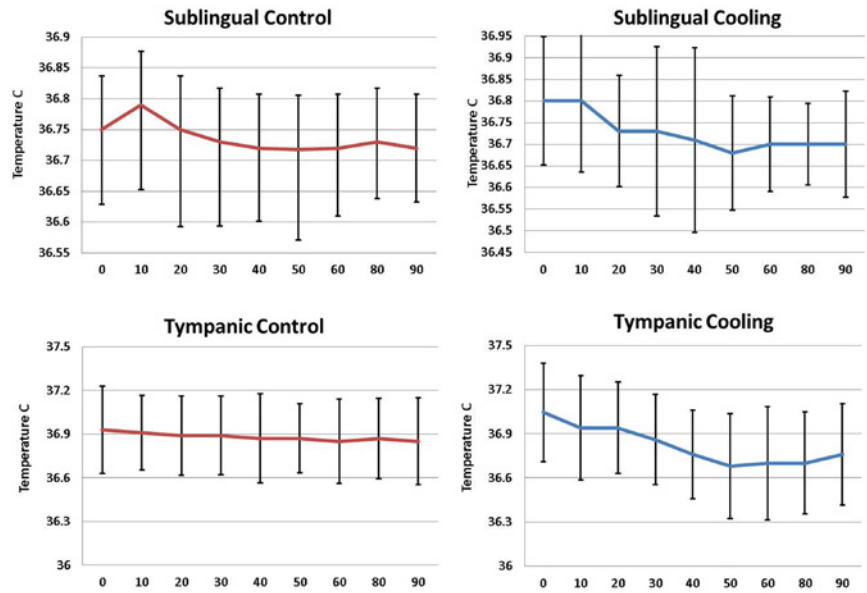

Figure 2. Graph showing the change in sublingual and tympanic temperatures over 90 min in healthy volunteers. Subjects were only cooled for 60 min after baseline measurements and were monitored 30 min after cooling. Error bars indicate standard deviation, SD.
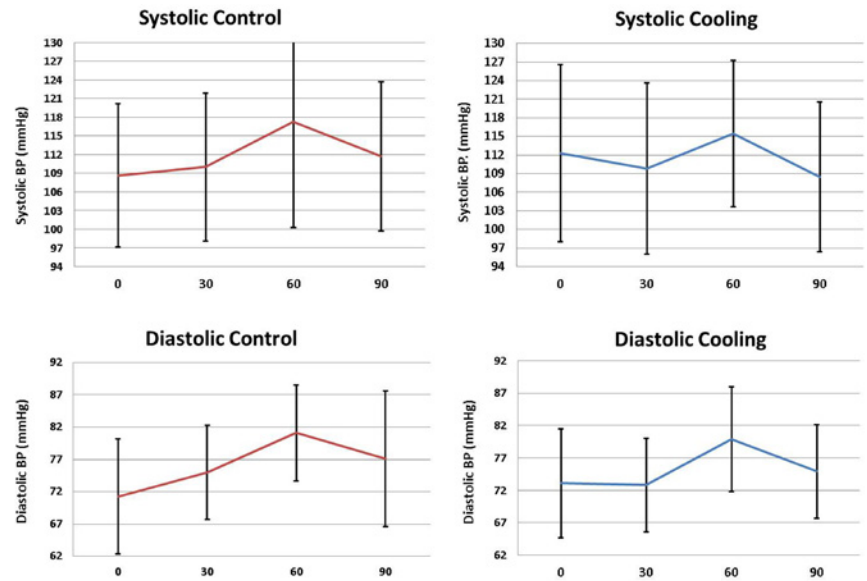

Figure 3. Time course of systolic and diastolic blood pressure during baseline, cooling phase, and 30 min post-cooling. Error bars indicate SD.

the room temperature pack was used was -0.08 (± 0.18) at the end of 60 min of wearing the cooling device and -0.08 (± 0.22) at 90 min the end of the session.

We performed the same analyses on sublingual temperatures with pack type and time-point as factors. The ANOVA revealed a main effect of time-point, $F_{8,80}$ = 3.21, p = 0.003, reflecting a decrease in temperature across the duration of both sessions; however, there was no interaction with pack type, $F_{8,80}$ = 0.48, p = 0.86, which suggests tympanic temperatures may be more sensitive to temperature changes related to the cooling helmet. The decrease

Table 1. Sublingual and tympanic temperature, systolic and diastolic blood pressure, heart rate, and pulse oximetry, during baseline, 60 min of treatment, and 30 min post treatment in healthy volunteers. BPM - beats per min.

VARIABLE	Baseline	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes	80 minutes	90 minutes
SUBLINGUAL (°C)				COOLING/CONTROL PHASE					
Cooling	36.80 (± 0.14)	36.79 (± 0.18)	36.73 (± 0.13)	36.73 (± 0.19)	36.71 (± 0.21)	36.68 (± 0.13)	36.70 (± 0.10)	36.70 (± 0.09)	36.70 (± 0.12)
Control	36.74 (± 0.12)	36.79 (± 0.13)	36.75 (± 0.15)	36.73 (± 0.13)	36.72 (± 0.12)	36.71 (± 0.14)	36.72 (± 0.11)	36.73 (± 0.09)	36.71 (± 0.08)
TYMPANIC (°C)									
Cooling	37.01 (± 0.34)	36.93 (± 0.35)	36.94 (± 0.94)	36.86 (± 0.31)	36.76 (± 0.28)	36.68 (± 0.35)	36.70 (± 0.38)	36.70 (± 0.34)	36.76 (± 0.33)
Control	36.93 (± 0.30)	36.91 (± 0.26)	36.90 (± 0.27)	36.89 (± 0.27)	36.86 (± 0.87)	36.87 (± 0.23)	36.85 (± 0.29)	36.87 (± 0.27)	36.85 (± 0.27)
PULSE Oxygen (%SpO$_2$)									
Cooling	97.5 (± 2.0)	97.5 (± 2.0)	97.1 (± 1.0)	97.6 (± 1.0)	97.8 (± 1.4)	97.3 (± 1.8)	97.5 (± 1.6)	97.8 (± 1.6)	97.5 (± 1.8)
Control	97.7 (± 1.1)	97.7 (± 1.1)	97.5 (± 1.2)	97.5 (± 1.2)	97.6 (± 1.2)	97.7 (± 1.7)	98.1 (± 1.1)	98.3 (± 0.78)	98.5 (± 1.0)
HEART RATE (BPM)									
Cooling	67.5 (± 8.5)	68.1 (± 10.3)	68.1 (± 10.5)	69.2 (± 10.6)	67.3 (± 11.0)	68.1 (± 10.1)	69.5 (± 9.6)	66.5 (± 10.7)	65.7 (± 10.4)
Control	63.3 (± 11.7)	63.3 (± 10.0)	64.3 (± 9.7)	65.1 (± 8.8)	63.6 (± 10.6)	63.9 (± 11.9)	65.0 (± 9.3)	61.3 (± 11.8)	61.2 (± 11.2)
DIASTOLIC									
Cooling	73.1 (± 8.4)			72.8 (± 7.2)			79.3 (± 8.1)		74.9 (± 7.2)
Control	71.3 (± 8.9)			75.0 (± 7.3)			81.1 (± 7.4)		77.1 (± 10.5)
SYSTOLIC									
Cooling	112.3 (± 14.3)			109.8 (± 13.7)			115.4 (± 11.7)		108.4 (± 12.1)
Control	108.6 (± 11.5)			110.0 (± 11.9)			117.3 (± 17.0)		111.7 (± 12.0)

in sublingual temperature when the cold temperature pack was used was -0.13 (± 0.17) at the end of 60 min of wearing the helmet and -0.12 (± 0.21) at 90 min the end of the session. The decrease in sublingual temperature when the room temperature pack was used was -0.02 (± 0.11) at the end of 60 min of wearing the helmet and -0.01 (± 0.08) at 90 min the end of the session.

To determine when a significant decrease in cooling occurred while wearing the cooling device with the frozen ice pack, we performed planned one-tailed comparisons between tympanic temperature at baseline and the other time-points. There was a significant decrease in tympanic temperature beginning at 30 min and at all later time-points (i.e., 40 min - 90 min), ts (10) ≥ 1.93, ps ≤ 0.041. No significant decreases were observed between tympanic temperature at baseline and other time-points when the room temperature water pack was used, ts (10) ≤ 1.44, ps ≥ 0.091.

Planned one-tailed comparisons between the baseline sublingual temperature and the other time-points were also performed. There was a significant decrease in sublingual temperature beginning at 20 min and at time-points 50 min and later (i.e., 50 - 90 min), ts (10) ≥ 1.99, ps ≤ 0.037. No significant decreases were observed between tympanic temperature at baseline and other time points when the room temperature pack was used, ts (10) ≤ 1.49, ps ≥ 0.084.

Physiological measurements

Descriptive statistics for all physiological measurements, including systolic and diastolic blood pressure, peripheral oxygen saturation, and heart rate, at each time point during "Cold Day" and "Room Temperature Day" are presented in Table 1. All recorded measurements are within the normal values for healthy adults.

Cognitive measurements

To measure the impact of cooling with the frozen ice pack and room temperature water pack on participant's cognitive abilities, we performed a two-way repeated measures analysis of variances (ANOVA) with pack type

Table 2. Cognitive tasks administered on *BrainBaseline*. Speed task measures processing speed performance in milliseconds. Stroop task measures executive function as switch cost in milliseconds. N-Back task, including 1-Back and 2-Back, measures working memory performance accuracy as percent correct.

VARIABLE	BASELINE (SD)	60 MINUTES (SD)	90 MINUTES (SD)
SPEED			
Cooling	355.7 (± 54.5)	358.0 (± 46.2)	342.9 (± 34.3)
Control	344.8 (± 42.1)	339.9 (± 31.6)	341.6 (± 37.0)
STROOP			
Cooling	178.5 (± 85.1)	102.2 (± 69.4)	117.5 (± 60.1)
Control	130.9 (± 125.1)	126.0 (± 56.0)	117.2 (± 76.3)
1-BACK			
Cooling	99.5 (± 1.6)	99.0 (± 2.1)	99.5 (± 1.6)
Control	94.1 (± 8.0)	97.6 (± 3.6)	98.6 (± 2.5)
2-BACK			
Cooling	94.4 (± 8.0)	90.9 (± 8.4)	92.4 (± 10.9)
Control	94.0 (± 8.4)	95.9 (± 3.6)	96.0 (± 5.0)

and time-point as factors for each of the three tasks: Speed, Stroop, and N-back. The mean performance levels and standard deviations for each task are presented in Table 2. For the Speed task, the ANOVA revealed that mean reaction time on the task did not change as a result of pack type, $F_{1,10} = 1.00$, $p = 0.34$, or time-point, $F_{2,20} = 0.46$, $p = 0.64$, and there was no interaction, $F_{2,20} = 0.59$, $p = 0.57$, suggesting that processing speed remained relatively stable during both sessions. For the Stroop task, the switch cost was calculated by subtracting the reaction time for incongruent trials from congruent trials to obtain a measure of performance. The ANOVA revealed that performance on the task did not change as a result of pack type, $F_{1,10} = 0.15$, $p = 0.71$, or time-point, $F_{2,20} = 1.64$, $p = 0.22$, and there was no interaction, $F_{2,20} = 2.27$, $p = 0.13$, suggesting that inhibition and executive function processes remained relatively stable during both sessions. For the N-back task, percent correct was calculated for the 1-back and 2-back conditions. On the 1-back, the ANOVA revealed a main effect of pack type on accuracy, $F_{1,10} = 10.58$, $p = 0.01$, but not time-point, $F_{2,20} = 1.87$, $p = 0.19$, and there was no interaction, $F_{2,20} = 1.78$, $p = 0.21$. Since there was a main effect of pack type, post hoc comparisons using

the Bonferroni correction were performed. These tests revealed no significant differences in accuracy due to pack type at each of the time-points, $ts(10) \leq 2.18$, $ps \geq 0.054$. It is likely that baseline differences between performance at baseline when the frozen ice pack was used (M = 99.5%) versus when the room temperature water pack was used (M = 94.1%) contributed to the main effect of pack type; however, this also means that the observed variability at baseline was greater than the change in performance as a result of the pack type. On the 2-back, the ANOVA revealed that accuracy on the task did not change as a result of pack type, $F_{1,10} = 1.21$, $p = 0.30$, or time-point, $F_{2,20} = 0.12$, $p = 0.89$, and there was no interaction, $F_{2,20} = 2.42$, $p = 0.11$, suggesting that working memory remained relatively stable during both sessions.

Discussion

Successful clinical management of concussions is challenging because of the multiple and complex pathophysiological processes. Therefore, head and neck cooling may be a practical and effective strategy to optimize brain temperature during the acute phase of sports-related concussions, and may potentially enhance the recovery and minimize

short and long term cognitive and behavioral complications.

Our study demonstrated temperature decreases occurred when wearing the cooling helmet over the duration of the experiment when the cold pack and room temperature pack were used. More cooling occurred when using the cold pack. Significant differences were observed when the cold pack was used between baseline and time-points after about 30 min, and the difference was maintained over the duration of the session. Significant differences were not observed when the room temperature pack was used between baseline and the individual time-points. Importantly, the decrease in temperature was not associated with disruption in other physiological or cognitive measures.

In general, there are several methods used to accomplish brain cooling and these include intranasal [31], endovascular [32], intravenous infusion of cooled fluids [33], and body surfacing cooling [34]. However, these methods are neither practical nor feasible in athletics, because they would either have to be done by a licensed professional, or would be too cumbersome in the field of play. Thus, selective head and neck cooling is an intriguing alternative.

Sports-related concussions have been a growing issue in sports worldwide and more research has shown the consequences of long-term complications from repetitive hits over a lifetime [4, 5, 7, 35, 36]. Diagnosis and evaluation of a concussion ranges from various cognitive tests [37], MRI [38-40], blood biomarkers [41], and specialized equipment [42-44]. In summary, there is no golden test that an athlete could take to diagnose a sports concussion. In addition, very little data supports existing treatments for concussions. This is mainly due to the fact that mTBI is a multifaceted disease and is difficult to approach from a singular perspective.

In a previous study, our group showed an average temperature reduction of 1.84°C (range 0.9 - 2.4°C) in patients with severe brain injuries [11]. In the setting of the present study, local cooling is performed with close contact to the external ear. Therefore, tympanic and sublingual readings should be interpreted as a

surrogate of a local cooling effect at superficial regions, including skin and the external ear.

Although this may seem like a small drop in temperature, it still may be clinically relevant, especially when treating a sports related mTBI. Recent publications by Miyauchi *et al.*, and Titus *et al.*, demonstrates that mild hypothermia treatment (between 35 and 36°C) immediately after head impact may prove beneficial in the long term because of brain temperature management [25]. This data seems to suggest that in sports like football and boxing where repetitive head impacts are inevitable and body temperatures are elevated, development of a cooling therapeutic protocol for use after practices or games could be invaluable for preservation of long-term brain health. In a recent review that our group wrote, we describe in great detail the use of selective head and neck cooling in athletics, and the powerful impact that it may have specifically on sports related concussions [45].

Exposure to a cold stimulus increases systolic and diastolic blood pressure in healthy volunteers [25, 46, 47]. One study reported an immediate increase in blood pressure with the onset of cooling [47], while another study showed no relevant blood pressure changes [46]. In our study, we show a gradual increase in both systolic and diastolic blood pressure in both sessions. However, this increase in blood pressure was well within the normal of a healthy adult, and was no reason for concern. We did not observe an increase in heart rate or pulse oximetry over that same time. We may assume that the increase in blood pressure in both sessions was due to the fact that each subject wore near infrared spectroscopy (NIRS)

probes on the frontal lobes which caused some discomfort over time and this was reported in the comfort questionnaire that each subject answered during the session (data not shown). Further research is necessary to determine cooling effect on blood pressure before this could be possibly used as a therapeutic treatment.

Limitations of the study

This is a small observational study designed to obtain data on the cooling device in healthy humans before investigating the clinical potential for sports-related concussions. It has fulfilled its initial purpose. To lessen the risks of detrimental outcomes from sport-related concussions, a multidisciplinary scientific approach is required. This would include understanding the length of cooling required post-injury to bring temperature back to normothermia, because factors such as body mass index, length of hair and gender may have an effect on cooling. Active and selective brain cooling for sports related concussions merits scientific evaluation for its potential therapeutic benefits as well as any possible drawbacks.

Conclusion

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 of recurrent mTBIs in athletes has drawn increased media attention. Recent data strongly suggest the damaging synergism between brain

temperature elevation and mTBIs, and the role that cerebral hypothermia may have on delineating short-term and long-term complications [24,27,48]. Therefore, optimizing brain temperature management post-injury using cooling technology such as the WElkins EMT (continuous long-term cooling) or the Catalyst™ Cryohelmet™ (intermediate short-term cooling) may represent a sensible, practical, and effective strategy to potentially enhance recovery and minimize the subsequent cognitive deficits. In this study we demonstrate that this cooling method worked in sedentary, non-active, healthy subjects. The next step is to determine the effectiveness of this type of cooling in the athletic world by examining how quickly core temperature could be reduced post workouts/practice in non-mTBI athletes. Further development of 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. In quoting a great commentary by Kochanek and Jackson: "It might be time to let cooler heads prevail" [48].

Acknowledgments

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