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Heat stroke is a life-threatening illness that is characterized clinically by central nervous system dysfunction, including delirium, seizures, or coma and severe hyperthermia. Rapid cooling and support of multi-organ function are the most effective clinical treatments, but many patients experience permanent neurological impairments or death despite these efforts. The highest incidence of heat stroke deaths occurs in very young or elderly individuals during summer heat waves, with ~200 deaths per year in the United States. Young, fit individuals may experience exertional heat stroke while performing strenuous physical activity in temperate or hot climates. Factors that predispose to heat stroke collapse include pre-existing illness, cardiovascular disease, drug use, and poor fitness level. For decades the magnitude of the hyperthermic response in heat stroke patients was considered the primary determinant of morbidity and mortality. However, recent clinical and experimental evidence suggests a complex interplay between heat cytotoxicity, coagulation, and the systemic inflammatory response syndrome (SIRS) that ensues following damage to the gut and other organs. Cytokines are immune modulators that have been implicated as adverse mediators of the SIRS, but recent data

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HIGHLIGHTED TOPIC | *Mechanisms and Modulators of Temperature Regulation*

Heat stroke: Role of the systemic inflammatory response

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Leon LR, Helwig BG. Heat stroke: Role of the systemic inflammatory response. *J Appl Physiol* 109: 1980–1988, 2010. First published June 3, 2010; doi:10.1152/japplphysiol.00301.2010.—Heat stroke is a life-threatening illness that is characterized clinically by central nervous system dysfunction, including delirium, seizures, or coma and severe hyperthermia. Rapid cooling and support of multi-organ function are the most effective clinical treatments, but many patients experience permanent neurological impairments or death despite these efforts. The highest incidence of heat stroke deaths occurs in very young or elderly individuals during summer heat waves, with ~200 deaths per year in the United States. Young, fit individuals may experience exertional heat stroke while performing strenuous physical activity in temperate or hot climates. Factors that predispose to heat stroke collapse include pre-existing illness, cardiovascular disease, drug use, and poor fitness level. For decades the magnitude of the hyperthermic response in heat stroke patients was considered the primary determinant of morbidity and mortality. However, recent clinical and experimental evidence suggests a complex interplay between heat cytotoxicity, coagulation, and the systemic inflammatory response syndrome (SIRS) that ensues following damage to the gut and other organs. Cytokines are immune modulators that have been implicated as adverse mediators of the SIRS, but recent data suggest a protective role for these proteins in the resolution of inflammation. Multi-organ system failure is the ultimate cause of mortality, and recent experimental data indicate that current clinical markers of heat stroke recovery may not adequately reflect heat stroke recovery in all cases. Currently heat stroke is a more preventable than treatable condition, and novel therapeutics are required to improve patient outcome.

exertional heat stroke; heat stress; hyperthermia; cytokines; systemic inflammatory response syndrome

HEAT STROKE IS A DEBILITATING illness characterized by a myriad of inflammatory, coagulation, and tissue abnormalities whose severity and time course of progression varies widely between individuals. Heat stroke has traditionally been defined by patient symptoms that present at the time of clinical admission, which include profound central nervous system (CNS) abnormalities (e.g., delirium, seizures, coma) and severe hyperthermia [core temperature typically but not always >40°C; (90)]. The goal of aggressive clinical treatments is to normalize body (core and skin) temperature and CNS function as rapidly as possible, but ~30% of heat stroke survivors experience permanent decrements in neurological and peripheral tissue function despite these efforts (1, 25). Recent epidemiological studies of short- and long-term heat stroke outcome indicate that multi-organ system dysfunction continues to manifest in patients following clinical treatment, which increases the risk of mortality during the ensuing months and years of recovery (1,

25, 84). The inability to properly anticipate, diagnose, and treat the long-term sequelae of heat stroke is a serious limitation of modern medicine that reflects our limited understanding of the pathophysiological mechanisms mediating tissue injury. This review provides a summary of the current understanding of the role of the systemic inflammatory response in the long-term sequelae of heat stroke and addresses knowledge gaps that need to be bridged to develop more effective diagnostic and therapeutic strategies to mitigate morbidity and mortality in this syndrome.

HEAT STROKE INCIDENCE AND MORTALITY

Heat stroke occurs during exposure to high environmental temperatures or while performing strenuous work and is classified as passive (also referred to as "classic") or exertional in nature. Passive heat stroke is experienced primarily by immunocompromised individuals, such as the very young or elderly, with high mortality rates reported by the popular press during annual heat waves (25, 28). Preexisting conditions, such as mental illness, alcoholism, or drug use (e.g., diuretics, anticholinergics) may compromise an individual's physiological adjustments to heat stress and increase the incidence of passive

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heat stroke (63, 65, 82). Athletes (e.g., marathon runners, race car drivers), occupational workers (e.g., fire fighters, agricultural workers), and military personnel are highly motivated populations at risk for exertional heat stroke while performing strenuous physical work or exercise in temperature or hot climates. The incidence of exertional heat stroke is influenced by a multitude of factors, including pre-existing illness, drug use (e.g., alcohol, amphetamines, ecstasy), and wearing protective clothing (e.g., uniforms in athletes) that limits heat dissipation.

Exposure to hot weather is considered one of the most deadly natural hazards in the United States in unacclimatized and immunocompromised individuals (20). It was estimated that between 1979 and 2002, heat stroke claimed more American lives than the combined effects of hurricanes, lightning, earthquakes, floods, and tornadoes (19). During this time period, the U.S. reported 4,780 heat-related deaths that were stratified by age with 6% in children <15 yr, 50% in persons aged 15–64 yr, and 44% in persons >65 yr of age. Despite these reports, heat stroke incidence is difficult to determine due to varying definitions that result in misdiagnosis. Heat stroke mortality rates are determined from medical examiner reports that define a "heat-related death" as that in which exposure to high ambient temperature either caused or significantly contributed to death based on the exclusion of other causes of hyperthermia (27). Estimates of heat-related mortality rates represent cases that occurred during annual heat waves when regional temperatures remained elevated over several days or weeks. In 2003, Europe experienced 22,000–45,000 heat-related deaths during a summer heat wave in which the average temperature was 3.5°C above normal during a 2-wk period (57, 76). However, the death toll from heat exposure per se is misleading, as many heat stroke victims in Europe succumbed to multi-organ system failure during the weeks, months, and years following the heat event despite hospital treatment (1). Similarly, military heat stroke patients showed ~2-fold increased mortality risk from cardiovascular, kidney, and liver failure within 30 years of hospitalization compared with patients hospitalized for a non-heat related illness (84). A recent epidemiological study identified a variety of factors that are associated with increased incidence of exertional heat illness, including sex (women > men), geographic region of origin (Northern > Southern states), and race/ethnicity [Caucasian > African American (18)]. Although the mechanisms responsible for long-term decrements in organ function are thought to be related to a systemic inflammatory response that ensues following heat-induced damage to the gut and other organs, we still know very little regarding the pathophysiological mediators that cause multi-organ system failure (Fig. 1).

AGING

Passive heat stroke is most commonly reported in elderly individuals that are immuno- or physiologically compromised and exposed to climatic heat stress during summer heat waves (1, 25, 28). During the 2003 heat wave in France, ~15,000 individuals died from heat stroke, which was thought to be a consequence of the large aged population (~10,000 people over 100 years old) and a lack of air conditioning in homes and hospitals (1, 28). Heat strain imposes large cardiovascular demands on the body as blood flow is shunted from core organs
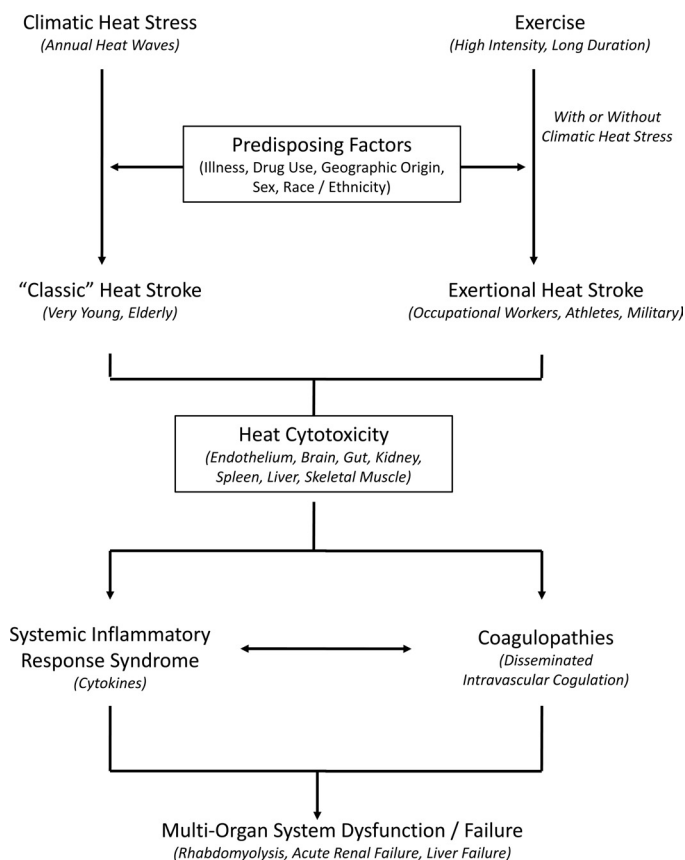

Fig. 1. Summary of environmental and predisposing factors that interact to cause "classic" (passive) and exertional heat stroke. Classic heat stroke is commonly observed in very young children or the elderly during annual heat waves. Exertional heat stroke is observed in young, healthy individuals that are performing a high rate of metabolic work in temperate or hot conditions. Predisposing factors, such as illness, drug use (e.g., anticholinergics, antidiurectics, ecstacy), geographic region of origin (Northern>Southern), sex (women>men), and race (Caucasian>African American) are confounding factors that increase the incidence of both forms of heat stroke. Following heat stroke collapse, heat cytotoxicity to the brain and peripheral organs initiates the coagulation cascade and a systemic inflammatory response syndrome that may culminate in multi-organ system failure and death.

to the skin to dissipate excess heat to the environment. Physiological decrements with aging may include impairment of baroreceptor reflex modulation (80), lower sweating rate and longer onset to sweating (43), and diminished renal and splanchnic sympathetic nerve discharge (44). Minson et al. (62) demonstrated that older men relied on a higher percentage of their cardiac chronotropic reserve compared with young men during heat exposure. This finding may have particular relevance to those individuals experiencing a heat wave with a pre-existing condition, such as coronary artery disease (62). Pre-existing illness is also a confounding factor in aged populations. During the 1995 heat wave in Chicago, 57% of heat stroke patients had evidence of infection on clinical admission (25). Chronic inflammatory conditions may impede the body's ability to respond to a subsequent stressful event by inhibiting the appropriate adaptive immune response that would protect against organ dysfunction. Thus the high death toll due to excessive heat per se may be small compared with that caused by the aggravation in severity of a pre-existing condition. The interaction of all of these factors in heat stroke mortality

complicates the etiology of this syndrome in aged populations and limits the success of traditional medical interventions.

THE SYSTEMIC INFLAMMATORY RESPONSE

In 2002 a new definition of heat stroke was introduced that suggested multi-organ system failure was due to the combined effects of heat cytotoxicity, coagulopathies, and a systemic inflammatory response syndrome (SIRS; 9). The primary cardiovascular response to heat exposure is an increase in skin blood flow that promotes heat loss and reduces the rate of heat gain from the environment. Increased skin blood flow is accompanied by a fall in splanchnic blood flow as a compensatory mechanism to maintain blood pressure. Hyperthermia is also associated with reduced cerebral blood flow (CBF), which may account for presyncopal signs or CNS abnormalities (68). The SIRS is regarded as a response to bacterial infection that ensues following damage to the gut and other organs following prolonged reductions in splanchnic blood flow. The resultant ischemic environment promotes nitrosative and oxidative stress that causes tight junctions of the gut to become "leaky." Gram-negative and -positive bacteria that are normally contained in the gut lumen are then able to freely cross the tight junction barrier and enter into the systemic circulation (26, 32, 36, 49). The liver is an important clearance organ for endotoxin (15, 67), suggesting an association between liver damage and circulating endotoxin levels in heat stroke patients and animal models. As an example, during football practice a young athlete had a body temperature of 40.6°C and high circulating levels of endotoxin that were associated with hemorrhagic necrosis of his liver (35). Manipulations that render experimental animals endotoxin-tolerant following a peripheral injection of LPS (a cell wall component of endotoxin) or endotoxin-"free" with antibiotic therapy are effective in improving short-term (<24 h) heat stroke survival rates (17, 30, 32). However, the efficacy of antibiotic therapy is inversely related to the severity of heat exposure, as antibiotics did not protect primates with core temperatures >43.8°C (32). Therefore, the systemic inflammatory response to endotoxin leakage appears to be an important component of the heat stroke syndrome but must be considered in relation to the effects of heat cytoxicity alone, which can cause irreversible organ damage and death in the early stages (32). As will be discussed below, the heat stroke syndrome is comprised of a wide range of thermoregulatory, coagulation, immune, and tissue injury responses with limited understanding of the endogenous mechanisms that predispose individuals to morbidity and mortality.

Body temperature responses. At the time of heat stroke collapse, the severity of hyperthermia varies widely between individuals, with reported core temperature values ranging from ~41 to ~47°C (7, 12, 21, 37, 38, 56). Core temperatures of elderly heat stroke victims are often less than ~41°C at the time of collapse. This appears to be due to physiological impairments that predispose to collapse, such as decrements in cardiovascular function (46), prescription drug use [e.g., diuretics (1)], pre-existing inflammatory conditions (25), or limited access or use of air conditioning systems (1). Well-conditioned athletes may tolerate hyperthermia without adverse side effects due to training-induced heat acclimatization effects on cellular protective mechanisms (60). However, heavy clothing and/or pre-existing infections may also predis-

pose to heat stroke collapse in this otherwise healthy, fit population (35, 59, 74, 78).

The body temperature responses observed during heat stroke recovery consist of hypothermia and/or fever, but are not as well-recognized as those observed at the time of collapse. Patients may show a rapid undershoot of body temperature to <37°C in response to cooling therapy, which is thought to be due to a loss of thermoregulatory control following heat-induced damage to the preoptic area of the anterior hypothalamus [POAH; the main thermoregulation control site (14, 58)]. However, there is scant histological evidence to support the hypothesis that the POAH is damaged in heat stroke patients that present with hypothermia, despite evidence of extensive damage to other CNS regions (e.g., cerebellum) and peripheral organs (33, 39, 58). In experimental animal models, hypothermia is a natural heat stroke recovery response that occurs in the absence of cooling treatment and is associated with behavioral and autonomic thermoeffector responses that support its development (42, 53). In mice, the prevention of hypothermia caused an increase in intestinal damage and mortality, suggesting it is a protective response that is important for recovery (52, 89). The Q_{10} effect states that each 10°C change in body temperature is associated with a two- to threefold change in enzymatic reaction rates. On the basis of this relationship, hypothermia is thought to minimize energy demands and reduce generation of harmful reactive oxygen species that would otherwise cause tissue injury following heat exposure (36).

Recurrent hyperthermic episodes have been documented in heat stroke patients and animal models during the hours, days, and weeks of recovery (52, 58). The early recurrence of hyperthermia in patients was regarded as a compensatory peripheral vasoconstriction response to cooling of the skin surface with ice packs, whereas protracted episodes were thought to be due to disturbances in CNS thermoregulatory control (58). To our knowledge, the mechanism(s) mediating recurrent hyperthermia in patients has never been examined in detail; yet antipyretic drugs (e.g., acetaminophen) are often used by physicians to treat immediate or recurrent hyperthermia in heat stroke patients (16, 25, 61). Mice show delayed hyperthermia ~24 h after severe heat stroke collapse and this response is associated with increased metabolic heat production and elevated circulating levels of the pro-inflammatory cytokine IL-6 (i.e., a known fever inducer), suggesting it may be a true fever response (51, 53). Interestingly, mice that are unable to rewarm from hypothermia to develop fever succumb to severe heat stroke (52). The biphasic thermoregulatory response displayed by patients and mice during heat stroke recovery is similar to that observed during sepsis, suggesting that similar physiological mechanisms may be mediating these responses (54, 66). Unfortunately, few studies have examined the regulated nature of these recovery responses and they continue to be regarded as manifestations of thermoregulatory "instability" despite a paucity of data to directly support this hypothesis (58).

Coagulopathies. Disseminated intravascular coagulation (DIC) is a common complication of heat stroke that is initiated following thermal injury to the vascular endothelium and is regarded as an important mechanism of heat stroke morbidity and mortality (8, 64; Fig. 2). In vitro studies have shown that heat (43–44°C) directly activates platelet aggregation and
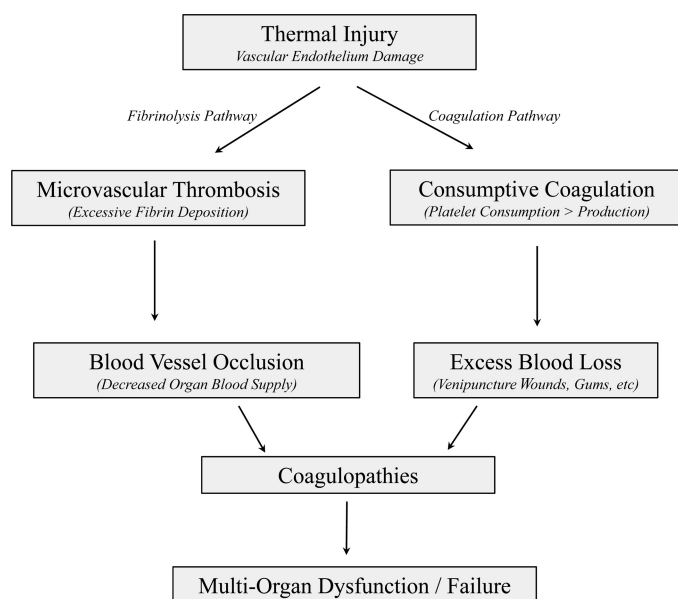
Thermal Injury
Vascular Endothelium Damage

Fibrinolysis Pathway   *Coagulation Pathway*

Microvascular Thrombosis
(Excessive Fibrin Deposition)

Consumptive Coagulation
(Platelet Consumption > Production)

Blood Vessel Occlusion
(Decreased Organ Blood Supply)

Excess Blood Loss
(Venipuncture Wounds, Gums, etc)

Coagulopathies

Multi-Organ Dysfunction / Failure

Fig. 2. Mechanisms of disseminated intravascular coagulation (DIC). Thermal injury to the vascular endothelium initiates the coagulation and fibrinoloysis pathways. Excess fibrin deposition may lead to vascular thrombosis in the arterioles and capillaries leading to occlusion of the blood supply to the organ bed. As coagulation proceeds, platelets and coagulation proteins are consumed at a faster rate than they are produced, resulting in blood loss from multiple tissue sites (e.g., venipuncture wounds, gums). The combined effects of vessel occlusion and excess blood loss result in coagulopathies leading to multi-organ dysfunction.

causes irreversible hyperaggregation following cooling (31, 88). Early in heat stroke, widespread activation of coagulation stimulates excess deposition of fibrin in the arterioles and capillaries along with platelet aggregation that leads to microvascular thrombosis. Although rapid cooling of the heat stroke patient may normalize fibrinolysis, coagulation often persists until platelets and coagulation proteins are consumed at a faster rate than they are produced (2, 4). Consumptive coagulation may lead to excessive, prolonged bleeding from multiple tissue sites (e.g., venipuncture sites, gums) and is associated with fatal outcome (46). In the Paris heat wave of 2003, a link was established between elevated circulating levels of pro-inflammatory cytokines, neutrophil activation, and coagulation in elderly heat stroke patients (41). Endotoxin and cytokines are thought to activate leukocytes and endothelial cells to amplify the coagulation cascade and participate in the progression of DIC.

Cytokines. 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 receptor antagonist of IL-1), IL-6, soluble IL-6 receptor (sIL-6R), IL-8, IL-10, IL-12, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and sTNFR concentrations are commonly observed at the time of heat stroke collapse or shortly after cooling (7, 11, 12, 37, 38, 51). Elevated IFN-inducible gene expression and IFN-γ levels are a clinical measure of viral or intracellular bacterial infection and are evident in exertional heat stroke patients with pre-existing infections (79). Although circulating levels of IL-6 and TNF correlate with heat stroke severity, few studies have examined the dynamic relationship of these cytokines with their soluble receptors. The sIL-6R may potentiate endogenous IL-6 effects by increasing the concentration of available IL-6 signaling receptors on cell membranes [known as a transignaling effect (48)] or reducing IL-6 signaling through competitive binding with IL-6 receptors already present on the cell membrane (77). IL-6 shows reciprocal changes with respect to the sIL-6R from the time of clinical admission to postcooling, but the manner in which interactions between these proteins alter heat stroke outcome remains unknown (37). Similarly, circulating levels of TNF-α and -β were undetectable at the time of clinical admission in a small cohort of heat stroke patients ($n = 3$), but sTNFR concentrations were higher in survivors than nonsurvivors (37). Since the sTNFR antagonizes endogenous TNF actions, it was suggested that TNF has detrimental actions in the SIRS (37). However, recent cytokine neutralization studies suggest that a reinterpretation of cytokine actions in the heat stroke syndrome is needed. That is, IL-6 and TNF double receptor knockout mice (i.e., mice that cannot produce IL-6 or generate TNF-mediated cellular signaling) showed higher mortality rates than their wild-type controls following heat stroke collapse (51). These data suggest that baseline (permissive) actions of these cytokines (or their downstream targets) are essential for resolution of the SIRS (51). Overall, data from correlation studies have misinterpreted the role of cytokines in the SIRS and it is now recognized that these immune modulators elicit protective actions in vivo that are probably time and tissue specific.

Multi-organ system dysfunction. A hallmark symptom of heat stroke is CNS dysfunction that manifests as mental status changes, including confusion, delirium, combativeness, seizures, or coma at the time of collapse. Brain hyperthermia is a consequence of increased cerebral metabolic rate, overall activation of the brain, and a reduction in cerebral blood flow (CBF; 68). The resultant increase in blood-brain barrier permeability is thought to facilitate the leakage of proteins and pathogens from the systemic circulation into the brain. Cerebral edema was associated with headache, coma, the absence of normal reflexive responses, and multi-organ system dysfunction in 27- to 76-yr-old heat stroke patients that collapsed during a summer heat wave in Israel (81). Despite rapid cooling, ~30% of heat stroke survivors experience permanent neurological impairments that may be related to cerebellar atrophy and infarcts (1, 25).

Peripheral tissue damage associated with heat stress includes acute renal failure, gut ischemia, blood clots within the stomach and small intestine, cytoplasmic protein clumping in the spleen, and a form of skeletal muscle injury known as rhabdomyolysis (13, 22, 51). Acute renal failure is an almost universal finding that is accompanied by decrements in function within 24 h of intensive care unit presentation (72). In exertional heat stroke patients, rhabdomyolysis may exacerbate renal dysfunction due to the toxic effects of myoglobin on the kidney nephrons and the resultant overproduction of uric acid (3, 55, 71, 86). Rhabdomyolysis is usually detectable as reddish-brown urine, but can lead to coagulopathy and death in asymptomatic patients. Although liver failure is one of the widely recognized conditions associated with heat stroke, damage to this organ may not peak until 24–48 h after heat exposure (33, 45, 50). Disruptions in liver function are

typically evident as fatty liver changes (22, 50) or disturbances in plasma glucose homeostasis that present as hyperglycemia or hypoglycemia (8, 29, 70). Liver dysfunction may also contribute to increased circulating endotoxin levels due to the important bacterial clearance function of this organ (67). Unfortunately, many heat stroke patients require liver transplantation, and the use of antipyretic drugs, such as acetaminophen, has been associated with failure of this organ (33, 39, 40, 75, 83).

CLINICAL INDEXES OF HEAT STROKE RECOVERY

Recent epidemiological studies suggest that current clinical indexes of organ function may not be sensitive enough to detect peripheral damage resulting in organ dysfunction in the ensuing years of recovery. Following the 2003 heat wave in France, many survivors experienced decrements in functional status within 1 to 2 years following treatment and mortality rates increased from 58% at *day 28* of hospitalization (mean hospital stay was 24 days) to 71% by the 2nd year of recovery (1). An epidemiological study of military exertional heat stroke patients showed ~40% increased mortality risk from cardiovascular, kidney, and liver failure within 30 years of hospitalization compared with individuals treated for a non-heat related illness (84). Traditional clinical markers of organ dysfunction include high circulating levels of creatine kinase (CK; skeletal muscle), blood urea nitrogen (BUN; kidney), aspartate aminotransferase (AST; liver), and alanine aminotransferase (ALT; liver). However, because these biomarkers are released by a variety of organs and/or tissues and altered by heat as well as exhaustive exercise, they may not be sensitive diagnostic
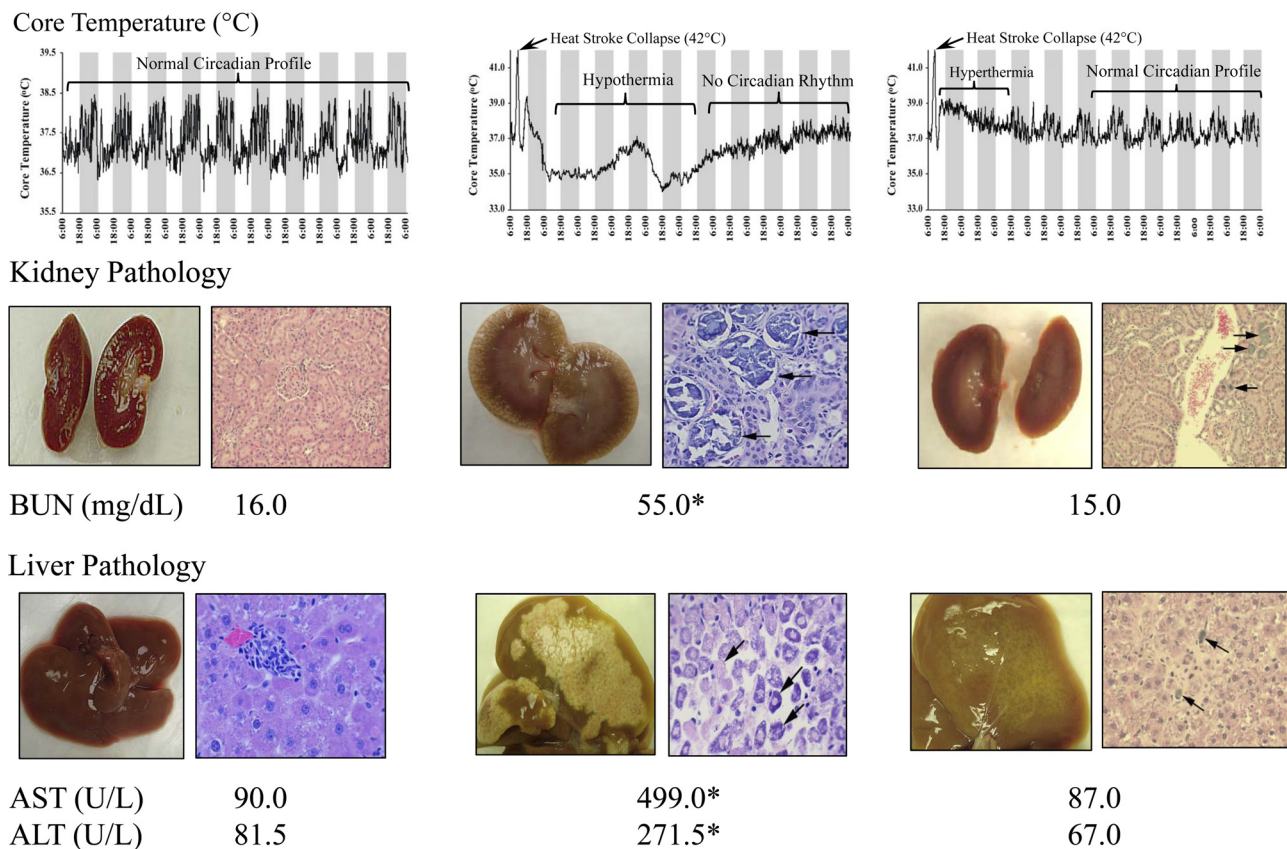

Fig. 3. Representative data showing that traditional clinical measures of tissue injury do not always accurately reflect the presence of peripheral organ damage. Male Fischer 344 rats were instrumented with intraperitoneal radiotelemetry devices for continuous sensing of core temperature (±0.1°C) during 10 days of heat stroke recovery. On *day 10*, circulating levels of blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were compared with gross morphology and histological damage (hematoxylin and eosin staining) of the kidney and liver. Representative core temperature tracings (*top*), kidney pathology and BUN levels (*middle*) and liver pathology, AST and ALT levels (*bottom*) from one control (*left*) and two heat stroke rats (*middle* and *right*; core temperature = 42.0°C at collapse) are shown. *Left*: the control (nonheated) rat displayed a normal circadian core temperature profile through 10 days with low daytime (~37°C) and high nighttime (~38°C) values. The kidney and liver showed normal gross and histological appearance and circulating levels of BUN, AST, and ALT were within the normal range. *Middle*: after heat stroke collapse, the rat displayed profound hypothermia (~34–35°C) through 5 days of recovery and then rewarmed to ~37°C by *day 10* of recovery, but failed to re-establish a normal circadian rhythm. Gross appearance of the kidney and liver indicated tissue damage, which was confirmed by histological analysis. The kidney showed bilateral renal tubular degeneration with protenuria, and multifocal necrosis of hepatocytes was evident in the liver (indicated by black arrows in representative photomicrographs). High circulating BUN, AST, and ALT levels accurately reflected the extensive histological damage to these organs. *Right*: after heat stroke collapse, the rat displayed hyperthermia (~39°C) through *day 3* and then re-established a normal circadian core temperature profile through 10 days of recovery. Gross appearance of the kidney and liver suggested residual damage in these organs, which was confirmed histologically as bilateral mineralization and protenuria in the kidney and extramedullary hematopoiesis with mineralization of hepatocytes (indicated by black arrows in representative photomicrographs). Circulating levels of BUN, AST, and ALT levels were virtually identical to controls and did not accurately reflect the persistence of tissue damage in this animal. These data demonstrate that traditional clinical biomarkers of organ function are not always sensitive enough to accurately indicate recovery from heat stroke at the organ level. Gray shading in core temperature graphs represents 12-h lights-off, active period. *Values elevated above control.

indicators of tissue injury in all heat stroke victims (34). For example, high circulating levels of CK may reflect a variety of clinical conditions, such as rhabdomyolysis, myocardial infarction, or acute renal failure (71, 85). Since BUN is secreted by the liver and removed from the blood by the kidneys, high circulating levels may be due to dysfunction of either of these organs. AST and ALT are used as clinical markers of liver function in heat stroke patients despite release from multiple tissues (e.g., liver, skeletal muscle).

Obviously, it is not ethical or feasible to directly assess tissue injury in heat stroke patients, such that reliance on circulating biomarkers is necessary in a clinical setting. However, experimental animal models can be used to more precisely determine the sensitivity of circulating biomarkers for assessing organ damage during recovery from heat stroke. Using a conscious rat model, we recently observed a dissociation between core temperature profiles; circulating BUN, AST, and ALT levels; and the presence of histological damage to the kidney and liver at 10 days of heat stroke recovery (Fig. 3). Specifically, altered core temperature profiles and elevated circulating levels of BUN, AST, and ALT were used as measures of severe kidney and liver injury, but these indexes were not sensitive enough to detect damage to these organs in a moderate heat stroke case (Fig. 3). Taken together, recent findings from epidemiological studies and data from our rodent heat stroke model indicate that reliance on traditional clinical biomarkers for assessment of organ (dys)function may result in misdiagnosis of heat stroke recovery status. Unfortunately, it is often difficult for physicians to accurately determine organ function in heat stroke patients and they must rely on circulatory and physiological measurements to assess recovery and determine appropriate treatment options. Therefore, animal models will be required to further delineate the pathophysiological mechanisms mediating multi-organ system dysfunction and identify sensitive diagnostic tools and efficacious clinical treatments to prevent heat stroke morbidity and mortality.

PREVENTION AND TREATMENT

Heat stroke is currently more preventable than treatable. The most effective preventive measures include acclimatization to the heat, reduction in the duration and extent of physical activity, rescheduling of activities to cooler times of the day, increased consumption of nonalcoholic fluids, and removing vulnerable populations, such as those with pre-existing viral or bacterial infections, from the heat stress environment. Fan cooling has not shown protection against heat stroke and is associated with increased thermal discomfort at ambient temperatures >38°C (47). Consistent with this, elevated death toll from the 2003 heat wave in France was due to the
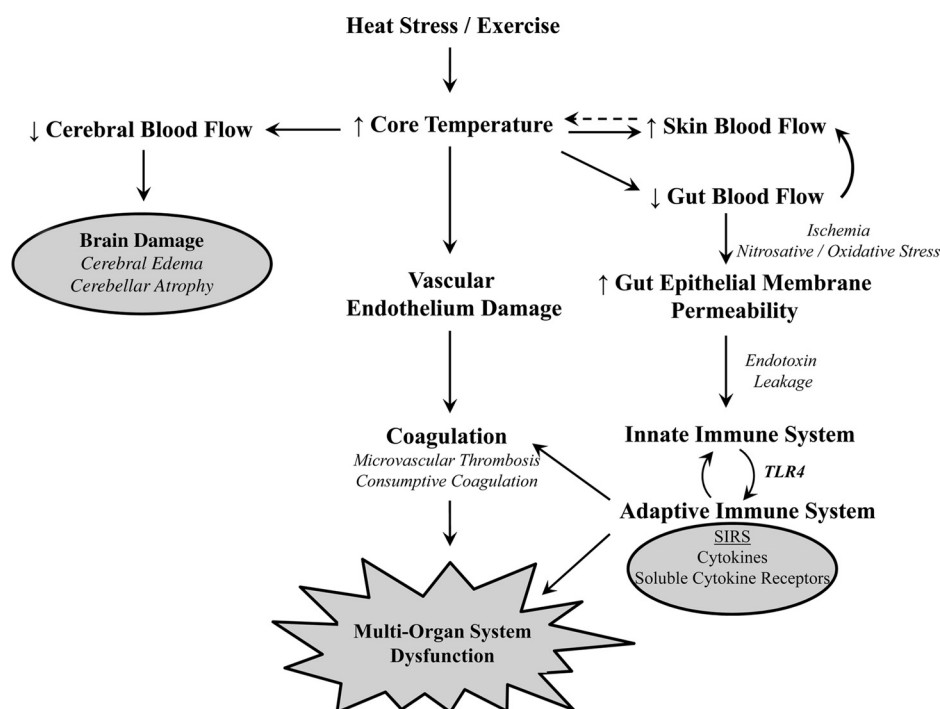

Fig. 4. Summary of heat stroke pathophysiological changes that culminate in multi-organ system dysfunction and death. Heat stress and/or exercise cause an increase in core temperature, which stimulates multiple reflexive adjustments. Skin blood flow is increased to facilitate heat loss to the environment and is an important negative feedback pathway (dashed arrow) to limit hyperthermia. A decrease in gut blood flow facilitates the redistribution of blood to the skin surface. Prolonged reductions in gut blood flow stimulate oxidative/nitrosative stress and cause the gut epithelial barrier membrane to become ischemic. Gut ischemia causes the tight junctions of the gut to become leaky, allowing endotoxin to leak from the gut lumen into the systemic circulation. The innate and adaptive immune systems sense and respond to endotoxin (through toll-like receptors, such as TLR4) and stimulate the production of cytokines and other immune modulators. High body temperature causes thermal injury to the vascular endothelium and initiates the coagulation/fibrinolysis pathways that lead to occlusion of the arterioles and capillaries (microvascular thrombosis) or excessive bleeding (consumptive coagulation). The systemic inflammatory response syndrome (SIRS) and coagulation pathways interact to cause multi-organ system failure and death if not rapidly treated and resolved. 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. Gray shading indicates hypothetical mechanisms of injury, but clinical and experimental data are limited.

high aged population and lack of air conditioning in homes and hospitals (1).

Heat stroke onset requires aggressive clinical treatments consisting of rapid cooling and supportive therapies, such as fluid resuscitation to stabilize organ function. Few controlled studies have been conducted examining the efficacy of anti-cytokine, anti-endotoxin, or anti-coagulation drugs on patient outcome with heat stroke. However, clinical trials of sepsis suggest that these therapies need to be viewed with cautious optimism. Multicenter clinical trials of >6,200 patients showed no benefit of anti-endotoxin antibodies, ibuprofen, platelet activating factor receptor antagonist, anti-TNF monoclonal antibody, or IL-1ra on all-cause mortality from sepsis (24, 69). There are several explanations for negative results from anti-cytokine therapies, including the possibility of no pathophysiological role for cytokines in multi-organ system failure, failure to neutralize the protein (due to a lack of biological activity, competition by other mediators, inadequate anatomical distribution), compensatory increase of other mediators with similar activities, inappropriate timing or duration of therapy, or the need for combination therapies (73). The transient nature of cytokine production and/or clearance rates and lack of correlation between serum levels and disease severity complicates treatment scenarios. Nonsteroidal anti-inflammatory drugs have potent antipyretic and anticoagulant properties, but these drugs have not been tested in controlled laboratory or clinical studies to determine their efficacy on heat stroke-related outcomes. Recombinant human activated protein C (rhAPC) has been approved in the United States for the treatment of severe sepsis and has anti-inflammatory and anticoagulant properties that warrant consideration for the treatment of heat stroke. In heat stroke patients and experimental models, rhAPC attenuated inflammation, resolved multi-organ system dysfunction, and improved survival (5, 10, 23). However, the efficacy of rhAPC was dependent on the timing of administration and specific characteristics of the patient population and did not protect against mortality in all heat stroke models, indicating that additional studies are needed to warrant its use as a heat stroke treatment (10, 23, 87).

CONCLUSIONS

Heat is a leading cause of natural-hazard death in the United States as evidenced by the profound morbidity and mortality associated with recent heat waves (6, 19, 20). Recent research has indicated heat stroke survivors have a significant elevation in their 30-yr mortality rate when compared with individuals never experiencing a heat stroke. Despite this, knowledge of the pathophysiology of heat stroke is severely limited as is our understanding of the mechanisms of the SIRS that predispose to morbidity and mortality (Fig. 4). Currently there is a paucity of data supporting the efficacy of current clinical treatments and there is a dire need for more efficacious therapeutics. The use of novel biotechnologies, including radiotelemetry, genomic, and proteomic analyses, will be critical in advancing our knowledge of heat stroke pathophysiology. These technologies combined with novel in vivo, in vitro, and in silico models will be critical to enhancing our understanding of the SIRS and developing of novel strategies to reduce the morbidity and mortality associated with heat stroke.

REFERENCES

1. **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.
2. **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.
3. **Bagley WH, Yang H, Shah KH.** Rhabdomyolysis. *Intern Emerg Med* 2: 210–218, 2007.
4. **Barbui T, Falanga A.** Disseminated intravascular coagulation in acute leukemia. *Semin Thromb Hemost* 27: 593–604, 2001.
5. **Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr.** Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 344: 699–709, 2001.
6. **Borden KA, Cutter SL.** Spatial patterns of natural hazards mortality in the United States. *Int J Health Geogr* 7: 64–76, 2008.
7. **Bouchama A, Al-Sedairy S, Siddiqui S, Shail E, Rezeig M.** Elevated pyrogenic cytokines in heatstroke. *Chest* 104: 1498–1502, 1993.
8. **Bouchama A, Hammami MM, Haq A, Jackson J, Al-Sedairy S.** Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med* 24: 1173–1178, 1996.
9. **Bouchama A, Knochel JP.** Heat stroke. *N Engl J Med* 346: 1978–1988, 2002.
10. **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.
11. **Bouchama A, Ollivier V, Roberts G, Al MF, 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.
12. **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.
13. **Bouchama A, Roberts G, Al MF, El-Sayed R, Lach B, Chollet-Martin S, Ollivier V, Al BR, 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.
14. **Boulant JA.** Hypothalamic neurons regulating body temperature. In: *Handbook of Physiology, Section* 4: Environmental Physiology. Bethesda, MD: Am Physiol Soc, 1996, p. 105–125.
15. **Bradfield JW.** Control of spillover. The importance of Kupffer-cell function in clinical medicine. *Lancet* 2: 883–886, 1974.
16. **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.
17. **Bynum G, Brown J, Dubose D, Marsili M, Leav I, Pistole TG, Hamlet M, LeMaire M, Caleb B.** Increased survival in experimental dog heat-stroke after reduction of gut flora. *Aviat Space Environ Med* 50: 816–819, 1979.
18. **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.

19. **CDC.** Heat-Related Mortality—Arizona, 1993–2002, and United States, 1979–2002. *Morbid Mortal Weekly* 54: 628–630, 2005.

20. **CDC.** Heat-Related Deaths—United States, 1999–2003. *Morbid Mortal Weekly* 55: 796–798, 2006.

21. **Chang DM.** The role of cytokines in heat stroke. *Immunol Invest* 22: 553–561, 1993.

22. **Chao TC, Sinniah R, Pakiam JE.** Acute heat stroke deaths. *Pathology* 13: 145–156, 1981.

23. **Chen CM, Hou CC, Cheng KC, Tian RL, Chang CP, Lin MT.** Activated protein C therapy in a rat heat stroke model. *Crit Care Med* 34: 1960–1966, 2006.

24. **Deitch EA.** Animal models of sepsis and shock: a review and lessons learned. *Shock* 9: 1–11, 1998.

25. **Dematte JE, O'Mara K, Buescher J, Whitney CG, Forsythe S, Mc-Namee T, Adiga RB, Ndukwu IM.** Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 129: 173–181, 1998.

26. **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.

27. **Donoghue ER, Graham MA, Jentzen JM, Lifschultz BD, Luke JL, Mirchandani HG.** Criteria for the diagnosis of heat-related deaths: National Association of Medical Examiners. Position paper. National Association of Medical Examiners Ad Hoc Committee on the Definition of Heat-Related Fatalities. *Am J Forensic Med Pathol* 18: 11–14, 1997.

28. **Dorozynski A.** Chirac announces investigation into heat wave's death toll. *BMJ* 327: 465, 2003.

29. **Drobatz KJ, Macintire DK.** Heat-induced illness in dogs: 42 cases (1976–1993). *J Am Vet Med Assoc* 209: 1894–1899, 1996.

30. **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.

31. **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.

32. **Gathiram P, Wells MT, Brock-Utne JG, Gaffin SL.** Antilipopolysaccharide improves survival in primates subjected to heat stroke. *Circ Shock* 23: 157–164, 1987.

33. **Giercksky T, Boberg KM, Farstad IN, Halvorsen S, Schrumpf E.** Severe liver failure in exertional heat stroke. *Scand J Gastroenterol* 34: 824–827, 1999.

34. **Goddard CJ, Warnes TW.** Raised liver enzymes in asymptomatic patients: investigation and outcome. *Dig Dis* 10: 218–226, 1992.

35. **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.

36. **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.

37. **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.

38. **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.

39. **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.

40. **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.

41. **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.

42. **Hutchison VH.** Critical thermal maxima in salamanders. *Physiol Zool* 34: 92–125, 1961.

43. **Inoue Y, Shibasaki M, Ueda H, Ishizashi H.** Mechanisms underlying the age-related decrement in the human sweating response. *Eur J Appl Physiol Occup Physiol* 79: 121–126, 1999.

44. **Kenney MJ, Fels RJ.** Sympathetic nerve regulation to heating is altered in senescent rats. *Am J Physiol Regul Integr Comp Physiol* 283: R513–R520, 2002.

45. **Kew M, Bersohn I, Seftel H, Kent G.** Liver damage in heatstroke. *Am J Med* 49: 192–202, 1970.

46. **Khogali M.** Epidemiology of heat illnesses during the Makkah Pilgrimages in Saudi Arabia. *Int J Epidemiol* 12: 267–273, 1983.

47. **Kilbourne EM, Choi K, Jones TS, Thacker SB.** Risk factors for heatstroke. A case-control study. *JAMA* 247: 3332–3336, 1982.

48. **Knupfer H, Preiss R.** sIL-6R: more than an agonist? *Immunol Cell Biol* 86: 87–91, 2008.

49. **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.

50. **Leon LR.** Heat stroke and cytokines. *Prog Brain Res* 162: 481–524, 2007.

51. **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.

52. **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.

53. **Leon LR, Gordon CJ, Helwig BG, Rufolo DM, Blaha MD.** Thermoregulatory, behavioral, and metabolic responses to heat stroke in a conscious mouse model. *Am J Physiol Regul Integr Comp Physiol* 299: R241–R248, 2010.

54. **Leon LR, White AA, Kluger MJ.** Role of IL-6 and TNF in thermoregulation and survival during sepsis in mice. *Am J Physiol Regul Integr Comp Physiol* 275: R269–R277, 1998.

55. **Line RL, Rust GS.** Acute exertional rhabdomyolysis. *Am Fam Physician* 52: 502–506, 1995.

56. **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.

57. **Luterbacher J, Dietrich D, Xoplaki E, Grosjean M, Wanner H.** European seasonal and annual temperature variability, trends, and extremes since 1500. *Science* 303: 1499–1503, 2004.

58. **Malamud N, Haymaker W, Custer RP.** Heat Stroke: clinico-pathologic study of 125 fatal cases. *Mil Surg* 99: 397–449, 1946.

59. **Maron MB, Wagner JA, Horvath SM.** Thermoregulatory responses during competitive marathon running. *J Appl Physiol* 42: 909–914, 1977.

60. **McClung JP, Hasday JD, He JR, Montain SJ, Cheuvront SN, Sawka MN, Singh IS.** Exercise-heat acclimation in humans alters baseline levels and ex vivo heat inducibility of HSP72 and HSP90 in peripheral blood mononuclear cells. *Am J Physiol Regul Integr Comp Physiol* 294: R185–R191, 2008.

61. **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.

62. **Minson CT, Wladkowski SL, Cardell AF, Pawelczyk JA, Kenney WL.** Age alters the cardiovascular response to direct passive heating. *J Appl Physiol* 84: 1323–1332, 1998.

63. **Misset B, De JB, Bastuji-Garin S, Gattolliat O, Boughrara E, Annane D, Hausfater P, Garrouste-Org, 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.

64. **Mustafa KY, Omer O, Khogali M, Jamjoom A, Gumaa KA, Abu el-Nasr N, Gader MA.** Blood coagulation and fibrinolysis in heat stroke. *Br J Haematol* 61: 517–523, 1985.

65. **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.

66. **Newcomb D, Bolgos G, Green L, Remick DG.** Antibiotic treatment influences outcome in murine sepsis: mediators of increased morbidity. *Shock* 10: 110–117, 1998.

67. **Nolan JP.** Endotoxin, reticuloendothelial function, and liver injury. *Hepatology* 1: 458–465, 1981.

68. **Nybo L.** Exercise and heat stress: cerebral challenges and consequences. *Prog Brain Res* 162: 29–43, 2007.

69. **Opal SM, Fisher CJ Jr, Dhainaut JF, Vincent JL, Brase R, Lowry SF, Sadoff JC, Slotman GJ, Levy H, Balk RA, Shelly MP, Pribble JP, LaBrecque JF, Lookabaugh J, Donovan H, Dubin H, Baughman R, Norman J, DeMaria E, Matzel K, Abraham E, Seneff M.** Confirmatory

interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 25: 1115–1124, 1997.

70. **Paidas CN, Mooney ML, Theodorakis NG, De Maio A.** Accelerated recovery after endotoxic challenge in heat shock-pretreated mice. *Am J Physiol Regul Integr Comp Physiol* 282: R1374–R1381, 2002.

71. **Patel DR, Gyamfi R, Torres A.** Exertional rhabdomyolysis and acute kidney injury. *Phys Sportsmed* 37: 71–79, 2009.

72. **Pease S, Bouadma L, Kermarrec N, Schortgen F, Regnier B, Wolff M.** Early organ dysfunction course, cooling time and outcome in classic heatstroke. *Intensive Care Med* 35: 1454–1458, 2009.

73. **Remick DG.** Cytokine therapeutics for the treatment of sepsis: why has nothing worked? *Curr Pharm Des* 9: 75–82, 2003.

74. **Roberts WO.** Death in the heat: can football heat stroke be prevented? *Curr Sports Med Rep* 3: 1–3, 2004.

75. **Saissy JM.** Liver transplantation in a case of fulminant liver failure after exertion. *Intensive Care Med* 22: 831, 1996.

76. **Schar C, Jendritzky G.** Climate change: hot news from summer 2003. *Nature* 432: 559–560, 2004.

77. **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.

78. **Smalley B, Janke RM, Cole D.** Exertional heat illness in Air Force basic military trainees. *Mil Med* 168: 298–303, 2003.

79. **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.

80. **Stauss HM, Morgan DA, Anderson KE, Massett MP, Kregel KC.** Modulation of baroreflex sensitivity and spectral power of blood pressure by heat stress and aging. *Am J Physiol Heart Circ Physiol* 272: H776–H784, 1997.

81. **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.

82. **Varghese GM, John G, Thomas K, Abraham OC, Mathai D.** Predictors of multi-organ dysfunction in heatstroke. *Emerg Med J* 22: 185–187, 2005.

83. **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.

84. **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.

85. **Wallimann T, Hemmer W.** Creatine kinase in non-muscle tissues and cells. *Mol Cell Biochem* 133–134: 193–220, 1994.

86. **Wang AY, Li PK, Lui SF, Lai KN.** Renal failure and heatstroke. *Ren Fail* 17: 171–179, 1995.

87. **Warren HS, Suffredini AF, Eichacker PQ, Munford RS.** Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med* 347: 1027–1030, 2002.

88. **White JG.** Effects of heat on platelet structure and function. *Blood* 32: 324–335, 1968.

89. **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.

90. **Winkenwerder M, Sawka MN.** Disorders due to heat and cold. In: *Cecil Medicine*, edited by Goldman L and Ausiello D. Philadelphia: Elsevier Science, 2007, p. 763–767.