White Paper –
A Brief Introduction to Therapeutic Temperature Management

Introduction

The human body strives for homeostasis, which is the normal condition and normally occurs at a core body temperature of 37˚C but may vary approximately 0.5˚C up or down between individuals. Normal temperature (normothermia) can thus typically vary between 36.5˚ and 37.5˚C and is commonly in the lower range in the elderly. In this temperature range, our enzymes, metabolic processes and organs function optimally and we feel comfortable.

Core body temperature is strictly controlled by a thermostat, located in a central region of the brain called the hypothalamus, and regulation of core body temperature is achieved by a conventional feedback system between the hypothalamus and the periphery. This feedback system is roughly grouped into an involuntary autonomic response and a voluntary behavioral response. The behavioral response is the most powerful and includes putting on warm clothes, building shelters or turning up the heat. Autonomic defense mechanisms include sweating and vasodilation in case of fever to get rid of heat while shivering and vasoconstriction are efficient to protect against cold. Thermoreceptors sense changes in temperature and are found in the skin, liver and skeletal muscles. Those sensing cold are 3-4 times more common than the ones sensing heat. The skin, particularly hands, feet and face are rich in thermoreceptors that inform the hypothalamus when skin temperature changes followed by activation of defense mechanisms. Thermoregulation is thus strictly controlled and also preserved in the elderly although after the age of 80, defense mechanisms seem to be weakened.

Infection and inflammation

A physiological temperature increase often occurs secondary to an infection or as a response to severe stress. For example, an infection typically triggers the release of endogenous cytokines (pyrogens) from leukocytes to the blood stream. These pyrogens will eventually reach the brain and trigger the hypothalamus to increase the core body temperature in order to optimize the fight against the invading infectious organisms (bacteria, virus). In order to increase core body temperature, several tightly regulated mechanisms are activated, among them vasoconstriction, shivering and pooling of blood from periphery to the core. A new homeostasis is eventually achieved but now at a higher core body temperature. Eventually, and typically when the infection is under control, the thermostat again settles for a core body temperature in the normal range of 36.5-37.5˚C. To allow for this temperature drop,

tightly regulated mechanisms are again activated leading to loss of heat by sweating, vasodilation and pooling of blood to the periphery.

Severe stress, like suffering from stroke, trauma or cardiac arrest will also trigger the release of pyrogens to the blood stream that will increase the core body temperature and fever will develop through the very same mechanisms, this time without being triggered by bacteria or virus. This response, which is mainly inflammation, will thus lead to fever as part of a normal physiological response, but has also been shown to be detrimental to a vulnerable, ischemic brain. There are numerous animal studies demonstrating that the combination of fever and ischemic injury to the brain is an undesirable combination since it may aggravate brain injury. The link between fever and aggravated brain injury has also been demonstrated for the human brain, both in stroke and in cardiac arrest patients.

The responsible mechanisms for the aggravation of brain injury when fever is present are several and include increased production of reactive oxygen species (ROS), dysregulation of Ca-homeostasis, mitochondrial dysfunction, increased glutamate-toxicity and increased oxygen demand. The full picture of all detrimental pathways and how they interact is, however, not yet known.

Hyperthermia (fever) and hypothermia

Increased core body temperature or fever has several definitions and there is no consensus what is correct. The lowest definition of fever is 37.8˚C, the highest is 38.3˚C, and 38˚C is commonly referred to as fever as well. A common definition of fever in the general ICU is 38.3˚C while fever in the neuro-ICU is often set at a lower level due to the association between higher temperatures and aggravated brain injury.

Decreased core body temperature or hypothermia is commonly defined as a temperature at or below 35˚C. A range down to 32˚C is defined as mild hypothermia, a temperature between 32˚C down to 28˚C is defined as moderate hypothermia while a temperature below 28˚C is defined as severe hypothermia. Profound hypothermia, which is sometimes used during vascular surgery in circulatory arrest, is defined as a temperature below 20˚C. The coldest known cardiac arrest survivor had an initial core body temperature of 13.8˚C after having been submerged in ice-cold water in northern Norway, she had a complete neurological recovery except for some remaining peripheral neuronal injury.

Hypothermia can be divided in accidental hypothermia and induced hypothermia. We already learned about the patient who was found in cardiac arrest with an initial body temperature of 13.8˚C, this is accidental hypothermia and must be avoided. Accidental hypothermia in trauma victims is part of a vicious triad that includes coagulopathy and acidosis as well and associated with increased mortality.

Induced hypothermia and TTM

Induced hypothermia means that a lower body temperature than normal is induced by means of external or internal devices, cold fluids, drugs or a combination of these tools. When hypothermia is induced as part of a medical intervention, it is referred to as induced or therapeutic hypothermia. A more commonly used terminology today is targeted or therapeutic temperature management (TTM).

There is overwhelming evidence from animal studies that TTM protects against ischemia-reperfusion injury. In humans, TTM is an established intervention in neonatal asphyxia and to some extent in adult cardiac arrest, while evidence is still lacking in stroke and acute myocardial infarction. Failed hypothermia trials in traumatic brain injury (TBI) has resulted in recommendations not to induce hypothermia in TBI patients, but most agree that fever should be avoided and TTM targeting normothermia is therefore recommended practice in TBI in many hospitals.

After out-of-hospital cardiac arrest followed by return of spontaneous circulation (ROSC) and admission to hospital, most patients are spontaneously hypothermic with temperatures in the 35-35.5˚C range, a condition called permissive hypothermia. In the old days, these patients were actively warmed using hot air and heavy blankets but this has fortunately stopped. Instead, we should consider this an opportunity and a potentially protective response and keep the patient at this low temperature or let him or her slowly drift towards 36˚C, at which temperature we should initiate active TTM with the help of a medical device. These devices come in different shapes and can deliver either external or internal heat exchange in order to keep the patient at a set temperature, commonly at 36˚C. In addition, comatose patients after cardiac arrest should always be sedated, preferably with short-acting sedatives and opiates. These drugs will also lower the shivering threshold by approximately 1˚C and facilitate care in the ICU during the first 24-36 vulnerable hours after cardiac arrest.

Which device should we use?

The principal difference among the TTM devices currently used today is whether one should choose an external cooling device applied to the body with circulating water and a feedback system, or an internal device inserted in a large vein allowing for intravascular heat exchange.

A third method is the intranasal cooling method developed by the Lund-based company, QuickCool AB, where thin balloons are applied in the nasopharynx through the nostrils. Cold water is allowed to circulate through the balloon catheters. This innovative solution cools the nasopharynx and the large vessels that pass nearby through heat exchange. The QuickCool® System is a novel and promising TTM device that is easy to use, portable and patient friendly.

All three methods should be combined with administration of sedative drugs and opioids to maximize comfort and to minimize stress during the intervention that typically lasts for 24-36 hours.

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Dr. Friberg is a Professor and Consultant in Anesthesia and Intensive Care Medicine at Skåne University Hospital in Malmö and Lund, Sweden. Dr. Friberg's PhD-work at the Laboratory for Experimental Brain Research at Lund University involved studies on brain ischemia in different rodent models and the role of the mitochondrial permeability transition pore in ischemic cell death. His current research is primarily centered on various aspects of post-resuscitation care, ranging from identification of cardiac arrest by medical dispatchers, quality of pre-hospital care and initial care and neuro-prognostication after admission to the ICU.

Additionally, he is responsible for SWECRIT, a biobank for critically ill patients in the Skåne Region.

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