Accidental hypothermia

A review on the underlying physiological and pathophysiological mechanisms and treatment of accidental hypothermia

5. årsoppgave – Med 3590
Medisinstudiet
University of Tromsø

Brage Håheim
Medisinstudent

Torkjel Tveita, MD, Ph.d
Supervisor

Tromsø, Norway

30th May, 2014

Abstract:

Accidental hypothermia is a rare condition with few deaths per year, but hypothermic patients have a 30% chance of dying. The past 15-20 years there has been an increased understanding of how hypothermia affects human physiology and may cause life-threatening conditions like arrhythmias, cardiovascular shock and pulmonary edema. New understanding of underlying mechanisms of hypothermia-induced complications have led to new clinical guidelines and improved survival rates the last 20-30 years. This review will briefly focus on the underlying physical and physiological mechanisms for maintaining temperature homeostasis. The main goal is to give a detailed look on how hypothermia affect human physiology and give a review of the research done on the underlying mechanisms of hypothermia and rewarming associated complications, with an emphasis on heart and cardiovascular complications.

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Introduction

Man is a tropical endothermic animal not naturally adapted to live in cold environments. The thermo-neutral zone for a naked man at rest lies between 27ºC and 31ºC and our optimal core temperature is 37ºC. Despite these limitations, we have conquered and settled in the most remote and cold places on the planet. In order to live and thrive in temperatures lower than 27ºC we have physiological mechanisms to produce heat and prevent heat loss. Our body saves heat by vasoconstriction and produce heat by increasing metabolism and muscle work. We have also developed (technical) equipment to help us keep warm and shelter us from nature.

Hypothermia occurs when our body fails to react with the proper physiological response, when our equipment fails to shelter us from the cold, or when the forces of nature exceed our body or equipment ability to hinder heat loss. In physiology and medicine hypothermia is defined as a deliberate or accidental drop in core temperature below 35ºC.

In my thesis description, I stated I would shed light on the clinical effect of hypothermia and the pathophysiological mechanism behind hypothermia/rewarming associated contractile dysfunction. I intended to base this on research done by my advisor Torkjel Tveita and his collaborators, including my own research.

The main aim of this thesis is to describe the pathophysiological effects hypothermia has on human physiology and how hypothermia-induced organ dysfunction cause clinical challenges when treating hypothermic patients. Focus will be on to what extent hypothermia alters cardiac function and the consequences this may have for cardiac physiology, and for choices of drugs or invasive techniques when treating hypothermic patients.

A secondary aim of this thesis is to look at hypothermia in a bigger picture than just physiological, pathophysiological and the clinical effects. The thesis will look at the physical mechanisms of how heat is transferred, how it is affected by climate and how

the body responds to cold. A final goal of this thesis is to describe the hypothermic patient.

Due to the narrative form this thesis will not be able to draw a scientific conclusion based on objective observations. The conclusion will try to sum up the thesis with some key points on where the field of hypothermia is today and point out what knowledge is needed in the future to further improve survival of hypothermic patients.

The paper will not focus on therapeutic hypothermia, but it is evident that many of the same physiological phenomena occur in both therapeutic and accidental hypothermia. Time will not be spent on explaining basic scientific principles and therefore the reader is expected to have a basic understanding of the classical scientific disciplines as well as an advanced understanding of medicine prior to reading this thesis.

Methods and work process

This thesis is a narrative based on information in papers and literature I have read as a part of my research the last four years. Much of the literature and publications originate from our laboratory at University of Tromsø.

All work was done independently. Torkjel Tveita did revision on the final version of the thesis before submission.

I have read the main body of supporting literature over a period of four years. I have worked with the experimental aspects of hypothermia research for some years and through this work collected most of the literature. Despite having read the literature on hypothermia before, I had to go through my library and re-read most of the articles to write this thesis. Since I choose to focus on the aspects of hypothermia outside my research, I had to explore and find literature on scientific fields of which I have no or little prior knowledge. I found it difficult to find and validate the strength of research in fields where I have little knowledge and my collection of literature has been collected in an unstructured manner.

I had hoped to spend less time on writing than I did, but I ended up spending a full 12 weeks on writing alone. I started out without a text disposition or a clear idea on what

the focus of the text should be. This resulted in several failed attempts and I ended up rewriting the thesis several times because of this. The final form of the thesis was chosen due to the natural progression from basic physiology, then pathophysiology, and ending up with clinical problems and treatment of hypothermia.

I chose not to focus on my own research as I intended when I wrote my project description. The reason for this decision was made when I started to explore other branches of hypothermia to include in my general discretion of hypothermia. My research has in a large degree revolved around cell signaling pathways in cardiac muscle, but hypothermia contains many interesting aspects worthy of understanding. When I started writing, I discovered aspects of hypothermia I did not know before, but found interesting. I realized I wanted to explore these aspects further to get broader understanding about hypothermia and to put hypothermia in a bigger picture with aspects like thermodynamics, thermoregulation, climate, and epidemiology.

Chapter 1:
Thermodynamics and climate

The human body strives to maintain homeostasis. Claud Bernard described the concept of homeostasis in 1865. Homeostasis comes from the Greek words "homoios" and "stasis" meaning "similar" and "standing still". The concept of physiological homeostasis describes the complete process in which the human body strives to maintain the optimal microenvironment for its cells and organs. The fight for homeostasis can be seen between the cells and the rest of the organ, the organ and the organism, and the organism against the external environment. Homeostasis is achieved by tightly regulating everything from blood pH, glucose or electrolytes to body temperature. The branch of biology called physiology tries to explain how all these regulatory systems work together to maintain homeostasis in response to change in environmental factors The next chapter will go in depth on how the body senses and responds to changes in environmental temperature in order to prevent heat-loss.

The human body has an extensive thermoregulatory system keeping us at an optimal core temperature. Thermoregulation is fundamentally based on the balance between thermogenesis and heat loss. A disturbance in this balance causes fever/heat shock on one side and hypothermia on the other. As describe above, if the hypothalamus senses an increase or decrease in body temperature, effector organs produce heat or increase heat loss, respectively(1).

This chapter aims to describe the factors determining the homeostasis of temperature. The first part will explain the physical phenomena of heat-transfer and how different climate will affect the body's ability to generate heat loss to the environment. The second and third part will focus on the how the body is able to sense temperature reduction and respond to maintain temperature homeostasis by thermogenesis or reduced heat loss.

Physics and thermodynamics

The relationship between heat production and heat transfer can be explained by the heat balance equation: $(M-W) - (R+C+E) = S$

Heat production or thermogenesis consists of metabolism (M) minus work done on the environment (W). Heat transfer consists of radiation (R), convection (C) and evaporation (E) together this sum up to net heat storage (S)(2). In the following chapter, I will explain in depth how the physical phenomenon transfers heat from or to our bodies. These physiological mechanisms are important to have knowledge about in order to understand how the thermoregulatory effector-organs work.

Conduction

Conduction is the process of heat-transfer directly from a place of high temperature to a place of lower temperature, without changing the material transferring the heat. Although heat transfer by conduction is mostly unimportant in normal physiological thermoregulation, immersion in water increase conductance by up to 4-fold. This will be discussed in more detail later.

Radiation

The transfer of heat by radiation is the release of electromagnetic waves in the infrared spectrum. The infrared waves are created when molecules randomly collide and emit photons. At higher temperatures increased rate of molecular collision increases photon emission and more heat is radiated to the environment. The environment also radiates heat upon us. The degree of radiation between the body and the environment can be described with a mathematical formula:

$$\underbrace{\frac{R}{\frac{kcal}{h}}} = \underbrace{\frac{h_{radiative}}{\frac{kcal}{h*°C*m^2}}} * \underbrace{\left(\bar{T}_{skin} - T_{radiant}\right)}_{°C} * \underbrace{A_{radiative}}_{m^2}$$

The rate and direction of heat radiation R is dependent on the radiative heat-transfer coefficient ($h_{radiative}$), the difference in temperature between the skin and the environment (T_{skin}-$T_{radiant}$) and on the area of the skin exposed to the environment ($A_{radiative}$)(2)

Convection and wind chill effect

Convection is the movement of heat by movement of a medium. The movement of warm blood from the core to the skin or the rise of heated air from the body are both examples of convection(2). Convection is mathematically expressed as:

$$C = h_{convective} * (\overline{T}_{skin} - T_{ambient}) * A_{convective}$$

$$\widehat{\frac{kcal}{h}} \qquad \widehat{\frac{kcal}{h * °C * m^2}} \qquad \widehat{°C} \qquad \widehat{m^2}$$

The rate and direction of heat convection I is dependent on the convection heat-transfer coefficient ($h_{convective}$), the difference in temperature between the skin and the environment (T_{skin}-$T_{ambient}$) and on the area of the skin exposed to the environment ($A_{convetive}$). Like radiative heat transfer, the rate of convection is dependent on the difference between skin and environmental temperature.

Convection can be classified as natural or forced(2). The rise of heated air is an example of natural convection. The removal by wind or a fan is an example of the latter. Forced convection is the explanation behind the wind chill effect. The rapid removal of the heated air increases convection and in a cold climate cools the body effectively(3). The wind chill effect can be described with the use of the wind chill index formula:

$$T_{wc} = 13.12 + 0.6215T_a - 11.37V^{+0.16} + 0.3965T_aV^{+0.16}$$.

This describes the relationship between the ambient temperature (T) and the wind speed in km/h (V). An example of this is if the air temperature is -10ºC and the wind speed 30km/h, the effective temperature experienced on the body will be -20ºC (4) .

Evaporation and heat index

Evaporation is the process of changing the physical form of a substance from liquid to gas. In physiology, this is usually limited to water evaporation. The process is energy consuming and evaporation alone can remove all excess heat produced during exercise. The energy removal during evaporation equals 58 kcal per 1g of water. The sweat glands can secrete 30g fluid /min or 1800g/hr. Evaporation can thus remove 1000 kcal/h or 1,1kW from the body. This is a power drainage equivalent to that of a small electrical heater. Evaporation is the only heat exchange process dependent on the environment water vapor pressure rather than the environment ambient temperature(2):

$$E = h_{evaporative} * \left(\overline{P}_{skin} - P_{ambient}\right) * A_{evaporative}$$

$$\widehat{\frac{kcal}{h}} \qquad \widehat{\frac{kcal}{h*°C*m^2}} \qquad \widehat{mmHg} \qquad \widehat{m^2}$$

Since the rate of evaporation (E) is dependent on the gradient between skin humidity (P_{skin}) and ambient environment humidity ($P_{ambient}$) the rate of evaporative heat loss is maintained even at high ambient temperatures. In humid environments, evaporative heat loss is reduced and heat storage increased. This effect is called heat index and can mathematically be expressed as:

$$HI = -42.37 + 2.04T + 10.14R - 0.22TR - 6.83x10^{-3}T^2$$
$$-5.48x10^{-2}R^2 + 1.22x10^{-3}T^2R + 8.52x10^{-4}TR^2 - 1.99x10^{-6}T^2R^2$$

This equation is a result of regression analysis and shows the effect of temperature (T) and relative humidity I on heat index(5).

An example of heat index is the effect of throwing water on a hot sauna oven and feel how fast the air gets scolding hot. This is due to two factors: The first is due to our reduction in evaporation and reduction in heat loss due to increased air humidity. Secondly, humid air has a greater ability to store heat than dry air and makes it warmer.

Heat index can also have the opposite effect. Due to the high heat capacity of humid air, cold humid air will absorb heat at a higher rate from the body. This is the explanation of why the relative temperature is colder when the humidity is high.

Heat storage

Our body strives to keep its core at a constant temperature. The result of the processes described above is heat loss or heat storage. With the knowledge of thermogenesis (M-W) and heat loss (R+C+E) we can calculate the net gain or loss in body temperature at different conditions. Since the specific heat of body tissue (0.83) is a constant and body weight (BW) normally spans from 50-150kg in the adult human being it's the relationship between thermogenesis and heat loss that determine the net heat storage.

$$\frac{\frac{\Delta \overline{T}_{body}}{\Delta t}}{\frac{\widehat{°C}}{h}} = \frac{\frac{(M-W)-(R+C+E)}{0.83 * \text{ BW}}}{\frac{kcal/h}{[kcal/(kg°C]x \text{ kg}}}$$

If we study the formula more closely we notice that both hypothermia and hyperthermia can occur by an internal (M-W), external (R+C+E) heat load, or heat loss, or a combination of the two.(2).

Internal heat load is created by increased heat production metabolism and work. Overheating occur when metabolism and heat production from work excides the body's capacity to dissipate heat. This occurs in cases of severe fever or in overheating during exercise. Internal heat loss occurs when the body can´t increase its metabolism and thermogenesis to meet the requirements to maintain core temperature, even in environmental temperatures within the thermoneutral zone. This internal cause of heat loss is the basis of chronic hypothermia often witnessed in elderly and the chronically ill.

External heat load or loss is determined by how the environmental factors change radiation, convection and evaporation. If these factors exceed the body's ability compensate it is at risk of overheating or becoming hypothermic.

Effects of climate on heat transfer
The following scenarios illustrate how changes in weather and climate affect how heat is transferred from the body to the environment.

Winter in Tromsø, Norway: The cold and humid environment
In Tromsø, Norway, the combination of humid and cold climate is common during winter. Its climate is classified as subarctic by the Köppen climate classification. The mild winters with more precipitation are atypical compared to the classic subarctic climate description. The coastal climate prevents the temperatures to drop far below -5°C during winter and the average temperature in December is -0, 7°C with a daily average precipitation of 15,1mm. At 69° north Tromsø experience polar night from

November 27th to January 15th and the sun never sees the horizon. The coast of northern Norway is exposed to harsh winds from the Norwegian and Barents Seas. The city of Tromsø is naturally protected from these winds by mountains, but still has an average wind speed of 3,9 m/s in December.

Radiation

Because of ambient temperatures below freezing and no sunlight in the winter, the radiative heat load from the environment to the body is negative. The body thus loses heat by radiation.

Convection

Due to windy conditions all year around and the severe winter storms caused by the polar low pressures, the wind chill effect is important in northern Norway.

Evaporation

When the ambient temperature is low, the thermoregulatory system shuts down sweat production and secretion. However, in the case of a cold environment with high air humidity, the humidified water molecules easily condensates in contact with our skin. The water evaporates on the skin causing us to feel cold.

Winter in Verkhoyansk, Russia: The cold and dry environment
The coldest place on earth with a year around population is Verkhoyansk in the republic of Yakutia in eastern Russia. Verkhoyansk, like Tromsø, is in the subarctic climate category. Unlike Tromsø, Verkhoyansk is inland and dominated by year around high air pressure. These high pressures give a stable climate with very little precipitation and wind. The average precipitation during winter months is only 6 mm per month and the temperatures in January averages -47ºC.

Radiation

In these temperatures, the difference between body temperature and the environment is great. Radiative heat loss from the body to the environment is large.

Evaporation

Since there is no air humidity and heat index factor is absent, there is no condensation of air humidity on the skin and due to the low temperatures, there is no sweat contributing to heat loss.

Convection

Due a stable high pressure, there is little forced convection by wind, but the natural conductance still continues. Warmed air around the body rises and is replaced by cold air, contributing to convection.

Immersion in water

A common way to suffer accidental hypothermia is by immersion in water. During immersion, heat transfer by radiation and evaporation is reduced to almost zero. On the other hand, conduction is increased by 400%. Convection also increases if the water is moving. Heat loss is still dependent on the difference in temperature of the body and the water. The heat capacity of water is 70% higher than air, which increase the rate of heat transfer. All of these factors make immersing humans in cold water an effective measure of cooling and hypothermia occur rapidly(2).

Chapter2:
Thermoception, thermoregulation and thermogenesis

The last chapter focused on the fundamental thermodynamic phenomena the body has to relate to when regulating its temperature. Humans have evolved an elaborate system of thermoreceptors and effector organs to regulate its temperature. This enables us to sense temperature and the possibility of heat production, all controlled by the hypothalamus. The next chapter will focus on the molecular and physiological fundament on how the body defends itself against hypothermia by thermosensation and thermogenesis.

Thermosensitive molecules and thermoreceptive neurons

Thermoreceptors are found through out the body, but are mainly divided in peripheral and central receptors. This next section focuses on the difference between the peripheral and the central thermoreceptors and how they relay in the central nervous system.

Peripheral thermoreceptors

The peripheral thermoreceptors in the skin consist mostly of cold receptors and to some degree warmth receptors.

Signals from peripheral thermoreceptors are carried by both fast, myelinated, Aδ-fibers and slow, unmyelinated, C-fibers. Cold receptors carry signals by Aδ-fibers and signals from the warmth receptors are carried by slow C-fibers. Slow C-fibers, and sometimes also fast Aδ-fibers, carry nociceptive and pain signals from both warmth and cold receptors(6).

These fibers enter the spinal cord and synapses with interneurons on lamina I, II and V in the dorsal horn of the gray matter in the spinal cord. Then they cross the spinal cord at the same level as they enter and bundle together in the spinothalamic and the spinoreticulo-hypothalamic tracts (6) . Neurons carrying temperature signals can end up in two main areas of the brain: the insular cortex or hypothalamus.

Insular cortex

Signals ending up in the insular cortex are important in giving us a sensation of skin and visceral temperatures, and to discriminate and localized changes in temperatures. Before terminating in the insular cortex the signals follow the spinothalamic tract uninterrupted to the thalamus where it relays once in the posterior lateral area. A second pathway is possible with a double relay in the parabrachial nucleus in the brainstem and ventromedial nucleus of the thalamus.

Hypothalamus

The signals ending up in the hypothalamus are important in the homeostatic control of temperature. These signals follow the spinoreticulo-hypothalamic tract and end relay and integrate with dendrites of warmth-sensitive central thermoreceptors in the periventricular striatum and medial forebrain bundle before terminating in the preoptic anterior part of the hypothalamus(1,7).

Central thermoreceptors

In addition to the peripheral thermoreceptors the hypothalamus has its own thermosensitive neurons. The central thermoreceptors, unlike the peripheral thermoreceptors, consist almost solely of warmth sensitive neurons. These neurons have their soma in the preoptic anterior part of the hypothalamus and project their dendrites horizontally with one pole in the periventricular space by the third ventricle, and the second pole in the midbrain bundle. This orientation allows temperature to be monitored both close to the surface and in the viscera. When the cold sensitive neurons enter the hypothalamus they relay with these warmth sensitive neurons. The sum of these signals is interpreted by the hypothalamus as the body temperature. This makes determining a true core temperature difficult. Since the hypothalamus use signals from the whole body to determine body temperature, different parts of the body can have large variation in temperature. If the hypothalamus registers a discrepancy between the peripheral and the central temperature, or if the core temperature deviates from set point, relevant thermoregulating action are initiated(1,7).

The transient receptor potential superfamily (TRP)

The molecular background to understand how thermosensitive neurons work can be understood by looking at their use of the transient receptor potential family of proteins

(TRP). The TRP can be found in all thermosensitive neurons and the different subtypes of TRP determine the neurons sensitivity to different temperatures.

These proteins are mixed, inward, cationic ion channels responding to changes in temperature. In cold receptors the influx of cations is increased inversely with lowered temperatures depolarizing the membrane at a higher frequency as temperature falls.(8) The TRP-channels have two important functions; the first is to detect changes in ambient environment and core body temperature. This information is important to make the correct physiological response in order to maintain homeostasis. The second function is to detect when the changes in ambient or body temperature reaches dangerously high or low levels. Some of the TPRs are able to change their signals from being evoked by cold or warm temperatures to pain or nociceptive stimuli (2).

The most common TRP ion channel in cold receptors is TRP ankyrin 1 (TRPA1) and TRP melastatin 8 (TRPM8). The TRPM8 ion channel is also activated by menthol. This is why eating menthol or rubbing it on your skin gives a sensation of cold. The activity of TRPM8 follows a bell shape curve with low frequencies at temperatures above 40°C and below 17°C and a maximal firing rate at temperatures between 20-30° C. Below 17°C the TRPA1-channel takes over cold signaling. This channel is not activated by menthol like the TRPM8, but is important in signaling nociceptive cold signals(7,8).

Warmth-receptors are associated with other proteins in the TRP-family. Examples of these are TRPM2, 4, 5 and TRPV1-4. TRPV binds vaniloids. One of the chemical structures binding to this receptor is capsicin, the chemical making chili peppers hot, burning and painful. The warmth-receptors communicate the heat signal in the same manner as the cold receptors. The TPR-proteins open unspecific cation channels in response to increased temperature, depolarizing the neuron. The different heat sensitive TRP-channels react to temperature in a graded manner. The TRPM4/M5 signal heat between 15°C -30°C, TRPV4: 28°C -40°C, TRPV3: 32°C -42°C, TRPV1: 41°C -55°C and TRPV2: >50°C Warmth-receptors also acts as receptors for nociceptive signals. Nociception is signaled by TRPV1 and TRPV2(7,8).

Energy expenditure, thermogenesis and physiological and behavioral reduction of heat loss

When the hypothalamus detects a reduction in ambient or core temperature, it triggers thermogenesis and heat saving mechanisms. Thermogenesis is an energy demanding process where chemical energy is utilized to release heat. This section will explore how the body utilizes different mechanisms to either produce heat or reduce heat loss.

Energy expenditure can be divided in three main groups: obligatory energy expenditure, expenditure from physical activity and adaptive thermogenesis(9).

Obligatory energy expenditure:

Obligatory energy expenditure is the required energy to maintain normal cellular function in a resting human, not performing work in a thermo-neutral environment. This is the standard metabolic rate (SMR). The SMR can change depending on degree of body stress and strain. During starvation the SMR is reduced by up to 40%, and by 10% during sleep(9).

Physical activity:

Expenditure from physical activity is the energy spent physically manipulating the surroundings. These processes all produce heat as a byproduct and contribute to thermogenesis. An athlete at VO_{2max} spend 1300 kcal/h, out of this 70-85% is transformed to heat [ref]. 300kcal is used as work on the environment, for instance running or moving a heavy object. This is the heat we need to get rid off when we go for a run or do heavy work.

Adaptive thermogenesis:

The two groups mentioned above are functional groups where the end goal is cellular function and performance of work on the environment. Due to the nature of biochemical processes heat is produced as a byproduct. The adaptive thermogenic group only contributes to thermogenesis, but with as little effect on the environment as possible. The main effectors to produce heat are shivering, brown adipose tissue and diet-induced thermogenesis.

Shivering

Shivering is controlled by its own primary motor center. This lies in the dorso-medial area of the hypothalamus, close to the third ventricle. It is inhibited by neurons from the pre-optic cortex. This area is excited by cold signals from the peripheral thermoreceptors. (10) . According to Horvath et al shivering starts when the skin temperature reaches 29°C, and general shivering starts at a skin temperature of 27,1°C. Shivering creates heat by exciting both a muscle and its opposing antagonist. The creation of force causes heat to be produced by increased metabolic activity and ATP production. Shivering can increase global oxygen consumption 5-fold (11) , but is not nearly as effective in producing heat as physical activity.

Diet-induced thermogenesis

Diet-induced thermogenesis is a natural phenomenon occurring when digesting food. It is the result of the metabolic reactions taking place when digesting nutrients. Its is defined, according to Westerterp: "the increase in energy expenditure above fasting level divided by the energy content of the food ingested and is commonly expressed as a percentage"(12).

Brown adipose tissue

Although brown adipose tissue is almost non-existent in the adult human, it has been discovered by several investigators and is believed to take a small part in thermoregulation(13). It is important in thermogenesis in newborn and some animals. Brown adipose tissue is tangled in sympathetic nerve fibers. During a cold response, these fibers trigger the brown adipose tissue, via noradrenaline to trigger Uncoupling protein-1. This protein works in the mitochondria by allowing H^+ to leak across the mitochondrial matrix. This results in lack of ATP production and increased metabolic action through glycolysis and Krebs cycle aimed at producing heat only(9).

Behavioral changes and clothing

As explained earlier, some of the temperature signals reach our consciousness and gives us a sensation of cold or warmth. Based on these signals we make behavioral changes. The precise manner of how these signals are transferred and interpreted is not known(1). Since our physiological mechanisms can't prevent heat loss outside of

the thermoneutral zone for an extended period of time, we have to take action. These changes vary from putting on clothes, lighting a fire or increase non-shivering thermogenetic activity.

Clothing helps us prevent heat loss by protecting the body from wind and rain, reducing convective, evaporative and radiative heat loss. The most important effect of clothing is creating an air-filled space between the skin and the garment. This air pocket works as a buffer against the cold and prevent convective and radiative heat transfer(14).

Physiological changes

Physiological heat preservation is triggered as the hypothalamus registers a fall in skin or core temperature. This is mediated through sympathetic nerves and causes peripheral vasoconstriction, reduced sweating and contraction of smooth muscle in hair on the skin giving us goose bumps(2). These are all measurements aimed at reducing the effect of radiation, evaporation and convection rather than increasing temperature. Vasoconstriction reduces convection of heat from the core to the skin surface. Radiation from the skin to the environment is lowered as peripheral blood flow is reduced. This peripheral vasoconstriction also aims to secure body temperature to the core organs like the brain and heart. The erection of dermal hare helps isolate the skin by trapping air between the skin hair and reducing radiation and convection.

Summary

The last two chapters have shown how thermodynamics move heat from the body and how the body responds by manipulating thermodynamics or by thermogenesis. The sum of these processes is one's body temperature. Hypothermia can develop through both external and internal causes. External hypothermia is caused by an overwhelming heat loss by extreme external factors and often occur to younger people having a skiing accident, falling asleep drunk outside or fishermen falling into the sea. Thermoregulation consequently tries to improve thermogenesis and stop heat loss, but fails. Internal hypothermia happens when the body cannot maintain homeostasis at "normal" temperatures, and occur mostly in chronically ill patients and elderly people

Chapter 3
Epidemiology of hypothermia

Mortality data from the Center for Disease Control in the USA show that hypothermia was a low mortality in the population(15). With a death rate of only 0.30/100 000 per year hypothermia mortality is low compared to large killers like cancer or cardiovascular disease with an annual death rate of 184/100 000 and 191/100 000 (16,17).

Studies from the 1970s show an estimated lethality from hypothermia of 30-80%(18). Lately, studies show that total lethality has fallen to around 30%(19). Hypothermic patients are a heterogenic population and total lethality rate is a poor measure for the complexity surrounding chance of survival. The next chapter will focus on the heterogeneity among hypothermic patients and what defines the different groups of patients.

The hypothermic patient

Roeggla et al found in their data of 80 hypothermic patients in Vienna between 1991 and 1998 that the mean age of patients of was 55 years of age. 52% of patients were male, 14% were homeless and 35% were found indoors . This is consonant with the findings of Megarbane et al in their data of 81 hypothermic patients. The mean age was 65 years of age, 50% were male, and 79% were found indoors . The total mortality of the hypothermic patients in data of Roeggla et al was 34%, versus 35% mortality in Megarbane et al. Van der Ploeg et al found the same among 84 hypothermic patients in Amsterdam, Netherlands. In their data 84% is male with a mean age of 47 years of age. 22% was found indoors(20). The total mortality rate is similar to that of Roeggla and Megarbane with 28%.

Taylor et al found, based on autopsy data from 63 hypothermia deaths in Alabama, USA, occurring between 1983 – 1999, that death by hypothermia falls within two main groups; the old and comorbid and the young intoxicated(21).

The old and comorbid found indoor versus the young intoxicated found outdoors

The three studies mentioned above show that 22% - 35% of hypothermic patients are found indoors. According to Roeggla et al the mean age of the patients found indoors was 69 years versus 50 years in those found outdoors. Also Megarbanes et al found similar numbers with a mean age of 67 years in those patients found indoors and 42 years in those found outdoors. They found that the patients found indoors had a significantly higher rate of associated illnesses. 19% were alcohol or drug intoxicated 30% had septicemia, 27% had neuropsychiatric disorders, 13% had hypothyroidism/hypoglycemia, 5% had cardiac arrhythmias, and 6% had other unspecified pathological states. In the victims found outdoors, the associated illnesses were significantly different. 76% of the patients had alcohol or drug intoxication, 6% had septicemia, 12% had neuropsychiatric disorders and 6% had hypothyroidism/hypoglycemia. The mortality in the indoors group is significantly higher than the patients found outdoor(22). Megarbanes et al. found a mortality rate of 44% in the indoor versus 6% in the outdoors group(22). Roeggla et al showed a mortality of 81% in the indoors group against 11% in the outdoors group(19).

The discrepancy in mortality between the outdoors and indoors group has been written off due to the large numbers of comorbidity and the high age among the patients found indoors(19,22). Elderly patients have altered responses to changes in temperature. They have a lower tendency to induce thermoprotective measures, to prevent heat loss, and to start thermogenesis(23). This predisposes the elderly to chronic hypothermia. The elderly have a higher rate of comorbidity, which predispose them to hypothermia and to complications during rewarming.

In patients found outdoors, evidence of alcohol or drug intoxication was found in 76% of them. An explanation of the lower mortality might be the protective effect on alcohol on cardiac function during hypothermia , but studies have not shown a correlation between blood alcohol level and improved survival in hypothermia patients

Trauma patients

Hypothermia is common among trauma patients and it is found to be an independent risk factor for death in trauma patients (24,25) . Wang et al found that 9,7% of their hypothermia patients had an additional trauma and not solely du to environmental

exposure(26). In the study by Van der Ploeg et al 47% of the hypothermia diagnoses were associated with trauma(20). Trauma patients are prone to hypothermia, these patients often suffer from conditions that impair their ability to reduce heat loss and produce heat by shivering or activity. Unconsciousness, hemorrhage, hypoxia and hypo-perfusion are all important factors predisposing trauma patients to hypothermia (27) . Wang et al found that the group of trauma patients with highest percentage of hypothermia was the second most traumatized group with a injury severity score between 3,5-4(26). Martin et. al found that among all of trauma patients in the US National Trauma Data Bank between 1993 – 200,5 1,9% where hypothermic. Mortality rate of hypothermic patients was 25% versus 3% in the patients with a core temperature >35ºC(28). Wang et al showed a linear relationship between degree of hypothermia and mortality in traumatic patients, with 100% mortality at core temperature <32ºC (26) . In Melbourne, Australia, Ireland et al found that 13,25% of 737 trauma patients were hypothermic upon hospital admission. A mortality of 29,9% was found in these patients versus 5,98% in non-hypothermic patients(25). In addition to having higher mortality, trauma patients stay longer in hospital and have a lower chance of being discharged to their home(25).

Summary

The data presented show that the lethality of hypothermia depended on other factors than just body temperatures. The victims of hypothermia are a heterogeneous group and survival rate is dependent on cohort. Age, comorbidity and associated traumatic accidents are all important factors when determining the severity of a hypothermic patient.

Few studies have looked at the interplay between factors like age, comorbidities, intoxication, and hypothermia. Thus, there is little knowledge about how the underlying mechanisms of hypothermia interact with the mechanisms of additional conditions.

This body of epidemiological data shows the importance of temperature measurement and prophylactic treatment against hypothermia in traumatized patients. Preventing hypothermia in the traumatic patient is key to improving survival rates and rehabilitation of these patients (24) .

Chapter 4:
The physiological effects of hypothermia

Human physiology is affected by hypothermia in a graded manner(29). Earlier clinical descriptions of grades hypothermia were based on its effect on human physiology with an emphasis on neurological symptoms and level of consciousness, and not on the clinical significance and complications of hypothermia(30). This chapter will focus on how human physiology is affected by hypothermia. The first part will elaborate on how hypothermia is defined and how it is graded. The remaining parts of this chapter will focus on how hypothermia affect individual organ systems and how this gives rise to clinical complications.

Grading of hypothermia

The grading system by Popovic from 1974 defines hypothermia as a core temperature below 35°C, and the international community across scientific branches still agrees on this definition of hypothermia(30,31). Although there is an international consensus about the definition of hypothermia there is still discrepancy on grading. Popovic divided hypothermia in mild (35°C- 32°C), moderate (32°C-22°C), deep (22°C- 8°C) and profound (< 8°C). Later Danzel, in 1994, divided hypothermia in mild (35°C - 32°C), moderate (32°C - 28°C), severe (28°C - 20°C), and profound (< 20°C)(32). This scaling is used in the European Resuscitation Council's guidelines for treating hypothermic patients. In 2009 Polderman and Herold proposed a more simplified scaling (33) . Mild hypothermia between 35°C - 34°C, moderate 34°C - 30°C, and severe < 30°C. This is the grading used by the American Heart Association and in the new University Hospital of Northern-Norway 2014 guidelines for treating accidental hypothermia (34,35). Poldermans grading is used because 30°C is acknowledged of as an important temperature in the clinical setting by grading anything below 30°C as severe. Rather than using Poldermans more clinical relevant grading system, I will use Danzels grading from 1994 when explaining the effects of hypothermia on the human physiology. The main difference between these to systems is that rather than focusing on the clinical aspects emphasizing 30°C as a critical temperature, Danzel is focusing on the physiological effects of hypothermia at different temperature intervals all the way down to and below 20°C.

Cellular changes

Hypothermia is unphysiological and damaging state and the body takes measures to protect itself from hypothermia. Hypothermia affects our cells with respect to cellular structure, ion handling and metabolism(36). Prolonged hypothermia damages cellular cytoskeletal and membrane integrity(37). The mechanism behind this is unknown, but change in the reactive oxygen species (ROS) balance and increased ROS production is believed to be important(36). An increase in ROS production is known to damage cellular structures(38)

Ion handling is affected by the reduced enzymatic Na^+/K^+-ATPase activity. This result in increased intracellular $[Na^+]$. Some investigators advocate other underlying mechanisms to explain the increased $[Na^+]_i$.. Boutilier ascribes it to increased H^+/Na^+-antiporter activity (36). Regardless of the underlying cause of increased $[Na^+]_i$, this is an important pathophysiological phenomenon leading to cytosolic calcium overload(36) and further cellular dysfunction.

Reduced enzymatic activity in glycolysis, Krebs cycle and oxidative phosphorylation during hypothermia impair cellular metabolism (39). Although different cell types differ in how they metabolically react to hypothermia, the general rule is that metabolism is reduced with 6% per 1ºC. At 28ºC metabolism is reduced 70-80%(29).

Cardiovascular system

The initial response by the body to hypothermia is a sympathetic drive causing tachycardia, peripheral vasoconstriction and increased cardiac contractility, resulting in increased cardiac output and oxygen consumption(14,40,41).

When temperature is lowered further bradycardia sets in, cardiac output and blood pressure are both reduced. At 28ºC heart rate is reduced by 50%, this severe bradycardia is due to reduced sympathetic activity by the autonomic nervous system(14). This in combination with reduced contractile function will significantly impair cardiac output. The molecular basis for this has been proposed to be decreased ATP production and reduced myofilament calcium sensitivity(42-44). When the sympathetic activity is reduced at <28ºC the vascular tone goes down. Due to the reduction in cardiac output the body depends on compensatory vasoconstriction to

maintain perfusion pressure. Reduction in vascular tone prevents this compensation and causes peripheral vasodilatation and a reduction in perfusion and blood pressure.

The electrophysiological changes due to hypothermia are clinically important and give rise to arrhythmias and, finally, asystole. At the onset of hypothermia there is little change in electrophysiology, but as the heart is cooled to 31ºC the conduction velocity of the heart is reduced as well as the repolarization, but the activation speed of the ventricle remains unchanged(45). This is reflected on an ECG as a prolongation of the PR-interval, the QT-time and a broadening of the QRS complex(41). In addition, reduced repolarization can be seen as a "J" or "Osborne" wave on an ECG, but has little clinical significance(46). The cellular basis for the reduced conduction and repolarization speed is not yet fully understood. Reduced enzymatic activity and the lower production of ATP, due to hypothermia might be an underlying mechanism. This would slow the Na^+/K^+-ATPase and hinder repolarization. Hypothermia also reduces the opening and closing of sodium channels, which slows the conduction of the Purkinje fibers(47).

The fibrillation threshold is lowest at around 30ºC. The mechanism behind this increased susceptibility to arrhythmias, and why it is greatest around 30ºC, is not yet fully understood(45). Reduced conduction speed in the ventricles versus the atrium, due to the slow nature of Purkinje fibers, might trigger a desynchronization between the atrium and the ventricles. The slowed repolarization in combination in with normal ventricular activation time at 31ºC might cause early after-depolarizations. These can trigger torsades de pointes, ventricular tachycardia or fibrillation (48) . Interestingly, at 17ºC conduction velocity, repolarization and ventricular activation time are all decreased and the fibrillation threshold is increased to normothermic levels. This suggests that the cause of the pro-arrhythmic state seen at 31ºC lies in the mismatch between repolarization, conduction velocity and activation time (45).

Respiratory system
The sympathetic drive at onset of hypothermia manifest itself initially as tachypnea, bronchial dilation, increased minute volume, and hyperventilation. As hypothermia progresses the respiratory center in the brain is depressed. At 34ºC sensitivity to CO_2 is reduced and, in combination with reduced CO_2 production, impairs spontaneous

respiration. The peripheral oxygen sensitive receptors in the aortic arch are still functioning at low temperatures. This ensures a working hypoxic respiratory drive which help stimulate the respiratory center and maintain spontaneous respiration. Around 25ºC spontaneous respiration eventually stops and apnea occurs(14).

At moderate hypothermia the ciliary function in the airways are impaired, predisposing to aspiration and pneumonia. When cold narcosis occurs at 30ºC, the protective airway reflexes become inoperative. This leaves the airways defenseless against aspiration and airway collapse(14,29,41).

There is little change in gas exchange during hypothermia, but there is an increase in anatomical and physiological dead space due to bronchial dilation.(49). These changes are small and not considered to contribute as a complication factor. Pulmonary edema has been reported, but is uncommon(41).

Acid-base balance

Hypothermia is associated with an acidotic state(50). The mechanism underlying the acid-base disturbances is bipartite, both respiratory and metabolic(51). With respect to the respiratory mechanism, hypothermia affects the chemical properties of CO_2.A decrease in temperature increases the solubility of CO_2. This shifts the chemical equilibrium between $CO_2 + H_2O$ and $HCO_3^- + H^+$ towards the right, producing more H^+. The limitation of H^+ production is the rate of dissociation of $CO_2 + H_2O$. Reduced temperatures lower dissociation rates, but this effect is not strong enough to hinder H^+ being formed. The net result of these changes is a decrease in pH.

The physiological result of severe hypothermia is respiratory depression with reduction in alveolar ventilation. This causes CO_2 to be retained increasing H^+ production(14,51).

The metabolic component is the result of lactate production from shivering and lowered tissue perfusion and reduction in liver enzyme conversion of lactate(51).

Endocrine system

The endocrine system reacts to immediate hypothermia by increasing metabolism and thermogenesis. The endocrine effector organs release thyroid hormones, cortisol, glucagon and catecholamines. This increases blood glucose, free fatty acids, inhibits insulin production and peripheral insulin responsiveness resulting in initial hyperglycemia(52). During prolonged and deeper hypothermia <28C the endocriological effector organs stop working. Shivering use glucose and during cooling this glucose is consumed, this in combination with impaired gluconeogenesis by the liver cause hypoglycemia. This can be observed after only a brief period of hypothermia(11,41). Since the blood glucose is not only dependent on gluconeogenesis and insulin production, but also on the metabolic rate of the patient, the rate of shivering and physical activity is important in determining how fast glucose is spent. Although most patients are hypoglycemic, clinical data show large differences between patients in blood glucose and insulin levels(14,41).

Cortisol, thyroid hormones and catecholamines levels are often unchanged and within the normal range during prolonged hypothermia, and may even be increased during rewarming(53). An explanation might due to a reduction in hormone release and, at the same time, an increase in hormonal half-time due to slowed drug and hormone metabolism during hypothermia.

Renal system
A major complication of hypothermia is cold-diuresis. It is one of the first clinical signs of moderate hypothermia and can increase urinary output 3-4 folds. The mechanism behind the increased renal output is still debated. The two main theories are hypervolemia and hyperosmolality. The hypervolemia theory claims that due to peripheral vasoconstriction there is a relative increase in blood pressure, which is detected by the renal and central autoregulation. The production of anti-diuretic hormone (ADH) from the pituitary is reduced and less water is reabsorbed in the renal collecting ducts(41,54).

The metabolic rate of the kidney is very susceptible to temperature. At <20C the metabolic rate is close to zero. The reduction in metabolism and subsequent oxygen consumption lowers enzymatic rate, hindering renal reabsorption of electrolytes. The

osmolality theory claims that the reduced metabolic rate in the kidney reduces reabsorption of the ultrafiltration. This results in osmolal diuresis. (41) .

The impaired renal metabolism contributes to the metabolic acidosis by reducing both HCO_3^- production and H^+ excretion.

Kidney failure is seen in 40% of hypothermic patients. The underlying mechanism has been attributed to prerenal causes, primarily due to hypothermia-induced hypoperfusion during rewarming. The kidneys are protected from hypoxia during hypothermia, but during rewarming there is a miss-match between oxygen consumption and demand causing acute tubular necrosis(41,55)

Hematology and coagulation

Hypothermia affects hematology in two important matters: The first is increased viscosity and hemoglobin concentration. Due to increased capillary leakage and cold-diuresis there is a loss of plasma volume, thus increased hematocrit(56). The hematocrit is increased with 2% for every 1ºC decline in body temperature. At temperatures in the severe range, the hematocrit can reach numbers as high as 50%(14,41).

Coagulation is affected by hypothermia. The coagulopathy caused by hypothermia is a feared complication and one of the reasons that hypothermic trauma patients have such high mortality compared to normothermic patients(27). Hypothermia affects coagulation by altering platelet aggregation and adhesion, but not platelet activation time. Platelet function is reduced by 33% at 33ºC, and do not worsen upon further cooling. How hypothermia cause decreased platelet aggregation and adhesion but not reduce the activation of platelet is not fully understood. Reduced thromboxane A2 synthesis have been proposed as one possible mechanism(57). Hypothermia can also induce thrombocytopenia due to platelet sequestration in the liver and spleen, as well as impaired hematopoiesis due to bone marrow suppression.

Moderate hypothermia do not significantly increase aPTT or INR(57). Studies have shown reduced enzymatic activity of individual coagulation factors at in moderate hypothermia. Despite the reduced enzymatic activity there is only a minor reduction

in aPTT and INR. At temperatures below 33ºC both aPTT and INR are significantly reduced and continues to increase down to 25ºC(57).

The clinical consequence of alternation of hematology and reduced coagulation activity during hypothermia is grave and feared(27). The reduced platelet activation and increased aPTT and INR make hemostasis in hypothermic a major difficult when treating bleeding hypothermic patients.

Summary

The previous chapter covered the effects of hypothermia on the major organ systems. The introduction advocated grading hypothermia with the scale used by Danzl, as this focus on the pure physiological phenomena occurring during hypothermia, focusing less on the clinical significance of the changes.

In the clinical setting, this grading is too complex and a less complicated one is needed. The acknowledgement of 30ºC as clinically important by Polderman and in new guidelines is based on the pathophysiological changes explained in this chapter. It seems that the physiological compensatory mechanisms are able to answer to changes caused by mild hypothermia. At around 30ºC these mechanisms are unable to maintain homeostasis and make way for life-threatening complications: loss of consciousness, the cardiovascular system fail to provide sufficient perfusion pressure, our endocrine system fails to maintain glucose and electrolyte balance, blood coagulation fails and our respiratory system and renal system cannot manage the excess H^+ resulting in acidosis.

Chapter 5:
Hypothermia-associated contractile dysfunction - "rewarming shock"

Rewarming from hypothermia is associated with several severe complications. Our research group at the University of Tromsø has since the early 1990s studied effects and pathophysiologic mechanisms of hypothermia-associated contractile dysfunction or "rewarming shock". Napoleon's army's chief surgeon, Moricheau-Beaupré, first described symptoms of rewarming shock in 1812. He described those patients who were rewarmed from severe hypothermia to suffer a vascular collapse with low blood pressure and hypoperfusion just prior to reaching 37ºC. Despite being described as early as 1812, little light has been shed on the underlying mechanism or treatment of "rewarming shock". Rewarming shock is an important complication when rewarming patients and one of the factors responsible for the high mortality(58).

Tveita et al conducted several experiments in the early and mid-1990s to describe rewarming shock and its effects on the heart and on global cardiovascular physiology. The next chapter will elaborate on this

Cardiac contractile function

Rewarming from hypothermia is associated with depressed cardiac contractile function. In vivo rat studies showed a reduction in cardiac output (CO) and stroke volume (SV) of 50% when rewarmed after 4 hours of hypothermia at 15ºC. Arterial pressure after rewarming remained unchanged, but total peripheral resistance was increased by 50%(59). Another rat experiments, aimed to look at blood composition and distribution after rewarming, showed a slight reduction in plasma volume, but not a significant change in blood volume. The plasma colloid pressure was also increased, indicating fluid loss. The distribution was significantly reduced in all tissues after rewarming(56).

Cardiac depression was also found in dogs after rewarming. 8 dogs where cooled, from 37ºC to 25ºC, and then rewarmed to 37ºC. This resulted in a reduction in mean aortic pressure (MAP), stroke work (SW) and preload-recruitable stroke work (PRSW) after rewarming, indicating hypothermia-induced cardiac dysfunction. Diastolic function was measured with the isovolumetric relaxation constant (τ), and

showed no difference after rewarming compared to baseline, indicating a preserved diastolic function(60).

Metabolism and ATP production

As explained earlier, hypothermia is known to reduce metabolism in eukaryote cells. The reduction in metabolism is improved upon rewarming, but Tveita et al showed a continued reduction in ATP production in cardiac cells upon rewarming(43).

A common cause to reduced ATP production is hypoxia, as it leads to ATP production from lactic acid, which yields less ATP. Kondratiev et al investigated oxygen delivery in tissue during hypothermia and rewarming. They found that oxygen was not a limiting factor when rewarming rats after prolonged hypothermia, with regard to cardiac function(61)

Change in metabolic substrate from fatty acids to glucose will also reduce ATP production per mole of oxygen in cardiac cells. Steigen et al. investigated the effect of hypothermia/rewarming on the myocardial capability to utilize fatty acids in oxidative phosphorylation. Fatty acid oxidation is often used as an indicator for cardiomyocyte health and metabolism(62). Cardiomyocyte damage and stress cause a shift in metabolic substrate from fatty acids to glucose (62). Steigen et al found a reduction in fatty acid and glucose oxidation during hypothermia. After rewarming, fatty acid oxidation was still reduced, while glucose oxidation was normalized. A second study preformed on isolated rat hearts found the same reduction in glucose and fatty acids during hypothermia, but after rewarming both glucose and fatty acid oxidation were reduced(63). In both these experiments cardiac function was depressed upon rewarming(63). Based on these finding Steigen concluded that cardiac dysfunction during rewarming is independent of cardiac substrate specificity(64).

The exact mechanism why metabolism is reduced when rewarming is still unclear. A possible explanation is mitochondrial dysfunction induced by hypothermia. Rewarming from hypothermia has proven to induce mitochondrial swelling, calcium overload and cytochrome C release. These are all factors indicating mitochondrial damage.

Myocardial ultrastructure

To investigate the effects of hypothermia on the integrity of myocardial cells Tveita el. al analyzed myocardial ultrastructure after rewarming using an electron microscope. They found a 72% increase in myocyte cytosolic volume and mitochondrial swelling by 42%. Investigations on the mitochondria showed mitochondria alteration of 48% in the rewarmed group(65). They argue that cellular swelling is a sign of increased $[Na^+]_i$. Although the exact mechanisms behind the increased $[Na^+]_i$ is still unknown, the reduction in Na^+/K^+-ATPase enzymatic activity have been proposed as the main mechanism. Some investigators point to other possible cellular mechanisms. Boutilier emphasize on the effect of cellular acidosis on the H^+/Na^+-antiporter (36) . A known result of increased $[Na^+]_i$ is the increase of $[Ca^{2+}]_i$ due to the influx of Ca^{2+} through the Na^+/Ca^{2+}-exchanger. Calcium overload can be seen in ischemia-reperfusion experiments, and is associated with reduced myocyte contractile function and cell viability(66). Kondratiev and Wold showed this increase in $[Ca^{2+}]_i$ in animals after rewarming from hypothermia(67,68).

Kondratiev and Wold found an increase in global intracellular calcium at onset of deep hypothermia. After four hours at 15ºC, there was a six-fold increase in intracellular calcium compared to before hypothermia. When rewarmed the calcium levels seemed to reduce, but there was no significant change in $[Ca^{2+}]_i$ between the hypothermic and the rewarmed rats (67,68) .

Dysfunctional β-receptors

Functioning β-receptors are important in maintaining cardiac function during physiological stress. Studies have been conducted with focus on the effect of epinephrine on the myocardium and probable alteration of the β-receptor during and after hypothermia. Studies done by Kondratiev and Han showed an altered response to epinephrine during and after hypothermia(69-71). When compared to normothermic controls a high dose of epinephrine (1,65ug/kg/min) increased mean arterial pressure, indicating epinephrine dependent vasoconstriction, with simultaneous absence of inotropic effect. Lower doses (0,4-1,25ug/kg/min) of epinephrine where able to produce an increase in cardiac output, but there was still a significant increase in total peripheral resistance compared to normothermic rats given epinephrine. Kondratiev concluded that these results are due to a mismatch

between β and α-receptor potency. During rewarming the α-mediated vasoconstrictive effect of epinephrine on vascular smooth muscle seems to be more potent that the positive inotropic effect of the β-agonism myocardium.

Han et al later studied the effect of the β-specific agonist isoprenaline before, during and after hypothermia(69). His findings correlated with Kondratievs, showing a decreased effect of β-stimuli on the heart after rewarming from hypothermia. He showed that at baseline rats exhibited a graded response to isoprenaline by increased CO, SV, HR and reduced TPR. Isoprenaline fail to produce the same response in rats during rewarming from hypothermia.

Isoprenaline cause vasodilation in the peripheral vessels, reducing vascular resistance. This was seen when isoprenalin as given to normothermic rats. After rewarming this effect was no longer present, even with a high dose (66 ng/kg/min). These data where interpreted by Han. et. al to indicate a failure in the β-reseptor cascade in vascular smooth muscle, creating an high vascular resistance. The reduction in cardiac contractility at low doses can also indicate β-reseptor desensitization in cardiomyocytes after hypothermia.

Altered myofilament calcium sensitivity
Han et al later showed in isolated papillary muscles a reduction of myofilament calcium sensitivity after rewarming from 1,5 hours of hypothermia. They showed that rewarmed isolated papillary muscle produced less force at higher Ca^{2+} levels than their controls. Lowering temperature is known to reduce myofilament calcium sensitivity(42). Han et al showed that the reduction is still present after rewarming. They looked at cardiac troponin I phosphorylation (cTnI) at the calcium sensitivity regulating sites Serine 23/24 on cTnI (72). They found a 40% increase in cTnI Ser23/24 phosphorylation after rewarming. Ser23/24 is a site, which is highly phosphorylated by protein kinase A (PKA), a downstream β-receptor second messenger. There is, seemingly, a conflict between the theory of β-dysfunction and cTnI-hyperphosphorylation. In normal physiology, Ser23/24 is mainly phosphorylated by PKA. After rewarming from hypothermia there is an increased Ser23/24 despite an apparent β-receptor dysfunction(44). This indicates a hypothermia-induced

mechanism causing increased Ser23/24 cTnI phosphorylation, other than downstream β-receptor stimulation.

Preliminary data from Haaheim et al have shown that the calcium activated Protein Kinase C (PKC) phosphorylate Ser23/24 during rewarming from hypothermia in mice(73). Cross-phosphorylation of PKC to Ser23/24 is unimportant in the normal physiology(74), but in hypothermia it seems to play a crucial role in Ser23/24 phosphorylation and thus myofilament calcium sensitivity.

Summary

The data and studies presented paint a picture of what happens to the heart during rewarming from hypothermia. It has become evident that the main component of "rewarming shock" is myocardial contractile dysfunction. The causal mechanism is unclear and multiple explanations exist. The most popular theories are: 1) Mitochondrial dysfunction due to mitochondrial and cellular calcium overload, resulting in subsequent reduced ATP production. 2) Reduced calcium sensitivity due to dysregulation of myofilament phosphorylation, reducing the amount of force produced at a given $[Ca^{2+}]_i$. 3) Impaired calcium handling, causing cellular calcium overload. 4) β-receptor dysfunction hindering a positive inotropic effect of epinephrine.

Continued investigation and search for these underlying mechanisms is needed to complete the picture and to explain the interplay between the different mechanistic explanations.

Chapter 6
Treatment of hypothermic patients

There has been a lack of consensus in the clinical community on how to treat hypothermic patients. In recent years, new guidelines have been written with emphasis on techniques and speed of rewarming. Both the European Resuscitation Council (ref) and American Heart Association came out with new guidelines 2010(31,34), and The University Hospital of Northern-Norway published their new guideline for rewarming from accidental hypothermia January 2014(35). These guidelines all emphasize on the importance of: "no patients is declared dead before they are warm and dead". This is based on clinical empirics where patients have been rewarmed from as low as 13,7°C and survived with close to no neurological sequel(75). Hypothermic patients with cardiac arrest should be treated with the same CPR algorithm with regard to compression technique and rate of ventilation. There is still debate regarding the use of vasopressors, fluid support, and inotropic and antiarrhythmic drugs in treating hypothermic patients. This chapter will elaborate on the different techniques of rewarming and the scientific evidence for use, or withholding the use, of these drugs.

Rewarming techniques

Rewarming from accidental hypothermia can be performed in several manners. The two main categories are invasive and non-invasive devices. Non-invasive methods like hot fluids to the skin and warm air blankets are the most common methods. These methods are easy to use, and non-invasive. The drawback is that they are not as efficient as invasive techniques and the patients need to be able to support their own circulation to distribute the rewarmed blood.

There are several invasive techniques to rewarm hypothermic patients. The most efficient, but also most invasive, are extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB)(76). The advantage with ECMO/CPB is that they can support circulation and oxygenation in addition to extracorporeal rewarming of the blood. Other invasive methods are infusion of warm fluids, and thoracic and/or peritoneal lavage. Thoracic lavage has shown to be an effective rewarming technique

in patients with stable circulation and in some cases of ventricular fibrillation and hypo perfusion . Infusion of fluid is not recommended as a rewarming method due to lack of effect and slow rewarming speed(35). The University Hospital of Northern-Norway just released their new guidelines for rewarming patients from accidental hypothermia. The recommendation is to treat hypothermic patients with body temperature >28ºC with stable circulation (>90 mmHg and sinus rhythm) using non-invasive rewarming methods. Since the primary hospitals in Northern-Norway do not have ECMO/CPB capability, patients with unstable circulation or body temperatures <28ºC are transported to Tromsø to be rewarmed on ECMO. Some investigators propose to use thoracic lavage when EMCO/CPB is not available and have shown good results in mortality and neurological outcome amongst survivors(77,78). Due to the lack of cardiopulmonary support in thoracic lavage and the high success rate in ECMO/CPB, thoracic lavage is considered an emergency solution. ECMO/CPB treatment in hypothermic patients with cardiac arrest has a success rate of 47%(76) and is thus the recommended treatment.

Drug therapy

An important part of critical care medicine is the support of vasoactive drugs and fluids infusions. Both the European Resuscitation Council and American Heart Association came out with new guidelines in 2010 with regard to cardiopulmonary resuscitation(31,34). They both advice withholding epinephrine and amiodarone in patients with cardiac arrest and a body temperature <30ºC. Northern-Norwegian guidelines, as well as the guidelines from University Hospital of Oslo, agree with this recommendation. In the case of hypotension and contractile dysfunction, they recommended the use of dopamine as the inotropic drug of choice. They recommend not using anti-arrhythmetics since these drugs have shown to have no effect on preventing the incidence of ventricular fibrillation in hypothermic patients with spontaneous circulation. With regard to fluid support, the recommendation is to use Ringer-Acetate and withhold the use of NaCl. The basis of this is the fear of worsening of metabolic acidosis by adding chloride(35).

Our research group at the University of Tromsø has over the last 25 years tested whether the commonly used drugs in critical care improve hemodynamic function in hypothermic animals. There has been a large focus on the use of inotropic drugs, with

a sharpened focus on beta-agonistic drugs like epinephrine. Studies on fluid support, anti-arrhythmic and other inotropic drugs have also been conducted. The last chapter in this thesis will focus of these findings and their clinical application.

Vasoactive drugs:

The previously explained findings of Kondratiev and Han on how epinephrine and isoprenaline affect hemodynamics and cardiac function during hypothermia and rewarming. They showed detrimental effect of a high dose of epinephrine during hypothermia and after rewarming(69,70). Later Filseth. et al showed a beneficial effect of dopamine during rewarming in pigs(79). Dopamine increased CO and reduced TPR with no change in MAP in pigs at 34 and 38ºC during rewarming after 1 hour at 25ºC. This indicates a beneficial effect of dopamine by increasing cardiac output while at the same time reducing vascular resistance.

As explained earlier Tveita et al found an increase in TPR after rewarming in untreated animals. A high TPR creates an increased afterload and is generally detrimental to the CO. To investigate the role of TPR on CO during rewarming, our laboratory utilized nitroprusside and diltiazem to reduce TPR during rewarming. Preliminary data from these experiments showed no improvement in CO after rewarming and a reduction in MAP after rewarming. There was also a higher lethality among these animals.

Fluid treatment:

Fluid resuscitation is important in treating intensive care patients with impaired circulation. Guidelines on treatment during hypothermia recommend the use of Ringer Acetate instead of NaCl due to fear of chloride overload inducing further metabolic acidosis(35). Preliminary data from Nilsen. et. al show improved CO, SV and reduced TPR in rats treated with the colloid fluid Dextran during rewarming. He concluded that the increased colloid pressure from Dextran infusion helped increase circulating blood volume and thus improving SV and CO.

Anti-arrhythmic drugs:

The prevention of arrhythmias during rewarming has been extensively studied. The importance of avoiding arrhythmia during rewarming is emphasized in the new

guidelines from University Hospital of Northern-Norway. Despite the central role antiarrhythmetics generally play in cardiology and emergency medicine, studies on common antiarrhythmic drugs like amiodarone, diltiazem and bretylium tosylate (80,81) have all failed to prevent ventricular fibrillation during rewarming. Amiodarone also fails to improve survival in hypothermic patients with arrhythmias(82). Furthermore, studies conducted to look at the effect on antiarrhythmic drugs to lower defibrillation threshold in ventricular fibrillation found no effect of antiarrhythmic drugs(83).

Summary

With the use of guidelines the treatment of hypothermic patients have been more standardized and evidence based. A recurring issue in pharmacological treatment of hypothermic patients is the alteration in pharmacokinetics and –dynamics. Consequently, this necessitates re-testing of drugs that are known to have a beneficial effect in normothermi. The last chapter has shown a handful of these experiments. Discoveries like that epinephrine lack beneficial effect in hypothermic patients or the lack of antiarrhythmic effect of antiarrhythmics are examples of the importance of experiments like this. This shows that there is more need to study how hypothermia alternates the effect of common used intensive care drugs.

Chapter 7

Thesis conclusion

Our understanding of hypothermia has increased over the past 20-30 year. The knowledge that hypothermia alters human physiology has been known for quite some time, but new ground has been broken with respect to understanding the mechanisms of *how* hypothermia changes human physiology and how this give rise to clinical complications. The increase in mechanistic understanding has improved the treatment of hypothermic patients and resulted in a reduction in total mortality from 80% to 30%. The impressive clinical examples of profoundly hypothermic patients being treated to complete recovery are a testimony to this.

Although the mortality of hypothermia is low, and increased survival rate, the importance of body temperature in elderly and trauma patients cannot be stressed enough. Despite an impressive decrease in lethality, these two groups of patients still have a poor chance of survival compared to other hypothermic patients. Despite the importance of comorbidity in hypothermia, little research focus has been directed on this interplay. How the underlying mechanisms of hypothermia interact with pathological mechanisms in different comorbid conditions in the chronically ill is unknown. In the same manner new guidelines and treatment algorithms now emphasize temperature and circulatory stability. Future guidelines might also implement comorbidities when assessing the medical severity in a hypothermic patient.

Despite great leaps in understanding underlying pathophysiology and mechanisms, we have only scratched the surface and much research is still needed. We now know there is a cardiac dysfunction associated with rewarming and many of the possible underlying mechanisms have been uncovered. The research on the hypothermic heart has lead to improved treatment by discovering how ubiquitously used drugs like epinephrine and amiodarone are detrimental to cardiac function in hypothermia. These finding help improve guidelines and move research forwards.

The focus on complications of accidental hypothermia has been on how the heart is affected by hypothermia. This makes sense in the emergency room, due to the importance of cardiac function. As described, hypothermia induces organ dysfunction

and failure. The underlying mechanisms to describe how and why this happens are still unknown. The body of scientific evidence on hypothermia-associated contractile dysfunction has led to new and improved. One can only assume that further research on mechanisms underlying organ dysfunction in other systems will provide new targets for pharmaceutical treatment and improved survival.

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