Long term health effects of sustained heat strain

Literature review

The start of another hot day at the Kirkush military training base in the desert of Iraq (photo: US Department of Defence)

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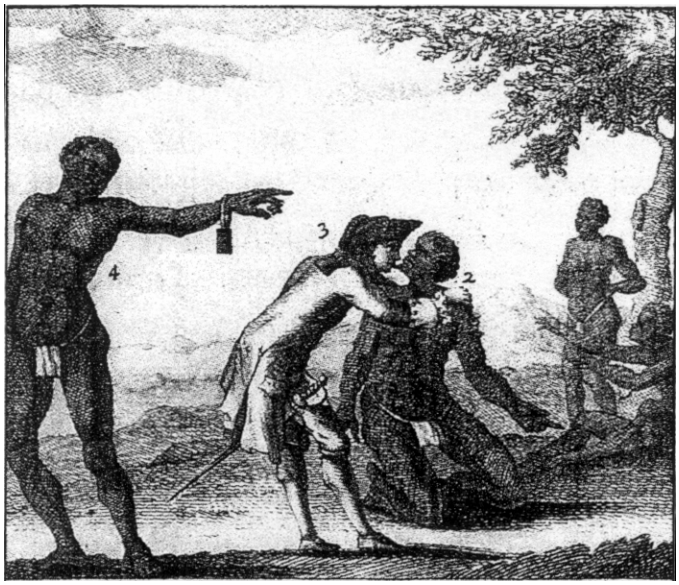

This picture shows a copper engraving made in 1764. In this scene an English slave trader licks the cheek of an African captive to taste his sweat before having him brought aboard the slave ship (Middleton, 1990). Moskowitz (1996) writes the following about this scene:

Presumably the saltiness of the African's sweat was used as a rough gauge for future short-term mortality aboard the slave ship. This was an important business consideration, since the slave trader was paid only for slaves delivered alive.

In his extensive article Moskowitz (1996) posts a hypothesis linking the harsh conditions in their original habitat and even more so during the slavery trade (high temperatures, low relative humidity and scarcely available drinking water) to a strong genetic predisposition to hypertension as seen in modern Afro Americans. It is assumed that this genetic predisposition was important for survival during the slavery trade, and thus due to natural selection the incidence of this "African gene" is high among modern Afro Americans.

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1 Introduction

A body core temperature in a narrow band around 37° C is essential for optimal functioning. This thermal balance can be acquired if heat gain is equal to heat loss. Under optimal conditions (nude and resting in an ambient temperature of 28° C) this equilibrium is maintained under control of minor fluctuations in skin blood flow. However, if the conditions are not optimal, such as during exercise in a hot environment, the heat strain can be enormous, resulting in increased skin blood flow, increased sweat rate, increased heart rate, several behavioural mechanisms and eventually an increased body core temperature (hyperthermia).

The acute effect of heat strain on the physiological system is evident, and results in reduced performance. This increased strain, with or without hyperthermia, results in an increased incidence of mortality and morbidity under the elderly and sick, as shown by Kunst et al. (1993) and Dematte et al. (1998). If heat strain results in hyperthermia it can even cause mortality and morbidity under healthy, well trained individuals (Coris et al., 2004).

Unfortunately, the long term effect of heat strain on health is unclear, which leaves us with many uncertainties such as: might it be expected that soldiers who served in the heat of Iraq will have physical complaints years later? How about workers exposed to the heat of ovens in the metal producing industries, miners and other employees with sustained heat strain? This thesis will focus on the long term health effects of sustained heat strain.

Heat strain is common in many occupations (table 1.1) as recognized by the National Institute for Occupational Safety and Health (NIOSH). In 1972 the NIOSH pointed out the need for research on the long term health effects of heat stress. Due to the rising environmental temperature the occurrence of heat strain will probably increase in some occupations. The Intergovernmental Panel on Climate Change (2001) predicts a global temperature rise of 1.4 – 5.8° C within this century, mainly due to the greenhouse effect.

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On a national level, governments are introducing new laws to make employers more responsible for the health of their employees, in order to minimize the negative effect of work on general health. The goal of these changes is to reduce sickness leave and thereby increasing productivity. Since employers are responsible for the pathologies caused by work done by their employees it is of special interest what the long term health effects of different occupations are. Unfortunately the recommendations of the NIOSH and the recent stimulus of governments did not result in extensive research into the field of heat strain and long term

health. To our knowledge there is no literature reviewing the long term health effects of sustained heat strain.

Sustained heat strain is defined as an increased thermoregulatory demand to balance heat gain with heat loss above the thermoneutral state, for a period of at least 6 months. Health is defined as the state of well-being and the absence of disease. However, the health effects discussed in this review can either be negative (making the body more susceptible for disease) or positive (strengthening the physiological system).

Recently the focus of research on thermoregulation has shifted from central to peripheral. This is seen in the amount of literature recently published on for example, the role of nitric oxide in vasodilatation, aquaporins in sweat and kidney function and heat shock proteins. In line with this current shift of focus, the peripheral thermoregulation will also be discussed next to the central thermoregulation. This thesis will also deal with the peripheral thermoregulation.

It was difficult to define an initial outline for this review since hardly any information on long term health effects of sustained heat strain is described in the literature. During the literature search articles related to the topic were searched with PubMed (www.ncbi.nlm.nih.gov), read and a concept of ordering was drafted afterwards. As a result this review starts by discussing the basic principles of thermal physiology (chapter 2). Chapter 3 will evaluate the physiological strain during hyperthermia. The next chapter (4) will give an overview of the physiological effects occurring up to 2 months after the heat strain exposure (short term physiological effects post heat strain). The long term health effects, defined as being longer than 2 months after heat strain exposure (long term health effects post heat strain), will be dealt with in chapter 5. This thesis will end with conclusions (chapter 6) where the problem will be evaluated. In this last chapter the reliability will also be discussed along with suggestions for future research.

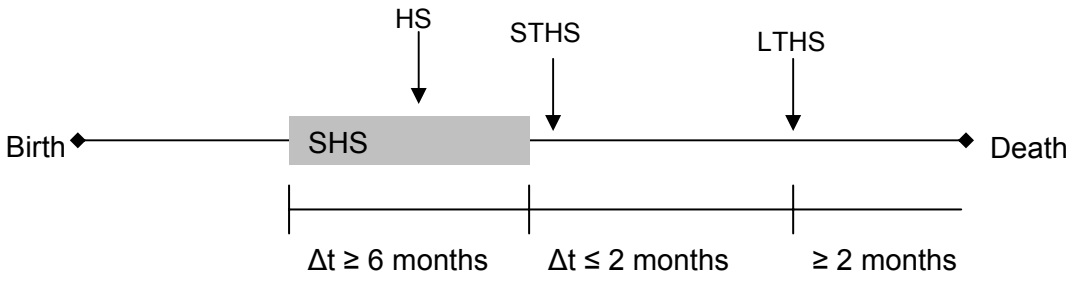


Figure 1.1: ***Chronologic overview of heat strain exposure and other periods which will be discussed in this thesis*****.** Somewhere in his/her life this person is exposed to sustained heat strain (SHS) for at least 6 months. During this exposure, the human physiological system adapts (HS). In some cases the sustained heat strain ends with mortality, as sometimes seen in the elderly and the sick after a period of extreme hot weather. Luckily, most people survive sustained heat strain. In the period shortly after the exposure (STHS) several adaptations to heat strain will be undone. The focus of this thesis will be the health effects of at least 2 months after the exposure (LTHS).

SHS: sustained exposure to heat strain;
HS: heat strain (chapter 3);
STHS: short term physiological effects post heat strain (chapter 4);
LTHS: long term health effects post heat strain (chapter 5).

2 Thermal physiology

To acquire a general insight in the human thermoregulation, first the heat balance will be discussed, followed by an overview of the mechanisms used by the human body to control the body core temperature (T_c).

2.1 Heat balance

Heat loss must be in balance with the heat gain in order to keep the T_c constant. To regulate the heat loss and gain the body uses different mechanisms. These mechanisms and its definitions according to the Glossary of terms for thermal physiology (2001) can be found below:

- Metabolic heat production (M): Rate of transformation of chemical energy into heat in an organism.
- Evaporative heat transfer (E): The rate at which heat energy is transferred by evaporation from or condensation on the skin and the surfaces of the respiratory tract.
- Convective heat transfer (C): The net rate of heat transfer in a moving gas or fluid between different parts of an organism, or between an organism and its external environment; it may develop and be amplified by thermal gradients and by forces such as wind, fans, pumps or body movement.
- Conduction heat transfer (K): The net rate of heat transfer in a solid material or a non-moving gas or fluid down a thermal gradient, within an organism, or between an organism and its external environment.
- Radiant heat exchange (R): The net rate of heat exchange by radiation between an organism and its environment.

The body heat balance equation is defined as:

$$S = M \pm E \pm C \pm K \pm R \qquad (2.1)$$

whereby S is negative or positive storage of heat.

A requirement for a constant T_c is that the heat storage is minimal ($S \approx 0$). The heat balance can be divided into dry heat loss and wet heat loss.

$$S = M \pm [\text{Wet Heat Loss}] \pm [\text{Dry Heat Loss}] \qquad (2.2)$$

Dry heat loss is achieved by convection, conduction and radiation. Evaporation is the only mechanism of wet heat loss. Wet heat loss becomes increasingly important if the ambient temperature proximate or exceeds 37° C. In this case dry heat loss is positive (heat is gained), and thus heat can only be lost by evaporation. With the evaporation of one gram sweat the skin looses 2426 Joule of heat (Wenger, 1972). However, relative humidity can severely impair wet heat loss.

This thesis deals with the situation whereby T_c is threatened to elevated above normal values for a prolonged period. In this situation the physiological strain is increased on the body in order to minimize the heat storage. This situation might or might not result in an increased T_c.

In addition to the theoretical model of the heat balance explained above, a more practical model of the heat balance can be used. This more practical heat balance model is divided into climate, clothing, exercise and individual factors, these factors can be further defined as done in table 2.1.

Table 2.1: ***Factors influencing the heat balance***

Heat balance	Climate	ambient temperature precipitation radiation relative humidity wind speed
	Clothing	air flow resistance insulation radiant characteristics water vapor resistance
	Exercise	duration efficiency intensity
	Individual factors	acclimatization or acclimation adaptation (genetically) pathology physical fitness resting metabolism

In order to understand the pathology related to sustained hyperthermia it must be well understood how the thermoregulatory system works. Therefore the general thermoregulation will be discussed next.

2.2 Thermoregulation

A constant T_c is essential for our survival, for instance, an increase of no more than 4° C of the T_c may result in heat stroke which sometimes results in death. Therefore it is important that the T_c is kept constant in a narrow band around 37° C. The basis of the thermoregulation is formed by the hypothalamus which is the most important structure of regulating T_c in that it coordinates the activity of other integrating mechanisms at lower levels of the neuraxis (Satinoff, 1978). Input for the hypothalamus is provided by thermoreceptors located in skin, spinal cord, muscles, splanchnic organs and most important located in the pre-optic anterior hypothalamus (Satinoff, 1978; Gisolfi & Wenger, 1984; Rowell, 1986 and Åstrand et al., 2003). The general idea is that the hypothalamus works as a thermostat that can be found in

a residence regulating the temperature of the residence (Gisolfi & Wenger, 1984). The resident can select a set point, for instance 19° C, on the thermostat. If the thermostat measures a temperature lower than the set point it will turn on the central heating system. If, on the other hand, the thermostat registers a temperature higher than the set point it will turn off the central heating system. However, it must be stressed that the concept of a set point is purely mathematical and that there are different set point for the different effector responses (Gisolfi & Wenger, 1984). This system is based on a constant *loss* of heat and can only actively raise the temperature. To maintain the T_c, humans can use several mechanisms to gain (thermogenesis) or loose heat, these effector responses are summarized in table 2.2. T_c is the most important factor in inducing mechanisms of thermogenesis or heat loss. However, also average skin temperature (T_{sk}) is of influence (Gisolfi & Wenger, 1984 and Parsons, 2003). The relation between T_c and T_{sk} and the effector response is often represented by formula 2.3 (Gisolfi & Wenger, 1984):

$$R - R_0 = a_1 * T_c + a_2 * T_{sk} - b \qquad (2.3)$$

whereby R is a thermoregulatory response, R_0 is a basal value of R, a_1 and a_2 are coefficients and b is a constant term. In human subjects the ratio a_1: a_2 is close to 9:1 for all of the heat dissipating responses (Gisolfi & Wenger, 1984). Based on formula 2.3 body temperature (T_b) can be defined as:

$$T_b = a * T_{sk} + (1 - a) * T_c \qquad (2.4)$$

whereby a is dependent of the skin to core ratio, as seen in figure 2.1. In a cold environment, skin blood flow decreases, which increases the insulative value of the skin. Thus, the skin assumes a greater role in determining T_b in a cool environment, reflected in values for a as high as 0.4. In a hot environment, T_{sk} and T_c are more alike, mostly due to a greater skin blood flow, resulting in lower values for a ($a \approx 0.2$).

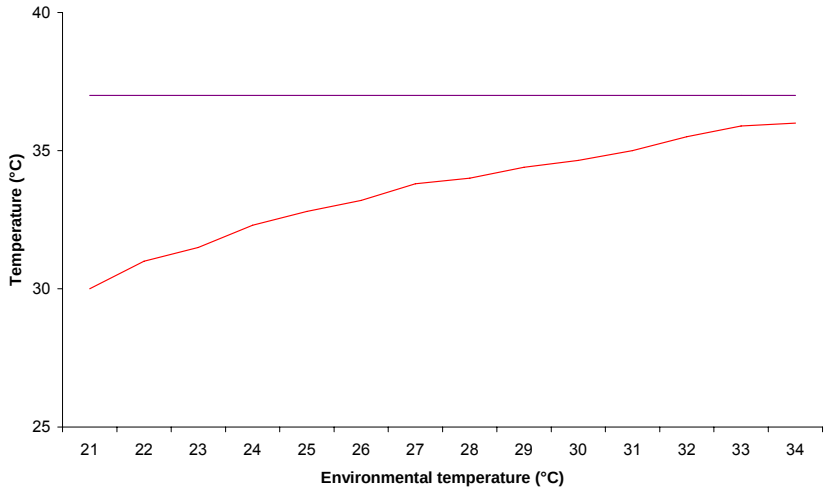


Figure 2.1: ***Skin to core temperature for different environmental temperatures.*** The purple line represents body core temperature and the red curve shows the skin temperature (derived from Gisolfi & Mora (2000)).

2.2.1 Heat loss

The first mechanism used to regulate T_c is based on vascular motor function or vasomotor control of the dermal arteries. Since most heat is lost in the skin due to dry and wet heat loss controlling the skin blood flow is very effective in correcting for minor changes in T_c. With a low T_c internally produced heat needs to be conserved. In order to accomplish this vasoconstriction of dermal arteries will take place (Rowell, 1986). Hereby the skin-core temperature gradient will increase. The effect of this system is to minimize heat loss to the environment. A second goal is to keep the warmth behind the subcutaneous fat layer. On the other hand, if the T_c is elevated vasodilatation will occur resulting in an increased skin blood flow. Thereby the skin blood flow might be increasing to as much as 8 $L*min^{-1}$ (Rowell, 1986). The effect of this reaction is to distribute heat over the whole body instead of only the core and thereby lowering the average temperature, as a result it decreases the skin to core gradient, which makes it easier to lose heat by dry and wet heat loss (Rowell, 1986). However, if a person needs to exercise while in a hyperthermic state the total blood volume will be distributed over more organs, thus the peripheral blood distribution increases. The result of this distribution is that less blood will reach the muscles, unless cardiac output (Q) increases. If the work intensity is sub maximal, Q can be increased by increasing hart rate (HR) or stroke volume (SV) or both, since Q is the product of HR and SV:

Table 2.2: ***Mechanisms of heat gain and loss***

Heat loss, high Tc
Vasomotor control
Sweating
Behavioral response
Heat adaptation / acclimatization / acclimation
Thermogenesis, low Tc
Nonshivering metabolism
Shivering metabolism
Behavioral response
Cold adaptation / acclimatization / acclimation

$$Q = HR * SV \qquad (2.5)$$

If more heat loss is necessary the sweating system comes into play. A disadvantage of this system is that in the course of a working day a person can sweat up to 7 L (Leithead & Lind, 1964). The consequence of sweating is that it will reduce the extracellular volume (hypovolemia), resulting in a smaller blood volume.

There are also several behavioural responses to hyperthermia. Opposed to behavioural responses to hypothermia, during hyperthermia the body reduces its heat gain. Examples of these behavioural responses are; taking off clothes, rest, moving to a sheltered area (shadow or protection from radiant heat sources) (Parsons, 2003). All together these behavioural responses will result in reduced productivity in a working situation.

If humans are exposed to hyperthermia their physiological system will adapt. Some phenotypic adaptations that will occur are increased sweat rate, reduced osmolarity of sweat, reduced heart rate and an increased plasma volume (Nielsen et al., 1993). These phenotypic adaptations will be discussed in more detail in the next chapter.

2.2.2 Thermogenesis

If the T_c is reduced the first physiological response is vasoconstriction. If vasomotor control is insufficient humans can increase their heat production in three different ways; non-shivering, shivering and voluntary (behavioural) thermogenesis (Marken Lichtenbelt & Daanen, 2003).

Non shivering thermogenesis is based on uncoupling proteins (UCP) which act upon membranes. There general function is to cause leakage in order to increase the metabolism of several pump systems. In animals this is seen in the mitochondrial inner-membrane in brown adipose tissue. In this case the UCP provide leakage for protons and thereby disturb the proton-gradient, to correct for this distortion the proton pump will increase their activity. Since none of all the biological processes have an efficiency of 100% some part of the energy converted will be lost as heat. Thus with an increase in activity of these pumps the heat production will be increased. UCP can also have an effect upon Ca^{2+} pump in skeletal muscles (Marken Lichtenbelt & Daanen, 2003).

Shivering thermogenesis are involuntary contractions of skeletal muscles. Result of increasing muscle activity is an elevated heat production. Voluntary thermogenesis is an increased activity level induced by the individual itself (Marken Lichtenbelt & Daanen, 2003), such as putting on clothing and searching for heat sources.

Phenotypic cold adaptation or acclimatization results in an increased metabolism and a greater skin to core temperature gradient (Marken Lichtenbelt & Daanen, 2003).

In this chapter the general thermal physiology was discussed, from the heat balance to the coordination of the regulation of T_c by the hypothalamus. The behavioural and physiological reactions to cold and heat strain were discussed. However, from the next chapter on only heat strain will be discussed. In the next chapter the physiological consequences and pathologies during sustained hyperthermia will be discussed in more detail.

3 Physiology and illness during heat strain

In the previous chapter the mechanisms were discussed by which fluctuations in T_c can be minimized. During a heat exposure, a physiological strain in placed on the body to minimize heat storage. This is often referred to as heat strain and will be discussed in the first paragraph of this chapter divided into thermal sweating and cardiovascular strain. In time these mechanisms will induce several physiological changes. Some of these physiological changes result in heat illness, as discussed in the second paragraph. Fortunately, other changes are beneficial for the survival of the individual during heat strain, referred to as physiological adaptations and discussed in the last paragraph of this chapter.

3.1 Heat strain

Heat strain is defined as a physiological demand placed on the body to counterbalance or minimize a rise in heat storage. The human body has two physiological systems to minimize heat storage; (i) cardiovascular and (ii) thermal sweating. If the body is in a thermoneutral environment the body temperature is regulated by increased or decreased skin blood flow. If heat strain increases thermal sweating comes into play. However, thermal sweating will be discussed first since it has a major impact on the cardiovascular system.

3.1.1 Thermal sweating

The cooling aspect of sweating is discussed in the previous chapter. This paragraph will focus on the acute effect of thermal sweating.

Two different sweat glands can be distinguished, apocrine and eccrine glands. The former are found in the armpits and pubic regions and are the cause of the distinctive odour in these regions. The later is found all over the body, however in fewer concentrations on the tights, soles and palms (Parson, 2003). The biggest difference is the way these glands are controlled. Apocrine glands are controlled by hormones, whereas eccrine glands are controlled by sympathetic nerves (Vander et al., 2001). For thermoregulation only the eccrine glands are important. These glands are mainly controlled by the hypothalamus. The consequence of severe sweating is often a reduced extracellular blood volume (hypovolemia) and sometimes (if only water is replaced) a reduced sodium concentration in the blood (hyponatremia).

3.1.1.1 Hypovolemia

Humans consist for 60 – 70% of water. This water is crucial for life, it is important as a transport medium, a medium in which biochemical reactions occur and for thermoregulation.

In the course of an average day 2600 ml of water is lost (Åstrand & Rodahl, 1987). This water is lost by evaporation from breathing, faeces, sweat and urine (table 3.1). However, a person experiencing heat strain can sweat up to 7 L in the course of a working day (Leithead & Lind, 1964). This will bring the total amount of daily water loss to 9 L! A practical problem in this example is replacing the water and salt loss. ISO 7033 (1989) provides limiting values for water loss during work in the heat, for non acclimatized workers the maximal loss is 4% of body weight and for acclimatized workers this value is 6%. A loss of 9 L is for an average person (75 kg) 12% of total body weight, thus unlimited and widely available water is vital. However, research has indicated that a loss of 2% of the total body fluid will impair cognitive and physical performance (Gisolfi & Wenger, 1984). Furthermore, hypovolemia causes a reduced blood pressure. The reduced blood pressure together with the increased peripheral blood distribution can severely impair the body's ability to regulate T_c and places a higher strain on the heart as explained above (2.2.1).

Tabel 3.1: ***Daily water loss***

Medium	Loss (ml)
Evaporation for lungs	400
Faeces	200
Sweat	500
Urine	1500
Total	2600

From: Astrand & Rodahl, 1987

3.1.1.2 Osmolarity

With the loss of water through sweating some electrolytes will be lost (mainly Na^+, Cl^- and K^+). Although sweat tastes very salt the osmolarity of sweat is much less than that of blood. If a person is sweating extensively its body water content will reduce. As a result, the osmolarity of the body fluid will increase. The kidneys have the function of regulating osmolarity of the body fluid, an important function since changed osmolarity can severely impair homeostasis. During extensive sweating the kidneys will secrete electrolytes into the bladder, to balance the osmolarity of the body fluid. Thus during sustained hyperthermia not only water replacement is important, but also the replacement of electrolytes, since the kidneys or other organs can only secrete electrolytes into the bladder and not visa versa. The American College of Sports Medicine (1996) recommends to; i) drink sufficient 24 hour before exercise, ii) drink 500 ml 2 hour before exercise, iii) start drinking early and try to replace all lost fluid or drink as much as possible, iv) serve fluid with a temperature between 15 and 22° C and v) replace carbohydrates and electrolytes in exercise lasting longer than 1 hour (30 – 60 $g*h^{-1}$ and 0.5 – 0.7 $g*L^{-1}$ respectively).

3.1.1.3 Hyponatremia

If only water (without electrolytes) is replaced during hyperthermia, the blood serum osmolarity (osmolality) and/or sodium concentration can drop, resulting in hypo-osmolality and/or hypotonic hyponatremia (also known as dilatational hyponatremia). Signs and symptoms of hyponatremia include confusion, disorientation, mental obtundation, headache,

nausea, vomiting, aphasia, disturbed co-ordination and muscle weakness (Montain, et al., 2001 and Murray et al., 2003). Unfortunately most of these signs and symptoms are also seen in heat illness (table 3.2). Untreated or wrongly treated hyponatremia can develop in seizure, coma, pulmonary oedema and cardiorespiratory arrest (Montain, et al., 2001). In the field it is seen that many cases of hyponatremia where wrongly determined to be heat illness. The treatment of developing heat illness is increasing fluid intake, in the case of hyponatremia hypo-osmolair fluid intake can increase the hyponatremia!

The replacement of electrolytes has long been underestimated. In the US army since 1988 an increase in hypo-osmolality and hyponatremia casualties is seen. It is not a coincidence that in 1988 a highly functional and portable fluid bladder was introduced in the US army (Camelbak). These Camelbaks reduce all hassle of hydration, simply drink through the tube which is connected to the bladder that is carried as a backpack. Running and drinking is, for example, less problematic. The coin side of the Camelbak is that the user is tempted to drink too much. Soldiers are usually instructed to drink when they feel unwell while exercising in heat (Montain, et al., 2001). This probably is the cause of the increase in hypo-osmolality and hyponatremia since 1988 in the US army. This problem can easily be solved by adding a NaCl concentration to the fluid used in the Camelbaks.

3.1.1.4 Regulation of body fluid status

The hypothalamus and kidneys are two important structures in regulating the fluid and salt balance. For a good understanding of the pathology related to hyperthermia knowledge of the hypothalamus and kidney are mandatory.

Hypothalamus

The hypothalamus integrates information from baroreceptors spread throughout the cardiovascular system and osmoreceptors located in the hypothalamus. Baroreceptors register blood pressure, which can decrease due to hypovolemia caused by sweating. Osmoreceptors register the concentration of ions in solution (osmolarity). The stimulation of one or both these receptors can produce the feeling of thirst and stimulation of the posterior pituitary gland to increase vasopressin production initiated by the hypothalamus. Vasopressin acts upon collecting ducts in the kidney, increasing their reabsorption of water. Thus vasopressin reduces the portion of the blood volume transferred to the bladder (Vander et al., 2001).

Kidney

In a 70 kg person about 180 L blood passes through the kidneys every day! The kidneys monitor the blood volume by registering the blood pressure in the juxtaglomerular cells. If the blood pressure is reduced the pressure on the juxtagolmerular cells is reduced as well, this

results in renine production. Renine stimulates the production of aldosterone by the adrenal cortex. Aldosterone acts upon the collecting ducts and stimulates the reabsorption of sodium and thereby the reabsorption water. However, different structures influence the production of renine, the central nervous system (CNS) through the sympathetic nerves, baroreceptors in the aorta by producing atrial natriuretic factor and the macula densa in the kidney (Vander et al., 2001).

A schematic overview of the reaction of aldosterone, vasopressin and kidney function in severe sweating can be found in figure 3.1.

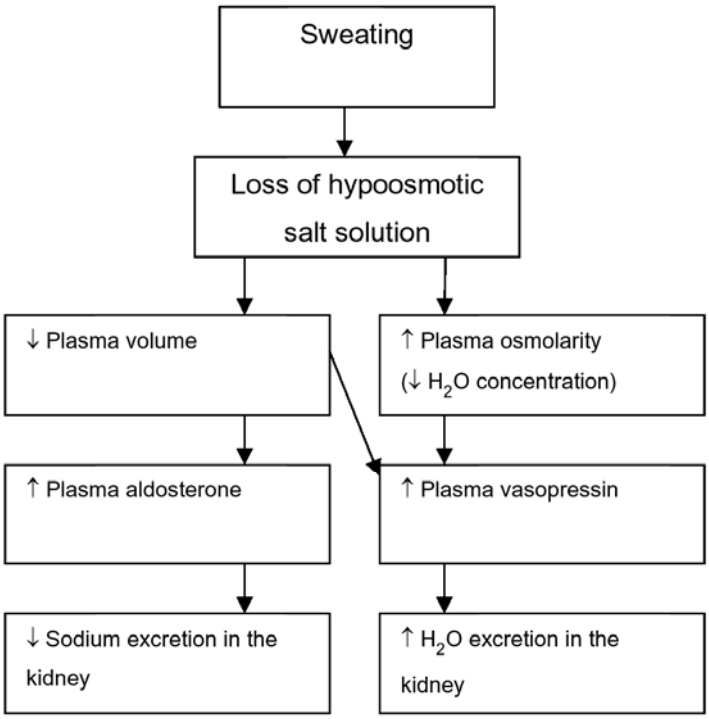


Figure 3.1: ***Effect of severe sweating on plasma concentrations of aldosterone and vasopressin and kidney function.***
From: Vander et al., 2001.

3.1.2 Cardiovascular strain

In many occupations heat strain coincides with physical activity. Sustained hyperthermia results in hypovolemia (due to sweating) and increased blood flow through the skin. Physical activity results in an increased blood need in the skeletal muscles. Thus the peripheral blood distribution increases while the total blood volume is unchanged or reduced. This will result in a reduced blood pressure. To correct for the blood pressure Q must be elevated. As explained earlier Q can be elevated by increasing HR and/or SV. Unfortunately this will result in a reduced maximal aerobic capacity and an increased cardiovascular strain during sub maximal aerobic exercise compared to exercise in a thermo neutral environment. This reduced blood pressure can also result in a reduced blood flow through the brains which in turn leads to fainting. This is not live threatening and will resolve itself when the person lies down, due to the horizontal position will increase the blood pressure due to the decreased influence of gravity on the circulatory system.

3.2 Heat illness

Heat strain can result in some acute heat related pathologies, heat cramps, heat exhaustion and heat stroke. These heat illnesses will be discussed in this paragraph. Older persons, children and patients with chronic disease or the poor physical conditioned are particularly susceptible to heat related illnesses (Wexler, 2002). However, also healthy and physically well conditioned individuals who are driving their thermoregulatory systems to the limits are susceptible to acute heat related pathologies. The signs and symptoms of these heat illnesses and the relationship with heat storage are depictured in figure 3.2. It must be kept in mind that the mentioned types of heat illness are not always easy to distinguish and often bland into each other.

3.2.1 Heat cramps

A common problem for athletes exercising in a hot environment is heat cramps. It is still unclear what the cause of these cramps is. However a commonly used explanation is a reduced sodium concentration due to extensive sweating in combination with too little or too much fluid intake (Wexler, 2002). Non acclimatized individuals have a greater risk of developing heat cramps because, as will be explained later, they sweat less but the sodium concentration of their sweat can be more than 10 times higher compared to acclimatized individuals (Wexler, 2002).

3.2.2 Heat exhaustion

The process of heat exhaustion is unclear. Heat exhaustion might relate to more than one factor, however, it is known that heat exhaustion coincides with an elevated T_c (Nielsen et al., 1993; Fuller et al., 1998; Gonzáles-Alonso et al., 1999 and Walters et al., 2000). Nybo & Nielsen (2001a) and Nielsen & Nybo (2003) postulated a hypothesis that central fatigue is involved in the aetiology of hyperthermia-induced fatigue which eventually leads to heat exhaustion. In their research they observed that exercise-induced hyperthermia reduced the voluntary activation of motorneurons during a sustained maximal muscle contraction. This hypothesis is strengthened by a study of Caputa et al. (1986) who found that brain temperature is a dominant factor affecting motor activity. There are several response for the rise in brain temperature, (i) temperature of the blood rises, and thus the blood will not be able to remove the same amount of heat from the brain as in a none heat strain condition; (ii) blood flow through the brain is reduced during hyperthermia (Nybo & Nielsen, 2001b; Nybo et al., 2002a and Nybo et al., 2002b) and (iii) cerebral metabolic rate and thus heat production in the brain is increased during hyperthermia (Nybo et al., 2002a and Nybo et al., 2002b).

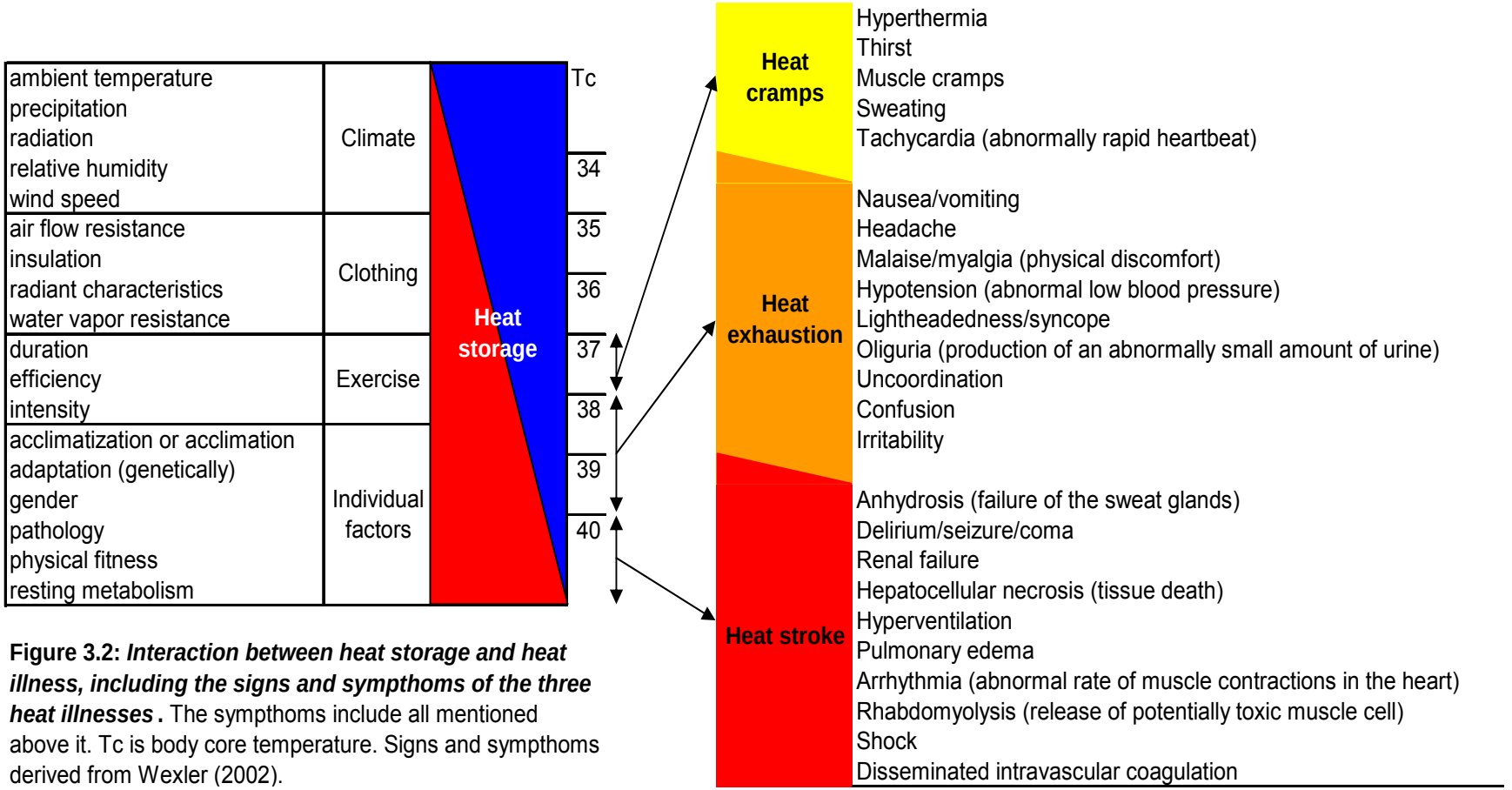


Figure 3.2: ***Interaction between heat storage and heat illness, including the signs and sympthoms of the three heat illnesses*****.** The sympthoms include all mentioned above it. Tc is body core temperature. Signs and sympthoms derived from Wexler (2002).

During heat exhaustion T_c reaches values between 38 and 40˚ C. If heat exhaustion is left untreated, heat stroke will most likely develop.

Important to notice is that performance in heat will decrease and the chance of developing any heat illness is reduced due to acclimatization.

3.2.3 Heat stroke

In addition to the signs and symptoms listed in figure 3.2 heat stroke is characterized by a T_c of 40˚C and up. Two types of heat stroke can be differentiated: i) Classic (or non exertional) heat stroke resulting from a high environmental temperatures; ii) Exertional heat stroke which is the result of excessive heat produced due to high metabolic demands, exertional heat stroke might, or might not coincides with heat stress. The elderly and the sick have a greater change to suffer from classic heat stroke in contrast to the healthy adult with high metabolic demands who have a greater chance of suffering from exertional heat stroke. If heat stroke is left untreated it will most likely result in death. Since exertional heat stroke is under recognized as a serious pathology it is the third leading cause of death among US high school athletes (Coris et al., 2004). However, if heat stroke is treated properly the mortality rate is low and most patients will recover completely. There are two theories that explain the mechanism of heat stroke, the first is know as the 'leaky gut theory' and focuses on the intestines. The second theory is called the 'burning brain' and recognizes the CNS as the primary organ resulting in the signs and symptoms as seen in heat stroke. Recently Gisolfi & Mora (2000) combined both theories in one working hypothesis. All three theories will be explained below.

3.2.3.1 Leaky gut theory

Bouchama & Knochel (2002) present a theory for developing heat stroke which will be summarized here. Important is the blood distribution which will increase in the skin (and muscles) and decrease in the gut. The reduced blood flow in the gut will result in local ischemia which causes intestinal hyper permeability. This alteration allows leakage of endotoxins, increased production of inflammatory cytokines that induce endothelial-cell activation and release of endothelial vasoactive factors such as nitric oxide, endothelins and other cytotoxins. These produced substances will influence the thermoregulation by raising the set point at which sweating is activated and by altering vascular tone, particularly in the splanchnic circulation, thereby precipitating hypotension, hyperthermia and heat stroke. Eventually this will lead to circulatory shock. DuBose et al. (2003) refers to heat illness without neurological abnormalities caused by strenuous exercise as exertional heat injury. Thereby they introduce a new heat illness positioned between heat exhaustion and heat

stroke. More important DuBose et al. (2003) recognizes the leaky gut theory as an actually occurring pathology, based on many cases of heat illness.

3.2.3.2 Burning brain theory

Another theory of heat stroke concentrates on the brain (Gisolfi & Mora, 2000). Hypotension can be the result of sustained hyperthermia and will cause a reduced cerebral blood flow (Nybo & Nielsen, 2001b; Nybo et al., 2002a and Nybo et al., 2002b). This combined with an increased brain temperature results in; i) deterioration of the blood-brain barrier, ii) deplete ATP in many neurons of the brain, iii) accumulation of neurotransmitters such as glutamate and dopamine. The accumulation of these neurotransmitters results in increased extracellular toxic quinones and an increase in the production of cytotoxic free radicals. These cytotoxic agents destroy neurons and thereby resulting in heat stroke.

An interesting ongoing discussion is whether selective brain cooling (SBC) takes place in humans. It is demonstrated that different animals (e.g. rabbits, dogs, cats, and sheep) can have a substantial lower brain temperature than the rest of the core under hyperthermic conditions. If SBC takes place in humans it can delay the onset of heat stroke, and if this mechanism is better understood it might result in protocols or articles preventing or reducing the (the effect of) heat stroke. The problem in this discussion is that brain temperature can not be measured directly in humans (Nielsen, 1988), due to ethical considerations.

3.2.3.3 Combined theory

Gisolfi and Mora (2000) combined these two theories (the leaky gut and the burning brain) into one working hypothesis of the cause of hyperthermia, as shown in figure 3.3.

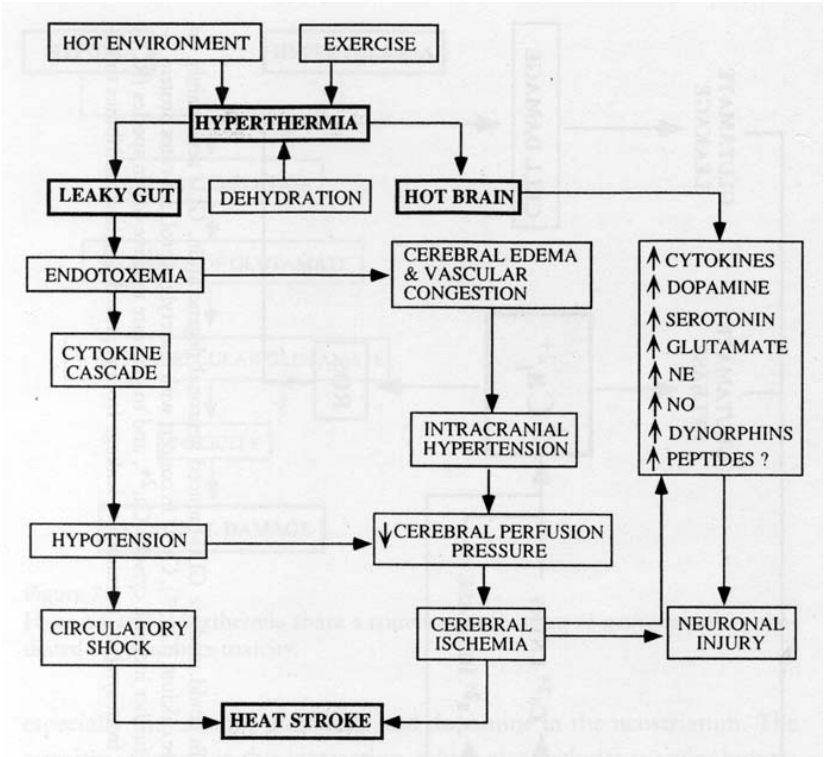


Figure 3.3: ***The combined effect of the leaky gut and burning brain theory as proposed by Gisolfi & Mora (2000).***

3.3 Physiological adaptations

Heat strain can also lead to beneficial physiological changes. These adaptations can be divided into (i) whole body changes that benefit

the organism during heat strain (acclimatization or acclimation) and (ii) cellular adaptation that increase cellular survival during heat exposure. Both mechanisms will be discussed below.

3.3.1 Acclimatization

Humans have a greater ability to adapt physiologically to heat compared to cold. It is believed that hyperthermia is the trigger of the adaptation to heat (Nielsen et al., 1997), also known as acclimatization or as acclimation in a laboratory setting. Complete acclimatization is achieved with daily 100 min. of moderate exercise for a period of 7 to 10 days (Pandolf, 1998). Some physiological adaptation and its time trial during a acclimatization period are depictured in figure 3.4. Nielsen and co-workers conducted a series of very extensive experiments (Nielsen et al., 1993 and Nielsen et al., 1997) in which they monitored acclimation process to dry and humid heat. In these experiments respectively 8 and 12 subjects exercised till exhaustion at 50% VO_2max, in a laboratory kept at 41˚C, 12% RH and 35˚C, 87% RH respectively. Both studies find an increased sweat rate, increased plasma volume, decreased heart rate and increased time to exhaustion, as a result of acclimation.

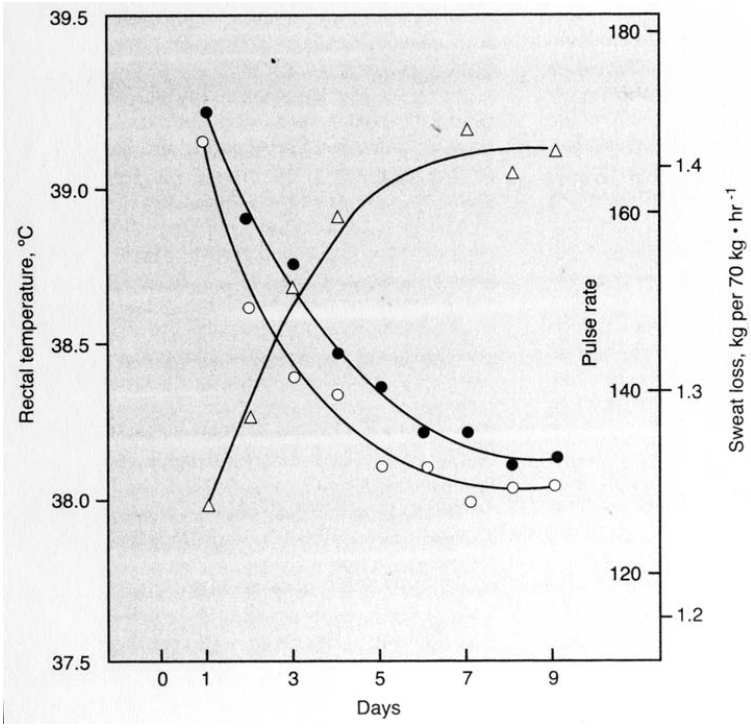


Figure 3.4: ***Physiological adaptations during the acclimatization process.*** Mean rectal temperature (●), heart rate (○) and sweat loss (Δ) in a group of men during a 9-day acclimatization period to heat. (Adapted form Lind & Bass, 1963.)

However, there are some discrepancies between these studies, it is only found in acclimation to humid heat that (i) cardiac output and stroke volume are not increased significantly and (ii) VO_2 at exhaustion is reduced. The unchanged cardiac output and stroke volume in acclimation to humid heat are explained by the various modes and intensities of exercise and to the fact that physical training induces changes that mimic acclimation responses. However, this doesn't seem to be a solid explanation since there is not much variation between subjects and protocol in both experiments. The explanation for the reduced VO_2 at exhaustion post

acclimation is coupled to the lower HR. This explanation is not completely satisfactory since HR is significantly reduced in both studies.

The results from these studies are in line with other research done to heat acclimation. In addition of these results there is evidence for a decreased T_c (Armstrong & Maresh, 1991; Pandolf, 1998 and Åstrand et al., 2003), a decreased T_{sk} (Armstrong & Maresh, 1991 and Åstrand et al., 2003), a decreased skin blood flow (Åstrand et al., 2003) and a decreased [NaCl] in sweat (Armstrong & Maresh, 1991), an overview can be found in table 3.2. These adaptations were also found by Nielsen et al. (1993) and/or Nielsen et al. (1997). However, in both studies Nielsen et al. did not find a reduced skin blood flow.

Table 3.2: ***Physiological adaptations to sustained exercise in dry and humid heat***

		Dry heat	Humid heat
[NaCl] of sweat	decrease	--	--
Body core temperature	decrease	--	--
Heart rate	decrease	--	--
Plasma volume	increase	++	++
Q and SV		+	o
Sweat rate	increase	++	++
Time to exhaustion	increase	++	+
VO2 at exhaustion		o	-

++/-- indicates an increase/decrease, +/- indicates a small (although significant) increase/decrease and o represents no change.
From: Armstrong & Maresh, 1991; Nielsen et al., 1993; Nielsen et al., 1997; Pandolf, 1998 and Åstrand et al., 2003.

3.3.2 Thermotolerance

So far the focus has been on the body as a whole. However, individual cells also respond to stress, by producing a family of proteins known as heat shock proteins (HSPs). These proteins are highly conserved: they occur in all organisms from bacteria and yeast to humans (Kregel, 2002). Different stressors can increase HSP concentration in the cell (figure 3.5). Examples of these stressors are; hyperthermia, hypothermia, ischemia-reperfusion, hypoxia, energy depletion, acidosis and reactive oxygen species formation (Kregel, 2002). HSPs were discovered in the 1960s while exposing cells to heat. Since that date these shock proteins are called *heat* shock proteins, although they are not only formed under heat shock. HSPs range in weight from 27 to 110 kDa[*] and are divided in 5 groups based on their weight. One of these groups is the HSP70 family. The HSP70 family is the most responsive to heat stress of all HSP groups (Horowitz, et al., 1997 and Kregel, 2002). The following protective functions have been attributed to HSP70 in a heat exposed cell; (i) the folding of proteins in various intracellular compartments, (ii) the maintenance of structural proteins, (iii) the refolding of misfolded proteins, (iv) translocation of proteins across membranes and into

[*] 1 Da = $1.7 * 10^{-24}$ g

various cellular compartments (chaperone function), (v) the prevention of protein aggregation, and (vi) the degradation of unstable proteins (Kregel, 2002).

In the case of cellular heat exposure above normal temperatures HSP70 starts to accumulate after some minutes (Xu, et al., 1996; Horowitz, et al., 1997 Kregel, 2002 and Moseley, 1997). Thus, after a sub lethal heat shock of a cell, HSP starts to accumulate. Interestingly these cells are able to withstand heat shocks that would be lethal in non heat shocked cells! However, it must be noted that thermotolerance is also possible without the accumulation of HSP (Moseley, 1996; Moseley, 1997 and Kregel, 2002). Despite this HSP are often coupled to thermotolerance (Moseley, 1996; Xu, et al., 1996; Horowitz, et al., 1997; Moseley, 1997 and Kregel, 2002). The process of thermotolerance is poorly understood as well as the role of thermotolerance in human acclimatization. More research into this field is ongoing.

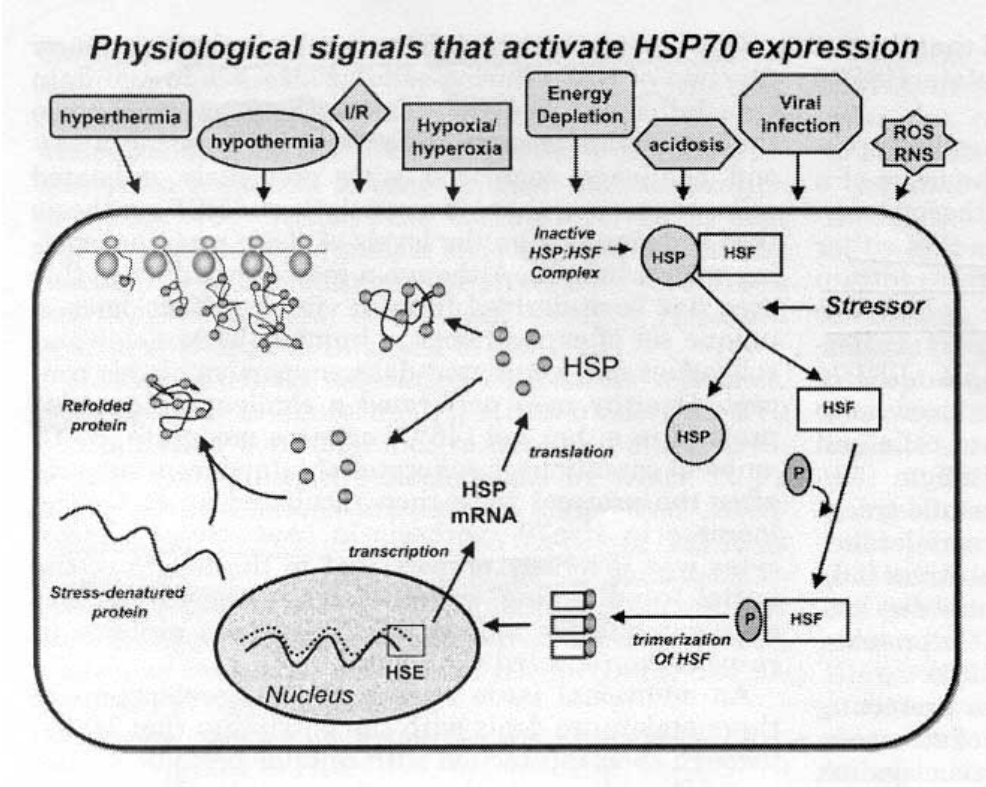


Figure 3.5: ***Physiological signals that activate HSP70 expression.*** Heat shock protein 70 (HSP70) is produced due to a cascade of reactions induced by several physiological causes, with heat shock factor (HSF) being an intermediate. I/R = ischemia-reperfusion; ROS = reactive oxygen species; RNS = reactive nitrogen species; HSE = heat shock element. (From Kregel, 2002.)

4 Short term physiological effects post heat strain

This chapter deals with physiological changes that take place after the exposure to heat strain. First acclimatization decay will be discussed, than heat related morbidity and mortality.

4.1 Decay of acclimatization

Most research done on the decay of acclimatization is less valid due to the use of small samples and/or inappropriate measurements (Armstrong & Maresh, 1991 and Pandolf, 1998). However, most adaptations will disappear in the course of 1 to 3 weeks (Armstrong & Maresh, 1991; Pandolf, 1998 and Åstrand et al., 2003). Pandolf (1998) writes in his review that acclimatization to dry heat in athletes will persist longer than acclimatization to humid heat. Acclimatization will also persist longer in physically active persons (Pandolf, 1998). This last point is not hard to understand while during physical activity the T_c is elevated, or at least heat stress is present. Since hyperthermia is the trigger for the acclimatization process (Nielsen et al., 1998) the acclimatization decay will be slowed due to physical activity.

4.2 Decay of thermotolerance

Cellular adaptation to heat, or thermotolerance, will persist for 2-7 days (Moseley, 1996 and Moseley, 1997). However, it is unclear how thermotolerance is related to thermoregulation in humans.

4.3 Heat related morbidity and mortality

Hyponatremia and hypo-osmolality can result in seizures, coma, pulmonary oedema and cardiorespiratory arrest (Montain et al., 2001 and Murray et al. 2003). There is at least one registered case of mortality due to hyponatremia (Montain et al., 2001). Unfortunately there is no research conducted on the morbidity solely due to hyponatremia and/or hypo-osmolality. However, hyponatremia and hypo-osmolality during hyperthermia can easily be prevented by drinking a fluid that has the same osmolarity as normally found in blood or cellular fluids.

Kunst et al. (1993) conducted a thorough research on outdoor air temperature and mortality in The Netherlands over a period of 8 years (1979 – 1987). They found an optimum temperature of 16.5° C whereby the mortality is lowest (figure 4.1). If ambient temperature increases an increase in mortality is seen. Kunst et al. (1993) corrected for mortality displacement (or harvesting effect) by monitoring mortality rates up to 30 days after. It was seen that in the 2 days after the increased temperature mortality rates would increase with 300%. However in the period from 3 to 30 days after the exposure the mortality rates would decrease with 150%. Thus the aggregate effect of increased temperature is 150% (300 –

150 = 150). This research was controlled for air pollution, which appeared not to have an influence on the mortality rate. Interestingly, an increase in relative humidity was not related to an increased mortality (figure 4.1). The lack of this relation is probably due to relatively low ambient temperatures. It is suggested that wet heat loss becomes important only when ambient temperature exceeds 28° C. Thus only with temperatures higher than 28° C relative humidity will influence mortality. At higher ambient temperatures, relative humidity does influence mortality rate (Leithead & Lind, 1964; Coris et al., 2004), as can be seen in figure 4.2.

The results of Kunst et al. (1993) are in line with other work done on mortality as a function of temperature (Ballester et al., 1997 and Becker & Weng, 1998). Although Ballester et al. (1997) found an optimum temperature of 24° C for the inhabitants of Valencia (Spain). Cultural differences are a good explanation for this discrepancy. It is also evident that the very young (Becker & Weng, 1998), the old (Becker & Weng, 1998) and the sick (Kunst et al., 1993; Ballester et al., 1997 and Becker & Weng, 1998) are most susceptible for high temperatures. The cause of increased mortality due to heat is unclear and research to this cause might save many lives in the future.

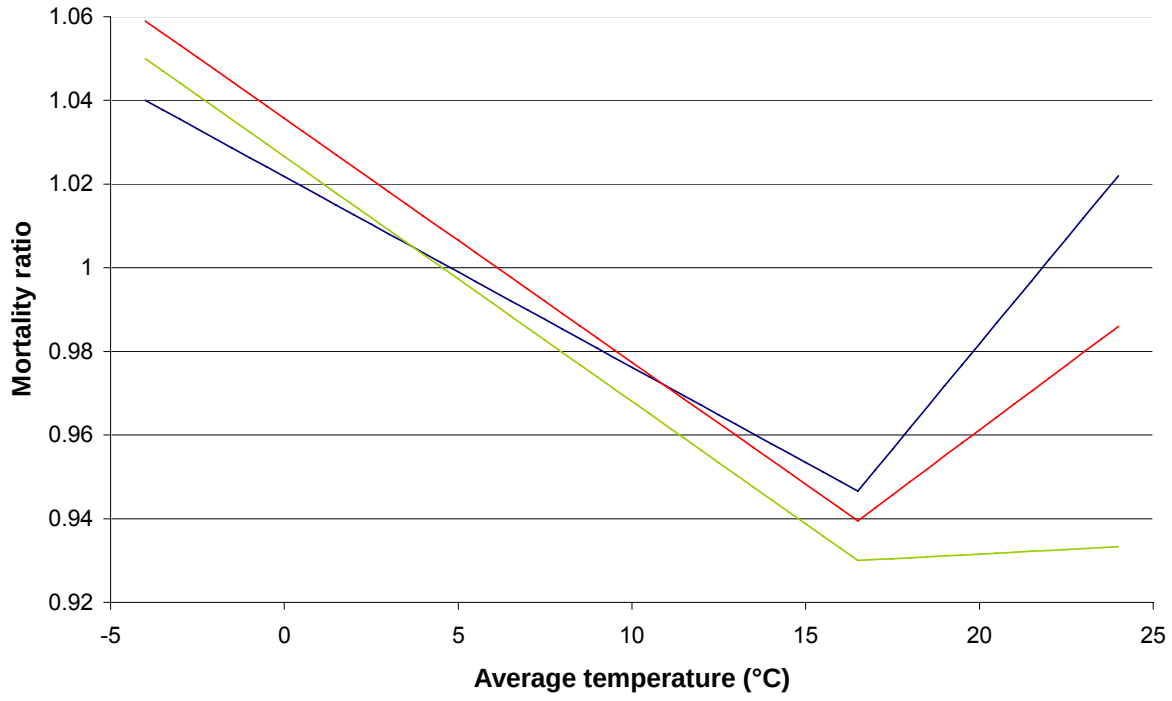


Figure 4.1: ***The relationship between mortality and average temperature in the period 0-6 days, with high humidity, strong wind and normal weather conditions respectively.***
Green curve: high humidity (= 88% / normal humidity = 79%);
Red curve: strong wind (= 4.1 $m*s^{-1}$ / normal wind=2.9 $m*s^{-1}$);
Blue curve: normal weather.
Overall average mortality ration is set to be 1.00.
(Derived from: Kunst et al., 1993).

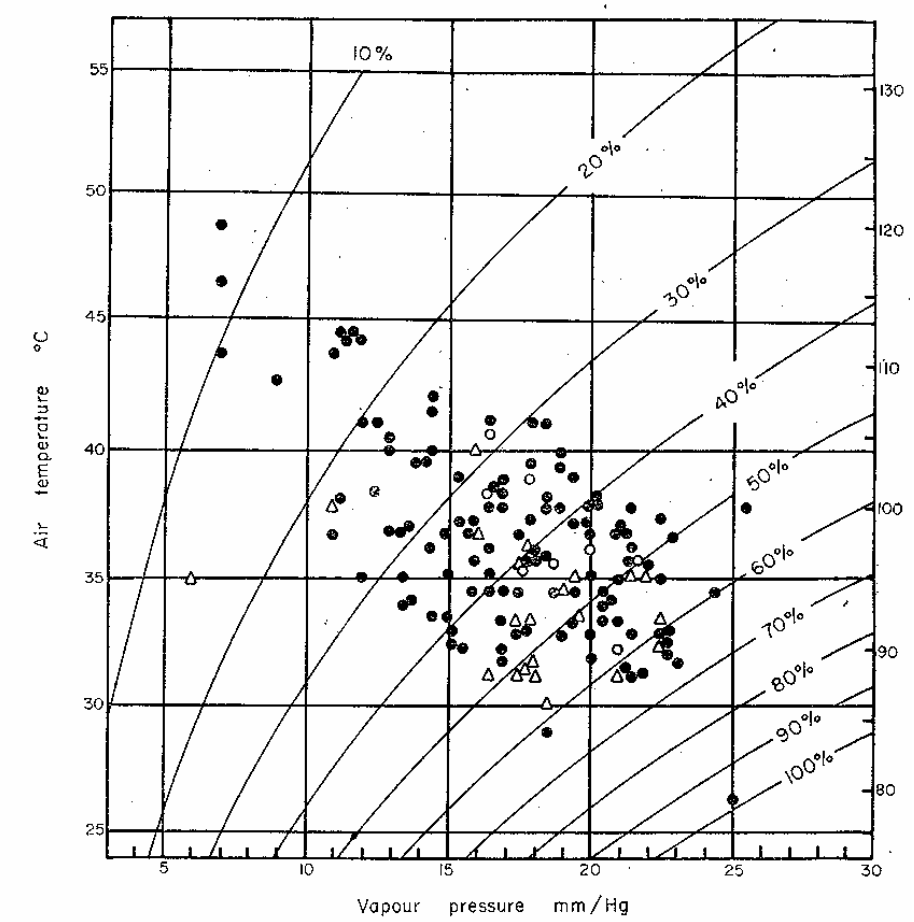


Figure 4.2: ***Humidity and maximum temperature on days of onset of cases of fatal heat stroke in US Army (1942-1944).***

Δ Subject engaged in heavy exercise in the sun, or had completed a march of 15 to 25 miles during the day.

● Subject engaged in average activity in the sun, i.e. drill, guard duty, or relatively short march; activity not known in few a cases.

○ Subject indoors during the day.

% Relative humidity.

From: Leithead & Lind, 1964.

5 Long term health effects post heat strain

The long term health effects of a sustained heat strain will be dealt with in this chapter. All organ systems which are suspected (based on literature search) to be influenced on the long term by sustained heat strain will be discussed. The following systems will not be discussed due to a lack of literature concerning long term health effects post heat strain: digestive, endocrine, immune, musculoskeletal and respiratory system. All other systems will be discussed below, the neurological system will be discussed in the paragraph 5.3 (thermoregulatory system). This chapter will end with a paragraph about neonatally induced thermotolerance.

Since little empirical longitudinal research have been conduced on this topic a large amount of scientific literature is used to speculate about the long term health effects of sustained heat strain. Recent topics related to thermoregulation will be explained in more detail if their role in the long term health effects are unclear. Examples of such a current subjects are aquaporins in kidneys and sweat glands.

5.1 Circulatory system

In the United States the prevalence and incidence of hypertension is much higher among African-Americans than American Caucasians (38% vs. 20% respectively and an incidence of 2-6 fold higher). Moskowitz (1996) demonstrates that the cause of this hypertension can be traced back to their original habitat and to the slavery trade. Fluid conservation is very important in high temperature environments in conjunction with limited water supply. It is speculated that some Africans are genetically adapted to this by producing an increased aldosterone concentration. According to Moskowitz (1996) this is beneficial in sustained heat stress conditions. However, under non heat stress conditions, as in many places in the Unites States this genetical adaptation results in hypertension. In time hypertension can cause heart failure.

However, next to this genetical predisposition there is no evidence of any long term effect of sustained heat strain on the circulatory system.

5.2 Urinary system

5.2.1 Aquaporins

Human consist for 60 – 70% of water (Åstrand & Rodahl, 1986), this water can diffuse freely through membranes. However, it was known for some time that transport speed of water through some membranes was higher than could be explained only by diffusion. In 1991

Agre and co-workers discovered de existence of water channels or aquaporins (AQPs) in membranes of erythrocytes. Since this discovery, at least 11 different AQPs have been identified, in different membranes and different species. Several types of AQPs are found in the urinary system. The urinary system is essential for life, like all the other organ systems, however, heat strain places a heavy burden on the urinary system. Sweating will at first cause an increase in osmolality since proportionally more water is lost than electrolytes. To bring the osmolality to normal levels the kidneys will absorb more electrolytes. In this process water transport through membranes are crucial, AQPs play an important role in this process (Nielsen et al., 2002 and Schrier & Cadnapaphornchai, 2003). Thus far research has revealed that the regulation of AQPs is a very dynamic process and regulated by hormones such as vasopressin. To date it is unknown whether heat strain has a long term effect on kidney AQPs, if there is any effect it is likely caused by its regulators such as vasopressin.

5.2.2 Nephrolithiasis

There appears to be a relationship between chronic dehydration due to work in the heat and nephrolithiasis (the development of kidney stones). Borghi et al. (1993) studied 236 employers of a glass plant in Italy exposed to heat (30° C WBGT) and 165 employers of the same factory not exposed to heat (25° C WBGT). The workers exposed to heat had no history of nephrolithiasis and worked for a minimum of 5 years in the same heat conditions. Urine analysis revealed an increased uric acid (722 vs. 482 $mg*l^{-1}$), decreased pH (5.3 vs. 5.6), increased specific gravity (1026 vs. 1021 $kg*m^{-3}$) and higher incidence of stone forming (8.5 vs. 2.4%). They concluded that the higher incidence of stone forming was caused by an insufficient fluid intake (dehydration). This is supported by an epidemiological survey that demonstrated a higher prevalence of nephrolithiasis in populations of hot climates (Parry & Lister, 1975). Better et al. (1978) studied workers exposed to heat and intense sunlight for at least 6 months a year and confirm a higher incidence of kidney stone disease. A sufficient fluid and salt intake seems to be the solution to this problem. However, athletes do not replace sufficient fluids voluntarily while exercising in a hot environment (Nielsen & Krog, 1994 and Murray, 1995). This is most likely also the case for employees working in hot environments. Increasing or keeping the productivity high might hinder fluid intake

There might also be a link between sunshine and nephrolithiasis. This link is formed by vitamin D, which is generated due to ultraviolet B radiation from sunlight and stimulates the absorption of calcium from the intestines (Holick, 2003). An increased vitamin D production can lead to an increased calcium concentration in the blood and thus to an increased calcium flux through the kidneys. An increased calcium flux through the kidneys coexists with an increase risk of nephrolithiasis (Shekarriz & Stoller, 2002). This hypothesis is postulated by

Parry & Lister (1975). Unfortunatly, too little research is conducted on sunlight and nephrolithiasis. However, if such a link might exist it can easily be prevented by using sunscreen (Holick, 2003).

5.3 Thermoregulatory system

Some research is conducted on the long term effect of heat stroke. Shapiro et al. (1979) examined 9 young men whom suffered from heat stroke 2 – 5 years earlier and 10 young men without a history of heat illness. They found significant differences in heart rate and rectal temperature between the two groups during exercise (40 and 80 W for 45 and 20 min. respectively) at room temperature (23° C, 50% RH) and high ambient temperature (40° C, 50% RH). VO_2 was significantly lower in the former heat stroke patients during the hot trial. Shapiro et al. (1979) could not explain this. There was no significant difference found in sweat rate. It was concluded that since the former heat stroke patients generated the same amount of external power (and even had a lower VO_2), their significant higher T_c might indicated an impaired transport of heat from the core to periphery.

The ability of former heat stroke patients to acclimate was the subject of a study from Armstrong et al. (1990). This study was conducted with 10 subjects who suffered from heat stroke 61 (± 7 SD) days earlier. The subjects together with a control group (n=5) performed walking exercise for 90 minutes on a treadmill in a conditioned room (5.6 km*hour^{-1}, 5% grade, 40.1° C and 25.5% RH) for 7 consecutive days. There were no significant differences found in HR, T_c, urine gravity between the former heat stroke patients and the controls at the start, during and at the end of the acclimation process. An interesting finding was that one former heat stroke patient still appeared to be clinical heat intolerant. This subject was discharged from the study but volunteered for the same test 11 months after the occurrence of the heat stroke, at this point the subject did not show any significant differences anymore with the controls.

Royburt et al. (1993) compared 21 young men with a history of heat stroke (6 months post hospitalization) with a closely matched control group without a history of heat stroke. From this study it was concluded that there were no differences between the two groups in psychological or physiological functioning.

Armstrong et al. (1990) and Royburt et al. (1993) found no difference between former heat stroke patients and control subjects in HR and T_c during exercise. However, there is one difference in subject characteristics between the studies of Shapiro et al. (1979) and Armstrong et al. (1990). The former heat stroke patients in the study of Shapiro et al. (1979) had a mass of 69 kg versus 85 kg in the study of Armstrong et al. (1990). Another difference

is the time spent in the conditioned room, which was 3 hours and 90 minutes respectively. The differences between the studies of Shapiro et al. (1979) and Royburt et al. (1993) are minimal since the physiological test used by the latter was based on the test used by Shapiro and co-workers. However, a more likely explanation is the date of occurrence of heat stroke. The subjects in the study by Shapiro et al. (1979) suffered from heat stroke around 1976 against 1988 in the study of Armstrong et al. (1990) and 1989 in the report of Royburt et al. (1993). A great body of literature concerning prevention and treatment of heat stroke has been published between 1976 and 1988. It could be that the response and treatment was faster and more efficient in the subjects used in the study of Armstrong et al. (1990). Lew et al. (2002) noticed that the response time and treatment are important factors in uncomplicated recovery. However, the response time is not mentioned in the three studies.

Thus it is not clear whether former heat stroke patients are more sensitive to heat after some recovery time. However, the former heat stroke patients used in the above mentioned studies suffered from exertional heat stroke. It must be noted that the fact that a history of heat stroke is included on all lists concerning elevated risk factors for heat illness (e.g. Gisolfi & Mora, 2003 and Coris et al., 2004) does not mean that heat stroke causes a degration of the thermoregulatory system. It is equally likely that former heat stroke patients had a degraded thermoregulatory system beforehand.

From research done during the 1995 heat wave in Chicago, which resulted in 600 excess deaths, only 52% of the former classic heat stroke patients survived the first year (Dematte et al., 1998)! Unfortunately none of these patients (n=58) recovered completely within a year. The authors concluded that near fatal classic heat stroke is associated with multiorgan dysfunction. It is hard to compare patients suffering from exertional and classic heat stroke, since the former affects healthy athletes (mostly soldiers) and the latter affects the elderly and the sick. Another problem is whether the casualties from classic heat stroke would have died shortly after the hyperthermia (mortality displacement or harvesting effect) and thereby exaggerating the effect. Thus patients suffering from classic heat stroke are less favoured, they have a 50% change to die in the first year after the occurrence of heat stroke and will most likely not recover completely within a year.

5.4 Reproductive system

No research has been conducted on the effect of a temporary hyperthermia exposure on the long term function of the reproductive system. All research concentrated on the acute effect of work in high ambient temperatures on the fertility or delayed conception. Rachootin & Olsen (1983) studied the effect of chemical, physical agents and work processes on infertility of males and females. They found that exposure to heat was associated wit a 1.8 times

greater risk of delayed conception. It was further found that spermatozoa have a greater change of showing more morphological abnormalities. This finding was explained by the fact that the optimum testicular temperature is 34 – 35° C for spermatogenesis and it is assumed that work in the heat will rise testicular temperature. In this study heat was not found to impair the reproductive system of females. Another study examined the fertility of male workers exposure to high temperatures (WBGT of 38° C) in different ceramic factories in Italy (Figà-Talamanca et al., 1992). They only found significant differences in last time to pregnancy and spermatozoa velocity, all being less well in the exposed workers. Although trends were found that (i) semen morphology and mortality and (ii) percentage of marriages without pregnancies are less well in the exposed workers.

The findings of the majority of the studies conducted on heat and fertility or delayed conception found that heat degrades the spermatogenesis with no effect on the reproduction system in females (Blair & Wilcox, 1986 and Mur et al., 1998). It is generally believed that temperature rise of the testicles is the direct cause of the degraded spermatogenesis. There is no evidence to assume that the negative effect on spermatogenesis will persist after the hyperthermia exposure. On the contrary, Procope (1965) exposed 12 married students to heat in a sauna bath. This resulted in a reduced sperm count. However, the sperm count recovered rapidly hereafter. Almost all human populations exhibit seasonal variation in births (Bronson, 1995 and Sharpe, 2000). This is partly explained by seasonal variation in the frequency of conception. Bronson (1995) also recognizes temperature as an important factor. With birth-rates lower 9 months after the summer season and higher 9 months after the winter season, indicates a recovery of the heat exposure.

There is evidence that hyperthermia can cause embryonic degeneration in rabbits (Cheng et al., 1999). They exposed 52 female white rabbits for 5 consecutive days to 8 hours of 33° C (10-30% RH) followed by 16 hours of 25° C (10-30% RH). After these 5 days the rabbits were removed from the experimental chamber, given hCG (to induce super ovulation) and paired overnight. 19 hours later embryos were recovered and cultured in vitro for 96 hours. After this period the embryos were examined and it was concluded that 40% of the embryos were degenerate. However, it is unknown whether this phenomenon exists in humans.

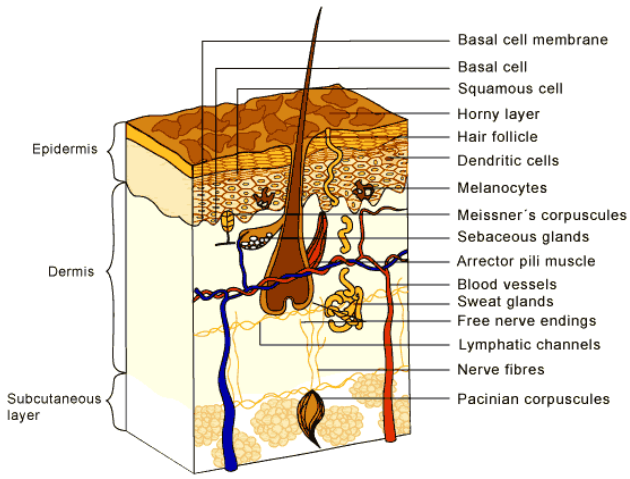
5.5 Skin system

The skin is the interface between the body and its environment and it is important in preserving homeostasis during environmental changes. As explained further above the skin is also essential in thermoregulation due to wet and dry heat loss. For a full understanding of this paragraph it is important to have some basic knowledge of the physiology of the skin. The skin is divided into different layers; epidermis, dermis and a subcutaneous layer.

The epidermis is the outer layer consisting mainly out of keratinocytes. There function is to provide a mechanical and chemical barrier. Of importance to this paragraph are also the Langerhans cells located in the epidermis. These cells mark other cells that don't belong to the individual, like antigens. In this Langerhans cells play an important immunological role (Vloten, et al., 2000).

The epidermal basale-membranezone provides the attachment of epidermis with the dermis. Another important feature is that molecules greater than 40 kDa can not pass through this membrane. The shape of the epidermal basale-membranezone is far from plain (figure 5.1), due to this accentuated membrane the surface area between the epidermis and dermis is greater than in the case of a plain surface (Vloten, et al., 2000).

The dermis is vasculated and it is in this layer that the blood flow is increased due to vasodilatation. Afferent and efferent nerve endings can also be found in this layer. However, the better part of the dermis consists of cells and fibres. Most of these cells are fibroblasts and there purpose is to synthesise the different type of fibres. The fibres in the dermis can be differentiated in three groups, collagen, elastine and reticuline fibres. The collagen fibres are important for this paragraph. Their function is to provide protection against external force and to provide elasticity of the skin (Vloten, et al., 2000).



Figuur 5.1: ***Skin structure***

5.5.1 Sweat gland and aquaporins

A sweat gland is a coiled tubular system which has the purpose of producing a hypotonic solution with a minimal osmolarity. As a filtering system a sweat gland is a more primitive version of a nephrone (kidney unit). Aquaporins (AQP) have an important function in the kidneys as explained above, how is this in sweat glands? Nejsum et al. (2002) where the first to prove the existence of AQP in sweat glands (referred to as AQP-5). To research the functionality of AQP-5 in sweat production they measured pilocarpine induced sweat rate in wild mice and AQP-5 missing mice. The AQP-5 lacking mice did not differ in number or morphological appearance of sweat glands. However, the wild mice had a higher number of visibly functional glands. From these results Nejsum et al. (2002) conclude that:

These studies establish an essential role (…) for AQP-5 in sweat production that may be of importance for understanding thermoregulation and the pathophysiology of hyperhidrosis or hypohisrosis.

Song et al. (2002) conducted a similar experiment and did not find a significant difference in sweat production. Therefore they conclude that although AQP-5 exists in sweat glands they do not seem to have a function. However, in these studies there was a major difference in administered pilocarpine, 50 $\mu g*kg^{-1}$ and 80 $mg*kg^{-1}$ respectively. The morphology and physiology difference of human sweat glands versus mice must also be taken into account in order to conclude anything from these and future studies in animals about the human sweat glands. Thus far the function of AQP-5 in human sweat glands is unclear, future research can perhaps link AQP-5 to a long term health effects due to sustained heat strain. To gain understanding about the function of AQP-5 in human sweat glands more research is needed.

5.5.2 Aging and carcinogenesis due to radiation

None of the studies done on the effect of high ambient temperature on the skin, differentiated temperature from radiation. Therefore the effect of temperature and radiation on development of skin disorders (dermatology) will be discussed in the same paragraph. It is generally believed that radiation is the primary cause of dermatological problems (Yost, 1992). Although ambient temperature, wind and humidity can accelerate the development of skin pathologies (Owens, 1978).

Although not necessarily coupled to hyperthermia, radiation is not necessarily coupled to hyperthermia but both will often coexist. Ultra violet (UV; λ= 100 – 400 nm) and infrared radiation (IR; λ= 750 - 10^5 nm) can induce several dermatological changes. UV light is mostly produced by the sun, IR is produced by heated objects and is present in cosmic radiation. An important long term health effect of UV and IR on the skin is aging (Benedetto, 1998). In the epidermis several changes are induced by UV and IR, of which decreased number of langerhans cells, ineffective pigmentation and decreasing contact surface between epidermis and dermis.

The effect of UV en IR on the dermis is hyperplasia of abnormal elastic tissue, increase in glycosaminoglycans, decreased capilarisation and destruction of sweat glands (Benedetto, 1998). The decreased capilarisation and destruction of sweat glands will impair thermoregulation. These changes are not directly induced upon exposure but are evident long after the exposure.

However, the most important effect of radiation on the skin is the development of cancer cells (carcinogenesis) (Page & Shear, 1988; Polla, 1990; Yost, 1992, Ichihashi, et al., 2003). Three types of cancer have been associated with UV and/or IR radiation; basal cell

carcinoma, squamous cell carcinoma and malignant melanoma (Yost, 1992). To avoid dermatological pathologies several organisations defined exposure limits, including the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and American Conference of Government Industrial Hygienists (ACGIH). The ICNIRP guideline for UV recommends a limit of 30 $J*m^{-2}$ for an 8 hour period. The ACGIH recommends a limit of 10 $mW*cm^{-2}$ for IR. Sisto et al. (2000) conducted research on radiation levels of employees of two traditional glass factories in Italy. Unprotected employees in these factories are exposed to high IR levels which exceeds the recommended limits of the ICNIRP with a factor 15! Protected clothing or other forms of shielding must be introduced for these employees.

However, people wearing clothing are more protected against radiation (Yost, 1992 and Ichihashi et al., 2003). This reduced risk especially accounts for soldiers who are mostly obligated to wear long trousers and long sleeve shirts.

Page & Shear (1998) makes notice of skin burns that can occur with a temperature of only 44˚C. The time of exposure and skin temperature are negatively linked. A temperature of 47˚C can cause skin burns in 45 minutes, whereas a higher skin temperature will need less time to cause skin burns. However, the literature doesn't give any cases of skin burn caused by hyperthermia (or another form of heat strain), therefore this will not be discussed further.

5.6 Neonatally induced thermotolerance

A very interesting study is done by Arjona et al. (1990). They exposed cockerels 5 days after birth to heat of 36° C for 24 hours, whereas normal brooding temperature 5 days after birth is 27° C. At day 43 and 44 after birth these cockerels and a control group were exposed to heat stress of 36° C for 8 hours each day, in contrast of the normal ambient temperature of 21° C. Interestingly there was no difference in mortality in the first 42 days between the exposed and control group (4 and 5% respectively). During the heat exposure on day 43 and 44 the mortality rate was significantly higher (4 and 20% respectively). They further found no differences in body temperature, surface to core ratio, weight, feed consumption, feed efficiency, plasma T_3 and T_4 levels and plasma glucose concentrations. However, there was a significant lower heterophil to lymphocyte ratio in the exposed group during day 43 and 44. This ratio corresponds to the stress level, this seems to suggest that the exposed cockerels were less affected by high ambient temperature as the control cockerels. Arjona and co-workers (1990) could not explain the difference of mortality rate in the exposed and control group. In 1997 Yahav et al. conducted a similar experiment and found a drastically reduced mortality rate during heat strain (36° C and 75% RH) in neonatally exposed chickens as opposed to the control group (47 and 65% mortality rate respectively). Interestingly Yahav et al. (1997) found a lower HSP syntheses rate in the neonatally exposed chickens (53 and

245% from base line values respectively) unfortunately they did not report the base line HSP values. Another interesting finding is the concentration of thyroid hormones (T_3 and T_4) in the blood, which were significaly lower in the neonatally exposed group compared to the control group. Yahav et al. (1996) explained the thermotolerance of the exposed chickens by an improved ability to reduce thyroid hormone concentration in the blood. Thyroid hormones are important in inducing the production of uncoupling proteins (UCP) and thereby stimulating heat production, as discussed in chapter 2. However, Arjona et al. (1990) did not find an increased thyroid hormone level. Zulkifli et al. (2003) exposed chickens at 4, 5 and 6 days after birth to food deprivation (FR) or to high temperatures 36° C (55% RH) for 1 hour from day 1 till day 21 (HT) or both (FRHT). All groups, including a control group were exposed to 39° C (55% RH) at day 35 after birth. They found a reduced heterophil/lymphocyte ratio and reduced HSP70 production during the exposure on day 35 in the neonatally exposed chickens compared with the controls. There were no differences between the FR, HT and FRHT groups, except for a higher body core temperature in the FRTH group at the end of the exposure on day 35. Thus not only neonatally exposure to heat can increase the thermotolerance later in life, food deprivation seems to have a similar effect. Thermotolerance can also be increased with cold exposure (Shinder, et al., 2002).

It appears that due to neonatally exposure to heat, thyroid hormone concentration in the blood decreases, HSP production is reduced and that mortality rate is lower during a heat exposure later in life (Arjona et al., 1990; Yahav et al., 1996 and Zulkifli et al. 2003). However, the mechanism underlying neonatally induced thermotolerance is not well understood and the research results are inconclusive, thus more research is needed in order to understand this mechanism. Furthermore the research of Arjona et al. (1990), Yahav et al. (1996) and Zulkifli et al. (2003) where conducted on young chickens and there is no evidence of neonatally induced thermotolerance in humans.

6 Conclusions

The purpose of this literature review was to investigate the long term health effects of sustained heat strain. Only a limited amount of literature has been published on this topic, and mainly focuses on heat stroke and nephrolithiasis. In general the long term health effects can be divided into negative (degration) or positive (adaptation). Based on research it can be concluded that long term effects of workers exposed to sustained heat strain for a period of at least 6 months have an increased risk of a degration of their physiological system compared with persons who are not exposed to heat strain. There is no evidence in the scientific literature for a positive long term health effect.

It appears that inhabitants and workers in hot environments have an increased risk of nephrolithiasis. It is generally believed that hyperthermia induced hypovolemia is the cause of this increased risk. Furthermore, an increased vitamin D production due to ultra violet B radiation can also be a cause of an increased risk of nephrolithiasis. There are some indications that persons suffering from exertional heat stroke have no impaired thermoregulation years later. However, these indications are controversial and need more research. Most persons suffering from classic heat stroke will show a degration of their physiological system months later. Hyperthermia of the male reproductive system will lead to a decreased sperm quality. However, there appear to be no long term effect, but more research is needed to investigate this. Skin exposure to (solar) radiation increases the risk for carcinogenesis in and aging of the skin. Arjona et al. (1990) revealed a relationship between heat stress 5 days after birth and an increased heat resistance 43 days after birth. This phenomenon is yet to be explained. There is no evidence that neonatally induced thermotolerance occurs in humans. More research is needed on this extraordinary topic.

Thus, sustained heat strain for at least 6 months might have a negative long term health effect. Due to the lack of literature on the long term health effects it was often impossible to link the results of different articles and postulate a (physiological) mechanisms inducing these long term health effects. However, more research into this field is needed and with this literature review I hope to stimulate research on subtopics which need more attention.

7.1 Summary

Employers are increasingly responsible for the health of their employees. Since many occupations take place under heat stress conditions the risk of sustained heat strain is increased in these employees. However, little is known about the long term health effects of sustained heat strain. It is the goal of this thesis to review the literature published on these long term health effects. Every organ system of the human body was investigated by reviewing the available literature found with PubMed. It was found that employees at hot jobs have an increased risk of; i) nephrolithiasis due to hypovolemia, ii) probably temporary degration of the spermatogenesis, iii) development of carcinogenesis in and aging of the skin due to (solar) radiation. In addition, complete recovery from exertional heat stroke is often described in the literature. Recovery from classic heat stroke appears to be more problematic. Another long term effect of sustained heat strain in new born chickens is neonatally induced thermotolerance, unfortunately this is not investigated in humans. Thus, sustained heat strain increases the risk of pathologies and/or impairs well being. However, more epidemiological research is needed to the long term health effects of sustained heat strain.

7.2 Samenvatting

Titel: De lange termijn effecten op de gezondheid van een langdurige warmtebelasting.

Werkgevers worden steeds meer verantwoordelijk gesteld voor de gezondheid van hun werknemers. Veel banen worden verricht onder hitte stress condities. Een gevolg van deze hitte stress is een verhoogde (thermo-)fysiologische belasting op het lichaam, ook wel warmtebelasting genoemd. Er is weinig bekend over de lange termijn effecten op de gezondheid van een langdurige warmtebelasting. Het doel van deze scriptie is een overzicht te geven van de tot nu toe gepubliceerde literatuur gerelateerd aan dit onderwerp. Alle orgaanstelsels van het menselijk lichaam zijn bestudeerd door aan gezondheid en warmtebelasting gerelateerde literatuur op te zoeken door middel van PubMed. Uit de resultaten blijkt dat arbeiders die blootstaan aan hitte belasting een grotere kans hebben op; i) nierstenen veroorzaakt door hypovolemia, ii) (waarschijnlijk tijdelijke) degeneratie van de spermatogenese, iii) ontwikkeling van kankergezwellen in en veroudering van de huid onder invloed van (zonne-) straling. Mensen die een klassieke hittestuwing opgelopen hebben blijken niet of slechts gedeeltelijk te herstellen. Kuikens blijken een verhoogde hitte weerstand te hebben wanneer zijn vlak na de geboorte worden blootgesteld aan hoge omgevingstemperaturen. Maar het is onduidelijk of dit fenomeen zich voordoet bij mensen. Samenvattend lijken arbeiders met een chronische warmtebelasting een grotere kans te hebben op het ontwikkelen van een pathologie en/of verlaging van de leefkwaliteit. Om meer inzicht te krijgen in deze lange termijn effecten is meer epidemiologisch onderzoek nodig.

8 Glossary

Acclimation: Physiological or behavioural changes occurring within an organism, which reduces the strain or enhances endurance of strain, caused by experimentally induced stressful changes in particular climatic factors.

Acclimatization: Physiological or behavioural changes occurring within the lifetime of an organism that reduce the strain caused by stressful changes in the natural climate.

Adaptation: Changes that reduce the physiological strain produced by stressful components of the total environment. This change may occur within the lifetime of an organism (*phenotypic*) or be the result of *genetic* selection in a species or subspecies.

Heat strain: A physiological demand placed on the body to counterbalance or minimize a rise in body core temperature (such as, increased heart rate and increased sweat rate).

Heat stress: Climatic conditions above the thermally neutral, resulting in heat strain.

Hyperthermia: An elevated body core temperature above the normal range. According to Mackowiak et al. (1992) this means a body core temperature of more than 37.7° C in healthy individuals. The raise in temperature can be caused by physical of pharmacological means.

Hypertension: An abnormally high blood pressure (systolic > 150 mmHg and diastolic > 95 mmHg).

Hypoosomolality: Low osmolarity of the blood serum (< 260 mOsm/kg).

Hyponatremia: Low plasma sodium concentration (< 135 mM).

Hypovolemia: Reduced extracellular volume.

Normothermia: The condition of a temperature regulator when its core temperature is within ± 1 standard deviation of the range associated with the normal post absorptive resting condition of the species in the thermoneutral zone.

Osmolality: Number of particles solved in blood serum without fibrinogens.

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