Heat Stroke

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ABSTRACT

Heat stroke is a life-threatening condition clinically diagnosed as a severe elevation in body temperature with central nervous system dysfunction that often includes combativeness, delirium, seizures, and coma. Classic heat stroke primarily occurs in immunocompromised individuals during annual heat waves. Exertional heat stroke is observed in young fit individuals performing strenuous physical activity in hot or temperature environments. Long-term consequences of heat stroke are thought to be due to a systemic inflammatory response syndrome. This article provides a comprehensive review of recent advances in the identification of risk factors that predispose to heat stroke, the role of endotoxin and cytokines in mediation of multi-organ damage, the incidence of hypothermia and fever during heat stroke recovery, clinical biomarkers of organ damage severity, and protective cooling strategies. Risk factors include environmental factors, medications, drug use, compromised health status, and genetic conditions. The role of endotoxin and cytokines is discussed in the framework of research conducted over 30 years ago that requires reassessment to more clearly identify the role of these factors in the systemic inflammatory response syndrome. We challenge the notion that hypothalamic damage is responsible for thermoregulatory disturbances during heat stroke recovery and highlight recent advances in our understanding of the regulated nature of these responses. The need for more sensitive clinical biomarkers of organ damage is examined. Conventional and emerging cooling methods are discussed with reference to protection against peripheral organ damage and selective brain cooling. Published 2015. *Compr Physiol* 5:611-647, 2015.

Introduction

Environmental heat exposure is a serious health hazard that is responsible for more deaths than all other natural disasters combined (73, 233, 243). Heat stroke incidence has increased dramatically during the past few decades and will continue to be a health concern as global climate change, expansion of urban environments, and increased lifespan are realized (70, 263). Heat stroke is clinically diagnosed as a severe elevation in body temperature that occurs in the presence of central nervous system (CNS) dysfunction and a history of environmental heat exposure or vigorous physical exertion (305, 403). The primary treatment for heat stroke is aggressive cooling for rapid normalization of body temperature since this strategy is associated with reduced risk of organ damage (385). However, many patients experience multi-organ dysfunction during the hours, days and weeks of recovery despite aggressive treatment, which increases the risk for long-term disability and death (18, 92, 238, 349, 390).

Emerging evidence suggests that multi-organ damage is a consequence of direct thermal injury to the tissues, coagulopathies, and development of a systemic inflammatory response syndrome (SIRS) that is stimulated by endotoxin, cytokines and other immune modulators [Fig. 1; (47, 214, 324)]. During the past few decades, considerable emphasis has been placed on delineating the actions of cytokines in the mediation of the pathophysiological responses to heat stroke (47, 50, 148, 152, 214, 223). Despite these efforts, there remain knowledge gaps in our understanding of the mechanisms mediating multi-organ damage, which has hindered identification of novel clinical strategies to treat this condition. The goal of this article is to provide a comprehensive review of emerging research developments that include: (1) identification of predisposing factors that may increase heat stroke risk; (2) mechanisms mediating thermoregulatory responses during recovery that occur in the absence of CNS damage; (3) the role of endotoxin in stimulation of the SIRS and endotoxin tolerance in reducing heat stroke risk in physically fit individuals; (4) circulating biomarkers used for clinical assessment of multi-organ damage in heat stroke patients; and (5) conventional and emerging cooling methods for clinical treatment and management.

The Heat Illness Continuum

Heat illnesses are best regarded as a series of conditions that exist along a continuum of increasing severity that progress from heat exhaustion to heat injury and heat stroke. There

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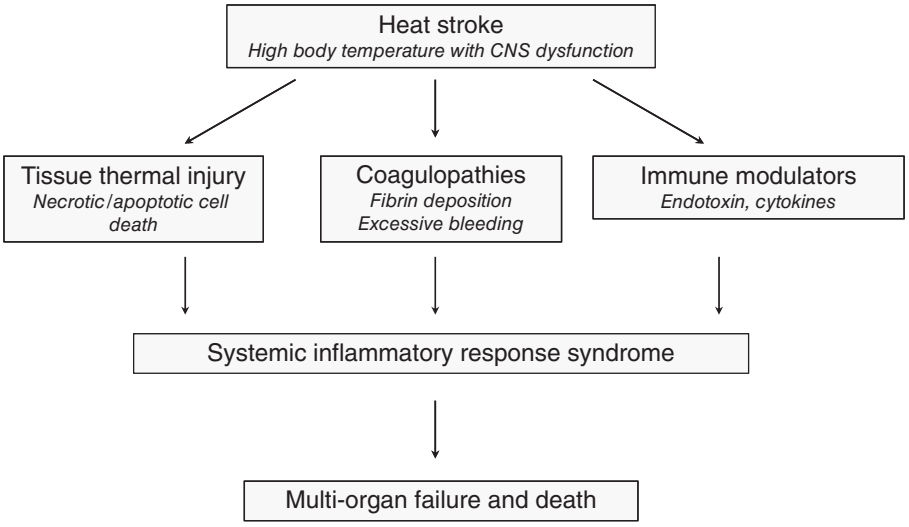

Figure 1 Schematic of the sequence of events occurring in response to heat stroke that stimulate a systemic inflammatory response syndrome that leads to multi-organ dysfunction and death.

are minor heat-related syndromes, such as heat rash and heat cramps that are not considered part of the heat illness continuum, but do commonly occur. This review is focused on the more severe conditions within the heat illness continuum with recognition that it may be difficult to distinguish between these entities early in the course of clinical manifestation.

Heat exhaustion is considered a mild to moderate form of heat illness that is characterized by an inability to sustain cardiac output, often accompanied by moderate to severe elevation of body temperature with dehydration and hot dry skin due to the absence of sweating [i.e., anhydrosis (403)]. The signs and symptoms of heat exhaustion include fatigue, dizziness, headache, nausea, vomiting, malaise, hypotension, and tachycardia with potential for collapse. Heat exhaustion can occur with or without exercise in hot environments and may progress to a moderately severe condition without associated organ damage. Heat exhaustion is often observed in the elderly as a result of medications (e.g., diuretics), inadequate water intake that leads to dehydration or preexisting cardiovascular insufficiency that predisposes to collapse. Treatment should consist of placing the individual in a recumbent position in a cool environment to normalize blood pressure. Oral fluid ingestion with electrolytes is often adequate for recovery, but IV fluid administration may be warranted in severely dehydrated individuals.

Heat injury is a more severe form of heat illness characterized by high body temperature with organ (e.g., kidney and liver) and tissue (e.g., gut and skeletal muscle) damage (403). Heat injury is an intermediate condition that involves more serious complications than heat exhaustion, but less severe complications than heat stroke. Organ dysfunction is typically not observed during the early time course of heat injury making it difficult to distinguish this condition from heat exhaustion. However, heat injury may progress to heat stroke if the patient is not rapidly cooled. Heat stroke is a life-threatening condition characterized by profound CNS dysfunction, organ (e.g., kidney and liver) and tissue (e.g., gut and skeletal muscle) damage with high body temperature (403). The onset of heat stroke is often acute without prodromal signs but can be gradual (over hours or seldom days) with nonspecific symptoms of weakness, loss of appetite, dizziness, fainting, nausea, vomiting, headache, and restlessness or confusion (47, 83, 107, 238). Neurological alteration is a main characteristic feature of heat stroke that is dominant early during clinical presentation as patients exhibit mental status changes that may include delirium, deep coma, and seizures (58, 413). Focal neurological signs are rare with cerebrospinal fluid usually normal; however, increased white blood cell counts have been observed.

Classic versus exertional heat stroke

Heat stroke may be further classified as "classic" or "exertional" depending on the etiology of the condition (Table 1). Classic heat stroke is observed primarily in sick and immunocompromised individuals (e.g., very young and elderly) with high morbidity and mortality rates observed during annual summer heat waves. Classic heat stroke is generally associated with exposure to hot environments in the absence of strenuous physical activity and hot, dry skin due to anhydrosis is common. Up to 60% of patients with classic heat stroke are hospitalized or found dead within one day of reported onset of illness, underlying the life-threatening character of this condition (68, 172). It is essential that clinical signs and symptoms of heat stroke are recognized promptly and rapid cooling is initiated.

Exertional heat stroke is typically observed in healthy, young, and otherwise physically fit individuals that collapse during exercise-heat stress (403). Anhydrosis is an uncommon finding in exertional heat stroke and many patients may cool spontaneously following collapse. The risk for exertional heat stroke is increased in individuals that are highly

Table 1 Comparison of Classic versus Exertional Heat Stroke

Characteristic	Classic	Exertional
Age	Very young, elderly	Young (15-50 years), healthy
Health	Often chronically ill	Typically healthy
Febrile illness	Unusual	Common
Weather condition	Heat wave	Temperate or hot
Activity	Sedentary	Sustained or heavy exertion
Medications or drug use	Diuretics, β-blockers, antihistamines, antidepressants	Ergogenic aids, ecstasy, cocaine
Sweating	Often absent	Often present
Acid-base disturbance	Mixed respiratory alkalosis and metabolic acidosis	Severe metabolic acidosis
Calcium	Normal	Hypocalcemia
Potassium	Normal	Hyperkalemia; hypokalemia (~30%)
Phosphate	Hypophosphatemia	Hyperphosphatemia
Blood glucose	Hyperglycemia	Hypoglycemia
Rhabdomyolysis	Rarely severe	Often severe
Acute renal failure	Uncommon (~5%)	Common (~25%)
DIC	Mild	Severe
CK	Mild elevation	Marked elevation
AST, ALT	Mild elevation	Marked

CK, creatine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DIC, disseminated intravascular coagulation.

motivated to perform strenuous physical activity in hot weather (e.g., military personnel, athletes, and occupational workers), indicating that behavioral influences are important to consider in the etiology of this condition (3). Physical effort unmatched to physical fitness was identified as a significant risk factor for exertional heat stroke (298). However, in many instances, exertional heat stroke occurs within the first 2 h of exertion and not necessarily at high ambient temperatures. The death rate from exertional heat stroke is relatively low (~3%-5%) compared to classic heat stroke, which is likely a consequence of preexisting medical conditions in the latter condition that increase thermoregulatory and cardiovascular strain (70, 342, 346, 350).

Heat stroke diagnosis

The diagnosis of heat stroke is largely clinical and based on the triad of hyperthermia, neurological abnormalities, and a history of exposure to hot and humid weather or vigorous muscle exertion. Disorders that can be mistaken for heat stroke include neuroleptic malignant syndrome, malaria, and meningitis. Neuroleptic malignant syndrome usually occurs in patients on neuroleptic medications and manifests as an extrapyramidal syndrome with autonomic dysfunction. Although malaria and meningitis rarely cause hyperthermia to the degree observed with heat stroke, specific workup diagnostic to rule them in or out should be performed for patients with a history of recent visits to an area endemic for falciparum, or where there has recently been an outbreak of meningitis. Neck rigidity is uncommon in heat stroke and cerebrospinal fluid is usually normal, although occasional pleocytosis has been observed.

Environmental heat stress and heat strain

Heat stress refers to conditions that increase body temperature whereas heat strain refers to the physiological responses that ensue as a consequence of heat exposure. Heat stress is typically described as compensable heat stress (CHS) or uncompensable heat stress (UCHS). CHS and UCHS are affected by biophysical (environment and clothing) as well as biological (hydration status and acclimatization) factors. CHS occurs when the rate of heat loss is in balance with heat production such that a steady-state core temperature can be sustained during physical activity. A physically fit individual wearing light clothing while exercising in moderate heat and low humidity conditions would typically experience CHS. Under these conditions, core temperature can be sustained at values substantially higher than normal (<40°C) for relatively long durations until dehydration or energy depletion occur. UCHS occurs when an individual's evaporative cooling requirements are not supported due to environmental or other conditions that impede cooling. An individual wearing heavy protective clothing while exercising in a hot, humid

environment would be expected to experience UCHS. Under UCHS conditions, core temperature will increase to the point of exhaustion. Even in individuals at low risk for UCHS, the physiological demands for increased heat dissipation during prolonged exercise-heat stress cannot be endured indefinitely and often lead to circulatory insufficiency and collapse at relatively mild temperatures.

There have been several attempts to develop a standardized heat stress index that takes into consideration environmental and physiological factors that affect physiological strain and safety limits for heat exposure. In 1905, Haldane advocated use of the wet bulb thermometer for determination of heat stress severity based on experiments conducted in Cornish tin and copper mines (141). Unfortunately, the wet bulb was somewhat ineffective in dry load conditions and failed to account for substantial radiant heat load. The wet bulb globe thermometer (WGBT) was introduced to overcome the limitations of the wet bulb alone by quantifying environmental heat stress based on the natural wet bulb, black globe (measure of radiant heat exchange), and dry bulb temperature (409). The WBGT remains the most widely accepted heat stress index in the world today, although its applicability across multiple environmental/work scenarios and the inconvenience of measuring globe temperature are limiting factors (105). Due to inherent limitations in the heat stress indices that exist today, efforts are ongoing to identify more appropriate measures that consider environmental (air temperature, air humidity, radiant heat exchange, and wind velocity), behavioral (metabolic rate and clothing), and biological (genetics and sex) factors as well as the physiological reactions to a given heat load [e.g., heart rate and body temperature (105, 258, 339, 340)]. The reader is directed to a number of reviews that describe heat stress indices in existence today and their limitations with respect to the number and complexity of interactions that need to be considered in their application (32, 63, 257, 288).

Avenues of heat exchange

In order for body temperature to remain constant during environmental heat exposure, heat loss must be equal to heat gain and/or heat production (e.g., during exercise-heat stress). For example, during physical exercise ~20% of metabolic energy is utilized for skeletal muscle contractions while the remaining ~80% is released as heat that must be dissipated to avoid an increase in body temperature. Cardiovascular adjustments are required to redirect blood flow from the heat-generating organs in the core to the skin surface where heat is dissipated to the environment by conduction, convection, radiation, or evaporation. The regulation of skin blood flow is a primary determinant of the effectiveness of heat transfer as are the biophysical properties of the surrounding environment that include air or water temperature, air or water motion, air humidity, and solar or ground radiation (114).

Dry heat exchange is achieved by nonevaporative mechanisms that include conduction, convection, and radiation. These mechanisms of heat exchange are only effective with a temperature gradient between the skin surface and the surrounding environment. Dry heat gain occurs when the environmental temperature exceeds skin temperature and dry heat loss occurs when skin temperature exceeds that of the environment. Conduction occurs when a body surface is in direct contact with a solid object and depends on thermal conductivity of the object as well as the amount of body surface area in contact with the object. Conduction is typically an ineffective mechanism of heat exchange due to behavioral adjustments (e.g., wearing of shoes) that minimize thermal exchange between the body and the object. Convective heat exchange is facilitated by movement of the surrounding air or water over the skin surface. The rate of convective heat transfer will be significantly increased by wind, but this effect varies depending on the type and amount of clothing. Water is a more effective medium than air for convective heat transfer due to its heat-transfer coefficient, which is ~25 times greater than air (371). Radiative heat exchange is electromagnetic energy that is exchanged between the body and surrounding objects and occurs independently of air temperature or velocity. All objects in our environment (sun, sky, ground, and man-made objects) absorb and emit thermal radiation, but clothing can reduce the radiant heat that impinges on the skin from these environmental sources. Evaporation is a major avenue of heat loss during exercise or when the environmental temperature is equal to or exceeds skin temperature. In humans, evaporative cooling is achieved as water secreted from sweat glands onto the skin changes into vapor and removes heat. Wetting of the skin from other water sources, such as rain or manual dousing will also facilitate evaporation for skin cooling. Approximately 580 kcal of heat is lost per liter of evaporated sweat although this cooling benefit will be negated if conditions fail to support evaporation causing sweat to accumulate on the skin surface (127). Arteriovenous anastomoses (AVAs) are collateral connections between adjacent blood vessels that increase the volume of blood delivered to a particular tissue. Small mammals, such as rodents, do not possess sweat glands, but achieve evaporative cooling by behavioral spreading of salivary onto nonfurred, highly vascularized skin surfaces (e.g., ears and paws). These areas of the body contain an abundance of AVAs and a high surface area to facilitate convective and evaporative heat loss.

Body heat storage (S) is affected by metabolic rate, work, and the four avenues of heat exchange in the following manner:

$$S = M - (\pm W) \pm (R + C) \pm K - E$$

Where M is metabolic energy (heat) production, W is concentric (positive) or eccentric (negative) mechanical work, $R+C$ is the rate of radiant and convective heat exchange, K is the rate of conduction, and E is the rate of evaporative heat loss. Body temperature will increase when S is positive (heat gain), decrease when S is negative (heat loss), and remain relatively stable when S equals zero (114).

Physiological temperature regulation

Humans and other homeotherms are capable of maintaining body temperature within a fairly narrow range (~35-41°C) despite large fluctuations in environmental temperature. The traditional view of the thermoregulatory control system is based on a "set-point" theory, which presumes that sensory receptors in the skin and core send thermal information to a central integrator, typically identified as the preoptic area of the anterior hypothalamus [POAH (53, 170, 292)]. Deviations of body temperature (the regulated variable) from the set-point temperature (the reference variable) within the POAH results in a "load error" that elicits graded heat loss or heat gain thermoeffector responses. The set-point temperature is often referred to analogously as a thermostat setting that controls all thermoregulatory responses. The magnitude of change in the heat loss or heat gain effector responses that are elicited following a change in heat storage is proportional to the displacement of body temperature from the set-point temperature. Thermal signals in the form of action potentials are generated within skin and core thermal receptors including warm- and cold-sensitive neurons within the POAH that change their firing rate in response to warming and cooling, respectively (53). Thermosensitivity of warm-sensitive neurons is determined by the rate of spontaneous depolarization between successive action potentials whereas sensitivity of cold-sensitive neurons is thought to be due to inhibitory input from nearby warm-sensitive neurons (417). A unique morphological characteristic of POAH thermosensitive neurons is the horizontal orientation of their dendrites toward other brain regions (e.g., third ventricle and medial forebrain bundle) that receive thermal signals from peripheral sites (136). The schematics of the thermoregulatory control system have been described in detail elsewhere (324).

A recent alternative theory suggests that thermoeffector responses are controlled "automatically" without a central integrator or reference to a set-point temperature. In this model, each sensory neuron is wired through a number of other neurons to an effector cell. Thermoeffector responses are elicited only when a large number of coordinated neural (sensory) networks send signals without the use of a central integrator to their respective thermoeffector cells (195, 196, 310). In this model, sensors are functioning as thermostats or comparators rather than true thermal sensory neurons that are regulated downstream from the POAH. Despite compelling architectural and functional evidence in support of this novel theory, it has not yet gained wide acceptance within the physiological community and the traditional set-point theory is the accepted model that will be relied on for this review.

Hyperthermia during exercise or heat stress occurs independently of an increase in the temperature set-point, which distinguishes this core temperature response from fever (Fig. 2). Hyperthermia generates a positive load error as body temperature exceeds the set-point temperature and elicits heat loss mechanisms to maintain thermal balance. Once exercise or heat stress ceases, heat loss exceeds heat production/heat gain and body temperature returns toward the set-point temperature until thermal balance is reestablished.

Fever is defined as a regulated increase in the temperature set point and is characterized by a negative load error that stimulates heat production (e.g., shivering and nonshivering thermogenesis) and heat conservation (e.g., use of blankets and vasoconstriction) to increase body temperature (166). The view of fever as an increase in the temperature set-point was first proposed by Liebermeister in the 1800s who demonstrated that the body temperature of a febrile rat returned to its previously elevated level after experimental warming or cooling of the POAH (219). Once fever is established and body temperature oscillates around the new elevated temperature set-point, there is a zero load error and the individual is considered normothermic (Fig. 2). Fever is a protective immune response displayed by endotherms and ectothermic vertebrates and invertebrates following exposure to environmental stimulants, such as pyrogens (e.g., endotoxin) and toxins (132, 133, 186). Fever is also observed in heat stroke patients and animal models during the days and weeks of recovery and is regarded as a response to endotoxin leakage from damaged gut membranes (212, 213, 238). Physicians have attempted to alleviate fever to heat stroke using the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), but there is currently no scientific evidence to support a role for the cyclooxygenase pathway (the targets of NSAIDs inhibition) in mediation of this response (34, 248, 321).

Hypothermia may occur as an unregulated or regulated phenomenon. Unregulated hypothermia represents the condition during which heat loss exceeds heat production and body temperature falls below the temperature set point (Fig. 2). Environmental cold exposure or anesthesia are common stressors that elicit unregulated decreases in body temperature, Regulated hypothermia (also referred to as anapyrexia) occurs in response to a regulated decrease in the temperature set-point that results in a positive load error and stimulation of heat loss mechanisms (e.g., vasodilation and splaying) to decrease body temperature [(166) Fig. 2]. The Q_{10} effect suggests that each 10°C change in body temperature will be associated with approximately twofold to threefold change in enzymatic reaction rates (377). Based on this relationship, a regulated decrease in body temperature is thought to protect against organ damage by reducing the production of harmful enzymatic end products (e.g., reactive oxygen species) that compromise tissue and cellular function. Small rodents often develop regulated hypothermia in response to severe environmental insults (e.g., hypoxia, dehydration, heat stroke, and toxins) whereas this response is less common in humans, perhaps due to body scaling issues (i.e., smaller surface area to body mass ratio) or clinical interventions that mask the response.

Core temperature measurements

There is no "absolute" core temperature value that can be relied on for a definitive assessment of heat stroke due to

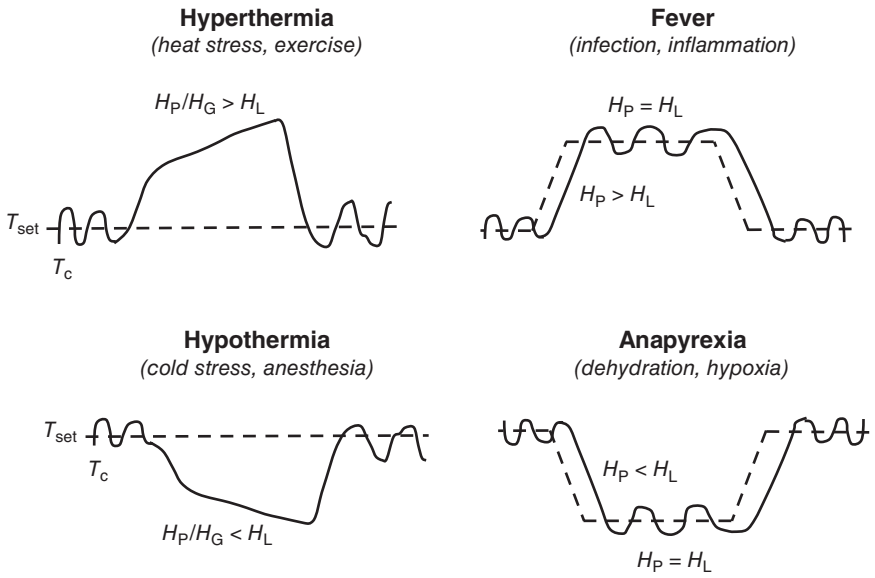

Figure 2 Theoretical concept of unregulated and regulated changes in core temperature (T_c) with reference to the temperature set point (T_{set}). (A) Hyperthermia represents an increase in T_c in the absence of a change in T_{set}. In response to climatic heat stress, exercise or the combination of these factors, heat gain (H_G), and/or heat production (H_P) exceed heat loss (H_L) and T_c rises above T_{set} as the organism becomes hyperthermic. Following removal from the heat, cooling or cessation of exercise, H_L exceeds H_G/H_P and T_c returns to baseline. (B) Fever is defined as a regulated increase in body temperature that is actively established and defended by behavioral and autonomic thermoeffector responses. An increase in heat conservation (H_C) and/or H_G and decrease in H_L stimulate a rise in T_c to a new elevated level. The rising phase of fever is associated with shivering (increases H_P), the use of blankets (increase H_C) until a new elevated level of T_c is attained. Note that while fever is maintained, T_c oscillates around T_{set} and the individual is considered normothermic with H_P=H_L. Once fever breaks, H_L exceeds H_C/H_P as the individual sweats, removes clothing, etc. to return T_c to the baseline level. *Reprinted, with permission, from* (209).

wide interindividual variability as well as temperature variability among different body sites. Temperature within a deep body region will vary as a function of the metabolic rate of surrounding tissues, local blood flow changes, and temperature gradients that exist between adjacent tissues. Skin temperature is the most accessible measurement, but is influenced by changes in blood flow, sweat secretion, environmental influences on heat exchange mechanisms (i.e., evaporative cooling and radiation) or inaccurate measurements such as occurs with a loss of sensor contact with the skin surface (352).

The ideal site for measurement of core temperature should be convenient, unbiased by the environmental conditions and reflective of small changes in arterial blood temperature. Esophageal temperature is considered the most accurate noninvasive measure of core temperature in humans that is rapidly responsive to changes in blood temperature, although this method is not feasible in unresponsive or combative heat stroke patients. Rectal temperature is slightly higher than esophageal temperature and responds more slowly to transient changes in core temperature, such as occurs during exercise. Tympanic auditory canal temperatures are biased by head skin temperature and provide values that may be higher or lower than steady-state rectal and esophageal temperatures (135, 241).

Radiotelemetry provides remote sensing of core temperature (as well as other physiological variables, such as heart rate and blood pressure), which has significantly improved experimental animal models by minimizing stress-hyperthermia in response to restraint and/or handling for rectal temperature measurements (215). These devices support analysis across consecutive circadian cycles throughout the lifetime of an animal, which has significantly improved our understanding of heat stroke-recovery responses in the past few decades. Radiotelemetry is also an effective method for core temperature measurements in human volunteers, although pill temperatures will vary as the pill travels through the gastrointestinal (GI) tract (130). The least reliable technology for core temperature measurement are temporal artery temperature scans, which are unrepresentative of rectal or core temperature (71, 115, 231, 312).

Epidemiology and risk factors

Heat waves are defined as three or more consecutive days during which the environmental temperature exceeds 32.2°C with the majority of heat illness hospitalizations observed within 24 h of the onset of these events (92, 262, 297). Extrinsic factors that may increase risk of classic heat stroke include clothing that impedes heat dissipation, poorly ventilated

Table 2 Risk Factors for Serious Heat Illness

Risk factor	Effect
Environmental factors	
Heat waves	Prolonged environmental heat exposure
High humidity	Impedes evaporative cooling
Lack of air movement	Impedes convective cooling
Urban heat islands	Higher intensity, longer duration environmental heat exposure
Lack of air conditioning	Impedes evaporative, convective cooling
Medications (classic)	
Diuretics	Dehydration and salt, potassium and calcium depletion
Anticholinergics (Atropine)	Impaired sweating
β-blockers (Propranolol)	Reduced blood pressure; reduced skin blood flow
Antihistamines	Impaired sweating
Antidepressants	Increased heat production
Alcohol	Diuresis, impaired vasomotor reflexes
NSAIDs (Aspirin, Acetaminophen)	Increased gut and liver toxicity
Drug Use (Exertional)	Increased activity and heat production, impaired sweating
Ergogenic aids (Ephedrine)	Increased heart rate and blood pressure; sweating or chills;
Ecstacy (MDMA)	increased muscle tension
	Increased heart rate and blood pressure; excessive sweating
Ritalin	Increased gut and liver toxicity
NSAIDs (Aleve)	
Compromised Health Status	
Viral or bacterial infection	Augmented hyperthermic response; immunocompromised
Fever	Augmented hyperthermic response
Skin disorders	Local inflammation; impaired sweating
Cardiovascular insufficiency	Orthostatic intolerance
Genetic conditions	
Malignant hyperthermia	Increased metabolic heat production
TLR4 polymorphisms	Endotoxin hyporesponsiveness

NSAIDs, nonsteroidal anti-inflammatory drugs; MDMA, 3,4-methylenedioxymethamphetamine; TLR, toll-like receptor.

residences, living alone with an inability or unwillingness to leave one's home, residing on the top floor of concrete buildings (heat rises and concrete traps heat), and lack of properly functioning air conditioning units, or refusal to use those units due to socioeconomic or other considerations [(45, 262) Table 2]. Urban dwellings are exposed to higher intensity and longer duration environmental heat exposure mainly due to concrete that traps heat, which does not rapidly dissipate with decreasing nighttime temperatures (81). Approximately 80% of the US population resides in metropolitan areas with the urban elderly particularly vulnerable to classic heat stroke due to physical frailty, limited financial resources, and/or isolation in their residences. Air conditioners are considered one of the most important protective factors for sedentary, elderly individuals, and the very young whereas fan cooling is an ineffective strategy (92, 262). Metropolitan cities experience higher temperatures than surrounding urban areas due to reduced vegetation and large areas of pavement ("urban heat islands"), which affects the manner in which water and heat are exchanged between the land and atmosphere (204). Temperatures may be 30 to 40°C higher on asphalt roads and roof tops compared to the surrounding air (110). Across the entire land mass of the United States, the surface temperature increased ∼0.3°C per century because of decreased vegetation during urban development (173).

Intrinsic risk factors for classic heat stroke include underlying illness, cardiovascular insufficiency, and use of alcohol and medications (Table 2). Concurrent infections may predispose to heat stroke as individuals develop a fever which is compounded by additional heat exposure or they may already reside in an immunocompromised state that limits their ability to rapidly resolve the systemic inflammatory response that ensues following heat stroke collapse (69, 200, 357). Infants are at increased risk for classic heat stroke due to high surface area to body mass ratio (accelerates heat gain), limited mechanisms of adaptive thermoregulation (e.g., suppressed behavioral adjustments), increased risk for dehydration, and preexisting respiratory infections. Cardiovascular insufficiency (regardless of age) compromises reflexive adjustments to environmental heat stress resulting in the inability to maintain adequate cardiac output, which predisposes to circulatory collapse (22, 200, 218, 382). Animal studies have also shown a reduction in thermotolerance in spontaneously hypertensive rats (405). Alcohol consumption is a risk factor due to metabolic stimulation and inhibition of vasomotor reflexes that normally facilitate heat dissipation. The majority of patients admitted to Chicago's Cook County Hospital during a July 1916 heat wave had consumed alcoholic beverages within 24 h preceding the event (122). The high elderly death rate (>600) during the Chicago 1995 heat wave was associated

with alcohol abuse, diuretics, aspirin use, hypertension, and preexisting infections (92). NSAIDs (e.g., naproxen and aspirin) are one of the most common prescription and over-the-counter medications used to treat physical ailments of the elderly. The effect of high environmental temperatures on NSAIDs toxicity has not been well-appreciated despite early reports showing increased aspirin toxicity (measured as lethality) in rats passively exposed to 36°C versus a thermoneutral environment (131).

Risk factors predisposing to exertional heat illness are often more difficult to identify since many victims are young, physically fit and collapse despite practicing sound heat mitigation procedures. Table 2 provides a list of predisposing factors for exertional heat stroke that have been categorized according to physiological limitations, environmental factors, organization practices, training schedules, and medical treatment practices. Although exertional heat stroke patients may cool spontaneously due to the cessation of metabolic heat production and a retained capacity to sweat, accurate diagnosis and rapid cooling are the most effective treatments to mitigate organ damage and ensure survival. Interestingly, many exertional heat stroke victims experience the same condition(s) multiple times with no adverse event, are concurrently exposed to the same condition as other individuals that did not experience heat stroke, and often collapse unexpectedly during the early stages of heat exposure (70,263). These observations suggest that some victims are more vulnerable on a particular day despite exposure to what might be considered an otherwise innocuous event. Approximately 50% of Marine Corps recruits that collapsed from heat stroke were considered low to medium risk suggesting that physical fitness, low body mass index, and/or heat acclimatization are not always sufficient protection (119). Anecdotal evidence suggests that prior bouts of illness or inflammation may increase the risk of exertional heat illness regardless of age, acclimatization status, or other known risk factors (119). In Singapore, a young victim had been ill for 3 days prior to collapsing from heat stroke while performing physical exercise in a relatively cool environment (78). The occurrence of exertional heat stroke during the early stages of an exercise bout suggests the victim was in an immunocompromised state on that particular day (70, 346). Carter et al. (70) showed under controlled laboratory conditions that cellulitis (i.e., friction blisters) was a predisposing factor to idiosyncratic hyperthermia in a young, healthy male volunteer during mild, low intensity exercise in a hot environment (Fig. 3). The rapid development of hyperthermia in some heat stroke victims suggests that fever from a preexisting illness may augment the normal hyperthermic response to exercise.

Several mechanisms have been proposed to account for increased heat stroke risk in individuals with recent illness or inflammation. Dehydration compromises thermoregulatory control mechanisms and was a risk factor in young male runners that suffered heat stroke following respiratory or GI illness (301). Yet dehydration alone cannot account for idiosyncratic cases of exertional heat illness since other

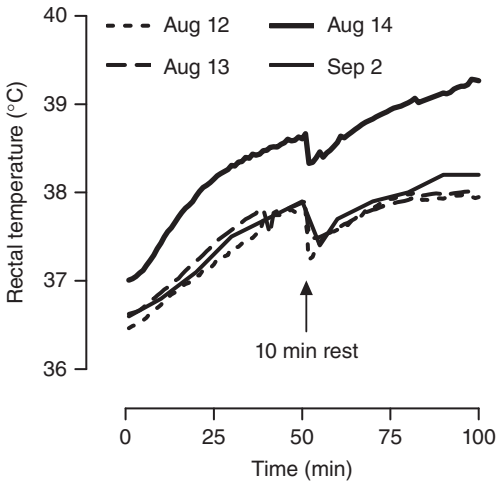

Figure 3 Idiosyncratic hyperthermia during mild, low-intensity exercise in a hot environment. Higher rectal temperature during exercise-heat stress on day 3 was associated with cellulitis. *Reprinted, with permission, from* (69).

subclinical conditions (e.g., cellulitis) that had no effect on hydration level were still associated with exacerbated hyperthermia during exercise-heat stress (70). Proinflammatory cytokines, such as interleukin (IL)-1β and IL-6 are known regulators of fever during infection and are often increased in the circulation and organs of heat stroke patients and animal models (50, 51, 210, 223). Experimental animals injected with *Escherichia coli* lipopolysaccharide (LPS; a nonproliferating component of the gram-negative bacteria cell wall) or *Salmonella enteritidis* LPS developed more rapid hyperthermia with more robust plasma IL-1β, tumor necrosis factor (TNF)α, and IL-6 responses as well as elevated liver enzymes during heat exposure compared to vehicle-injected controls (37, 143, 220). Infection and heat stroke induce similar thermoregulatory (e.g., fever and hypothermia) and inflammatory (e.g., heat shock proteins and cytokines) responses suggesting shared mechanisms may mediate the SIRS that culminates in multi-organ dysfunction or failure.

An alternative hypothesis suggests that prodromal viral illness may deactivate molecular inflammatory pathways that normally protect against organ damage during heat exposure (357). Viruses produce double-stranded RNA (dsRNA) during replication, which stimulates sickness behaviors associated with the "flu syndrome" (236). Interferon (IFN) is thought to mediate body temperature alterations (fever and hypothermia), anorexia, and lethargy in response to dsRNA, but IL-1, IL-6, and TNF have also been implicated in these sickness responses (109, 174, 176, 185, 237, 375). IFNγ was elevated in exertional heat injury victims and considered a potential biomarker of susceptibility to organ dysfunction (232, 357). Murine endothelial cells showed greater apoptotic death in response to heat shock when pretreated with IFNγ supporting a mechanistic role for this cytokine in cellular vulnerability (2). Marine Corps recruits that collapsed from exertional heat injury after a bout of viral illness (pneumonia and mononucleosis) showed higher IFN-inducible (IFI) gene expression

than individuals exposed to the same conditions that did not experience exertional heat injury (357). Similarly, sudden heat stroke death of young soldiers in the Israeli Army was precipitated by febrile illness, including upper respiratory infection, gastroenteritis, and meningitis during the two weeks prior to death (200). Convergent stimulation of cytokine or other inflammatory pathways that mediate sickness behaviors to infection may accelerate hyperthermia and exacerbate heat illness severity (47, 155, 186, 206).

The rapid development of hyperthermia that leads to heat stroke in otherwise low- to medium-risk individuals may be due to activation of neuronal pathways of thermogenesis in the liver following pathogen exposure (36). The liver reticuloendothelial system (RES) is comprised of monocytes, macrophages, and Kupffer cells that detect pathogens and stimulate the complement cascade for rapid, local production of prostaglandin E_2 [PGE_2 (36)]. The binding of locally produced PGE_2 to receptors on afferent (vagal) neurons projecting to the POAH are expected to evoke behavioral and autonomic mechanisms of heat production/heat conservation and inhibit mechanisms of heat loss for rapid generation of fever (36). Neuronal thermogenesis is an effective mechanism for rapid fever development during infection and could rapidly increase body temperature during heat exposure.

Skin disorders and burns

Skin is the largest organ of the body and an important area for effective heat exchange with the environment. There are a number of skin disorders that can adversely affect temperature control and increase susceptibility to heat illness. Miliaria rubra (also known as prickly heat, sweat rash, or heat rash) occurs when the sweat gland ducts become blocked with dead skin cells or bacteria (e.g., *Staphylococcus epidermidis*). Obstruction of the sweat glands causes eccrine secretions to accumulate in the ducts or leak into the deeper layers of the epidermis, causing a local inflammatory reaction associated with redness and blister-like lesions. This condition can increase heat illness risk when a large area of the skin is affected. Experimentally induced miliaria rubra (40%-70% of total body surface area) of healthy male volunteers increased body heat storage and reduced exercise performance time in a hot environment compared to the responses of individuals in a nonrash state (285). Exercise-heat intolerance may occur with miliaria rubra covering as little as 20% of the body surface and can persist up to 3 weeks after the rash appears to have resolved (284).

Sunburn is an epidermal and dermal reaction to ultraviolet radiation that causes skin injury (128). Sweating sensitivity, forearm, and back sweat rates were significantly lower 24 h after an artificial sunburn compared to responses observed in protected (control) body regions (283). Severe sunburn to major portions of the body may result in systemic toxicity as evidenced by symptoms including chills, fever, nausea, and delirium (158). Sunburn effects on sweating appear to be locally mediated and independent of any effects on CNS mechanisms of sudomotor control (283). Sunburn effects on the sweat glands and the dermal vasculature may persist beyond the period that the skin appears to be completely healed.

Burn-related injuries were reported in ~180,000 individuals in the United States from 2002 to 2012 with extensive skin grafts often required to treat the affected areas (14). The most common type of skin graft is referred to as split-thickness which consists of the entire epidermis and a portion of the dermis from a noninjured body site that is grafted to the burned area. Thermoregulatory control is dependent on full integrity of the skin including functional sweat glands and sweat ducts that maintain neural innervation and vascularization. Most split-thickness grafts do not contain functional sweat glands such that revascularization and neural control of blood flow must be reestablished at the grafted site for thermoregulatory control to be supported. There are several reports of higher rectal temperature and diminished thermal tolerance in patients with healed burns over 40% of their body (30, 314, 336, 338). In a small study ($N = 2$-3 patients per group), burns on 60% or greater surface area of the skin showed moderate increases in rectal temperature and heart rate, which did not differ from unburned subjects (21). Although these findings contradict other observations of the effect of burns on the human thermoregulatory response, additional studies are needed to confirm the findings from this small study. Davis et al. (88) showed attenuated cutaneous vasodilation at the grafted site of burn victims following whole body heating that persisted for >4 years after surgery. Conversely, vasoconstrictor responses to whole body cooling remained intact in grafted skin regardless of surgical recovery time (89). These findings suggest that grafted skin is capable of normal reinnervation of the cutaneous vasoconstrictor response, but the vasodilator limb of thermoregulatory control appears to be compromised. The mechanisms responsible for these selective vasomotor responses in skin grafted individuals remain to be elucidated. A comprehensive review of the cutaneous vascular and sudomotor responses in human skin grafts is provided elsewhere (86).

Malignant hyperthermia

Malignant hyperthermia (MH) is a pharmocogenetic disorder characterized by hypercapnia, tachycardia, metabolic acidosis, muscle rigidity, and late onset of hyperthermia (93). The MH syndrome is triggered by exposure to volatile anesthetics (e.g., halothane and isoflurane) or succinylcholine which induces massive release of calcium from the type I ryanodine receptor (RyR1) of the sarcoplasmic reticulum of skeletal muscle (277). cDNA cloning studies have identified three distinct isoforms of the RyR in mammalian tissues (246). RyR1 and RyR2 are abundantly expressed in skeletal and cardiac muscle whereas RyR3 is predominantly expressed in smooth muscle and epithelial cells with lower levels observed in neurons, skeletal and cardiac muscle (124). RyR1 and RyR2 share >60% amino acid sequence identity and respond similarly to

a number of substances including caffeine, Ca^{2+}, Mg^{2+}, and ATP (365). MH-susceptible individuals are identified by caffeine, halothane, or 4-chloro-m-cresol stimulation of skeletal muscle biopsies using an *in vitro* contracture test (313, 418).

Dantrolene is a postsynaptic skeletal muscle relaxant that inhibits calcium release from the sarcoplasmic reticulum by either direct or indirect interaction with the RyR1 receptor (287). Recent studies suggest that dantrolene may also interact with the RyR2 receptor although these interactions appear to be dependent on posttranslational modification of Ca^{2+} channels and/or gene expression of an accessory protein (290). Dantrolene sodium is currently the only effective pharmacologic treatment for MH and is used in conjunction with cessation of anesthesia and rapid cooling to prevent heat stroke in these patients. Mortality rates of untreated MH patients may exceed 90% but survival has significantly increased due to improved monitoring standards, early detection, and dantrolene treatment (227).

MH has been identified in several animal species, including dogs (274), boars (332), cats (29), and horses (13), but the most common experimental animal is a porcine model that possesses a single RyR1 gene mutation in skeletal muscle. These animals develop the MH syndrome in response to inhalational anesthetics as well as exercise, heat, and other stressors. Exposure to mild exercise prior to anesthesia accelerated progression of the MH syndrome and shortened the latency to death, suggesting inflammatory mediators released by skeletal muscle may predispose to MH (378). A small subset (~5%-10%) of MH patients also develop reactions to exercise, heat exposure, and emotional stress, which has led to the hypothesis that excessive Ca^{2+} release from the RyR1 is an underlying etiology for both MH and exertional heat stroke (93, 395). However, excessive skeletal muscle Ca^{2+} release has not been implicated as a mechanism of heat stroke pathophysiology in normal (non-MH) patients or animal models and dantrolene efficacy has not been established for heat stroke. Dantrolene was evaluated for efficacy of a nonexertional anesthetized canine heat stroke model (body temperature = 43°C), but failed to show an effect on cooling rate, hemoconcentration, prothrombin time (one of several clinical measures of disseminated intravascular coagulation; DIC), mean arterial blood gas responses, serum chemistries, or organ damage through 12 h of recovery (15). Similarly, therapeutic intervention of an immature pig heat stroke model (body temperature = 43°C) with dantrolene and conventional cooling did not significantly improve cardiovascular responses compared to conventional cooling methods alone (419). Moran et al. (256) reported enhanced cooling of rats following treatment with dantrolene compared to saline at the time of heat stroke collapse (body temperature ≤43°C), but the effect of dantrolene alone on the body temperature of nonheated control rats was not examined. In a sheep model of heat stroke, dantrolene did not provide a significant benefit compared to conventional cooling methods consisting of fluid resuscitation, sponging with room temperature water, mechanical fanning, and gastric lavage (419). Channa et al. (76) reported more rapid cooling time of heat stroke patients treated with dantrolene compared to conventional cooling methods alone, but neurological sequelae during recovery were virtually identical between groups. In a randomized double-blind controlled study of heat stroke patients, dantrolene sodium treatment had no effect on mean cooling times, complications, or recovery as determined by the mean number of hospital days (42).

With the exception of heat cramps, muscle rigidity is not an exertional heat stroke symptom of non-MH patients whereas this is one of the primary manifestations of the MH syndrome. As such, an inability to demonstrate efficacy of dantrolene for the treatment of heat stroke is likely due to differing etiologies for the development of these conditions. Prophylactic treatment with dantrolene also appears unwarranted as heat stroke patients often display heart, kidney, and liver dysfunction and chronic dantrolene treatment adversely affects the function of these organs (74, 205, 278, 290, 328).

Heat stroke complications

Despite normalization of core temperature with cooling, up to a third of heat stroke patients continue to display core temperature disturbances and progression to multi-organ system dysfunction or failure (42, 238). Complications may range from a sustained alteration of the level of consciousness to full-blown DIC, acute respiratory distress syndrome (ARDS), acute kidney, cardiac, GI, and liver dysfunction or failure (Table 3). Necropsy studies in human victims of classic and exertional heat stroke as well as animal heat stroke models suggest that end organ failure is primarily due to heat-induced necrotic and apoptotic cell death with contributions from widespread microthrombosis, hemorrhage, and inflammatory injury [(52, 61, 62, 238) Fig. 4].

Table 3 Frequency of Organ Dysfunction in 486 Classic Heat Stroke Patients Admitted to ICU During the United States and European Heat Waves

Organ dysfunction	Number of patients (*n*)	Frequency range (%)
CNS	418	80.3-100
Cardiovascular	255	43.4-65.2
Hematologic	275	3.6-75
Respiratory	415	47-98.8
Renal	307	34.9-74.6
Liver	141	0-2.4
Hospital mortality	486	21-65
Neurologic impairment at hospital discharge	141	33-100
Additional mortality at 1-year	39	9-28

Adapted from references (18, 92, 251).
Organ dysfunctions were defined as follows: Central Nervous System (GCS < 8); cardiovascular (need of vasoactive drugs); hematologic (platelet count < 150,000); respiratory (need for mechanical ventilation); renal (serum creatinine > 120 μmol/L); and liver (bilirubin > 20 μmol/L).

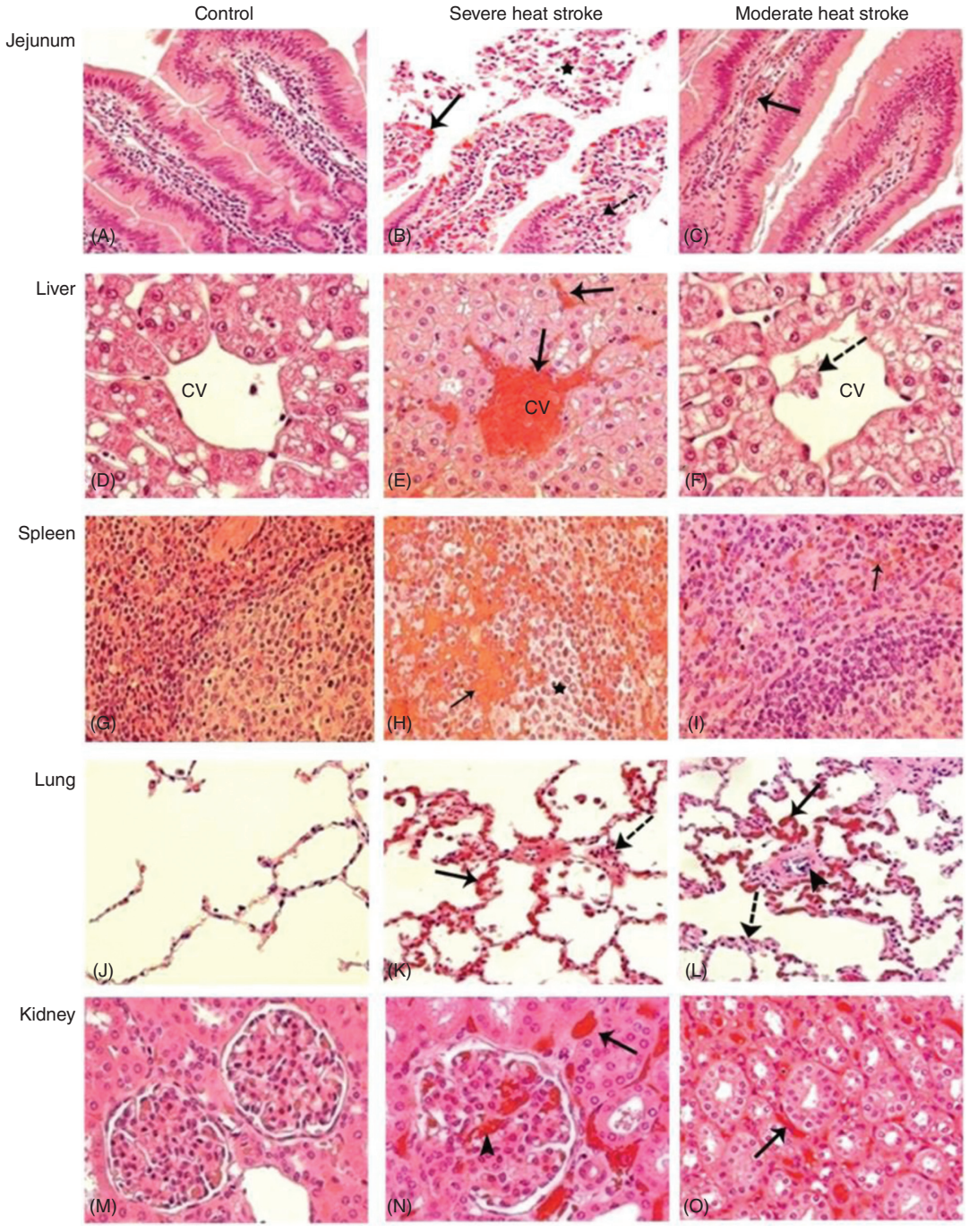

Figure 4 Hematoxylin and eosin (H&E) of multiple organ damage in heat stroke and control baboons. (A) H & E. Controls, no abnormalities (A, D, G, J, and M). Severe heat stroke baboons (B, E, H, K, and N) display vascular congestion and/or hemorrhage (straight arrows), thrombi (arrow-heads), increased inflammatory cells (dashed arrows), and disruption of architecture (asterisks). Moderate heat stroke shows similar changes but less severe (C, F, I, L, and O). *Reprinted with permission, from* (303).

Body temperature responses

Hyperthermia is the most outstanding feature of heat stroke and core temperature is often relied on to distinguish the level of heat severity. However, a low core temperature should not rule out heat stroke, if the history and physical findings are otherwise consistent with the diagnosis. Body temperature at the time of clinical presentation may vary considerably due to delayed measurement (cooling or other clinical interventions prior to temperature measurement), individual differences in acclimatization status, or different anatomical sties of temperature measurement. As such, the maximum recorded body temperature of heat stroke victims may show poor correlation

with the extent of organ damage. Rectal temperatures as high as 42.7°C were reported in competitive runners with no adverse clinical signs suggesting acclimatization to repeated hyperthermia during intensive training regimens provided protection against organ damage (240). Wide-ranging values have also been reported for lethal body temperature of experimental animals including monkeys [~44.5°C (120)], dogs [37.7-41.7°C (5, 101)], cats [~43.5°C (5)], sheep [43.7-44.0°C (142)], rats [40.4-45.4°C (5, 102, 159, 230, 279, 405)], mice [38.7-45°C (212, 402, 406)], and salamanders [~33°C (164)]. The wide variability in experimental heat stroke temperatures is largely a consequence of differences in experimental design, although species differences in body size and other physiological factors that affect heat exchange likely contribute.

The body temperature profile displayed during heat exposure in experimental animals is characterized as a triphasic hyperthermic curve. This response consists of a rapid increase in body temperature on initial heat exposure followed by establishment of an equilibrium plateau, which represents the period during which physiological and behavioral reflexes are stimulated to enhance heat loss and reduce heat gain. The final phase of hyperthermia is characterized by a rapid increase in body temperature due to thermoregulatory breakdown that leads to collapse (279). This body temperature response is predictable and highly reproducible among experimental models and has been used to identify strain and species differences in heat stroke tolerance (50, 211, 212, 220, 223, 405, 406).

It is unknown if the hyperthermic response of humans shows a similar triphasic profile. Thermal area (i.e., the area under the hyperthermia curve) represents the time–intensity relationship of heat exposure, which has been shown to correlate with heat stroke severity in a variety of animal models (52, 161, 212, 341). Similarly, rapid cooling for minimization of the area under the curve is the most effective treatment for heat stroke patients (72, 346, 407) In addition to the body temperature response to heat stroke, downstream signaling events initiate a complex cascade of inflammatory pathways that have been investigated as the ultimate mediators of multi-organ dysfunction and death (52, 207, 308).

Hypothermia and/or recurrent hyperthermia (also referred to as fever) are body temperature responses that are often displayed by heat stroke patients and animal models during the hours, days, and weeks of recovery (212,238,346). Aggressive cooling of heat stroke patients may cause a rapid undershoot of body temperature to <37°C whereas hypothermia to temperatures as low as ~30°C are commonly observed in small rodents allowed to passively cool (212, 213, 230, 311, 406). Hypothermia in heat stroke patients was suggested to be a dysregulated thermoregulatory response following thermal damage to the POAH (238). Yet, there is no clinical or experimental evidence to indicate that the POAH is damaged in response to heat stroke despite evidence of extensive histological damage to other CNS regions (125, 154, 213, 238). Malamud et al. (238) performed autopsy of 125 military exertional heat stroke victims and failed to detect histological damage to the POAH despite the occurrence of hypothermia, recurrent hyperthermia, cerebral edema, degeneration of the Purkinje cells of the cerebellum and extensive histological damage to peripheral organs, including the spleen, liver, and kidney. Experimental animal models often display hypothermia during heat stroke recovery, but recent evidence suggests this is a regulated response that occurs in response to a decrease in the temperature set point [Table 4 (213)]. Hypothermia in heat stroke mice occurred in the absence of histological damage to the POAH (219). The infrequent observation of hypothermia in heat stroke patients is not particularly surprising given the smaller surface area to body mass ratio of

Table 4 Hypothermia and Fever During Heat Stroke Recovery

Species	Body temperature after collapse	Hypothermia during recovery	Fever	References
Cat	NS	33.5, 35.0°C	NR	(5)
Guinea Pig	NS	37°C	NR	(5)
	43.9°C	34°C	NR	(311)
Mouse	42°C	32°C	NR	(406)
	38.7-41.9°C	29-35°C	NR	(402)
	42.4, 42.7, 43.0°C	29-32°C	~1°C (~8 h)	(90, 211-213)
Rat	41.5-42.8°C	35-36°C	NR	(230)
Salamander	33.7°C	10°C below controls (3 days)	—	(164)
Human	36.5-44°C	~1°C	>5°C above normal	(238)
	38.5-44°C	—	24 hours to 7 days	(22)
	38-42°C	—	37.4-38°C (3-21 days of recovery)	(346)

NS, not specified; NR, not recorded due to short observation period; —, body temperature response not observed; human maximum body temperature was recorded following cooling treatments.

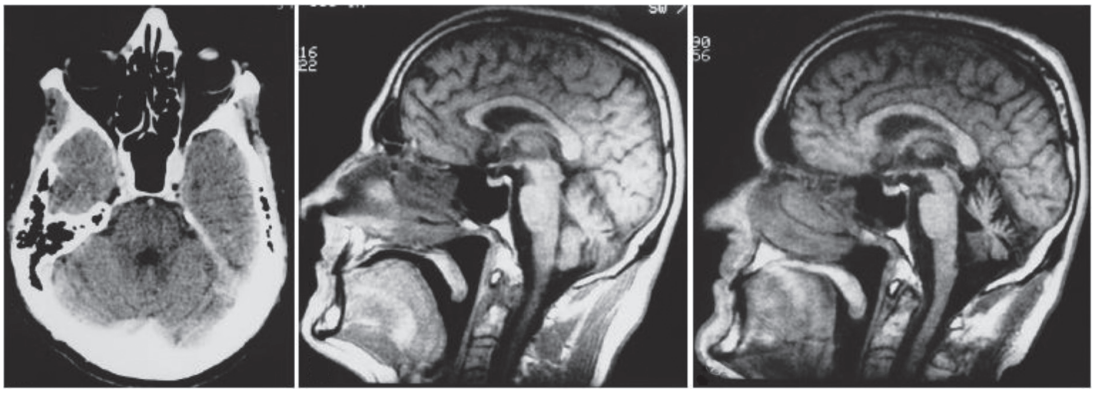

Figure 5 Cerebellar atrophy is a common heat stroke response shown by computer tomography (CT) scan. A 45-year-old man was unconscious and hyperthermic with convulsions at the time of hospital admission. (A) Cerebellum appeared normal 2 weeks following collapse, but showed progressive atrophy from 10 weeks (B) to 11 weeks (C) of recovery. Hypothalamic damage was not reported in this patient. *With, kind permission, from Springer Science and Business Media* (12).

humans compared to mice (creates a larger thermal inertia for heat dissipation) and the multitude of clinical interventions that may mask the response. It remains unknown if cooling of heat stroke patients to a hypothermic level will provide protection against organ damage, such as occurs with the use of clinically induced hypothermia for the treatment of other severe conditions, including cardiac arrest (167), traumatic brain injury (163), and stroke (97, 239).

The most common thermoregulatory response observed during heat stroke recovery of patients and animal models is recurrent hyperthermia [also referred to as rebound hyperthermia or fever; Table 4 (212, 238, 248, 346)]. A rapid increase in body temperature during the initial hours following heat stroke is typically regarded as a compensatory peripheral vasoconstriction response to cooling of the skin surface with ice packs; conversely, protracted episodes have traditionally been regarded as disturbances in CNS thermoregulatory control related to POAH damage (238). Similar to the discussion of hypothermia control, there is no evidence to support the hypothesis that recurrent hyperthermia is due to a lack of thermoregulatory control since patients and animal models that display this body temperature response do not exhibit POAH damage (213, 238, 346). Interestingly, exertional heat stroke patients rapidly reestablished hyperthermia following cessation of clinical cooling, which is reminiscent of Liebermeister's experimental observations of the reestablishment of fever in rats following experimental cooling of the POAH (219, 238). Fever in the most severe exertional heat stroke cases occurred within 3 days of collapse and was associated with petechial hemorrhages of the ventricle walls and hypothalamus [region not specified (346)]. Fever also occurred in mild heat stroke cases that did not experience histological damage to the POAH (346). The Purkinje cells of the cerebellum are particularly heat sensitive such that cerebellar atrophy is a common clinical observation that is associated with ataxia or other functional impairments [(12, 244) Fig. 5]. Severe CNS dysfunction (e.g., coma) was associated with cerebral edema that presented as a loss of gray-white matter discrimination, which was the only notable abnormality (366). Neurological impairments in heat stroke patients are thought to be a consequence of increased intracranial pressure from reduced cerebral blood flow, cerebral ischemia, and possibly intracranial hemorrhage (272). Despite the emergence of sensitive imaging technologies for clinical assessments, damage to the POAH region has not been documented in heat stroke victims that present with CNS and neurological abnormalities.

Fever represents an adaptive immune response to infection and inflammation whereas recurrent hyperthermia has been anecdotally associated with poor outcome in heat stroke patients. An amateur long-distance runner was hospitalized for 10 days following collapse from exertional heat stroke during a 6-mile foot race (248). Moderate fever (>38°C) was evident during the first 4 days of hospitalization, but on the 10th day the patient experienced convulsions and a rapid increase of body temperature to 41°C; rapid cooling and aspirin were ineffective in reducing body temperature and the patient died (248). The potent antipyretic actions of classic NSAIDs (such as aspirin) are attributed primarily to cyclooxygenase inhibition and reduced production of PGE_2, which is considered the POAH mediator of fever during bacterial infection. The inability of aspirin to inhibit the rapid rise in body temperature of the long-distance runner suggests this was not a true fever response, but rather a pathologic response to increased metabolic heat production induced by convulsions. Indomethacin is an NSAID with potent antipyretic actions in mice yet had no effect on the fever responses displayed by mice the day following classic heat stroke collapse [(34, 198, 199) Fig. 6]. Given the lack of NSAIDs efficacy on the fever response to heat stroke, additional research is required to delineate the mechanisms mediating this body temperature response during recovery. Many physicians treat

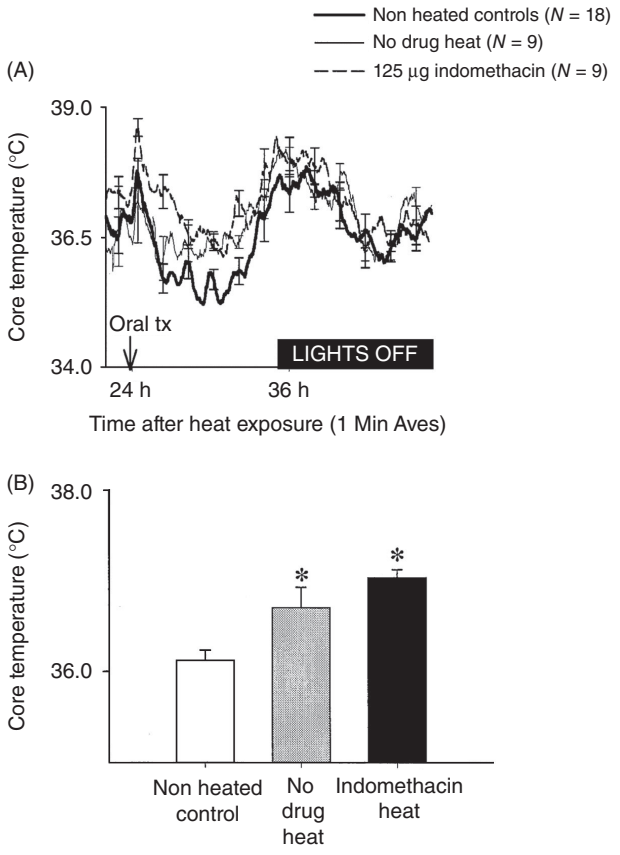

Figure 6 Mice display ~1°C fever the day following heat stroke that is not attenuated by prior treatment with the nonsteroidal anti-inflammatory drug, indomethacin. Responses compared to mice that received no drug or indomethacin in the absence of heat stroke. Indomethacin had no effect on normal (resting) core temperature. (A) Circadian core temperature responses; (B) 12-h average daytime responses. *Reprinted, with permission, from* (34).

heat stroke patients with NSAIDs, but these drugs are contraindicated for this condition due to potential toxic effects on the liver and the association of this treatment with the need for liver transplantation in some patients (125,153,154,321,389).

Cardiovascular dysfunction with heat stroke

The primary cardiovascular adjustment to heat stress is vasoconstriction of splanchnic blood flow with concomitant cutaneous vasodilation to facilitate heat dissipation (318). Reductions in splanchnic blood flow are mediated by thermal receptor stimulation and increased sympathetic activity with heat and exercise having additive effects on these responses (317). Hyperthermia, high skin blood flow and dehydration contribute to a reduction in venous pressure and diastolic filling, the latter of which is compensated with increased cardiac contractility in an attempt to maintain adequate stroke volume (59, 317, 362). The competing thermoregulatory and metabolic demands during heat stress can impose significant strain on the cardiovascular system that often results in syncope and orthostatic intolerance. Aged individuals are particularly susceptible to these symptoms due to preexisting cardiovascular insufficiency or medications that impede normal cardiovascular adjustments to heat stress (18,22,45,218). Austin and Berry (22) examined 100 cases of classic heat stroke and found cardiovascular illness in 84% of patients. Similarly, Levine (218) found classic heat stroke mortalities in the elderly (200 cases) to be associated with arteriosclerotic heart disease (72%) and hypertension (12%). During the European heat wave of 2003, France reported ~15,000 classic heat stroke deaths in 9 days with cardiovascular and pulmonary illnesses identified as contributing factors to the high death toll (18, 197, 251).

Cardiovascular abnormalities in heat stroke (regardless of age or other predisposing factors) may include a weak or irregular pulse, ventricular tachycardia, multiform ventricular premature complexes (PVCs) and arterial hypotension (101, 201, 247). Tachycardia and tachypnea are common and accompanied by hypotension in approximately one third of classic heat stroke cases (42). More detailed cardiac abnormalities have been reported in heat stroke patients than animal models and include PVCs, ST segment depression, and T-wave changes consistent with myocardial ischemia and infarction, sinus tachycardia, and hypo- or hypertension that present with or without global myocardial damage (7, 9, 85, 182, 238, 335, 337, 342, 346, 414). Hypocalcemia and hyperkalemia have been implicated in Q-T interval prolongation and S-T segment abnormalities, respectively, with heat stroke (7, 190). S-T segment alterations were observed in Bantu miners for up to ~5 months of recovery and thought to reflect myocardial injury as evidenced by subendocardial and myocardial hemorrhages with marked interstitial edema (182). Myocardial damage was associated with elevated venous pressure and pulmonary edema whereas subendocardial petechial hemorrhages and localized areas of myocardial necrosis are common autopsy findings (190, 238, 346). Yarom et al. (415) proposed that endomyocardial fibrosis may be an endemic condition in the tropics due to the toxic effects of prolonged environmental heat exposure on cardiac tissue. Rats exposed to 34°C and 40% humidity for up to 2 months displayed numerous cardiac histological changes including focal necrosis, cellular infiltration, and occasional calcification, but only slight fibrosis (415). Whereas diffuse S-T segment changes and myocardial ischemia are commonly reported, myocardial infarction is considered a rare consequence in young heat stroke survivors (117).

Dehydration and electrolyte disturbances

Sweat rates may range from 0.3 to ~3 L/h during athletic or occupational activities, depending on the environmental conditions, type, duration, and intensity of work (79, 178). Water depletion dehydration develops when the rate of water replacement is not adequate due to a mismatch between fluid intake and sweat loss, lack of water availability, or diuretic medications. If high sweat rates are maintained without adequate replenishment of lost water, this can cause electrolyte

imbalances that impede the efficiency of autonomic mechanisms of thermoregulatory control. Severe hypernatremic dehydration is associated with brain edema, intracranial hemorrhage, hemorrhagic infarcts, and permanent brain damage (259).

Sodium, potassium, calcium, and magnesium plasma concentrations are usually normal and hemoconcentration is uncommon with classic heat stroke (42, 43). This is in contrast to exertional heat stroke where hyponatremia, hypocalcemia, hyperkalemia, and hypoglycemia may occur (189, 348). Symptomatic hyponatremia is a relatively rare condition, but has been observed in marathon runners and military recruits during training exercises in response to overconsumption of hypotonic fluids with inadequate replacement of sodium losses (254, 273). Intracellular swelling as a consequence of hyponatremia may cause CNS dysfunction. Hypocalcemia has been attributed to rhabdomyolysis due to sequestration of calcium by the skeletal muscle, but may not be the only causal factor (191, 360). Potassium is a potent vasodilator of blood vessels to skeletal and cardiac muscle and excess loss of this electrolyte can lead to hypokalemia resulting in decreased sweat volume, cardiovascular instability and reductions in muscle blood flow that predispose to rhabdomyolysis (192, 334).

Hyperkalemia may be a consequence of release of potassium from liver or muscle or a shift of potassium from cells to plasma due to acidosis (64, 184, 361) and has been associated with heat stroke deaths during annual heat waves (360). Hyperkalemia has been implicated as a cause of ST-segment elevation and may precipitate these symptoms in classic heat stroke patients (217). Hypokalemia may be a consequence of overproduction of aldosterone, excessive sweating, or respiratory alkalosis resulting in polyuria and increased urinary potassium loss (360, 393). Potassium deficiency has been associated with increased lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and creatine phosphokinase activities in humans and dogs (193, 380). Potassium deficiency of various causes may be due to the loss of muscle cell membrane integrity or enhanced membrane permeability.

Acid base disturbances

Hyperventilation and elevation of core temperature will result in respiratory alkalosis, which may be masked in exertional heat stroke patients by metabolic acidosis due to increased glycolysis and hyperlacticacidemia (77, 261). Mixed respiratory alkalosis with metabolic acidosis is the predominant acid-base alteration in most patients with classic heat stroke (42, 92, 360). Acute compensatory respiratory alkalosis may occur in response to increased respiratory effort; after several hours, a mixed clinical picture of acidosis and alkalosis may lead to a predominant metabolic acidosis due to sustained organ damage. Severe metabolic acidosis is a common manifestation of exertional heat stroke and may be a consequence of an impaired ability of the liver to rapidly clear lactic acid from skeletal muscle for glucose conversion (189). Classic heat stroke was associated with respiratory alkalosis following by progressive metabolic acidosis and decreased bicarbonate levels at temperatures above 42°C in dogs (235). The presence of respiratory alkalosis, metabolic acidosis or both will be dependent on the contributing factors and duration of heat exposure. Elevated CO_2 with accompanying tissue acidosis and reduced pH may impair thermoregulation via excitation of hypothalamic warm-sensitive neurons that receive afferent input from peripheral chemo- and baroreceptors (367-369). Stimulation of warm-sensitive neurons within the POAH would cause a reduction in heat-loss responses and facilitate the development of severe hyperthermia during heat exposure. CO_2 effects on POAH neurons appear to be due to changes in pH as warm-sensitive neurons within hypothalamic tissue slices decreased their firing rate to isocapnic acidosis (i.e., normal CO_2 with decreased pH), but not isohydric hypercapnia [i.e., increased CO_2 with normal pH; Fig. 7 (404)].

Hematologic disturbances

Hematologic disturbances usually consist of leukocytosis, normal hematocrit values, and normal or low platelet counts (40). Leukocytosis is due to both neutrophilia and lymphocytosis. There is a significant alteration in the distribution of lymphocyte subsets reflected by a marked decrease in the ratio of T-helper cells (CD4) to –suppressor/cytotoxic cells (CD8) together with an increase in natural killer cells (CD16). Thrombocytopenia may be associated with DIC.

Coagulopathy is a common complication of severe heat stroke. It ranges from subclinical activation of coagulation and fibrinolysis to fatal hemorrhagic diathesis and widespread microthrombosis in most organs of the body at necropsy (11, 41, 238). A number of clinical studies attributed cell injury, end organ failure and death in heat stroke to excessive activation of coagulation and its extreme manifestation of DIC (11, 92, 104, 245, 251, 354). Microvascular thrombosis is characterized by fibrin deposition and/or platelet aggregation that occludes arterioles and capillaries (216). Coagulopathy may worsen during the first few days after cooling and result in bleeding diathesis (11, 78, 238). Bleeding diathesis (also known as consumptive coagulation) is characterized by excessive blood loss as the consumption of platelets and coagulation proteins outpaces production (20, 28). Heat stroke patients may experience hemorrhagic complications such as prolonged bleeding from venipuncture sites or other areas, including the gums (183). Thermal injury to the vascular endothelium is considered the primary event that initiates coagulation in heat stroke patients (41, 47, 260). *In vitro* heat exposure (43-44°C) was shown to activate platelet aggregation and cause irreversible hyperaggregation that persisted despite cooling (113, 400). Treatment of cancer patients with whole body hyperthermia treatment at body temperatures as low as 39°C was associated with decreased fibrinogen and plasminogen, altered factor VII activity at 41.8°C and decreased platelet concentrations through 18 h of recovery

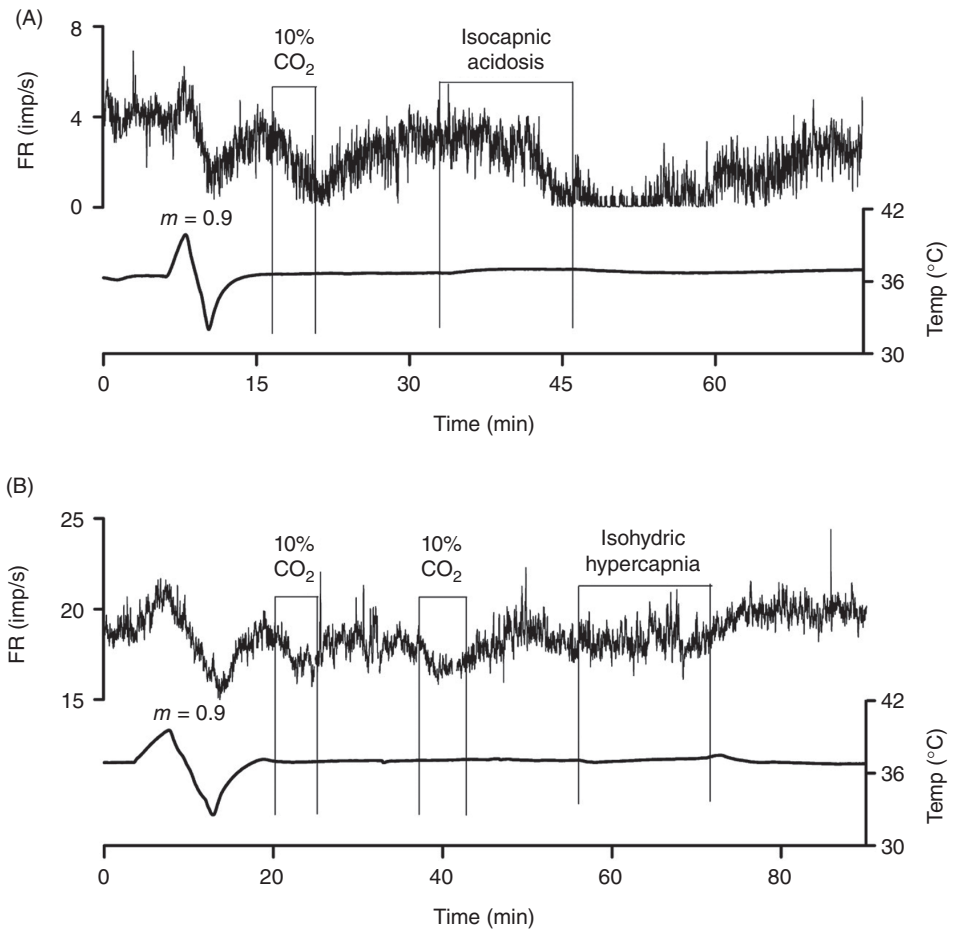

Figure 7 Firing rate responses of two warm-sensitive neurons in a preoptic hypothalamic tissue slice. Each record shows spontaneous firing rate (impulses/s) and tissue slice temperature (°C) with thermal coefficient expressed as $imp \cdot s^{-1} \cdot {}^{\circ}C^{-1}$ (A) Decreased firing rate of a warm-sensitive neuron during hypercapnia and isocapnic acidosis. (B) Decreased firing rate of a warm-sensitive neuron to two hypercapnic exposures with no response during isohydric hypercapnia. *Reprinted, with permission, from* (404).

(363). Experimental studies in baboons demonstrated that the tissue factor/factor VII pathway initiates the activation of coagulation (38, 303). Importantly, its complete neutralization with a tissue factor/factor VII pathway inhibitor failed to decrease cellular injury and organ dysfunction, suggesting that coagulation activation is not a prerequisite of cell injury, organ failure, and death in classic heat stroke (38).

IL-1, TNF, activated protein C (APC) and high mobility group box 1 (HMGBI) have all been implicated in the regulation of coagulation, anticoagulation, and fibrinolytic pathways. Cytokine modulation of DIC is supported by several lines of evidence including: (i) increased plasma levels of IL-1β, IL-6, and TNF in patients with DIC, with high IL-6 correlating with organ failure (386-388), (ii) IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, and TNF-induced alteration in coagulation (23, 169, 264, 293, 379), and (iii) efficacy of neutralizing cytokine antibodies for attenuation of coagulation (282, 327). In the Paris heat wave of 2003, a link was established between elevated circulating levels of proinflammatory cytokines, neutrophil activation, and coagulation in elderly classic heat stroke patients (162). HMGB1 is a 30 kDa protein constitutively expressed in the nuclei of eukaryotic cells. HMGB1 signals through advanced glycation end-products (RAGE) and Toll-like receptor (TLR)2 and TLR4 to induce nuclear NF-κB translocation for transcriptional control of cytokines (253, 286, 394, 411). HMGB1 in combination with thrombin causes excess fibrin deposition in glomeruli, prolonged clotting times, and increased sepsis mortality compared to thrombin alone (165). Tissue factor is a cell surface receptor expressed by monocytes and vascular endothelial cells; increased expression of tissue factor results in initiation of the coagulation cascade. Tissue factor expression is stimulated by IL-1α, IL-1β, IL-6, IL-8, TNF, leukemia inhibitory factor, IFNγ, and monocyte chemoattractant protein (MCP)-1 whereas TGFβ, IL-4, IL-10, and IL-13 inhibit this protein (91, 157, 264, 293, 331). HMGB1 stimulated vascular endothelial cells to express tissue factor mRNA and protein in a concentration- and time-dependent manner (234). This response was attenuated following neutralizing antibody blockade of RAGE, TLR2, and TLR4 receptors

indicating the effects of HMGB1 are mediated through these receptors (234). HMGB1 stimulated tissue factor expression on monocytes and inhibited the APC pathway *in vitro* (165). Cytokines can also modulate the protein C-protein S anticoagulation pathway at several levels, preventing proteolytic cleavage of several factors (Va and VIIIa) involved in the coagulation pathway (299, 410).

Gut Epithelial Permeability and Bacterial Translocation

The primary cardiovascular response to heat exposure is an increase in skin blood flow, which facilitates dry heat loss to the environment and a reduction in total body heat storage. Increased skin blood flow is facilitated by a reduction in splanchnic blood flow, which is a compensatory response to maintain mean arterial pressure while blood is shunted to the skin surface for thermoregulatory control. The GI mucosa normally protects the systemic environment from bacterial products contained within its lumen. However, sustained restrictions in splanchnic blood flow results in ATP depletion, hypoxia, free radical production, acidosis, and cellular dysfunction that makes the GI mucosa "leaky" allowing gram-negative and gram-positive bacteria to translocate into the portal or systemic circulation (126, 145-147). Oxygen tension is naturally lower at the tip of the intestinal villus compared to arterial blood. A blood flow reduction is expected to decrease tissue oxygenation and increase mucosal acidosis leading to epithelial cell injury (26, 280). Hyperthermia in combination with cellular hypoxic stress has been associated with GI damage that promotes bacterial translocation into the systemic circulation (145, 203). Large regional zones of hypoxic cells in the intestinal mucosa of rats were particularly evident in the villi (145). The high metabolic rate of the upper intestine compared to the other regions suggests this region would be more susceptible to hypoxia (345). *In vitro* models have demonstrated that hyperthermia alone (typically in the same range as that associated with intestinal damage *in vivo*) is sufficient to cause epithelial barrier disruption or damage and changes in tight junction protein expression that may be a mechanism that mediates increased permeability (98, 203, 271). Direct comparison between *in vitro* hyperthermia and *in vivo* heat stroke indicated that the pattern of intestinal injury differs between these models, although it may simply be a consequence of more prolonged, severe heat exposure in most cell culture systems (271).

It has been suggested that hyperthermia during heat exposure results from an inability to dissipate heat as well as an increase in the temperature set point that initiates fever in response to endotoxin leakage from damaged gut membranes (143, 144). Fever in combination with heat exposure will accelerate the increase in body temperature resulting in more rapid collapse to heat stroke. Several studies examined the effect of a peripheral injection of LPS on the body temperature response of experimental animal models during heat exposure. In a rat model of heat stroke, low and high doses of LPS had no effect on body temperature to heat stress, whereas moderate doses improved thermal tolerance by shifting the critical thermal maximum (the minimum lethal body temperature) from 42.7 to 43.1°C (67). Conversely, indomethacin is a potent inhibitor of LPS-induced fever that had no effect on heat-induced hyperthermia suggesting the temperature set point was not altered during heat exposure (67). Rabbits injected with LPS showed a significantly faster increase and longer duration of hyperthermia than vehicle-treated animals once they were returned to a temperate environment (37). Indomethacin abated hyperthermia during heat exposure of rabbits, which differed from the lack of effect of this NSAID on the response of rats to a similar combination of stimuli. Additional experimentation will be required to determine if discrepancies in the effect of NSAIDs on hyperthermia during LPS and heat exposure is due to nonspecific effects of the drug on normal body temperature or species-specific responses that remain to be elucidated (37, 323).

The liver RES is the major clearance site for endotoxin and this function is likely responsible for inconsistencies in the ability to detect circulating endotoxin under mild or moderate heat stroke conditions. In a rat model of classic heat stroke, chemical (zymosan), bacterial (endotoxin), and environmental (prior heat stress) stimulation of the RES was effective in reducing heat stroke mortality whereas inhibition of the RES worsened outcome (103). However, there appears to be a core temperature threshold above which the RES may no longer function optimally due to heat-induced damage that causes liver dysfunction. Splanchnic blood flow is decreased at temperatures of ~40°C but compromised liver function is typically not observed until core temperature exceeds ~41 to 42°C (54, 78, 180). Hall et al. (147) showed an association between increased oxidative stress and portal endotoxemia in rats heated to a colonic temperature of 41.5°C, but circulating endotoxin was undetectable. In primates, elevations in circulating endotoxin were detectable as core temperature approached 41.5°C with a precipitous increase observed at ~43.0°C (120). Few studies have cultured bacteria from classic heat stroke patients, but LPS was observed in the circulation of patients with core temperature ~42°C (51). A fatal exertional heat stroke patient that experienced hyperthermia >43°C presented with circulating endotoxin and gram-negative sepsis that was associated with severe necrosis of the liver (134).

Physically fit individuals may be more resistant to heat stroke due to bacterial tolerance that develops following endotoxin exposure during repeated bouts of strenuous physical activity. Training adaptations were associated with lower circulating endotoxin and elevated anti-inflammatory cytokine levels compared to those observed in untrained individuals (333). Endurance trained rats were able to perform more work, sustain a greater thermal load and experience higher rectal temperatures than untrained rats prior to collapsing from exhaustion (111). Training not only reduced the rate of rise in body temperature, but imparted a survival advantage at body

temperatures up to ~42.6 to 43°C (111). Importantly, these rats were trained for 6 weeks in a cool environment to prevent repeated hyperthermia exposures indicating that thermal tolerance was not the mechanism responsible for improved heat stroke survival (111). Physically trained sheep showed improvements in cardiovascular capacity, as evidenced by higher cardiac output and lower heart rate, that was associated with increased blood flow to the brain and ileum during heat exposure (322). Indomethacin attenuated hyperthermia of sedentary, but not fit sheep suggesting training improved gut barrier membrane integrity and reduced intestinal endotoxin leakage and the induction of fever during heat exposure (322).

Despite the potential benefits of physical training, ultraendurance activities are often associated with symptoms that mimic those observed in severely ill (e.g., septic or heat stroke) patients. Increased circulating endotoxin levels in patients can manifest as several types of symptoms including dizziness, nausea, fever, and GI complaints that may include vomiting and diarrhea (381). Severe diarrhea and vomiting may occur with exertional heat stroke (151). Ultraendurance athletes often report GI problems such as intestinal cramps, diarrhea, or blood loss in the feces that may be indicative of increased intestinal permeability (60, 177, 300, 302, 364). The majority (~81%) of runners participating in the Comrades Marathon showed high circulating endotoxin levels following completion of the race that correlated with the incidence of nausea, vomiting, and/or diarrhea (56). Although endotoxemia after strenuous or ultraendurance exercise has been reported, this finding does not always correlate with gut symptoms (25, 255). Increased LPS and IgG anti-LPS levels did not correlate with GI symptoms during running or cycling in ironman triathletes (171). Decreased IgG antiendotoxin levels during the days following long distance athletic events suggests continual leakage of endotoxin is occurring during the protracted recovery period (56, 171). Ibuprofen use the day prior or during a 160-km ultramarathon race was associated with 106% increase in plasma LPS levels compared to athletes that did not use the drug (267). Race time, GI discomfort, muscle damage, and perception of muscle soreness did not differ between groups (267). NSAIDs have not been shown to alleviate muscle soreness or muscle damage following contraction-induced muscle injury (99, 291, 374), but increased GI permeability and decreased kidney glomerular filtration rate have been observed (106, 202, 320, 351). These findings suggest that NSAIDs usage may exacerbate organ damage with exertional heat stroke, but this hypothesis has not been tested.

Oral antibiotics were effective in reducing hyperthermia and the incidence of endotoxemia in several heat stroke models. The rise in core temperature and incidence of endotoxemia in rabbits was reduced with oral antibiotics (65). Dogs pretreated with an antibiotic regimen that reduced gut lumen bacterial content experienced more than threefold increase in classic heat stroke survival compared to untreated controls [rectal temperature ~43.5°C (66)]. In primates, pretreatment with anti-LPS hyperimmune serum was effective in reversing mortality following severe classic heat stress, but the protective effect was no longer evident with ~0.3°C further increase in rectal temperature [43.5 vs. 43.8°C (121)]. Therefore, heat cytotoxicity alone may account for mortality under extreme heat stroke conditions. Dubose et al. (102) reported similar findings in endotoxin-tolerant rats which were protected from classic heat stroke mortality under moderate, but not severe heat stress.

Systemic Inflammation and Organ Damage

The systemic inflammatory response syndrome

The sequelae of classic and exertional heat stroke are thought to be a consequence of high tissue temperatures and underperfusion of the vascular beds that induces oxidative/nitrosative stress and cellular damage (203). Prolonged heat exposure can compromise cardiovascular adjustments and lead to exercise-induced syncope, myocardial ischemia and circulatory failure. Endotoxemia following reduced perfusion of the viscera and resultant cytokine production have been implicated in a SIRS that often culminates in multi-organ dysfunction syndrome and death (47). Histological damage to the gut, kidney, liver, and other peripheral organs are common with both classic and exertional heat stroke, but the molecular inflammatory mechanisms mediating these changes remain poorly understood (18, 238, 347).

A standard clinical heat panel comprised of a Comprehensive Metabolic Profile, Complete Blood Count (CBC), creatine kinase (CK), and urinalysis is currently used to assess organ damage during heat stroke hospitalizations (276). Physicians are reliant on circulating and physiological measurements for acute management of heat stroke; however, these are not always reliable indicators of residual organ damage and may result in a return to normal activities or return to "play" despite increased risk of a subsequent heat event (275, 390). Provided below is a description of current clinical biomarkers of organ damage as well as additional biomarkers that are not currently used for heat stroke assessment, but may improve diagnostic accuracy of heat stroke severity.

Biomarkers and mediators of organ damage

Traditional clinical biomarkers of damage include high circulating CK levels (skeletal muscle), blood urea nitrogen (BUN; kidney), AST (liver), and ALT (liver). Many of these biomarkers are altered by heat as well as exhaustive exercise and released by multiple organs and tissues, which limits their diagnostic value for accurate clinical assessment of organ damage (129). High circulating CK levels may be indicative of rhabdomyolysis, myocardial infarction, muscular dystrophy, or acute renal failure (289, 391). BUN is reflective of blood urea content, which is secreted from the liver and removed by the kidneys. As such, elevated BUN concentrations may be

indicative of impaired liver or renal function. Alternatively, high BUN levels may be unrelated to heat stroke as they are increased with fever, burns, and consumption of high protein diets (4, 315). AST and ALT are common clinical biomarkers of liver function in heat stroke patients despite multiple tissue sources and occasional false-negative results. AST is released by the liver as well as skeletal muscle and may be reflective of congestive heart failure, viral hepatitis, mononucleosis, or muscle injury. ALT is released by red blood cells as well as the liver, heart, skeletal muscle, kidney, and brain. Unfortunately, many heat stroke patients have preexisting conditions that elevate biomarkers in the absence of heat stress, which limits their reliability for accurate organ damage assessment in these patients (129, 139, 344). Furthermore, exercise may induce similar inflammatory mediators as heat stress suggesting that distinctions between these stimuli may depend on the level as well as the pattern of release (160, 179). High enzyme levels are often observed during the acute phase of recovery in classic heat stroke patients whereas they tend to peak later (~24-48 h) during recovery in exertional heat stroke patients (140).

Rhabdomyolysis is a form of skeletal muscle injury caused by the leakage of muscle cell contents into the circulation or extracellular fluid. Myoglobin released from damaged muscle cells is filtered and metabolized by the kidneys. Elevations of circulating CK concentration indicative of muscle injury are observed in classic heat stroke patients; however, overt rhabdomyolysis with acute kidney injury occurs more frequently with exertional heat stroke. The renal threshold for filtration of myoglobin is exceeded with severe muscle damage causing protein to appear in the urine as a reddish-brown color (112). Myoglobin toxicity to the kidney nephrons causes overproduction of uric acid, leading to acute renal failure, coagulopathy, and death if not rapidly detected and treated (24, 112, 226, 289, 393). Clinical markers of rhabdomyolysis include myoglobin, CK, adolase, LDH, ALT, and AST, which are influenced by several additional factors [type, intensity, and duration of exercise, gender, temperature, altitude (82, 249, 309)].

HMGB1 is secreted by necrotic cells as well as oxidative stress-challenged macrophages (294, 325, 370). Peak plasma HMGB1 levels were detected in exertional heat stroke patients within 6 to 13 h of clinical presentation and showed a positive correlation ($r = 0.798$) with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (373). The APACHE II score is not specific to heat stroke, but is a clinical classification system used to determine disease severity of ICU patients (187). Receiver operating characteristic curve (ROC) analysis identified HMGB1 as having similar sensitivity and specificity as the APACHE II score for prediction of heat stroke lethality (373). In a rat classic heat stroke model, plasma and liver HMGB1 levels were significantly increased at 77 min of heat exposure (body temperature = 43°C) and correlated with plasma ALT and AST (372). Pretreatment with a HMGB1 monoclonal antibody significantly attenuated plasma ALT, AST, IL-1β, IL-6, and TNFα and alleviated liver pathology as evidenced by reduced swelling of hepatic sinusoid endothelial cells (372). The ability of anti-HMGB1 antibody to attenuate gut barrier dysfunction, decrease bacterial translocation, and lower circulating cytokine concentrations following hemorrhage shock suggests this strategy may be a potential therapeutic to ameliorate morbidity of heat stroke patients (412).

The paucity of early, noninvasive, predictive biomarkers of organ damage has impeded identification of effective treatments to mitigate organ damage in a timely manner. Therefore, the identification of new circulating biochemical markers is required to aid in more accurate diagnosis and treatment of heat stroke. Two new biomarker candidates include neutrophil gelatinase-associated lipocalin (NGAL; also known as 24p3, uterocalin or neu-related lipocalin) and cardiac troponin I (cTnI). NGAL is purported to overcome limitations of relying on serum creatinine for early diagnosis and prognostication of acute kidney injury as well as myocardial infarction with heat stroke (6, 326). NGAL is produced in renal tubular cells as well as intestinal tissues and liver, but shown to be an accurate predictor of the development of acute kidney injury and mortality in a number of clinical conditions (6, 138). In patients with ST-segment elevation myocardial infarction, high circulating NGAL levels were a significant predictor for long-term mortality and major adverse cardiovascular events (6). Marathon runners showed approximately fivefold increase in urine NGAL suggesting a link between cardiovascular exhaustion and changes in renal filtration function with exhaustive exercise (242). NGAL was also identified as a robust, accurate and early sentinel marker of liver injury to bacterial infection and NSAIDs toxicity (376). A standardized point-of-care kit is available for plasma NGAL measurements with quantitative results available within ~15 min from small blood volumes whereas urine NGAL is measurable with an immunoassay that provides results within 35 min (95). As such, NGAL is a novel sensitive biomarker of organ damage that has the potential for integration into current standards of clinical care for heat stroke

Cardiac troponin I (cTnI) is a highly conserved protein that is present exclusively in cardiac muscle and has higher sensitivity than CK-MB or troponin T for detection of cardiac myocyte damage (1,17). Exertional heat stroke was associated with cTnI levels in a dog that experienced systolic hypotension, multiform PVCs, and irregular myocardial echogenicity with poor left ventricular systolic function (247). Loewenstein et al. (229) proposed fingerstick testing of cTnI for point-of-care assessment of acute coronary syndrome, but the feasibility of this methodology for the determination of cardiac damage with heat stroke remains to be determined.

Multi-Organ Damage During Heat Stroke Recovery

Encephalopathy

Figure 8 provides schematic representation of the mechanisms that are thought to mediate multi-organ damage in response to

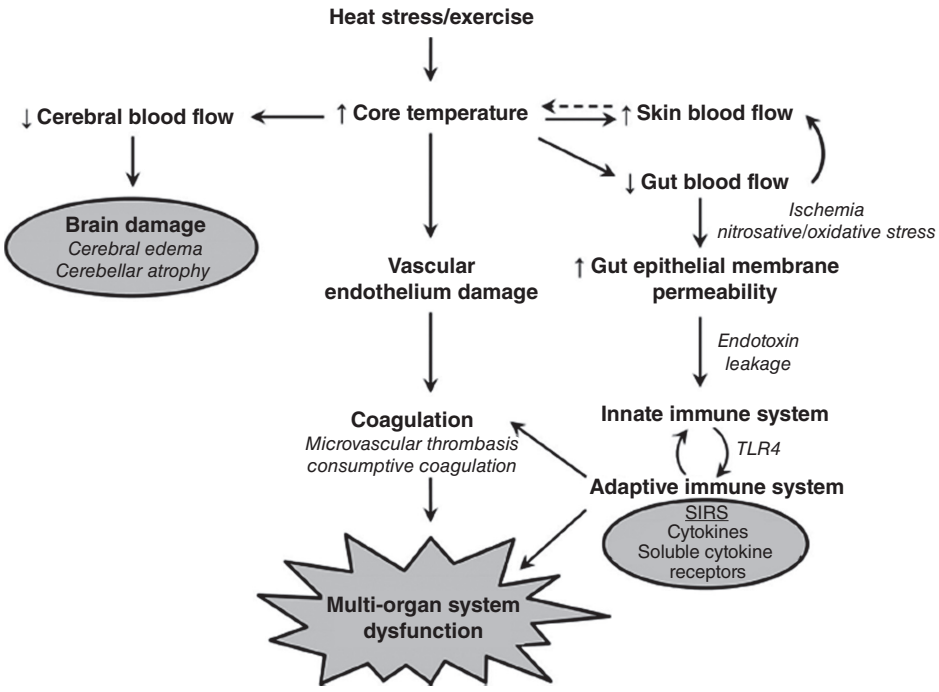

Figure 8 Mechanisms implicated in the pathophysiological responses to heat stroke that often culminate in multi-organ damage and failure. Hyperthermia causes a reduction in cerebral blood flow that may be the initiating stimulus for increased blood brain barrier permeability and brain injury. Hypothalamic damage has been thought to mediate hypothermia and/or recurrent hyperthermia during heat stroke recovery, although there are no clinical or experimental data to support this hypothesis. Skin blood flow is increased during heat exposure to facilitate heat loss to the environment and limit hyperthermia. This response is supported by a decrease in gut blood flow that facilitates redistribution of blood to the skin surface. Gut ischemia causes the gut to become "leaky," which facilitates passage of endotoxin into the systemic circulation. Cytokines, chemokines, and other inflammatory mediators are thought to be initiated by immune responses to endotoxin. Thermal injury to the vascular endothelium and initiation of coagulation/fibrinolysis pathways leads to arteriole and capillary occlusion (microvascular thrombosis) or excessive bleeding (consumptive coagulation). Gray shading represents hypothetical mechanisms of injury. *Reprinted with permission, from* (214).

heat stroke. Heat stroke severity is primarily attributable to the extent of injury incurred by the brain, gut, kidney, liver, and skeletal muscle (specific to exertion). Encephalopathy is a universal manifestation of heat stroke, occurring abruptly and can be severe in most of the cases. This is perhaps the reason why this illness is labeled as a stroke (189, 348, 413). Brain hyperthermia is a consequence of whole-body hyperthermia inducing an increase in cerebral metabolic rate, and a reduction in cerebral blood flow (272). The encephalopathy improves dramatically by cooling in 70% to 90% of heat stroke patients (42, 413). The remainder do not regain consciousness and/or develop seizures or focal motor deficit (413). The blood-brain barrier allows the selective entry of substances (e.g., glucose) into the brain while blocking the entry of other substances (e.g., bacteria). Increased blood brain barrier permeability facilitates protein and pathogen leakage from the systemic circulation into the brain, but neurological impairments are considered a consequence of increased intracranial pressure and autonomic dysfunction that culminates in cerebral ischemia or hemorrhage (272). Postmortem analysis reveals an edematous brain with patches of congestion and petechial hemorrhages (83, 221, 238). Comparable histologic findings of neuronal cell death and Purkinje cells shrinkage and disappearance were reproduced in non-human primate model of heatstroke (Fig. 9). The mechanisms of CNS injury are not well understood but studies in an experimental rat model of classic heat stroke identified ischemia as a major cause and demonstrated that it is secondary to increased intracranial pressure and decreased cerebral flow, resulting in extensive neuronal injury (83, 222-224). Persistent functional disability attributed in large part to neurologic damage is observed in 76% to 100% of the patients that survived classic heat stroke after 1- and 2-years follow-up period, respectively, after hospital discharge (18, 92, 189, 238, 413).

The most conspicuous histological damage to the CNS of heat stroke patients includes progressive degeneration of neurons in the cerebellum and cerebral cortex with congestion, edema, and microhemorrhages at autopsy (238, 346). To date, there are no clinical or experimental studies demonstrating structural damage to the POAH following heat stroke [(213, 238, 346, 366) Table 5]. In the 1995 Chicago heat wave, atrophy, infarcts of the cerebellum, and edema were evident in elderly classic heat stroke victims. Computerized tomography (CT) scans also revealed a severe loss of gray-white

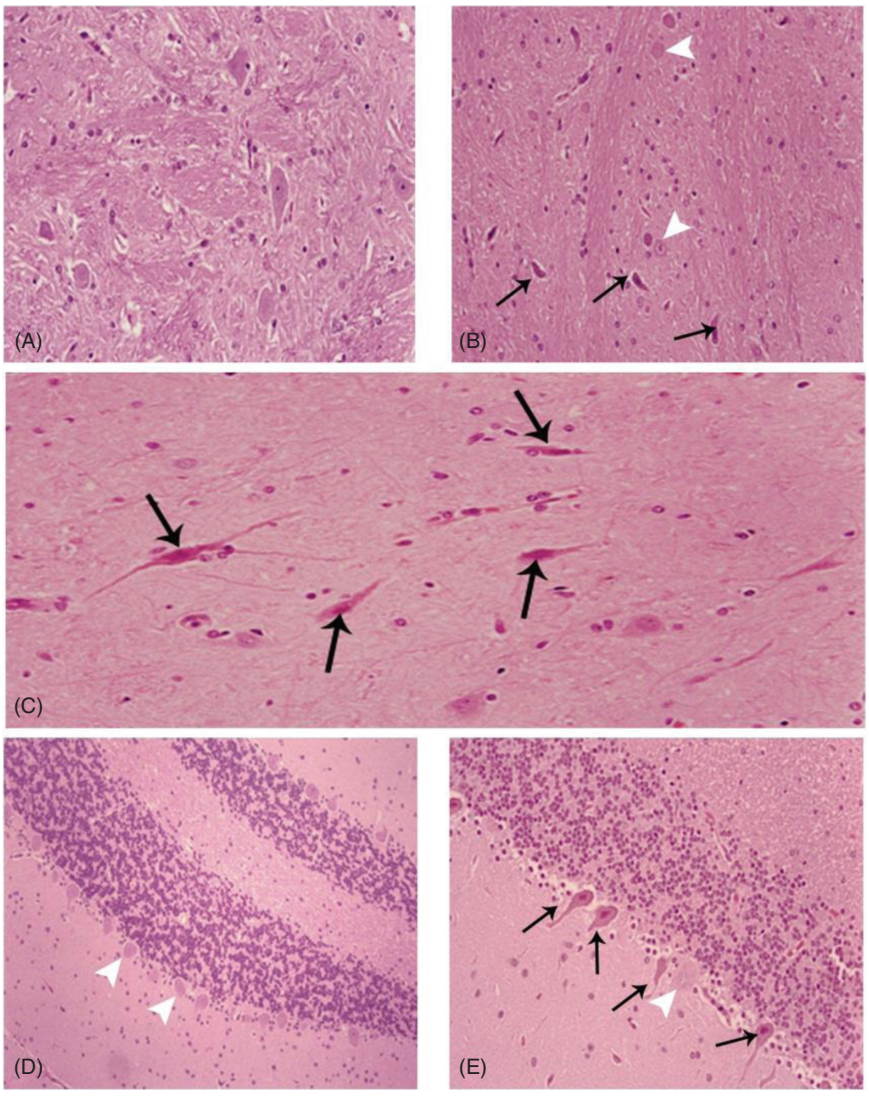

Figure 9 Hematoxylin and eosin stain of tissue sections in control and heat stressed study groups. BRAIN: (A) Normal pallidum in sham-heated controls; (B) early neuronal necrosis (arrows) in scattered neurons. Normal neurons (white arrowheads) in moderate heat stroke; (C) widespread neuronal necrosis (arrows) in severe heatstroke; (D) normal cerebellum: normal Purkinje cells (white arrowheads) in sham-heated controls; (E) early Purkinje cells necrosis (solid arrows) and normal Purkinje cells (white arrowheads) in moderate heat stroke. *Reprinted, with permission, from* (52).

matter discrimination (GWMD), which was associated with headache, coma, the absence of normal reflexive responses and multi-organ dysfunction (366). The loss of GMWD is a consequence of increased brain water content, which is in line with the occurrence of edema in heat stroke victims. Cytoplasmic eosinophilia and nuclear pyknosis in the scattered neurons of the hippocampus and pallidum as well as in the Purkinje cells were observed in severely classic heat stroked baboons (50). The Purkinje cells of the cerebellum appear to be particularly sensitive to heat injury with the progression of cerebellar atrophy readily apparent in magnetic resonance images of heat stroke victims that experienced ataxia or other functional impairments (12, 244).

Gut injury

Figure 10 shows micrographs of sloughing and histological damage to epithelial gut membranes that are thought to facilitate endotoxin leakage into the systemic circulation (203). Dilation of the central lacteals of intestinal villi are commonly observed at temperatures >41.5°C (52, 147, 203, 210). Regional differences in GI susceptibility are observed in a variety of species during acute heat stroke recovery (52, 271, 416).

Regional differences in GI damage are expected to affect the type of immune response that is elicited during heat stroke recovery since the species and density of bacteria differ along the length of the intestine (271, 392). Bacteria known to

Table 5 Brain Injury in Heat Stroke Patients

Age/gender	Body temperature (°C)	Imaging technique(s)	Abnormal findings
41/M	NR	DWI	Corpus callosum and cerebellum lesions (day 4); cerebellar atrophy (day 90)
		CT scan; MRI	Cerebellar atrophy
75/F	42.2°C	MRI	Brainstem and cerebellar atrophy (month 2; year 1)
39/M	42°C	MRI	None
39/F	41.1°C	MRI, CSF	None
53/F	40°C	MRI	Normal (admission); cerebellar and cerebral atrophy (month 2)
46/M	42°C	High *b*-value DWI MRI	Bilateral dentate nuclei lesions Cerebellar atrophy (day 44)
50/F	43.2°C	CT scan	Normal (day 7); cerebellar atrophy (month 5)
45/M	42.7°C	MRI	Normal (2 weeks); cerebellar atrophy (years 1 and 2)
44/F	42.1°C	CT scan (admission; month 3); MRI (day 3)	Normal Normal
2/F	NR	MRI	Cerebellar, parietooccipital, and hippocampi lesions (day 5)
18-41/M&F	≤41°C	H&E (autopsy)	Cerebral edema; neuronal degeneration; reduced Purkinje cells; lack of hypothalamic damage; cerebral hemorrhages
66/M	42.5°C	H&E (autopsy)	Total Purkinje cell loss; normal hypothalamus
79/F	42.9°C	CT scan H&E (autopsy)	Cerebral edema (day 2) Neuronal degeneration in hippocampus, parietal cortex, thalamus, cerebellum, spinal cord
36/M	>42°C	Pneumoencephalography (year 11)	Mild cerebral and moderate cerebellar atrophy

CSF, cerebrospinal fluid; CT, computed tomography; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; NR, not reported. Year of follow-up is shown in parentheses.

translocate across the GI mucosa include *E. coli, Klebsiella pneumonia*, and *Pseudomona aeuruginosa*, although these are most commonly observed in severely ill patients presenting with complicating infections (399,401). Bacterial cultures are not routinely performed in heat stroke patients and many studies have failed to detect circulating endotoxin using traditional assays such as the Limulus amoebocyte lysate test (80, 147).

Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs) that aid in the maintenance of a healthy gut barrier, while also recognizing pattern associated molecular patterns on the cell surface of endotoxin and other invading pathogens (168, 252, 383). Ten human and 12 mouse TLRs have been identified and the specific pathogenic ligands that activate these PRRs are known. In the 1960s, a spontaneous mutation in the TLR4 gene was discovered in C3H/HeJ mice, which has been an important animal model to determine the role of TLR4 in endotoxin and heat stroke responsiveness. C3H/HeJ mice displayed more profound and sustained hypothermia, more rapid induction of circulating IL-1β, IL-6, TNFα, HMGB1 levels, more severe liver damage, and increased classic heat stroke mortality than wild-type mice during 72 h of recovery (90). Purified A box protein (a specific antagonist of HMGB1) protected C3H/HeJ mice from lethality when provided immediately prior to heat exposure (90). Given that TLR4 polymorphisms exist in humans, this may be one (of several) genetic factors that predispose to mortality during the systemic inflammatory response to heat stroke (16, 108).

Rhabdomyolysis and kidney injury

Exertional heat stroke is often associated with rhabdomyolysis. Rhabdomyolysis is most often observed with novel, strenuous overexertion, and clinical evidence suggests that dehydration increases the likelihood or severity of acute renal failure associated with this condition (10,27). Acute renal failure is a common complication of severe exertional heat stroke occurring in ∼25% to 30% of patients (188, 238, 346). Elevations of circulating CK concentration indicative of muscle injury are observed in classic heat stroke patients; however, overt rhabdomyolysis with acute kidney injury occurs more frequently with exertional heat stroke (154).

In patients that survive >24 h, severe hypotension, dehydration, BUN, and oliguria are associated with tubular

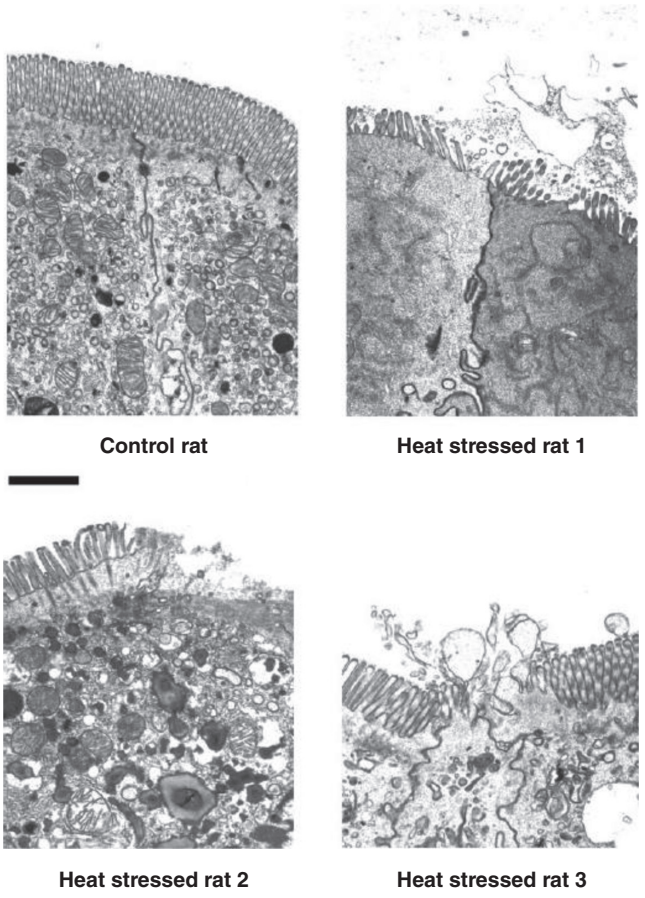

Figure 10 Transmission electron micrographs of small intestinal epithelial cells of heat stroked rats. Partial photograph of adjacent enterocytes showing damage to the microvilli of heat stroke rats compared to controls. *Reprinted, with permission, from* (203).

necrosis or intertubular edema of the kidney (238). Red and white cells are usually present in the urine along with hyaline and granular casts as well as mild to moderate proteinuria (330). Reduced renal blood flow subsequent to heat-induced hypotension, hypohydration, and peripheral vasodilation are contributing factors to renal dysfunction along with direct thermal injury (330). A decrease in renal blood flow is due to active renal sympathetic nerve activity and will be greater if the individual is exercising in the heat and dehydrated (295). Myoglobinuria and elevated blood viscosity resulting from DIC may further contribute to acute oliguric renal failure (296, 330, 355, 384). The incidence of acute renal failure ranges from 5% in classic heat stroke to 25% in exertional heat stroke.

Acute lung injury

Acute lung injury ranges from mild hypoxemia to ARDS (92, 104, 189). The incidence of ARDS ranges from 10% to 23% with a classic heat stroke mortality rate of 75% in a single study (92, 104). The development of DIC was a major risk factor (104). Pulmonary edema is a consistent finding in a baboon classic heat stroke model and is found at autopsy in 60% of classic and exertional heat stroke cases (238, 303).

Liver injury

The time course of liver damage differs from that of the other organs and is often not observed until several days following heat exposure (94, 266, 319). Liver damage of exertional heat stroke patients was characterized by centrilobular degeneration and necrosis with parenchymal damage that was only evident at >30 h of recovery (238). Liver injury is characterized by an early increase in AST and LDH which peak after 3 to 4 days, and increase in bilirubin by the second or third day.

Elevated bilirubin levels reflect hemolysis as well as hepatic dysfunction and remain elevated for several days. Histologic findings consist of centrilobular necrosis with extensive cholestasis (154). Rare cases of fulminant liver failure have been described (154). Liver damage with heat stroke is thought to be a result of the damaging effects of hyperthermia in combination with hypoxia, ischemia, and/or DIC (180, 181). Similar combinatorial factors contributing to liver dysfunction have been reported in sepsis patients (96). Fatty liver changes are due to an inability of mitochondria to utilize fat or may reflect enhanced breakdown of fat and are typically observed in the most severe cases (78, 206). Hyperglycemia or hypoglycemia may be due to dysfunction of phosphoenolpyruvate carboxykinase, which is a regulatory enzyme of the liver's gluconeogenic pathway (41, 206, 210). Bacteria are rarely cultured from the systemic circulation and this may merely be a consequence of resident macrophages in the lungs and liver eliminating micro-organisms from the central venous and portal blood, respectively (268, 269). As such, liver dysfunction may contribute to increased circulating endotoxin levels in heat stroke patients due to the bacterial clearance function of this organ (55, 269). Acute liver failure is documented in 5% of exertional heat stroke patients with hypophosphatemia a predictive biomarker of this condition (118, 189). Liver transplantation has been suggested as a potential treatment for exertional heat stroke patients although patients have succumbed despite this treatment; others with recurrent and/or extensive liver damage have displayed complete biochemical and histologic recovery without transplantation (31, 33, 153, 154, 321, 358, 359). Treatment of heat stroke patients with antipyretic drugs, such as acetaminophen (e.g., Tylenol) has been associated with hepatic failure and the need for liver transplantation (125, 153, 154, 321, 389). The benefit of liver transplantation for exertional heat stroke patients remains controversial due to poor and limited results of the procedure; therefore, proper interpretation of prognostic criteria is crucial before considering a patient for this surgical intervention as reviewed in (140).

Despite clinical treatment, organ dysfunction often persists for several months or years and increases the risk of mortality. The France 2003 heat wave was associated with increased mortality rates from day 28 of hospitalization (58%)

through the second year of recovery [71% (18)]. Military exertional heat stroke patients showed approximately twofold to threefold increased risk of death from cardiovascular, kidney, and liver disease within 30 years of hospitalization (390). Clinical responses occurring shortly after heat stroke collapse and clinical presentation are generally recognized and treatable. However, those occurring during the months and years following hospitalization are underreported and the mechanisms responsible for long-term decrements in organ function remain poorly understood.

Cytokines and Chemokines

Cytokines are a class of immune modulators that have been implicated in the adverse consequences of the SIRS based on data correlating high circulating levels of these proteins with heat stroke morbidity and mortality. Increased circulating levels of IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra, a naturally occurring antagonist of IL-1), IL-6, soluble IL-6 receptor (sIL-6R), IL-8, IL-10, IL-12, IFNγ, TNFα, and soluble TNF receptor (sTNFR) I and II concentrations are commonly observed at the time of heat stroke collapse or shortly after cooling (39,46,50-52,148,149,152,210,211,223, 232). The reader is referred to a recent review that describes these responses in more detail (324). There appears to be an association between high IFNγ levels or high IFI gene expression and preexisting viral infection in classic and exertional heat stroke patients (39, 357). Elevated IFI gene expression and IFNγ levels are a clinical measure of viral or intracellular bacterial infection that were observed in exertional heat stroke patients with preexisting infections [e.g., mononucleosis and pneumonia (357)]. Anecdotal evidence and controlled laboratory studies in humans and animal models suggest that concurrent or preexisting inflammatory or infectious conditions may increase heat stroke risk (37, 69, 143, 225). This effect may be due to the potentiation of hyperthermia during the early stages of heat exposure or deactivation of cytokine pathways that normally protect against cellular damage (2, 69, 357). Murine endothelial cells experienced greater apoptotic death in response to heat shock following pretreatment with IFNγ supporting a mechanistic role for this cytokine in cellular vulnerability (2).

The most consistent cytokine observation has been correlation of high circulating IL-6 levels with heat stroke morbidity/mortality. IL-6 is typically elevated in 100% of classic heat stroke patient populations, levels tend to be highest in patients that do not survive, and sustainment of high IL-6 levels during cooling is correlated with heat stroke severity (39, 52). Yet, IL-6 knockout mice showed a tendency toward increased heat stroke mortality compared to their wild-type counterparts suggesting this cytokine has anti-inflammatory actions that are required for recovery (208). Unfortunately, few studies have examined the dynamic relationship of IL-6 (or other cytokines) with their soluble receptors in the heat stroke syndrome (148). Soluble cytokine receptors act as agonists or antagonists of cytokine actions and their role in the SIRS to heat stroke remains to be identified. It has been suggested that the sIL-6R can function as an agonist or antagonist of IL-6 actions depending on the ratio of this protein to IL-6 in the circulation or the immediate cellular milieu (194, 329). Since mortality of IL-6 knockout mice was observed at hypothermia depth when maximal circulating concentrations of IL-6 and the sIL-6R were observed in wild-type mice, the actions of IL-6 at this time point of heat stroke recovery are difficult to delineate (210, 211). Thus, while baseline (permissive) actions of IL-6 appear to be essential for heat stroke survival, there remains poor understanding of IL-6 actions within the cytokine "milieu" or the downstream signaling events that mediate multi-organ failure and death.

Unfortunately, limitations in our understanding of the actions of cytokines in heat stroke are not unique to IL-6, but also exist with respect to TNF actions in this syndrome. An intriguing study conducted in classic heat stroke patients (a small cohort study of $N = 3$) showed increasing sIL-6R and sTNFRII levels (a natural antagonist of TNF) in nonsurvivors compared to survivors from 6 to 24 h of recovery, respectively, following hospital admission (232). These findings suggest TNF has protective anti-inflammatory actions, which is congruent with the response of TNFR knockout mice (mice that do not express TNF receptors) that experienced greater mortality than their wild-type controls during the second day of heat stroke recovery (207). Taken together, our current understanding of the role of cytokine in the SIRS to heat stroke suggests that high circulating levels may contribute to morbidity, but permissive actions appear to be essential for survival. Additional studies are required to determine the time course of cytokine actions as well as the complex network of interactions occurring in the cellular milieu that determine organ (dys)function during progression of the SIRS.

Chemokines (*chemo*tactic cyto*kines*) are a family of proteins that control leukocyte migration and activation for host immune surveillance during homeostatic and inflammatory conditions. The chemokine family is divided into functionally related subgroups with CC and CXC chemokines representing the largest groups with receptors localized to several cell types in the periphery and CNS. Most chemokines are considered proinflammatory due to the association with T-helper 1 (Th1) cell infiltrate and Th1 cytokine expression (e.g., IFNγ, IL-2, and IL-12) at the site of inflammation (316). DNA microarray analysis of heat shocked peripheral blood mononuclear cells from healthy adults showed decreased expression of macrophage inflammatory protein (MIP)-1α, and β, IFNβ2, and IL-2, but the effect of these changes on protein translation were not investigated (356). Military recruits that developed exertional heat stroke during training exercises displayed significant elevations of several cytokines (IL-1β, TNFα, IL-6, IFNγ, IL-2R, IL-4, and IL-10) and chemokines (IL-8, monocyte chemoattractant protein [MCP]-1, and RANTES) during active cooling following clinical admission (232). IL-6, IFNγ, IL-2R, and MCP-1 were positively correlated with the Simplified Acute Physiology Score, but were independent of the

degree of hyperthermia [~41°C (232)] and all cytokines and chemokines returned to control levels during the acute recovery phase. Blood neutrophils and monocytes isolated from classic heat stroke patients that collapsed during the 2003 France heat wave displayed significantly increased basal IL-8 production *ex vivo*, which was indicative of an activated state of these cells (162). *Ex vivo* stimulation of neutrophils with LPS induced significantly greater IL-8 production in heat stroke patients compared to controls and correlated with reactive oxygen species generation (162). In a mouse model of heat stroke, cytokine (IL-1β, IL-6, and TNFα) and chemokine (MCP-1, MIP-1α and β, and CX3CR1) gene expression profiles in the POAH coincided with expression of glial activation markers, suggesting glia or infiltrating macrophages are a source of these proteins in this brain region (34). Interestingly, increased cytokine and chemokine gene expression changes were observed despite a lack of histological damage to the POAH suggesting these may be compensatory inflammatory changes that are important for heat stroke recovery (34). Table 6 summarizes the direction of changes observed in cytokines and chemokines during heat stroke recovery.

Treatment

There are two main objectives in treating heat stroke: immediate cooling with concomitant support of airways, breathing, and circulation and the management of late or postcooling complications. No pharmacological treatment has been found to be beneficial. Antipyretics have no role in heat stroke and may be toxic to the liver, whereas experimental findings in a primate classic heat stroke model do not support the clinical use of corticosteroids or activated protein C in the prevention or treatment of classic heat stroke (48, 49).

Cooling methods

The primary treatment for heat stroke is to reduce body temperature as quickly as possible since there is ample evidence, albeit indirect, that the severity of tissue damage is related to both the duration and degree of hyperthermia (57, 84, 385). Rapid dissipation of heat is accomplished by increasing the temperature gradient (conduction), water vapor pressure (evaporation), and velocity of air (convection) between the skin and the surrounding air (47). Several external or internal techniques have been devised based on these principles [Table 7 (44, 353)]. Heat stroke prognosis is quite good with an early diagnosis and rapid cooling whereas risk of morbidity/mortality is higher with delayed or ineffective cooling (57, 84, 305).

Conventional cooling techniques

Conductive cooling

This is a direct transfer of heat down a temperature gradient from the body to cooler objects (e.g., ice) in direct contact with the skin. Immersion in an ice-water bath, cooling blanket, or packing the whole or part of the body in ice chips or slush, for example, ice packs to the groin, neck, and axillae, have been used (218, 401). Since all these methods result in skin vasoconstriction, vigorous massaging of the skin is recommended.

Evaporative cooling

This is based on the physical principle that the conversion of 1.7 ml of water to a gaseous phase consumes 1 kcal of heat (107, 397, 408). The efficiency of evaporative cooling depends on a high water-vapor pressure gradient accomplished by continuously spraying the skin with water and blowing hot air to keep it warm (107, 397, 408). Based on this principle of dissipation of heat, a special bed has been developed to accelerate evaporative cooling from warm skin (397), whereby finely atomized water under pressure and at 15°C temperature is sprayed over the whole body surface. The spray is combined with warm air at 45°C to maintain skin temperature around 30 to 33°C thereby preventing vasoconstriction. This maximizes both skin blood flow and vapor pressure gradients between skin and the air. This cooling method has been used on victims of classic heat stroke during the pilgrimage to Makkah. In the absence of such a bed, effective cooling can be achieved as follows: place the naked patient on his or her side (to avoid aspiration) and cover as much skin area as possible with fine gauze sheets (8), spray the gauze intermittently with water at room temperature to keep the skin temperature at 30 to 33°C, while continuously fanning the patient.

Other cooling methods

These include infusion of cold normal saline or ringer lactate solution, iced gastric, bladder, and colonic lavage (18, 92, 251). Peritoneal lavage have been investigated in animals and used infrequently in humans.

Novel cooling techniques

A rapidly increasing number of new generation cooling devices have been emerging following the findings that induced-hypothermia may be beneficial in patients' postcardiac arrest to prevent and/or attenuate anoxic brain damage (Table 7). These cooling devices include catheters using ice-cold fluids circulating in a closed circuit, transnasal system designed to cool selectively the brain, and cold-air or water pads and blankets controlled with sophisticated algorithms. These new cooling devices may prove to be beneficial to patients with heat stroke by accelerating cooling and improving patient's comfort. However, their efficacy must be rigorously tested in hyperthermic patients and not just extrapolated from studies on induced-hypothermia, because these are two distinct pathophysiological conditions.

Selection of optimal cooling methods

There is no evidence to support the superiority of any one cooling technique for the treatment of heat stroke patients

Table 6 Cytokine and Chemokine Gene and Protein Expression Changes to Heat Stroke

	Response	Heat stroke	Whole body/*in vitro* hyperthermia
Cytokines			
IFNα	↑	(357)	
IFNβ	↓	(356)	(304)
IFNγ	↑	(39, 232)	
	↔		(100, 304)
IL-1β	↑	(34, 39, 75, 223, 224, 228, 232, 398)	(87, 116, 343)
	↔	(50)	(281)
IL-1α	↑	(35, 51, 265, 308)	
IL-1ra	↑	(50, 152)	
sIL-1RI	↑	(155)	
sIL-1RII	↑	(155)	
IL-2	↑	(123)	
IL-2R	↑	(149, 232)	
IL-4	↑	(232)	
	↔	(50)	
IL-6	↑	(34, 39, 116, 148, 152, 232, 307, 308)	
	↓	(356)	
	↔		(281)
sIL-6R	↓	(148)	
	↑	(211)	
IL-10	↑	(46, 50, 232, 307, 308)	
IL-12	↓	(50, 210)	
TNFα	↑	(34, 51, 75, 232)	(87)
	↓	(398]	(35, 137, 281)
	↔	(35, 50, 148)	
TNFβ	↔	(148)	
sTNFRI	↑	(50, 148)	(306)
sTNFRII	↑	(50, 148, 152)	(306)
G-CSF	↑	(307)	
Chemokines			
MCP-1	↑	(34, 232)	
MIP-1α	↓	(34, 356)	
MIP-1β	↑	(34)	
MIP-2	↑	(356)	
RANTES	↑	(232)	
C3aR1	↓	(34)	
CX3CR1	↔	(34)	

IFN, interferon; IL, interleukin; IL-1ra, IL-1 receptor antagonist; sIL-1R, soluble IL-1 receptor; sIL-6R, soluble IL-6 receptor; TNF, tumor necrosis factor; sTNFR, soluble tumor necrosis factor receptor; G-CSF, granulocyte colony stimulating factor; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T cell expressed and secreted; C3aR, complement component 3a receptor; CX3CR1, fractalkine receptor. Asterisk indicates gene expression, rather than protein was measured.

Table 7 Conventional and Emerging Cooling Methods

Methods of cooling
Conventional cooling techniques
*Cooling based on conduction**
Ice pack applied to head, neck, and groin
Immersion in cold water
Cold water or air circulating cooling blankets
Cooling based on evaporation and convection
Fanning undressed patient at room temperature (20-22°C)
Wetting of the body surface during continuous fanning
Use of body-cooling unit†
Cooling based on conduction and convection
Infusion of normal saline or ringer lactate solution at 4°C
Iced gastric, colonic, bladder, and peritoneal lavage
Novel cooling techniques‡
Water circulating gel coated energy transfer pads
Central veins cooling catheters using ice-cold fluids circulating in a closed circuit
Extracorporeal circulation cooling system
Selective brain cooling using intranasal nasal delivery of a mixture of high flow gas and cold liquid

*Conductive cooling lower the skin temperature <30°C, triggering cutaneous vasoconstriction and shivering. Keeping skin temperature around 33°C with concomitant spray of tepid water or hot air and/or vigorous massaging of the skin is recommended.
†A body-cooling unit is a special bed that sprays atomized water at 15°C and warm air at 45°C over the whole body surface to keep the temperature of the wet skin between 32 and 33°C.
‡New generation of cooling methods used for the induction of hypothermia postcardiac arrest. Their efficacy has not been tested in heat stroke.

(44, 353). Two recent systematic reviews failed to identify robust randomized clinical trials, and found that most of the studies were observational case-series. Nevertheless, their findings suggest that immersion in iced water is effective among young people, military personnel, and athletes with exertional heat stroke. There is no optimal cooling technique in classic heat stroke. The effects of noninvasive, evaporative, or conductive-based cooling techniques, singly or combined, appeared to be comparable. There is also no evidence of a specific endpoint temperature at which to halt cooling. A rectal temperature of less than 39°C appears to be safe in terms of mortality in heat stroke but associated long-term morbidity, particularly neurological, has not yet been established. Induced hypothermia has shown promise for several neurological and cardiovascular emergencies, including acute stroke and postcardiac arrest. This therapeutic has not been evaluated for effectiveness with classic or exertional heat stroke, but may be effective for cooling severe refractory cases of hyperthermia (19, 156, 270).

Management

The management of heat stroke pre- and in-hospital is summarized in Table 8.

Table 8 Diagnosis and Management of Heat Stroke

A. Diagnosis
- **1** Exposure to high ambient temperature (heat wave, summer time, closed car, and occupational hazard) or strenuous exercise
- **2** Alteration in mental status (delirium, seizures, or coma)
- **3** Core temperature > 40°C measured with rectal probe

B. Management of hyperthermia and concomitant resuscitation
- **1** *Hyperthermia*
  - **a.** Move the patient to a cooler place, and remove his or her clothing
  - **b.** Immerse young patients with exertional heatstroke in cold water, if not available, continuous dousing with cold water. Initiate external cooling‡: in elderly patients with classic heat stroke using cold packs on the neck, axillae, and groin; continuous fanning; and spraying of the skin with water at 25 to 30°C.
  - **c.** Monitor core and skin temperature during cooling and keep skin temperature 30 to 33°C. Halt cooling when core temperature <39°C.
  - **d.** Transfer the patient to an emergency department
- **2** *Initial resuscitation*
  - **a.** Position an unconscious patient on his or her side and clear the airway; consider elective intubation if inability to protect the airways.
  - **b.** Administer oxygen at 4 L/min to enhance arterial oxygen saturation >90%
  - **c.** Give isotonic crystalloid (normal saline)

C. Supportive therapy
- **1** *Encephalopathy*
  - **a.** Endotracheal intubation for impaired gag or cough reflexes
  - **b.** Benzodiazepines to control seizures
- **2** *Acute circulatory failure*
  - **a.** Administer Crystalloids to keep mean arterial pressure >65 mmHg
  - **b.** Consider vasopressors therapy if fluid fails to improve blood pressure, heart rate, and organ perfusion (urine output)
- **3** *Rhabdomyolysis and acute kdney injury*
  - **a.** Expand volume with normal saline and administer intravenously furosemide, and sodium bicarbonate to prevent myoglobin-induced renal injury
  - **b.** Monitor serum potassium and calcium levels and treat hyperkalemia to prevent life-threatening cardiac arrhythmia
- **4** *Disseminated intravascular coagulation*
  Fresh frozen plasma and platelets can be given to control active bleeding
  Heparin has been used but its efficacy and safety remain to be proved
- **5** *Acute respiratory distress syndrome*
  Intubation and mechanical ventilation should be instituted immediately
  Positive end-expiratory pressure (PEEP) may be necessary to achieve adequate oxygenation
- **6** *Liver failure*
  Depletion of clotting factors and encephalopathy should be treated with standard therapy. Occasionally, orthotopic liver transplant is necessary.

Pre-hospital management

Rectal temperature should be measured promptly in patient with mental status alteration during strenuous exercise or exposed to a high ambient temperature. The patient should be moved to a cooler place immediately (preferably indoors) and his/her clothing removed. Cooling measures are started *in situ* and must continue throughout transportation to a hospital. Young people, military personnel, and athletes with exertional heat stroke should be immersed immediately in iced-water or alternatively doused with tap water. Elderly with classic heat stroke should be fanned continuously and the skin can be kept wet with water. Alternatively, cold packs can be placed on the neck, in the axillae and the groin.

In-hospital management

Once in the emergency room, the rectal temperature should be monitored continuously, preferably with a thermistor probe. This should be inserted into the rectum to a depth of 20 cm to obtain a core temperature (189). Skin temperature should also be monitored as it is essential to keep it around 33°C (397). Cooling is continued until the core temperature is below 39°C (42, 189). The cooling method used should be the one with which the emergency room staff are most familiar. While cooling the patient, arterial blood gas, serum electrolyte concentrations, CBC, lactic acid level, and coagulation profile should be determined. Resuscitative measures similar to those used in other conditions may be needed in heat stroke, but cooling takes priority.

Organ support

Central nervous system

The treatment of neurologic complications in heat stroke is directed at the contributory factors responsible for the encephalopathy (hyperthermia, dehydration, cerebral and hypoperfusion). Unfortunately, the neuropathologic substrates (cerebral edema, punctuate hemorrhages, and neuronal necrosis) are not amenable to treatment. Agitation and seizures may be treated with parenteral diazepam or lorazepam. Sustained coma with impaired gag and cough reflexes may require endotracheal intubation to protect the airways and general supportive care such as restoration of normal blood pressure and prevention of hypoxia. The value of hyperventilation, mannitol, the administration of steroids, or the initiation of intracranial pressure monitoring is unclear.

Cardiovascular

Hypotension usually responds to volume replacement with crystalloid and to cooling. In rare cases, hemodynamic monitoring may be necessary, so that fluids or inotropic support can be titrated.

Pulmonary

Airway intubation and mechanical ventilation should be based on a clinical assessment of the patient rather than arterial blood gas determinations because of the difficulty in defining normality in hyperthermic conditions. However, oxygen should be provided at a sufficiently high concentration with high flow or a rebreath mask to achieve an arterial oxygen saturation greater than 90%. If severe hypoxemia persists, as in the patient with the common complications of aspiration pneumonitis and ARDS, intubation and mechanical ventilation should be instituted immediately. Positive end-expiratory pressure may be necessary to achieve adequate oxygenation.

Renal system and electrolytes

Rhabdomyolysis should be treated with adequate fluid replacement to maintain a good urine blood flow (2-3 ml/kg/h). Alkalinization may be helpful to prevent myoglobin-induced renal failure. Hyperglycemia and hypophosphatemia observed in classic heat stroke subside after cooling with no specific treatment (42). Hypo- or hyperkalemia associated with ECG changes should be treated as usual with careful administration of potassium or glucose, insulin, calcium, and $NaHCO_3$, according to standard guidelines. Complex electrolyte imbalance, severe lactic acidosis and anuric renal failure may require early hemodialysis.

Coagulopathy

Bleeding is common in heat stroke patients and hemorrhagic diathesis is constant in fatal cases. The bleeding is due to depletion of antithrombin III, protein C, and platelets secondary to DIC (11). Fresh frozen plasma and platelets should be administered to control active bleeding. Heparin has been used to treat DIC, but its efficacy and safety remain to be proved (396).

Gastrointestinal

Vomiting and diarrhea are commonly seen in patients with heat stroke and cease after cooling, with no specific treatment. Vomiting predisposes the unconscious heat stroke patient to aspiration. This can be avoided by placing the patient in the lateral decubitus position during cooling. Liver failure with depletion of clotting factors and encephalopathy should be treated with standard therapy. Occasionally, orthotropic liver transplant is necessary (154).

Outcome

The hospital mortality rate in classic heat stroke ranges from 10% to 65% whereas that of exertional heat stroke is 3% to 5% (342, 346). The prevalence of functional impairment with varying degrees of severity in near-fatal classic heat-stroke ranges from 76% to 100% at hospital discharge. The

functional disability is sustained with no improvement or even worsening after 1- and 2-years follow-up period (18, 92). The heterogeneity of patients may account for such wide ranges in functional outcome, including neurologic as well as mortality; hence, there is a need to develop an index of heat stroke severity at presentation that would allow comparison of across studies. Several indices have been proposed, but universal acceptance and application of a single paradigm to evaluate heat stroke etiology does not currently exist (175, 250, 298). Similarly, several clinical and biochemical prognostic factors which may identify those patients more likely to succumb have been proposed, however none have been validated yet (189). These factors include age, degree of hyperthermia, neurological symptoms (42), plasma concentrations of liver and muscle enzymes [AST, CPK, respectively (189)], cytokines [IL-6 (39)], and the presence of lactic acidosis (150).

Multivariate analysis (hazard ratio and 95% confidence interval) identified the presence at admission of anuria (5.24; 2.29-12.03), coma (2.95; 1.26-6.91), cardiovascular failure (2.43; 1.14-5.17), high body temperature (1.01; 1.00-1.49), prolonged prothrombin time, (2.44; 1.65-3.63), and use of vasoactive drugs (1.50; 1.01-2.23) within the first day in the ICU, as significant independent variable for heat stroke mortality (18, 251).

Conclusions

As discussed in this review, there remain significant gaps in our understanding of the pathophysiological mechanisms that mediate multi-organ damage to heat stroke. However, recent research efforts highlight a number of promising new approaches for prevention and/or treatment of this condition. For several decades, endotoxin leakage across ischemic damaged gut membranes was thought to be the primary stimulus for initiation of the SIRS that leads to multi-organ damage. However, the inability to consistently detect circulating endotoxin in heat stroke patients and animal models suggests other factors need to be considered in the etiology of this syndrome. Similarly, the use of more sensitive imaging technologies for the assessment of brain injury indicates that POAH damage should not be considered the sole causal factor for core temperature disturbances during recovery. Recent focus on the identification of novel risk factors and organ damage biomarkers suggest that heat stroke shares similar etiologies and downstream effects as other injurious conditions. As such, thermal injury is best viewed as the initiating stimulus of the heat stroke syndrome with the effectiveness of innate and adaptive immune responses determining the time course of resolution of the SIRS and the extent of multi-organ damage. Rapid and aggressive cooling of heat stroke patients continues to be an effective strategy for the mitigation of organ damage on clinical admission, but induced hypothermia should be tested for its efficacy in preventing anoxic brain damage, as its protection has been demonstrated for other severe clinical conditions.

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References

1. Myocardial infarction redefined–a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 21: 1502-1513, 2000.
2. Abello PA, Buchman TG. Heat shock-induced cell death in murine microvascular endothelial cells depends on priming with tumor necrosis factor-alpha or interferon-gamma. *Shock* 2: 320-323, 1994.
3. Abriat A, Brosset C, Bregigeon M, Sagui E. Report of 182 cases of exertional heatstroke in the French Armed Forces. *Mil Med* 179: 309-314, 2014.
4. Adams KF, Jr., Uddin N, Patterson JH. Clinical predictors of in-hospital mortality in acutely decompensated heart failure-piecing together the outcome puzzle. *Congest Heart Fail* 14: 127-134, 2008.
5. Adolph EF. Tolerance to heat and dehydration in several species of mammals. *Am J Physiol* 151: 564-575, 1947.
6. Akcay AB, Ozlu MF, Sen N, Cay S, Ozturk OH, Yalcn F, Bilen P, Kanat S, Karakas MF, Isleyen A, Demir AD, Sogut S, Covic A, Kanbay M. Prognostic significance of neutrophil gelatinase-associated lipocalin in ST-segment elevation myocardial infarction. *J Investig Med* 60: 508-513, 2012.
7. Akhtar MJ, al-Nozha M, al-Harthi S, Nouh MS. Electrocardiographic abnormalities in patients with heat stroke. *Chest* 104: 411-414, 1993.
8. Al-Aska AK, Abu-Aisha H, Yaqub B, Al-Harthi SS, Sallam A. Simplified cooling bed for heatstroke. *Lancet* 1: 381, 1987.
9. al-Harthi SS, Nouh MS, al-Arfaj H, Qaraquish A, Akhter J, Nouh RM. Non-invasive evaluation of cardiac abnormalities in heat stroke pilgrims. *Int J Cardiol* 37: 151-154, 1992.
10. Al-Khawashki MI, Mustafa MKY, Khogali M, El-Sayed H. Clinical presentation of 172 heat stroke cases seen at Mina and Arafat. In: Khogali M, Hales JRS, editors. *Heat Stroke and Temperature Regulation*. New York: Academic Press, 1983, pp. 99-108.
11. al-Mashhadani SA, Gader AG, al Harthi SS, Kangav D, Shaheen FA, Bogus F. The coagulopathy of heat stroke: Alterations in coagulation and fibrinolysis in heat stroke patients during the pilgrimage (Haj) to Makkah. *Blood Coagul Fibrinolysis* 5: 731-736, 1994.
12. Albukrek D, Bakon M, Moran DS, Faibel M, Epstein Y. Heat-stroke-induced cerebellar atrophy: Clinical course, CT and MRI findings. *Neuroradiology* 39: 195-197, 1997.
13. Aleman M, Riehl J, Aldridge BM, Lecouteur RA, Stott JL, Pessah IN. Association of a mutation in the ryanodine receptor 1 gene with equine malignant hyperthermia. *Muscle Nerve* 30: 356-365, 2004.
14. AmericanBurnAssociation. American Burn Association National Burn Repository (2012 Report) Chicago, IL: 2012.
15. Amsterdam JT, Syverud SA, Barker WJ, Bills GR, Goltra DD, Armao JC, Hedges JR. Dantrolene sodium for treatment of heatstroke victims: Lack of efficacy in a canine model. *Am J Emerg Med* 4: 399-405, 1986.
16. Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, Frees K, Watt JL, Schwartz DA. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. *Nat Genet* 25: 187-191, 2000.
17. Archer J. Cardiac biomarkers: A review. *Comp Clin Pathol* 12: 121-128, 2003.
18. Argaud L, Ferry T, Le QH, Marfisi A, Ciorba D, Achache P, Ducluzeau R, Robert D. Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. *Arch Intern Med* 167: 2177-2183, 2007.
19. Arrich J, Holzer M, Herkner H, Mullner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 9: CD004128, 2009.
20. Asakura H, Suga Y, Yoshida T, Ontachi Y, Mizutani T, Kato M, Ito T, Morishita E, Yamazaki M, Miyamoto K, Nakao S. Pathophysiology of disseminated intravascular coagulation (DIC) progresses at a different rate in tissue factor-induced and lipopolysaccharide-induced DIC models in rats. *Blood Coagul Fibrinolysis* 14: 221-228, 2003.

21. Austin KG, Hansbrough JF, Dore C, Noordenbos J, Buono MJ. Thermoregulation in burn patients during exercise. *J Burn Care Rehabil* 24: 9-14, 2003.
22. Austin MG, Berry JW. Observations on one hundred cases of heat stroke. *J Am Med Assoc* 161: 1525-1529, 1956.
23. Baars JW, de Boer JP, Wagstaff J, Roem D, Eerenberg-Belmer AJ, Nauta J, Pinedo HM, Hack CE. Interleukin-2 induces activation of coagulation and fibrinolysis: Resemblance to the changes seen during experimental endotoxaemia. *Br J Haematol* 82: 295-301, 1992.
24. Bagley WH, Yang H, Shah KH. *Rhabdomyolysis. Intern Emerg Med* 2: 210-218, 2007.
25. Baker B, Gaffin SL, Wells M, Wessels BC, Brock-Utne JG. Endotoxaemia in racehorses following exertion. *J S Afr Vet Assoc* 59: 63-66, 1988.
26. Balzan S, de Almeida Quadros C, de Cleva R, Zilberstein B, Cecconello I. Bacterial translocation: Overview of mechanisms and clinical impact. *J Gastroenterol Hepatol* 22: 464-471, 2007.
27. Bar-Or O. Children and physical performance in warm and cold environments. *Adv Pediatr Sport Sci* 1: 117-129, 1984.
28. Barbui T, Falanga A. Disseminated intravascular coagulation in acute leukemia. *Semin Thromb Hemost* 27: 593-604, 2001.
29. Bellah JR, Robertson SA, Buergelt CD, McGavin AD. Suspected malignant hyperthermia after halothane anesthesia in a cat. *Vet Surg* 18: 483-488, 1989.
30. Ben-Simchon C, Tsur H, Keren G, Epstein Y, Shapiro Y. Heat tolerance in patients with extensive healed burns. *Plast Reconstr Surg* 67: 499-504, 1981.
31. Berger J, Hart J, Millis M, Baker AL. Fulminant hepatic failure from heat stroke requiring liver transplantation. *J Clin Gastroenterol* 30: 429-431, 2000.
32. Beshir MY, Ramsey JD. Heat stress indices: A review paper. *Internat J Indust Ergonom* 3: 89-102, 1988.
33. Bianchi L, Ohnacker H, Beck K, Zimmerli-Ning M. Liver damage in heatstroke and its regression. A biopsy study. *Hum Pathol* 3: 237-248, 1972.
34. Biedenkapp JC, Leon LR. Increased cytokine and chemokine gene expression in the CNS of mice during heat stroke recovery. *Am J Physiol Regul Integr Comp Physiol* 305: R978-R986, 2013.
35. Blake D, Bessey P, Karl I, Nunnally I, Hotchkiss R. Hyperthermia induces IL-1α but does not decrease release of IL-1α or TNFα after endotoxin. *Lymphokine Cytokine Res* 13 (5): 271-275, 1994.
36. Blatteis CM. The onset of fever: New insights into its mechanism. *Prog Brain Res* 162: 3-14, 2007.
37. Blatteis CM, Ungar AL, Howell RB. Thermoregulatory responses of rabbits to combined heat exposure, pyrogen and dehydration. In: Milton AS, editor. *Temperature Regulation: Recent Physiological and Pharmacological Advances*. Basel: Springer, 1994, pp. 71-72.
38. Bouchama A, Al-Mohanna F, Assad L, Baturcam E, Eldali A, Owaidah T, Dehbi M. Tissue factor/factor VIIa pathway mediates coagulation activation in induced-heat stroke in the baboon. *Crit Care Med* 40: 1229-1236, 2011
39. Bouchama A, al-Sedairy S, Siddiqui S, Shail E, Rezeig M. Elevated pyrogenic cytokines in heatstroke. *Chest* 104: 1498-1502, 1993.
40. Bouchama A, al Hussein K, Adra C, Rezeig M, al Shail E, al Sedairy S. Distribution of peripheral blood leukocytes in acute heatstroke. *J Appl Physiol* 73: 405-409, 1992.
41. Bouchama A, Bridey F, Hammami MM, Lacombe C, al-Shail E, al-Ohali Y, Combe F, al-Sedairy S, de Prost D. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost* 76: 909-915, 1996.
42. Bouchama A, Cafege A, Devol EB, Labdi O, el-Assil K, Seraj M. Ineffectiveness of dantrolene sodium in the treatment of heatstroke. *Crit Care Med* 19: 176-180, 1991.
43. Bouchama A, Cafege A, Robertson W, al-Dossary S, and el-Yazigi A. Mechanisms of hypophosphatemia in humans with heatstroke. *J Appl Physiol* 71: 328-332, 1991.
44. Bouchama A, Dehbi M, Chaves-Carballo E. Cooling and hemodynamic management in heatstroke: Practical recommendations. *Critical care (London, England)* 11: R54, 2007.
45. Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. Prognostic factors in heat wave related deaths: A meta-analysis. *Arch Intern Med* 167: 2170-2176, 2007.
46. Bouchama A, Hammami MM, Al Shail E, De Vol E. Differential effects of in vitro and in vivo hyperthermia on the production of interleukin-10. *Intensive Care Med* 26: 1646-1651, 2000.
47. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 346: 1978-1988, 2002.
48. Bouchama A, Kunzelmann C, Dehbi M, Kwaasi A, Eldali A, Zobairi F, Freyssinet JM, de Prost D. Recombinant activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. *Arterioscler Thromb Vasc Biol* 28: 1318-1325, 2008.
49. Bouchama A, Kwaasi A, Dehbi M, Al Mohanna F, Eldali A, El-Sayed R, Tbakhi A, Alzahrani AS, Roberts AG. Glucocorticoids do not protect against the lethal effects of experimental heatstroke in baboons. *Shock* 27: 578-583, 2007.
50. Bouchama A, Ollivier V, Roberts G, Al Mohanna F, de Prost D, Eldali A, Saussereau E, El-Sayed R, Chollet-Martin S. Experimental heatstroke in baboon: Analysis of the systemic inflammatory response. *Shock* 24: 332-335, 2005.
51. Bouchama A, Parhar RS, el-Yazigi A, Sheth K, al-Sedairy S. Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. *J Appl Physiol* 70: 2640-2644, 1991.
52. Bouchama A, Roberts G, Al Mohanna F, El-Sayed R, Lach B, Chollet-Martin S, Ollivier V, Al Baradei R, Loualich A, Nakeeb S, Eldali A, de Prost D. Inflammatory, hemostatic, and clinical changes in a baboon experimental model for heatstroke. *J Appl Physiol* 98: 697-705, 2005.
53. Boulant JA. Hypothalamic neurons regulating body temperature. In: Fregly MJ, Blatteis CM, editors. *Handbook of Physiology, Section 4: Environmental Physiology*. New York: Oxford University, 1996, pp. 105-125.
54. Bowers WD, Jr., Hubbard RW, Leav I, Daum R, Conlon M, Hamlet MP, Mager M, Brandt P. Alterations of rat liver subsequent to heat overload. *Arch Pathol Lab Med* 102: 154-157, 1978.
55. Bradfield JW. Control of spillover. The importance of Kupffer-cell function in clinical medicine. *Lancet* 2: 883-886, 1974.
56. Brock-Utne JG, Gaffin SL, Wells MT, Gathiram P, Sohar E, James MF, Morrell DF, Norman RJ. Endotoxaemia in exhausted runners after a long-distance race. *S Afr Med J* 73: 533-536, 1988.
57. Brodeur VB, Dennett SR, Griffin LS. Exertional hyperthermia, ice baths, and emergency care at the Falmouth Road Race. *J Emerg Nurs* 15: 304-312, 1989.
58. Broessner G, Beer R, Franz G, Lackner P, Engelhardt K, Brenneis C, Pfausler B, Schmutzhard E. Case report: Severe heat stroke with multiple organ dysfunction - a novel intravascular treatment approach. *Crit Care* 9: R498-R501, 2005.
59. Brothers RM, Bhella PS, Shibata S, Wingo JE, Levine BD, Crandall CG. Cardiac systolic and diastolic function during whole body heat stress. *Am J Physiol Heart Circ Physiol* 296: H1150-H1156, 2009.
60. Brouns F, Saris WH, Rehrer NJ. Abdominal complaints and gastrointestinal function during long-lasting exercise. *Int J Sports Med* 8: 175-189, 1987.
61. Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR. Role of brain insulin receptor in control of body weight and reproduction. *Science* 289: 2122-2125, 2000.
62. Bruunsgaard H, Skinhoj P, Qvist J, Pedersen BK. Elderly humans show prolonged in vivo inflammatory activity during pneumococcal infections. *J Infect Dis* 180: 551-554, 1999.
63. Budd GM. Wet-bulb globe temperature (WBGT)–its history and its limitations. *J Sci Med Sport* 11: 20-32, 2008.
64. Burnell JM, Scribner BH, Uyeno BT, Villamil MF. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. *J Clin Invest* 35: 935-939, 1956.
65. Butkow N, Mitchell D, Laburn H, Kenedi E. Heat Stroke and endotoxaemia in rabbits. In: Hales JRS, editor. *Thermal Biology*. New York: Raven Press, 1984, pp. 511-514.
66. Bynum G, Brown J, Dubose D, Marsili M, Leav I, Pistole TG, Hamlet M, LeMaire M, Caleb B. Increased survival in experimental dog heatstroke after reduction of gut flora. *Aviat Space Environ Med* 50: 816-819, 1979.
67. Caputa M, Dokladny K, Kurowicka B. Endotoxemia does not limit heat tolerance in rats: The role of plasma lipoproteins. *Eur J Appl Physiol* 82: 142-150, 2000.
68. Carré N, Ermanel C, Isnard H, Ledrans M. Décès par coup de chaleur dans les établissements de santé en France: 8 aout-19 aout 2003. *Bulletin Epidémiologique Hebdomadaire N°* 45-46: 226-227, 2003.
69. Carter RIII, Cheuvront SN, Sawka MN. A case report of idiosyncratic hyperthermia and review of U.S. Army heat stroke hospitalizations. *J Sport Rehabil* 16: 238-243, 2007.
70. Carter R, III, Cheuvront SN, Williams JO, Kolka MA, Stephenson LA, Sawka MN, Amoroso PJ. Epidemiology of hospitalizations and deaths from heat illness in soldiers. *Med Sci Sports Exerc* 37: 1338-1344, 2005.
71. Casa DJ, Becker SM, Ganio MS, Brown CM, Yeargin SW, Roti MW, Siegler J, Blowers JA, Glaviano NR, Huggins RA, Armstrong LE, Maresh CM. Validity of devices that assess body temperature during outdoor exercise in the heat. *J Athl Train* 42: 333-342, 2007.
72. Casa DJ, McDermott BP, Lee EC, Yeargin SW, Armstrong LE, Maresh CM. Cold water immersion: The gold standard for exertional heatstroke treatment. *Exerc Sport Sci Rev* 35: 141-149, 2007.
73. CDC. Heat-Related Deaths – United States, 1999–2003. *Morbid Mortal Weekly* 55: 796-798, 2006.
74. Chan CH. Dantrolene sodium and hepatic injury. *Neurology* 40: 1427-1432, 1990.

75. Chang DM. The role of cytokines in heat stroke. *Immunol Invest* 22: 553-561, 1993.
76. Channa AB, Seraj MA, Saddique AA, Kadiwal GH, Shaikh MH, Samarkandi AH. Is dantrolene effective in heat stroke patients? *Crit Care Med* 18: 290-292, 1990.
77. Chao NHH. Clinical presentation of heat disorders. In: Yeo PPB, Lin NK, editors. *Heat Disorders*. Singapore: Headquarters Medical Services., 1985, pp. 6-15.
78. Chao TC, Sinniah R, Pakiam JE. Acute heat stroke deaths. *Pathology* 13: 145-156, 1981.
79. Cheuvront SN, Carter R, III, and Sawka MN. Fluid balance and endurance exercise performance. *Curr Sports Med Rep* 2: 202-208, 2003.
80. Chung NK, Shabbir M. Cytokine levels in patients with previous heat-stroke under heat stress. *Mil Med* 164: 306-310, 1999.
81. Clark JF. Some effects of the urban structure on heat mortality. *Environ Res* 5: 93-104, 1972.
82. Clarkson PM. Case report of exertional rhabdomyolysis in a 12-year-old boy. *Med Sci Sports Exerc* 38: 197-200, 2006.
83. Clowes GH, Jr., O'Donnell TF, Jr. Heat stroke. *N Engl J Med* 291: 564-567, 1974.
84. Costrini A. Emergency treatment of exertional heatstroke and comparison of whole body cooling techniques. *Med Sci Sports Exerc* 22: 15-18, 1990.
85. Costrini AM, Pitt HA, Gustafson AB, Uddin DE. Cardiovascular and metabolic manifestations of heat stroke and severe heat exhaustion. *Am J Med* 66: 296-302, 1979.
86. Crandall CG, Davis SL. Cutaneous vascular and sudomotor responses in human skin grafts. *J Appl Physiol (1985)* 109: 1524-1530, 2010.
87. D'Oleire F, Schmitt CL, Robins HI, Cohen JD, Spriggs D. Cytokine induction in humans by 41.8 degrees C whole-body hyperthermia. *J Natl Cancer Inst* 85: 833-834, 1993.
88. Davis SL, Shibasaki M, Low DA, Cui J, Keller DM, Purdue GF, Hunt JL, Arnoldo TB, Kowalske KJ, Crandall CG. Impaired cutaneous vasodilation and sweating in grafted skin during whole-body heating. *J Burn Care Res* 28: 427-434, 2007.
89. Davis SL, Shibasaki M, Low DA, Cui J, Keller DM, Wingo JE, Purdue GF, Hunt JL, Arnoldo BD, Kowalske KJ, Crandall CG. Sustained impairments in cutaneous vasodilation and sweating in grafted skin following long-term recovery. *J Burn Care Res* 30: 675-685, 2009.
90. Dehbi M, Uzzaman T, Baturcam E, Eldali A, Ventura W, Bouchama A. Toll-like receptor 4 and high-mobility group box 1 are critical mediators of tissue injury and survival in a mouse model for heatstroke. *PLoS One* 7: e44100, 2012.
91. Del Prete G, De Carli M, Lammel RM, D'Elios MM, Daniel KC, Giusti B, Abbate R, Romagnani S. Th1 and Th2 T-helper cells exert opposite regulatory effects on procoagulant activity and tissue factor production by human monocytes. *Blood* 86: 250-257, 1995.
92. Dematte JE, O'Mara K, Buescher J, Whitney CG, Forsythe S, McNamee T, Adiga RB, Ndukwu IM. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 129: 173-181, 1998.
93. Denborough M. Malignant hyperthermia. *Lancet* 352: 1131-1136, 1998.
94. Deutsch M, Koskinas J, Emmanuel T, Kountouras D, Hadziyannis S. Heat stroke and multi-organ failure with liver involvement in an asylum-seeking refugee. *J Emerg Med* 31: 255-257, 2006.
95. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl* 241: 89-94, 2008.
96. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: Interaction between coagulation and inflammatory processes. *Crit Care Med* 29: S42-S47, 2001.
97. Dietrich WD, Kuluz JW. New research in the field of stroke: Therapeutic hypothermia after cardiac arrest. *Stroke* 34: 1051-1053, 2003.
98. Dokladny K, Moseley PL, Ma TY. Physiologically relevant increase in temperature causes an increase in intestinal epithelial tight junction permeability. *Am J Physiol Gastrointest Liver Physiol* 290: G204-G212, 2006.
99. Donnelly AE, Maughan RJ, Whiting PH. Effects of ibuprofen on exercise-induced muscle soreness and indices of muscle damage. *Br J Sports Med* 24: 191-195, 1990.
100. Downing JF, Martinez-Valdez H, Elizondo RS, Walker EB, Taylor MW. Hyperthermia in humans enhances interferon-gamma synthesis and alters the peripheral lymphocyte population. *J Interferon Res* 8: 143-150, 1988.
101. Drobatz KJ, Macintire DK. Heat-induced illness in dogs: 42 cases (1976-1993). *J Am Vet Med Assoc* 209: 1894-1899, 1996.
102. DuBose DA, Basamania K, Maglione L, Rowlands J. Role of bacterial endotoxins of intestinal origin in rat heat stress mortality. *J Appl Physiol* 54: 31-36, 1983.
103. DuBose DA, McCreary J, Sowders L, Goode L. Relationship between rat heat stress mortality and alterations in reticuloendothelial carbon clearance function. *Aviat Space Environ Med* 54: 1090-1095, 1983.
104. el-Kassimi FA, Al-Mashhadani S, Abdullah AK, Akhtar J. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. *Chest* 90: 571-574, 1986.
105. Epstein Y, Moran DS. Thermal comfort and the heat stress indices. *Ind Health* 44: 388-398, 2006.
106. Farquhar WB, Morgan AL, Zambraski EJ, Kenney WL. Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. *J Appl Physiol (1985)* 86: 598-604, 1999.
107. Ferris EB, Blankenhorn MA, Robinson HW, GE C. Heat Stroke: Clinical and Chemical Observations on 44 Cases. *J Clin Invest* 17: 249-261, 1938.
108. Feterowski C, Emmanuilidis K, Miethke T, Gerauer K, Rump M, Ulm K, Holzmann B, Weighardt H. Effects of functional Toll-like receptor-4 mutations on the immune response to human and experimental sepsis. *Immunology* 109: 426-431, 2003.
109. Fortier ME, Kent S, Ashdown H, Poole S, Boksa P, Luheshi GN. The viral mimic, polyinosinic:polycytidylic acid, induces fever in rats via an interleukin-1-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol* 287: R759-R766, 2004.
110. Frumkin H. Urban sprawl and public health. *Public Health Rep* 117: 201-217, 2002.
111. Fruth JM, Gisolfi CV. Work-heat tolerance in endurance-trained rats. *J Appl Physiol* 54: 249-253, 1983.
112. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 61: 141-152, 1982.
113. Gader AM, al-Mashhadani SA, al-Harthy SS. Direct activation of platelets by heat is the possible trigger of the coagulopathy of heat stroke. *Br J Haematol* 74: 86-92, 1990.
114. Gagge AP, Gonzalez RR. Mechanisms of heat exchange: Biophysics and physiology. In: Blatteis CM, Fregly MJ, editors. *Handbook of Physiology Environmental Physiology*. Bethesda, MD: American Physiological Society, 1996, pp. 45-84.
115. Ganio MS, Brown CM, Casa DJ, Becker SM, Yeargin SW, McDermott BP, Boots LM, Boyd PW, Armstrong LE, Maresh CM. Validity and reliability of devices that assess body temperature during indoor exercise in the heat. *J Athl Train* 44: 124-135, 2009.
116. Ganta CK, Blecha F, Ganta RR, Helwig BG, Parimi S, Lu N, Fels RJ, Musch TI, Kenney MJ. Hyperthermia-enhanced splenic cytokine gene expression is mediated by the sympathetic nervous system. *Physiol Genomics* 19: 175-183, 2004.
117. Garcia-Rubira JC, Aguilar J, Romero D. Acute myocardial infarction in a young man after heat exhaustion. *Int J Cardiol* 47: 297-300, 1995.
118. Garcin JM, Bronstein JA, Cremades S, Courbin P, Cointet F. Acute liver failure is frequent during heat stroke. *World J Gastroenterol* 14: 158-159, 2008.
119. Gardner JW, Kark JA, Karnei K, Sanborn JS, Gastaldo E, Burr P, Wenger CB. Risk factors predicting exertional heat illness in male Marine Corps recruits. *Med Sci Sports Exerc* 28: 939-944, 1996.
120. Gathiram P, Gaffin SL, Brock-Utne JG, Wells MT. Time course of endotoxemia and cardiovascular changes in heat-stressed primates. *Aviat Space Environ Med* 58: 1071-1074, 1987.
121. Gathiram P, Wells MT, Brock-Utne JG, Gaffin SL. Antilipopolysaccharide improves survival in primates subjected to heat stroke. *Circ Shock* 23: 157-164, 1987.
122. Gauss H, Meyer KA. Heat stroke: Report of one hundred and fifty-eight cases from Cook County Hospital, Chicago. *Am M Med Sci* 154: 554-564, 1917.
123. Gern JE, Jayman JR, Goldberg LI, Murphy PA, Lederman HM. Temperature is a powerful promoter of interleukin 2 transcription. *Cytokine* 3: 389-397, 1991.
124. Giannini G, Conti A, Mammarella S, Scrobogna M, Sorrentino V. The ryanodine receptor/calcium channel genes are widely and differentially expressed in murine brain and peripheral tissues. *J Cell Biol* 128: 893-904, 1995.
125. Giercksky T, Boberg KM, Farstad IN, Halvorsen S, Schrumpf E. Severe liver failure in exertional heat stroke. *Scand J Gastroenterol* 34: 824-827, 1999.
126. Gisolfi CV. Is the GI system built for exercise? *News Physiol Sci* 15: 114-119, 2000.
127. Gisolfi CV, Wenger CB. Temperature regulation during exercise: Old concepts, new ideas. *Exerc Sport Sci Rev* 12: 339-372, 1984.
128. Glazer SF. Adverse reactions to sunlight. *Compr Ther* 7: 44-49, 1981.
129. Goddard CJ, Warnes TW. Raised liver enzymes in asymptomatic patients: Investigation and outcome. *Dig Dis* 10: 218-226, 1992.
130. Goodman DA, Kenefick RW, Cadarette BS, Cheuvront SN. Influence of sensor ingestion timing on consistency of temperature measures. *Med Sci Sports Exerc* 41: 597-602, 2009.
131. Gordon C. *Temperature Regulation in Laboratory Rodents*. New York: Cambridge, 1993.
132. Gordon CJ. Thermoregulatory aspects of environmental exposure to anticholinesterase agents. *Rev Environ Health* 11: 101-117, 1996.
133. Gordon CJ. Behavioral thermoregulatory response to chlorpyrifos in the rat. *Toxicology* 124: 165-171, 1997.

134. Graber CD, Reinhold RB, Breman JG, Harley RA, Hennigar GR. Fatal heat stroke. Circulating endotoxin and gram-negative sepsis as complications. *JAMA* 216: 1195-1196, 1971.
135. Greenleaf JE, Castle BL. External auditory canal temperature as an estimate of core temperature. *J Appl Physiol* 32: 194-198, 1972.
136. Griffin JD, Saper CB, Boulant JA. Synaptic and morphological characteristics of temperature-sensitive and -insensitive rat hypothalamic neurones. *J Physiol* 537: 521-535, 2001.
137. Grunenfelder J, Zund G, Schoeberlein A, Schurr U, Frisullo R, Schmid ER, Maly F, Turina M. Expression of adhesion molecules and cytokines after coronary artery bypass grafting during normothermic and hypothermic cardiac arrest. *Eur J Cardiothorac Surg* 17: 723-728, 2000.
138. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. *Am J Kidney Dis* 54: 1012-1024, 2009.
139. Haber MM, West AB, Haber AD, Reuben A. Relationship of aminotransferases to liver histological status in chronic hepatitis C. *Am J Gastroenterol* 90: 1250-1257, 1995.
140. Hadad E, Ben-Ari Z, Heled Y, Moran DS, Shani Y, Epstein Y. Liver transplantation in exertional heat stroke: A medical dilemma. *Intensive Care Med* 30: 1474-1478, 2004.
141. Haldane JS. The influence of high air temperatures: No. 1. *J Hyg* 5: 494-513, 1905.
142. Hales JR, Khogali M, Fawcett AA, Mustafa MK. Circulatory changes associated with heat stroke: Observations in an experimental animal model. *Clin Exp Pharmacol Physiol* 14: 761-777, 1987.
143. Hales JRS, Nagai M. Endotoxemia is normally a limiting factor in heat tolerance. *Pharmacology of Thermoregulation*. Giessen, Germany: 1994.
144. Hales JRS, Sakurada S. Heat tolerance. A role for fever? *Ann NY Acad Sci* 856: 188-205, 1998.
145. Hall DM, Baumgardner KR, Oberley TD, Gisolfi CV. Splanchnic tissues undergo hypoxic stress during whole body hyperthermia. *Am J Physiol* 276: G1195-G1203, 1999.
146. Hall DM, Buettner GR, Matthes RD, Gisolfi CV. Hyperthermia stimulates nitric oxide formation: Electron paramagnetic resonance detection of NO-heme in blood. *J Appl Physiol* 77: 548-553, 1994.
147. Hall DM, Buettner GR, Oberley LW, Xu L, Matthes RD, Gisolfi CV. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. *Am J Physiol Heart Circ Physiol* 280: H509-H521, 2001.
148. Hammami MM, Bouchama A, Al-Sedairy S, Shail E, AlOhaly Y, Mohamed GE. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. *Crit Care Med* 25: 1314-1319, 1997.
149. Hammami MM, Bouchama A, Shail E, al-Sedairy S. Elevated serum level of soluble interleukin-2 receptor in heatstroke. *Intensive Care Med* 24: 988, 1998.
150. Hart GR, Anderson RJ, Crumpler CP, Shulkin A, Reed G, Knochel JP. Epidemic classical heat stroke: Clinical characteristics and course of 28 patients. *Medicine (Baltimore)* 61: 189-197, 1982.
151. Hart LE, Egier BP, Shimizu AG, Tandan PJ, Sutton JR. Exertional heat stroke: The runner's nemesis. *Can Med Assoc J* 122: 1144-1150, 1980.
152. Hashim IA, Al-Zeer A, Al-Shohaib S, Al-Ahwal M, Shenkin A. Cytokine changes in patients with heatstroke during pilgrimage to Makkah. *Mediators Inflamm* 6: 135-139, 1997.
153. Hassanein T, Perper JA, Tepperman L, Starzl TE, Van Thiel DH. Liver failure occurring as a component of exertional heatstroke. *Gastroenterology* 100: 1442-1447, 1991.
154. Hassanein T, Razack A, Gavaler JS, Van Thiel DH. Heatstroke: Its clinical and pathological presentation, with particular attention to the liver. *Am J Gastroenterol* 87: 1382-1389, 1992.
155. Helwig BG, Leon LR. Tissue and circulating expression of IL-1 family members following heat stroke. *Physiol Genomics* 43: 1096-1104, 2011.
156. Hemmen TM, Lyden PD. Induced hypothermia for acute stroke. *Stroke* 38: 794-799, 2007.
157. Herbert JM, Savi P, Laplace MC, Lale A. IL-4 inhibits LPS-, IL-1 beta- and TNF alpha-induced expression of tissue factor in endothelial cells and monocytes. *FEBS Lett* 310: 31-33, 1992.
158. Holti G. Measurements of the vascular responses in skin at various time intervals after damage with histamine and ultra-violet radiation. *Clin Sci (Lond)* 14: 143-155, 1955.
159. Hubbard RW, Bowers WD, Jr., Mager M. A study of physiological, pathological and biochemical changes in rats with heat- and/or work-induced disorders. *Isr J Med Sci* 12: 884-886, 1976.
160. Hubbard RW, Criss RE, Elliott LP, Kelly C, Matthew WT, Bowers WD, Leav I, Mager M. Diagnostic significance of selected serum enzymes in a rat heatstroke model. *J Appl Physiol Respir Environ Exerc Physiol* 46: 334-339, 1979.
161. Hubbard RW, Matthew WT, Linduska JD, Curtis FC, Bowers WD, Leav I, Mager M. The laboratory rat as a model for hyperthermic syndromes in humans. *Am J Physiol* 231: 1119-1123, 1976.
162. Huisse MG, Pease S, Hurtado-Nedelec M, Arnaud B, Malaquin C, Wolff M, Gougerot-Pocidalo MA, Kermarrec N, Bezeaud A, Guillin MC, Paoletti X, Chollet-Martin S. Leukocyte activation: The link between inflammation and coagulation during heatstroke. A study of patients during the 2003 heat wave in Paris. *Crit Care Med* 36: 2288-2295, 2008.
163. Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 358: 2447-2456, 2008.
164. Hutchison VH, Murphy K. Behavioral thermoregulation in the salamander *Necturus maculosus* after heat shock. *Comp Biochem Physiol* 82A: 391-394, 1985.
165. Ito T, Kawahara K, Nakamura T, Yamada S, Abeyama K, Hashiguchi T, Maruyama I. High-mobility group box 1 protein promotes development of microvascular thrombosis in rats. *J Thromb Haemost* 5: 109-116, 2007.
166. IUPS. Glossary of terms for thermal physiology. *Jap J Physiol* 51: 245-280, 2001.
167. Janata A, Holzer M. Hypothermia after cardiac arrest. *Prog Cardiovasc Dis* 52: 168-179, 2009.
168. Janeway CA, Jr., Medzhitov R. Innate immune recognition. *Annu Rev Immunol* 20: 197-216, 2002.
169. Jansen PM, Boermeester MA, Fischer E, de JI, van der PT, Moldawer LL, Hack CE, Lowry SF. Contribution of interleukin-1 to activation of coagulation and fibrinolysis, neutrophil degranulation, and the release of secretory-type phospholipase A2 in sepsis: Studies in nonhuman primates after interleukin-1 alpha administration and during lethal bacteremia. *Blood* 86: 1027-1034, 1995.
170. Jessen C. Interaction of body temperatures in control of thermoregulatory effector mechanisms. In: Fregley MJ, Blatteis CM, editors. *Handbook of Physiology Environmental Physiology*. Bethesda, MD: American Physiological Society, 1996, pp. 127-138.
171. Jeukendrup AE, Vet-Joop K, Sturk A, Stegen JH, Senden J, Saris WH, Wagenmakers AJ. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. *Clin Sci (Lond)* 98: 47-55, 2000.
172. Jones TS, Liang AP, Kilbourne EM, Griffin MR, Patriarca PA, Wassilak SG, Mullan RJ, Herrick RF, Donnell HD, Jr., Choi K, Thacker SB. Morbidity and mortality associated with the July 1980 heat wave in St Louis and Kansas City, Mo. *JAMA* 247: 3327-3331, 1982.
173. Kalnay E, Cai M. Impact of urbanization and land-use change on climate. *Nature* 423: 528-531, 2003.
174. Kapas L, Bohnet SG, Traynor TR, Majde JA, Szentirmai E, Magrath P, Taishi P, Krueger JM. Spontaneous and influenza virus-induced sleep are altered in TNF-alpha double-receptor deficient mice. *J Appl Physiol* 105: 1187-1198, 2008.
175. Kark JA, Burr PQ, Wenger CB, Gastaldo E, Gardner JW. Exertional heat illness in Marine Corps recruit training. *Aviat Space Environ Med* 67: 354-360, 1996.
176. Katafuchi T, Kondo T, Yasaka T, Kubo K, Take S, Yoshimura M. Prolonged effects of polyriboinosinic: Polyribocytidylic acid on spontaneous running wheel activity and brain interferon-alpha mRNA in rats: A model for immunologically induced fatigue. *Neuroscience* 120: 837-845, 2003.
177. Keeffe EB, Lowe DK, Goss JR, Wayne R. Gastrointestinal symptoms of marathon runners. *West J Med* 141: 481-484, 1984.
178. Kenefick RW, Cheuvront SN, Sawka MN. Thermoregulatory function during the marathon. *Sports Med* 37: 312-315, 2007.
179. Kew M, Bersohn I, Seftel H. The diagnostic and prognostic significance of the serum enzyme changes in heatstroke. *Trans R Soc Trop Med Hyg* 65: 325-330, 1971.
180. Kew M, Bersohn I, Seftel H, Kent G. Liver damage in heatstroke. *Am J Med* 49: 192-202, 1970.
181. Kew MC, Minick OT, Bahu RM, Stein RJ, Kent G. Ultrastructural changes in the liver in heatstroke. *Am J Pathol* 90: 609-618, 1978.
182. Kew MC, Tucker RB, Bersohn I, Seftel HC. The heart in heatstroke. *Am Heart J* 77: 324-335, 1969.
183. Khogali M. Epidemiology of heat illnesses during the Makkah Pilgrimages in Saudi Arabia. *Int J Epidemiol* 12: 267-273, 1983.
184. Kilburn KH. Muscular origin of elevated plasma potassium during exercise. *J Appl Physiol* 21: 675-678, 1966.
185. Kimura M, Toth LA, Agostini H, Cady AB, Majde JA, Krueger JM. Comparison of acute phase responses induced in rabbits by lipopolysaccharide and double-stranded RNA. *Am J Physiol* 267: R1596-R1605, 1994.
186. Kluger MJ. Fever: Role of pyrogens and cryogens. *Physiol Rev* 71: 93-127, 1991.

187. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med* 13: 818-829, 1985.
188. Knochel JP. Environmental heat illness. An eclectic review. *Arch Intern Med* 133: 841-864, 1974.
189. Knochel JP. Heat stroke and related heat stress disorders. *Dis Mon* 35: 301-377, 1989.
190. Knochel JP, Beisel WR, Herndon EG, Jr., Gerard ES, Barry KG. The renal, cardiovascular, hematologic and serum electrolyte abnormalities of heat stroke. *Am J Med* 30: 299-309, 1961.
191. Knochel JP, Caskey JH. The mechanism of hypophosphatemia in acute heat stroke. *JAMA* 238: 425-426, 1977.
192. Knochel JP, Dotin LN, Hamburger RJ. Pathophysiology of intense physical conditioning in a hot climate. I. Mechanisms of potassium depletion. *J Clin Invest* 51: 242-255, 1972.
193. Knochel JP, Schlein EM. On the mechanism of rhabdomyolysis in potassium depletion. *J Clin Invest* 51: 1750-1758, 1972.
194. Knupfer H, Preiss R. sIL-6R: More than an agonist? *Immunol Cell Biol* 86: 87-91, 2008.
195. Kobayashi S. Temperature-sensitive neurons in the hypothalamus: A new hypothesis that they act as thermostats, not as transducers. *Prog Neurobiol* 32: 103-135, 1989.
196. Kobayashi S, Hori A, Matsumura K, Hosokawa H. Point: Heat-induced membrane depolarization of hypothalamic neurons: A putative mechanism of central thermosensitivity. *Am J Physiol Regul Integr Comp Physiol* 290: R1479-R1480; discussion R1484, 2006.
197. Kosatsky T. The 2003 European heat waves. *Euro Surveill* 10: 148-149, 2005.
198. Kozak W, Archuleta I, Mayfield KP, Kozak A, Rudolph K, Kluger MJ. Inhibitors of alternative pathways of arachidonate metabolism differentially affect fever in mice. *Am J Physiol Regul Integr Comp Physiol* 275: R1031-R1040, 1998.
199. Kozak W, Conn CA, Kluger MJ. Lipopolysaccharide induces fever and depresses locomotor activity in unrestrained mice. *Am J Physiol Regul Integr Comp Physiol* 266: R125-R135, 1994.
200. Kramer MR, Drori Y, Lev B. Sudden death in young soldiers. High incidence of syncope prior to death. *Chest* 93: 345-347, 1988.
201. Krum SH, Osborne CA. Heatstroke in the dog: A polysystemic disorder. *J Am Vet Med Assoc* 170: 531-535, 1977.
202. Lambert GP, Broussard LJ, Mason BL, Mauermann WJ, Gisolfi CV. Gastrointestinal permeability during exercise: Effects of aspirin and energy-containing beverages. *J Appl Physiol* 90: 2075-2080, 2001.
203. Lambert GP, Gisolfi CV, Berg DJ, Moseley PL, Oberley LW, Kregel KC. Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress. *J Appl Physiol* 92: 1750-1761, 2002.
204. Landsberg HE. Man-Made Climatic Changes: Man's activities have altered the climate of urbanized areas and may affect global climate in the future. *Science* 170: 1265-1274, 1970.
205. Langeron O, Coirault C, Fratea S, Orliaguet G, Coriat P, Riou B. Effects of dantrolene on the diaphragm muscle of the normal and myopathic hamster. *Br J Anaesth* 81: 553-555, 1998.
206. Leon LR. Heat stroke and cytokines. *Prog Brain Res* 162: 481-524, 2007.
207. Leon LR. The thermoregulatory consequences of heat stroke. Are cytokines involved? *J Therm Biol* 31: 67-81, 2006.
208. Leon LR. The use of gene knockout mice in thermoregulation studies. *J Therm Biol* 30: 273-288, 2005.
209. Leon LR. Thermoregulatory responses to environmental toxicants: The interaction of thermal stress and toxicant exposure. *Toxicol Appl Pharmacol* 233: 146-161, 2008.
210. Leon LR, Blaha MD, DuBose DA. Time course of cytokine, corticosterone, and tissue injury responses in mice during heat strain recovery. *J Appl Physiol* 100: 1400-1409, 2006.
211. Leon LR, Dineen S, Blaha MD, Rodriguez-Fernandez M, Clarke DC. Attenuated thermoregulatory, metabolic, and liver acute phase protein response to heat stroke in TNF receptor knockout mice. *Am J Physiol Regul Integr Comp Physiol* 305: R1421-R1432, 2013.
212. Leon LR, DuBose DA, Mason CW. Heat stress induces a biphasic thermoregulatory response in mice. *Am J Physiol Regul Integr Comp Physiol* 288: R197-R204, 2005.
213. Leon LR, Gordon CJ, Helwig BG, Rufolo DM, Blaha MD. Thermoregulatory, behavioral, and metabolic responses to heatstroke in a conscious mouse model. *Am J Physiol Regul Integr Comp Physiol* 299: R241-R248, 2010.
214. Leon LR, Helwig BG. Heat stroke: Role of the systemic inflammatory response. *J Appl Physiol* 109: 1980-1988, 2010.
215. Leon LR, Walker LD, DuBose DA, Stephenson LA. Biotelemetry transmitter implantation in rodents: Impact on growth and circadian rhythms. *Am J Physiol Regul Integr Comp Physiol* 286: R967-R974, 2004.
216. Levi M, Ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 341: 586-592, 1999.
217. Levine HD, Wanzer SH, Merrill JP. Dialyzable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis. *Circulation* 13: 29-36, 1956.
218. Levine JA. Heat stroke in the aged. *Am J Med* 47: 251-258, 1969.
219. Liebermeister C. *Vorlesungen Uber Specielle Pathologie und Therapie*. FCW Vogel, 1887.
220. Lim XJ, Li YJ, Li ZL, Zou F, Lin MT. Pre-existing lipopolysaccharide may increase the risk of heatstroke in rats. *Am J Med Sci* 337: 265-270, 2009.
221. Lin MT. Heatstroke-induced cerebral ischemia and neuronal damage. Involvement of cytokines and monoamines. *Ann N Y Acad Sci* 813: 572-580, 1997.
222. Lin MT, Kao TY, Jin YT, Chen CF. Interleukin-1 receptor antagonist attenuates the heat stroke-induced neuronal damage by reducing the cerebral ischemia in rats. *Brain Res Bull* 37: 595-598, 1995.
223. Lin MT, Kao TY, Su CF, Hsu SS. Interleukin-1 beta production during the onset of heat stroke in rabbits. *Neurosci Lett* 174: 17-20, 1994.
224. Lin MT, Liu HH, Yang YL. Involvement of interleukin-1 receptor mechanisms in development of arterial hypotension in rat heatstroke. *AmJPhysiol* 273: H2072-H2077, 1997.
225. Lin XJ, Li YJ, Li ZL, Zou F, Lin MT. Pre-existing lipopolysaccharide may increase the risk of heatstroke in rats. *Am J Med Sci* 337: 265-270, 2009.
226. Line RL, Rust GS. Acute exertional rhabdomyolysis. *Am Fam Physician* 52: 502-506, 1995.
227. Litman RS, Rosenberg H. Malignant hyperthermia: Update on susceptibility testing. *JAMA* 293: 2918-2924, 2005.
228. Liu CC, Chien CH, Lin MT. Glucocorticoids reduce interleukin-1á concentration and result in neuroprotective effects in rat heatstroke. *JPhysiol* 527 (Pt 2): 333-343, 2000.
229. Loewenstein D, Stake C, Cichon M. Assessment of using fingerstick blood sample with i-STAT point-of-care device for cardiac troponin I assay. *Am J Emerg Med* 31: 1236-1239, 2013.
230. Lord PF, Kapp DS, Hayes T, Weshler Z. Production of systemic hyperthermia in the rat. *Eur J Cancer Clin Oncol* 20: 1079-1085, 1985.
231. Low DA, Vu A, Brown M, Davis SL, Keller DM, Levine BD, Crandall CG. Temporal thermometry fails to track body core temperature during heat stress. *Med Sci Sports Exerc* 39: 1029-1035, 2007.
232. Lu KC, Wang JY, Lin SH, Chu P, Lin YF. Role of circulating cytokines and chemokines in exertional heatstroke. *Crit Care Med* 32: 399-403, 2004.
233. Luber G, McGeehin M. Climate change and extreme heat events. *Am J Prev Med* 35: 429-435, 2008.
234. Lv B, Wang H, Tang Y, Fan Z, Xiao X, Chen F. High-mobility group box 1 protein induces tissue factor expression in vascular endothelial cells via activation of NF-kappaB and Egr-1. *Thromb Haemost* 102: 352-359, 2009.
235. Magazanik A, Shapiro Y, Shibolet S. Dynamic changes in acid base balance during heatstroke in dogs. *Pflugers Arch* 388: 129-135, 1980.
236. Majde JA. Viral double-stranded RNA, cytokines, and the flu. *J Interferon Cytokine Res* 20: 259-272, 2000.
237. Majde JA, Kapas L, Bohnet SG, De A, Krueger JM. Attenuation of the influenza virus sickness behavior in mice deficient in Toll-like receptor 3. *Brain Behav Immun* 24: 306-315, 2010.
238. Malamud N, Haymaker W, Custer RP. Heat Stroke: Clinico-pathologic study of 125 fatal cases. *Mil Surg* 99: 397-449, 1946.
239. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 336: 540336-540546, 1997.
240. Maron MB, Wagner JA, Horvath SM. Thermoregulatory responses during competitive marathon running. *J Appl Physiol* 42: 909-914, 1977.
241. McCaffrey TV, McCook RD, Wurster RD. Effect of head skin temperature on tympanic and oral temperature in man. *J Appl Physiol* 39: 114-118, 1975.
242. McCullough PA, Chinnaiyan KM, Gallagher MJ, Colar JM, Geddes T, Gold JM, Trivax JE. Changes in renal markers and acute kidney injury after marathon running. *Nephrology (Carlton)* 16: 194-199, 2011.
243. McGeehin MA, Mirabelli M. The potential impacts of climate variability and change on temperature related morbidity and mortality in the United States. *Environ Health Persp* 109: 185, 2001.
244. McLaughlin CT, Kane AG, Auber AE. MR imaging of heat stroke: External capsule and thalamic T1 shortening and cerebellar injury. *AJNR Am J Neuroradiol* 24: 1372-1375, 2003.
245. Meikle AW, Graybill JR. Fibrinolysis and hemorrhage in a fatal case of heat stroke. *N Engl J Med* 276: 911-913, 1967.
246. Meissner G. Ryanodine receptor/Ca2+ release channels and their regulation by endogenous effectors. *Annu Rev Physiol* 56: 485-508, 1994.
247. Mellor PJ, Mellanby RJ, Baines EA, Villiers EJ, Archer J, Herrtage ME. High serum troponin I concentration as a marker of severe myocardial damage in a case of suspected exertional heatstroke in a dog. *J Vet Cardiol* 8: 55-62, 2006.

248. Mendeloff AI, Smith DE. Extreme physical effort in summer heat followed by collapse, stupor, purpura, jaundice and azotemia. *Am J Med* 18: 659-670, 1955.
249. Mikkelsen TS, Toft P. Prognostic value, kinetics and effect of CVVHDF on serum of the myoglobin and creatine kinase in critically ill patients with rhabdomyolysis. *Acta Anaesthesiol Scand* 49: 859-864, 2005.
250. Minard D. Prevention of heat casualties in Marine Corps recruits. Period of 1955-60, with comparative incidence rates and climatic heat stresses in other training categories. *Mil Med* 126: 261-272, 1961.
251. Misset B, De Jonghe B, Bastuji-Garin S, Gattolliat O, Boughrara E, Annane D, Hausfater P, Garrouste-Orgeas M, Carlet J. Mortality of patients with heatstroke admitted to intensive care units during the 2003 heat wave in France: A national multiple-center risk-factor study. *Crit Care Med* 34: 1087-1092, 2006.
252. Modlin RL, Brightbill HD, Godowski PJ. The toll of innate immunity on microbial pathogens. *N Engl J Med* 340: 1834-1835, 1999.
253. Mollnes TE. High mobility group box-1 protein–one step closer to the clinic? *Crit Care* 12: 168, 2008.
254. Montain SJ, Sawka MN, Wenger CB. Hyponatremia associated with exercise: Risk factors and pathogenesis. *Exerc Sport Sci Rev* 29: 113-117, 2001.
255. Moore GE, Holbein ME, Knochel JP. Exercise-associated collapse in cyclists is unrelated to endotoxemia. *Med Sci Sports Exerc* 27: 1238-1242, 1995.
256. Moran D, Epstein Y, Wiener M, Horowitz M. Dantrolene and recovery from heat stroke. *Aviat Space Environ Med* 70: 987-989, 1999.
257. Moran DS, Epstein Y. Evaluation of the environmental stress index (ESI) for hot/dry and hot/wet climates. *Ind Health* 44: 399-403, 2006.
258. Moran DS, Shitzer A, Pandolf KB. A physiological strain index to evaluate heat stress. *Am J Physiol* 275: R129-R134, 1998.
259. Musapasaoglu H, Agildere AM, Teksam M, Tarcan A, Gurakan B. Hypernatraemic dehydration in a neonate: Brain MRI findings. *Br J Radiol* 81: e57-e60, 2008.
260. Mustafa KY, Omer O, Khogali M, Jamjoom A, Gumaa KA, Abu el-Nasr N, Gader MA. Blood coagulation and fibrinolysis in heat stroke. *BrJ Haematol* 61: 517-523, 1985.
261. Mustafa MK, Khogali M, Gumaa K. Respiratory pathophysiology in heat stroke. In: Khogali M, Hales JRS, editors. *Heat Stroke and Temperature Regulation*. New York: Academic Press, 1983, pp. 119-127.
262. Naughton MP, Henderson A, Mirabelli MC, Kaiser R, Wilhelm JL, Kieszak SM, Rubin CH, McGeehin MA. Heat-related mortality during a 1999 heat wave in Chicago. *Am J Prev Med* 22: 221-227, 2002.
263. Nelson NG, Collins CL, Comstock RD, McKenzie LB. Exertional heat-related injuries treated in emergency departments in the U.S., 1997-2006. *Am J Prev Med* 40: 54-60, 2011.
264. Neumann FJ, Ott I, Marx N, Luther T, Kenngott S, Gawaz M, Kotzsch M, Schomig A. Effect of human recombinant interleukin-6 and interleukin-8 on monocyte procoagulant activity. *Arterioscler Thromb Vasc Biol* 17: 3399-3405, 1997.
265. Neville AJ, Sauder DN. Whole body hyperthermia (41-42 degrees C) induces interleukin-1 in vivo. *Lymphokine Res* 7: 201-206, 1988.
266. Ng'walali PM, Kibayashi K, Yonemitsu K, Ohtsu Y, Tsunenari S. Death as a result of heat stroke in a vehicle: An adult case in winter confirmed with reconstruction and animal experiments. *J Clin Forensic Med* 5: 183-186, 1998.
267. Nieman DC, Henson DA, Dumke CL, Oley K, McAnulty SR, Davis JM, Murphy EA, Utter AC, Lind RH, McAnulty LS, Morrow JD. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav Immun* 20: 578-584, 2006.
268. Nieuwenhuijzen GA, Haskel Y, Lu Q, Berg RD, van Rooijen N, Goris RJ, Deitch EA. Macrophage elimination increases bacterial translocation and gut-origin septicemia but attenuates symptoms and mortality rate in a model of systemic inflammation. *Ann Surg* 218: 791-799, 1993.
269. Nolan JP. Endotoxin, reticuloendothelial function, and liver injury. *Hepatology* 1: 458-465, 1981.
270. Nolan JP, Morley PT, Hoek TL, Hickey RW, Advancement Life support Task Force of the International Liaison committee on R. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation. *Resuscitation* 57: 231-235, 2003.
271. Novosad VL, Richards JL, Phillips NA, King MA, Clanton TL. Regional susceptibility to stress-induced intestinal injury in the mouse. *Am J Physiol Gastrointest Liver Physiol* 305: G418-G426, 2013.
272. Nybo L. Exercise and heat stress: Cerebral challenges and consequences. *Prog Brain Res* 162: 29-43, 2007.
273. O'Brien KK, Montain SJ, Corr WP, Sawka MN, Knapik JJ, Craig SC. Hyponatremia associated with overhydration in U.S. Army trainees. *Mil Med* 166: 405-410, 2001.
274. O'Brien PJ, Cribb PH, White RJ, Olfert ED, Steiss JE. Canine malignant hyperthermia: Diagnosis of susceptibility in a breeding colony. *Can Vet J* 24: 172-177, 1983.
275. O'Connor FG, Casa DJ, Bergeron MF, Carter R, 3rd, Deuster P, Heled Y, Kark J, Leon L, McDermott B, O'Brien K, Roberts WO, Sawka M. American College of Sports Medicine Roundtable on exertional heat stroke–return to duty/return to play: Conference proceedings. *Curr Sports Med Rep* 9: 314-321, 2010.
276. O'Connor FG, Williams AD, Blivin S, Heled Y, Duester PA, Flinn SD. Guidelines for return to duty (play) after heat illness: A military perspective. *J Sports Rehabil* 16: 227-237, 2007.
277. O'Sullivan GH, McIntosh JM, Heffron JJ. Abnormal uptake and release of Ca2 +ions from human malignant hyperthermia-susceptible sarcoplasmic reticulum. *Biochem Pharmacol* 61: 1479-1485, 2001.
278. Ogburn RM, Myers RL, Burdick GE. Letter: Hepatitis associated with dantrolene sodium. *Ann Intern Med* 84: 53-54, 1976.
279. Ohara K, Furuyama F, Isobe Y. Prediction of survival time of rats in severe heat. *J Appl Physiol* 38: 724-729, 1975.
280. Oliver SR, Phillips NA, Novosad VL, Bakos MP, Talbert EE, Clanton TL. Hyperthermia induces injury to the intestinal mucosa in the mouse: Evidence for an oxidative stress mechanism. *Am J Physiol Regul Integr Comp Physiol* 302: R845-R853, 2012.
281. Ostberg JR, Taylor SL, Baumann H, Repasky EA. Regulatory effects of fever-range whole-body hyperthermia on the LPS-induced acute inflammatory response. *J Leukoc Biol* 68: 815-820, 2000.
282. Paleolog EM, Delasalle SA, Buurman WA, Feldmann M. Functional activities of receptors for tumor necrosis factor-alpha on human vascular endothelial cells. *Blood* 84: 2578-2590, 1994.
283. Pandolf KB, Gange RW, Latzka WA, Blank IH, Kraning KK, II, Gonzalez RR. Human thermoregulatory responses during heat exposure after artificially induced sunburn. *Am J Physiol* 262: R610-R616, 1992.
284. Pandolf KB, Griffin TB, Munro EH, Goldman RF. Heat intolerance as a function of percent of body surface involved with miliaria rubra. *Am J Physiol* 239: R233-R240, 1980a.
285. Pandolf KB, Griffin TB, Munro EH, Goldman RF. Persistence of impaired heat tolerance from artificially induced miliaria rubra. *Am J Physiol* 239: R226-R232, 1980b.
286. Park JS, Svetkauskaite D, He Q, Kim JY, Strassheim D, Ishizaka A, Abraham E. Involvement of toll-like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. *J Biol Chem* 279: 7370-7377, 2004.
287. Parness J, Palnitkar SS. Identification of dantrolene binding sites in porcine skeletal muscle sarcoplasmic reticulum. *J Biol Chem* 270: 18465-18472, 1995.
288. Parsons KC. International heat stress standards: A review. *Ergonomics* 38: 6-22, 1995.
289. Patel DR, Gyamfi R, Torres A. Exertional rhabdomyolysis and acute kidney injury. *Phys Sports Med* 37: 71-79, 2009.
290. Paul-Pletzer K, Yamamoto T, Ikemoto N, Jimenez LS, Morimoto H, Williams PG, Ma J, Parness J. Probing a putative dantrolene-binding site on the cardiac ryanodine receptor. *Biochem J* 387: 905-909, 2005.
291. Peterson JM, Trappe TA, Mylona E, White F, Lambert CP, Evans WJ, Pizza FX. Ibuprofen and acetaminophen: Effect on muscle inflammation after eccentric exercise. *Med Sci Sports Exerc* 35: 892-896, 2003.
292. Pierau FK. Peripheral thermosensors. In: Fregley MJ, Blatteis CM, editors. *Handbook of Physiology Environmental Physiology*. Bethesda, MD: American Physiological Society, 1996, pp. 85-104.
293. Pradier O, Gerard C, Delvaux A, Lybin M, Abramowicz D, Capel P, Velu T, Goldman M. Interleukin-10 inhibits the induction of monocyte procoagulant activity by bacterial lipopolysaccharide. *EurJImmunol* 23: 2700-2703, 1993.
294. Qin S, Wang H, Yuan R, Li H, Ochani M, Ochani K, Rosas-Ballina M, Czura CJ, Huston JM, Miller E, Lin X, Sherry B, Kumar A, Larosa G, Newman W, Tracey KJ, Yang H. Role of HMGB1 in apoptosis-mediated sepsis lethality. *J Exp Med* 203: 1637-1642, 2006.
295. Radigan LR, Robinson S. Effects of environmental heat stress and exercise on renal blood flow and filtration rate. *J Appl Physiol* 2: 185-191, 1949.
296. Rajan SF, Robinson GH, Borwer JD. The pathogenesis of acute renal failure in heatstroke. *South Med J* 66: 330-333, 1973.
297. Ramlow JM, Kuller LH. Effects of the summer heat wave of 1988 on daily mortality in Allegheny county, PA. *Public Health Rep* 105: 283-289, 1990.
298. Rav-Acha M, Hadad E, Epstein Y, Heled Y, Moran DS. Fatal exertional heat stroke: A case series. *Am J Med Sci* 328: 84-87, 2004.
299. Redl H, Schlag G, Adolf GR, Natmessnig B, Davies J. Tumor necrosis factor (TNF)-dependent shedding of the p55 TNF receptor in a baboon model of bacteremia. *Infect Immun* 63: 297-300, 1995.
300. Rehrer NJ, Brouns F, Beckers EJ, Frey WO, Villiger B, Riddoch CJ, Menheere PP, Saris WH. Physiological changes and gastro-intestinal symptoms as a result of ultra-endurance running. *Eur J Appl Physiol Occup Physiol* 64: 1-8, 1992.
301. Richards R, Richards D, Whittaker R. Method of predicting the number of casualties in the Sydney City-to-Surf fun runs. *Med J Aust* 141: 805-808, 1984.
302. Riddoch C, Trinick T. Gastrointestinal disturbances in marathon runners. *Br J Sports Med* 22: 71-74, 1988.

303. Roberts GT, Ghebeh H, Chishti MA, Al-Mohanna F, El-Sayed R, Bouchama A. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: A study in baboon model. *Arterioscler Thromb Vasc Biol* 28: 1130-1136, 2008.
304. Roberts NJ, Jr. Differential effects of hyperthermia on human leukocyte production of interferon-alpha and interferon-gamma. *Proc Soc Exp Biol Med* 183: 42-47, 1986.
305. Roberts WO. Managing heatstroke: On-site cooling. *Phs Sportsmed* 20: 17-28, 1992.
306. Robins HI, Grosen E, Katschinski DM, Longo W, Tiggelaar CL, Kutz M, Winawer J, Graziano F. Whole body hyperthermia induction of soluble tumor necrosis factor receptors: Implications for rheumatoid diseases. *J Rheumatol* 26: 2513-2516, 1999.
307. Robins HI, Kutz M, Wiedemann GJ, Katschinski DM, Paul D, Grosen E, Tiggelaar CL, Spriggs D, Gillis W, d'Oleire F. Cytokine induction by 41.8 degrees C whole body hyperthermia. *Cancer Lett* 97: 195-201, 1995.
308. Rodriguez-Fernandez M, Grosman B, Yuraszeck TM, Helwig BG, Leon LR, Doyle FJ, III. Modeling the intra- and extracellular cytokine signaling pathway under heat stroke in the liver. *PLoS One* 8: e73393, 2013.
309. Rogers MA, Stull GA, Apple FS. Creatine kinase isoenzyme activities in men and women following a marathon race. *Med Sci Sports Exerc* 17: 679-682, 1985.
310. Romanovsky AA. Thermoregulation: Some concepts have changed. *Am J Physiol Regul Integr Comp Physiol* 292: R37-R46, 2007.
311. Romanovsky AA, Blatteis CM. Heat stroke: Opioid-mediated mechanisms. *J Appl Physiol* 81: 2565-2570, 1996.
312. Ronneberg K, Roberts WO, McBean AD, Center BA. Temporal artery temperature measurements do not detect hyperthermic marathon runners. *Med Sci Sports Exerc* 40: 1373-1375, 2008.
313. Rosenberg H, Antognini JF, Muldoon S. Testing for malignant hyperthermia. *Anesthesiology* 96: 232-237, 2002.
314. Roskind JL, Petrofsky J, Lind AR, Paletta FX. Quantitation of thermoregulatory impairment in patients with healed burns. *Ann Plast Surg* 1: 172-176, 1978.
315. Rosner MH. Urinary biomarkers for the detection of renal injury. *Adv Clin Chem* 49: 73-97, 2009.
316. Rossi D, Zlotnik A. The biology of chemokines and their receptors. *Annu Rev Immunol* 18: 217-242, 2000.
317. Rowell LB. Cardiovascular adjustments to thermal stress. In: Shephard JT, Abboud FM, editors. *Handbook of Physiology: The Cardiovascular System, Peripheral Circulation and Skin Blood Flow*. Bethesda, MD: American Physiological Society, 1983, pp. 967-1023.
318. Rowell LB. Cardiovascular aspects of human thermoregulation. *Circ Res* 52: 367-379, 1983.
319. Rubel LR. Hepatic injury associated with heatstroke. *Ann Clin Lab Sci* 14: 130-136, 1984.
320. Ryan AJ, Chang RT, Gisolfi CV. Gastrointestinal permeability following aspirin intake and prolonged running. *Med Sci Sports Exerc* 28: 698-705, 1996.
321. Saissy JM. Liver transplantation in a case of fulminant liver failure after exertion. *Intensive Care Med* 22: 831, 1996.
322. Sakurada S, Hales JRS. A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. *J Appl Physiol* 84: 207-214, 1998.
323. Satinoff E. Salicylate: Action on normal body temperature in rats. *Science* 176: 532-533, 1972.
324. Sawka MN, Leon LR, Montain SJ, Sonna LA. Integrated physiological mechanisms of exercise performance, adaptation, and maladaptation to heat stress. *Compr Physiol* 1: 1883-1928, 2011.
325. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 418: 191-195, 2002.
326. Schiffl H, Lang SM. Update on biomarkers of acute kidney injury: Moving closer to clinical impact? *Mol Diagn Ther* 16: 199-207, 2012.
327. Schmid EF, Binder K, Grell M, Scheurich P, Pfizenmaier K. Both tumor necrosis factor receptors, TNFR60 and TNFR80, are involved in signaling endothelial tissue factor expression by juxtacrine tumor necrosis factor alpha. *Blood* 86: 1836-1841, 1995.
328. Schneider R, Mitchell D. Dantrolene hepatitis. *JAMA* 235: 1590-1591, 1976.
329. Schobitz B, Pezeshki G, Pohl T, Hemmann U, Heinrich PC, Holsboer F, Reul JM. Soluble interleukin-6 (IL-6) receptor augments central effects of IL-6 in vivo. *FASEB J* 9: 659-664, 1995.
330. Schrier RW, Hano J, Keller HI, Finkel RM, Gilliland PF, Cirksena WJ, Teschan PE. Renal, metabolic, and circulatory responses to heat and exercise. Studies in military recruits during summer training, with implications for acute renal failure. *Ann Intern Med* 73: 213-223, 1970.
331. Schwager I, Jungi TW. Effect of human recombinant cytokines on the induction of macrophage procoagulant activity. *Blood* 83: 152-160, 1994.
332. Seeler DC, McDonell WN, Basrur PK. Halothane and halothane/succinylcholine induced malignant hyperthermia (porcine stress syndrome) in a population of Ontario boars. *Can J Comp Med* 47: 284-290, 1983.
333. Selkirk GA, McLellan TM, Wright HE, Rhind SG. Mild endotoxemia, NF-kappaB translocation, and cytokine increase during exertional heat stress in trained and untrained individuals. *Am J Physiol Regul Integr Comp Physiol* 295: R611-R623, 2008.
334. Senay LC, Jr. Relationship of evaporative rates to serum [Na+], [K+], and osmolarity in acute heat stress. *J Appl Physiol* 25: 149-152, 1968.
335. Seraj MA, Channa AB, al Harthi SS, Khan FM, Zafrullah A, Samarkandi AH. Are heat stroke patients fluid depleted? Importance of monitoring central venous pressure as a simple guideline for fluid therapy. *Resuscitation* 21: 33-39, 1991.
336. Seth P, Juliana P. Exertional heat stroke in a marathon runner with extensive healed deep burns: A case report. *Int J Emerg Med* 4: 12, 2011.
337. Shahid MS, Hatle L, Mansour H, Mimish L. Echocardiographic and Doppler study of patients with heatstroke and heat exhaustion. *Int J Card Imaging* 15: 279-285, 1999.
338. Shapiro Y, Epstein Y, Ben-Simchon C, Tsur H. Thermoregulatory responses of patients with extensive healed burns. *J Appl Physiol Respir Environ Exerc Physiol* 53: 1019-1022, 1982.
339. Shapiro Y, Pandolf KB, Avellini BA, Pimental NA, Goldman RF. Physiological responses of men and women to humid and dry heat. *J Appl Physiol Respir Environ Exerc Physiol* 49: 1-8, 1980.
340. Shapiro Y, Pandolf KB, Goldman RF. Sex differences in acclimation to a hot-dry environment. *Ergonomics* 23: 635-642, 1980.
341. Shapiro Y, Rosenthal T, Sohar E. Experimental heatstroke. A model in dogs. *Arch Intern Med* 131: 688-692, 1973.
342. Shapiro Y, Seidman DS. Field and clinical observations of exertional heat stroke patients. *Med Sci Sports Exerc* 22: 6-14, 1990.
343. Shen RN, Hornback NB, Shidnia H, Wu B, Lu L, Broxmeyer HE. Whole body hyperthermia: A potent radioprotector in vivo. *Int J Radiat Oncol Biol Phys* 20: 525-530, 1991.
344. Sherman KE. Alanine aminotransferase in clinical practice. A review. *Arch Intern Med* 151: 260-265, 1991.
345. Sherratt HS. The metabolism of the small intestine. Oxygen uptake and L-lactate production along the length of the small intestine of the rat and guinea pig. *Comp Biochem Physiol* 24: 745-761, 1968.
346. Shibolet S, Coll R, Gilat T, Sohar E. Heatstroke: Its clinical picture and mechanism in 36 cases. *Q J Med* 36: 525-548, 1967.
347. Shibolet S, Lancaster MC, Danon Y. Heat stroke: A review. *Aviat Space Environ Med* 47: 280-301, 1976.
348. Simon HB. Hyperthermia and heatstroke. *Hosp Pract (Off Ed)* 29: 65-68, 73, 78-80, 1994.
349. Sithinamsuwan P, Piyavechviratana K, Kitthaweesin T, Chusri W, Orrawanhanothai P, Wongsa A, Wattanathum A, Chinvarun Y, Nidhinandana S, Satirapoj B, Supasyndh O, Sriswasdi C, Prayoonwiwat W, Phramongkutklao Army Hospital Exertional Heatstroke Study T. Exertional heatstroke: Early recognition and outcome with aggressive combined cooling–a 12-year experience. *Mil Med* 174: 496-502, 2009.
350. Smalley B, Janke RM, Cole D. Exertional heat illness in Air Force basic military trainees. *Mil Med* 168: 298-303, 2003.
351. Smetanka RD, Lambert GP, Murray R, Eddy D, Horn M, Gisolfi CV. Intestinal permeability in runners in the 1996 Chicago marathon. *Int J Sport Nutr* 9: 426-433, 1999.
352. Smith AD, Crabtree DR, Bilzon JL, Walsh NP. The validity of wireless iButtons and thermistors for human skin temperature measurement. *Physiol Meas* 31: 95-114, 2010.
353. Smith JE. Cooling methods used in the treatment of exertional heat illness. *Br J Sports Med* 39: 503-507; discussion 507, 2005.
354. Sohal RS, Sun SC, Colcolough HL, Burch GE. Heat stroke. An electron microscopic study of endothelial cell damage and disseminated intravascular coagulation. *Arch Intern Med* 122: 43-47, 1968.
355. Sohol RS. Heatstroke: An electron microscopic study of endothelial cell damage and disseminated intravascular coagulation. *Arch Intern Med* 122: 43-48, 1968.
356. Sonna LA, Gaffin SL, Pratt RE, Cullivan ML, Angel KC, Lilly CM. Effect of acute heat shock on gene expression by human peripheral blood mononuclear cells. *J Appl Physiol* 92: 2208-2220, 2002.
357. Sonna LA, Wenger CB, Flinn S, Sheldon HK, Sawka MN, Lilly CM. Exertional heat injury and gene expression changes: A DNA microarray analysis study. *J Appl Physiol* 96: 1943-1953, 2004.
358. Sorensen JB, Ranek L. Exertional heatstroke: Survival in spite of severe hypoglycemia, liver and kidney damage. *J Sports Med Phys Fitness* 28: 108-110, 1988.
359. Sort P, Mas A, Salmeron JM, Bruguera M, Rodes J. Recurrent liver involvement in heatstroke. *Liver* 16: 335-337, 1996.
360. Sprung CL, Portocarrero CJ, Fernaine AV, Weinberg PF. The metabolic and respiratory alterations of heat stroke. *Arch Intern Med* 140: 665-669, 1980.

361. Spurr GB, Barlow G. Tissue electrolytes in hyperthermic dogs. *J Appl Physiol* 28: 13-17, 1970.
362. Stohr EJ, Gonzalez-Alonso J, Pearson J, Low DA, Ali L, Barker H, Shave R. Effects of graded heat stress on global left ventricular function and twist mechanics at rest and during exercise in healthy humans. *Exp Physiol* 96: 114-124, 2011.
363. Strother SV, Bull JM, Branham SA. Activation of coagulation during therapeutic whole body hyperthermia. *Thromb Res* 43: 353-360, 1986.
364. Sullivan SN. The gastrointestinal symptoms of running. *N Engl J Med* 304: 915, 1981.
365. Sutko JL, Airey JA. Ryanodine receptor Ca2+ release channels: Does diversity in form equal diversity in function? *Physiol Rev* 76: 1027-1071, 1996.
366. Szold O, Reider-Groswasser II, Abraham RB, Aviram G, Segev Y, Biderman P, Sorkine P. Gray-white matter discrimination - a possible marker for brain damage in heat stroke? *Eur J Radiol* 43: 1-5, 2002.
367. Tamaki Y, Nakayama T. Effects of air constituents on thermosensitivities of preoptic neurons: Hypoxia versus hypercapnia. *Pflugers Arch* 409: 1-6, 1987.
368. Tamaki Y, Nakayama T, Kanosue K. Effects of peripheral chemo- and baro-receptor denervation on responses of preoptic thermosensitive neurons to inspired CO2. *Pflugers Arch* 414: 495-499, 1989.
369. Tamaki Y, Nakayama T, Matsumura K. Effects of carbon dioxide inhalation on preoptic thermosensitive neurons. *Pflugers Arch* 407: 8-13, 1986.
370. Tang D, Shi Y, Kang R, Li T, Xiao W, Wang H, Xiao X. Hydrogen peroxide stimulates macrophages and monocytes to actively release HMGB1. *J Leukoc Biol* 81: 741-747, 2007.
371. Toner MM, Mcardle WD. Human thermoregulatory responses to acute cold stress with special reference to water immersion. In: Fregly MJ, Blatteis CM, editors. *Handbook of Physiology, Section 4: Environmental Physiology*. New York: Oxford University, 1996, pp. 379-397.
372. Tong H, Tang Y, Chen Y, Yuan F, Liu Z, Peng N, Tang L, Su L. HMGB1 activity inhibition alleviating liver injury in heatstroke. *J Trauma Acute Care Surg* 74: 801-807, 2013.
373. Tong HS, Tang YQ, Chen Y, Qiu JM, Wen Q, Su L. Early elevated HMGB1 level predicting the outcome in exertional heatstroke. *J Trauma* 71: 808-814, 2011.
374. Trappe TA, White F, Lambert CP, Cesar D, Hellerstein M, Evans WJ. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am J Physiol Endocrinol Metab* 282: E551-E556, 2002.
375. Traynor TR, Majde JA, Bohnet SG, Krueger JM. Sleep and body temperature responses in an acute viral infection model are altered in interferon type I receptor-deficient mice. *Brain Behav Immun* 20: 290-299, 2006.
376. Tugendreich S, Pearson CI, Sagartz J, Jarnagin K, Kolaja K. NSAID-induced acute phase response is due to increased intestinal permeability and characterized by early and consistent alterations in hepatic gene expression. *Toxicol Pathol* 34: 168-179, 2006.
377. van't Hoff JH. Lectures on theoretical and physical chemistry. Part 1. Chemical dynamics. London: London Edward Arnold, 1898.
378. van den HC, Lister D, Muylle E, Ooms L, Oyaert W. Malignant hyperthermia in Belgian Landrace pigs rested or exercised before exposure to halothane. *Br J Anaesth* 48: 821-829, 1976.
379. van der Poll T, Buller HR, ten CH, Wortel CH, Bauer KA, van Deventer SJ, Hack CE, Sauerwein HP, Rosenberg RD, ten Cate JW. Activation of coagulation after administration of tumor necrosis factor to normal subjects. *N Engl J Med* 322: 1622-1627, 1990.
380. Van Horn G, Drori JB, Schwartz FD. Hypokalemic myopathy and elevation of serum enzymes. *Arch Neurol* 22: 335-341, 1970.
381. Van Leeuwen PA, Boermeester MA, Houdijk AP, Ferwerda CC, Cuesta MA, Meyer S, Wesdorp RI. Clinical significance of translocation. *Gut* 35: S28-S34, 1994.
382. Vandentorren S, Suzan F, Medina S, Pascal M, Maulpoix A, Cohen JC, Ledrans M. Mortality in 13 French cities during the August 2003 heat wave. *Am J Public Health* 94: 1518-1520, 2004.
383. Vasselon T, Detmers PA. Toll receptors: A central element in innate immune responses. *Infect Immun* 70: 1033-1041, 2002.
384. Vertel RM, Knochel JP. Acute renal failure due to heat injury: An analysis of 10 cases associated with a high incidence of myoglobinuria. *Am J Med* 43: 435-451, 1967.
385. Vicario SJ, Okabajue R, Haltom T. Rapid cooling in classic heatstroke: Effect of mortality rates. *Am J Emerg Med* 4: 394-398, 1986.
386. Wada H, Ohiwa M, Kaneko T, Tamaki S, Tanigawa M, Takagi M, Mori Y, Shirakawa S. Plasma level of tumor necrosis factor in disseminated intravascular coagulation. *Am J Hematol* 37: 147-151, 1991.
387. Wada H, Tamaki S, Tanigawa M, Takagi M, Mori Y, Deguchi A, Katayama N, Yamamoto T, Deguchi K, Shirakawa S. Plasma level of IL-1 beta in disseminated intravascular coagulation. *Thromb Haemost* 65: 364-368, 1991.
388. Wada H, Tanigawa M, Wakita Y, Nakase T, Minamikawa K, Kaneko T, Ohiwa M, Kageyama S, Kobayashi T, Noguchi T, et al. Increased plasma level of interleukin-6 in disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 4: 583-590, 1993.
389. Wagner M, Kaufmann P, Fickert P, Trauner M, Lackner C, Stauber RE. Successful conservative management of acute hepatic failure following exertional heatstroke. *Eur J Gastroenterol Hepatol* 15: 1135-1139, 2003.
390. Wallace RF, Kriebel D, Punnett L, Wegman DH, Amoroso PJ. Prior heat illness hospitalization and risk of early death. *Environ Res* 104: 290-295, 2007.
391. Wallimann T, Hemmer W. Creatine kinase in non-muscle tissues and cells. *Mol Cell Biochem* 133-134: 193-220, 1994.
392. Walter J, Ley R. The human gut microbiome: Ecology and recent evolutionary changes. *Annu Rev Microbiol* 65: 411-429, 2011.
393. Wang AY, Li PK, Lui SF, Lai KN. Renal failure and heatstroke. *Ren Fail* 17: 171-179, 1995.
394. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, Manogue KR, Faist E, Abraham E, Andersson J, Andersson U, Molina PE, Abumrad NN, Sama A, Tracey KJ. HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 285: 248-251, 1999.
395. Wappler F, Fiege M, Steinfath M, Agarwal K, Scholz J, Singh S, Matschke J, Schulte Am Esch J. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology* 94: 95-100, 2001.
396. Weber MB, Blakely JA. The haemorrhagic diathesis of heatstroke. A consumption coagulopathy successfully treated with heparin. *Lancet* 1: 1190-1192, 1969.
397. Weiner JS, Khogali M. A physiological body-cooling unit for treatment of heat stroke. *Lancet* 1: 507-509, 1980.
398. Welc SS, Clanton TL, Dineen SM, Leon LR. Heat stroke activates a stress-induced cytokine response in skeletal muscle. *J Appl Physiol* 115: 1126-1137, 2013.
399. Wells CL. Relationship between intestinal microecology and the translocation of intestinal bacteria. *Antonie Van Leeuwenhoek* 58: 87-93, 1990.
400. White JG. Effects of heat on platelet structure and function. *Blood* 32: 324-335, 1968.
401. Wiest R, Rath HC. Gastrointestinal disorders of the critically ill. Bacterial translocation in the gut. *Best Pract Res Clin Gastroenterol* 17: 397-425, 2003.
402. Wilkinson DA, Burholt DR, Shrivastava PN. Hypothermia following whole-body heating of mice: Effect of heating time and temperature. *Int J Hyperthermia* 4: 171-182, 1988.
403. Winkenwerder M, Sawka MN. Disorders due to heat and cold. In: Goldman L, Ausiello D, editors. *Cecil Medicine*. Philadelphia: Elsevier Science, 2007, pp. 763-767.
404. Wright CL, Boulant JA. Carbon dioxide and pH effects on temperature sensitive and insensitive hypothalamic neurons. *J Appl Physiol* (in press): 2006, pp. 1357-1366.
405. Wright G, Knecht E, Wasserman D. Colonic heating patterns and the variation of thermal resistance among rats. *J Appl Physiol Respir Environ Exerc Physiol* 43: 59-64, 1977.
406. Wright GL. Critical thermal maximum in mice. *J Appl Physiol* 40: 683-687, 1976.
407. Wyndham CH, Strydom NB, Cooke HM, Maritz JS, Morrison JF, Fleming PW, Ward JS. Methods of cooling subjects with hyperpyrexia. *J Appl Physiol* 14: 771-776, 1959.
408. Wyndham CH, Strydom NB, Cooke HMea. Methods of cooling subjects with hyperpyrexia. *J Appl Physiol* 14: 771-776, 1959.
409. Yaglou CP, Minard D. Control of heat casualties at military training centers. *AMA archives of industrial health* 16: 302-316, 1957.
410. Yamamoto K, Shimokawa T, Kojima T, Loskutoff DJ, Saito H. Regulation of murine protein C gene expression in vivo: Effects of tumor necrosis factor-alpha, interleukin-1, and transforming growth factor-beta. *Thromb Haemost* 82: 1297-1301, 1999.
411. Yang H, Wang H, Czura CJ, Tracey KJ. HMGB1 as a cytokine and therapeutic target. *J Endotoxin Res* 8: 469-472, 2002.
412. Yang R, Harada T, Mollen KP, Prince JM, Levy RM, Englert JA, Gallowitsch-Puerta M, Yang L, Yang H, Tracey KJ, Harbrecht BG, Billiar TR, Fink MP. Anti-HMGB1 neutralizing antibody ameliorates gut barrier dysfunction and improves survival after hemorrhagic shock. *Mol Med* 12: 105-114, 2006.
413. Yaqub BA. Neurologic manifestations of heatstroke at the Mecca pilgrimage. *Neurology* 37: 1004-1006, 1987.
414. Yaqub BA, Al-Harthi SS, Al-Orainey IO, Laajam MA, Obeid MT. Heat stroke at the Mekkah pilgrimage: Clinical characteristics and course of 30 patients. *Q J Med* 59: 523-530, 1986.
415. Yarom R, Levy E, Horowitz M. Myocardial pathology in rats exposed to prolonged environmental heat. *Cardiovasc Res* 24: 982-986, 1990.

416. Yu J, Yin P, Liu F, Cheng G, Guo K, Lu A, Zhu X, Luan W, Xu J. Effect of heat stress on the porcine small intestine: A morphological and gene expression study. *Comp Biochem Physiol A Mol Integr Physiol* 156: 119-128, 2010.
417. Zhao Y, Boulant JA. Temperature effects on neuronal membrane potentials and inward currents in rat hypothalamic tissue slices. *J Physiol* 564: 245-257, 2005.
418. Zorzato F, Fujii J, Otsu K, Phillips M, Green NM, Lai FA, Meissner G, MacLennan DH. Molecular cloning of cDNA encoding human and rabbit forms of the Ca2+ release channel (ryanodine receptor) of skeletal muscle sarcoplasmic reticulum. *J Biol Chem* 265: 2244-2256, 1990.
419. Zuckerman GB, Singer LP, Rubin DH, Conway EE, Jr. Effects of dantrolene on cooling times and cardiovascular parameters in an immature porcine model of heatstroke. *Crit Care Med* 25: 135-139, 1997.