



# Common Misconceptions in Classic and Exertional Heat Stroke

# 5

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## 5.1 A Long History of Heat Stroke

Heat stroke is a complex physiological condition that has plagued humankind for centuries. It is considered one of the oldest known medical conditions with descriptions of human death from heat exposure dating back to the earliest writings of man [1]. Sunstroke was an early term that was mentioned several times in the Bible in reference to the death of farmers as well as armored fighting forces ~1000 B.C. [2]. Fever in men and madness of dogs later became correlated with the summer appearance of Sirius, the Dog Star of the constellation Canis Major, from which stems the phrase “dog days” of summer (~3000 B.C.). The term “siriasis” was later introduced into the medical literature in reference to all heat illnesses and remained the preferred term well into the twentieth century [3]. Despite this long history of the debilitating effects of heat stroke, there still remain gaps in our understanding of the complex etiological factors (e.g., host immunity, environment, physical injury) that predispose to collapse, as well as the mechanisms mediating the wide array of organ responses. Within the last decade, considerable effort has been put forth attempting to identify mechanisms of multi-organ injury that may lead to the identification of novel targeted clinical therapies to mitigate morbidity and hasten recovery. While much progress has been realized in this realm, much also remains to be discovered. The purpose of this chapter is to identify misconceptions that have permeated the scientific literature and clouded our judgement as to the pathophysiologic basis for the devastation that wreaks havoc on multiple organ systems following heat stroke collapse.

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## 5.2 Heat Illness Defined

The responses to exercise-heat stress can be categorized as minor “heat-related” conditions versus exertional heat “illnesses.” An abbreviated list of minor heat-related conditions includes physiological hyperthermia of exercise, exercise-associated muscle cramps (EAMCs, also known as heat cramps), and heat syncope. Note that these conditions are not categorized as heat illness per se, that is, they occur typically, but not always, during environmental heat exposure, but are usually not severe enough to place an individual at increased risk for true heat illness. Physiological hyperthermia of exercise may occur in hot or temperate environments as a natural response to the increase in metabolic heat production that occurs during exercise. That is because only ~20% of energy during exercise is used for skeletal muscle contractions, while the remaining ~80% is released as heat. As long as the rate of heat loss remains in balance with heat production, an elevated, although steady-state body core temperature can be sustained for a relatively long period until extreme dehydration or energy depletion occurs. Body core temperatures in excess of 40.6 °C have been reported in conditioned athletes and these individuals will cool naturally upon the cessation of exercise with no adverse effects [4]. EAMCs or heat cramps occur following strenuous exercise and appear as brief, recurrent, and often agonizing skeletal muscle cramps of the limbs and trunk, although smooth, cardiac, and diaphragm muscles are not involved. Cramps may be precipitated by vigorous use of affected skeletal muscles and may recur in the same individual, but are not associated with significant complications and do not predispose to exertional heat illness. EAMCs often occur in salt-depleted persons during a period of recovery (up to many hours) after prolonged, intense sweating [5]. The mechanism of EAMC is not fully understood. It has been suggested that EAMCs are due to electrolyte depletion, but this is based mainly on anecdotal and observational studies rather than sound experimental evidence [6, 7]. Malignant hyperthermia (MH) is a genetic condition characterized by a mutation in the ryanodine I receptor (RyR1) that normally regulates  $\text{Ca}^{2+}$  flux in skeletal muscle [8]. Whether there is a connection between EAMCs, MH, and complications associated with exertional heat illness or exertional rhabdomyolysis is a hypothesis that has been recently introduced and will be discussed further in this chapter [9–12]. Heat syncope is a temporary circulatory insufficiency due to pooling of blood in the peripheral veins (typically the lower extremities), which reduces diastolic filling of the heart resulting in inadequate cerebral perfusion. Heat syncope often, but not always, occurs after prolonged standing or cessation of exercise in hot weather with symptomatology ranging from lightheadedness to a loss of consciousness. Dehydration may be a contributing factor to heat syncope, but body core temperature is typically not elevated, and victims will re-establish cerebral perfusion and recover rapidly once seated or supine.

Heat “illnesses” are best described as a spectrum of conditions with overlapping features that exist on a continuum and often lead to severe organ damage or death if not rapidly recognized and effectively treated. In World War II, attempts were made to provide distinct categories, with associated symptoms, for each of the various

**Table 5.1** Definition of exertional heat illness

Condition	Definition	Symptoms
Heat exhaustion (HE)	Inability to sustain cardiac output to meet combined demands of increased skin blood flow for heat dissipation and blood flow for the metabolic requirements of exercising skeletal muscle and vital organs	Undue fatigue, transient ataxia, dizziness, headache, nausea, vomiting, malaise, tachycardia, hyperventilation, and transient mildly impaired cognition
Exertional heat injury (EHI)	A condition intermediate between HE and EHS with clinical evidence of end-organ injury	More sustained mild confusion and disorientation than HE with elevated core body temperature
Exertional heat stroke (EHS)	Serious, life-threatening condition characterized by central nervous system (CNS) dysfunction in the presence of severe hyperthermia	Delirium, agitation, inappropriate aggressiveness, convulsions, or coma. Core body temperature (i.e., rectal) >40 °C, although reliance on a specific rectal temperature value is not advised

severities of heat illness, but we recognize today that it is difficult to regard them as discrete disorders with their own distinct pathogenesis. For the purposes of this chapter, discussion will be focused primarily on exertional heat illnesses, which typically occur in young, healthy, fit individuals engaging in physical activity in hot or temperate environments. Exertional heat illnesses are categorized as heat exhaustion (HE), exertional heat injury (EHI), and exertional heat stroke (EHS) as highlighted in Table 5.1 [13].

HE is a mild to moderate condition that occurs when cardiac output can no longer be sustained due to competing demands for increased skin blood flow for heat dissipation vs. blood flow to support skeletal muscle contractions and vital organ function. Hypovolemia due to dehydration may contribute to the development of HE. Symptoms typically consist of fatigue, transient ataxia, dizziness, headache, and nausea with most individuals recovering following the cessation of physical activity, removal from the heat, and adequate hydration. EHI is a condition that is intermediate in severity between HE and EHS with patients exhibiting more sustained mild confusion and disorientation. It may be difficult to distinguish EHI from HE during the first few hours of illness without a clinical evaluation for end-organ dysfunction (e.g., acute kidney injury), which is not present with HE. EHI patients will maintain thermoregulatory control, but active cooling is recommended to accelerate organ function recovery. EHS is a serious, life-threatening condition characterized by central nervous system (CNS) dysfunction (e.g., delirium, agitation, inappropriate aggressiveness, convulsions, or coma) that occurs in the presence of severe hyperthermia. The co-occurrence of CNS dysfunction with hyperthermia is necessary to distinguish EHS from other conditions, such as exercise-associated hyponatremia (EAH), that may not present with increased body core temperature but has similar symptomology as EHS at the time of presentation. EAH is a consequence of hyper-hydration and high stress in which antidiuretic hormone levels are often significantly elevated. Symptomology similar to EHS includes acute mental status changes, seizures, coma, headache, confusion, visual disturbances/changes, nausea, and recurrent vomiting. Due to these overlapping

**Table 5.2** Comparison of classic and exertional heat stroke

Patient characteristics	Classic	Exertional
Age	Young children or elderly	15–45 years
Health	Chronic illness common	Usually healthy
Recent febrile illness or immunization	Uncommon	Not uncommon
Prevailing weather	Recent, prolonged heat waves	Variable
Activity	Sedentary	Strenuous exercise
Drug use	Diuretics, antidepressants, anticholinergics, phenothiazines	Usually none, sometimes ergogenic stimulants or cocaine
Sweating	Usually absent	Typically present
Lactic acidosis	Uncommon	Common
Acute kidney injury	Fairly rare (<5%)	Common (~30%)
Rhabdomyolysis	Unusual	Common, may be severe
Hyperuricemia	Mild	Variable
Potassium	Usually normal	Hypo- or hyperkalemia may be present
Calcium	Usually normal	Hypocalcemia not uncommon
Disseminated intravascular coagulation (DIC)	Mild	May be marked
Glucose	Hypoglycemia common	Variable; hyper- or hypoglycemia may be present

features, the presence of hyperthermia with CNS dysfunction is the important distinguishing characteristic of EHS.

Although many of the clinical manifestations of classic heat stroke (CHS) will overlap with EHS, CHS is a condition most commonly experienced by vulnerable individuals, such as the elderly or very young (Table 5.2).

These individuals either have pre-existing conditions (i.e., illness, medication use, cardiovascular insufficiency) or lack the behavioral mechanisms to escape prolonged heat exposure during annual heat waves (e.g., children or pets in vehicles). CHS is a condition that occurs under resting conditions, thus eliminating the influence of skeletal muscle heat production and/or overuse injury from the clinical pathology (i.e., rhabdomyolysis). Perhaps one of the most intriguing aspects of heat stroke, whether exertional or classic in nature, is frequent reports of the victim collapsing under conditions that he/she had been exposed to many times before, or while others were concurrently exposed to the same condition without incident [14, 15]. This suggests that these victims were inherently more vulnerable on that particular day or some unique circumstance triggered the heat stroke event. There are individual and environmental factors that have been recognized to increase heat stroke risk, but it is difficult to “score” or assign cumulative risk since any combination of factors may be present on a particular day and will vary among individuals (Table 5.3).

The main distinction between CHS and EHS is the presence of physical exertion and the participation of skeletal muscles in the etiology of the latter condition. The role that skeletal muscles play in EHS etiology remains debatable, but a consensus is the occurrence of extensive skeletal muscle damage with EHS, a condition that is

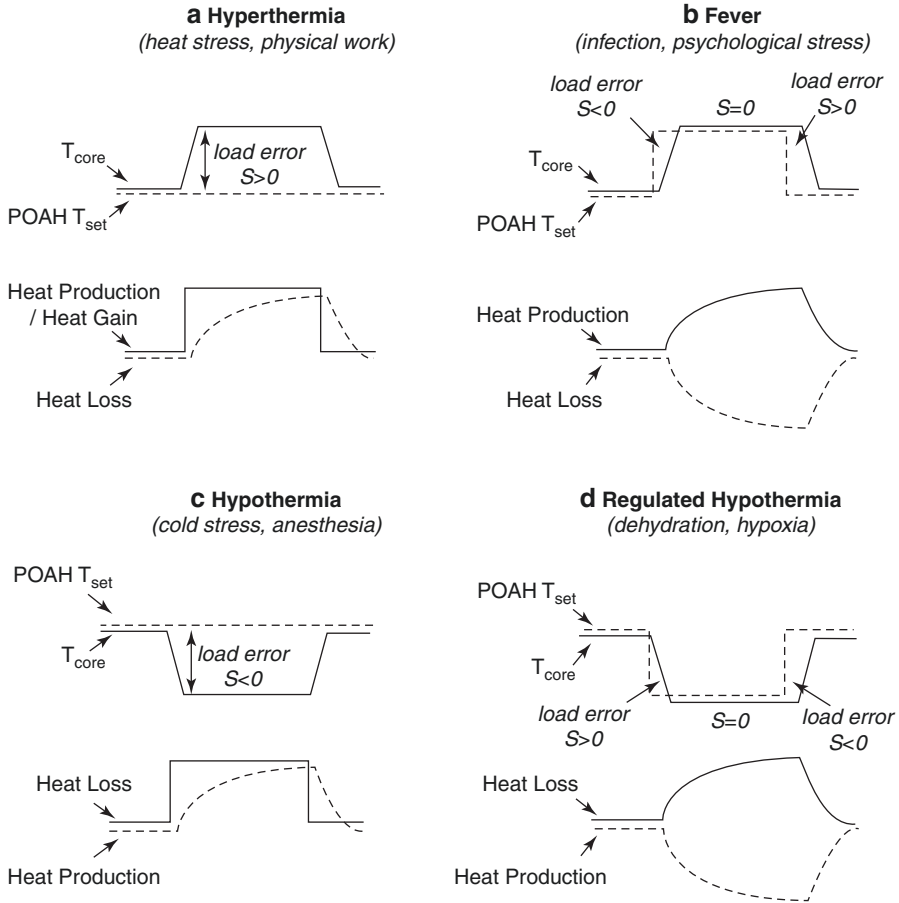
**Table 5.3** Individual and environmental risk factors for exertional heat illness

Congenital	Functional	Acquired
<i>Individual</i>		
Anhidrosis	Low physical fitness	Dehydration
Ectodermal dysplasia	Low work efficiency for task	Sleep deprivation
	High body mass index (BMI)	Infection
	Lack of heat acclimatization	Prior heat illness
		Febrile illness
		Burn graft
		Miliaria rubra/sunburn
		Alcohol use
		Supplement use
		Medication
<i>Environmental</i>		
High ambient temperature/wet bulb globe temperature (WBGT)		
Previous day heat stress		
High humidity		
Lack of air movement		
Lack of access to air conditioning/cool respite		
Lack of shelter or shade		
Clothing		

normally absent in CHS. Clinically relevant muscle damage is also known as rhabdomyolysis which is defined by rapid (*rhabdo*) skeletal muscle (*myo*) breakdown (*lysis*) resulting in the leakage of intramuscular content such as electrolytes, purines, enzymes, and myoglobin into the circulation [16]. As renal failure can be a consequence of rhabdomyolysis, it is considered part of the multi-organ dysfunction that often characterizes EHS. For the remainder of this chapter we will discuss five misconceptions associated with EHS and CHS that have permeated the scientific literature and seem to have clouded our judgement as to the pathophysiologic basis for the devastation that wreaks havoc on multiple organ systems following heat stroke collapse. We present the most current literature on the topic and highlight the evidence, or lack thereof, behind each misconception.

### 5.2.1 Misconception #1: The Severity of Heat Stroke Can Be Defined by a Critical Body Core Temperature Value at the Time of Collapse

Medical textbooks [13], research studies [17–19], athletic position statements [20, 21], and military regulations [22, 23] are almost universal in defining the body core temperature of heat stroke (whether CHS or EHS) as >40 °C. Interestingly, fever during an infectious illness can also cause body core temperature to exceed 40 °C, but does not always invoke the same warnings as heat stroke. Perhaps this is due to regulated (fever) vs. unregulated (hyperthermia) increases in body core temperature being mediated by opposing thermoregulatory and cardiovascular adjustments such that fever is tolerated (in most cases) whereas severe hyperthermia is not (Fig. 5.1).



**Fig. 5.1** Diagrammatic representation of unregulated (left side) and regulated (right side) body core temperature ( $T_{core}$ ) and set point temperature ( $T_{set}$ ) changes in response to environmental stimuli. **(a)** Hyperthermia is an increase in  $T_{core}$  that occurs independent of a change in  $T_{set}$  as heat gain (heat stress) and heat production (physical exertion) are increased. **(b)** Fever is a regulated increase in  $T_{core}$  in response to an upward setting of  $T_{set}$ . **(c)** Hypothermia is the mirror image of hyperthermia, whereas **(d)** regulated hypothermia is the mirror image of fever

Because it has been reported that heat stroke victims collapse with a wide range of body core temperatures, it is now widely recognized that the absolute value is not a sensitive predictor of severity, and what could be considered extreme temperatures are survivable if active cooling is implemented rapidly and effectively. Furthermore, there are reports of highly trained athletes experiencing temperatures as high as  $\sim 42^{\circ}\text{C}$  [4] with no adverse consequences, which is thought to be due to the protective effect of training and acclimation. These examples highlight the complicated nature of heat stroke and indicate that the pathology is not just a consequence of high body core temperature but is due to multiple interacting factors that include

tissue ischemia/reperfusion injury, a systemic inflammatory response syndrome (SIRS), coagulation, and other physiological disturbances.

There are a multitude of factors that may be responsible for the wide range of body core temperature values associated with heat stroke. While it is tempting to rank risk factors according to the magnitude of impact on the heat stress response, the difficulty is that many exist concurrently and in unique combinations that are not always predictable, recognizable (i.e., subclinical infection), or universally present in a population under observation. Physical effort unmatched to physical fitness was identified as a significant risk factor for EHS [24]. In many instances, EHS occurs within the first 2 h of exertion and not necessarily at high ambient temperatures. Additional risk factors may include, but are not limited to, circadian rhythmicity, site of body temperature measurement, different times of clinical presentation, presence of pre-existing or concurrent illness, heat acclimatization state, physical fitness, type of physical activity, clothing ensemble, as well as a number of environmental factors (e.g., solar load, relative humidity; for a thorough review on the topic, see Leon and Bouchama [19]).

The ideal site for the measurement of body core temperature should be convenient, unbiased by the environmental conditions and reflective of small changes in arterial blood temperature. Temperature within a deep body region will vary due to different metabolic rates of surrounding tissues, local blood flow changes, and temperature gradients between adjacent tissues. Skin temperature is the most accessible measurement, but is influenced by changes in blood flow, sweat secretion, environmental effects on heat exchange mechanisms (i.e., evaporative cooling and radiation), or inaccurate measurements such as occurs with a loss of contact with the skin surface [25]. Esophageal temperature is considered the most accurate noninvasive measure of body core temperature in humans because it is rapidly responsive to changes in blood temperature. Unfortunately, this method is not feasible in unresponsive or combative heat stroke patients so other methods must be relied upon under these conditions; because of this limitation, rectal temperature is considered the gold standard for the measurement of body core temperature in heat stroke patients. The only considerations are that rectal temperature will be slightly lower than esophageal temperature because it responds more slowly to transient changes in core temperature, which could result in an underestimation of the response. Interestingly, rectal temperature tends to be  $\sim 0.8$  °C lower than esophageal temperature even during cooling interventions [26]. There is also the procedural caution that perforation of the rectum can occur in those individuals who are not trained in the use of rectal probes. For this reason, many rely on tympanic auditory canal temperatures, which are simple to obtain, but are biased by head skin temperature and provide values that may be higher or lower than steady-state rectal and esophageal temperatures [27, 28].

One of the more intriguing aspects of heat stroke is the remarkable inter-individual (i.e., within a species or strain) variability of the hyperthermic response that is observed during heat exposure. Large inter-individual variability is readily apparent in animal models, despite the absence of pre-existing risk factors (e.g., specific pathogen free or disease free) or their genetic similarity as many are several

generations inbred [29–36]. Despite controlling for immune health, genetic diversity, environmental temperature, humidity and lighting, feed and water intake, body weight and age, there still exists quite wide variability in the maximum body core temperature that is associated with CHS or EHS collapse [20–22, 28]. This has been shown for a number of species including cats, guinea pigs, mice, rats, and salamanders (for a review, see Leon [38]). These findings suggest an inherent variability in how organisms respond to environmental heat stress on any given day, which is difficult if not nearly impossible to predict or define. Basically, something is just different for that organism, whether animal or human, on that particular day relative to other individuals with the same exposure or the same physiological and genetic make-up. It is conceivable that we will never be able to precisely elucidate what those factors are, or when they might arise, but can be sure that reliance on a specific body core temperature value is not the panacea for heat stroke prevention that we wish it to be.

### 5.2.2 Misconception #2: Heat Stroke Causes a “Failure” of Thermoregulatory Control Due to Hypothalamic Injury

Hyperthermia is the body core temperature disturbance that occurs *during heat exposure*, whereas hypothermia and/or recurrent hyperthermia (also referred to as rebound fever) are often observed *during recovery*. In humans, hypothermia is typically a direct response to active cooling that represents a rapidly correctable undershoot of body core temperature (e.g.,  $<37^{\circ}\text{C}$ ). This rebound hypothermia is typically regarded as an adverse response, but there is speculation that a mild hypothermia ( $\sim 32\text{--}34^{\circ}\text{C}$ ) could provide protection against tissue injury as has been shown with cardiopulmonary bypass and other conditions [4, 39]. This rationale has resulted in the suggested practice of inducing hypothermia in the most serious EHS cases as a treatment strategy to protect against liver failure (personal communication to LR Leon). A protective effect of hypothermia has been demonstrated by small rodents that develop protracted (several hours) *regulated* hypothermia ( $<35^{\circ}\text{C}$  and often as low as  $30^{\circ}\text{C}$ ) when left to passively cool in a temperate environment. If rodents are prevented from developing this response, CHS mortality is significantly increased [29]. During the recovery period, a fever-like response ( $\geq 24$  h after collapse) may also be observed, which is typically transient in nature, but can be associated with poor outcome in humans [29, 40].

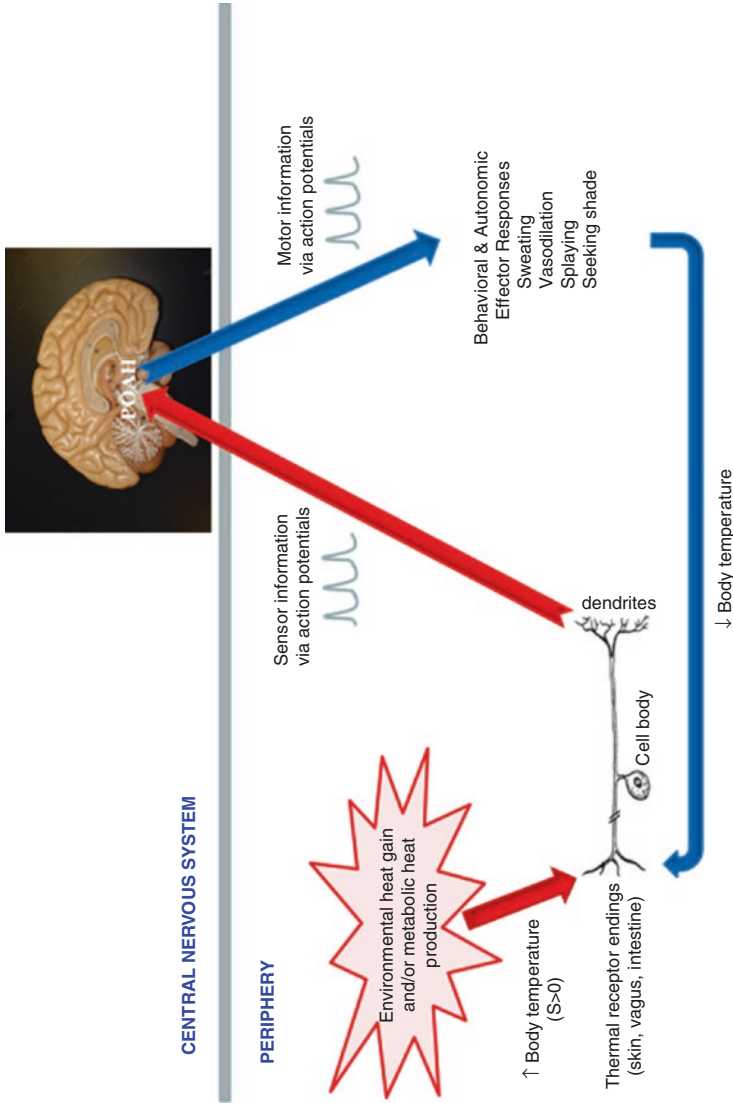
All of the body core temperature disturbances described above have been traditionally regarded, and are still mentioned today, as a reflection of heat-induced injury to the preoptic anterior hypothalamic (POAH) region of the brain, which many consider the main CNS site for temperature regulation. In particular, this hypothesis suggests that prolonged heat exposure causes POAH *injury* that results in a “failure” of thermoregulatory control that manifests as severe hyperthermia during heat exposure as well as hypothermia and/or recurrent fever during heat stroke recovery. We contend that severe hyperthermia during heat exposure is a



consequence of failure of the cardiovascular system to support competing blood flow demands to the skin, organs, and skeletal muscle such that heat dissipation cannot keep up with heat gain and heat production. On the other hand, a recent report in rats showed glutamine and monoamine imbalances that correlated with neuroinflammation in the hypothalamus at the point of collapse with severe CHS [41]. These imbalances may account for transient POAH “dysfunction” that explains the development of hypothermia during the immediate recovery period (e.g., during active or passive cooling). For example, behavioral analysis of severe CHS mice in a temperature gradient indicated that the thermoregulatory feedback loop was altered in some way following collapse—either due to a breakdown of the afferent (sensory) relay of information or inability of the POAH to integrate the sensory information to make corrective effector actions as highlighted in Fig. 5.2 [42].

We are not aware of any permanent disturbances in thermoregulation of severe CHS or EHS patients or animal models that would suggest irreversible thermal injury to the POAH. Furthermore, there are no clinical or experimental data that show injury to the POAH to account for more protracted hypothermia or rebound fever episodes during the days or weeks of recovery. Malamud et al. [43] provided the most striking clinical data from 125 fatal military EHS cases that exhibited no damage to the POAH despite extensive damage to other CNS regions. In fact, there were several noteworthy observations from this study: First, EHS in these patients was defined as CNS dysfunction with body core temperature  $>41.1$  °C, rather than the current definition of  $>40$  °C; second, body core temperature at the time of hospital admission ranged from 36.1 °C, presumably due to active cooling, to 43.9 °C; third, shock rather than the degree of hyperthermia was the best prognostic index; fourth, rises in body core temperature following active cooling (ice packs, etc.) were interpreted as a persistent disturbance in thermoregulation; yet, the lack of demonstrable damage (in the hypothalamus) in these patients differed from injury in other portions of the brain. The emergence of sensitive imaging technologies has provided more detailed examination of the CNS abnormalities experienced by EHS patients but has also failed to detect damage to the hypothalamus despite detectable, and in some cases, quite severe injury to the cortex, thalami, paraventricular nucleus, cerebellum, and third ventricle [44, 45].

While the hypothalamus may not be grossly damaged, investigators have shown increases in pyknotic neurons along with significant elevation in inflammatory mediators such as NF- $\kappa$ B, interleukin (IL)-1 $\beta$ , cyclooxygenase (COX)2, and glial fibrillary acidic protein (GFAP) following severe heat stress [41]. Similarly, there is a body of literature that contends heat stroke is due to damage caused by brain ischemia, inflammation, and neuronal damage [36, 37]. While inflammatory markers are increased following heat stress, it is still unknown if this is the cause of temperature dysregulation at the time of collapse. Obtaining these data in human populations will prove to be challenging, as heat stroke is unpredictable and collecting data at the point of collapse especially in an area such as the hypothalamus is difficult, if not impossible.



**Fig. 5.2** Negative feedback loop of body core temperature regulation. Thermal receptor endings in the skin and other anatomical sites detect increases in skin and body core temperature during environmental heat stress and/or metabolic heat production (exercise). Sensory information is sent via action potentials through ganglions to the POAH. The POAH acts as a thermoregulatory integration center and compares peripheral temperature changes to the set point temperature. A load error is generated that evokes graded behavioral and autonomic effector responses to aid in the dissipation of heat for the return of body core temperature toward homeostasis

### 5.2.3 Misconception #3: Hyperthermia During Heat Exposure Is a Fever Response to Endotoxin Leakage from the Gut and/or Leakage of Intramuscular Content

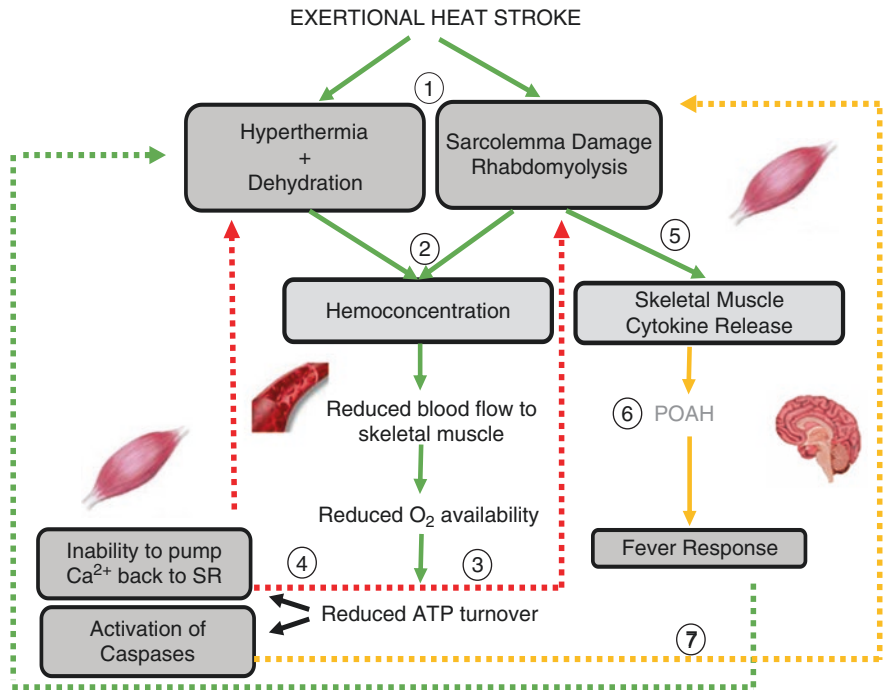
One of the major misconceptions regarding CHS or EHS is that endotoxemia, or the presence of endotoxin in the circulation, is a universal phenomenon observed in all animal models and patients. This misconception was based on early reports that showed reductions in splanchnic blood flow at temperatures as low as 40 °C [46], which falls in line with the definition of heat stroke. As blood flow is diverted from the splanchnic circulation to the skin for heat dissipation, gut epithelial membranes experience nitrosative and oxidative stress that degrades tight junction integrity to facilitate endotoxin leakage into the portal circulation. Whereas the liver reticuloendothelial system normally clears endotoxin, under severe CHS or EHS conditions, heat-induced dysfunction or injury to the liver may compromise the ability to perform this function. It is under these severe conditions, often associated with liver failure, that endotoxemia has been observed. For example, a young football player who collapsed and died from EHS presented with significant endotoxemia as well as hemorrhagic liver necrosis and body core temperature of 40.6 °C [47]. Similarly, circulating endotoxin showed a precipitous increase in primates under CHS conditions once body core temperatures exceeded the fatal level of 43.0 °C [48]. Liver injury was not assessed in this study, but is typically detectable at body core temperatures ranging from ~ 42 to 43 °C [49–51]. Endotoxin neutralization studies in dogs, rabbits, and rats have shown a protective effect of antibiotics and endotoxin tolerance against heat stroke mortality, but once again these were lethal models with temperatures at or above the threshold where liver injury would be expected [48, 52, 53]. In contrast to these studies, a mouse CHS model that induced body core temperature as high as 42.7 °C did not correlate with detectable levels of circulating endotoxin despite significant gut histological injury [29, 37]. This was mostly likely due to a lack of liver injury, once again supporting the hypothesis that dysfunction of this organ is a primary mechanism for endotoxemia. Similarly, Chung et al. [54] failed to show increased endotoxin in former heat stroke patients who were subsequently exposed to a 60-min heat stress that only caused body core temperature to increase to <39.5 °C.

We propose three alternative interpretations for the role of endotoxin in the heat stroke response. First, endotoxemia is not a universal phenomenon and is manifest under the most severe, typically chronic exposure conditions that lead to organ (primarily liver) failure. As mentioned above, this has been shown in several animal models and patients, although it does conflict with several recent reports showing a correlation between indirect biomarkers of gut leakage (namely, intestinal fatty-acid binding protein, or I-FABP) with endotoxin-like symptoms with exercise heat-stress or EHS [30]. However, caution is warranted in the interpretation of these findings due to the potential lack of sensitivity and specificity of I-FABP (or other biomarkers) as measures of endotoxin leakage and reliance on correlation studies that do not equate to causality. Second, we do not believe that endotoxin leakage is a major contributor to hyperthermia *during heat exposure* under most

conditions (i.e., lack of pre-existing conditions or significant organ injury). That is, there is little evidence to support the contention that endotoxin leakage during heat exposure is inducing an increase in the POAH temperature set point for fever development. This is based on a number of studies that have failed to show a consistent effect of non-steroidal anti-inflammatory drugs (NSAIDs, i.e., fever inhibitors) on the hyperthermic response during heat exposure. NSAIDs are a class of over-the-counter and prescription drugs that are the most widely prescribed worldwide. NSAIDs efficacy for improved heat tolerance (*during heat exposure*) has been examined in animal models and men working in hot environments with contradictory results. In animal models, indomethacin (a prescription NSAID) or sodium salicylate (aspirin) improved heat tolerance by inducing a lower rate of body core temperature rise, suggesting this was at least partially a true fever response [55, 56]. Prostaglandins (PGs), which are the main mediators of endotoxin-induced fever, have been shown to contribute to active cutaneous vasodilation in humans suggesting their release via endotoxin stimulation in the heat could affect hyperthermia and heat tolerance [57, 58]. However, Jacobsen and Bass [59] failed to show an effect of a high chronic dose of sodium salicylate on skin temperature or pulse rate of men walking in a hot environment, yet the hyperthermic response was *potentiated* (rather than inhibited) suggesting an alternative mechanism for this response [59]. More recently, Audet et al. [32] showed that indomethacin had no effect on the body core temperature response of mice during the development of CHS, but significantly increased mortality due to toxic effects on the gut mucosa that caused excessive hemorrhaging. Given that many athletes use NSAIDs as potential performance enhancing drugs, the advantage of this strategy for heat mitigation is questionable and the probability of gut injury is concerning. One can suppose that under conditions of NSAIDs usage with heat exposure, endotoxemia, fever, and gut and/or liver injury are likely consequences.

The third intriguing possibility is that extensive skeletal muscle damage (i.e. rhabdomyolysis) during exercise triggers a pyrogenic response similar to fever [60, 61] leading to further increases in body core temperature and EHS—note that in this instance, exertional rhabdomyolysis is inducing a regulated increase in body core temperature that is distinct from the hyperthermia induced by heat stress or endotoxemia per se. Fever is caused by the release of endogenous pyrogens (e.g., IL-1 $\beta$  and IL-6, among others; reviewed in [62]) that leads to a subsequent rise in PGs. PGs, whether produced systemically or locally within the POAH, raise the thermoregulatory set point triggering multiple behavioral and autonomic responses to induce fever. Endogenous antipyretics such as arginine vasopressin, glucocorticoids, IL-10, and TNF- $\alpha$  are also released to modulate fever and prevent it from reaching dangerous levels [62, 63]. Conversely, hyperthermia due to exertion and heat stress occurs because the metabolic heat production of active skeletal muscles and the environmental source of heat surpasses the body's capacity to exchange heat to the surroundings, thus driving an increase in body core temperature (Fig. 5.3).

Patients with exertional rhabdomyolysis often exhibit fever symptoms, which may be a consequence of skeletal muscle damage that induces a fever in the absence of environmental heat stress. That is, the pyrogenic response may be elicited directly



**Fig. 5.3** Integrative model of EHS. (1) EHS is associated with whole-body hyperthermia and (sometimes) dehydration and sarcolemma damage; (2) reductions in plasma volume and leak of intracellular content lead to hemoconcentration; (3) reduced ATP turnover due to reduced blood flow and oxygen delivery to skeletal muscle leads to (4) inability to pump calcium back to the sarcoplasmic reticulum and activation of caspases; (5) this results in sustained muscle contractions and further sarcolemma damage which leads to (6) cytokine release into the circulation leading to (7) fever response via POAH in the CNS which further enhances hyperthermia and dehydration. The arrows stand for a “traffic light” system where red = poor evidence; yellow = some evidence; and green = strong evidence

by cytokines released from inflammatory cells as well as skeletal muscle [64–66]. The stimulus for cytokine release by skeletal muscle may be an increased epinephrine and norepinephrine response [67, 68], triggered by exercise of sufficient intensity, and/or via direct sarcolemma damage [69]. An alternative pathway for cytokine release from skeletal muscle may arise from the presence of endotoxin in the circulation as mentioned earlier in this section. Endotoxemia has been observed in more chronic CHS, although not universally (see above) [70], and has been shown to lead to cytokine release (i.e., IL-6, IL-1 $\beta$ , IL-8) from inflammatory cells and other tissues including skeletal muscle. Cytokines released into the circulation can trigger PG production via COX enzyme with PGE<sub>2</sub> considered the main mediator of fever [61]. Evidence for exercise-induced muscle damage that induces a pyrogenic response is provided in studies that administered NSAIDs in exercising humans and rodents [61, 71, 72]. NSAIDs block COX activity and have been shown to halt the increase in body core temperature during exercise in temperate environments

suggesting that a component of the elevation in body core temperature may partly have a fever-like origin [61, 72]. On the other hand, the use of NSAIDs during exposure to heat stress has been shown to enhance organ damage while having no effect on the rise in body core temperature (i.e., hyperthermia rather than fever) during heat exposure [32]. Another point worth highlighting is that pyrogenic cytokines are also observed in CHS [36], which suggests that tissues other than the skeletal muscle, presumably inflammatory cells, are major players in this form of elevated body core temperature. Nevertheless, the extent by which the exercise-induced pyrogenic response is enhanced by skeletal muscle damage and thus contributes to hyperthermia leading to EHS is not yet known and warrants further investigation.

#### **5.2.4 Misconception #4: Cytokines Are Adverse Mediators of the Systemic Inflammatory Response Syndrome**

The severity of multi-organ dysfunction with EHS is thought to be a consequence of cytokines, such as IL-6, that induce a SIRS. IL-6 and TNF- $\alpha$  are typically regarded as pro-inflammatory (e.g., adverse) mediators of the SIRS due to studies that have demonstrated endotoxemia- or sepsis-like symptoms and initiation of the acute phase response following injection, as well as the correlation of high circulating levels with heat stroke severity in clinical and laboratory settings [47, 73, 74]. The misconception that cytokines are solely adverse mediators of the SIRS, and do not provide any protective advantage, is based almost exclusively on correlation studies that have shown high circulating concentrations (e.g., IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$ ) with morbidity and mortality, which is more evident in CHS than EHS [17, 70, 75–80]. The most consistent observation has been the correlation of high circulating IL-6 levels with heat stroke death in primates and patients. IL-6 is typically elevated in 100% of CHS patients [75], levels tend to be highest in those who do not survive [75, 77, 79], and sustainment of high IL-6 levels during cooling in primates correlated with heat stroke severity [17, 75]. Yet, there are two aspects of these studies that warrant caution in our interpretation of cytokines (IL-6 or others) in the heat stroke syndrome: First, the majority of the early CHS studies showed a (typically weak) correlation of high circulating cytokine levels with heat stroke symptoms, but failed to show a causal relationship between these responses. Whereas more recent animal studies have closed this gap and shown, with the use of exogenous cytokine treatment or gene knockout technology, that IL-6 and TNF have protective functions that enhance performance in the heat and improve survival during recovery, respectively [81, 82]. As such, IL-6 and TNF- $\alpha$ , as well as other cytokines, appear to have both pro- and anti-inflammatory actions that depend on the cytokine milieu in which they function as well as the concentration that is achieved (likely) at the local, tissue level [38]. Second, the contribution of circulating soluble cytokine receptors on the actions of these proteins has virtually been ignored, despite early evidence of their potential protection for CHS survival. For example, CHS survivors had higher levels of soluble TNF receptors (sTNFRs; natural antagonists of TNF actions) than non-survivors, suggesting a detrimental effect of high TNF levels in

these patients [77]. Note that the binding of TNF to the sTNFR occurs only at high concentrations suggesting that the pro-inflammatory effects are concentration-dependent. The soluble IL-6R (sIL-6R) plays a different role in that it will integrate into cell membranes that do not contain the receptor to make them responsive to IL-6 via ubiquitously expressed glycoprotein 130 (GP130) receptor. The role of the sIL-6R in CHS pathophysiology has not been clearly delineated, but increased circulating sIL-6R correlated with effective cooling in patients supporting a protective effect on outcome.

Clearly, additional research is needed to understand the complex nature of cytokine actions in CHS and EHS. Not only are current misconceptions based primarily on correlation studies, but the differences in the etiology and time course of cytokine responses between CHS and EHS suggest that these immune modulators may function differently with these two conditions. Perhaps the misunderstanding of cytokine actions in heat stroke is based on their known role with endotoxemia, which has always been considered the initiating stimulus for the SIRS. As new research unfolds to further delineate the role of endotoxin and novel approaches continue to be employed to study cytokine actions, the interplay of these responses will become clearer.

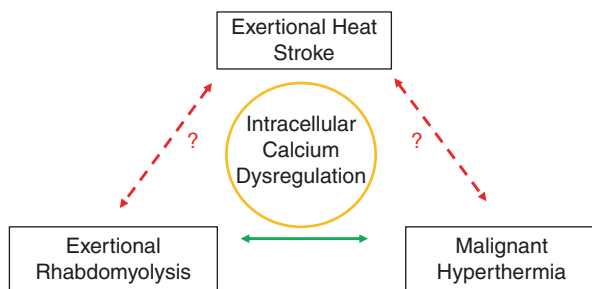
### **5.2.5 Misconception #5: EHS, Exertional Rhabdomyolysis, and Malignant Hyperthermia Are Triggered by Similar Mechanisms of Calcium Dysregulation in the Skeletal Muscle**

Controversy exists regarding the molecular events resulting in extensive sarcolemma damage leading to clinically relevant exertional rhabdomyolysis, mainly when it is associated with EHS, but these events seem to involve intracellular calcium ( $\text{Ca}^{2+}$ ) dysregulation of some sort. For instance, exertional rhabdomyolysis is believed to share similarities with another myopathy known as malignant hyperthermia (MH) [8, 83, 84]. MH is a reaction triggered by anesthetic drugs (e.g., halothane, enflurane, isoflurane, sevoflurane, desflurane) that causes sustained skeletal muscle contractions (in a positive feedback loop) that drive body core temperature toward heat stroke levels if not rapidly treated. The syndrome is associated with a mutation in the ryanodine 1 receptor (RyR1), which causes dysregulation in  $\text{Ca}^{2+}$  homeostasis, namely, increased  $\text{Ca}^{2+}$  influx in skeletal muscle. This influx of  $\text{Ca}^{2+}$  triggers skeletal muscle contractions resulting in metabolic heat production that can lead to severe whole-body hyperthermia. Presumably, this  $\text{Ca}^{2+}$  dysregulation due to mutation of the RyR1 receptor in the sarcoplasmic reticulum would be present in those at increased risk of EHS and exertional rhabdomyolysis and this would conveniently separate responders and non-responders in terms of susceptibility to these conditions [85, 86]. The majority of evidence for this relationship among MH, exertional rhabdomyolysis, and EHS comes from case reports [87, 88]. For instance, Hopkins et al. reported a case where two men in the military service, who previously experienced EHS episodes, tested as MH susceptible after their skeletal

muscle samples were submitted to an *in vitro* contracture test (IVCT) in response to caffeine and halothane challenges. The authors concluded that abnormalities seen in both EHS and MH were similar, but not identical [88]. Tobin et al. [87] suggested an association between MH and EHS with a case report of a 12-year-old boy who displayed signs of MH during surgery for a humerus fracture. Eight months later, the boy displayed signs and symptoms of EHS after a football match-play at an ambient temperature of 26 °C. Body core temperature at the time of arrival at the hospital was >42.2 °C. Postmortem analysis of the DNA from the patient, and their parents, revealed mutations of the RyR1 gene [87]. Wrappler et al. observed an association between exertional rhabdomyolysis and MH by performing IVCT in patients with previous history of exertional rhabdomyolysis. Ten out of 12 subjects with previous episodes of exertional rhabdomyolysis were classified as MH-susceptible [84]. Even though these studies indicate a possible association among EHS, exertional rhabdomyolysis, and MH, the sample size was too small to establish causality. More recently, a study explored the link between EHS and MH in a larger cohort of subjects [12]. Skeletal muscle samples were collected from military personnel who previously experienced EHS and submitted the skeletal muscle samples to an IVCT. Authors observed a high prevalence of MH susceptibility in those who experienced EHS previously, presumably indicating that Ca<sup>2+</sup> dysregulation is part of the EHS syndrome. Indeed, there is no direct evidence of Ca<sup>2+</sup> dysregulation in EHS, at least when exertional rhabdomyolysis is absent. Even though exertional rhabdomyolysis could be part of the multi-organ dysfunction that often characterizes EHS, and perhaps those with a genetic mutation are at elevated risk of developing EHS and exertional rhabdomyolysis, there are several aspects of exertional rhabdomyolysis and EHS that are incongruent with the conclusion that these syndromes share similar mechanisms related to RyR1 myopathy such as MH. In summary, MH, exertional rhabdomyolysis, and EHS may display a common feature of loss of intracellular Ca<sup>2+</sup> control (although yet to be demonstrated with EHS), it is unlikely that they share a single common genetic predisposition. As pointed out later in this chapter, there are other features of both EHS and exertional rhabdomyolysis that can trigger intracellular Ca<sup>2+</sup> dysregulation and are independent of a MH genotype (Fig. 5.4).

EHS involves a physiological crisis characterized by increased energy demand, whole-body hyperthermia, and often sweat-induced dehydration, all of which can

**Fig. 5.4** Intracellular calcium dysregulation is a common feature of both exertional rhabdomyolysis and malignant hyperthermia. But whether it is present in exertional heat stroke requires further evidence





potentially result in exertional rhabdomyolysis, as highlighted in Fig. 5.3, and other stress responses such as reactive oxygen species formation as reviewed by King et al. [89]. The misconceptions concerning EHS-related rhabdomyolysis revolve around the extent by which each of these factors contributes to the exertional rhabdomyolysis syndrome in those experiencing EHS. A potential alternative mechanism involved in exertional rhabdomyolysis and EHS is the fact that hyperthermia decreases muscle blood flow due to a competition for the available cardiac output between skin, for thermoregulation, and active muscles, which can make skeletal muscles ischemic during exercise [90]. A reduction in O<sub>2</sub> delivery decreases ATP turnover in muscle—despite a reported compensatory increase in O<sub>2</sub> extraction in hyperthermia [91]—which can presumably increase intramuscular Ca<sup>2+</sup> content due to an inability to actively transport Ca<sup>2+</sup> back to the endoplasmic reticulum. Increased intramuscular Ca<sup>2+</sup> leads to the activation of proteolytic enzymes (i.e., caspases) that contribute to skeletal muscle breakdown seen in exertional rhabdomyolysis.

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### 5.3 Conclusion

We have focused on the five most common misconceptions regarding heat stroke that arise from a combination of lack of evidence, the misinterpretation of inconclusive studies, and reliance on other conditions with similar pathophysiology as CHS or EHS. There are extensive data in the literature indicating that the body core temperature response to heat exposure varies widely and is not a sensitive predictor of CHS or EHS. Due to a variety of different thermoregulatory disturbances at the time of collapse, or during the early periods of recovery, heat stroke has been thought to cause injury to the POAH, which is considered the main thermoregulatory center of the brain. This misconception persists despite autopsy of 125 military EHS patients who showed that the POAH was the one region of the brain that did not experience overt injury. It is possible that the technique used to examine injury at that time was not advanced to detect subtle changes, yet more sophisticated imaging techniques continue to support those original findings from over 70 years ago. Why the misconception that the POAH is damaged continues to persist today remains a mystery. Cytokine release in response to endotoxemia has been purported by many authors (including those of this chapter) to be key stimulators of the SIRS with heat stroke. However, perhaps the error on our part has been to present that hypothesis as a universal finding, whereas data are showing that endotoxemia is not a universal finding and cytokines can be both pro- and anti-inflammatory in their actions. Finally, even though extensive rhabdomyolysis is part of the EHS syndrome, there is no evidence that intramuscular content leakage leads to a pyrogenic response that contributes to EHS. Furthermore, EHS, exertional rhabdomyolysis, and MH do not share a single mutation (i.e., RyR1 receptor), even though calcium dysregulation may be present in each syndrome. The take home message from this summary of misconceptions is that heat stroke is a complex condition with multiple, overlapping etiologies and mechanisms that are not readily understood and continue to perplex physicians and researchers in terms of the most effective prevention (beyond cooling) and

treatment strategies. While initially disappointing to realize, we view this as an exciting opportunity to explore new methodologies and approaches to solve this mystery once and for all!

**Disclaimers** The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense. Any citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement of approval of the products or services of these organizations.

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