Heat Transfer Capabilities of Surface Cooling Systems for Inducing Therapeutic Hypothermia

by

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ABSTRACT

Therapeutic Hypothermia has emerged as a strong neuroprotective treatment for ischemic patients after myocardial infarction and stroke. Body surface cooling systems allow for a simple non-invasive method to induce therapeutic hypothermia in ischemic patients. The performance of three body surface cooling systems were compared in this study. They were 1) Arctic Sun with ArcticGel pads (AS); 2) Blanketrol III with Maxi-Therm Lite blankets (BL); and 3) Blanketrol III with Kool Kit (KK). The purpose of this study was to test the hypothesis that the Blanketrol III with the Kool Kit provides the most heat transfer due to its tighter fit and increased surface area in highly perfused areas of the body (e.g., the torso) compared to the other two systems. Eight participants were enrolled and cooled on three separate occasions (one for each condition). Shivering was not inhibited. Participants were cooled until either: 1) core temperature (T_{co}) reached 35°C; 2) 120 minutes elapsed; or 3) the participant or researcher wished to stop for any reason. Heat loss was the main performance measure. Heat loss was transiently highest with AS at the start of cooling, but there were no differences between systems at the end of cooling. AS also produced a significant reduction in ΔT_{co} in comparison to the KK condition from 30 to 60 minutes of cooling ($p < 0.05$) and the BL condition from 60 to 120 minutes ($p < 0.05$). Results suggest that each of the cooling systems had its own benefits and limitations. Heat transfer capabilities of each system is dependent on the cooling pump unit and the design of the water-perfused covers. Both cooling pump units in this study had similar performances in their ability to reduce water temperature (output temperature was 4°C). However, the Blanketrol III unit likely had a greater flow rate and therefore may have more cooling power. AS had an early transient advantage in heat removal, but this effect decreased over the course of cooling and may represent a minimal advantage in longer periods of cooling that are recommended in guidelines

CHAPTER 1: INTRODUCTION

BACKGROUND

Cerebral ischemia, also known as cerebrovascular ischemia, occurs when there is a lack of blood flow to the brain. The reduction/interruption of blood flow to the brain reduces energy production abilities available to cerebral tissues, thus forcing these tissues to rely on less efficient anaerobic energy production [1]. The reduced energy production in cerebral tissues initiates a cascade of events resulting in excitotoxicity, inflammation, and free radical production [2, 3]. Causes of cerebral ischemia can be categorized into different types which include thrombotic, embolic, or hypoperfusion [4]. The region of impact of cerebral ischemia can also vary, as focal ischemia is confined to a specific area of the brain and global ischemia affects a wider area due to drastically reduced cerebral blood flow [4]. Cardiovascular complications impacting the brain can range from a single event such as a cardiac arrest or stroke to longer chronic diseases such as diabetes mellitus [5, 6].

Therapy for ischemic strokes can be divided into reperfusion and neuroprotection. Reperfusion therapies are treatments that restore blood flow and effective methods include cardiopulmonary resuscitation, intravenous administration of thrombolytic drugs, and surgical endovascular thrombectomies [7]. Neuroprotective therapies are those that interrupt the cellular, biochemical, and metabolic processes that lead to brain injury during ischemia and include the use of medications, surgery, or hypothermia [8]. Therapeutic Hypothermia (TH) has emerged as a strong neuroprotective therapy and it has been validated in laboratory and clinical settings [3, 9, 10]. The American Heart Association, European Resuscitation Council, and the International Liaison Committee on Resuscitation all provide post-resuscitation guidelines and recommendations that support the use of TH in patients post-cardiac arrest [11-13]. These

guidelines define TH as a controlled reduction of the body's core temperature to roughly 32°C–36°C for a minimum duration of 24 hours.

The neuroprotective properties of TH offer protection against ischemic conditions in various ways. One protective factor of brain cooling is the reduced oxygen consumption and preserved energy stores for the neurons [14]. Preserving the brain's energy could reduce the downstream effects of ionic imbalances and reduce the risk of acidosis. TH has also been shown to: mitigate damage to endothelial cells and increases in blood-brain barrier permeability [15]; reduce hydroxyl radical production [16]; and improve post-ischemia glucose utilization [17]. Furthermore, TH has shown the ability to suppress glutamate release/sensitivity in ischemic rat brains [18, 19]. This could attenuate the severity of excitotoxicity during the ischemic cascade by reducing/inhibiting the action of degradative enzymes on neurons. Finally, when blood flow is reduced during ischemia, microvascular narrowing occurs and results in an overshoot of blood flow, temporarily reducing cerebral blood flow upon reperfusion [20]. TH mitigates this microvascular change and allows for improved circulation upon reperfusion [20]. It is the combination of these neuroprotective mechanisms that make TH an effective treatment for ischemic patients.

An issue associated with TH is the difficulty in cooling the human body. Thermoregulatory responses to cooling have been described in several review articles [21-23], so a quick summary will demonstrate the difficulty that cooling the body poses for TH. First, the large mass of the human body makes it difficult to change core temperatures, as it requires a large cold stimulus to reduce core temperature. Tissue composition is also a barrier, as the layers of adipose, muscle, and connective tissue insulate the body and protect its core organs from severe heat loss. Another major challenge to core cooling is the body's thermoregulatory

responses. Skin cooling triggers peripheral vasoconstriction and shivering thermogenesis. Vasoconstriction reduces the heat loss from the skin, while shivering results in increased metabolic heat production to maintain or even increase core temperature. Sudden cooling of the skin also initiates thermoregulatory responses to increase ventilation, heart rate, cardiac output, and mean arterial pressure. These thermoregulatory responses counteract the cooling stimulus imposed on the body and allow for continual management of heat production. This allows the body to maintain a relatively constant core temperature of approximately 37±0.5°C.

Another issue with TH is the method used for cooling. Methods used for body cooling are classified into either central cooling or surface cooling. Central cooling introduces cold fluids into a patient's circulation and uses conductive heat transfer to cool one's core temperature. Central cooling techniques have been shown to be the most effective method for cooling, but they are an invasive technique that pose a risk to the patient [24]. Surface cooling techniques use external, non-invasive, applications of cold stimuli to induce core cooling. The effectiveness of these surface cooling methods is dependent on the surface area and thermal conductivity of the cooling surfaces.

Due to its promising use in a clinical setting, specific methods of surface cooling will also be explored. Forced air cooling involves moving cooled air across the skin surface and uses convection and conduction as a means of heat transfer. Forced air is not as effective at cooling patients as other methods available, due to the limited thermal conductive properties of air [25]. Water immersion involves having a patient sit in cooled water and relies on conductive heat transfer to reduce core temperature. Although water presents a much higher (about 25 times) thermal conductivity than air, this method is impractical for patients in a clinical setting. Ice packs have also been used, but they have not been shown to be reliable in maintenance of cooled

core temperature [25]. Ice packs also run the risk of skin lesions and freezing tissue while requiring constant supervision. Finally, cold-water perfusion systems have been identified as an ideal application of surface cooling [24]. These cooling systems are comprised of a cooling pump unit which circulates cooled water through a water-perfused cover. It has been shown to be effective in various laboratory and clinical settings [24-27]. While it also uses conduction and convection as a means of cooling, cooling covers offer increased thermal conductivity compared to air with its use of water.

Two commercial cooling systems that are commonly used in clinical setting are: 1) The Blanketrol III Hyper-Hypothermia Temperature Management System with Maxi-Therm Lite blankets (placed under and on top of the patient) (Gentherm Medical, Cincinnati) and 2) The Arctic Sun Temperature Management System (Becton, Dickinson and Company, Mississauga) with ArcticGel pads covering the back and sides of the torso, thighs, and stomach. Both these cooling systems have been demonstrated to be effective in laboratory settings [26-28]. A new attachment, the Kool Kit, has been developed for the Blanketrol III cooling pump unit. The Kool Kit has an increased surface area and improved fit available for cooling compared to the other two devices; it includes a head wrap, a vest and lower body pad. However, it has not been researched or compared to the two systems mentioned above. The purpose of this study was to determine the cooling system with the greatest heat removal capacity and identify the factors that benefit or limit each system's heat transfer capabilities. We hypothesized that the Blanketrol III with the Kool Kit would provide the most heat transfer capabilities due to its tighter fit and increased surface area in highly perfused areas compared to the standard Blanketrol III and Arctic Sun systems. In an ideal situation, this study would examine core cooling rates induced by the three devices in non-shivering participants. Shivering would be inhibited with the

administration of Meperidine [29-31] . However, this requires physicians to administer the drug and monitor the participants. Due to the strain on the medical community because of COVID-19, our medical collaborators were not available to participate in these trials for the foreseeable future. Because shivering was present in each condition, an equal comparison was made between the three cooling systems' heat transfer performance. The results of this study were used to infer the heat removal capabilities of each system on non-shivering patients. Thus, this study focused on the cooling capacity of each unit, with the assumption that the unit with the most heat transfer capabilities in shivering participants will be most effective in non-shivering patients.

CHAPTER 2: REVIEW OF LITERATURE

INTRODUCTION

Due to its promising potential to be used as a neuroprotective therapy for ischemic patients, a thorough review of TH was conducted to understand what is currently known and unknown about its use. To accomplish this, a literature review examined current understandings within the field of research regarding the use of TH for ischemia caused by strokes and myocardial infarctions. Gaps in the research were also identified to ensure uniform progression of its understandings. This will promote continual optimization and standardization of TH as a future therapy for ischemic patients and promote understanding of its potential abilities within clinical settings.

PHYSIOLOGICAL INDICATIONS

Ischemia (or ischaemia) is the restriction of blood supply to tissues, resulting in a shortage of blood and oxygen that is needed for cellular metabolism [32]. The majority of clinical ischemic patients are the result of a myocardial infarction or ischemic stroke [32]. The brain is one of, if not the most, important organ in the human body as it regulates essentially all neurological functions required for necessary body function. This makes tissues in the brain essential for continued body function and making it a significant concern in the threat of ischemia. The significance of ischemia on body functions warrants major investigation into neuroprotective treatments to reduce the risk of cerebral cellular death during ischemia.
Since the early 2000's, the idea of neuroprotection has generated much enthusiasm and has triggered a significant amount of research focused on its use in ischemic patients [33]. The goals of neuroprotective therapies are to reverse or halt particular pathways in the ischemic cascade,

but with improved understanding, no single agent is thought to be able to affect the entire cascade [34]. One of the most compelling neuroprotective strategies to be investigated is TH, as it shows the ability to reduce the amount of cellular damage during hypoxic conditions and show post-ischemic neurological improvement in comatose patients [35]. With this continued understanding, both the ischemic cascade and the mechanism of neuroprotection appear to be significant in the use of TH as a treatment, thus an overview of each was conducted.

Ischemic Cascade

The ischemic cascade is a complex sequence of biochemical reactions that are initiated by the cessation of blood flow in the brain. The specific details of the ischemic cascade have been studied extensively, but an overview of several studies will be summarized. The fundamental consequence of the ischemic cascade is the result of an energy deficiency [36]. Brain tissue has a relatively high consumption rate of oxygen and glucose, and it relies almost entirely on aerobic energy production to meet its requirements [1]. Due to the reduced oxygen transport to cerebral tissues during ischemia, neurons are unable to maintain energy demands using aerobic respiration. To adjust to the reduction in aerobic respiration, the cell relies on anaerobic energy production means which produce Adenosine Triphosphate (ATP) and lactate [37]. As the energy production continues to be insufficient to maintain healthy cellular functions, energy-dependent transporters such as the sodium/potassium and calcium pumps are unable to maintain ionic balance [36]. This results in increased sodium and calcium concentrations inside the cell. The increased concentrations of positively charged ions results in depolarization of the cell and promotes hyperexcitability in neurons to stimulate the release of excitatory neurotransmitters like Glutamate [38]. Glutamate receptors (including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and (AMPA) and N-methyl-D-aspartate (NMDA)

receptors further increase calcium concentrations in post-synaptic cells and cause them to continually depolarize resulting in a continual sequence of hyperexcitable neurons [38]. Reduced action of glutamate reuptake proteins also promotes higher levels of extracellular glutamate, thus contributing to further depolarization of neighboring neurons through activation of AMPA and NMDA receptors [39]. In the event of continual energy depletion: membrane potential is lost, lactate acidosis occurs, and neurons and glia depolarize [39]. As an important secondary messenger, Ca^{2+}'s intracellular level increase triggers excitotoxicity, which is a series of catabolic processes mediated by proteases, lipases, and nucleases that breakdown essential proteins, membranes, and nucleic structures, respectively [40]. The production of free radicals and reactive oxygen species further contribute to cellular damage and apoptotic processes [41]. Finally, in response to the high concentrations of ions in the cerebral tissues, water begins to flow passively into the tissue and leads to cerebral edema [42].

It is important to note that not all aspects of the brain are equally impacted by the ischemic cascade. In the core of the ischemic brain, cerebral blood flow is reduced approximately 20% [43]. Cells in this vicinity of the brain are destroyed quickly by the cessation of ionic homeostasis [44]. Between this damaged core and the peripheral brain areas lies the penumbra, which is an area of the brain with limited blood flow and partially preserved energy metabolism [44]. It has been demonstrated in animals that given sufficient time and no treatment, the penumbra can progress to tissue death due to ongoing excitotoxicity [44]. Thus, the primary goal of neuroprotection should be to save the ischemic penumbra. Although there is evidence that the penumbra exists in human stroke patients [45, 46], the magnitude and dynamics of the penumbra are less understood [44].

Neuroprotective mechanisms

The neuroprotective mechanisms of TH offer protection against ischemic conditions in various ways. Research has identified the impact of brain cooling in significant cell death pathways including excitotoxicity, apoptosis, inflammation, and free radical production [2, 3]. One of the most notable impacts of cooling the brain is that it appears to reduce oxygen consumption and preserves energy stores for the neurons [14]. The decreased metabolic requirements of O_2 for cerebral tissues (CMR_{O2}) during brain cooling can be demonstrated using the Q_{10} principle. The Q_{10} principle uses a temperature coefficient (Q_{10}), which is a ratio of O_2 consumption rates at two temperatures separated by 10°C (Higher rate/Lower rate). One can use Q_{10} to determine duration of protection using TH during an ischemic episode. Duration of protection is equal to the duration of the ischemic episode (minutes) multiplied by the Q_{10} for the associated 10°C temperature interval. For example, the Q_{10} of the body is approximately 2, while the brain has been associated with values exceeding 3 [47]. It has been shown in canines that the Q_{10} of the brain increases from 3 (between 37°C and 28°C) to 4.9 (between 28 and 18°C) [48]. This suggests that if the brain could survive an ischemic incident for 5 min at 37°C, then cooling to 28°C would provide 15 minutes of protection (5 mins x 3), while cooling the brain from 28-18°C would provide 72.5 minutes (5 mins x 3 x 4.9). This is based solely on the decreased CMR_{O2}. Preserving the brain's energy can significantly reduce the downstream consequences of ionic imbalances and reduce the risk of cellular death. The preservation of energy stores also mitigates the consequences of increased lactate production from anaerobic energy production and the development of acidosis.

TH has also been shown to mitigate the ischemia-induced damage to endothelial cells and increases in blood-brain barrier permeability [15]. It has also demonstrated the ability to reduce

hydroxyl radical production and improve post-ischemia glucose utilization [16, 17]. Brain cooling may also impact glutamate release during the ischemic cascade. It has been shown that the cooling of an ischemic rat brain suppressed almost all glutamate release while also reducing the number of AMPA and NMDA receptors after global ischemia [18, 19]. This may potentially attenuate the severity of excitotoxicity during the ischemic cascade and offer protection to the cerebral cells under ischemic conditions. Finally, when blood flow is reduced during ischemia, microvascular narrowing occurs. This results in an overshoot of blood flow (hyperemia) when reperfusion is initiated, followed by a temporary reduction in cerebral blood flow [20]. TH mitigates this microvascular change in the brain during ischemia and allows for improved circulation when blood flow is restored [20]. It is the combination of these neuroprotective mechanisms that make TH an effective treatment for ischemic patients.

THERAPEUTIC HYPOTHERMIA INDICATIONS

The theory of reducing core temperature in the treatment of ischemic patients originated from research on ischemic animals, which demonstrated that lowering brain temperature could significantly reduce cerebral oxygen demand and neuronal death in anoxic conditions [37, 49-54]. These findings motivated the design of two foundational prospective clinical trials showing that mild hypothermia improved neurological outcomes and reduced mortality of ischemic comatose patients at 6 months post-cardiac arrest [9, 10]. These findings triggered significant interest in the use of cooling as a means of protecting the brain in anoxic conditions. Since then, TH has been extensively studied in the laboratory and is one of the most effective neuroprotectants studied to date [3]. TH has developed into a recommended practice for clinical use among health care providers and emergency medical services. The American Heart

Association, European Resuscitation Council, and the International Liaison Committee on Resuscitation all provide post-resuscitation guidelines and recommendations that support the use of TH in comatose patients, post-cardiac arrest [11-13]. More recent research has shifted towards understanding the specific mechanisms involved in the neuroprotective effects of TH [55, 56]. Although there has been significant support for the use of TH on out of hospital cardiac arrests (OHCA), studies showing the benefit of TH in non-shockable rhythms are mixed [57-59]. For patients who experience an in-hospital cardiac arrest (IHCA), data also appears to show no benefit from the use of TH [55, 60]. However, it is important to note that the use of TH after resuscitation of IHCA is rare, as less than 3% of the patients in these studies were treated with TH, and only 50% of these patients achieved goal temperatures.

These studies provided support for the development of the most effective cooling method and inspired future studies to explore its use. Early pre-clinical and clinical studies show that TH could be a strong neuroprotective method for the treatment of ischemic patients [61]. Currently, research has shifted towards the specific considerations required in efficiently fostering TH.

METHODOLOGICAL CONSIDERATIONS OF THERAPEUTIC HYPOHTERMIA

The next section of this literature review will explore current understandings of the methodological considerations in the use of TH. This literature review will explore specific understandings regarding initiation timing, methods of cooling, and target temperatures related to the use of TH. Each area under consideration will be explored for its impact in the practice of TH

Timing of Intervention Initiation

The practicality of TH within clinical practices is an important aspect of measuring its effectiveness, so the optimal timing for TH initiation will be explored first. From the discussion

thus far, it is important to understand why intervention timing is significant. Recall that the results of ischemia are reduced oxygen and energy transport to the brain tissues resulting in cellular death. It is, therefore, logical to suggest that earlier interventions would benefit the ischemic patients, as patients could maintain energy stores longer and reduce the risk of a prolonged ischemic cascade. The time interval between the occurrence of ischemia and ensuing resuscitative measures can vary immensely depending on location and time of day. Therefore, a thorough understanding of optimal initiation of TH would be useful.

Current understandings of TH intervention timing suggest that early initiation and fast achievement of TH are mixed. Some studies have concluded that early achievement of TH reduces hypoxic brain injury and produces favored positive neurological outcomes [62, 63]. In one study, it was concluded that for every 1 hour in delay to initiation of cooling, the risk of death increased by 20% [64]. Another study also concluded that the odds of poor neurological outcome increased significantly with each 5-min delay in initiating TH and with every 30-min delay in achieving target temperature [63]. This suggests that there may be an inherent benefit to earlier TH initiation from increased survival rates and improved neurological outcomes. While benefits have been noted from TH's early intervention, it is important to note that there is significant evidence that shows earlier initiation of TH may not have an impact on patient outcomes. Despite showing significant differences in core temperatures upon hospital arrival between intervention and control groups, subsequent randomized trials have been unable to demonstrate any significant benefits in survival or neurologic outcomes [65-68].

Overall, it appears that there are mixed results regarding the timing of intervention, thus more research is needed to understand its importance [69]. Timing of intervention may have a significant impact on improved neurological outcomes of ischemic patients; thus, it is important

to conclusively understand its role in administering TH. Another significant finding in the literature was the importance of elapsed time between ischemia and return of circulation. Multiple studies concluded that time to return of circulation played a significant factor in determining survival rates [64, 65]. This is an important distinction, as it is replicated in most of research on cardiac arrest survival [33]. Reducing time to return of circulation should be a priority in cardiac patient management, as it will serve to improve patient survival rates.

Methods of Cooling

As explained in the introduction, current methods of TH can be divided either central cooling or surface cooling. Available literature will be reviewed to understand and compare the use of specific cooling methods within each category. Central cooling techniques involve the introduction of cold fluids into a patient's circulation and use conductive heat transfer to cool one's core temperature. Central cooling methods include techniques such as intravascular catheters, peritoneal lavage devices, and extracorporeal circulation. Many studies using intravascular cooling devices have reported rapid cooling rates and highly reliable maintenance of core temperature, which suggests that it is an effective way to achieve and maintain hypothermic temperatures [25]. The main disadvantage with using central cooling techniques is that they are invasive and present risks to the patient through the intravascular procedures. The main risks of using central cooling methods are catheter-related thrombosis and the risk of infection [25]. Some of the more specific techniques, such as extracorporeal circulation, are impractical in clinical settings.

Surface cooling involves techniques for cooling patients through the application external cooling mechanisms on the surface of the skin. As mentioned in the introduction, the effectiveness of these surface cooling methods is dependent on the surface area and thermal

conductivity of the approach. Specific methods of surface cooling will be explored. Forced air cooling is one surface cooling technique that involves moving cooled air across the skin surface and uses convection and conduction as a means of heat transfer. Forced air is not as effective at cooling patients as other methods available, due to the limited thermal conductive properties of air [25]. Water immersion is another surface cooling method that involves having a patient sit in cooled water and uses conductive heat transfer to reduce core temperature. Although water presents a better thermal conductivity than air, this method is impractical for patients in a clinical setting. Ice packs have also been used, but they have not been shown to be reliable in maintenance of cooled core temperature [25]. Ice packs directly on the skin also run the risk of skin lesions and burns. Finally, perfused water or gel blankets is a technique that has been identified as an ideal application of surface cooling [24]. It has been shown to be effective in various laboratory and clinical settings [24-27]. While it also uses conduction and convection as a means of cooling, cooling blankets offer increased thermal conductivity compared to air with its use of fluids like water. In consideration of limitations for surface cooling techniques, skin surface cooling will induce a shivering response which will counteract the loss of heat. However, medications can be used to inhibit shivering in patients, making the technique still an effective treatment option [31].

There have been many studies that have compared the performance of central and surface cooling methods, so a summary of their findings will be discussed [25, 70-72]. In comparing the two methods of cooling, most research suggests that central cooling methods display superior outcomes in key performance standards such as cooling rates and temperature maintenance. However, despite the superior performance of central cooling, studies found that it did not seem to impact the final outcomes of patients. In studies that compared neurological outcomes, there

were no significant differences in outcomes between groups. A meta-analysis reviewed the comparison of central versus surface cooling techniques in 20 different studies [72]. In the context of the included studies, there was found to be no significant differences between populations, time to return of circulation, and interventions; thus, the participants of the 20 studies were deemed comparable. The analysis found that central cooling was superior in terms of cooling rates, cooling efficiency, and temperature stability in comparison to the measured surface cooling techniques. However, it also concluded that there was no significant difference in health outcomes (death, neurological function, etc.) between either technique. Although survival rates may be similar due to the non-significant difference between time to return of circulation (as already discussed), the important distinction is the lack of significant difference in neurological outcomes. Despite the worse performance, surface cooling techniques can achieve similar outcomes as central cooling without the risk of infection and catheter-related thrombosis. Further research into the clinical comparison of both techniques could serve to support this conclusion, but current research understandings suggest that surface cooling is the favored technique.

Target Core Temperature

Optimal core temperature for TH is another important methodological consideration in the application of its treatment. In the initial ground-breaking studies on TH, the target core temperature that was used in cardiac arrest patients was approximately 32-34 °C [9, 10]. Despite the significant clinical benefit seen with TH in these studies, research on an optimal core temperature for TH has yielded mostly mixed results. This literature review will begin by reviewing the literature comparing hypothermia and normothermia and comparisons of hypothermic core temperatures.

Literature comparing hypothermic patients to normothermic patients has been well established through the application of several Randomized Clinical Trials (RCTs) and cohort studies [9, 10, 73-76]. The hypothermic temperatures of these studies varied from approximately 32-34 °C but displayed effective treatment outcomes. Evidence strongly suggests that reduced core temperatures following an ischemic episode significantly improves neurological outcomes and mortality rates after treatment in comparison to normothermic core temperatures. The strong indication for TH is documented within literature in comparison to normothermic temperatures, thus it has become a recognized treatment for ischemic patients. With the understanding that TH improves neurological outcomes and survival rates compared to normothermia, literature has shifted its focus towards the understanding of an optimal core temperature for TH.

Literature for an optimal target temperature for TH is mixed [77-79]. Literature has been largely unsuccessful at demonstrating significant outcome differences between core temperatures ranging from 32-36 °C [77, 78]. One of the most significant findings on optimal core temperatures for TH was demonstrated by a large RCT, where unconscious adults after out-of-hospital cardiac arrests were randomly assigned to targeted temperature management at either 33°C or 36°C [77]. The primary measure was all-cause mortality through the end of the trial, while secondary measures included a combination of poor neurologic function or death at 180 days. The randomized trial found that there was no significant difference in survival rates or neurological function in each temperature group after 180 days. Although not as sound, there is also some evidence suggesting that lower core temperatures may be more beneficial. A smaller randomized trial measured unconscious cardiac arrest patients and compared the impacts of 32°C and 34°C core temperatures [79]. Findings reported an improved 6-months mortality ($p = 0.03$) favoring 32 °C. When restricting analysis to those with shockable rhythms, the data showed

improved good outcomes favoring 32 °C (p = 0.029). However, the patients assigned to the 34 °C arm received less CPR by bystanders, had longer downtimes and tended to have worse admission Glasgow Coma Scores (GCS). GCS can range from 3 (completely unresponsive) to 15 (responsive). The score is used to monitor hospitalized patients and track their level of consciousness, as lower GCS scores are correlated with higher risk of death. These results suggest that there may not be an optimal temperature for therapeutic hypothermia, but more research is required to confirm this conclusion. Current guidelines, and the initial groundbreaking studies, only consider temperatures from 32-34 °C as recommended [61]. The fact that a 36°C core temperature did not show any difference with the 33°C group suggests that the optimal range may wider than previously thought. Overall, findings suggest that there is a need for continued research in optimal cooling temperatures. Results appear to be mixed, as there is evidence supporting and opposing optimal temperatures.

MEASUREMENT OF HEAT BALANCE

The final section of this literature review will explore the understanding of heat balance. To maintain a relatively stable core temperature of approximately 37±0.5°C (98°F), the human body relies on important thermoregulation control. Thermoregulation represents an important ability of the body to manage and balance the amounts of heat produced in the body with the amounts lost. For heat production, the body relies on important behaviours such as shivering thermogenesis and mechanical work. These behaviours allow for heat to be created and counteract the amounts of heat loss. Heat loss can be attributed to the impacts of conduction, convection, radiation, and evaporation [80]. Conduction is the transfer of heat from warm to cool objects that are in direct contact. Convection is the transfer of heat by movement of a fluid (gas,

liquid) across a warmer or colder surface. Radiation is the transfer of heat in the form of electromagnetic energy between two objects of different temperatures. Finally, evaporation is a transfer of heat from the vaporization of a liquid into a gas. Each of these methods play an integral role in the net heat loss of the human body. Note that conduction, convection, and radiation can result in heat gain if the body is receiving the transfer of heat, but evaporation (sweating, breathing, etc.) will only result in heat loss from the body.

In resting conditions and in a neutral climate, heat balance in the body can be conceptually understood with the following equation:

$H_{Produced} = H_{Lost}$

While this equation works under the assumption that Heat production and loss are completely balanced, it does provide a general understanding of what the body is working to achieve. At the point where heat production can match the heat loss, the resting internal core temperature is approximately 37±0.5°C. In circumstances where $H_{Produced} > H_{Lost}$, the body internal core temperature will be above resting core temperature such as during exercise or in a patient with a fever. In circumstances where $H_{Produced} < H_{Lost}$, core temperature will drop below average such as during hypothermia. This means that even if processes such as shivering or physical work fail to maintain the amount of heat being lost, core temperature will continue to fall. Many processes inside the body function optimally at an internal temperature of 37±0.5°C, thus it is important for the body to maintain these temperatures. In the context of TH and understanding the role of heat balance, TH is a purposeful increase in H_{Lost} to reduce core temperature.

In a laboratory setting, $H_{Produced}$ and H_{Lost} can be monitored to understand the dynamics of heat balance. Heat production can be monitored by measuring oxygen consumption (VO_2), while heat loss can be monitored by measuring Heat flux.

Heat Production

$\dot{V}O_2$ can be used to estimate energy expenditure associated with thermogenesis through the metabolism of fats and carbohydrates [81]. VO_2 has been used widely across research to measure shivering activity, as it can be measured practically with the use of a metabolic cart that monitors a participant's inspired and expired air. Because of the relatively low heat production from non-shivering sources in cold environments, such as brown adipose tissue, $\dot{V}O_2$ provides an effective estimate for the measurement of shivering thermogenesis activity [81]. Using a metabolic cart, VO_2 in L/min and respiratory exchange ratio (RER) can be determined to calculate metabolic heat production (M) in Watts (W) using the following equation:

$M\ (W) = VO_2 * 69.7 *[4.686 + [(RER - 0.707) * 1.232]]$ [82]

This equation allows for the determination of quantity of heat production from shivering thermogenesis and the understanding of the dynamics of heat balance under the influence of TH.

Heat Flux

Heat flux (HF) is the flow of thermal energy per unit area per unit time, and can be effectively measured using heat flux transducers [83]. In understanding heat flux to be the flow of thermal energy, one can understand the way heat flux is measured using heat flux transducers. Measuring heat flow with the use of transducers can be visualized using Ohm's law where current (flow) is equal to the difference in voltage divided by the resistance. Heat flux can be visualized similarly, as current (I) can be replaced with heat flux, voltage difference (ΔV) can be

replaced with temperature difference (ΔT), and resistance (R) can be thermal resistance (TR). The idea can be understood in the following equation:

$I = \frac{\Delta V}{R}$ (Ohm's Law) → $HF = \frac{\Delta T}{TR}$ (Heat Flux)

This means that if one could know the thermal resistance of a transducer and the difference in temperature on either side, one could determine the heat flux at a given site. In heat flux transducers, these variables are determined using a thermopile, which is a succession of thermocouples connected in series. Each thermocouple consists of two different metals (usually copper and constantan) with electric and magnetic fields (EMFs) that produce different voltages when thermal energy flows through them. Since the transducer has a known thermal resistance and the voltage difference is representative of the temperature difference, heat flux can be determined for the area of the transducer. This information is delivered to a computing system capable of analyzing the information, which calibrates the heat flux over the surface area of the transducer (approximately $1cm^2$) to a $1m^2$ surface area in W/m^2. With the heat flux of a specific site on the body (HF_T), Body Surface Area (BSA), and anatomical fraction (F) one can use the following equation to determine the heat flux of specific anatomical locations:

$HF\ (W) = HF_T\ (W/m^2) \times BSA\ (m^2) \times F\ (\%) \times 0.01$

Under the assumption that heat flux is constant in specific areas of the body (i.e., arms, legs, chest, etc.), one can determine the heat flux of all anatomical areas using their fractional percentage of total body surface area. The heat flux of each anatomical area can also be summarized to determine total body heat flux. In calculating the total heat flux, one can have a good estimate of heat loss and the dynamics of heat balance.

RESEARCH GAPS

As has been highlighted throughout the discussion of this literature review, current understandings of therapeutic hypothermia are mixed. Its effectiveness is supported by significant amounts of literature; however, there is a need for better understanding within specified methodological considerations (timing, optimal temperature, etc.). Future research should strive to continue studies into these important considerations to ensure that the practice of TH is optimal and standardized. Future research should also move into more clinical trials to provide stronger levels of support for the use of therapeutic hypothermia.

CONCLUSION

In conclusion, therapeutic hypothermia appears to be an effective treatment option in the care of post-cardiac arrest and stroke patients. Physiological and academic indications support the use of therapeutic hypothermia in the treatment of ischemic patient, showing potential for improved health outcomes. Current methodological considerations appear to be mixed in their levels of understanding, thus suggesting further research is required into specific areas. Finally, future research should move towards more clinical trials to provide an improved understanding of TH in a clinical setting. Although current insights appear promising, the future potential of therapeutic hypothermia is yet to be understood.

CHAPTER 3: METHODS

PARTICIPANTS

The experimental protocol has been approved by the University of Manitoba Education/Nursing Research Ethics Board [Protocol # HS23118 (B2019:076)] and was registered in ClinicalTrials.gov (NCT04332224). Prior to participation, a signed informed consent was obtained. To achieve 90% power (a = 0.05, 1-tailed test; ß = 0.10; power index of 2.92), the sample size required to detect a statistically significant difference (mean ± SD) between cooling conditions was eight subjects. Eight healthy (4 males and 4 females; aged 21-26 years) were enrolled in the study.

MEASUREMENTS

For each trial, subjects wore a swimsuit and were instrumented by research staff in ambient lab temperature (~22°C). Barometric pressure in the lab was approximately 757 mmHg during each trial. Data were collected from each participant, which included age, body fat percentage, weight, and height. This data was used for the calculation of body surface area. Body fat percentage was measured using a body composition analyzer (InBody 270, CA, USA)

Esophageal temperature (T_{es}) was measured with a disposable esophageal thermocouple (Mon-a-therm) inserted through the nose, to midway down the esophagus at the level of the heart. This site provides the best noninvasive measure for intracardiac (or core) temperature.

Cutaneous heat flux (W/m^2) and skin temperature (°C) were measured using twelve heat flux discs (Concept Engineering). The discs (2 cm in diameter) were taped to the skin at the following sites: forehead, dorsum of the head, left anterior chest, right anterior abdomen, right scapula, left lower back, left anterior upper arm, right posterior upper arm, left anterior thigh,

right posterior thigh, right anterior lower leg, and left posterior lower leg. According to previous work in our lab, flux was defined as positive when heat traversed from the skin toward the environment (i.e., heat loss).

Oxygen consumption was continuously measured with a metabolic cart (Parvo Medics, Utah, USA). Participants wore a face mask, which collected their expired breath during the baseline and cooling period. Time at which participant started shivering was also noted.

Outflow water temperature and flow rate of the cooling pump unit was collected every 5 minutes from the start of cooling.

Subjective cold discomfort was collected from participants using the Cold Discomfort Scale (CDS) where participants could rank subjective cold discomfort from 0 (slightly cold) to 10 (unbearably cold) [84] . Participants were allowed to choose any half integer between 0 to 10, which totaled to 21 possible options to choose from. Subjective data were collected at the start of cooling for each trial and every 15 minutes until completion. After the completion of all three trials, participants were also asked to rank the three cooling conditions from the coldest to the least cold.

COOLING CONDITIONS

Each participant experienced three separate conditions, one for each of the three commercial cooling systems: 1) Arctic Sun 5000 with the ArcticGel™ pads; 2) Blanketrol III with Maxi-Therm Lite blankets; and 3) Blanketrol III with Kool Kit. For each condition, the participant lay supine on a bed and was covered in the cooling system with a cotton blanket placed overtop (Figure 4). Each cooling system was applied according to manufacturer

recommendations and set to the same specified water temperature (4°C). All systems were not turned on until the start of the cooling period.

Arctic Sun

The Arctic Sun™ 5000 Temperature Management System with the ArcticGel™ pad (AS) (Figure 1) is a thermal regulating unit that circulates temperature controlled water through conductive hydrogel coated pads [85]. The hydrogel coated pads are designed to cover the back and sides of the torso, abdomen, and thighs on the patient. The flowing water allows for conductive and convective heat transfer and the controlled temperature of patients. The company (Becton, Dickinson and Company) claims that the AS allows for fast initiation of treatment, simple programming abilities, and easy to access treatment data [85].

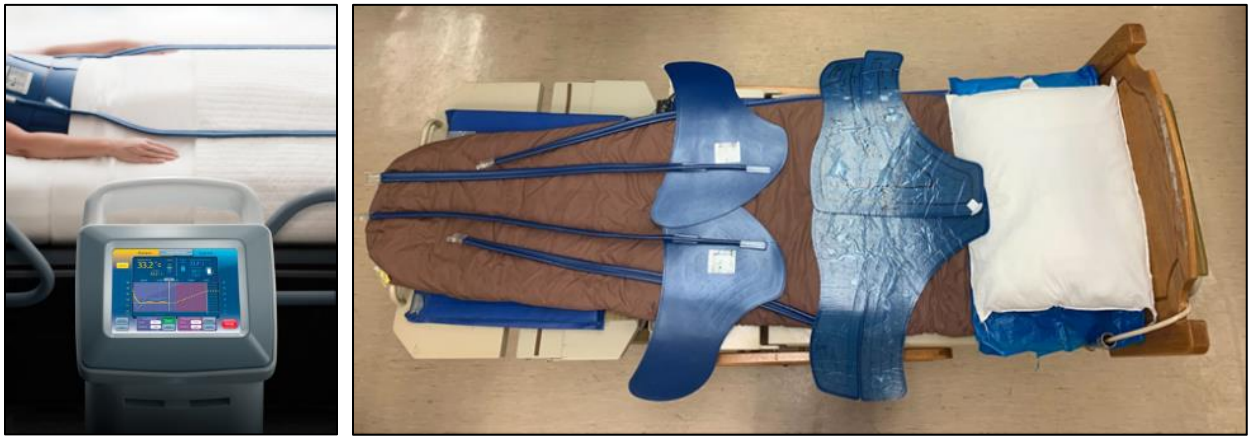

Figure 1. The Arctic Sun™ 5000 Temperature Management System with ArcticGel™ pads. [86]

Blanketrol III with Maxi-Therm Lite Blankets

The Blanketrol III with Maxi-Therm Lite blankets (BL) (Figure 2) is a cooling system that circulates temperature-controlled water through perfused blankets that are in contact with a patient's skin [87]. The system is composed of a heater/cooler, a compressor, a circulating pump

and two whole body blankets [87]. Each of the two blankets are approximately 1.5 meters in length and approximately covers the patient from the neck to the feet (depending on patient size). The cooling system is designed to control the temperature of the patient using conductive and convective heat transfer with the patient's skin. The company (Gentherm Inc.) suggests that this unit has an operator-friendly interface, a high flow rate for tight temperature control, and specific programmable temperature selections that can be used in a variety of medical departments [87].

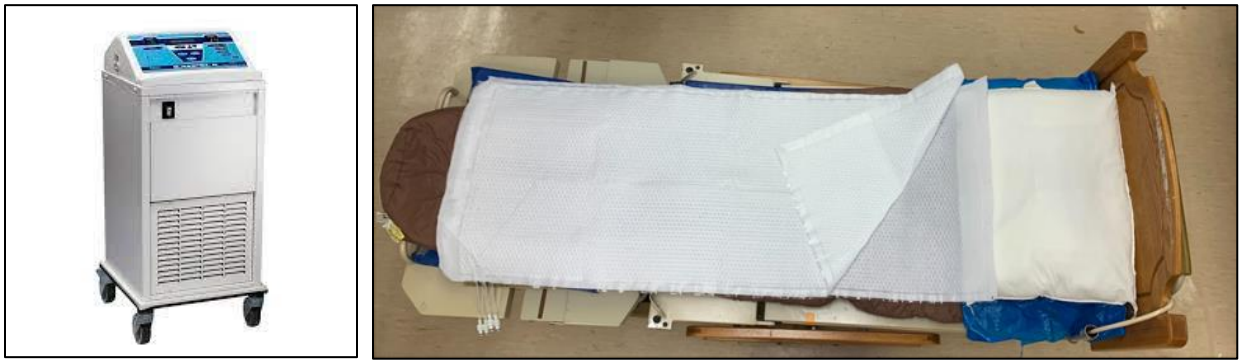

Figure 2. Blanketrol III Hyper-Hypothermia Temperature Management System with Maxi-Therm Lite blankets. [87]

Blanketrol III with Kool Kit

A new cooling cover system has been developed for the Blanketrol III called the Kool Kit (KK) (Figure 3). The Kool Kit includes a head wrap, a vest, and a lower body pad (placed on top of the patient's lower body). The lower body pad covers the patient from the waist to approximately the knees (depending on size of patient). The company (Gentherm Inc.) claims that the random flow design of the blankets/wraps ensures that the therapy will be constantly delivered regardless of the patient's positioning [88]. The company also suggests that the benefits of the Kool Kit include covering a wide range of patients, individually adjustable blankets

allowing for easy access to the skin, and quick cooling initiation set to a tenth of a degree [88]. It should be noted however, that the effectiveness of the Kool Kit has not been quantified or compared to the current two systems mentioned above.

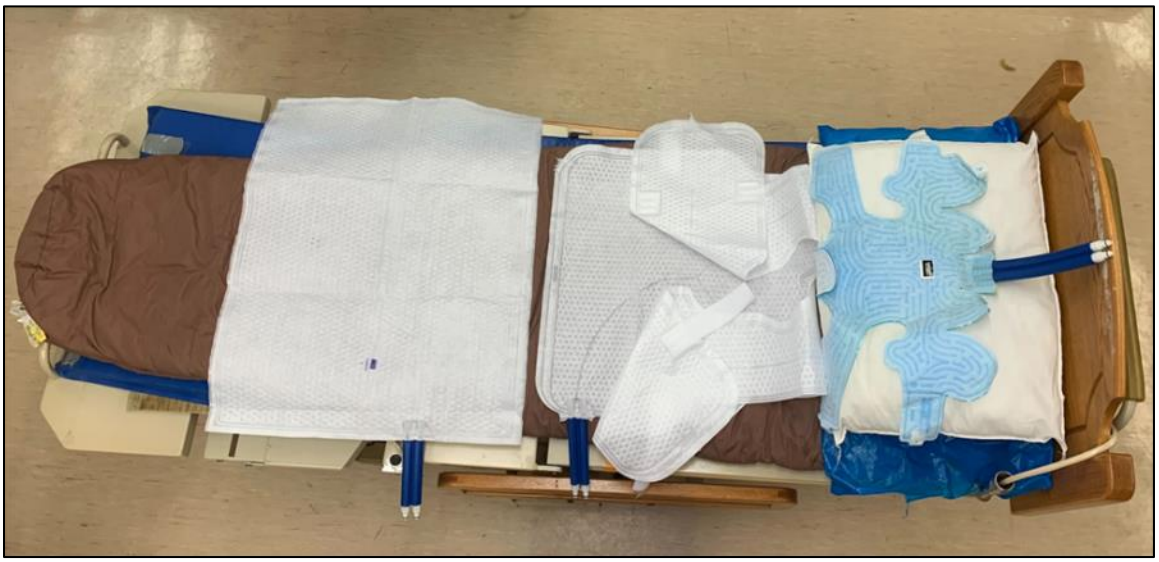

Figure 3. Kool-Kit® whole body cooling cover. [88]

PROTOCOL

Each participant was cooled on three different occasions. The subjects were cooled at the same time of the day to control for circadian effects. The order of trials followed a randomized balanced design, with all 6 possible orders of conditions being employed at least once.

After instrumentation, the participants lay down quietly, and baseline measurements were recorded for 10 minutes at an ambient room temperature (~22°C). An example of instrumented participants covered in cooling system is shown in Figure 4. Participants were then cooled until either: 1) core temperature reached 35°C; 2) 120 minutes elapsed; 3) the participant wished to stop for any reason; or 4) a researcher advised termination for any reason. Upon completion of

the experiment, participants were removed from the cooling condition and rewarmed by entering a warm bath of approximately 41°C until core temperature returned to normal (36.5-37°C).

Figure 4. Instrumented participants covered in cooling systems. Left image, participant wearing AS prior to start of baseline measurements. Right image, participant covered in blanket wearing KK at the start of baseline.

Due to the uneven distribution of water entering the BL and KK, one side of the body was receiving freshly cooled water and the other side receiving body-warmed water (See Appendix A-D). This would be an issue when collecting data with heat flux discs applied to only one side of the body at each site, as measurements from one side of the body were being used to assume heat flux and skin temperature on the contralateral side of the body. To account for a possible over/under-estimation of measurements, the delivery and return hoses to the pads/blankets were switched after approximately 1 hour of cooling to ensure both sides received freshly cooled water. The delivery and return hoses were not switched during the AS trials due to the design of the pads and their ability to provide uniform and an even distribution of water around the surface area of the gel pad (See Appendix E and F).

DATA ANALYSIS

Change in core temperature (ΔT_{co}) was calculated by determining the difference in T_{co} compared to T_{co} at the start of cooling (time 0). Metabolic rate was calculated from oxygen consumption (VO_2) by using the following equation:

$$M\ (W) = VO_2 \cdot 69.7 \cdot \{[4.686 + [(RER - 0.707) \cdot 1.232]\}\ [82]$$

Heat flux for each site (W/site) was calculated from flux values for each transducer (W/m^2) as follows: $HF_{site}\ (W) = HF_{disc}\ (W/m^2) \cdot$ Body Surface Area (m^2) $\cdot$ Regional% $\cdot$ 0.01.

The following regional percentages were assigned based on a previous study (See Figure 5) [83]: forehead, 4%; dorsum of the head, 5%; left anterior chest, 9%; right anterior abdomen, 9%; right scapula, 9%; left lower back, 9%; left anterior upper arm and hand, 9%; right posterior upper arm and hand, 9%; left anterior thigh, 9%; right posterior thigh, 9%; right anterior lower leg and foot, 9%; and left posterior lower leg and foot, 9% (e.g., 99% of BSA); the missing 1% refers to the groin area. Heat flux values for all the measured sites were added to determine total heat flux for areas under each cooling unit. Average total heat flux was calculated for each condition.

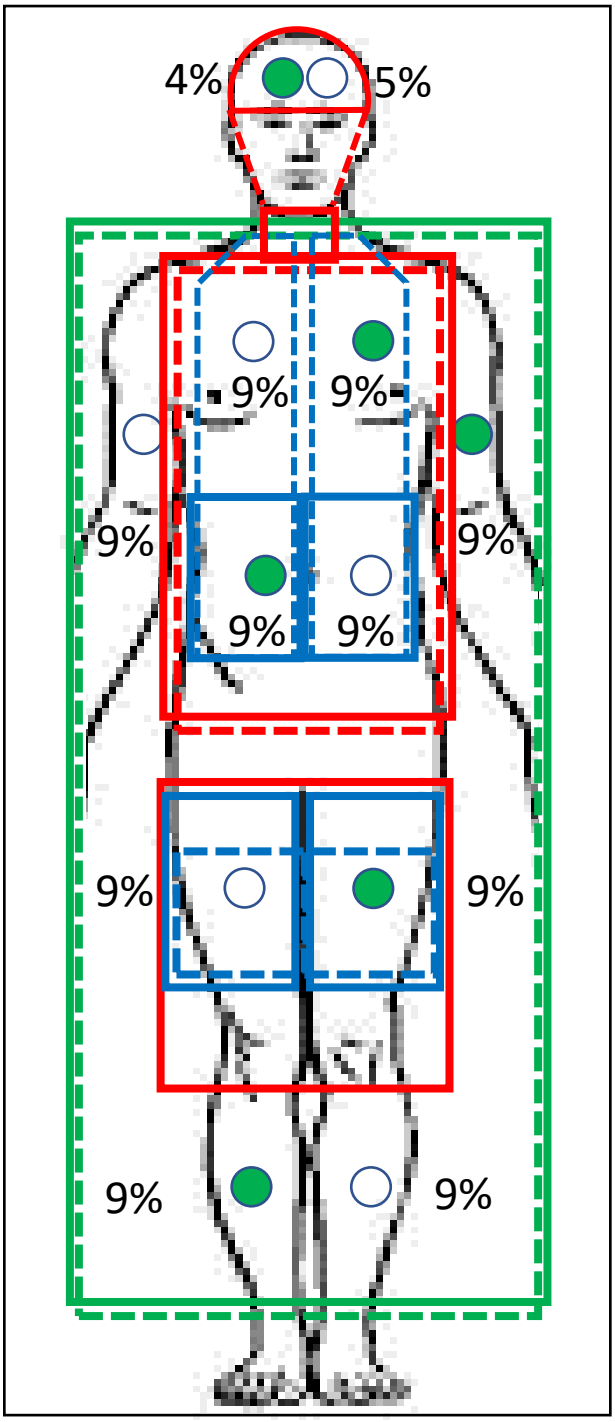

Figure 5. Locations of water-perfused covers and heat flux discs with their regional BSA%. Covers: solid lines anterior, dotted lines posterior; green, Maxi-Therm Lite blankets; red, Kool Kit; blue, ArcticGel pads. Disks: closed circles anterior; open circles, posterior.

Regional heat flux was calculated by grouping heat flux values into three separate groups: 1) head; 2) upper body; and 3) lower body. Regional head heat flux was calculated by adding heat flux values from the forehead and dorsum of head. Regional upper body heat flux was calculated by adding left anterior chest, right anterior abdomen, right scapula, left lower back, left anterior upper arm and hand, and right posterior arm and hand. Regional lower body heat flux was calculated by adding left anterior thigh, right posterior thigh, left anterior lower leg and foot, right posterior lower leg and foot

Mean skin temperature was calculated as a weighted mean using the following equation:

T_{sk} (°C) = T_{disc} (°C) · Regional% · 0.01.

Regional percentages were identical to the ones used for calculating HF. Regional skin temperatures were then calculated for the same areas as the regional HFs and included the same regions within each group.

Data from the three trials were compared as follows: all measurements were compared with a one-way repeated measures analysis of variance approximately every 30 minutes of cooling (0, 30, 60, 85, and 120 minutes). Two participants ended their trials early (at approximately 85 minutes). Therefore, it was decided to perform a one-way ANOVA for repeated measures at 85 minutes to compare all subjects' data prior to having dropouts. After collecting data, it was also decided to perform a one-way ANOVA for repeated measures at 8 minutes due to a potential significant difference between conditions. Post hoc analysis for significant differences between treatments was accomplished using Tukey's test. For participants' cold rankings, a one-way analysis of variance on ranks (Kruskal-Wallis Test) was used to test for significant differences. Results are reported as means ± SD; $p \leq 0.05$ identifies statistically significant differences.

CHAPTER 4: RESULTS

Eight healthy subjects (4 female, 4 male) (age, 23.8 ± 1.8 y; height, 158.8 ± 34.6 cm; mass, 89 ± 41.8 kg; body surface area (BSA), 1.9 ± 0.4 m^2; and body fat, 21.9 ± 9.2%) participated. Average cooling time for all trials was 112.3 ± 13.6 min (range 86-120 min).

Table 1. Subject information.

Participant	1	2	3	4	5	6	7	8	Mean	SD
Sex	F	M	M	M	M	F	F	F		
Age (y)	23	24	26	21	24	22	24	26	23.8	1.8
Height (cm)	154.5	173	184	193	170	167	160	163	170.6	34.6
Weight (kg)	58.7	79.1	104.1	123.1	64.4	71.9	50.6	66.5	77.3	41.8
BF (%)	33.9	13.4	13	26.6	13.2	34.5	15.9	24.4	21.9	9.2
BSA (m^2)	1.52	1.91	2.26	2.52	1.8	1.79	1.48	1.7	1.9	0.4

TOTAL HEAT FLUX

AS had a significantly higher total heat flux during baseline measurements. Heat loss was transiently highest with AS at the start of cooling. For most of the remainder of cooling, HF for BL and AS was greater than for KK ($p < 0.05$) (Figure 6). There were no differences between systems at the end of cooling.

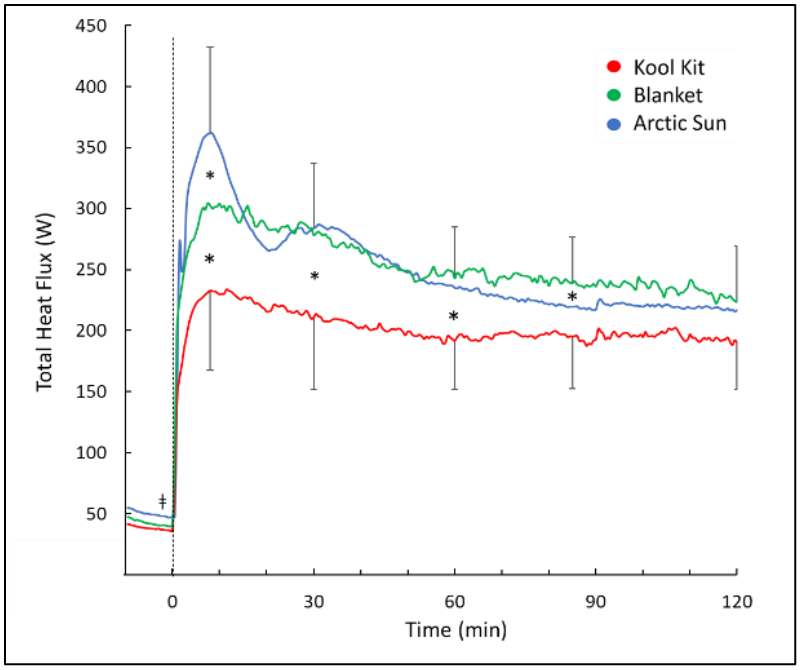

Figure 6. Total heat flux during 120 minutes of cooling with three cooling systems. Time 0 indicates start of cooling. For clarity, SD bars are only included for top and bottom lines. * Separates values that are significantly different from each other; ǂ AS > KK ($p < 0.05$).

REGIONAL HEAT FLUX

There were no significant differences in HF_{Head} between the three conditions during baseline. KK had a significantly higher HF_{Head} compared to AS and BL from 0 to 85 minutes of cooling ($p < 0.05$) (Figure 7).

There was a significant difference between AS and KK and AS and BL during baseline measurements. AS HF_{UB} was greater than KK and BL at 8 minutes ($p < 0.05$) but was only greater than KK at 30 minutes of cooling ($p < 0.05$). After that, there were no significant differences between conditions.

There were no significant differences in HF_{LB} between the three conditions during baseline. HF_{LB} was higher with AS than BL throughout the entire cooling period ($p < 0.05$). BL also had a significantly higher HF_{LB} compared to KK from 8 to 85 minutes of cooling (8-60 min,

$p < 0.001$; 85 min, $p < 0.05$). BL also had a significantly higher HF_{LB} than AS at 85 minutes of cooling compared to AS ($p < 0.05$)

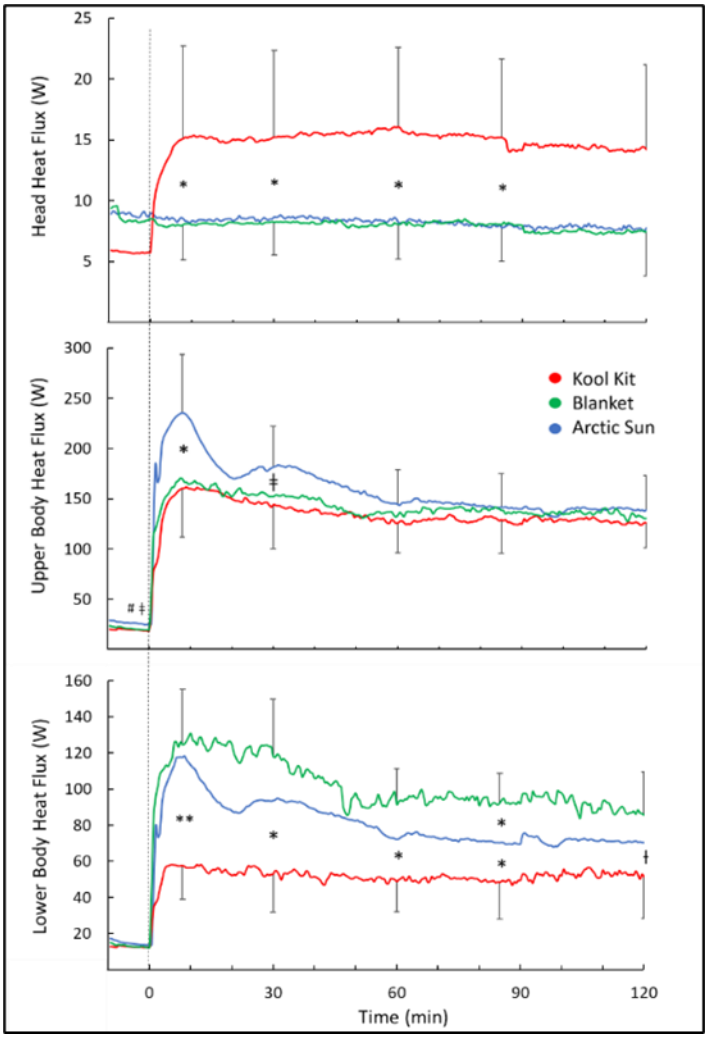

Figure 7. Regional heat flux during 120 minutes of cooling with three cooling systems. Top, head heat flux; middle, upper body heat flux; bottom, lower body heat flux. Time 0 indicates the start of cooling. For clarity, SD bars are only included for top and bottom lines. * Separates values that are significantly different (*$p < 0.05$; **$p < 0.01$); ǂ BL > KK ($p < 0.05$); ǂ AS > KK # AS > BL ($p < 0.05$).

CORE TEMPERATURE

There were no significant differences between conditions during baseline measurements. Average cooling time for AS was 112.5 ± 13.9 min (range 90-120 min). Mean T_{co} dropped from 36.9 ± 0.3°C to 36.5 ± 0.4°C at a rate of -0.3 ± 0.2°C/hr (Figure 8). Average cooling time for BL was 112.5 ± 13.9 min (range 90-120 min) and mean T_{co} dropped from 37.0 ± 0.3°C to 36.9 ± 0.4°C at a rate of -0.04 ± 0.15°C/hr. Average cooling time for the KK was 112.0 ± 14.9 min (range 86-120 min) and mean T_{co} dropped from 36.9 ± 0.3°C to 36.8 ± 0.6°C at rate of -0.07 ± 0.36°C/hr. There were no significant differences for T_{co} between the three conditions at the start of cooling. AS showed a significant reduction in ΔT_{co} in comparison to the KK condition from 30 to 60 minutes of cooling ($p < 0.05$) and the BL condition from 60 to 120 minutes ($p < 0.05$). AS also showed a significantly greater core cooling rate (-0.37 ± 0.15°C/hr) than both KK (-0.29 ± 0.22°C/hr) and BL (-0.21 ± 0.14°C/hr) from 30 minutes onward ($p < 0.05$).

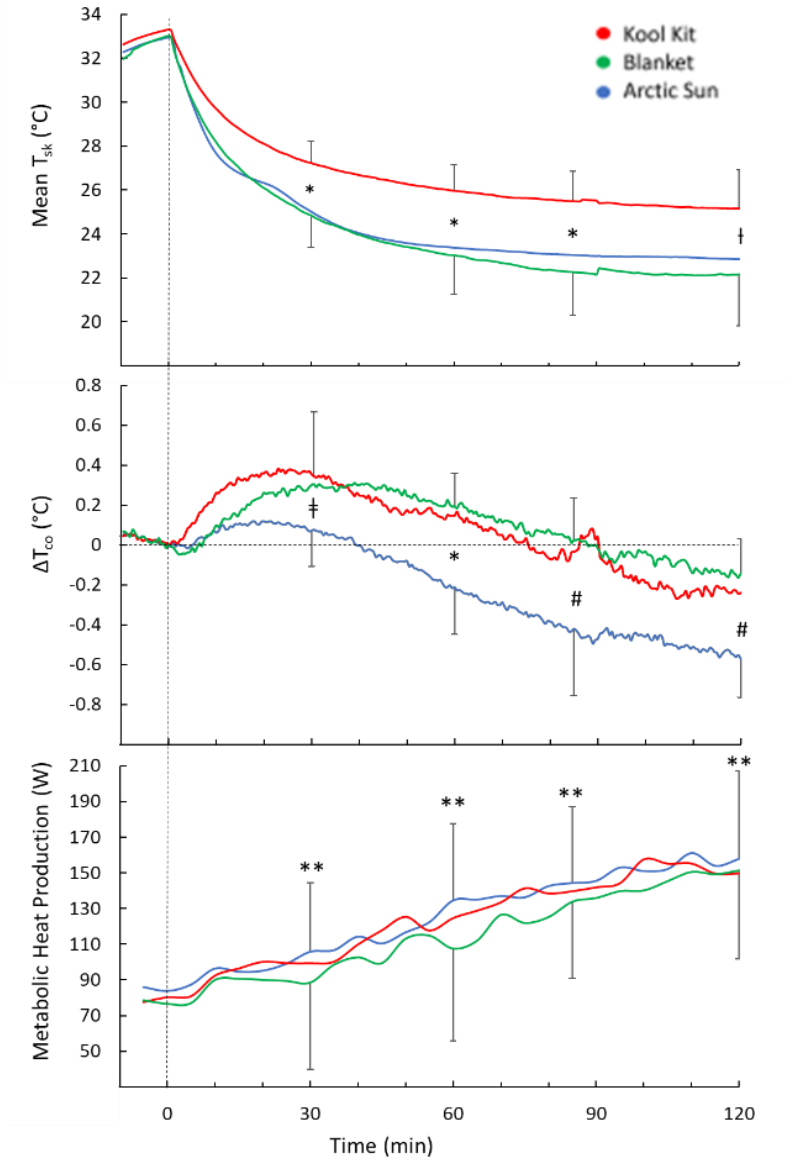

Figure 8. Top, mean skin temperature (T_{sk}); middle, change in core temperature (ΔT_{co}), and bottom, metabolic heat production during 120 minutes of cooling with three cooling systems. Time 0 indicates the start of cooling. For clarity, SD bars are only included for top and bottom lines. * Separates values that are significantly different; ǂ KK > BL; ǂ KK > AS; # AS < BL; ** different than baseline, ($p < 0.05$).

MEAN SKIN TEMPERATURE

No significant differences were found for mean T_{sk} between the three conditions after baseline measurements (Figure 8). Mean T_{sk} was significantly higher in in the KK condition

compared to AS and BL from 30 to 85 minutes ($p < 0.05$). Mean T_{sk} of KK was only significantly higher than BL at 120 minutes ($p < 0.05$). AS mean T_{sk} dropped from 32.9 ± 0.6°C to 22.8 ± 1.1°C. BL T_{sk} dropped from 33.0 ± 0.6°C to 22.2 ± 2.4°C. KK T_{sk} dropped from 33.3 ± 0.7°C to 25.2 ± 1.7°C.

METABOLIC HEAT PRODUCTION AND SHIVERING

No significant differences were found for metabolic heat production between the three conditions after baseline measurements (Figure 8). Metabolic heat production increased similarly in all conditions. Heat production was significantly greater than baseline after 30 minutes and continued to increase by about 85% by the end of the cooling period ($p < 0.05$). All participants subjectively reported shivering with a mean cooling time of 30 minutes (range 5-105 min).

REGIONAL SKIN TEMPERATURE

Head skin temperature (T_{Head}) was found to be significantly lower in KK compared to both AS and BL after baseline measures ($p < 0.001$ and $p < 0.05$ respectively) (Figure 9). KK also had a significantly lower T_{Head} compared to AS and BL for the entire duration of cooling ($p < 0.05$). AS had a significantly lower T_{Head} compared to BL at 60 and 85 minutes of cooling ($p < 0.05$). There were no significant differences found for upper body skin temperature (T_{UB}) between all three conditions throughout cooling. There was also no significant difference found for lower body skin temperature (T_{LB}) between all three conditions during baseline measures. AS and BL demonstrated a significantly lower T_{LB} compared to KK for the entire period of cooling ($p < 0.001$). BL had a significantly lower T_{LB} from 85 to 120 minutes ($p < 0.05$).

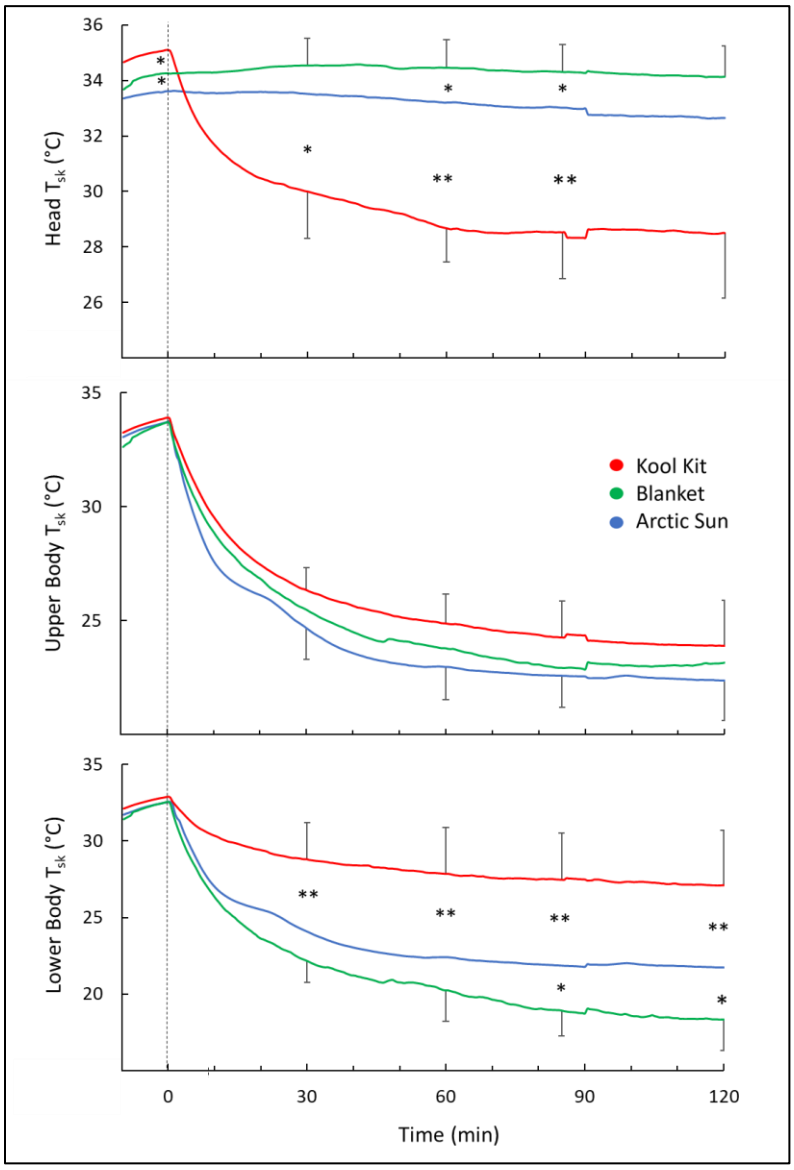

Figure 9. Regional T_{sk} during 120 minutes of cooling with three cooling systems. Top, head; middle, upper body; bottom, lower body. Time 0 indicates the start of cooling. For clarity, SD bars are only included for top and bottom lines. * Separates values that are significantly different (*$p < 0.05$; **$p < 0.01$).

OUTFLOW WATER TEMPERATURE AND FLOW RATE

Outflow water temperature was similar in all conditions, decreasing rapidly for 30 minutes and then more gradually for the remaining 90 minutes of cooling (Figure 10). The

cooling pump flow rate was only displayed by the Arctic Sun unit (Figure 11). The Blanketrol III cooling pump unit used a visual indicator wheel to confirm there was water flow but did not provide a quantitative flow rate.

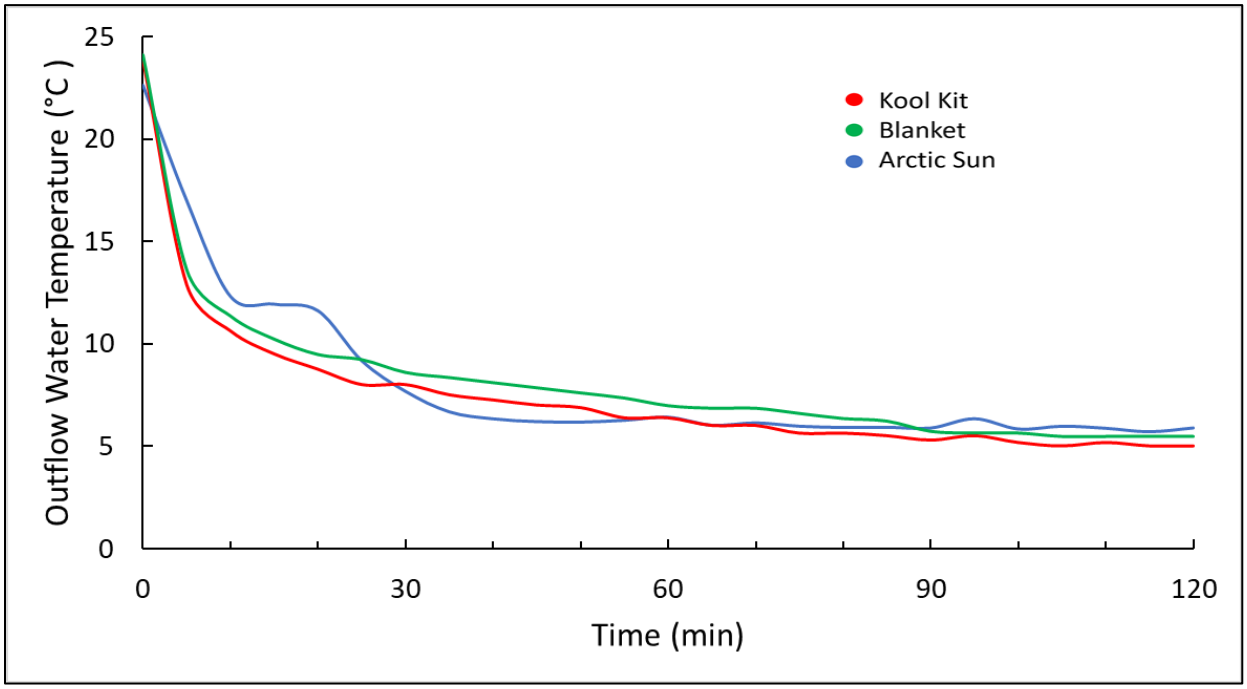

Figure 10. Mean outflow water temperature of each cooling pump unit after starting the cooling function (n=8 for each unit).

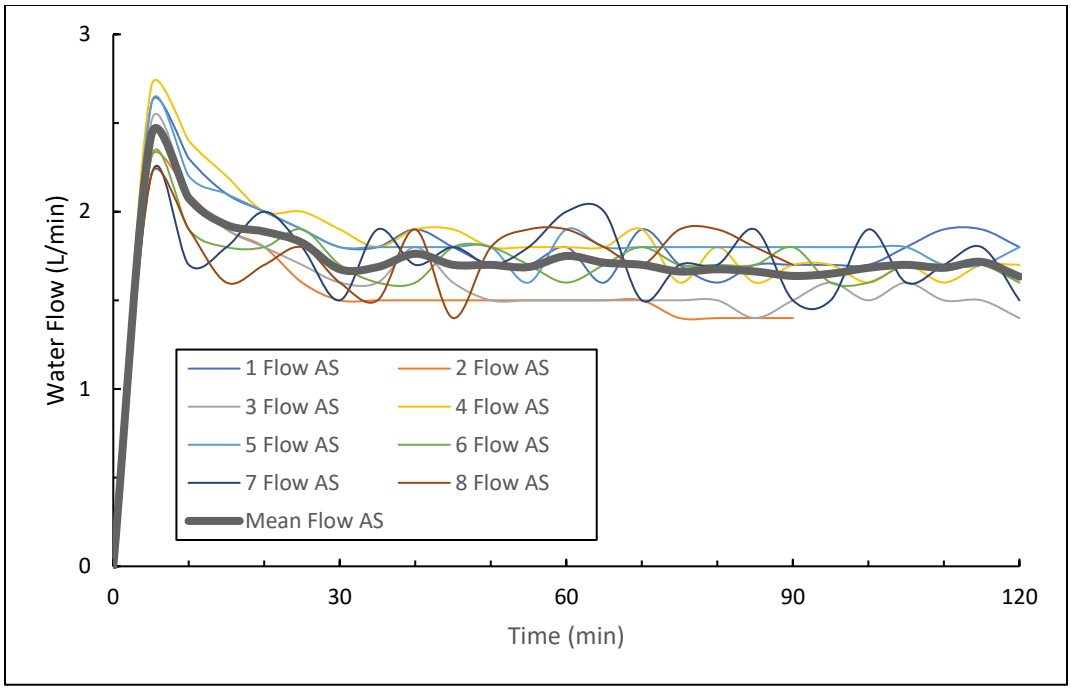

Figure 11. Individual and mean flow rates for the Arctic Sun cooling pump unit.

COLD DISCOMFORT

Cold discomfort increased similarly during cooling in all three conditions (Figure 12).

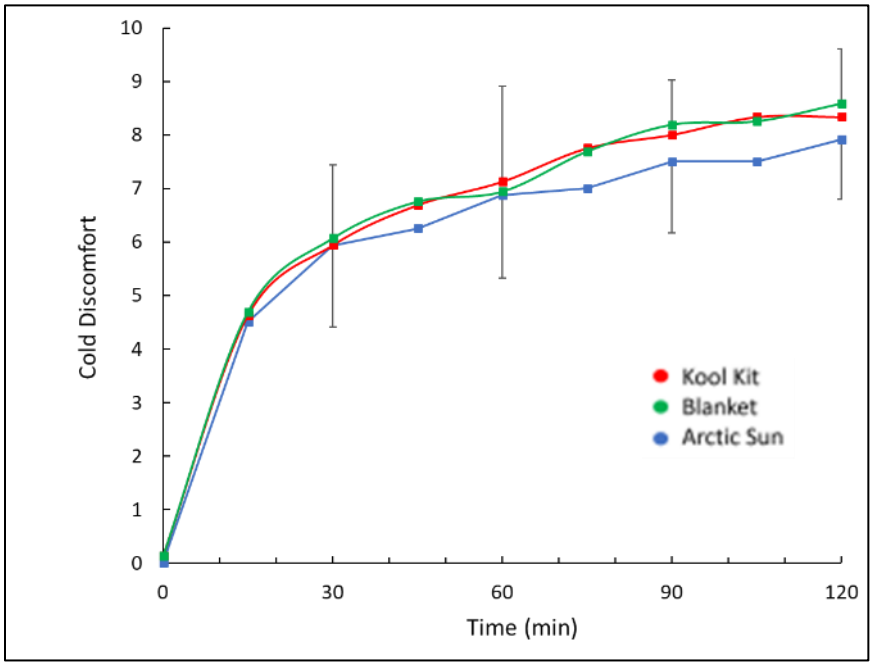

Figure 12. Cold discomfort scale during 120 minutes of cooling with three cooling conditions. For clarity, SD bars are only included for top and bottom lines. * Separates values that are significantly different (*p < 0.05; **p < 0.01).

COLD RANKING

There were no significant differences in cold ranking between three cooling conditions (Table 2).

Table 2. Cold condition ranking from most cold to least cold. S, subject number; 1, coldest condition; 2, second coldest condition; 3, least cold condition (NS)

Ranking	S1	S2	S3	S4	S5	S6	S7	S8
1	KK	KK	KK	AS	KK	BL	BL	BL
2	AS	AS	AS	BL	AS	AS	AS	KK
3	BL	BL	BL	KK	BL	KK	KK	AS

CHAPTER 5: DISCUSION

While several previous investigations have separately demonstrated the efficacy of the AS [28, 89-93] and BL [94, 95], this is the first study that we are aware of that compared the performance of both of these established cooling systems as well as the newer KK water-perfused covers.

The heat transfer capabilities of the cooling systems in this investigation are a result of the components making up each cooling system. In this discussion, heat flux will be understood using the following equation:

$$HF = \frac{k(SA)\Delta T}{L}$$

Where HF is heat flux in W, k is thermal conductivity in W/m°K, SA is surface area in m^2, ΔT is the temperature gradient between two isothermal surfaces in °K, and L is the distance between the two isothermal planes in m. According to this equation, heat flux is directly proportional to k, SA, and ΔT (which are all affected by the cooling systems) while it is inversely proportional to L.

Recall that each cooling system is composed of 1) a cooling pump unit; and 2) a water-perfused cover. Each system's performance is governed by the advantages and limitations of these two major components (See Figure 13). Within the cooling pump unit of each system, the effectiveness of heat transfer is influenced primarily by two major factors: 1) water temperature and 2) water flow rate. Additionally, the heat transfer of the cover is primarily influenced by its size, surface material, tightness of fit, and surface design and adhesion of the cover (Figure 13).

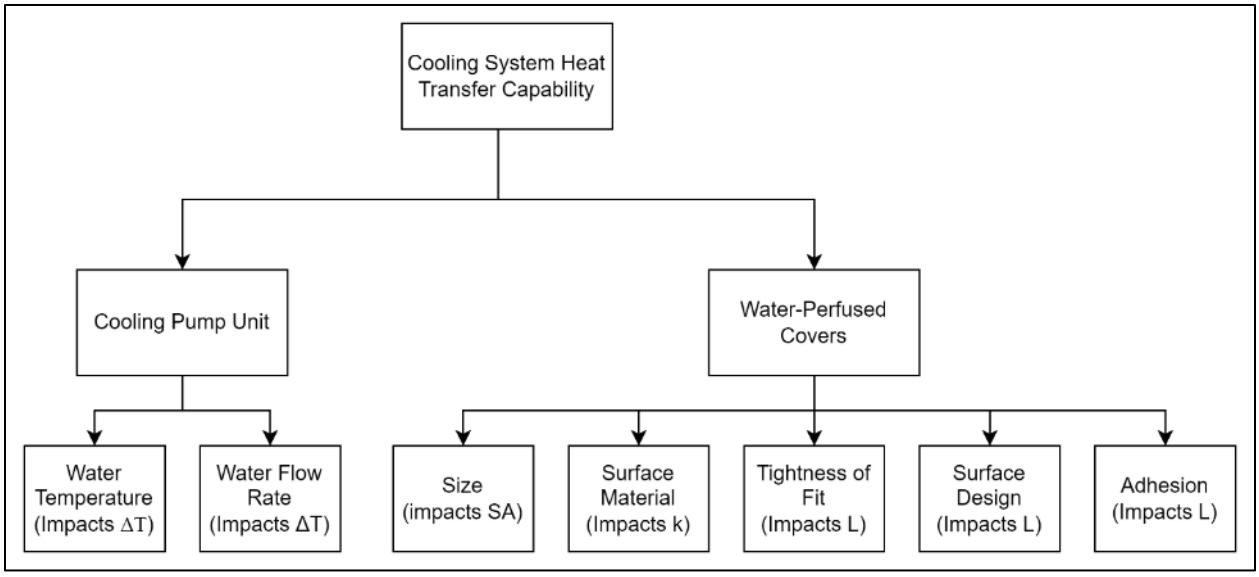

Figure 13. Factors impacting system heat transfer capability. Specific factors in parentheses.

The performance comparison made during this study is based on several key measures collected during cooling. While the main goal of these cooling systems is to reduce a patient's core temperature for an extended period, heat flux provides a useful understanding of a system's heat transfer capability. Total heat flux was the foremost performance measure of this investigation, and it was determined that AS removed heat more efficiently during the early minutes of cooling compared to KK and BL (See Figure 6). This advantage was maintained over KK for approximately 60 minutes but decreased over time, eventually showing no difference between the three conditions at the end of the cooling protocol (120 minutes). TH guidelines suggest active cooling for a minimum for 24 hours, which means this transient advantage is probably minimal [11-13].

The cooling pump unit affects heat flux through changes in outflow water temperature and flow rate (See Appendix G and H). A decrease in outflow water temperature increases ΔT and heat loss. As noted earlier, there were no significant differences in outflow temperature between the three cooling pump units. Increased water flow rate increases heat loss. Flow rates

cannot be compared since only the AS unit displayed flow rate. However, company specifications indicate that flow rates should be >2.27 L/min for the Blanketrol III and >1.70 L/min for the Arctic Sun. As Figure 11 indicates, the AS system performed within specifications (e.g., ~1.7 L/min). It is assumed that the Blanketrol unit also performed within specifications. Therefore, the Blanketrol unit may have more cooling power.

As described briefly above, the water-perfused covers affect heat flux through factors such as: cover size, surface material properties, tightness of fit, surface design, and adhesion. These factors are compared for the three covers in Table 3.

Table 3. Relative rankings of the three conditions for each factor that impacts heat transfer of water-perfused covers. ↑↑, highest ranking; ↑, higher ranking; -, lowest ranking. In parentheses, factors affecting heat transfer: SA, surface area; k, thermal conductivity; and L, distance.

Factor	**AS**	**BL**	**KK**
Size (SA)	-	↑↑	↑
Surface Material (k)	↑↑	-	-
Tightness of Fit (L)	↑↑	-	↑
Surface Design (L)	↑	-	-
Adhesion (L)	↑	-	-

The size of the cover impacts the heat transfer by affecting SA. The BL blankets had the largest SA (Figure 5). The two blankets covered approximately 90% of total BSA and included anterior and posterior coverage from the base of the participant's neck to their feet. The KK head wrap, vest, and blanket has less SA (approximately 50% of total BSA). The AS pads covered only about 36% of total BSA. The results of these characteristic SA coverages are shown in Figure 7. KK had a higher HF_{Head} during cooling because it was the only condition with active cooling of the head. Early on in cooling, AS had a significantly higher HF_{UB} than KK and BL despite having somewhat less upper body SA (Figure 7). This effect will be explored more later

as it may be explained by other qualities of the perfused-covers. Finally, BL had higher HF_{LB} than KK which is consistent with the substantially increased lower BSA coverage (36% and 9% respectively).

The surface material properties impact the heat transfer capabilities of the covers by affecting thermal conductivity (k). The k value for the hydrogel used in the ArcticGel pads was approximately 0.33-0.51 W/m°K, while the k value for the plastic and non-woven fabric of BL and KK covers was approximately 0.14-0.36 W/m°K [96, 97]. Thus, thermal conductivity of the AS covers is 2 to 3 times that of the BL and KK covers.

The tightness of fit impacts the heat transfer capabilities of the covers by affecting the average L (e.g., the average distance between the skin and the cover). Covers with a tighter fit around the surface of the skin have a reduced L (related to air gaps between the skin and cover) and thus an increased HF. The AS pads gave the best fit around the surface of the skin and allowed for direct contact with the hydrogel and skin surface, thus L was essentially 0 and disappears from the equation. In comparison, the adjustable vest and head wrap of the KK proved to be effective at making direct skin contact around the torso and head but was less effective over the lower body. The BL blankets notably lacked a tight fit over the participant's anterior skin surface. The participant's body weight provided a means of improving skin contact underneath the participant, but the blanket on top of the participant was much looser. The effect of a tighter fit may explain the early increased HF_{UB} of AS compared to BL despite having less SA coverage (Figure 7).

Surface design and adhesion also impact heat transfer by affecting L. The surface designs of the two types of covers are shown in Figure 14. The AS pad is rigid and therefore remains flat when water flows through it. However, the Blanketrol covers are not rigid and water flow causes

a quilting effect, thus some areas are in direct skin contact while others are not. This means that the average L for AS pads is less than the L for the Blanketrol pads. Adhesion also affects the average value of L. The average L is 0 for AS pads but not for the Blanketrol covers.

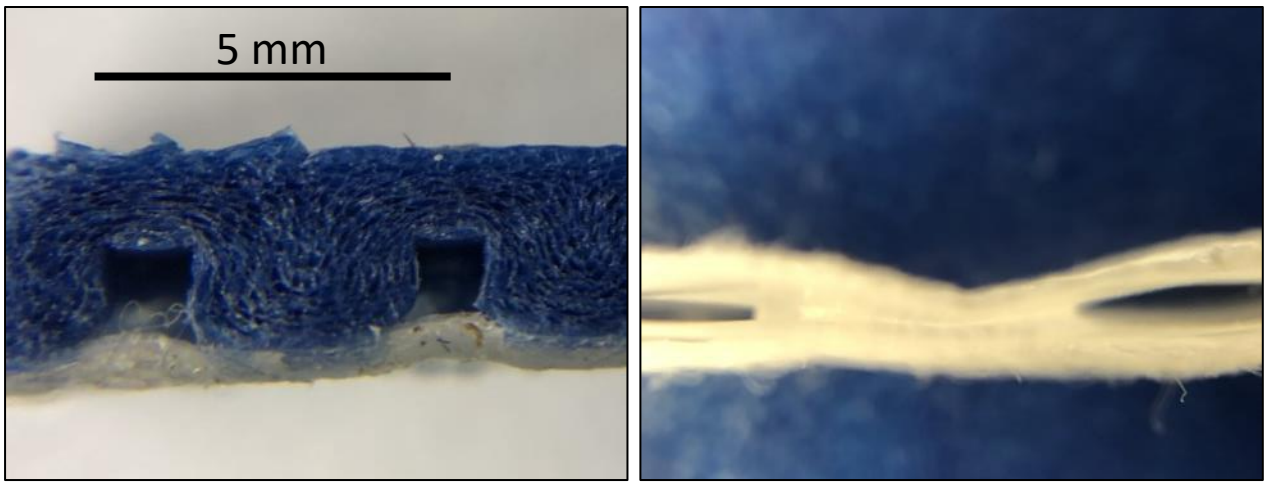

Figure 14. Cross section of the Maxi-Therm Lite blanket (left) and ArcticGel pad (right). The surface of the Maxi-Therm blanket is non-woven fabric covering a plastic lining and the surface of the ArcticGel pad is hydrogel.

The other measures of this study reflect the heat flux findings. Mean T_{sk} was significantly higher in KK throughout cooling in comparison to the other two conditions (Figure 8). The outcome for mean T_{sk} replicates the total HF (Figure 6), as KK with less total HF resulted in higher skin temperatures. Regional skin temperatures (Figure 9) also reflect results from regional skin HF (Figure 7). KK had a significantly higher HF_{Head} than AS and BL, which resulted in KK having a significantly lower T_{Head}. AS and BL HF_{UB} was similar for most of cooling, and it resulted in a similar T_{UB}. T_{LB} was significantly higher in KK throughout cooling (Figure 9), which reflects the lower HF_{LB} (Figure 7). AS T_{LB} was also significantly higher than BL after approximately 85 minutes of cooling. Once again, these results mirror the significantly higher HF_{LB} of AS at 85 minutes (Figure 7 and 9).

Additionally, AS decreased ΔT_{co} significantly more than KK and BL (Figure 8). AS was better able to resist the early rise of ΔT_{co} compared to the other two conditions. After approximately 30 minutes, AS also reduced ΔT_{co} at a faster rate compared to KK and BL (Figure 8). Despite only showing an advantage in HF during early cooling, the AS was more effective at reducing core temperature than BL. One possible reason for this effect on ΔT_{co} may be due to the location of cooling. Although total HF was similar between AS and BL, recall that BL had substantially more surface area coverage than AS. This increased SA coverage for BL was mostly on the extremities of the participants. For example, AS only had coverage on the thighs and torso while BL had SA coverage on the thighs, lower legs, feet, torso, arms, and hands. Despite this difference in lower and upper body coverage, HF_{LB} and HF_{UB} were similar for most of cooling (Figure 7). The larger decrease in ΔT_{co} for AS suggests that concentrated cooling on the torso may have a larger impact on reducing core temperature compared to removing similar amounts of heat from a larger surface area.

PRACTICAL IMPLICATIONS

One possible improvement noted by researchers is suggested for the vest used for KK. It was noted that even with the current adjustable straps of the vest, researchers had a difficult time ensuring a tight fit on the participants involved in this study. It is recommended that the KK vest adds Velcro strips on the anterior portion of the vest, so all connections are at the same level (black lines on Figure 15). We also suggest adding Velcro to back side of the right arm pit flap (blue line on Figure 15) so the chest flap can connect at any position on either the blue or black Velcro strips.

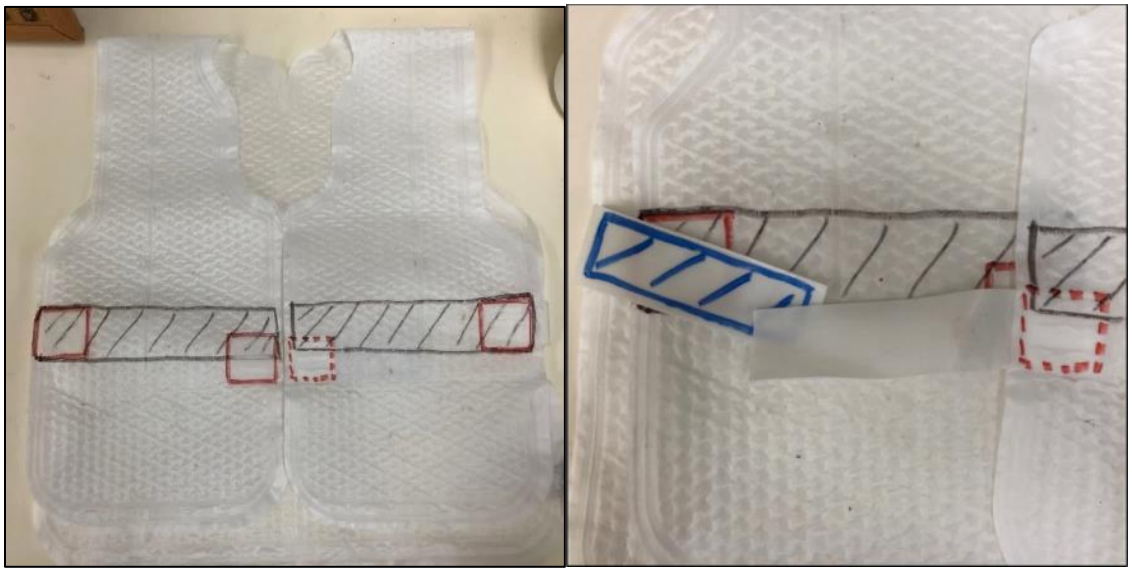

Figure 15. Suggested improvements for Kool Kit vest. Red solid line, existing Velcro; dotted red line, chest flap connection; black solid line, suggested new Velcro strap; blue line, suggested Velcro on top of chest strap.

CONCLUSION

In conclusion, results suggest that each of the cooling systems has its own benefits and limitations. Heat transfer capabilities of each system is dependent on the cooling pump unit and water-perfused covers. Both cooling pump units in this study had similar performances in their ability to reduce water temperature. However, the Blanketrol III unit likely has a greater flow rate and therefore may have more cooling power. Although the size of the AS pads limits its surface area coverage, the advantageous surface material, tight fit, surface design, and adhesion make it effective at removing heat. AS had an early transient advantage in heat removal, but this effect decreased over the course of cooling and may represent a minimal advantage in longer periods of cooling that are recommended in guidelines. The two BL covers cover the largest surface area, but the effectiveness of heat transfer was limited by its surface material, loose fit,

surface design, and lack of adhesion. Finally, the size and tight fit of the KK gave it effective coverage around the torso and head, but the cover is limited by its surface material, surface design, and lack of adhesion.

Some of the limitations of this study include participant demographics and the presence of shivering. The participants were young healthy adults and may not be representative of the populations that often require therapeutic hypothermia. These patients are often older and have greater mass and surface area. Larger patients would be more difficult to cool compared to the participants enrolled in this study. They may also have increased heat loss due to their increased BSA. Future research should seek to confirm the results of this study by testing larger sample sizes and populations that are more representative of TH patients. Future studies should also aim to compare the performance of cooling systems when shivering is inhibited, as it will be more characteristic of clinical practice.

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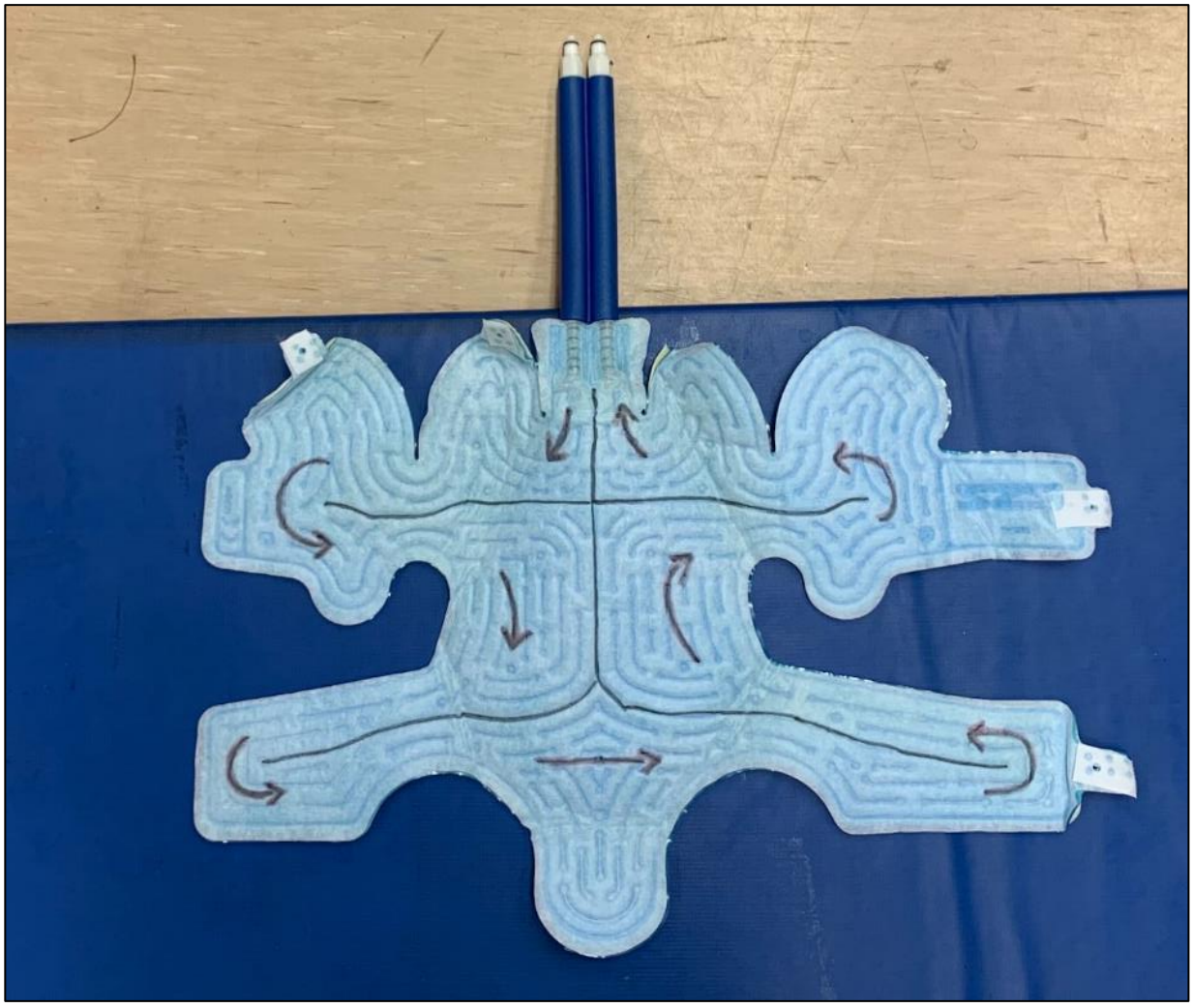
APPENDICES

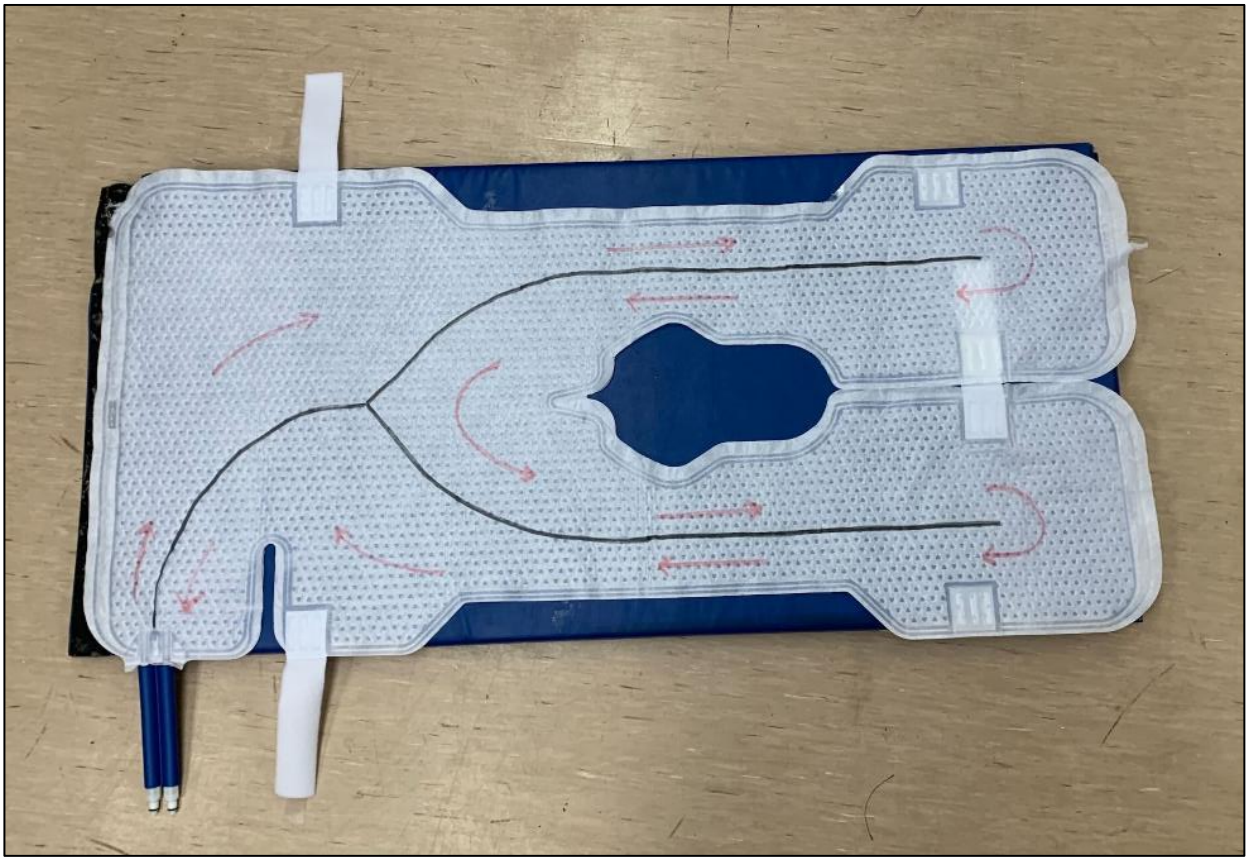
APPENDIX A

Water flow of Kool Kit head wrap (Black line, flow barrier; Black arrow, direction of water flow; note that flow can be reversed by switching inflow and outflow hoses).



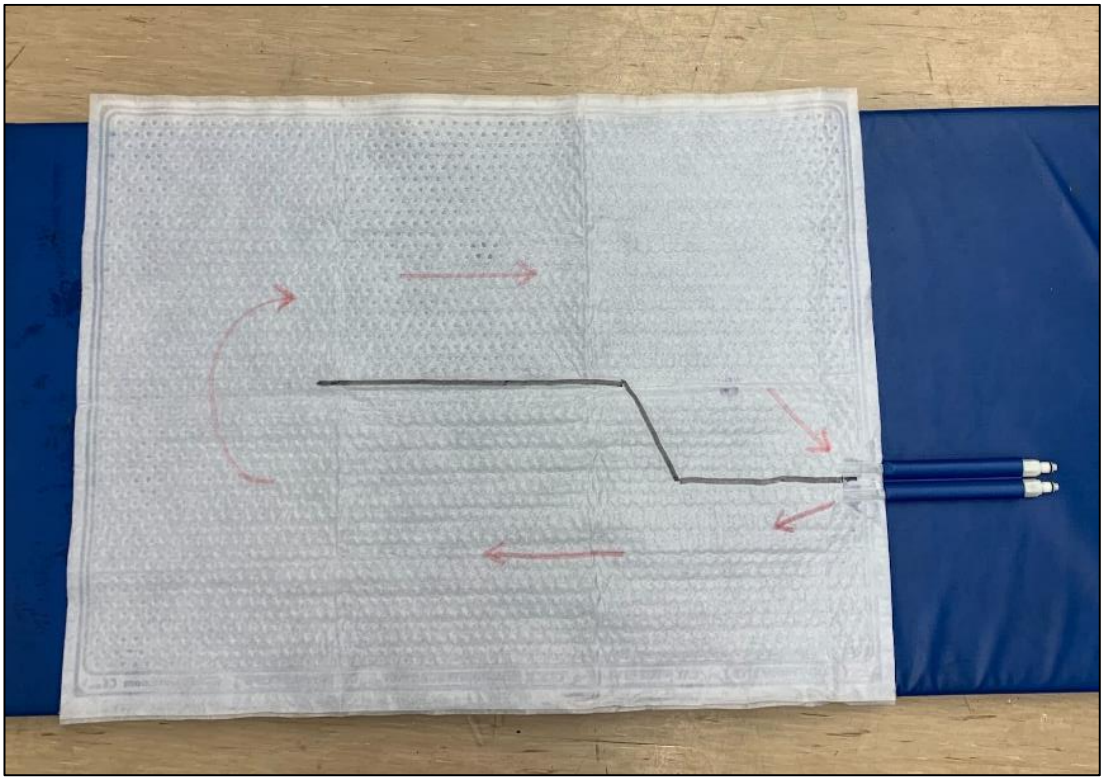
APPENDIX B

Water flow of Kool Kit vest (Black line, flow barrier; Red line, direction of water flow; note that flow can be reversed by switching inflow and outflow hoses).



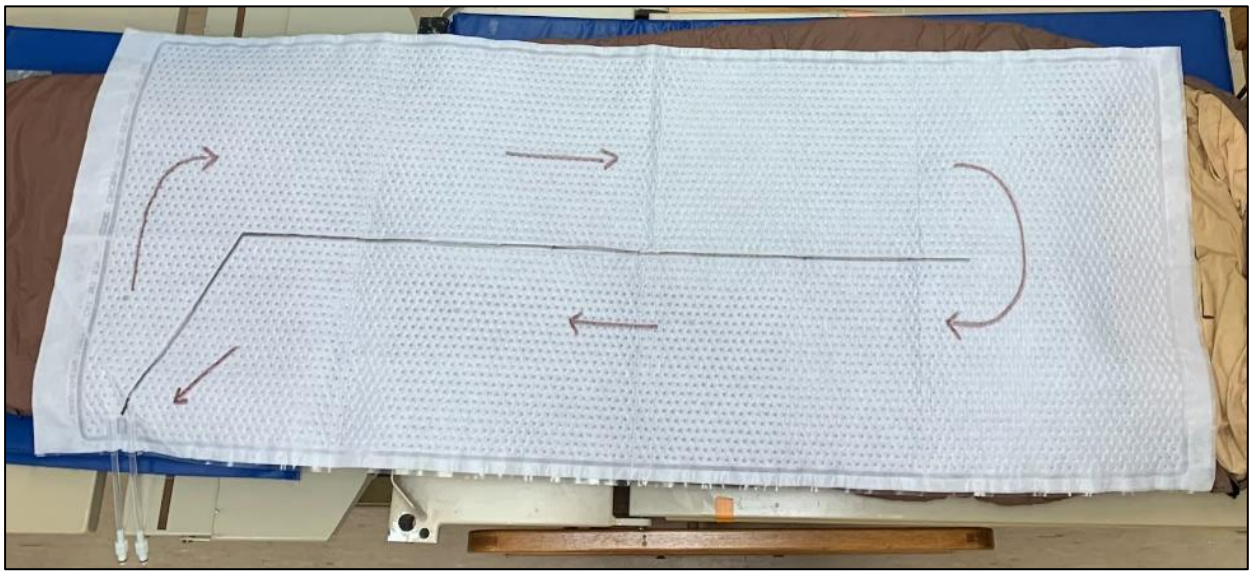
APPENDIX C

Water flow of Kool Kit blanket (Black line, flow barrier; Red line, direction of water flow; note that flow can be reversed by switching inflow and outflow hoses).



APPENDIX D

Water flow of Maxi-Therm Lite blanket (Black line, flow barrier; Red line, direction of water flow; note that flow can be reversed by switching inflow and outflow hoses).



APPENDIX E

Water flow of ArcticGel thigh pad (Black line, flow barrier; Black arrow, direction of water flow; note that flow can be reversed by switching inflow and outflow hoses).

APPENDIX F

Water flow of ArcticGel back/torso pad (Black line, flow barrier; Black arrow, direction of water flow; note that flow can be reversed by switching inflow and outflow hoses).

APPENDIX G

Schematic diagram of Arctic Sun 5000 Temperature Management System

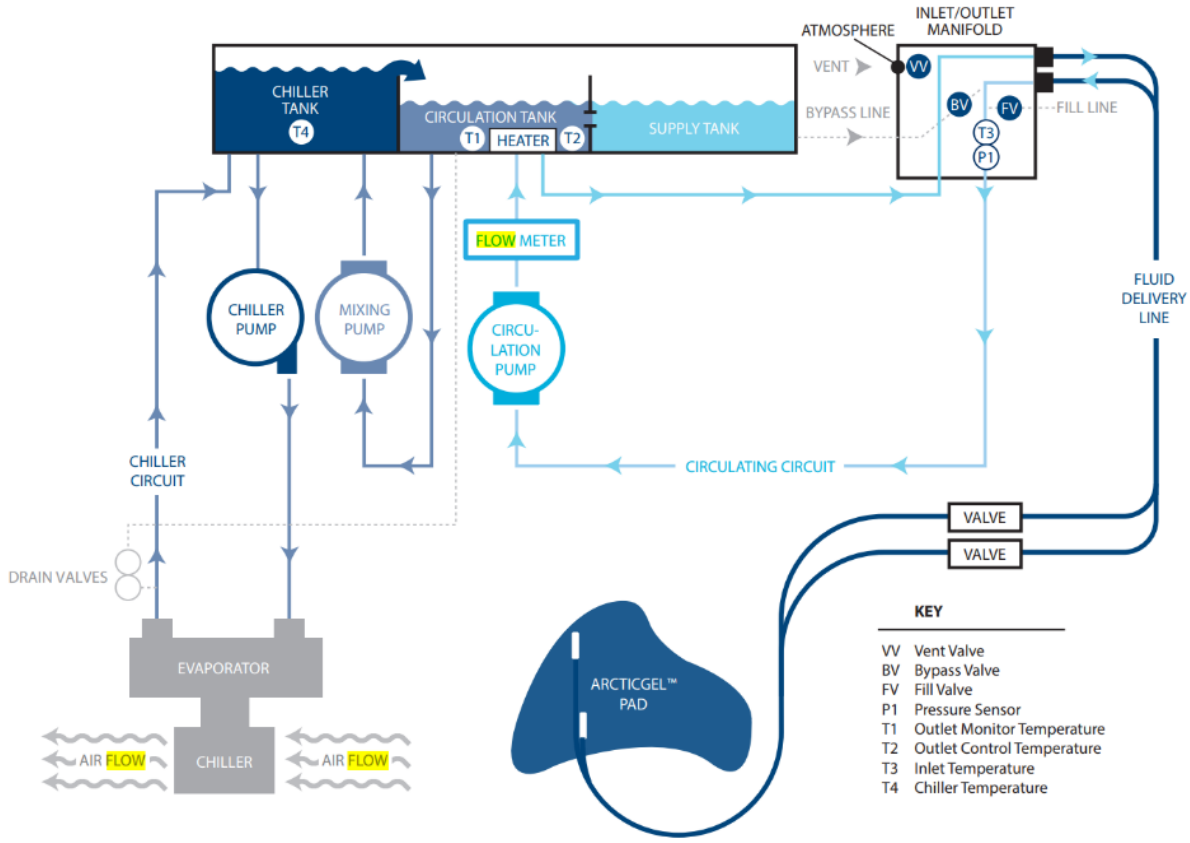


Fig. 2-1 The Hydraulic Schematic

APPENDIX H

Water flow diagram of the Blanketrol III Hyper-Hypothermia System