New Insights into Hyperthermia and Heat Illness: Brain Salvage

In their Excessive Heat Events Guidebook last updated 2016[1], the United States Environmental Protection Agency noted 1700-1800 deaths[2,3] annually in the United States attributable to heatstroke. Ten times that number suffer long-term or permanent injury as a result of near-heatstroke damage to brain and other organs.

Fire departments, implementing NFPA 1584[A4] standard thermal rehabilitation measures, have led the way reducing the incidence of catastrophic heat illness events with their periodic cooling protocols to reduce heat stress. These protocols have proven so successful they are now adopted by athletic trainers as *per-cooling* in recent international meta-analytic reviews and consensus statement recommendations[5,6,7,8,9,10,11,12]. Military and industrial safety recommendations now echo similar periodic cooling for all participants exerting themselves in hot humid conditions. Safety supervisors must still pay close scrutiny to Heat Index indicators in assessment of thermal risk for participants[4].

The recognition and treatment of hyperthermia on-site has improved since the 1970's with greatly improved early recognition of hyperthermic stress symptoms and faster execution of cooling measures. Introduction of mandatory protocols designed to limit thermal stress has resulted in shorter periods of exertion in the heat with mandatory regular water breaks and cool-down periods[4]. These have done much to reduce the incidence of severe thermal stress events such as heat exhaustion and heat stroke.

Even so, athletes and soldiers make headlines as they continue to collapse on the field and die. Fatigue and confusion induced by heat stress still causes accidents plaguing Industrial Safety Officers. Slips, trips, and falls in firefighters results from that same heat-stress fatigue while the long-term cumulative heat stress of fire suppression duty is impacting firefighter longevity. All this still happens despite close supervision by all counterparts of Fire Department Health and Safety Officers.

Despite vast improvements in periodic cooling, important data from the experimental physiology, aerospace, and neurology/neurosurgery communities remains unrecognized in current detection and emergent treatment of hyperthermia victims in the field. We must look to the very basics of temperature measures and what they really mean, how the body attempts to maintain temperature balance in heat, and what happens to our brain and body as those mechanisms fail. Only then can we understand and improve heat stroke prevention by more effective recognition and therapy of heat illness in the field.

[A] NFPA 1584- National Fire Protection Agency Standard on the rehabilitation process for members during emergency operations and training exercises. This Standard defines the ideal periodic cooling process of thermal rehabilitation for firefighters.

Brain, at only 2% of body mass, receives 20% of all cardiac output. Brain metabolism accounts for 20% of all oxygen consumption and 25% of all glucose utilization[13,14] in the body. With such a high oxidative metabolism, heat production in the brain is very high in humans, and thus a greater challenge to effectively cool than other mammals[14].

Advances in the treatment of moderate traumatic brain injury (i.e. concussions) since the 2000 has shown brain temperature is ***always*** greater than true core body temperature by 0.1-0.6°C (0.18-1.08°F)[15] under normal conditions. But neurophysiology studies in traumatic brain injury have also shown brain can vary its temperature from true core (pulmonary artery) body temperature by as much as ±3.0°C (±5.4°F)[14,15,16], especially in the setting of brain injury. While elevation of brain temperature is proven true in traumatic brain injury, it appears also to be true in heat stroke and vascular stroke[17].

Dangers of Brain Hyperthermia

Brain is ***the*** most sensitive organ of the entire body to excessive heat[18,19,20,50]. Brain has been shown to protect itself during hyperthermia by *selective brain cooling* mechanisms (see section below). As these mechanisms begin to fail under excessive heat conditions, brain cells and their connections begin to 'cook' as protein denaturation. The net effect is *thermal stress illness* or just plain *heat illness*– 'prickly heat' to heatstroke- with all their associated sequelae.

Human protein begins to denature at 105.8°F (41.0°C), some denaturation becoming irreversible by 106.3°F (41.3°C)[21,22,23]. Heatstroke and near-heat stroke events 'cook' the delicate and tiny (0.3-2.2 micrometers) connections between brain cells, the dendrites. Even when thermal damage is not severe enough to destroy brain cells, the dendrite connections can be impaired or destroyed. When dendrites are damaged or destroyed, communication between brain cells is impaired or even terminated if heat-induced damage is severe.

This is a basis for long-term dysfunction and mental impairments suffered by heat-stroke survivors. EPA estimates for every heat stroke death, there is an average of 10 heat-stroke survivors with long-term disabilities[1].

Yet even minor increases in brain temperature can yield the first malignant changes of brain hyperthermia. As hyperthermia raises core temperature above 38.1°C (100.6°F), the *tight junctions* of the brain's blood vessels begin to separate, causing a leak of intra-vascular water from those blood vessels into the interstitial spaces of the brain- *cerebral.*[14,46,50] The greater the brain's temperature, the greater the leak, resulting in worsened *cerebral edema*[46]. When relatively minor, this brain swelling is the cause the heat-induced headaches so often experienced by firefighters, athletes, soldiers, and industrial workers during exertion in hot humid conditions.

These 'heat headaches' usually resolve in a matter of minutes to hours after core temperature returns to normal. But if *brain temperature* (T_{BRAIN}) increases further, increasing cerebral edema causes increasingly severe symptoms of *heat illness*[46]. Furthermore, brain hyperthermia induces heat-proportional drops in systemic blood pressure with increasing pulse[28,19], made worse by dehydration. Above 40.0°C, increasing T_{BRAIN} is associated with severe and malignant changes, derived from increasing cerebral edema, heat-induced cerebral blood vessel spasm, worsened by hypotension-induced brain ischemia, and disruption of the brain's ability to regulate body and brain temperature[24,25,26,27].

As cerebral edema worsens, nausea and vomiting, shortness of breath, disorientation, decreased consciousness, delirium, lethargy, seizures, hypertonia, hypotonia, focal deficits, automatisms, and coma may occur[28,29]. Constricted pupils become almost universally present[27]. The cerebellum, integrating and coordinating movement, is particularly sensitive to hyperthermia[30], and manifests in the discoordination (slips, trips, falls) seen with the onset of heat exhaustion. When severe brain hyperthermia causes brain cerebellar damage, permanent ataxia is the result[29,31].

Concurrent with increasing T_{BRAIN}, dangerous vascular changes affecting the brain's blood supply are occurring[18]. Increasing hyperthermia can cause spasm of the brain's blood vessels resulting in a heat-proportional decrease in brain blood flow. This decreased blood flow is worsened by a hyperthermia-induced drop in systemic blood pressure and carotid artery vasospasm, thus limiting brain perfusion and metabolism[19]. This combination of limited cerebral perfusion and cerebral edema leads to the clinical symptoms of impaired cognition, confusion, disorientation, and other altered level-of-consciousness symptoms[27]. Further decreases in cerebral perfusion result in worsening brain hypoxia, ischemia, and kicks off a cascade of serotonin release, further vascular smooth muscle spasm, platelet aggregation, blood vessel occlusion, and even further cerebral edema. The summation of these can lead to brain infarction and permanent coma in heatstroke. When immediate death in heatstroke occurs, it is usually overwhelming cerebral edema[32].

Thus the mandate for Health and Safety Officers in the fire department, Athletic Trainers in athletics, and Safety Officers in the military and industry to screen their charges for hyperthermia symptoms as above. These safety managers are tasked with recognition of the symptoms of thermal stress illness and instituting immediate effective therapy to prevent the progress to heat exhaustion and even heat stroke. Rarely recognized data from experimental physiology on *selective brain cooling, thermal hyperpnea, transpulmonary cooling* (covered below), and recent neurophysiology data on the effects of brain cooling may greatly help make this important job easier, with the promise of better recognition and interventions for hyperthermia. But first is needed a better understanding of temperature measures themselves.

Temperature Measurements

Brain temperature (T_{BRAIN}) is *the* most critical temperature measurement in thermal stress illness[50]. It is *the* temperature best predicting heat exhaustion and heat stroke as well as best indicating response to therapy for dangerous hyperthermia[14]. Unfortunately, T_{BRAIN} is impossible to obtain except by direct temperature probe placement on or in the brain[14,15]. Except neurosurgery in a sterile operating theater, these direct measurements of T_{BRAIN} are impossible to obtain, especially in the field. T_{BRAIN}, under stable normothermic conditions, is usually 0.3-0.4°C above core body temperature (T_{CORE}) and varies directly with it. But under dangerous hyperthermia or brain injury, T_{BRAIN} can vary as much as ±3.0°C from T_{CORE}[14].

Physiologists, anesthesiologists, and intensive care physicians define T_{CORE} as the temperature where collection of all body heat and maximum blood temperature accumulates before cooling in the lungs can reduce blood temperature. This occurs before oxygenated blood in the lung is then pumped through the heart to the rest of the body. This maximum-blood-temperature collection point is the *pulmonary artery* where all blood returning from exercising muscles and organs gathers before being sent to the lungs for oxygenation, removal of CO_2, and exchange of heat in the lung.

A catheter with thermistor inserted into the pulmonary artery yields the invasive *pulmonary artery temperature* (T_{PA}). This is the temperature critical care physicians rely upon when exact *core body temperature* (T_{CORE}) measurements are essential to a patient's care. Under normal conditions T_{CORE} is usually a very good approximation of T_{BRAIN}, partially tracking T_{BRAIN} during the dynamic temperature changes of exercise. Compared with T_{BRAIN} and its varying range in exertion, T_{CORE} as T_{PA} has the *second* best record for tracking T_{BRAIN} changes.

Rectal temperature (T_{REC}), often presumed to be T_{CORE}, approximates T_{PA} only in the most stable of temperature situations and only with slower changes and long equilibration times, such as fever. T_{REC} lags behind T_{PA} considerably and poorly predicts T_{PA} during the rapid rise of T_{PA} in hard exertion. T_{REC} also lags behind falling T_{PA} during cool-down in thermal rehabilitation. T_{REC} has gained much accord over the decades from its use in febrile children, as it cannot be spat out like an oral thermometer. But T_{REC}, in the tracking of T_{PA} as T_{CORE} during dynamic exercise, remains a poor predictor of T_{CORE} and an especially poor predictor of T_{BRAIN}.

Other temperature measurements possible during dynamic exercise generally range between T_{PA} and T_{REC} as accurate predictors and trackers of T_{CORE}. In sequence from best to poorest, these are *esophageal temperature* (T_{ES}), *oral temperature* (T_O), and radiothermotelemetry-based gastrointestinal temperature (T_{GI}). The only temperature measure less accurate than T_{REC} in dynamic exercise is

skin temperature (T_{SKIN}), a measurement Sessler[33] calls "random number generators" instead of any meaningful measure of body temperature.

You should note tympanic membrane (eardrum) temperature (T_{TM}) is not mentioned in this list. T_{TM} has a uniquely special and close relationship to T_{BRAIN} but less to T_{CORE}, explained below. T_{TM} is measured at the eardrum, the closest measure of temperature to the base of the brain, and T_{TM} does track the movement of T_{BRAIN} closely. One would therefore assume T_{TM} to be the perfect approximation of T_{BRAIN}. To understand why it is not, the phenomenon of *selective brain cooling* must first be understood.

Selective Brain Cooling

Selective brain cooling has been a controversial mechanism[34,35,36,37,38,39,40,41,42,43], now confirmed[14,15], by which brain partially controls its own temperature independent of the rest of the body, especially during exertion in heat. In lower mammals, such brain temperature management is accomplished by 'panting' when overheated. In this manner, blood temperature is vented through the lung and cooled before that blood is sent to the organs, first among them, brain. Whether or not humans can similarly lower brain temperature has been a heated debated in the experimental physiology community since the 1970's[44,45,46,47,48,49], but is now generally agreed *selective brain cooling* does occur in humans[14,15,50]. This seems to be accomplished by two separate mechanisms:

Head and Face Perspiration

During hyperthermia, sweat pours over the face and scalp, cooling the skin by evaporation and the venous blood within[34,37,51]. This cooled venous blood of the scalp then drains downward into the skull and directly to the brain, cooling the surface and deeper portions of the brain itself before the cooled venous blood returns, via the jugular veins, to the heart. Emissary veins of the scalp have no vasoconstrictive capacity[52] and drain directly through the skull to the venous sinuses deep in the brain, cooling the surface and deep structures of the brain.

Facial veins can reverse their normal outward drainage such that perspiration-cooled venous blood can then drain inward directly to the base of the brain[37,53], cooling the thalamus and, especially important, the hypothalamus- the thermal control center of the brain. This cooled venous blood helps maintain T_{BRAIN} at lower temperature than T_{CORE}. Keeping the hypothalamus at a lower temperature helps the hypothalamus maintain control of sweating and activity, thereby preventing excessive body temperature accumulation during exertion in heat.

Thermal Hyperpnea/ Transpulmonary Cooling

When T_{CORE} begins to rise above 38.5°C, the brain excites an adjunctive cooling mechanism known as *thermal hyperpnea*[54,55,56], a form of *transpulmonary cooling*[57,58,59,60]. Here a rising $T_{CORE} \geq 38.5°C$ induces hyperventilation to the point of respiratory alkalosis well outside normal breathing and body chemoregulation set-

points[38]. This is well beyond the need to supply the body with oxygen or eliminate carbon dioxide. Why?

Thermal hyperpnea allows the body to dump excess heat through lung exhalation, cooling the bloodstream and thereby organs fed by that bloodstream, first among them, the brain. This is directly analogous to *panting* recognized in lower mammals, a mechanism they use to cool brain as well.

Lungs have a surface area ~59 times the skin surface area. A person 183 cm tall and weighing 78.1kgs has a Body Surface Area (BSA) of 2.0 m^2. Yet they will have a Lung Surface Area (LSA) of 118m^2 ± 11m^2.[61] Inhaled air entering the lung will exchange its oxygen and pick up carbon dioxide in the alveolar air sacs surrounded by capillary blood flow. All that separates the air from the capillary blood in the alveoli is the microscopically thin alveolar wall- approximately 400-1000 nanometers- the same measure used to size viruses. Thus rapid transfer of blood heat to outside air is much faster and more efficient through the lung than venting blood heat through skin sweat with skin's intervening insulating fat layer keeping body heat within.

When T_{CORE} rises above 38.5°C (101.3°F), *thermal hyperpnea* begins. The increased surface area of the lung allows increased dissipation of heat during hyperventilation. This expansive lung surface exchange area separates blood and air by less than 1 micron when venting blood-heat to air, versus the much longer blood-to-skin distance of millimeters to a centimeter to get blood heat vented to outside air by skin sweat. Therefore blood heat is much more easily vented to outside air through the lung than skin during *thermal hyperpnea*. Thus *thermal hyperpnea* mechanism, as a form of *transpulmonary cooling*, is very effective during *thermal stress* as an adjunctive cooling mechanism to *selective brain cooling* for T_{BRAIN}.

Normally the lung will act to conserve body heat[62], but in the setting of hyperthermia, the lung has the ability to act as an accessory mechanism for elimination of excess body heat[63]. This drives the hyperventilation of *thermal hyperpnea* seen in exercising athletes, military personnel, hot industrial workers, and firefighters in fire suppression training and duty.

Recent brain cooling research in experimental physiology labs has shown *transpulmonary cooling* through the lung can achieve cooling of T_{CORE} 4 to 6 times faster than skin cooling in the normothermic.[60,61] T_{CORE} lowering by *transpulmonary cooling* in *thermal hyperpnea* occurs even faster in hyperthermia.

Tympanic Membrane (T_{TM}), Rectal (T_{REC}), and Brain (T_{BRAIN}) Temperatures

T_{BRAIN} is central to all *heat illness* and heatstroke. But T_{BRAIN} cannot be accurately obtained in the field; therefore we must rely on the closest T_{BRAIN}

approximation. Many have assumed this to be rectal temperature (T_{REC}) in past research[64,65], but physiology data indicates T_{REC} is not the best approximation of T_{BRAIN}[66,67,68,69,70]. Even the best T_{CORE} measure, pulmonary artery (T_{PA}) temperature, while 0.1-0.4°C lower than T_{BRAIN} at normothermia and rest, begins to diverge from T_{BRAIN} as *selective brain cooling* mechanisms come into play with increasing hyperthermia from exertion. When brain injury, such as traumatic brain injury or heat stroke, occurs, T_{CORE} and T_{BRAIN} may diverge as much as 3°C[14].

While stably reproducible and an excellent measure of depot heat, T_{REC} suffers from slow response to dynamic heat changes in exercise[69,70,71]. Body heat from exercise accumulates in the bloodstream and is eliminated by sweat or transpulmonary cooling (thermal hyperpnea). One might presume the semi-invasive esophageal temperature (T_{ES}) is the best estimate to track the dynamic heat changes of T_{CORE} in estimating T_{BRAIN}, especially when one must judge the risk of rising exertional heat or the effectiveness of therapy treating heat exhaustion and heat stroke. Yet we know in hyperthermia, T_{CORE}'s tracking of T_{BRAIN} is not fully reliable[72]. How can we reliably judge the dynamic changes of body temperature and accurately predict when hyperthermia has become dangerous? Or know if and when our treatment for hyperthermia is effective?

For all its variances and "inaccuracy", properly calibrated and executed tympanic membrane temperature (T_{TM}) may be that measure[68,69,70] of T_{BRAIN}. First proposed by Benzinger[29] and later Cabanac[20], T_{TM} has a number of qualifications for readily available field approximations of T_{BRAIN}. Mariak et. al.[73,] placed thermocouples on the brain and tympanic membrane of neurosurgical patients after surgery. Even with surface cooling of the face, T_{BRAIN} and T_{TM} remain highly correlated, much better than the correlation of T_{BRAIN} with T_{ES} or T_{REC}[73]. Questions as to T_{TM} being highly affected by cooling of the head were answered when T_{BRAIN} as *subdural brain temperature* (T_{SD}) was measured against T_{TM} during face cooling and without face cooling. T_{TM} was the only extra-cranial temperature measurement that statistically and significantly highly correlated with T_{SD}, whether T_{SD} moved up or down. T_{ES} somewhat correlated with T_{SD}, but that correlation was not statistically significant. T_{TM} correlation with T_{SD} was very highly significant[73].

Mariak et al. also noted T_{TM} runs closer to the temperature of central and basal segments of the brain, rather than the brain's surface[73]. This is easy to understand as a common blood supply flows to the eardrum and the base of the brain surrounding the hypothalamus. Branches of the internal carotid artery supply both structures: the deep auricular branch of the internal maxillary artery, the stylomastoid branch of the posterior auricular artery, and the tympanic branch of the internal maxillary artery[30]. Thus T_{TM} shares a close common arterial blood supply and has the closest proximity of any external measurement to the basal brain. T_{TM} *tracks* equal movement in T_{BRAIN} without *being* T_{BRAIN} in measurements taken as T_{TM} is always lower than actual T_{BRAIN} due to *selective brain cooling* mechanisms.

In conditions where T_{ES} (a close substitute for T_{PA})> 38.5°C, T_{ES} and T_{TM}, in still air, are seen to move together and temperature measurement values almost equalize[8]. But if air is moving across the head, T_{TM} will be lower than T_{ES}, reflecting the effects of *selective brain cooling* by evaporative cooling of the scalp and face and resulting in lowering T_{BRAIN}, as described by Mariak[57] and others[68].

Therefore, we see the very "inaccuracy" of T_{TM} is actually its strength in evaluating the hyperthermic athlete, firefighter, worker, or soldier. T_{TM} is the closest approximation of the dynamic changes in T_{BRAIN} (much closer than T_{REC}) in *exertional heat stress* that is available in the field. Though also reflecting efforts to cool the brain, increasing T_{TM} towards 40°C (104.0°F) indicates approach of failure of *selective brain cooling* and onset of heat illness. This failure is confirmed by neurological or psychological changes in the victim. T_{TM} is *the* essential measure of T_{BRAIN} in the evaluation of *heat illness* and tracking T_{BRAIN} changes in the evaluation and treatment of hyperthermia. Once reaching 40°C, effective cooling mechanisms are needed emergently to bring down T_{BRAIN} to prevent permanent brain damage.

Diagnosis: Thermal Stress Illness / Heatstroke

Obviously T_{BRAIN} is not an accessible temperature in the field or even the Emergency Department. T_{REC} may be misleading, and T_{TM} will be lower than T_{BRAIN} even though it moves with T_{BRAIN}. So how do you know who needs treatment?

As a former emergency physician and Base Station Director, we never had primary decisions of heat stroke based solely on temperature. We looked at the patient. If outside conditions were warm (high Heat Index) and the patient had been exercising in the heat, but now had an altered level of consciousness and high temperature by any measure (usually T_{TM}), we assumed imminent heat stroke and treated for it. While we would proceed concurrently with ruling out hypoglycemia, stroke, drugs, and other possible causes of altered level of consciousness, we assumed severe *heat illness* when exercising participants suddenly becoming "odd" during or after exertion. You must think *heat illness* first and begin treatment immediately. T_{BRAIN} can be in excess of whatever temperature you can obtain and, in heat stroke, **increased time to treatment = increased damage to brain and body function**[17].

Therapy: Effective Hyperthermia Reduction for Brain and Body

Cold Water Immersion (CWI) for Critical Hyperthermia:

But not all is bad news for victims of hyperthermia. Hyperthermia can cause the brain to swell, cerebral arteries to spasm, and result in systemic hypotension and brain ischemia. *But immediate brain cooling can reverse these changes quickly*, limiting brain damage and its resulting permanent disability. Rapid reduction of T_{BRAIN} quickly begins to tighten loosened brain arterial *tight junctions*. This stops water translocation into the brain and enhances water resorption out of the brain, reducing *cerebral edema*. Cerebral arteries spasmed by heat begin to relax,

improving blood flow to the brain and washing out ischemic by-products with fresh oxygenated blood, thereby salvaging endangered brain cells[17,74]. These improvements limit the development and extent of stroke symptoms. Cooling of the brain also begins to reverse hyperthermia-induced hypotension throughout the body, improving blood pressure and perfusion of blood to all organs, including brain. But just like CPR, **time to resuscitation is life!** Brain cells begin to die by 5 minutes of complete ischemia in CPR. In heat stroke, the time frame is not much longer. **Faster cooling of brain = increased brain heat resuscitation and salvage[17]**.

Cold-water immersion is, and has been, the 'gold standard' treatment for imminent or existing heat stroke over many decades. Stress has been upon immersing the body in cold water, but equal treatment of the head and its brain has been absent.

Knowledge of *selective brain cooling* mechanisms has shown that cooling facial and scalp skin and veins, draining directly to the brain, can be used for effective brain cooling during hyperthermia. It only makes sense to augment that cooling mechanism by pouring ice water continuously over the face and scalp to achieve far greater cooling. This creates colder venous blood draining into the brain for greater, faster and more direct brain cooling than could ever be accomplished by torso cooling with ice-water to cool blood in the skin that only *eventually* cools the brain.

Therefore, when T_{BRAIN} may be rising rapidly with high T_{TM}, personality or mentation changes are occurring, and heatstroke may be imminent, CWI *must* be employed. Pouring ice-water *continuously* over the face and scalp must be used to effect the fastest possible cooling of T_{BRAIN} through cooling face and scalp venous drainage. Veins of the face and scalp cannot spasm in the cold[36,52,75], so the colder the water, the faster the brain cooling. Pouring ice water over the head frequently shortens the time to return of victim consciousness and orientation to just minutes. This effects major improvements in brain cooling and salvage in heat stroke victims. **Rapid brain cooling = less heatstroke-induced disability and damage= greater brain salvage[17].**

Periodic Cooling (Per-Cooling/Thermal Rehabilitation) Advances:

While *Per-Cooling* is 'new' to athletic training[5,6,7,8,9], it is a closely related practice to *Thermal Rehabilitation* used by firefighters during fire suppression or training for decades. A simple periodic rest period with fan cooling and ingestion of electrolyte fluids during fire suppression duty has greatly reduced the incidence of severe and critical heat stress events within the firefighting community. However, periodic Per-Cooling and Thermal Rehabilitation still currently rely solely upon skin surface cooling for their beneficial effects, just like CWI for heatstroke. *More can be done*.

At lesser levels of thermal stress, perspiration remains our common natural cooling mechanism for control of body temperature. But increasing cooling of the face and scalp can lower the temperature of venous blood draining into and cooling the brain. Neither forget our accessory cooling mechanism, *thermal hyperpnea*, that form of *transpulmonary cooling* still useful outside the ice-bath. Cooling through the lung is rapid, quickly cooling the circulating bloodstream. And the first organ receiving such cooled blood is brain!

Firefighters in thermal rehabilitation and breathing a ~15.6°C airstream (also cooling face and scalp) have reported rapid return of thermal relief sensation while T_{TM} cooled from 40.1°C to 36.7°C in as little as 11 minutes[76]. Uniformly, these firefighters experienced a sensation of 'chill' when T_{TM} began to drop to 36.7°C. Those experiencing this degree of periodic cooling in all burn evolutions spontaneously reported no heat headaches, no nausea, and no exhaustion at the end of 6 burn evolutions in a single day. T_{TM} was shown to drop 0.56°C every 2-3 minutes during MAC[B] hood thermal rehabilitation[78].

Currently in press[77] is a crossover-design study of athletes cooling after exercise in hyperthermic condition in a heat chamber (40°C). Participants in this experiment cooled post-exercise either by fan plus fluids or by placing the head inside a MAC cooling hood producing a 22.2°C airstream for head and transpulmonary cooling. Note this MAC airstream temperature is higher than preferred Thermal Rehab parameters. Normal post-exercise rehydration was utilized in both groups.

This study compared MAC hood cooling to CWI as a single emergency cooling measure for heatstroke, as measured by T_{TM} and T_{REC}. The MAC hood was not equal to CWI as measured by T_{REC} as MAC hood cooling was only 0.07°C/min T_{TM} compared to 0.15°C/min. T_{REC} in CWI. It was the changes in T_{TM} and the participants' response in thermal stress perception that are most significant. MAC hood use resulted in a far more rapid and statistically significant reduction in T_{TM} over the course of the first 10-minutes of *per-cooling*, with lower overall T_{TM}. Significantly, participants utilizing the MAC hood spontaneously reported greater thermal stress relief than standard post-exercise cooling.

It should be noted this study examined MAC hood cooling using T_{REC} instead of T_{GI}, as T_{REC} is the current 'gold standard' used by many groups to assess critical hyperthermia. However, T_{REC} is known to be slower and less accurate a measure of T_{CORE} than T_{GI}, so the estimation of the efficacy of the MAC hood in reducing T_{CORE}

[B] MAC= *microenvironmental air chiller*- a system providing a continuous and cold but limited airstream at least 11.1°C colder than ambient air drawn into the system. Nominal range for current MAC units is in the 15.6°C range. These MAC systems are single-pass, non-air-recirculating cooling devices. MAC systems can be used for air-hypercooling purposes in outside heat and humidity so long as the cold airstream is confined to limited areas requiring cooling, such as the head and neck. Without recirculation of air through the evaporator, MAC systems do not recirculate contaminants nor viruses among users so long as separate hoods are used for each user.

may be underestimated. Worse yet, the 40°C conditions of the experiment exceeded the designed operational range (< 35°C) for the MAC device.

As T_{TM} tracks T_{BRAIN} in time (while still lower than T_{BRAIN}), the rapid drop in T_{TM} of Adams' study in the first 10-minutes indicates the MAC hood, when combined with adequate rehydration, may offer significant advantages for periodic cooling with minimal interference for all hyperthermic working communities. Regular periodic cooling appears to offer better thermal stress relief and improved cognition and complex task assessment. Lowering of T_{TM} indicates critical lowering of T_{BRAIN} and T_{CORE} overall in hyperthermic exercising conditions where the MAC hood is used for *per-cooling*. Because periodic cooling rapidly lowers T_{TM} in a MAC hood, the resultant lowering of T_{BRAIN} should also lower the incidence of critical heat illness and the need for CWI.

For periodic cooling (*per-cooling* and Thermal Rehabilitation) in a MAC hood, best results appear when the airstream is below 21.1°C, and best in its nominal range of 15.6°C. Such results are currently achieved by industrial *microenvironmental air-chilling* (MAC) units. A single MAC hood over the head can cool face and scalp as well as cooling lung in *transpulmonary cooling*. This is the optimal combination for rapid cooling of T_{BRAIN} in periodic cooling. Actual studies[76,78] of firefighters during live fire training in MAC hoods show T_{TM} drops averaging 0.4-0.5°C/minute and complete thermal rehabilitation times of 10-minutes or less to T_{TM} less than 37.2°C. Firefighters, utilizing these MAC devices during live fire training and multiple thermal rehabilitation sessions, report increased stamina, absence of headaches and nausea, increased alertness, and less exhaustion even after 6 sequential burn evolutions[80].

While this review is intended to address exertional heat stroke and severe heat illness for multiple working communities, the principles of brain protection provided by *hypothermia* have broader implications and applications. Per Wang et. al.[14], speaking of induced brain *hypothermia* after traumatic brain injury: "…brain hypothermia, with its broader, pleiotropic effects, represents the most potent neuroprotectant in laboratory studies". Thus *hypothermic* brain protection in heat illness promotes brain protection even down to the genetic level[79].

Brain *hypothermia* has already been proven to prevent post-trauma reperfusion damage in moderate traumatic brain injury (concussions). Similar brain *hypothermia* trials are now being explored for potential similar benefits in vascular stroke and possibly even severe heatstroke victims[17].

Such results have not been limited to firefighter training nor fire suppression duty. Noteworthy results were obtained from the Florida Regional, National, and World Finals of the Firefighter Combat Challenge Competition. This extreme firefighter competition normally sends 10-25 participants to the Emergency Department for exertional heat illness during any competition. During the 2019 competitions events, MAC units were used for thermal rehabilitation in three events.

No participants in any of these three events required E.D. visits for heat illness or other hyperthermic events.

Video interviews at the World Final of the Firefighter Combat Challenge in 2019 show actual responses of firefighters to MAC hood thermal rehabilitation. These videos can be viewed at the following web addresses:

https://www.youtube.com/watch?v=IjXBznyZHNs
1-minutes video of a firefighter at thermal rehabilitation in the World Finals of Firefighter Combat Challenge 2019.

https://www.youtube.com/watch?v=KbU6uB_b3H4
6-minute video of multiple participants after using Polar Breeze® in the thermal rehabilitation tent in the World Finals of Firefighter Combat Challenge 2019.

Hyper-Cooling Device Options

Refrigerant Based Options:

The MAC units of the Adams' and incomplete Blackstone studies were *Polar Breeze*® MAC machines. *Polar Breeze*® also makes compatible hoods for face/scalp/transpulmonary cooling with these MAC devices. These are single-pass air refrigeration machines that do not recirculate any cooled air through its system. This eliminates risk of contamination spread between users. Thus each user should have his or her individual hood to minimize the risk of viral contamination during this current Covid-19 pandemic.

Any common (non-MAC) enclosed air-conditioned pod used for per-cooling or thermal rehabilitation relies upon partially-cooled air recirculating through the evaporator for repeated cooling, thus *eventually* working air temperature down to cold air. However, the air-recirculation of a common air-conditioner also recirculates contaminants and viruses in that air. This air-recirculation becomes a risk for all users within the same small air-conditioned space as well as any subsequent users.

Ice-Based Options:

Refrigerant-based industrial MAC devices such as *Polar Breeze*® are purpose-built hyper-cooling machines for periodic cooling. But ice-based devices can also produce an acceptable result on an emergent basis. Passage of an outside ambient airstream through a sufficiently long column of crushed ice can produce a cold airstream in the 60°F range. This hyper-cooled airstream can be used in emergent face/scalp and transpulmonary cooling for periodic or emergency cooling when early *heat illness* symptoms begins to show in the victim.

Such ice-based units can be very effective for emergency cooling, even though they can only produce hyper-cooled air for a limited period of time (30-60 minutes) before ice replenishment is required. These are less expensive but still

effective for emergency use, though they require constant attention (for ice-water removal and replenishing crushed ice) if used for anything beyond true emergencies in a single individual. Currently the only ice-based MAC device is *Pol-Air*™, a cooling device for general aviation.

Other fan-driven ice-based coolers do not produce the cooling equal to the *Pol-Air*™ MAC unit. These non-MAC coolers also require recirculation of the air through the ice unit to reach cool temperatures within a confined space. Similar to air-conditioned spaces, such air recirculation also re-circulates contaminants and air-borne viruses within that space, a danger in this current pandemic. However, these devices can reach temperatures in the 15.6°C range with continuous recirculation of the ice-cooled air in a sufficiently small space.

Therapy Application

When CWI is used in evolving heatstroke or other critical heat illness, ice-water cooling of the head is a very important addition to CWI for cooling T_{BRAIN}. This facial and scalp cooling directly cools T_{BRAIN} (by mechanisms above) and thereby aids prevention of terrible consequences of heatstroke damage, permanent disability, and death. Ice-water immersion in CWI is still the treatment of choice in heatstroke. But the victim should remain in the CWI tank, even after return of consciousness, until T_{TM} shows a drop at least to 39.4°C or lower. I have seen victims removed from CWI while T_{TM} still read above 41.1°C after the victim regained consciousness as the resuscitation team prematurely prepared to move the victim to an Emergency Department via ambulance.

As a former Emergency Physician, I caution you not to do this. The Emergency Department will not have an ice-bath immediately available for CWI and a hot brain is still swelling and 'cooking' its dendrites. I encourage you to keep the victim in CWI until T_{TM} is under 39.4°C and preferably at 38.3°C or less with continuous ice-water rinsing of the face and scalp. If a cold-air MAC or similar device is available, this also should be used *with CWI* as combination cooling therapy. Cooling through the lungs and skin effects faster lowering of T_{BRAIN} and T_{CORE}. Such rapid lowering to a normalized temperature is important in reduction of heat stroke damage and disability. **Rapid brain cooling = greater heat stroke salvage**[17].

Postscript Note for Doubters:

For those still scoffing at this new data and who still believe all organs must be cooled equally for maximum heat stroke survival, I point out a 100-year old cancer treatment, *Therapeutic Hyperthermia*, still in use today. In this therapy, a chemotherapy drug is intravenously infused before the patient is placed under a general anesthetic. The patient is then heated to high body temperature, thereby increasing the killing effectiveness of the chemotherapy drug on cancer cells. When used in the United States, T_{PA} (true core temperature) may be raised as high as

42.8°C for periods up to one hour. In Germany, T_{PA} may be raised as high as 45.0°C[80], a temperature well into heat stroke range. Yet these patients do not suffer brain or organ damage as a result of such extreme body temperatures. Why?

This is because the head and face are continuous sprayed with cold water to keep T_{BRAIN} below denaturation range[81] during *Therapeutic Hyperthermia* treatment. Organ failure due to hyperthermia does not occur. Thus lowering T_{BRAIN} by effective cooling of the face and scalp, as well as transpulmonary cooling, offer an effective therapy to prevent the catastrophic sequelae from heat stroke and critical heat illness.

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