

## **The Physiology of Mammalian Temperature Homeostasis**

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**Objectives:** The purposes of this monograph are to: 1) describe the unique features of mammalian thermoregulation, 2) emphasize the importance of behavior and passive heat transfer as thermoregulatory mechanisms, and 3) propose a noninvasive alternative to general surface temperature manipulation as a means for effective treatment of heat- and cold-stressed individuals.

### **Preface**

Mammalian temperature regulation has been the subject of scientific investigation since the advent of thermometers that could be inserted into an orifice of the body. Thousands of research articles, review articles, and book chapters have been written on the subject. A substantial portion of the *Handbooks of Physiology Section 4: Environmental Physiology* (American Physiological Society, 1996) deals with temperature regulation and is a comprehensive reference resource. Several more condensed detailed monographs of mammalian thermoregulation have also been published (e.g., Clark and Edholm, 1985; Gordon, 1993; Jessen 2000) and every animal physiology and medical physiology textbook has a section dedicated to temperature (e.g., Guyton and Hall, 2000; Schmidt-Nielsen, 1997), as do most college general biology textbooks (e.g., Purves et al., 2003). This current monograph is a focused, concise description of mammalian temperature regulation as it relates to temperature management of humans in emergency medical situations. Unless specifically referenced, the materials presented here have been compiled from the general reference sources listed above.

### **Introduction**

Humans, unlike other species of mammals, are found in most terrestrial biomes of the planet: from temperate tropical rainforests to arid hot subtropical deserts and cold polar tundra. Humans have the ability to rapidly transfer from one biome to another. What makes humans unique is not the physiological capacity to tolerate a wide range of environmental conditions, rather it is the ability to create and occupy survivable microenvironments in otherwise inhospitable regions. Most mammals are limited to narrow thermal niches and have specific physiological adaptations that enable survival in those particular niches. These adaptations are modifications and/or amplifications of physiological characteristics common to all mammals. An understanding of the basic thermophysiology of mammalian temperature regulation should enable the development and implementation of effective means for treating thermal maladies in humans.

Most mammals, including humans, maintain relatively constant internal temperatures despite changes in ambient conditions and fluctuations in internal heat production. To achieve this end, an individual must be able to: 1) protect the internal milieu from external thermal challenges and 2) dissipate excess internally produced heat. Heat balance, the ability to match heat loss and heat

gain, is achieved by the appropriate activation of specific thermoregulatory effector mechanisms. Responses to thermal challenges fall into two categories: behavioral and autonomic. Behavioral responses involve conscious sensing of the internal and external environmental conditions and selecting the optimal thermal microclimate from those available. Autonomic responses include changes in vasomotor tone, evaporative cooling (sweating, panting, or saliva spreading), and metabolic heat production (exercise, shivering, and/or non-shivering thermogenesis).

Heat balance must be achieved without exhausting limiting resources: metabolic fuel in the cold and body water content in the heat. If the cost of maintaining core body temperature exceeds the storage capacity of the limiting resource, the individual will not survive. The activation of the various thermoregulatory effector mechanisms is hierarchical and minimizes resource expenditure. Behavioral responses and adjustments in passive heat transfer through changes in local circulation require little resource expenditure, while evaporative heat loss and metabolic heat production mechanisms are more resource costly. Thus, when thermally challenged, behavioral and vasomotor responses precede the activation of heat production and water loss responses. The resource-expensive responses are reserved for extreme conditions that cannot be accommodated by behavioral and passive responses.

An example of the complex thermoregulatory challenges that mammals can face is provided by black bears indigenous to the sub-Arctic regions. Annual temperature cycles in the sub-Arctic regions are extreme: winters are cold and food is scarce, summers are warm and food is abundant. Animals that do not migrate must endure these annual cycles. Black bears, as seasonal hibernators, are inactive and hypometabolic in the winters and, thus, metabolic heat production is lowest during the coldest environmental conditions (Nelson et al., 1973, Barnes et al., 1999). Despite the reduced metabolic activity and behavioral quiescence, black bears maintain relatively high core temperatures throughout the winter (Barnes et al., 1999). The relatively high core temperatures are enabled largely by a thick coat of fur and a layer of subcutaneous fat that protect the internal tissues from the external cold. Heat loss is further minimized by passing respiratory gasses through nasal turbinates, a dense matrix of thin-wall calcified structures in the snout which form a network of small-diameter channels. The ebb and flow of air through the turbinates creates a heat trap that reduces respiratory heat loss.

In the spring when the black bear emerges from hibernation the challenges to the thermoregulatory system are reversed, going from protecting against the external cold to preventing overheating. Bears neither shed their fur nor alter their subcutaneous insulation upon emergence from hibernation. The insulation that enables a high core temperature throughout the cold winters also limits heat dissipation capacity during the warm summers. Yet, despite the 4-6 fold increase in basal metabolic rate and periodic increases in metabolic effort associated with motor activity (up to 10 fold over basal metabolic rate), these animals maintain a relatively stable internal environment.

To survive such extreme annual environmental temperature and activity cycles, these animals must be able to dissipate internally produced heat despite the insulation layers. Only limited regions of a bear's body surface lack external insulation: the pads of the feet, the tip of the snout and the tongue. Underlying these exposed surfaces are unique vascular structures capable of delivering large volumes of blood directly to the subcutaneous space. In bears, thermoregulatory vasomotor responses are confined to these radiator-like vascular structures underlying the non-insulated body surface regions (Tøien et al., 1999). Similar radiator-like structures underlie non-

insulated surfaces of most terrestrial mammals, including humans (Baker, 1982; Bergersen, 1993; Gemmell and Hales, 1977; Heath, 1998; Tattersall and Milson, 2004; Jessen, 2001).

### **The physics of mammalian temperature regulation**

Heat is produced internally in mammals as a byproduct of cellular metabolism and is lost to the environment across the body surface. Homeothermy is maintained by controlling the transfer of the internally generated heat to the body surface.

Heat is lost from the surface of an object through radiation, conduction, convection and evaporation. Radiant heat transfer occurs in the absence of contact between objects. Conductive heat transfer occurs between physical objects (solids liquids or gases) in contact with one another. Radiation and conduction are fixed physical phenomena that cannot be manipulated, but are a function of the temperature differential between the body surface and the environment. Convection, heat transfer associated with the movement of a fluid (both liquid and gaseous), and evaporation, the conversion of a material from a liquid state to a gaseous state, enhance heat transfer from the body surface. Convection and evaporation in biological systems can be manipulated by adjusting fluid movement (convection) or delivering an expendable fluid to the interface surface (evaporation).

Convection influences both external heat transfer between the body and the surrounding environment and internal heat transfer between various tissues and regions of the body. *Natural convection* occurs when a warm object is placed in a still body of cool fluid or gas. The cooler medium in direct contact with the warm object takes up heat from the object, becomes more buoyant and rises. This upward streaming of the warmed fluid carries heat away from the object. Natural convection can be reduced by compartmentalizing the fluids surrounding an object and thereby limiting the range of the upward streaming capacity. External insulation reduces convective heat loss from the body surface while cell membranes effectively eliminate natural convection within the tissues of the body.

*Forced convection* is the increase in heat transfer by the passage of a medium over the surface of an object. Blood flow is movement of fluid inside the body and adds a forced convective component to heat transfer within the body. In this case, the objects which are subject to heat transfer are cells. Blood flow through metabolically active tissues increases heat transfer between the active cells and the cooler tissues and fluids surrounding them. At rest, blood flow is primarily directed to the metabolically active visceral organs and, thus, heat produced by those organs is conserved within the body core. During exercise, blood flow through active muscles transfers heat out of the muscles. Similarly, blood flow through the subcutaneous space delivers heat to the skin.

### **Thermophysiology**

Mammals have evolved mechanisms for harnessing the heat released as a byproduct of cellular metabolism to generate a stable internal thermal environment. The adaptations that enable mammalian survival without excessive resource expenditure for thermoregulation are insulation, respiratory gas heat traps, and a mechanism for efficient passive heat dissipation.

#### *Insulation*

Insulation impedes heat transfer and can be external or internal. External insulation, in the form of fur or clothing, has a thermal conductivity similar to that of still air. In fact, fur by itself does

not provide substantial insulation value, rather, it is the still air trapped by the fur that provides the insulation (Hammel, 1955). The fur fibers interrupt natural convective heat transfer. Except in humans, external insulation represents a fixed resistance to heat loss which cannot be altered in response to changing thermal demands. Some animals adapt to seasonal climate changes by shedding their fur and replacing it with a more seasonally appropriate insulation layer.

Subcutaneous insulation is provided in part by adipose tissue. A limiting factor for the utility of adipose tissue as insulation is the weight-to-insulation value ratio. Fat, per unit of insulation, substantially outweighs air. The insulation value of adipose tissue is an order of magnitude lower than that of fur and air. Adipose layers must be substantially thicker and heavier than fur layers to achieve the same insulation value. Blubber (adipose tissue) is the particularly efficient insulation of marine mammals. Sea water provides a relatively constant thermal environment: water which never drops below freezing. However, water has approximately 25 times the heat capacity of air. Marine animals must maintain a thick layer of insulation despite the relatively mild temperatures of the sea. Water and blubber have approximately the same density and blubber is near-neutral buoyancy in water. Thus, weight and bulk of the insulation is not a limiting factor for marine animals. Subcutaneous insulation has two advantages over external insulation: 1) it is relatively incompressible which is of value for marine mammals that dive to great depths, and 2) the resistance to heat flow through subcutaneous insulation layers can be varied by adjusting blood flow through the insulation to the skin surface (Muack, 2003). The ability to adjust the heat transfer through the insulation layer enables the matching of heat loss to heat gain despite varying levels of internal heat production.

Blood flow through tissues largely determines the insulative properties of the tissues. The thermal conductivities of all animal tissues are of a similar magnitude (Hensel and Bock, 1955). Adipose tissues, in general, have low capillary density and are poorly perfused. In the absence of blood flow, heat transfer through the tissues is negligible. It is lack of blood flow through the adipose tissues that provides a substantial portion of its insulating capacity.

Subcutaneous insulation is not confined to adipose tissues. Any tissues that are poorly perfused become insulators. Tissue perfusion determines local heat transfer and enables delivery of heat to (or removal from) a body region. Blood flow through lean tissue is determined by the metabolic demands of the tissue. Therefore, any part of the body that is metabolically quiescent provides an insulating effect.

Insulation not only protects animals from the cold, but also impedes the transfer of heat into the body. In hot regions, external insulation deflects solar radiation away from the skin surface and reduces the flow of heat from the surface of the insulation layer to the skin. Subcutaneous insulation, similarly, retards the transfer of heat from the skin surface into the body core (Jessen, 2001).

#### *Respiratory heat conservation*

The gas exchange surface area of the alveoli in an adult human is roughly 40-60 times that of the total skin surface area (lungs 55-100 m<sup>2</sup> vs. skin 1-2 m<sup>2</sup>). All of the circulating blood passes through the gas exchange surfaces of the lungs and, in resting humans, air in the lungs is turned over 10-12 times per minute. Without an adaptive mechanism to prevent heat loss, heat exchange between the circulating blood and the air at the gas exchange surface would be problematic.

Heat loss through respiration is minimized by the geometry of the airways, the ebb and flow pattern of air movement through the airways and the low heat capacity of air. The upper airway passages warm and humidify the inspired air (Wolf et al., 2004). In the nasal passages inspired air comes in contact with warm and moist nasal mucosa and is rapidly warmed and humidified, while expired air returns some of the heat and moisture to the nasal epithelium. The bronchial tree serves to further isolate the gas exchange surfaces from the external thermal environment. A factor for heat transfer between an air stream and the conduit it is flowing through is the surface area of the conduit. The greater the surface area, the greater the heat transfer. The bronchial tree branches from a single large diameter airway to a plurality of micro airways connecting to clusters of alveoli. There are about 23 branches to the bronchial tree. The tremendous surface area in the bronchial tree eliminates thermal differences between the air stream and the tissues before they reach the gas exchange surfaces.

*Thermal compartmentalization: Core organs vs. peripheral tissues*

Table 1. Tissue mass distribution and metabolic heat production.

Organ	% of body weight	% resting heat production	
Kidneys	0.45	<b>7.7</b>	7.7
Heart	0.45		10.7
Lungs	0.9		4.4
Brain	2.1		16.0
Splanchnic Organs <sup>a</sup>	3.8		33.6
Skin	7.8	<b>92.3</b>	1.9
Muscle	41.5		15.7
Other <sup>b</sup>	43.0		10.0
			<b>72.4</b>

<sup>a</sup> abdominal organs not including kidneys.  
<sup>b</sup> bone and connective tissues.

From Ashoff et al. 1971

The thermal core of a mammal is defined as those inner tissues of the body whose temperatures are not changed in their relationship to each other by circulatory adjustments and changes in heat dissipation to the environment (Commission for Thermal Physiology, 2001). The thermal core consists of the brain and the organs of the chest and abdomen - heart, lungs, kidneys, liver, spleen, gastrointestinal tract, etc. The thermal core organs account for only 6 - 10% of the total body mass. These core organs are characterized by relatively high and constant levels of metabolic

activity and account for roughly 75% of the total metabolic heat production during rest (Table 1) (Ashoff, 1971; Heymsfield, 2000).

Peripheral tissues, as opposed to core organs, are defined as the skin, mucosal surfaces, and underlying tissues whose temperatures may deviate from core temperature (Commission For Thermal Physiology, 2001). Peripheral tissues such as skin, fat, bone, skeletal muscle, and connective tissue are characterized by relatively low resting metabolic activity. The peripheral tissues make up over 90% of the total body mass, but generate less than 35% of the resting metabolic heat production (Ashoff 1971, Heymsfield, 2000). On a per unit mass basis, resting peripheral tissues are essentially metabolically silent compared to the core organs.

*Blood flow.*

Blood volume and cardiac output in mammals are insufficient to uniformly perfuse all tissues in the body (Folkow and Neil, 1971). Blood volumes range between 5 and 10% of total lean body mass (5-6 liters in adult humans). Cardiac output in a resting human is about 5 l/min so that the total blood volume circulates at a turnover rate of one cycle per minute. All blood passes through the chambers of the heart and the lungs. The distribution of the systemic blood is in accordance with local tissue metabolic demand. At rest, the thermal core organs are the metabolically active

Table 2. Systemic blood flow distribution in a resting human.

Organ	% of body weight	% blood flow	
Kidneys	0.45	21.4	<b>64.3</b>
Liver	2.2	25.0	
Brain	2.1	13.4	
heart	0.43	4.5	
Skin	7.0	3.6	<b>35.7</b>
Muscle	41.5	16.1	
Remainder <sup>a</sup>	46.5	16.1	
<sup>a</sup> bone, connective tissue, splanchnic organs except liver			
From Folkow and Niel 1971			

tissues and, thus, they are preferentially perfused (Folkow and Niel 1971). The four most heavily perfused organs (kidneys, liver, heart and brain) make up only 5% of the total body mass but receive almost two-thirds of the total cardiac output during rest (Table 2). In contrast, peripheral tissues are metabolically quiescent and poorly perfused during rest rendering these tissues an effective insulation layer.

#### *Heat production and blood flow during exercise.*

During exercise, total metabolic oxygen consumption may increase 10-fold (Kozlowski et al, 1985). However, metabolic activity only increases in the active muscles during exercise

(Gonzalez-Alonso et al, 2000; Krstrup et al. 2001, 2003). The metabolic activities of the thermal core organs remain relatively constant. Cardiac output increases are proportional to total metabolic effort while blood flow follows the local metabolic demand. As a result, a 10 fold increase in skeletal muscle cellular metabolism results in a similar increase in local blood flow to the working muscles. Since circulation is a closed loop system in which all of the cardiac output returns to the heart, the bulk of the heat produced by working muscles is returned to the body core and is not dissipated directly to the environment (Gonzalez-Alonso et al, 2000; Kenney, 2003).

#### *Heat dissipation*

Heat is lost to the environment across the body surface. Heat produced by the thermal core, or returned to the thermal core from active peripheral tissues, must be delivered to the body surface to be dissipated to the environment. Heat carried in the circulating blood cannot be delivered beyond the confines of the circulatory system and, thus, cannot effectively be conveyed across external insulation layers.

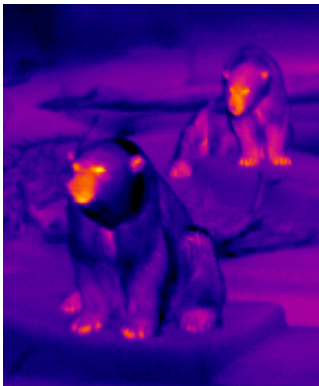


Figure 1. An infrared image of two polar bears at the San Francisco Zoo. The brighter the color the warmer the surface temperature. Note: Only the snout and foot pads are noticeably different from the surrounds.

Most terrestrial mammals possess some form of external insulation. Only the limited skin regions that lack insulation have direct contact with the environment. Therefore, heat loss occurs primarily across the non-insulated body surfaces that are directly exposed to the environment (Figure 1) (Baker, 1982; Bergersen, 1993; Gemmell and Hales, 1977; Heath, 1998; ; Jessen, 2001; Johnson 2002; Mauck et al, 2003; Saad et al, 2001; Tattersall and Milson, 2004). The rate of heat loss across these exposed surfaces is determined by the amount of internal heat delivered via the blood to the exposed surfaces and the magnitude of the thermal gradient across the exchange surface (blood temperature - environmental temperature). Heat loss can be regulated by controlling blood flow to the non-hairy skin regions.

*Specialized Heat Exchange Vascular Structures.*

Circulation through the skin serves two major functions: nutrition of the skin tissue and heat transfer (Greenfield, 1983; Roddie, 1983). These two functions have different hemodynamic requirements. Nutrient exchange requires slow movement of blood through thin-walled, small-diameter vessels with walls permeable to small molecules. Heat exchange requires the movement of large volumes of blood through vessels closely apposing a body surface. Accordingly, two types of vascular structures are found in the skin of mammals: 1) nutritive units consisting of arterioles, capillaries, and venules, and 2) heat-transfer units consisting of venous plexuses (dense networks of thick-walled, large-diameter venules) and arteriovenous anastomoses (AVAs; vascular communications between small arteries and the venous plexuses).

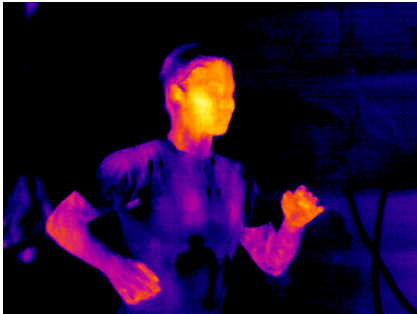


Figure 2. An infrared image of a female runner after 45 min. of exercise in a 23°C environment. Note that the palms of the hand and the face are substantially warmer than the rest of the body surface.

The heat-transfer vascular units and nutritive vascular units are anatomically distinct and have mutually exclusive functions. Nutritive vascular units are uniformly distributed throughout the skin, whereas the heat exchange units are found only in the non-insulated skin regions which in humans are the palms of the hands, the soles of the feet, the ears, and non hairy regions of the face (Figure 2) (Bergersen, 1993; Gemmell and Hales, 1977; Saad, 2001). They also exist in the footpads and tongues of dogs (Baker, 1982), ears of elephants (Phillips and Heath, 1992) and rabbits (Ootsuka et al., 2003), and tails of rodents (Heath, 1998, Johnson 2002). In the human hand, AVAs and associated venous plexuses are found under the nail beds, the tips of the digits, the palm, and the palmar surface of the fingers. AVAs and venous plexuses are absent from

the dorsal surface of the fingers and hand (Roddie, 1983). The dimensions of venous plexuses determine the blood volume capacity of a heat exchange region while the AVAs control the blood flow through the venous plexuses.

The heat exchange-vascular units do not contribute to the nutrition of surrounding tissues, and the nutritive units are not directly active in temperature regulation. The thermoregulatory vascular units enable direct heat transfer from the body core to the surrounding environment (Krauchi et al., 1999,2000). Blood passing through these heat exchange units is delivered directly from the heart via the arterial system and is delivered back to the heart via venous return.

Blood flow through the heat exchange vascular units is extremely variable. It has been estimated that blood flow into the venous plexuses can range from near zero in cold stress to as much as 60% of the total cardiac output during heat stress (Greenfield, 1983; Johnson and Proppe, 1996). Constriction of the AVAs thermally isolates the body core from the environment. Conversely, dilation of the AVAs promotes a free exchange of heat between the body core and the environment.

**Temperature Homeostasis**

Mammalian temperature regulation is mediated by the central nervous system and specifically by the hypothalamus. Destruction of hypothalamic tissue impairs thermoregulation (Hammel, 1968; Satinoff, 1978). If the hypothalamus is damaged, an individual's ability to thermoregulate

becomes compromised: body temperature rises in warm environments and falls in cold environments.

The hypothalamic temperature controller (i.e., the thermostat) receives afferent input about the thermal condition of the body (feedback), compares this thermoafferent information with a set point signal, and generates appropriate output commands that activate effector mechanisms (Hammel, 1968; Heller, et al., 1978). Feedforward input to the thermoregulatory system allows for coordinated changes in effector mechanisms by modifying the set points of the thermostat in anticipation of the immediate future needs of the individual. The long list of inputs that affect the regulated set points include time of day, sleep state, activity levels, exercise, acclimatization, presence of pyrogens, season, ambient temperature, and satiety.

Thermoafferent inputs to the temperature controller originate from thermosensors located in the skin, various core regions, and locally in the hypothalamus (Crawshaw 1980; Fusco et al., 1961; Heller, 1978, 1983). Although the thermoafferent input from different sensors all contribute to the generation of appropriate responses, some of the inputs are more critical than others for eliciting thermoregulatory responses. An important function of the temperature controller is to prioritize the inputs from the various sources.

Information about one's thermal environment is extremely important for the functioning of the thermoregulatory system (Wyss et al., 1974). In humans, conscious perception of hot and cold from cutaneous thermoreceptors is the primary input driving behavioral thermoregulatory responses (Frank 1999). If one perceives the environment to be uncomfortably warm or cold, one will either move to a more comfortable location or will change the insulation layer by adding or removing clothing. Cutaneous thermoreceptors also provide inputs that drive autonomic thermoregulatory effector responses (Crawshaw et al., 1975; Hales et al., 1985).

A high-priority input to the thermoregulatory control system is local brainstem temperature (Crawshaw 1980; Fusco et al., 1961; Hammel, 1968; Hammel et al., 1973; Heller, 1978, 1983). The effects of local brain region temperature manipulations on thermoregulatory control have been well worked out in animal studies. Minute areas of the brain can be experimentally heated or cooled by use of a thermode, a small implantable device through which heated or cooled water can be circulated. The preoptic anterior hypothalamic area (POAH) has been identified as the principal area where local temperature manipulation can affect thermoregulatory function. Local heating or cooling of the POAH can elicit appropriate thermoregulatory responses that result in a large change in the heat content of the body as a whole. Cooling of the POAH stimulates vasoconstriction and increases metabolic heat production. This results in a rise in overall body temperature. Heating the POAH stimulates vasodilation and evaporative heat loss mechanisms, resulting in a decrease in overall body temperature.

Each thermoregulatory effector mechanism has a unique POAH temperature-activation threshold. The threshold for the onset of shivering is lower than the threshold for vasoconstriction, and the threshold for sweating is higher than the threshold for vasodilation. POAH response thresholds are influenced by ambient conditions. For example, the local POAH temperature threshold for shivering is increased at cooler ambient temperatures and decreased in warmer environments. However, changes in POAH temperature can elicit appropriate thermoregulatory responses irrespective of the skin temperatures (i.e., a decrease in POAH temperature can elicit shivering in a warm environment).

Deep body tissue sites that can be manipulated to elicit thermoregulatory responses are not limited to the hypothalamic brain regions. Thermosensors do exist in the spinal cord and some deep tissues. Therefore, a thermal load imposed on the body core elicits thermoregulatory responses for two reasons – activation of local thermosensors and eventually activation of POAH thermosensors as the thermal load is distributed by the circulation. Application of a cold load by ingestion or infusion of a large quantity of cold fluids can elicit vasoconstriction and increase metabolic heat production (Frank et al., 1999). However, the magnitude of the thermal load necessary to elicit a given response when delivered to the body core is considerably larger than when POAH temperature is manipulated directly.

The priority hierarchy for eliciting thermoregulatory responses is straightforward. Local brainstem temperatures are of the highest priority, followed by core temperatures, while input from the skin temperature sensors is of lowest priority. This means that when the thermal core organs are within an acceptable temperature range, the system will respond to skin surface input. However, when the core temperatures deviate from the acceptable range, responses to the internal thermal conditions will take precedence over the external environment.

#### *Basal Metabolic Rate and the Thermoneutral Zone*

The thermoneutral zone is defined as the environmental temperature range in which the resting metabolic rate of an animal is low and independent of environmental temperature (Commission for Thermal Physiology, 2001). Basal metabolic rate reflects the amount of energy required to perform necessary metabolic functions other than thermoregulation and exercise. When the heat produced by basal metabolic activity is insufficient to meet the thermal demands of the resting animal, supplemental endogenous heat can be generated through voluntary exercise, involuntary muscle activity (shivering), or nonshivering thermogenesis. Similarly, when the conditions are such that basal metabolic heat production exceeds heat dissipation capacity, metabolic efforts will increase to enhance heat dissipation. The thermoneutral zone for a given species or individual can vary depending on a number of parameters including insulation, acclimation, time of year and day, fat accumulation, and satiety.

#### *Thermoregulatory Effector Mechanisms*

##### Behavioral Thermoregulation

An animal that possess the ability to move has the ability to respond to adverse environmental conditions by selecting or creating an optimal microenvironment makes it possible to remain within its thermoneutral zone. Behavioral thermoregulatory responses include seeking shade during the heat of the day, burrowing up during excessive cold, changing posture and orientation to the sun (basking on a cold morning), shuttling between the sun and shade or between still and moving air, group huddling, and the application of superficial water to the skin surface by wallowing. A unique human behavioral thermoregulatory response is the ability to alter our external insulation on demand by changing clothing layers. Successful behavioral thermoregulation eliminates the need for utilizing metabolically expensive thermogenic or thermolytic responses.

##### Autonomic Thermoregulation

*Vasomotor Tone.* Within the thermoneutral zone, the core temperature of a resting individual is regulated by adjusting vasomotor tone. Vasomotor tone determines blood flow through the subcutaneous heat exchange vasculature structures and, thus, the transport of heat from the

thermal core to the skin surface. Vasoconstriction reduces heat transfer, vasodilation increases heat transfer. When the thermal core is within an acceptable temperature range, vasomotor tone is responsive to changes in ambient temperature. Increases in ambient temperature stimulate vasodilation; decreases in ambient temperatures, vasoconstriction. However, should core temperature deviate from the desired level, appropriate vasomotor responses based on the core temperature will prevail irrespective of ambient conditions. Even in a cold environment, an increase in the core temperature (e.g., during exercise) can elicit vasodilation and sweat onset (Pergola et al., 1996; Wyss et al., 1974). Conversely, placing a hypothermic post-anesthesia patient in a local warm environment will have little effect on vasomotor tone (Ereth et al., 1992). In the first example, the elevated core temperature drives vasodilation despite ambient conditions. In the latter example, the artificially lowered core temperature elicits vasoconstriction despite the warm ambient conditions.

*Thermogenesis.* When vasomotor responses are insufficient, metabolically costly responses are activated. The thermal neutral zone is bounded by a lower critical temperature, below which resting metabolic rate increases. The increase in metabolic rate is proportional to the difference between ambient temperature and the lower critical temperature. Endothermic animals have only a limited metabolic heat production capacity. With acute exposure to extreme cold or prolonged exposure to milder cold, heat loss from the body will exceed the capacity to produce heat and the temperature of the body core will drop.

*Evaporative Heat Loss.* The thermal neutral zone is also bounded by an upper critical temperature, above which resting metabolic rate (and water loss) increases. When necessary, an individual can increase heat dissipation by evaporative heat loss. The modality for evaporative heat loss is dependant on species. Some mammals sweat, some pant, while others spread saliva across the general skin surface (Furuyama, et al., 2003). All of these strategies result in a net decrease in water content of the body.

Evaporative heat loss is costly in terms of fluid loss and is, at best, a means for extending short term survival of acute heat stress (Swaka et al., 2001). Plasma is the immediate source of water for evaporative heat loss. The fluid loss associated with evaporative heat loss causes a reduction in plasma volume. Reduction in plasma volume (dehydration), in turn, inhibits heat dissipation responses. A high rate of sweating does not prevent increases in core temperature. In fact, with progressive dehydration, core temperatures must rise to higher temperatures to maintain equivalent levels of evaporative heat dissipation.

### **The treatment of heat- and cold-maladies in humans - conventional methods**

Thermal maladies can occur when the thermoregulatory system is overwhelmed by severe environmental conditions or when the thermoregulatory system has been compromised (e.g., by anesthesia or trauma). In a normal conscious individual, hypothermia is the result of prolonged exposure to a cold challenge. Since vasoconstriction occurs prior to the activation of thermogenic mechanisms, inherent in the condition of hypothermia is maximal vasoconstriction. While vasoconstriction is an appropriate response to minimize heat loss from the thermal core, it also impedes the transfer of heat from the skin surface to the body core. Because deviations of core temperature override input about the thermal environment, application of heat to the general skin surface of a hypothermic individual has little effect on vasomotor tone. The vasoconstrictive blockade to heat transfer prevents the superficially applied heat from accessing the thermal core of a hypothermic individual (Ereth et al., 1993, Giesbrecht and Bristow, 1998).

Hyperthermia occurs when heat dissipation mechanisms are overwhelmed by environmental conditions, excessive internal heat production, inhibition of the heat dissipation mechanisms, or a combination of these conditions. Exercise in a hot environment, the inability to escape a heat stress, physical activity wearing inappropriate insulation, dehydration, and pharmacological manipulations all can contribute to the generation of hyperthermia. Inherent in the condition of hyperthermia is that an individual's heat dissipation mechanisms have reached maximum capacity.

The goal in treating heat-related conditions is to restore normothermia in a timely manner using minimally invasive techniques. Methods for treating cold stress or hypothermia include passive external rewarming, active external rewarming, inhalation rewarming, and active internal rewarming (see Lazar, 1997). Passive external rewarming is suitable for treating mildly cold-stressed individuals and entails minimizing heat loss by removing the individual from the cold environment and providing insulation around the body. Heat for rewarming the body core is generated endogenously through shivering thermogenesis. Increases in core temperature of 0.4°C to 2°C per hour have been reported for recovery under minimal treatment conditions (e.g., passive external rewarming).

Active external rewarming includes the application of heat to the general skin surface. Heat can be applied using hot water bottles, heated blankets, radiant heat sources, forced hot air, or water-bath immersion. While active external rewarming techniques are effective for delivering heat to the skin surface, vasoconstriction prevents the applied heat from penetrating rapidly to the thermal core. The rewarming rates of the thermal core regions using active rewarming are similar to those reported for passive external rewarming. A potential danger with applying heat directly to the skin of a hypothermic individual is the risk of surface burns.

Inhalation rewarming, the breathing of warmed humidified gases, has been proposed as a means for delivering a thermal load to the thermal core, but has been shown to provide little benefit (Mekjavic, 2002). The fact that airway rewarming is generally ineffective is not surprising given that a major function of the respiratory tract is to minimize heat and water loss through respiration (see respiratory heat conservation section). Rewarming rates similar for those reported for passive rewarming techniques (1 -2.5°C/hr) have been reported for inhalation rewarming. Similar rewarming rates have also been reported for more invasive pleural irrigation, gastrointestinal lavage, and peritoneal dialysis techniques (See Lazar, 1997).

Active core rewarming techniques are the most invasive and most effective for rapidly raising body core temperatures because such techniques provide direct access to the circulating blood and avoid the vasoconstrictive heat transfer blockade. Extracorporeal rewarming of blood by cardiopulmonary bypass or hemodialysis is the most effective (and most drastic) of the invasive rewarming techniques. Increases in core temperature of up to 10°C/hr have been reported for extracorporeal rewarming techniques during cardiopulmonary bypass (Walpoth et al., 1997). Recent development of catheter-based heating and cooling systems provide another means for direct manipulation core temperatures, however, these techniques are extremely invasive. An obvious downside of these invasive techniques is that they are risky surgical procedures that cannot be applied outside of a surgical setting.

Treatment of heat stress or hyperthermia involves enhancing heat loss capacity, and the treatment is generally determined by the severity of the condition (Bouchama and Knochel, 2002; Kashmeery, 1992; Simon, 1993). Physical cooling methods include removal of insulating clothing, removing the source of the heat stress (i.e., moving the individual to a cool shaded environment), increasing convective heat loss using fans, and/or increasing evaporative heat loss by sponging the general skin surface with tepid water or alcohol. Immersion in ice water is the most effective means of physical cooling, but also the most extreme. Other emergency treatments include intravenous or intraperitoneal administration of cool fluids, gastric lavage and ice water enemas, and even extracorporeal circulation (Simon, 1993).

All of the above listed treatments for heat-related disorders assume that: 1) the skin surface has equivalent heat exchange capacity, and 2), if a thermal load applied to the general skin surface is an insufficient treatment, then invasive measures are in order. If a thermal load could be delivered directly to the thermal core in a non-invasive manner, most heat related disorders could be easily treated.

### A novel approach to treatment of heat-related disorders.

The challenge is to deliver a thermal load to the body core despite the inherent resistance of the mammalian thermoregulatory system to such manipulations. The heat exchange vascular structures seem to be an ideal vector for delivering a thermal load to the body core. Over 50 years ago it was demonstrated that heat could be effectively extracted from the body core through the hands and feet (Greenfield et al., 1951 a and b). When the fingers of a resting individual were immersed in cold water, local blood flow fell initially to near zero. However, after about 10 minutes blood flow started to rise again exceeding the resting value. This rise in blood flow was not maintained and blood flow continued to rise and fall throughout the cold exposure (the Hunting Response). At the time it was speculated that the objective of the vasomotor cycling was for the prevention of cold damage to the local tissues, which was accomplished at a considerable heat loss from the body - a fall in esophageal temperature of 0.6°C in 9 minutes (Greenfield et al., 1951b).

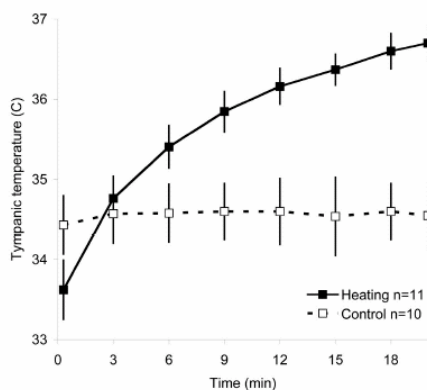


Figure 3.  $T_{ty}$  during recovery after SCUBA dives. Closed symbols: warming by delivery of heat through the palm of one hand, open symbols: control treatment. The temperature of the water flowing through the device separated the experimental from control treatments (45-46 °C for the experimental treatments, 25-30 °C for the controls). The subjects remained clad in their wet suits during treatments. From Grahn and Heller, 2004.

It has also been demonstrated that increases in transmural pressure by exposure to local subatmospheric pressure increased blood flow through the fingers and toes (Coles 1957; Coles and Greenfield 1955). These determinations were made calorimetrically by measuring heat loss from the fingers and toes. Increasing transmural pressure (by creating a local subatmospheric pressure environment) by up to 50 mm Hg resulted in an increase in heat loss (and thus, blood flow) through the hand (Coles and Greenfield, 1956). Additional increases in pressure differentials resulted in a decrease in heat loss (and thus, blood flow) through the hand (Coles and Greenfield, 1956). It was also demonstrated that while sub-atmospheric pressure expanded the blood volume in the hand, blood flow through the distended vessels could be controlled by

manipulations of local skin temperatures and general skin temperatures (Coles and Peterson, 1957). Coles and Peterson concluded that, by decreasing vascular resistance through local heating or general body surface heating (of normothermic individuals), blood flow through the hand could be increased without affecting blood volume in the hand. These results demonstrated that while the local application of sub-atmospheric pressure increased the standing volume of blood in the vascular structures of the hand, it was the temperature manipulations that determined blood flow through the vasculature structures. The temperature manipulation effects were independent from the pressure manipulation effects.

We reasoned that the combined application of subatmospheric pressure and an appropriate thermal load to a hand or foot would provide direct access to the thermal core of a heat- or cold-stressed individual. This would enable the development of equipment that could provide the controlled delivery of appropriate thermal loads directly to the thermal core of humans. With circulation intact, the palm of the hand can tolerate prolonged exposure to local temperatures as high as 46°C without thermal injury. However, if the circulation is arrested, thermal injury will ensue. It was reasoned that the application of water at temperature below the burn/pain threshold, but sufficient to elicit a local vasomotor response, and 40-50 mmHg subatmospheric pressure to the hand of a hypothermic/cold stressed individual would enable the delivery of heat directly to the body core. Using this technique it was demonstrated that effective restoration of normothermia could be achieved in hypothermic post-surgical patients (Grahn et al., 1997) and cold-stressed healthy subjects (Figure 3) (Grahn and Heller 2004; Soreide et al., 1998). The rates of core temperature recovery were similar to those reported for the immersion of the both hands and both feet of hypothermic individuals in warm water (42-45°C) (Vanggaard et al., 1999). Rates of rewarming in both of these studies were 5-6 times as rapid as reported for conventional non-invasive rewarming methods.

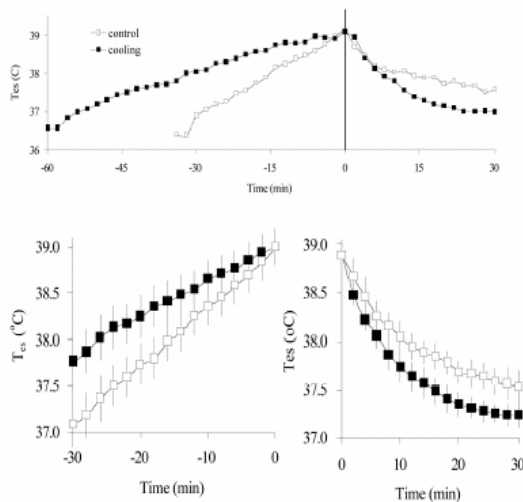


Figure 4. Esophageal temperature ( $T_{es}$ ) during exercise and recovery in a hot room. The rate of  $T_{es}$  rise during exercise was decreased with cooling which enabled longer duration exercise bouts. Closed symbols: cooling through one hand, open symbols: control treatment. Top panel: an example of one subject. Bottom panel: Group results (mean + SEM,  $n=5$ ) of  $T_{es}$  during the last 30 min of exercise (left) and post-exercise recovery (right). From Grahn and Heller, 2004.

Relaxation of vasomotor tone has been demonstrated to be an effective means for enhancing heat loss in animals (Berner et al., 1991). Immersion of the hands and forearms has also been demonstrated to affect heat balance in humans (Allsopp et al, 1991; House et al., 1997). Manipulation of the heat exchange vasculature of a hand or foot, using subatmospheric pressure, enhances heat loss from a heat stressed individual (Figure 4) (Grahn and Heller, 2004; Hagobian, 2004). The mechanical distention of the heat-exchange vasculature structures maximizes the heat exchange capacity of these structures and, as in the case of treating cold stress, the critical core regions that are normally hardest to reach are the first to receive the cooling benefit.

A consideration for using the heat exchange vascular structures for the treatment of heat related disorders is the local vasomotor responses to changes in local skin temperature (Bergersen et

al., 1997). The temperature of the thermal load applied to skin overlying the mechanically dilated tissues is critical for ensuring blood flow through the heat exchange vascular structures. Even in heat stressed individuals the application of cold water to the local skin surface will elicit a local vasoconstrictive response. Likewise, in cold stressed individuals the temperature of the local skin surface must be high enough to elicit a local vasodilation response.

The use of the heat exchange vascular structures to deliver a thermal load to the body core is inherently safe. When treating a cold stressed individual, an initial vasoconstriction limits the distribution of the delivered heat to the body core, but as the thermal core reaches normothermia, a peripheral vasodilation occurs and the excess heat delivered by the treatment can be dissipated from body via the untreated heat exchange vascular structures. Similarly, when a heat stressed individual's core has been restored to normothermia, local vasoconstriction will prevent a further drop in core temperature. The delivery of a thermal load to a body through selected heat exchange vascular structures is self-limiting and presents no danger of inducing a thermal overshoot which could result in a subsequent hyper- or hypo-thermic state.

### **Summary and Conclusions**

The mammalian thermoregulatory system enables minimal energy expenditure to maintain a relatively stable internal thermal condition despite large variations in environmental conditions and internal heat generation. Thermoregulatory anatomical structures include: 1) insulation to protect against external thermal challenges, 2) thermal capacitance in the airways to minimize respiratory heat loss, and 3) radiator-like vascular structures which penetrate the insulation barrier and enable the controlled release of internally accumulated heat. Primary heat exchange occurs through specialized heat exchange-vascular structures that underlie the non-insulated body surfaces. In humans these heat exchange vascular structures are found exclusively underlying the palms of the hands, soles of the feet, the ears, and the hairless skin surfaces of face.

The treatment of hypo- and hyperthermia requires effective delivery of a thermal load to the body core. It is possible to deliver heat directly to the thermal core in a non-invasive manner via the heat exchange vascular structures. To effectively utilize these heat exchange vascular structures, it is necessary to control blood flow through them. We are currently exploring the use of a combined application of subatmospheric pressure and an appropriate thermal load directly to the heat exchange surfaces of the hands and feet to treat heat- and cold-related maladies.

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### **Conflict of Interest Disclosure:**

Patent have been issued for the technology disclosed in this manuscript [D. Grahn and H.C. Heller (Inventors); Stanford University (Assignee)], and Stanford University has entered into licensing agreements with AVAcore technologies, Inc. and Dynatherm Medical, Inc., for the commercialization of the technology. Included in the license is a royalty agreement that grants Stanford University a percentage of the net sales of the technology, which will be shared by the

University and the inventors. D. Grahn and H.C. Heller are founders of AVAcore Technologies but receive no ongoing compensation from the company.

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