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A Feasible, Near-Term Approach to Human Stasis for Long-Duration Deep Space Missions

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Abstract

Recent medical progress is quickly advancing our ability to induce torpor, a deep sleep hibernation-like state, in humans for extended periods of time. The authors propose to place crew and passengers in a prolonged hypothermic state during space-mission transit phases (outbound and Earth-return) to significantly reduce the system mass, power, habitable volume, and medical challenges associated with long-duration space exploration. The process and application is based on an emerging medical practice known as Therapeutic Hypothermia (TH) or Targeted Temperature Management (TTM). TH is a medical treatment in which an injured patient's body temperature is lowered to 32-34°C (89-93°F) in order to slow the body's metabolism and minimize ischemic injury. This paper focuses on the medical aspects associated with achieving this induced torpor state for deep space missions. The authors have assembled a team of experts in multiple medical specialties to access the feasibility of extended duration hypothermia and administration of TPN, overcoming the long-term medical complications that may occur, and advantages of placing the crew in hibernation. Detailed descriptions of the current state-of-the-art for each process, recommendations from the medical team, and discussions of medical advantages and potential medical challenges are presented. Designs for crew support systems that can enable prolonged stasis periods in deep space habitats are also discussed.

Acronyms/Abbreviations

GCR	Galactic Cosmic Radiation
H2S	Hydrogen Sulfide
HBE	Harris-Benedict Equation
ICP	Intra-Cranial Pressure
ISS	International Space Station
IV	Intra-Venous
NIAC	NASA Innovative Advanced Concepts
NMES	Neuro-Muscular Electrical Stimulation
PICC	Peripherally Inserted Central Catheter
SPE	Solar Particle Events
TBI	Traumatic Brain Injury
TH	Therapeutic Hypothermia
TPN	Total Parenteral Nutrition
VIIP	Vision Impairment and Intracranial Pressure

1 Introduction

The idea of suspended animation for interstellar human spaceflight has often been posited as a promising far-term solution for long-duration spaceflight. A means for full cryo-preservation and restoration remains a long way off still. However, recent medical progress is quickly advancing our ability to induce deep sleep states (i.e. torpor) with significantly reduced metabolic rates for humans over extended periods of time.

The authors propose that placing crews in an inactive, torpor state can provide significant benefits towards advancing our spaceflight capabilities. Torpor can be safely achieved by placing the body in a mild hypothermic state. This practice is a common and well-understood medical procedure called Therapeutic Hypothermia (TH) or Targeted Temperature Management (TTM). TH is a medical treatment in which a patient's body temperature is lowered to 32-34°C (89-93°F) in order to slow the body's metabolism. TH is being used routinely in hospitals around the world with broad application to reduce the impact of traumatic body injuries. To support prolonged periods of torpor needed for spaceflight, body nutrition and hydration provided via Total Parenteral Nutrition (TPN) is advocated. TPN is a medical process in which patients are fed intravenously with fluids delivered via a central venous catheter. Long-term TPN is often used to treat patients suffering the extended consequences of an accident, surgery, or digestive disorder.

TH is a proven and ischemic treatment for traumatic injuries; however, it has not been applied for non-critical care purposes due to current lack of purpose (i.e. no practical need). The opportunity exists to advance TH in this capacity to enable and enhance our human spaceflight capability. With this concept, we have the potential to simultaneously solve multiple exploration challenges.

In July 2013, the NASA Innovative Advanced Concepts (NIAC) Program awarded the authors with a Phase I study to investigate the feasibility and systems-level impact of applying this medical technology to human spaceflight, specifically for human missions to

Mars [1]. In July 2016, the authors were awarded a Phase II study to continue research on this promising concept and technology.

In papers presented at IAC 2014 and IAC 2015, the authors presented the results of initial feasibility and systems-level impact studies of applying this medical technology to near-term exploration-class missions to Mars [2], and to far-term settlement-class missions to Mars [3].

2 Background

2.1 Rationale and Goal

While TH is currently used as a short term medical treatment, an extrapolation from 14-day cycles to periods of weeks and months may be achievable in the next 10-20 years based on the rapid progress, understanding, and extension of this process over the relatively short period of time it has been studied and employed in medicine.

Though longer-term stasis is not without its own difficulties and challenges, the current complications associated with hypothermia therapy are likely compounded by the fact that this therapy is being used as a treatment for people with severe medical complications (e.g. neonatal encephalopathy, increased intracranial pressure, heart failure, traumatic injuries, etc.).

Due to the current lack of need or rationale in medical treatments to maintain TH beyond 10-14 days, longer periods have not been formally studied. While no medical procedure is without some risk, the known complication rates and the severity in which these complications occur should be significantly reduced when applied to healthy individuals.

2.2 Challenges of Human Spaceflight

The human body is not naturally adapted and designed for survival in the space environment. Microgravity, exposure to solar and galactic radiation, and long-term social isolation all present difficult challenges for the design of a settlement-class mission to Mars.

Due to the microgravity environment, significant bone demineralization and muscle atrophy occurs over time. These can seriously impact the performance and health of the astronauts [4]. Average bone loss rate on the Russian Mir Space Station was measured to be 1-2% per month [5]. During a Mars mission, crew members could lose up to 40% of muscle strength even with exercise [6]. In addition, prolonged exposure to microgravity can lead to elevated Intra-Cranial Pressure (ICP), which can cause persistent vision

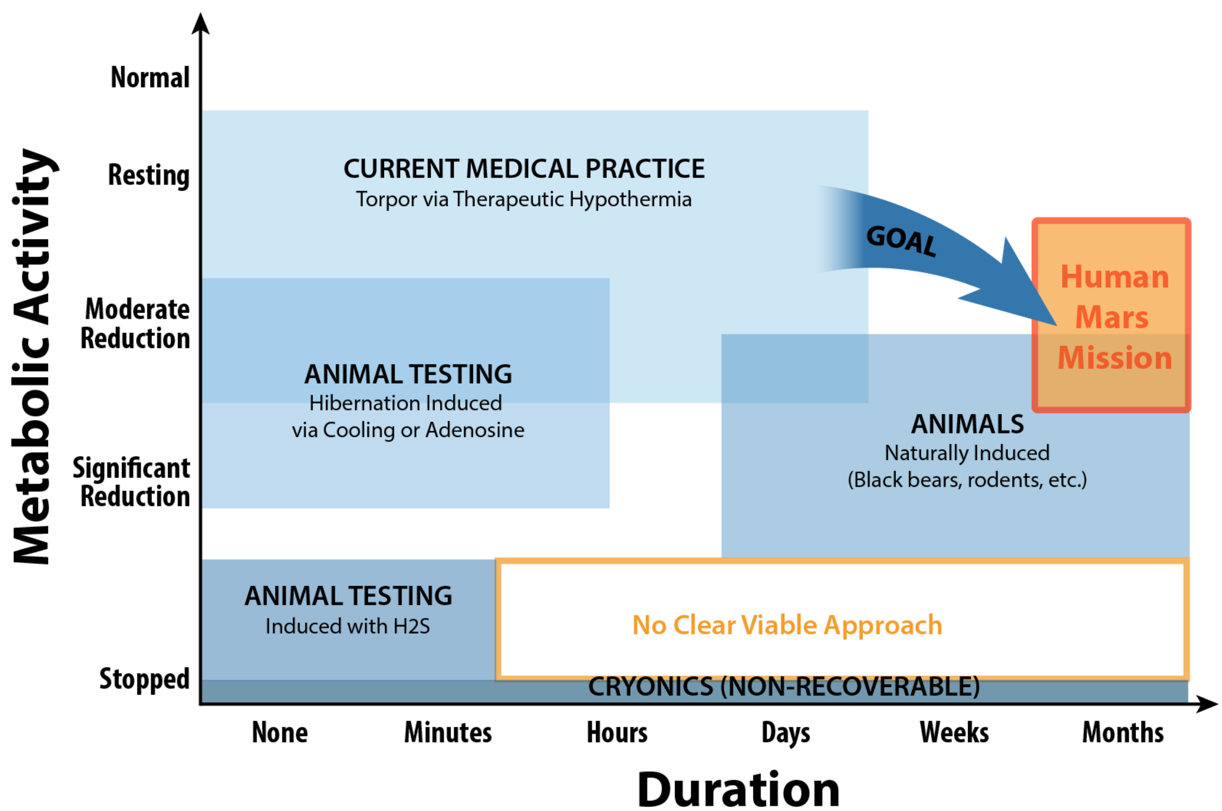

Figure 1. Medical Knowledge Spectrum

issues both during and after spaceflight, in some cases for years after returning to Earth. Experiments on elevated ICP and its effects on vision are currently being researched on the International Space Station (ISS) as a part of the NASA Vision Impairment and Intracranial Pressure (VIIP) program [7].

Traveling in space away from the protective atmosphere and magnetic field of the Earth exposes astronauts to both Solar Particle Events (SPE) and Galactic Cosmic Radiation (GCR). Left unprotected, this radiation exposure can damage the central nervous system, skin, and body organs as well as ultimately increase an astronaut's risk of cancer in the long term [8]. SPEs originate from the sun and occur intermittently. It is generally possible to receive notification of the event in advance and place the crew in small shielded compartment. GCR consists of a continuous, omnidirectional stream of very high-energy particles that originated from outside our solar system. For space travel, it is currently mass-prohibitive to provide adequate shielding against GCR, so alternative approaches and technologies must be used.

Spaceflight introduces other health complications such as spinal elongation, disrupted circadian rhythm, and altered immune systems. All of these problems are compounded with mission duration. The adverse health effects of operating in a high stress environment can also not be ignored. Decreases in immune function, nutrient absorption, interruption in sleep patterns, and effects on cognitive abilities are all well-known results of the physiologic response to stress. Space travel is a high stress activity in low-Earth orbit, and would likely be even more so on a mission that left the immediate safety and support of the Earth.

Long duration spaceflight also introduces psycho-sociological issues. A mission lasting 2 or more years may be difficult both socially and emotionally for the crew members. At typical crew sizes of only 4-8 members, interpersonal conflicts are likely to amplify as the mission progresses. Data recorded by astronauts on the ISS for missions of only 1-year in duration have shown a significant increase in recorded conflicts during the latter half of the mission [6]. Results from the 2010-2011 Russian-ESA-Chinese Mars500 experiment with a 6-member "crew" held in isolation for 520-days also indicated interrupted sleeping patterns, depression, lethargy, and even willful isolationism [8].

NASA is currently studying the psycho-social impacts of long term isolation with their Hawaii Space Exploration Analog and Simulation (HI-SEAS) program. The most recent of these simulations, HI-SEAS IV, began on 28 August 2015 and will last one year [9].

On the medical side, there are challenges with simply providing treatment (e.g. emergency medical care) and having the necessary equipment and expertise on hand. To date, a major medical emergency has never occurred in space. On a Mars mission, communications with the crew can also take anywhere from 4 to 24 minutes, depending on the relative position of Earth and Mars. In an emergency situation, this puts the crew in a position of having to make swift medical decisions with minimal or no input from remote support staff such as program managers, engineers, and medical teams.

2.3 Advantages of Torpor

Placing the crew in an inactive, hibernation state affords many advantages for deep space missions. With the crew in hibernation, the total pressurized volume required for habitation and living quarters is significantly reduced. In addition, many ancillary crew accommodations (e.g. food galley, cooking and eating supplies, exercise equipment, entertainment, etc.) can be eliminated. Additionally, a person in torpor has reduced metabolic rates, and therefore requires less consumable food, water, and oxygen.

Applying torpor to these missions will also minimize psychological challenges for crew. After boarding the transfer vehicle in Earth orbit, the crew of a Mars mission can simply sleep through the 6 to 9 month in-space transfer to Mars, and be woken once they have arrived in Mars orbit.

Having the crew inactive and stationary during the mission also provides some flexibility to habitat design that can help solve or mitigate a number of the health issues stemming from long-duration spaceflight. One approach to eliminating these risks is by rotating the habitat element to induce an acceleration field inside the crew cabin, thus simulating gravity. This concept of artificial gravity is not new - spinning habitats have been considered from the earliest days of human space exploration, and have been featured heavily in both engineering studies and works of science fiction. For an active crew, this often means creating a habitat in which the crew can "stand up" in the induced gravity field. Such a habitat must be large enough to not impart a significant acceleration gradient across a crew member, otherwise the crew can become disoriented or suffer other ill health effects. With a stationary crew, however, the crew can be "lying down" in the induced gravity field, significantly reducing the size requirements of the habitat and avoiding issues with gravity gradients.

The crew can also be better protected from radiation if they remain stationary for the duration of the mission. Rather than shielding the entire habitable volume from radiation, the habitat can be designed in a way to minimize radiation exposure in the exact locations where the crew will be located. This can be accomplished through the combination of consumables placement and additional radiation shielding as necessary [10].

3 Hibernation in Nature

3.1 Types of Hibernation

There are three ways that organisms are known to hibernate in nature: obligate hibernation, facultative hibernation, and torpor.

Obligate hibernators spontaneously enter hibernation regardless of the ambient temperature or their access to food. In these creatures their core body temperature drops to environmental levels and heart/respiration rates will slow drastically. This form of hibernation is also characterized by periods of sleep with periodic arousals where the body temperature and heart rate return to normal levels to pass waste (e.g. marmots, arctic ground squirrel).

Facultative Hibernators only enter hibernation when they are either cold stressed, food deprived, or both for survival purposes (e.g. Prairie Dogs). In doing so these animals are able to awaken and eat during warmer days when food may be available.

Torpor is defined as a deep sleep state that is induced by active metabolic suppression with minimal decrease in body temperature to save energy over the winter period. Black bears are the most famous example of this type of hibernation. Due to the minor decrease in body temperature and physiologic function black bears have minimal systemic effects from hibernation and are able to fully arouse over a very short period of time.

3.2 Hibernating Animals

Table 1 provides a listing of mammals that are known to hibernate or enter torpor states. Of particular interest is the black bear's ability to re-absorb nitrogen waste (from urea contained in urine) internally and thus prevent muscle atrophy. The dwarf lemur is also significant as one of a handful of known primate hibernators. During hibernation periods lasting up to 5 months, Lemurs can reduce their metabolic rate to just 2% of their active state.

3.3 Artificially Induced Hibernation

There are three possible approaches for inducing a hibernation-like state in animals and humans that have been studied over recent years: temperature-based, chemical/drug-based, and brain-synaptic-based.

Temperature-based cooling approaches have the largest body of medical data available for humans and is a well-understood and commonly used clinical procedure. While our current assumed approach for inducing torpor uses this technique, it could easily be supplemented or enhanced with the other identified options with little or no impact to the overall habitat designs and architecture.

3.3.1 Temperature-based

Torpor is achieved by lowering the body core temperature through either invasive cooling (infusing cooled IV fluids), or conductive cooling (e.g. gel pads placed on body or evaporative gases in the nasal and oral cavity).

3.3.2 Chemical/Drug-based

In 2011, Scientists at Univ. Alaska successfully induced hibernation by activating adenosine receptors (5'-AMP) in arctic ground squirrels. More recent studies on rats have yielded similar results. While this "hibernation molecule" has had mixed experimental results when used on its own, when used in conjunction with temperature based induction it has yielded very promising results [11].

Inhaled Hydrogen Sulfide (H2S) has also been shown in recent studies to induce a deep hibernation state within mice by binding to cells and reducing their demand for oxygen [12].

Table 1. Hibernating Animals [11]

Species	**Category**	**Duration (months)**	**Comments**
Black Bear	Carnivora	3 to 6	Minimal body temp. reduction, consumes 25-40% body mass Nitrogen waste from body is recycled, preventing muscle atrophy
Arctic Ground Squirrel	Rodentia	Up to 6	Experiences significant body temperature reductions Heart rate can decrease to as low as 1 beat per minute
Marmot	Rodentia	4 to 8	Body temperature remains at ambient for days to weeks, followed by a brief return cycle (< 24 hr) to higher body temperature
Prairie Dog	Rodentia	4 to 5	Can spontaneously awaken to eat on warmer days
Groundhog	Rodentia	Up to 6	Moderate body temperature changes Heart-rate slows to approximately 4 beats per minute.
Dwarf Lemur	Primate	4 to 5	Can reduce metabolic rate to 2% of "active" rate First known primate to hibernate

3.3.3 Brain Synaptic-based

Current research shows significant decreases in the number of dendritic spines along the whole passage of apical dendrites in hibernating creatures. Whether this is an initiating factor for hibernation or a result of other metabolic processes is still being investigated [13,14].

3.4 Latest Experimental Data

There is such a wealth of clinical date on TH that ILCOR, American Heart Association, and American Association for Pediatrics guidelines support the use of 24-72 hour cycles of TH cooling for cardiac arrest, neonatal encephalopathy, and refractory increased ICP [15,16]. More interesting is the limited data that is now available for prolonged uses of TH.

Chinese studies showed evidence of increased benefit from prolonged TH (up to 14-days) without increasing the risk of complication [17]. Recent studies confirm this data [18].

The goal of both of these studies study was to investigate the protective effects of long-term (3-14 days) mild hypothermia therapy (33-35°C) on patients with severe Traumatic Brain Injury (TBI). In half the patients in the mild hypothermia group, body temperatures were cooled to 33-35°C for 3-14 days. Rewarming commenced when the individual patient's ICP returned to the normal level. Body temperatures in 44 patients assigned to a normothermia group were maintained at 37-38°C. Each patient's outcome was subsequently evaluated one year later. Approximately one year after TBI, the mortality rate and the rate of unfavorable outcome was significantly reduced in the mild hypothermia group. In the normothermia group, the mortality rate was 50% higher and the rate of favorable outcome was 40% lower. The data produced by these studies demonstrated that long-term mild hypothermia therapy significantly improved outcomes in patients with severe TBI [19,20].

The U.S. military is also actively funding research in this area to support the warfighter, with the goal of being able to extend the time period to transfer an injured person to receive proper medical care. Additionally, the National Institute of Health has funded research in this area in support of the same general objective [21].

Despite initial encouraging results with Hydrogen Sulfide on mice producing a brief hibernation-like/suspended animation state, more recent clinical trials were suspended after subsequent studies did not show this effect occurring in larger animals [19,22].

Unfortunately, none of the aforementioned efforts are focused on achieving extended durations of torpor or considering the applicability of this science to human space flight.

3.5 Evidence Supporting Ability and Recovery

Real-world evidence offers encouragement that this process can be expanded from days to weeks or even months once fully understood. Consider the well-publicized case of Mitsutaka Uchikoshi from Japan in 2006. He was found after 24 days of exposure to freezing temperatures, unconscious in a hibernation state after a mountain hiking accident. His body temperature had dropped to 22°C (71°F) and his pulse was undetectable. Upon arrival at a hospital and undergoing medical rewarming, he woke up and has since made a full recovery [23].

In 1999, 29-year-old Dr. Anna Bagenholm was revived after her heart was stopped for 3 hours after being submerged under the ice in a skiing accident. Her body temperature quickly dropped to 14°C and she had entered a torpor state, enabling her to survive the accident [24]. There is also the astounding case of Erika Norby, a one-year old, who in 2002 was revived after her heart stopped beating for over two hours. An accident left her exposed to -20°C weather conditions and her core temperature had dropped to 17°C [25,26].

More recently in the news was the miraculous survival of a 16-year-old boy who stowed away in the wheel hub of a Boeing 747 travelling to Hawaii. He survived freezing temperatures and very low oxygen levels occurring at the 38,000 ft flight altitude for several hours and recovered with no medical complications. Doctors speculate that his body quickly entered a hibernative state due to the rapid temperature drop thus permitting him to survive at the minimal oxygen levels [27].

These cases are indicators of the resiliency of the human body and what it appears to be an inherent, natural ability to assume some form of a hibernation state the correct environmental conditions. Through medical science and technology, we can identify and understand these exact conditions to recreate them as needed to induce similar effects for the purposes of achieving the human exploration of space.

4 Medical Application of Body Cooling

4.1 History

Body cooling as a therapy for traumatic injury has been theorized, and even tested, since antiquity. The Greek physician Hippocrates, arguably the world's first modern doctor, advocated the packing of wounded soldiers (especially those with head injuries) in snow and ice (400 BCE) for transport to army hospitals [28]. In 1810, Napoleonic surgeon Baron Dominique Jean Larrey tested this theory after noting that wounded officers who were kept closer to the fire survived less often than the minimally pampered infantrymen on the outskirts on the camp and therefore exposed to much cooler ambient temperatures.

Table 2. Milestones in Development of Therapeutic Hypothermia [28]

Year	Description
1945	First medical articles concerning use of hypothermia published
1955	Division of Medical Sciences, NRC symposium on the Physiology of Induced Hypothermia, sponsored by U.S. Army, Navy, and Air Force
1980	Animal studies prove that mild hypothermia acts as a general neuro-protectant following a blockage of blood flow to the brain
2002	Two landmark human studies published simultaneously by the New England Journal of Medicine
2003	American Heart Association endorses the use of TH following cardiac arrest
2005	Protocols for use of TH for prenatal infants established
2009	RhinoChill® IntraNasal cooling system enters clinical trials

4.2 *Modern Usage*

The "modern" era of Therapeutic Hypothermia was initiated by the U.S. Military during World War II. Table 2 shows a timeline of the most significant events in the formation of current TH protocols.

The first medical article concerning hypothermia was published in 1945. In the 1950s hypothermia was employed during intracerebral aneurysm surgery to help create a bloodless field. Because most of the early research on TH focused on placing patients in a deep hypothermia (body temperature between 20-25°C (68-77°F), numerous serious and life threatening side effects were noted, and hypothermia was viewed as impractical in most clinical situations.

By the 1980s animal studies were showing the ability of mild hypothermia to act as a neuroprotectant. As noted above, the 1999 skiing accident of Anna Bågenholm's (her heart stopped for three hours and her body temperature dropped to 13.7°C prior to being resuscitated, without any adverse effects) kick-started a new interest in TH. By 2002 two landmark human studies were published by the New England Journal of Medicine that showed the positive effects of mild hypothermia following cardiac arrest [29]. Currently, almost every major hospital around the world includes hypothermic therapies in their care for critically ill patients. There are even some researchers that argue that hypothermia provides better neuroprotection than any drug treatment [30]. By 2005 multiple studies had also shown that hypothermia is a highly effective treatment for preterm and newborn infants suffering from birth asphyxia, significantly increasing the chance of survival without brain damage [31].

4.3 *Therapeutic Hypothermia*

TH is a medical treatment that lowers a patient's body temperature in order to help reduce the risk of ischemic injury to tissue following a period of insufficient blood flow. Initial use on a limited basis started in 1980's, but since 2003 TH has become a staple of Critical Care for newborn infants suffering from fetal hypoxia and for adults suffering from head trauma, neurological injuries, stroke and cardiac arrest. Benefits of hypothermic therapy have been well proven, and it is inexpensive to implement and use. Standard protocols for the use of TH exist in most major medical centers throughout the world [32].

4.3.1 *State-of-the-Art Usage*

Hypothermic therapy is being used routinely and with broader application in hospitals to reduce the impact of traumatic body injuries. Therapeutic Hypothermia use can be divided into six primary treatment categories: Neonatal encephalopathy, Cardiac arrest, Ischemic stroke, Traumatic brain or spinal cord injury without fever, Neurogenic fever following brain trauma, and increased intracranial pressure refractory to other treatments. Additionally, this type of cold therapy is the only known medical treatment to be clinically proven to prevent brain damage and improve mortality for newborns experiencing oxygen deprivation due to underdeveloped lungs.

4.3.2 *Medical Procedure*

In simple terms there are four aspects to the hypothermic process and stasis induction: initial body cooling, sedation, nutrition/hydration, and rewarming. Patients are actively cooled to a mild hypothermic state (defined as a core temperature between 32-34°C (89-93°F). While various cooling approaches exist, there is no evidence demonstrating the superiority of any one cooling method over another [33]. Shivering (a muscle activation response that tries to rewarm the body) is commonly suppressed with a very low-level

Table 3. Cooling and Rewarming Target Temperatures and Inducement Times

Parameter	Cooling	Rewarming
Target Temperature	32-34°C (89-93°F)	36-37°C (97-98°F)
Rate of Change	0.5°C (1°F) per hour	0.5°-2°C (1-4°F) per hour
Time Required	6 hours	2 to 8 hours

infusion of propofol and fentanyl, with or without the intermittent treatment of benzodiazepines (e.g. midazolam). Patients are then maintained in this torpor like state until significant improvement is noted in their medical status. The patient is then rewarmed to normal body temperatures, with continued medical treatment as a standard critical care patient. Table 3 shows an example of a typical cooling and warming timeline.

4.3.3 Temperature and Vital Signs Monitoring

Core body temperature should be monitored continuously during TH. The most common method of measurement is via central venous temperature, but several other options are available, including esophageal, bladder, or rectal probes. Esophageal temperature is the most accurate surrogate method [33].

Basic vital sign monitoring is required during therapeutic hypothermia. This normal includes a 12 lead ECG to monitor cardiac activity, a central line monitor and measure systemic blood pressure and an indwelling catheter or urine collection system to monitor urine output to measure for dehydration.

4.4 Body Thermal Management Systems

Torpor is achieved by decreasing a crewmember's core temperature to approximately 34°C (93°F). There are several ways that this can be accomplished. Regardless of technique, all of the systems are low mass, low power, and can be automated. And as discussed above, multiple studies show that there is no evidence demonstrating the superiority of any one cooling method over another [33].

4.4.1 Invasive

Invasive techniques involve the insertion of a double lumen catheter into a major vascular structure. In most cases this cooling catheter would be inserted into the crew's femoral vein. A cooled saline solution is then circulated through either a metal coated tube or a balloon located in the catheter body. The saline cools the patient's whole body by lowering the temperature of a patient's blood through conduction cooling. No cooled fluid actually enters the patient's blood stream. The CoolGard 3000™ with IcyT Catheter by ZOLL Medical, as shown in Figure 2, is an example of an invasive system currently in use. While these systems are very effective at controlling body temperature, they are typically used for shorter term stasis periods and not desirable for longer induction periods.

4.4.2 Non-Invasive

An alternative to the aforementioned invasive procedure is a non-invasive technique that involves circulating cold water through a blanket, skull cap, or body pads. This method lowers the core temperature exclusively by cooling a crewmember's skin, requiring no clinician performed invasive procedures. Although this technique of temperature management dates back to the 1950s, it still remains in use today. The treatment also represents the most well studied means of controlling body temperature. The ArcticSun 5000™ by Medivance, Inc. is an example of an approved and widely used non-invasive system. The primary drawback of this system is the need for long-term contact of the blankets and pads with the skin which could cause surface erosion. These pads also need to be changed every seven days per manufacture recommendations.

4.4.3 Trans Nasal Evaporative Cooling

A new novel cooling approach that does not require access to a major vein or prolonged placement of cooling pads is called trans-nasal evaporative cooling. For this system, a cannula (small plastic tube) would be inserted into the crewmember's nasal cavity. This is used to deliver a spray of coolant mist that evaporates directly underneath the brain and base of the skull. As blood passes through the cooling area, it reduces the temperature throughout the rest of the body. The coolant mist is only used as needed to adjust the body temperature to within the target range. The RhinoChill™ system created by BeneChill, as shown in Figure 3 is an example of a trans nasal evaporative system currently in use.

4.4.4 Environmental

The unique cold environment of space would allow cooling the astronauts core temperature by lowering the temperature of the entire habitat. Temperature stability could then be achieved through conductive warming through bedding pads with embedded heating elements, similar to the KOALA System™ produced by NovaMed Inc. (see Figure 4).

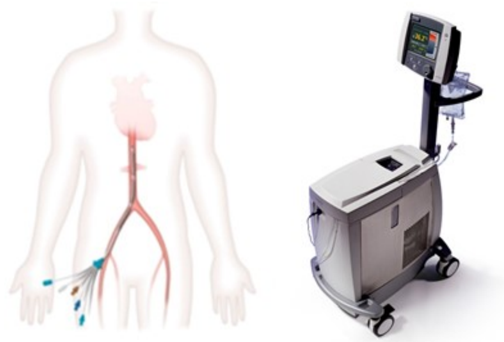

Figure 2. CoolGard 3000R™ with IcyT Catheter by ZOLL Medical [34]

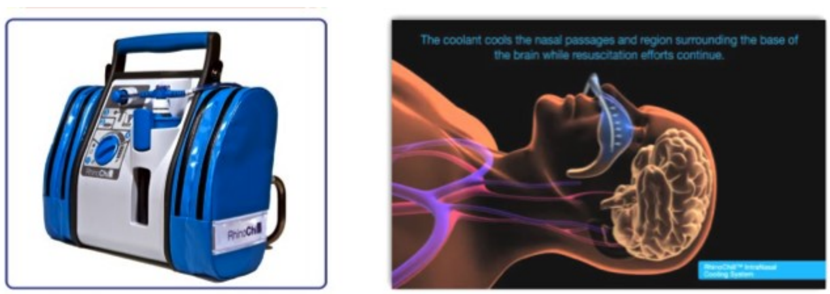

Figure 3. RhinoChill™ System by BeneChill, Inc. [35]

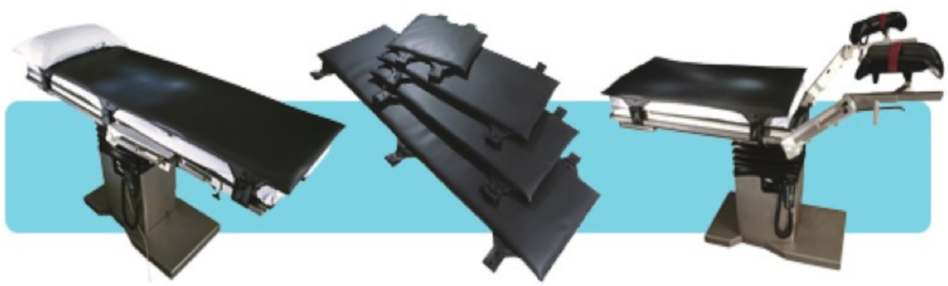

Figure 4. KOALA System™ by NovaMed Inc. [36]

5 Hydration and Nutrition

All the nutrition and hydration needs for a person in torpor can be provided by a liquid solution and administered through an Intra-Venous (IV) line directly into the body. This process is known as Total Parenteral Nutrition (TPN). The solution contains all nutrients that the body needs to maintain full physiologic function. It is fed slowly through a permanent IV line to the body over a period of hours and is routinely used in numerous post-surgery and oncological treatments where the individual has digestive issues or cannot process foods normally. Short-term TPN is used if a person's digestive system has shut down (for instance due to peritonitis or post-operative ileus), and there are concerns about nutrition during an extended hospital stay.

Long-term TPN is often used to treat people suffering the extended consequences of an accident, surgery, or digestive disorder. Cancer patients and preterm infants are routinely on TPN for months at a time. While most patients usually recover enough to stop TPN use, there are circumstances where patients obtain all of their nutrition solely from TPN for years. Long-term parenteral nutrition requires a tunneled central venous catheter or a Peripherally Inserted Central Catheter (PICC). A tunneled catheter is preferable, since infections are more common among patients receiving parenteral nutrition at home through a PICC. Also, while single lumen central venous catheters should be dedicated solely for the infusion of parenteral nutrition, multiple lumen central venous catheters need only one port for this purpose [37].

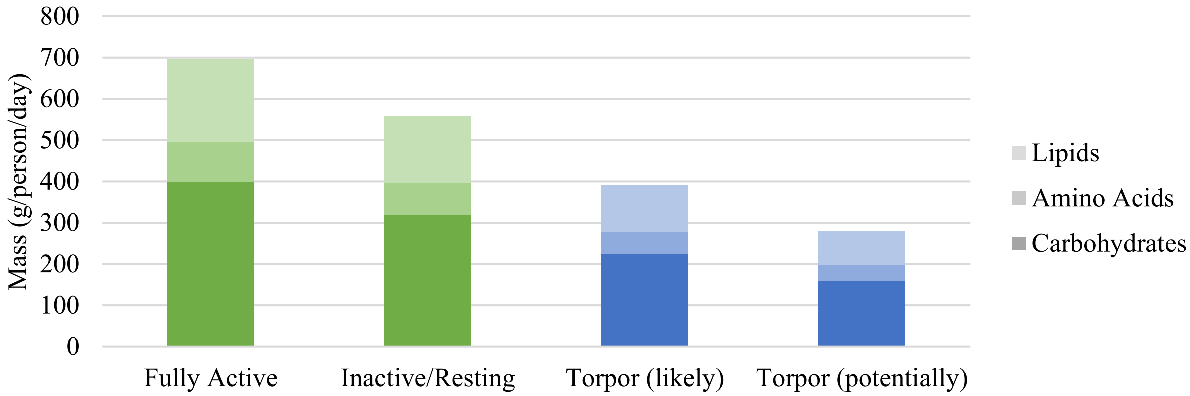

Figure 5. TPN Dosage Rate vs. Activity Level for 80 kg (175 lbm) Male

5.1 *TPN Contents*

A typical or normal TPN mixture contains five different substances [37]: dextrose, amino acids and electrolytes, lipids, vitamins and trace elements, and glutamine. The exact concentration of each fluid in the TPN mixture can vary based on daily measurements of a person's vitals and blood chemistry to provide the ideal nutritional requirement.

5.1.1 *Dextrose*

Dextrose-containing stock solutions are available in a variety of concentrations and provide a majority of the caloric contribution of total parenteral nutrition.

5.1.2 *Amino acids and electrolytes*

Amino acid solutions contain most essential and nonessential amino acids. Electrolytes are contained in the buffer solution that is used to help administer the TPN. Most electrolytes are given with maintenance fluids and are not given with the TPN dose.

5.1.3 *Lipids*

Lipids are provided as an emulsion that is added to the mixture (three-in-one mixture).

5.1.4 *Vitamins and trace elements*

Multiple studies have been conducted evaluating the benefit of adding vitamins and trace minerals to TPN. These studies have not conclusively noted any benefit. However, given their safety, it seems reasonable to provide vitamins and trace elements to astronauts that would be undergoing prolonged TPN reliance of all nutrition needs. The optimal mixture of vitamins and trace elements is yet to be determined.

5.1.5 *Glutamine*

Glutamine is a precursor for DNA synthesis and is an important fuel source for rapidly dividing cells.

5.2 *Dosing*

The daily TPN requirement for the human body is a well understood science [38]. The standard protocol for calculating the dosage is to use the Harris-Benedict Equation (HBE) with additional adjustments for individual activity level (e.g. active, resting) and stress environment (e.g. recovering). The HBE estimates the basal metabolic rate and daily kilocalories needed and is a function of gender, body weight, and body height. The value obtained is designed to maintain the crew members' current body weight.

Figure 5 provides the required TPN mass per person per day based on a male crew member weighing 80 kg (175 lbm). Female crew members TPN requirements are slightly lower. The values shown for a fully-active and resting-state are provided based on the HBE. The torpor values of "likely" and "potential" represent further reductions in daily TPN requirements from the resting rate due to the lower metabolic rate that is expected in the stasis condition. [39]

5.3 *Administration*

TPN can be administered by continuous infusion over 24 hours or cyclic infusion over 12-14 hours. Cyclic infusion is used with a tapering-up period at the beginning and a tapering-down period at the end to avoid electrolyte and blood sugar complications. Infusion occurs via pump using either peripheral or central venous line [38].

While historically medical personnel have mixed TPN solutions manually, hardware has recently been developed to automate this process. These automated systems contain a nutrient bank that is used to mix daily doses of TPN based on weight, activity and lab analysis parameters.

The Pinnacle system, shown in Figure 6, is an automated TPN delivery system created by B. Braun Medical, Inc. It is a manually inputted and activated system that runs on a 115 V_{AC}, 60 Hz, 5.0 Amp electrical system. Control panel dimensions are height: 14.76 in, width: 11.77 in x depth: 1.93 in with a weight of 10.78 lbs. Pump dimensions are height: 28 in, width: 19.4 in x depth: 11.8 in with a weight of 30 lbs. Each nutrient reservoir contains a 2 L course container

Figure 6. Pinnacle System™ for Automated TPN Dispensing [40]

for mixing the final TPN solution. Discussions with Jessica Pitt, Product Director for Pinnacle, have shown that the system could be modified to include battery back-up and remote operation and control, as well as an increase in the nutrient source reservoir to any size desired. Little modifications would need to be made for this product to be space ready.

5.4 Monitoring

Routine monitoring of total parenteral nutrition includes measurement of fluid inputs and output and periodic laboratory studies. In the hospital environment patients have serum electrolytes, glucose, calcium, magnesium, and phosphate labs performed daily until they are stable. Once stable these labs are typically decreased to a weekly basis [38]. On a space mission, it is expected that more rigorous monitoring will be conducted with daily measurements taken.

5.5 Hydration Fluids

Current space missions carry large stores of water onboard for multiple uses. Unfortunately, limitations of mass, volume, storage space, shelf-life, transportation, and local resources do restrict the availability of such important fluids. Potable water can be recycled from water waste produced on the space module with basic filtration systems, but medical grade fluids require a much higher level of processing.

In 2010, NASA successfully tested the IVGEN system, as shown in Figure 7, on an actual space mission [41]. It is a handheld device that can convert regular drinking water to produce sterile, ultrapure water that meets the stringent quality standards of the United States Pharmacopeia for Water for Injection (Total Bacteria, Conductivity, Endotoxins, Total Organic Carbon). The device weighs 1 kg and is 2 cm long, 13 cm wide, and 7.5 cm high. One device can produce 1 L of medical-grade water in 21 minutes. The device contained one battery powered electric mini-pump, although a manually powered pump can be attached and used. Operation of the device is easy and requires minimal training.

In addition to creating IV fluids, the device produces medical-grade water, which can be used for mixing with medications for injection, reconstituting freeze-dried blood products for injection, or for wound hydration or irrigation.

6 Research Findings

6.1 Discussions with Medical Researchers and Practitioners

While Therapeutic Hypothermia and Total Parenteral Nutrition are well studied and often practiced medical procedures in every major medical center in the world, their use on healthy individuals over a long period of time in the space environment would be completely innovative. As no data exists at this time that we can use to answer some of the more pressing questions about long-term TPN and TH use, information can be extrapolated based on our current knowledge of these technologies. To address some of these issues, the authors consulted with several medical experts in multiple medical specialties to access the feasibility of long term use and overcoming the long-term medical complications that can occur.

6.1.1 Cognitive Function

Question: What effects would long-term TH have on cognitive function? When the astronauts awaken would they have a recovery period before they were fully mission ready?

Response: It is hard to determine if there are any direct effects of TH on cognitive function. Every patient that is currently placed into TH would already be suffering from impaired or decreased cognitive function due to their injuries, so it is not feasible to test the effects of TH alone on function without placing healthy individuals under TH with the specific goal to evaluate that effect. However, our clinical experts do not see any reason why TH should have significant effects on the cognitive function of the crew members.

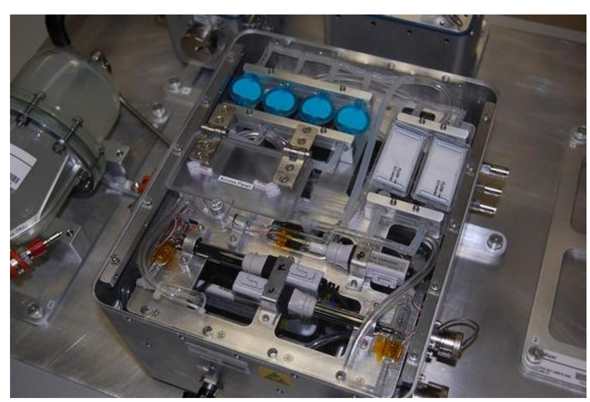

Figure 7. IVGEN System for Production of IV-grade Fluids [42]

6.1.2 Long Term Use

Question: What are your concerns about the long-term use (greater than 10-14 days) of TH and TPN?

Response: Electrolyte abnormalities caused by both TPN and TH were the consensus primary concern. However, all subspecialists agreed that this could be easily controlled by daily adjustments to TPN and maintenance fluids. The other primary concern was that, as a general rule, the longer that someone is under TH the slower and longer the rewarming process is. A majority of the risk associated with Therapeutic Hypothermia is not with initiation or maintenance of the TH state, but the rewarming process and the subsequent physiological effects that occur. Most experts agree at this time that shorter, repeat cycles of TH would be safer than single, long-term cycle.

6.1.3 Repeat Cycles

Question: What concerns exist about repeat cycles of TH?

Response: None of our experts had any concerns with shorter, repeat cycles. Everyone thought that they would be tolerated well and, as discussed above, would prefer this method to longer cycles.

6.1.4 Psychological Advantage

Question: Would placing an astronaut provide any Psychological Advantages?

Response: The Neurologist consulted by the authors feels that the mild sedation associated with TH would not only provide psychological advantages but also suggested that placing the astronauts in a Torpor state could be "mentally protective", meaning that it would put the brain in a sleep/standby mood that would not require constant stimulation for good brain health.

6.1.5 TH in Healthy Individuals

Question: How would healthy individuals tolerate TH compared to current TH patients?

Response: Our consultants feel that healthy individuals would tolerate TH much better than the current patient population. Without the confounders of medical complications, they feel that crewmembers would have less chance of bleeding and infection (such as pneumonia due to decreased effects on cilia function), could tolerate longer periods of TH, would be easier and safer to wake, and would recover from the torpor state more quickly.

6.1.6 Crewmember Bias

Question: Would some crewmembers be better suited than others for Torpor missions?

Response: There is a lot of medical evidence that shows that some people have less of a shivering response and physically handle both TH and the medications associated with its use better than others. There is obviously a genetic component to it, but our experts feel that this tolerance to cooling may be programmable. This would mean that you could test astronauts beforehand to see which ones better tolerate TH. You could also expose them to short periods of TH before the mission. This would "prime" them for Torpor and allow their bodies to become accustomed to the physiologic effects of TH. It would also prepare the crewmembers for the actual Torpor process, mentally decreasing their anxiety about the procedure.

Further work with the expert team of subspecialists assembled will enable us to address more questions and concerns like the ones above, as well as help guide research in the areas of prolonged TPN and TH in the space environment.

6.1.7 Existing Equipment

Question: Can current TH and TPN equipment be used for this mission?

Response: The RhinoChill™ system is an evaporative cooling system created by BeneChill, Inc. It uses a Hexan fluid compound and a nasal cavity cannula to deliver a spray of coolant mist that evaporates directly underneath the brain and base of the skull. It is a manually activated system (but automatically adjusts to regulate body temperature) that runs on a 115 VAC, 60 Hz, 6.0 Amp electrical system or a 4-hour battery pack. Total weight of the system is 10 lbs. Dimensions are height: 47 cm, width: 47 cm, depth: 18 cm. Discussions with Fred Colen, President and CEO of BeneChill, have shown that the system could be modified to include longer battery back-up and remote operation and control. Little modifications would need to be made for this product to be space ready.

The Koala System™ (by NovaMed, Inc.) is a conductive warming system currently used for warming patients during surgical operations. It is a manually activated system (but automatically adjusts to regulate body temperature) that runs on a 115 VAC, 60 Hz, 10.0 Amp electrical system. Weight for normal pad and control panel is approximately 7 lbs. In discussion with Peter Derrico, Head Researcher for Koala, indicated in a discussion that the system could be modified to include battery back-up and remote operation and control. In addition, due to the unique nature of the material the Koala warming pads could be modified to any shape, including bedding, padding or even uniforms. Little modifications would need to be made for this product to be space ready.

The ArcticSun 5000™ is a non-invasive cooling system produced by Bard Medical Inc. It is an automated system that runs on a 230 VAC, 50 Hz, 5.5 Amp (115 VAC, 60 Hz, 11.0 Amp Nominal) electrical system. Total weight of the operating console, coolant (3-4L of normal saline), and attachments is 47 kg (103 lbs). Dimensions are height: 89 cm), width: 36 cm, depth: 47 cm. In discussions with Sam Privitera, V.P. of New Product Development, indicated in a discussion that the system could be modified to include battery backup and remote operation and control. The system as currently constructed is not space ready at this time though due to the fact the console must remain upright to prevent coolant leakage.

6.1.8 *Effects of Rotating Environment*

Question: Can TH help minimize the adverse effects associated with placing the crew in a rotating environment to induce artificial gravity?

Response: Specific testing would be need to be conducted to determine what affects the sedative state of TH would have on increasing the level to which the crew would tolerate artificial gravity. However, our clinical experts expect that the disorientation caused by spinning would not physiologically affect an astronaut that was in a Torpor state. This would allow for the induction of an artificial gravity in space, potentially minimizing both muscle atrophy and bone density loss on the long mission to and from Mars.

6.2 *Medical Advantages for Spaceflight*

6.2.1 *Intracranial Pressure*

There is some evidence that TH may, itself, provide some health benefits to crews of a long-duration mission. TH has recently been recommended as a standard treatment for increased ICP that is refractory to normal treatment methods [43,44,45].

6.2.2 *Radiation*

Reports from a symposium sponsored by the U.S. Army and facilitated by the National Academy of Sciences in the 1950's presented reports of testing on animals that showed reductions in cancerous tumor growth and the effects of radiation during while in the torpor-state. The tumor growth and cell-damaging effects of the radiation were seen to resume upon warming of the animals [46,47].

6.2.3 *Muscle Atrophy*

Muscle atrophy is a major concern for astronauts on deep space missions. Very recent medical studies and testing on critically-ill comatose patients have indicated that neuromuscular electrical stimulation (NMES) can prevent any muscle atrophy due to disuse [48]. With the crew in an inactive state, NMES can be applied extensively to any muscle group via robotic manipulators and very low power electrical impulses.

6.3 *Potential Medical Challenges*

The key medical challenges to be researched and mitigated for extended Torpor periods with the use of TPN are listed in Table 4 below. The issue area, initiator or cause, and comment on the issue or identification of the solution is provided. Note that while there are a number of potential challenges associated with torpor, there are a number of general human spaceflight challenges that are not unique to torpor.

6.3.1 *Thromboembolism*

Thromboembolism, or the formation of blood clots in the blood stream, can occur with any prolonged IV access. Peripheral IVs are particularly associated with blood clots, which is why a tunneled IV line is preferred. Prevention of clot formation includes good sterile practices, using centrally placed long-term IV lines, and utilizing new technology for such as anti-coagulation impregnated IV equipment. Treatment for thromboembolism is done with heparin flushes through the line to dissolve any formed clots [49]. In addition, a known side effect of TH is a general decrease in clotting factor activity, which could provide protection from the formation of a thromboembolism as well [49].

6.3.2 *Bleeding*

As described above a known side effect of TH is a general decrease in clotting factor activity. There is no documented evidence of any bleeding requiring the

Table 4. Summary of Concept Medical Challenges

Issue	Initiator	Solution/Comments
Thromboembolism (Blood Clotting)	Prolonged sleep status and indwelling IVs	Periodic heparin flushes to dissolve clots, Clotting is generally reduced in TH state, Minimize IV access
Bleeding	Decrease in coagulation factor activity	Not a significant concern outside of trauma May decrease risk of thromboembolism
Infection	Temperature reduction in white blood cell activity	Minimize IV access, improved sterile techniques, use of tunneled catheters and antibiotic-infused catheters
Electrolyte Imbalances	Decreased cellular metabolism	Close monitoring and IV stabilization with TPN
Fatty Liver and Liver Failure	Long term TPN usage	Can alternate source of lipids to reduce risk
Other Complications (hypo/hyper glycaemia, bile stasis, etc.)	TPN and reduced metabolic rate	Augment TPN with insulin, exogenous CCK, etc.
Electrolyte Imbalances	Decreased cellular metabolism	Close monitoring and IV stabilization with TPN

stopping of TH in patients that were not trauma patients already suffering from significant internal or external bleeding at the initiation of treatment [49].

6.3.3 Infection

TPN requires long-term IV access for the solution to run through, and the most common complication is infection of this catheter [50]. Therapeutic hypothermia does not incur a risk of overall infection, but can increase the risk of pneumonia and sepsis if infection occurs [51]. Prevention of IV line infection includes good sterile practices, using centrally placed long-term IV lines, and utilizing new technology for such as antibiotic impregnated IV equipment [52]. New studies show that in the case of infection the IV line need not be removed as previously thought. Treatment for central line infection includes IV administered antibiotics and rewarming and waking from the Torpor state.

6.3.4 Electrolyte and Glucose Imbalances

As addressed multiple times above, TH can be associated with electrolyte imbalances in patients. The use of TPN and the associated laboratory testing and solution preparation would mitigate this complication.

6.3.5 Fatty Liver Disease

Fatty liver is usually a rare, long-term complication of TPN. The main cause of this is the use of linoleic acid (an omega-6 fatty acid component of soybean oil) as the major source of lipids. Research is currently underway that shows that alternate sources of lipids have a much lower risk of this complication. Fatty liver disease is usually benign in nature and can be corrected with adjustments in diet and exercise [53].

7 Implementation in Space

The required crew support systems are identified and demonstrated in Figure 8. The basic features and systems required to support an individual would include:

1. A central monitoring station for evaluating heart function and vital signs (e.g. 12-lead electrocardiogram).
2. A tunneled catheter for IV hydration, TPN administration and lab draws. A second line could be placed as a reserve in case of infection or damage to the other line.
3. Nasal thermal management system for TH if evaporative approach is used. (A multi-lumen catheter

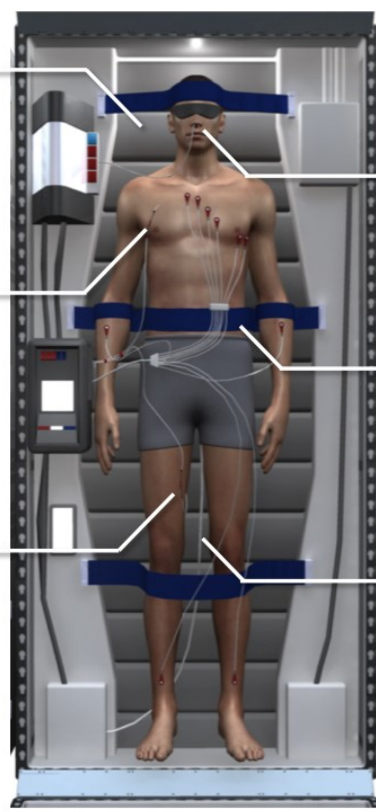

Figure 8. Implementation of Crew Support Systems

could be used for both cooling and IV hydration if that method is preferred).

4. Urine collection assembly and drain line.
5. Thermal warming pads to act as an additional thermoregulator, and to provide emergency waking support if needed.

Additionally, some loose-fit straps and bindings are used to minimize any movement in the habitat and keep the crew member in their respective alcove.

Torpor habitat designs include robotic arms. These manipulator arms are used to manage and manipulate the passenger lines, leads, and restraints during the mission. The arms can also be used to administer NMES therapy.

Torpor habitats can also be designed to rotate in order to induce an artificial gravity field. In this configuration, the crew will be accelerated into the padding on the torpor compartment; the sensed acceleration will be as if lying down in a gravity field. The crew are inclined slightly such that with respect to the gravity field, the head is slightly above the feet.

The acceleration field gradient is typically a concern in traditional artificial gravity habitat designs; the human body cannot tolerate a large acceleration gradient well. However, because the crew are stationary in the torpor-enabled habitat, the passengers can be placed nearly perpendicular to the acceleration vector, significantly reducing the acceleration gradient across the body.

8 Results Summary

Human patients have been placed in a continuous torpor state using TH protocols for periods up to 14-days. Prior to the start of the study, the team was only aware of TH being applied for up to 7-days. This longer duration is important because it makes viable approaches like the sentinel protocol with an active caretaker. Additionally, results from recent medical studies are also starting to suggest that increasing the administration of TH in clinical settings from current period of 2-3 days to 4-5 days may be warranted and beneficial.

According to our experts, humans can undergo multiple TH induction cycles with no negative or detrimental effects reported in either the near term recovery period or long term. In addition, repeat cycles may actually be tolerated better then single treatments as humans so some adaptability to the TH process.

Torpor has been shown to reduce cancerous tumor growth and the effects of radiation. Additionally, TH has recently been recommended as a standard treatment for increased ICP that is refractory to normal treatment methods. Both radiation exposure and ICP have been cited on NASA's Human Research Program and Risk Roadmap as major concerns.

Human patients have regularly received sustenance for extended durations (>1 year) from TPN, which can meet all hydration and nutritional needs. The administration of TPN is a well understood science within the medical community and is used at every major hospital.

Contrary to some opinions and concerns, based on over a dozen studies with hundreds of patients, there was no evidence suggesting that TPN promotes bacterial overgrowth, impairs neutrophil functions, inhibits blood's bactericidal effect, causes villous atrophy, or increases the risk of death due to gastrointestinal complications

All key hardware systems required (i.e. body cooling systems, TPN mixing and dispensing, space-based IV-grade solution generation, etc.) are currently available in non- or semi-automated forms. Conversations with medical system R&D divisions did not identify any immediate concerns or challenges with fully automating their hardware.

9 Future Work

In July 2016, NASA HQ's NIAC Program under the Space Technology Mission Directorate (STMD) awarded the authors with a follow-on, two-year grant to continue to investigate the feasibility and systems-level impact of advancing this medical technology for human spaceflight applications, specifically for human missions to Mars. As a part of this study, the authors have assembled a diverse research team including medical researchers, scientists, and former astronauts. The team will focus on five research areas: nutrition and intravenous support; metabolic rate studies; prolonged hypothermia physiological impacts; feasibility and evaluation of prolonged hypothermia in non-hibernating mammals; and hypothermia induction process and supporting hardware systems.

9.1 Nutrition and Intravenous Support

The use of TPN combined with prolonged hypothermia will be further evaluated. Specifically, the adaptation of current TPN practices for use in space will be examined. Any complications or side effects of usage and possible methods of prevention and treatment will be identified. Other analogs for adult hypothermia (e.g. comatose patients, neonatal care) where TPN is administered on inactive people will also be considered and evaluated to assess their impacts and applicability.

9.2 Torpor Metabolic Rate Studies

The benefits of combined chemical and thermal induced torpor for prolonged space travel evaluated. Specifically, the long term energy savings from metabolic suppression and cooling coupled with A1AR (adenosine) agonists will be studied.

9.3 Prolonged-Hypothermia Physiological Impacts

The possible medical complications associated with hypothermia-based torpor in the context of prolonged space travel will be investigated. The sensitivity and long-term impact on human physiology with application duration will also be evaluated. Furthermore, the risk mitigation potential of multiple induction cycles versus a single, long-duration cycle over an identical total time period will be considered.

9.4 Feasibility and Evaluation of Prolonged Hypothermia in Non-Hibernating Mammals

A multi-phased test plan for conducting prolonged-hypothermia evaluations in non-hibernating mammals that can advance our understanding and knowledge of the medical impacts of the technology will be developed. Many challenging questions remain as to the most effective means to induce cooling, maintain hypothermia, and the rate and process for rewarming. In addition, non-hibernating mammals lack the physiological processes to maintain adequate oxygenation, electrolyte and acid-base homeostasis, sufficient nutrition, and excretory functions during prolonged hypothermia.

9.5 Hypothermia Induction Process and Supporting Hardware Systems

Processes and options to facilitate rapid induction and (possible) rewarming for prolong hypothermia will be determined. The rationale for viability of extended use/application (i.e. long-term impacts on nasal passages, etc.) will be provided. Additionally, unique hardware modifications required for spaceflight adaptability of the non-invasive cooling systems, automated TPN systems, etc. will be identified. Consideration will be given to specific aspects such as long-term operation in microgravity, crew operation/manipulation of hardware, part reliability, etc.

10 Conclusions

Therapeutic Hypothermia (TH) is an established and rapidly evolving medical procedure that the medical community recognizes as a beneficial management tool for an increasing list of medical conditions. Human patients have been placed in a continuous torpor state using TH protocols for periods up to 14-days. Some limited testing in animals has shown that cancerous tumor growth and the effects of radiation may be significantly reduced and slowed during the torpor-state (on par with metabolic rate reduction). TH is also now recognized as an effective treatment in patients suffering from increased intracranial pressure (ICP) that is refractory to normal treatment methods.

Human patients have regularly received sustenance for extended durations (>1 year) from an all-liquid solution, called Total Parenteral Nutrition, which can meet all the body's hydration and nutritional needs. Furthermore, all key hardware systems required for TH and TPN are currently available in non- or semi-automated forms.

Enabling human stasis continues to appear as the most promising approach toward enabling manned exploration in deep space. Leveraging ongoing medical advancements with therapeutic hypothermia to support prolonged hypothermic stasis, combined with metabolic suppression, may provide a number of unique benefits and solve a variety of common engineering and medical challenges for space travel.

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