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Integrated Physiological Mechanisms of Exercise Performance, Adaptation, and Maladaptation to Heat Stress

Michael N. Sawka,[*1] *Lisa R. Leon,*[1] *Scott J. Montain,*[1] *and Larry A. Sonna*[2]

ABSTRACT

This article emphasizes significant recent advances regarding heat stress and its impact on exercise performance, adaptations, fluid electrolyte imbalances, and pathophysiology. During exercise-heat stress, the physiological burden of supporting high skin blood flow and high sweating rates can impose considerable cardiovascular strain and initiate a cascade of pathophysiological events leading to heat stroke. We examine the association between heat stress, particularly high skin temperature, on diminishing cardiovascular/aerobic reserves as well as increasing relative intensity and perceptual cues that degrade aerobic exercise performance. We discuss novel systemic (heat acclimation) and cellular (acquired thermal tolerance) adaptations that improve performance in hot and temperate environments and protect organs from heat stroke as well as other dissimilar stresses. We delineate how heat stroke evolves from gut underperfusion/ischemia causing endotoxin release or the release of mitochondrial DNA fragments in response to cell necrosis, to mediate a systemic inflammatory syndrome inducing coagulopathies, immune dysfunction, cytokine modulation, and multiorgan damage and failure. We discuss how an inflammatory response that induces simultaneous fever and/or prior exposure to a pathogen (e.g., viral infection) that deactivates molecular protective mechanisms interacts synergistically with the hyperthermia of exercise to perhaps explain heat stroke cases reported in low-risk populations performing routine activities. Importantly, we question the "traditional" notion that high core temperature is the critical mediator of exercise performance degradation and heat stroke. © 2011 American Physiological Society. *Compr Physiol* 1:1883-1928, 2011.

Introduction

Humans are tropical animals, and given access to shade and adequate water, healthy acclimated persons can tolerate extended exposure to virtually any naturally occurring environmental heat stress. By contrast, many occupational and military situations involve heat-stress conditions (due to microenvironments and/or performing strenuous muscular exercise) so severe that they cannot be tolerated for extended periods. Environmental heat stress increases the requirements for skin blood flow and sweating to dissipate body heat; when the environment is warmer than the skin, the body gains heat from the environment thus increasing the amount of heat that needs to be dissipated. Muscular exercise increases metabolic rate above resting levels, and also increases the rate at which heat must be dissipated to the environment. Even without environmental heat stress, muscular exercise can require a high cardiac output to support metabolism. When heat stress is combined with muscular exercise, the cardiovascular system may be pushed to its limit to simultaneously support the competing thermoregulatory demands for skin blood flow and metabolic demands of the contracting skeletal muscles. Therefore, environmental heat stress and muscular exercise can interact synergistically to degrade performance and induce serious heat illness.

Previous Handbook of Physiology articles in *Comprehensive Physiology* have provided detailed historical reviews regarding human thermoregulation and acclimation to heat stress (216, 220, 359), cardiovascular and endocrine adjustments (120, 192), and heat stroke (157); however, within the past decade, significant advances have been made regarding aerobic exercise performance in the heat, fluid-electrolyte needs during exercise-heat stress, molecular adaptations to exercise-heat stress, and pathophysiological events associated with exertional heat stroke. This article will review: (i) normal physiological responses to exercise-heat stress; (ii) the impact of heat stress on degrading aerobic exercise performance; (iii) newly identified adaptations associated with heat acclimation/acquired thermal tolerance that impact exercise-heat tolerance; (iv) new quantitative information regarding potential fluid-electrolyte imbalances during exercise-heat stress;

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Table 1 Risk of Hyperthermia (and Possible Exertional Heat Illness) for a Typical Marathon Racer Based on Wet Bulb Globe Temperature (WBGT) and Relative Humidity (RH)

Level of risk	Color code (Flag)	WBGT (@ RH of 100%)	WBGT (@ RH of 75%)	WBGT (@ RH of 50%)
Excessive	Black	>28°C	>29°C	>33°C
High	Red	24-28°C (73-82°F)	26-29°C (77-85°F)	28-33°C (82-92°F)
Moderate	Amber	18-23°C (65-72°F)	20-25°C (68-76°F)	24-27°C (75-81°F)
Low	Green	<18°C (<65°F)	<20°C (<68°F)	<24°C (<75°F)
Very low (some risk)	White	<10°C (<50°F)	<10°C (<50°F)	<10°C (<50°F)

Adapted from Gonzalez (141).

and (v) emerging insights into the etiology and pathogenesis of exertional heat stroke.

Heat Stress and Strain

Heat stress refers to environmental (including clothing) and metabolic conditions that tend to increase body temperatures; heat strain refers to physiological (e.g., body temperature) consequences of heat stress. The biophysical properties posed by the environment and clothing will determine if heat stress can be categorized as compensable heat stress (CHS) or uncompensable heat stress (UCHS) (126, 359). CHS exists when heat loss occurs at a rate in balance with heat production so that a steady-state core temperature can be achieved at a sustainable level for a requisite activity. CHS represents the vast majority of situations encountered by workers and athletes. UCHS occurs when the individual's evaporative cooling requirements exceed the environment's evaporative cooling capacity. During UCHS, an individual cannot adequately dissipate metabolic heat, so body temperature (heat strain) continues to increase until the person becomes exhausted or removes themselves from the UCHS situation (363). Examples of UCHS include boiler room work, wearing heavy protective clothing during activities in hot weather, and performing firefighting near the active fire.

Environmental heat stress and exchange

Wet Bulb Globe Temperature (WBGT) is commonly used to quantify environmental heat stress in occupational, military, and sports applications (141). The outdoor and indoor WBGT, natural wet bulb, dry bulb, and black globe temperature are related in the following manner:

1. outdoor WBGT = 0.7 natural wet bulb + 0.2 black globe = 0.1 dry bulb, and

2. indoor WBGT = 0.7 natural wet bulb + 0.3 black globe.

WBGT is an empirical index of climatic heat stress originally developed for resting comfort and later adapted for physical exercise. WBGT does not include any considerations for clothing or exercise intensity (metabolic rate) so it cannot predict heat exchange between a person and the climate.

During summer months, many geographical regions have WBGT values above 29°C (85°F) either through high humidity, as reflected in high wet bulb temperature, or through high air (dry bulb) temperature and solar load, as reflected in black globe temperature. By contrast, many occupational and military tasks are conducted in WBGT conditions above 35°C, such as in deep mining, boiler room work, and fire-fighting. In humid conditions, the WBGT underestimates heat stress risk, so different guidance indices should be used. Table 1 provides the relative risk of excessive hyperthermia and possibly heat illness for an athlete competing in a marathon race in hot weather (141). These WBGT risk levels are consistent with the number of marathon runners unable to finish the race and requiring medical attention from heat illness (331).

Physical exercise can increase metabolic heat production by 3- to 12-fold above the resting rate (~100 watt). Since skeletal muscle contraction is ~20% efficient, ~80% of expended energy is released as heat and must be dissipated from the body to avoid heat storage and increasing body temperature. To direct the heat to the periphery for subsequent dissipation to the environment, cardiovascular adjustments redirect blood flow from the body core to periphery. The heat delivered to the skin is transferred to the environment by conduction, convection, radiation, and evaporation. The effectiveness of these pathways is dependent on the biophysical properties of the environment (e.g., air or water) and include the temperature difference between the skin surface and the environment, the evaporative potential and solar conditions (126).

The nonevaporative (conduction, convection, and radiation) avenues are often collectively called dry heat exchange. Conduction is heat transfer between two solid objects in direct contact, and convection is heat exchange between a surface and a fluid, including air or water. Heat exchange by conduction or convection will occur as long as there is a temperature gradient between the body surface and contacting solid object or surrounding fluid. When in a standing position (walking or running) and wearing shoes, heat exchange by conduction is minimal, because the thermal gradients between the body and contacted solids are usually small. Convective heat exchange is facilitated if the surrounding medium (air or fluid) is moving (e.g., wind and water circulation) relative to the body surface. In air environments, convective heat transfer

can be significantly increased by wind (if clothing does not create a barrier), and for swimmers convective heat loss can be very large even when the difference between body surface and surrounding fluid temperature is small, since water's heat capacity is much greater than that of air (410). Heat loss by convection to air or water occurs when the air/water temperature is below body temperature; conversely, heat gain by convection from air or water occurs when the temperature exceeds that of the body.

Heat gain by radiation occurs when surrounding objects have higher surface temperatures than body surface temperature; and heat loss by radiation occurs when surrounding sun, sky, ground, or other large natural or manmade objects have lower surface temperatures than the body. The sense of warmth felt on very sunny days in mid-winter is an example of radiative heat gain. Evaporative heat loss occurs when liquid water phase changes into water vapor. When water is secreted onto the skin surface via sweat glands, accumulated on the skin by rain or splashing or evaporates from respiratory passages, the kinetic energy of the added water molecule motion (i.e., the latent heat of evaporation) removes body heat. Evaporative cooling is the primary means of heat removal during exercise, and is the sole means of heat removal when ambient temperature is equal or above skin temperature.

The interplay between factors that increase or decrease heat production and heat removal and the consequent impact on body heat storage is evident in the heat balance equation: $S = M - (\pm W) \pm (R + C) \pm K - E$, in which S = rate of body heat storage; M = rate of metabolic energy (heat) production; W = mechanical work, either concentric (positive) or eccentric (negative) exercise; $R + C$ = rate of radiant and convective energy exchanges; K = rate of conduction (important only when in direct contact with an object, such as clothing, or a substance, such as water); and E = rate of evaporative loss. The sum of these, heat storage, represents heat gain if positive, or heat loss if negative. Body temperature increases when S is positive, decreases when S is negative and remains constant when S equals zero (126).

Core, muscle, skin temperatures, and body heat content

Fundamental to the experimental study of human temperature regulation is the measurement of body core temperature. Core temperature is measured to either estimate input to thermoregulatory control, or to estimate average internal temperature to compute changes in heat storage (359). Brain (i.e., hypothalamic) temperature during exercise is probably similar or slightly higher than blood temperature (301). There is no one "true" core temperature because temperature varies among different sites inside the deep body. The temperature within a given deep body region depends upon: (i) the local metabolic rate of the surrounding tissues, (ii) the source and magnitude of local blood flow, and (iii) the temperature gradients between contiguous body regions. Considerable temperature gradients exist between and within different orifices, body cavities, and blood vessels.

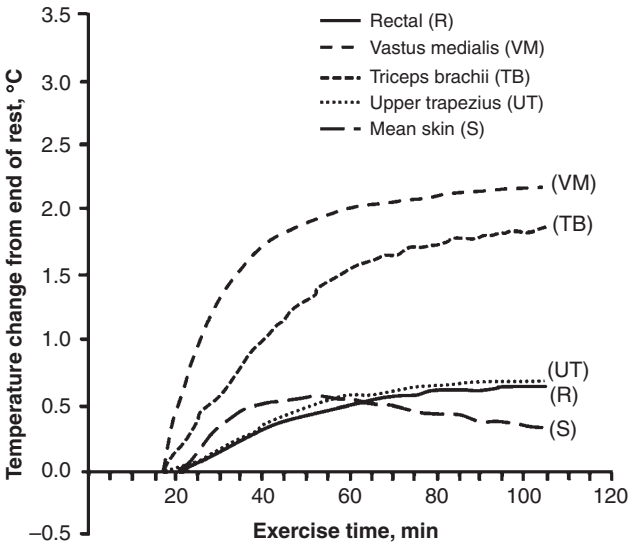

Figure 1 Active (vastus medialis) and inactive (triceps brachii) muscle temperatures relative to core and mean skin temperature changes during exercise. Reprinted (with permission) from Jay et al. (186).

For resting humans, internal organs and viscera within the body core produce about 70% of the metabolic heat. During dynamic exercise, however, skeletal muscles produce up to about 90% of the metabolic heat. Because metabolic heat sources change during exercise as compared to rest, temperature changes measured in one body region during exercise may be disproportionate to changes measured in other body regions. For example, during rest in a temperate environment, skeletal muscle temperature is lower than core temperature, but during exercise, the temperature within active skeletal muscle usually exceeds core temperature (203, 348). Figure 1 provides active (vastus medialis) and inactive (upper trapezius) muscle temperatures relative to core and mean skin temperatures during rest and exercise (186). While active skeletal muscles rapidly warm during exercise, the inactive skeletal muscles demonstrate only a modest increase in temperature (186). In addition, the active skeletal muscles have larger temperature increases medially than superficially (348). Blood that perfuses active skeletal muscles is warmed and carries the heat to other body regions, which consequently elevates core temperature.

Core temperatures vary among internal measurement sites. An ideal measurement site for core temperature should be convenient and unbiased by environmental conditions, and should rapidly and quantitatively reflect small changes in arterial blood temperature. Thermal physiologists often measure core temperature in the esophagus, rectum, gastrointestinal tract, tympanum, and auditory canal. Esophageal temperature responds rapidly and quantitatively to changes in central blood temperature and most thermal physiologists consider esophageal temperature to be the best noninvasive index of

core temperature for humans. Rectal temperature is slightly higher than esophageal values, and responds more slowly to rapid transients in core temperature, for example, the onset of exercise. Gastrointestinal "pill" temperatures provide similar steady-state values as rectal temperature, and respond more slowly than esophageal but faster than rectal measures (209); however, "pill" temperature values are more variable due to location changes as the pill travels within the gastrointestinal tract (152). Tympanic auditory canal temperatures can be either lower or higher than steady-state rectal and esophageal values, because tympanic-auditory canal temperatures are biased by head skin temperature (154, 252). Temporal artery temperature scans have been shown to be unrepresentative of either rectal or "pill" temperature either during or after exercise (64, 129 241, 336).

Skin temperature is measured for the purposes of: (i) calculating the mean body temperature for heat storage determinations, (ii) calculating sensible (radiative and convective) heat exchange and skin conductance, (iii) calculating skin blood flow requirements, and (iv) integrating an index of the skin temperature input to the thermoregulatory controller. Although the skin surface is easily accessed (unlike the core), measurement problems can occur because the skin represents the boundary between two media, tissue, and the ambient air. As a result, changes in skin temperature might result from physiological adjustments (cutaneous blood flow, sweat secretion, and evaporation) or alterations in the environment (air motion, temperature, and radiation). Generally, skin temperatures are measured from temperature sensors in contact with the skin's surface or from non-contact infrared methods. For the former method, care needs to be taken to insure that the temperature sensor remains in good thermal contact with the skin, since otherwise the measurement will be biased by the ambient temperature (382).

Although a single skin temperature measurement can be useful for biophysical calculations, thermal physiologists are more often interested in the average or mean skin temperature. The mean skin temperature represents the sum of weighted individual skin temperatures. Generally, the weighting is based on the percentage of body surface area that is represented by the body region from where the temperature is measured (259). For example, Hardy et al. (161) divided the body into 12 regions while Winslow and colleagues (432) divided the body into 15 regions for skin temperature measurements. Numerous investigators subsequently attempted to minimize the number of measurement sites necessary to obtain a valid estimate of mean skin temperature (259) and compared nine of these shortened equations which are used to estimate mean skin temperature. They recommended that when it is difficult to measure a large number of sites, the equation developed by Ramanathan (326) be used, where: mean skin temperature, $^{\circ}C = 0.3$ (chest + upper arm temperatures) + 0.2 (thigh + calf temperatures).

Mean skin temperature can also be calculated on regional weighting of the skin's thermal sensitivity and not on its percentage of body surface area (234, 282). It is reasoned that thermal receptors are not evenly distributed over the skin's surface, and warming of a body region having the greatest number of thermal sensors would have the greatest influence on altering thermoregulatory effector responses. Therefore, calculating mean skin temperature from thermal sensitivity weightings might provide a more meaningful index of the peripheral input into the thermoregulatory controller (282). However, there is disagreement whether mean skin temperature values differ significantly if calculated from regional thermal sensitivity weightings or regional body surface area weightings (234).

Body heat content is the product of mean body temperature and body heat capacity (body mass × tissue specific heat), with the latter being constant for any given body composition (258). Body heat content changes are usually estimated by measuring body temperature changes (thermometry) and values are rarely measured directly by calorimetry, as the latter approach is complicated and requires extensive sophisticated instrumentation (187). For thermometry, mean body temperature changes are estimated from weighted core and mean skin temperature measurements (126). Core temperature and mean skin temperature values are weighted by their anticipated relative size which varies reciprocally with cutaneous vasodilation and cutaneous vasoconstriction with core/skin weightings of 0.9/0.1, 0.79/0.21, and 0.66/0.34 in hot, warm/temperate, and cool conditions, respectively (359). For calorimetry, mean body temperature change is calculated from the difference between measured metabolic heat production (indirect calorimetry) and measured (direct calorimetry) heat exchange with the environment (383).

Recently, it was determined that a three-compartment (muscle, core, and skin temperatures) thermometry model predicted mean body temperature changes better than the traditional two-compartment (core and skin temperatures) thermometry model during exercise in temperate and warm conditions; but even when including invasive muscle temperature measurements this three-compartment thermometry model accounted for only ∼50% of the variance of mean body temperature from calorimetry measurements (186). Subsequently, Jay and colleagues (188) constructed a two-compartment thermometry model that employed "adjustment factors" to individually calibrate mean body temperature values from calorimeter measures. The optimally "adjusted" two-compartment models accounted for only ∼56% of the variance of mean body temperature from calorimetry measurements. The implications of these findings are that thermometry provides an inaccurate estimate of mean body temperature changes and therefore thermoregulatory models, forcing function analyses of thermoregulatory effector responses, and heat storage based on these measures are likely flawed. These inaccuracies are accentuated when comparing between different subjects (e.g., lean vs. obese), environmental conditions (e.g., warm vs. temperate), surface to volume ratios, and transient versus steady-state conditions (138). Therefore, thermometry should be employed with repeated measures designs for a given condition where it will

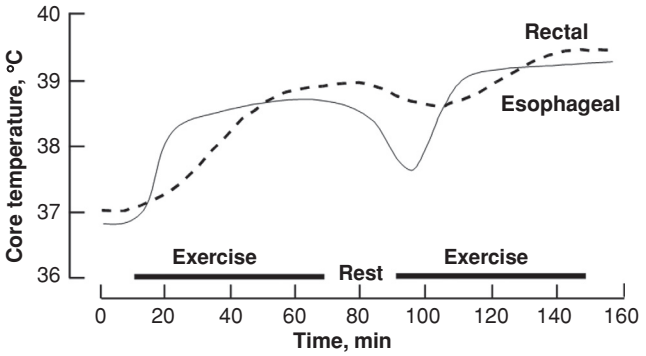

Figure 2 Core (rectal and esophageal) temperature during rest and aerobic exercise in the heat. Reprinted (with permission) from Sawka and Wenger (358).

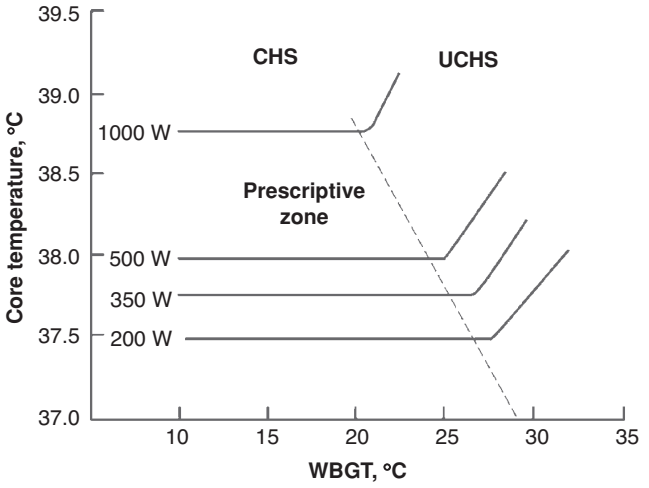

Figure 3 Possible core temperatures steady-state during aerobic exercise at metabolic rates of 200, 350, 500, and 1000 W at different environmental conditions. Reprinted (with permission) from Sawka et al. (360).

be adequate to determine treatment effects for heat storage or thermoregulatory input, while yielding absolute numbers that are inaccurate.

Core temperature response to exercise

Figure 2 illustrates the core (rectal and esophageal) temperature responses to two exercise bouts interspersed by a rest period (358). Skeletal muscle contraction immediately elevates heat production during muscular exercise, causing heat production to initially exceed heat dissipation, which results in heat storage and an elevated core temperature. As core temperature rises, heat-dissipating reflexes are elicited, and the rate of heat storage decreases, so that core temperature rises more slowly. Eventually, as exercise continues, heat dissipation increases sufficiently to balance heat production, and essentially steady-state values are achieved. When muscular exercise is discontinued, core temperature returns toward baseline levels, and with subsequent exercise the process is repeated. During exercise and recovery, both measures of core temperature show similar patterns but with somewhat different kinetics and absolute values (rectal temperature slower to respond and slightly higher).

During muscular exercise, the magnitude of core temperature elevation is proportional to the metabolic rate and largely independent of the environment over a wide range of conditions. Figure 3 illustrates the possible steady-state core temperature response of a semi-nude subject at metabolic rates of 200, 350, 500 and 1000 W (rest-, light-, moderate-, and heavy-intensity exercise, respectively). For athletes, the upper limit for sustained exercise is a metabolic rate of about 1000 W. For any person, the greater the metabolic rate, the higher their steady-state core temperature during exercise. The linear relationship between metabolic rate and core temperature is valid for a given person (controlling for factors like acclimatization and hydration), but does not always hold for comparisons between different people. These differences between people can be somewhat corrected by expressing metabolic rate as a relative exercise intensity (percent of maximal aerobic power) (15, 94). It is important to appreciate that the relationship between metabolic rate (absolute or relative exercise intensity) and steady-state core temperature is independent of the environment within a range of CHS conditions, referred to as the "prescriptive zone" (359). If a CHS condition falls outside the "prescriptive zone" a warmer environment will elicit an augmented steady-state core temperature elevation; and under a UCHS condition, core temperature will continue to rise as long as exercise is continued.

Physiological Temperature Regulation

Human core temperature is usually regulated within a narrow range (35-41°C) through two collaborative processes: behavioral and physiological temperature regulation. Behavioral temperature regulation operates through conscious alterations in behavior that influence heat storage, and includes modification of activity levels, clothing changes and seeking of shade or shelter. Physiological temperature regulation operates through responses that are independent of conscious voluntary behavior, and includes control of: (i) rate of metabolic heat production (e.g., shivering), (ii) body heat distribution via redistribution of blood flow between the core to the skin (e.g., cutaneous vasodilatation and constriction), and (iii) sweating. Conscious changes in behavior are likely linked to relative perceived exertion, thermal sensation/discomfort and other unquantifiable cues. Athletes may sometimes choose to ignore effective behavioral thermoregulation because of their motivation to complete a task or win in athletics; or with practice/experience develop strategies of managing these cues to optimize performance.

Thermoregulatory control

The function of the human thermoregulatory system is shown schematically in Figure 4 (360). This scheme presumes that

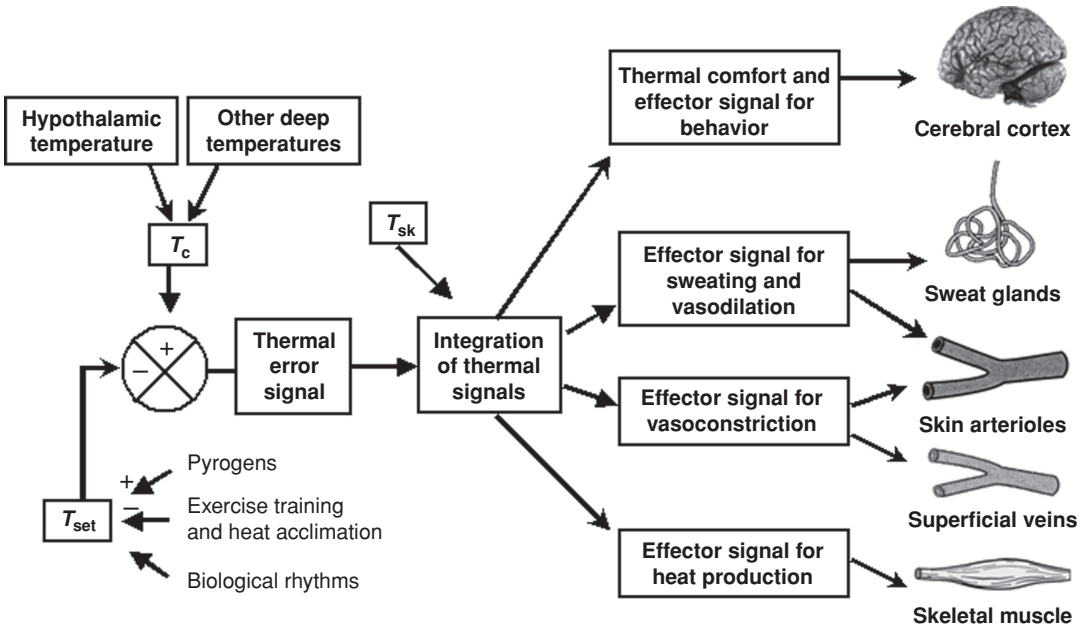

Figure 4 Schematic diagram of the thermoregulatory control system. T_{sk} represents skin temperature and T_c represents core temperature. Reprinted (with permission) from Sawka et al. (360).

there are sensory receptors in the core and skin that send thermal information to some central integrator, such as the preoptic anterior hypothalamus (POAH) (39, 189, 321). Any deviation between the regulated variable (body temperature) and a reference variable (e.g., "set-point temperature") in the POAH results in a "load error" that generates a thermal command signal to modify sweating and cutaneous vasodilatation responses during heat stress (359). The notion of such a thermal command signal is supported, first, by observations that for the thermoregulatory control of any one of the heat-dissipating responses, the ratio of the contributions of core and skin temperature inputs is the same for sweating and skin blood flow; and second, by observations that threshold temperatures for different thermoregulatory effector responses are shifted simultaneously, and to a similar degree, by factors such as biological rhythms, pyrogens, and heat acclimatization. It is useful to think of such similar and simultaneous shifts in thresholds for a number of different thermoregulatory responses as representing (or as being the result of) a shift in thermoregulatory "set point."

It is important to note that there is controversy as to whether a "set point" truly exists and there are alternate theories (166, 189, 334). A persuasive recent theory is that each thermoregulatory effector response is controlled by independent neuronal networks without a unified central integrator (so no integrated "set point") with coordination achieved by the common controlled variable of body temperature (334). This review will rely on the traditional view of a central integrator and "set point," but recognizes the existence of alternate hypotheses.

The traditional set-point theory is based on the idea that a disturbance in the regulated variable, that is, core temperature, elicits graded heat loss or heat gain responses. The "set-point" temperature, serves as a reference (analogous to a thermostat setting) in the control of all the thermoregulatory responses. Peripheral (skin) and central (brain, spinal column, and large vessels) thermal receptors provide afferent input into hypothalamic thermoregulatory centers (321), where this information is processed with a resultant "load error" and proportionate thermoregulatory command signal to initiate responses to reestablish and maintain heat balance (189). In addition, very small changes in POAH temperature elicits changes in the thermoregulatory effector response, as this area contains many warm- and cold-sensitive neurons which increase their firing rate in response to warming or cooling, respectively (39). The magnitude of change in heat loss (e.g., sweating, skin blood flow) response will be proportional to the displacement of the regulated variable (core temperature) from the thermoregulatory "set-point" temperature.

The weighting of "central" (core) and peripheral (mean skin) inputs for thermoregulatory control vary depending on environmental temperature (see preceding discussion of core and skin temperature weightings). During heat stress, a weighting of 90% core and 10% mean skin temperature is often used (278), which means that a change of 1°C in core temperature elicits about 9 times as great a change in thermoregulatory effectors' response as does a 1°C change in mean skin temperature. However, since skin temperature generally varies over a wider range than core temperature, the importance of skin temperature in thermoregulatory control is greater than suggested by the 9:1 ratio. The responsiveness of the thermoregulatory system to core temperature changes is necessary if the thermoregulatory system is to keep core temperature relatively constant, and the system's sensitivity to

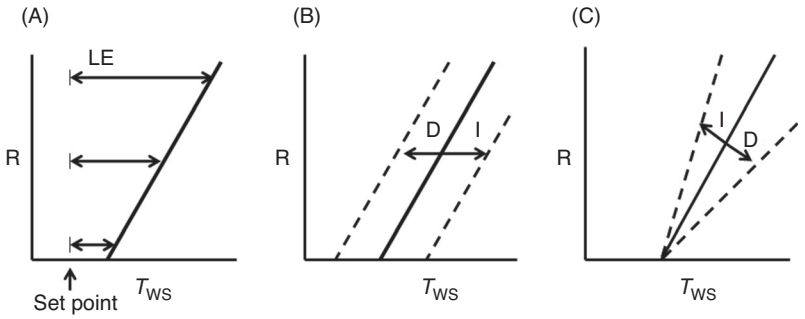

Figure 5 Schematic diagram of thermoregulatory effector (e.g., sweating rate and skin blood flow) responses (forcing function analysis with linear plots) to: (A) increased load error (LE), (B) parallel shift in threshold temperature suggesting change in "set point," and (C) slope or sensitivity changes suggesting peripheral modifications. LE, load error; D, decrease; and I, increase. Reprinted (with permission) from Gisolfi and Wenger (138).

mean skin temperature allows appropriate responses to large changes in environmental temperature while permitting little change in body core temperature.

To evaluate changes in thermoregulatory control during human experiments, forcing function analyses are typically employed (138). Forcing function analyses require that thermoregulatory effector responses—e.g., skin blood flow or sweating—and a weighted body temperature are continuously measured (requiring a rapidly responding core temperature measure that is similar to blood temperature) and then analyzed to determine the mean body temperature at which an effector response increases above some baseline (threshold temperature) and the change in slope (sensitivity) of the response once initiated (42, 70). Figure 5 shows forcing function analyses with linear plots of individual mean body temperature and associated effector (e.g., sweating or skin blood flow) responses to an increasing "load error" (left panel) and illustrates how a shift in threshold temperature (center panel) or a shift in sensitivity (right panel) might appear (138). Threshold temperature shifts are often interpreted as reflecting central nervous system-mediated changes in set point, while sensitivity shifts are often interpreted as changes in peripheral input to the thermoregulatory controller (138); however, such interpretations are not always the case (374). Thermoregulatory control (shifts in threshold and or sensitivity) changes have been reported to be associated with numerous factors including heat acclimatization (282), physical training (330), exercise intensity (404), dehydration (269), high altitude (210), age (10), sleep loss (354), sex hormones (392), circadian patterns (393), and baroreceptor unloading (182).

Exercise hyperthermia versus fever

Exercise and fever increase core temperature, but thermoregulatory control differs between these two conditions. Whereas exercise has no impact on the "set-point" temperature or the desired body temperature that the thermoregulatory control system is attempting to preserve, fever does. These differences between exercise and fever are illustrated in Figure 6 (394). With exercise, the threshold temperature (T_{set}) is unchanged and heat-dissipating responses are elicited as body (core and skin) temperature increases, until heat loss matches heat production and a new thermal balance is established. When exercise stops, heat loss exceeds heat production, so core temperature falls back toward the set point, thereby diminishing the signal eliciting the heat dissipation responses, and they decline to baseline levels, as thermal balance is eventually re-established. The elevated body temperature produced by exercise is called hyperthermia.

With fever, the primary event eliciting an increase in body temperature is an elevation of set-point temperature, which initially causes a negative load error or error signal. Heat-dissipating responses are inhibited and heat production and heat conservation (e.g., use of blankets) are stimulated to increase core temperature and correct the error signal. During the maintenance of fever, an individual is considered normothermic since a new thermal balance has been established in which heat production and heat loss are near (or slightly above) their values before the fever. When fever abates (set point returns to "normal"), heat-dissipating responses are increased and/or heat production and heat conservation are reduced until homeostatic thermal balance is re-established. If individuals perform exercise during fever, exercise-induced hyperthermia may be imposed above the fever temperature. Under these conditions, the core temperature elevation during exercise is expected to be the sum of the hyperthermia and fever.

Physiological Responses to Heat Stress

Sweating and evaporative heat loss

As ambient temperature increases, there is increasing dependence on sweating and evaporative heat loss to remove body heat. Eccrine glands are the primary source of sweat. The rate

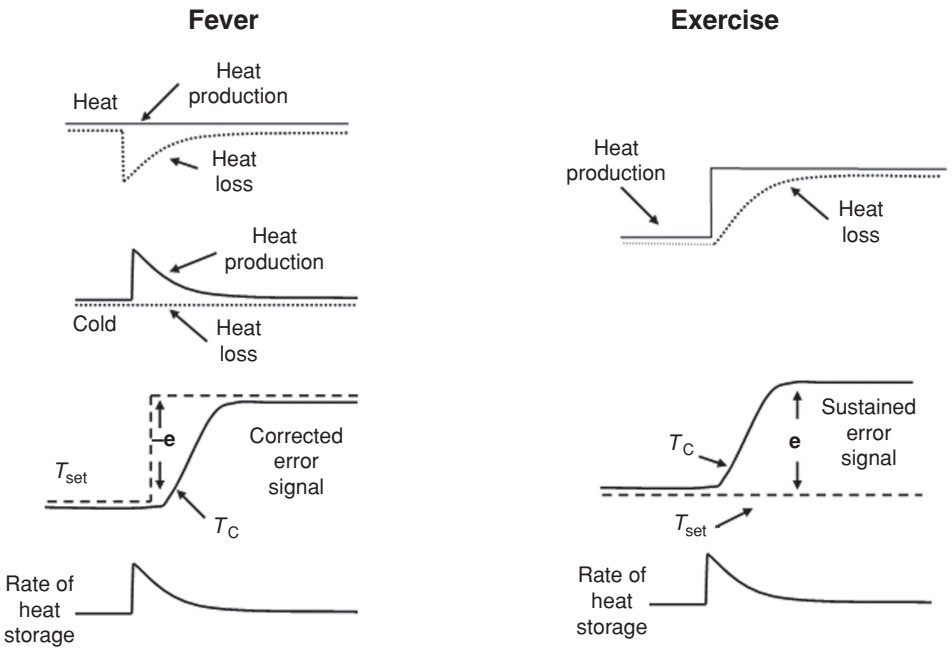

Figure 6 Differences between the elevation of core temperature in fever and during exercise. Reprinted (with permission) from Sawka and Wenger (358); redrawn (with permission) from Stitt (394) and Gisolfi and Wenger (138).

that sweat evaporates is determined by the gradient between the skin and air vapor pressures, and the coefficient of evaporative heat transfer—the wider the water vapor gradient, the greater the rate of evaporation for a given mass transfer coefficient (126). The sweat glands respond to thermal stress primarily through sympathetic cholinergic stimulation, but catecholamines and other neuromodulators such as vasoactive intestinal peptide, calcitonin gene-related peptide, and nitric oxide likely facilitate thermoregulatory sweating (374, 421). Warm skin enhances the sweat response (281) and this is likely mediated by both the increased local temperature and associated increased skin blood flow (430). Thermoregulatory sweating can begin within a few minutes after starting muscular exercise. Initially skin from the back and chest regions will have the greatest sweating rates for a given core temperature, then the limbs will subsequently increase their sweating rates (281). Heat acclimation may (379) or may not (318) further redistribute sweat recruitment from trunk-to-limbs. Regardless, as the sweating rate increases the initial response is to increase the number of sweat glands that are recruited and subsequently to increase the sweat secretion per gland. As a consequence, the sweat produced by a given body region is dependent on the density of sweat glands in that region and the secretion rate per gland (350).

Sweating and subsequent evaporation is a critical process in the thermoregulatory response to exercise. When an individual performs exercise at a 600-W metabolic rate, approximately 80% of the energy consumed becomes heat. As such, 480 W (0.48 $kJ \cdot s^{-1}$ or 28.8 $kJ \cdot min^{-1}$) must be dissipated to avoid heat storage. The specific heat of body tissue (the amount of energy required for 1 g of tissue to increase temperature by 1°C) approximates 3.5 $kJ \cdot {}^{\circ}C^{-1}$, so a 70-kg man has a heat capacity of 245 $kJ \cdot {}^{\circ}C^{-1}$. If this person performed exercise in a hot environment that enabled only evaporative heat loss but sweat was not secreted, body temperature would increase by approximately 1.0°C every 8.5 min (245 $kJ \cdot {}^{\circ}C^{-1}$/28.8 $kJ \cdot min^{-1}$). However, as the latent heat of evaporation is 2.43 $kJ \cdot g^{-1}$, secretion and evaporation of ~12 g of sweat (28.8 $kJ \cdot min^{-1}$/2.43 $kJ \cdot g^{-1}$) per minute, or 0.72 $liters \cdot h^{-1}$ would enable the heat to be transferred to the environment.

Sweating rates can be substantial during intense or prolonged physical exercise in the heat. Persons in very hot (e.g., desert) climates often have sweating rates of 0.3 to 1.2 $liters \cdot h^{-1}$ while performing occupational activities (4). Persons wearing protective clothing often have sweating rates of 1 to 2 $liters \cdot h^{-1}$ while performing light-intensity exercise in hot weather (75, 78, 271). Athletes training and competing produce a range of sweating rates as a consequence of the wide range of exercise intensities, task durations, clothing/equipment worn, and environmental conditions. Table 2 summarizes sweat rates observed among serious competitors across a range of sports, both in training and in competition (352). These data indicate that sweating rates from 0.5 to 2.0 $liters \cdot h^{-1}$ can be expected (25, 26, 43, 48, 89, 140, 251, 376, 390). The sweating rates for a given physical activity and environmental condition can be predicted from the following regression equation using the required evaporative cooling (E_{req}) and evaporative cooling capacity of the environment (E_{max}) values as input parameters (142): Sweating

Table 2 Observations of Sweat Rates in Various Sports

Sport	Condition	Sweat rate, liters·h^{-1} Mean	Range
Waterpolo (89)	Training (males)	0.29	(0.22-0.35)
	Competition (males)	0.79	(0.69-0.88)
Netball (43)	Summer training (females)	0.72	(0.45-0.99)
	Summer competition (females)	0.98	(0.45-1.49)
Basketball (43)	Summer training (males)	1.37	(0.9-1.84)
	Summer competition (males)	1.60	(1.23-1.97)
Soccer (376)	Summer training (males)	1.46	(0.99-1.93)
Soccer (251)	Winter training (males)	1.13	(0.71-1.77)
American Football (140)	Summer training (males)	2.14	(1.1-3.18)
Tennis (26)	Summer competition (males)	1.60	(0.62-2.58)
Tennis (25)	Summer competition (cramp-prone males)	2.60	(1.79-3.41)
Squash (48)	Competition (males)	2.37	(1.49-3.25)
XC- running (140)	Summer training (males)	1.77	(0.99-2.55)

Values are mean, plus (range), or (±95% reference range).
Adapted from Sawka et al. (352).

rate ($g \cdot m^{-2} \cdot h^{-1}$) = $147 + 1.527 \cdot E_{req} - 0.87 \cdot E_{max}$. This sweat rate prediction equation provides improved precision over a broader range of heat stress conditions and metabolic rates than previous prediction equations (371, 372).

Skin blood flow and dry heat loss

Blood transfers heat by convection from the deep body tissues to the skin. When core and skin temperatures are low enough that sweating does not occur, raising skin blood flow brings skin temperature nearer to blood temperature, and lowering skin blood flow brings skin temperature nearer to ambient temperature. Thus, the body can control dry heat loss by varying skin blood flow and thereby skin temperature. When sweating occurs, the tendency of skin blood flow to warm the skin is approximately balanced by the tendency of sweat evaporation to cool the skin. Therefore, after sweating has begun, skin blood flow serves primarily to deliver to the skin the heat that is subsequently removed by sweat evaporation. Skin blood flow and sweating thus work in tandem to dissipate heat.

The cutaneous circulation is affected by skin temperature by directly impacting on the vascular smooth muscle, and is affected by the skin and core temperatures via reflexes operating through the sympathetic nervous system from the thermoregulatory control centers (191). Human skin is under dual vasomotor control (192). The palm of the hand, sole of the foot, lips, ears, and nose are predominantly innervated by adrenergic vasoconstrictor fibers, and the vasodilatation that occurs in these regions during heat exposure is largely the result of withdrawing vasoconstrictor activity. Over most of the remaining skin areas (e.g., arm, leg, and torso) there is minimal vasoconstrictor activity at skin temperatures of ~39°C (405) and active vasodilatation during heat exposure depends on sympathetic innervations. The mechanisms responsible for active cutaneous vasodilatation are not fully understood, but believed to be mediated primarily by an unidentified cholinergic vasodilator associated with sweating and by other redundant mechanisms (66). The cholinergic cotransmitter may not be released from the sudomotor nerves as the time-frame for the initiation of sweating and active cutaneous vasodilation are similar but can occur concurrently, before or after each other (66). Other substances suggested to contribute to active cutaneous dilation include vasoactive intestinal peptide, nitric oxide, histamine, prostaglandins, substance P, and/or neurokinin-1 agonists (66, 170, 191, 192, 374).

Maximal whole-body skin blood flow measurements are not possible, but it has been estimated that skin blood flow can approach 8 liters·min^{-1} during heat stress (198, 340, 406). Skin blood flow responses are somewhat different at rest as compared to that observed when performing aerobic exercise during heat stress (147). Figure 7 schematically compares skin blood flow (as a percentage of maximum) responses during rest- and moderate-intensity exercises in the heat (147). Exercise increases vasoconstrictor tone (Fig. 7A) which increases the threshold temperature for vasodilatation (Fig. 7B) and reduces skin blood flow at high body temperatures (Fig. 7C) compared to rest (41, 190, 197, 202). These modified skin blood flow responses occur during exercise-heat stress because the cardiovascular system is challenged to simultaneously support both high skeletal muscle and skin blood flow. In addition, healthy aged (>60 years) persons demonstrate 25% to 50% reduction in skin blood flow due to: (i) reduced sympathetic output; (ii) modified presynaptic neurotransmitter synthesis; (iii) reduced vascular responsiveness and (iv) impaired signaling to endothelial and smooth muscle (169).

The core-to-skin gradient narrows as ambient temperature rises within the prescriptive zone of CHS. Therefore, in such conditions, greater vasodilatation has important implications for providing sufficient skin blood flow to preserve heat balance (198). The elevated core temperatures accompanying exercise-heat stress outside the prescriptive zone provide a

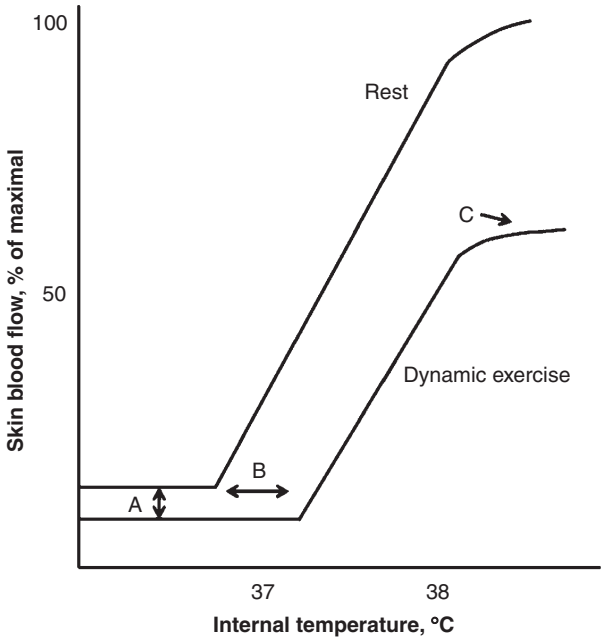

Figure 7 Schematic description of the thermoregulatory control of skin blood flow as modified by moderately intense exercise. Reprinted (with permission) from Gonzalez-Alonso et al. (147).

useful strategy to assist with heat transfer, as it widens the core-to-skin gradient and lessens the demand for skin blood flow. Table 3 illustrates the effect of different core and skin temperatures on the skin blood flow requirements if heat transfer is to be preserved (199). These estimates assume that blood entering and leaving the cutaneous vasculature is equal to core and skin temperatures, respectively (340). In the example, if the exercise-mediated heat production is 10 kcal·min^{-1} and core and skin temperatures are 38°C and 30°C, respectively, the skin blood flow requirement will be about 1.1 liters·min^{-1}. During heat stress that increases skin temperature up to 34° and 36°C, the minimal skin blood flow requirement to preserve the same heat transfer rate increases to ~2.2 liters·min^{-1} and ~4.4 liters·min^{-1}, respectively. However, if core temperature were 39°C, the skin blood flow requirements are lessened without compromising heat transfer. Thus, these examples clearly demonstrate how elevated skin temperatures (by warmer ambient or reduced evaporative cooling) increase skin blood flow requirements and how an elevated core temperature can reduce the skin blood flow requirement and cardiovascular strain associated with exercise-heat stress. This latter point is rarely appreciated in the sports medicine literature.

Table 3 Estimated Whole Body Skin Blood Flow (SkBF) Requirements* During Prolonged, Severe Running Exercise** at Different Body Core (T_c) and Skin (T_{sk}) Temperatures

T_c (°C)	T_{sk} (°C)	Gradient (°C)	SkBF, liters·min^{-1}
38	30	8	1.1
38	34	4	2.2
38	36	2	4.4
39	36	3	3.0

*Equation for skin blood flow: $Q_s = 1/C \times h/(T_c - T_{sk})$, where C = specific heat of blood ≈0.87 kcal·°C·liter^{-1}; h = heat production (kcal·min^{-1}); Q_s = skin blood flow (340).
**Net heat production (7.7 kcal·min^{-1}) estimated using 60-kg body mass and 325 m·min^{-1} running velocity (approximate pace for men's world class 42 km footrace) after subtracting for work (20% efficiency) and 50% dry and evaporative heat losses.
Adapted from Kenefick (199).

Cardiovascular support of thermoregulation

During exercise-heat stress, the primary cardiovascular challenge is to provide sufficient cardiac output to adequately perfuse skeletal muscle to support metabolism while simultaneously perfusing the skin to support heat loss (192, 344). These competing metabolic and thermoregulatory demands alter cardiac function (44) and distribution of the cardiac output (243). Figure 8 provides cardiovascular responses during sustained moderate-intensity (70% $\dot{V}o_2max$) exercise in

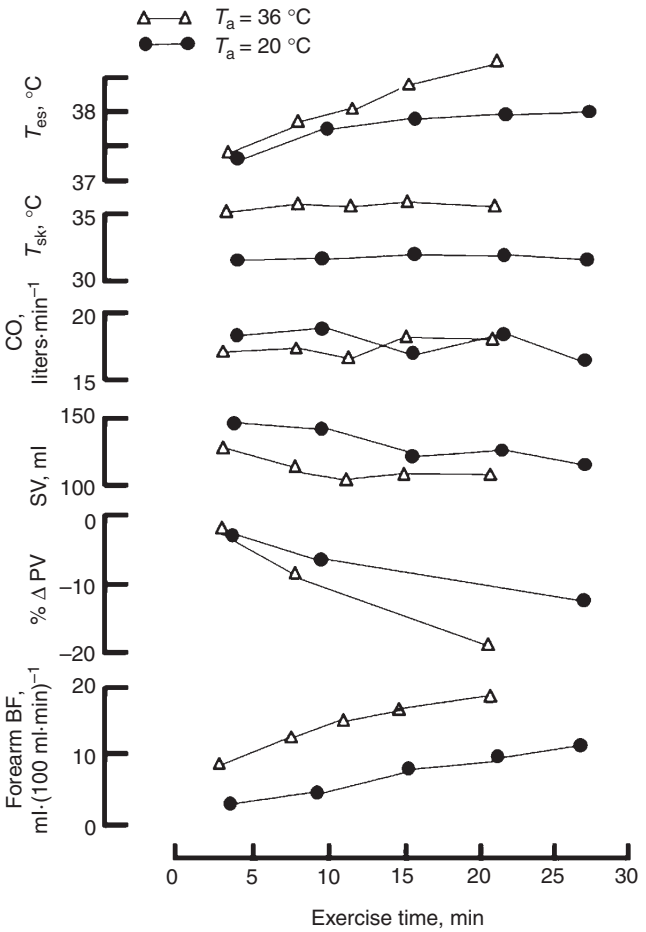

Figure 8 Cardiovascular responses during sustained moderate intensity (70% $\dot{V}o_2max$) exercise in temperate and hot conditions. BF, blood flow; PV, plasma volume; SV, stroke volume; CO, cardiac output; T_{sk}, skin temperature; T_{es}, esophageal temperature; and T_a, ambient temperature. Drawn (138) (with permission) from data presented by Nadel et al. (279).

temperate and hot conditions (138, 279). The high skin blood flow and plasma loss (percent change plasma volume) both act to reduce venous pressure and thus reduce cardiac filling (284, 339). In addition, a reduced diastolic filling time, from high heart rate, may contribute to the reduced stroke volume (121, 412). To compensate for reduced cardiac filling during rest and exercise, cardiac contractility increases to help sustain stroke volume (44, 284, 395). However, despite the increase in heart rate and contractility, stroke volume will usually decline, particularly if core-to-skin gradient is sufficiently narrow, as during sustained moderate-intensity exercise-heat stress (339, 344).

Heart rate is elevated for any given cardiac output during exercise-heat stress (126). Figure 9 illustrates the impact of skin temperature on the heart rate response to light-intensity exercise (77). Skin temperature was manipulated by a water perfused suit, while core temperature remained relatively constant (~37.5°C), so the core-to-skin temperature gradient progressively narrowed as skin temperature increased. This paradigm results in substantial increases in skin blood flow and displacement of blood into the periphery likely resulting in reduced venous pressure and rate of cardiac filling. In this experiment, raising mean skin temperature from 32 to 35°C elevated heart rate by ~26 bpm, and raising T_{sk} from 32 to 36°C elevated heart rate by ~49 bpm. Therefore, the warmer the skin and narrower the core-to-skin gradient, the greater the heart rate elevation and cardiovascular strain.

Figure 10 demonstrates the impact of graded exercise intensity on the cardiovascular responses during hot and temperate conditions (338, 343). During light-intensity exercise, the cardiac output was sustained with a lower blood pressure (mean aortic pressure) in the hot environment. During high-intensity exercise, the cardiac output could not be sustained compared to levels achieved in temperate conditions (145, 343). Therefore, during exercise-heat stress the cardiovascular system is pushed to its limits (more easily than in temperate conditions) and the ability to perfuse skeletal muscle and cerebral blood flow (CBF) can be compromised (145, 147, 298, 301, 327).

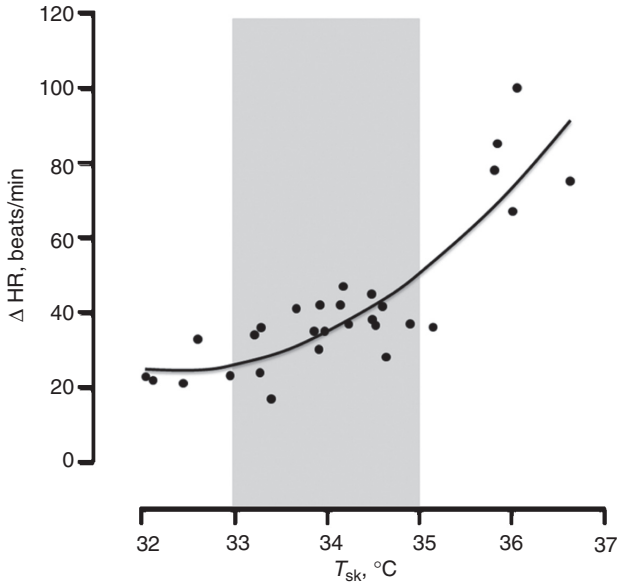

Figure 9 The impact of high skin temperature on elevating heart rate during light-intensity exercise. Reprinted (with permission) from Cheuvront et al. (77).

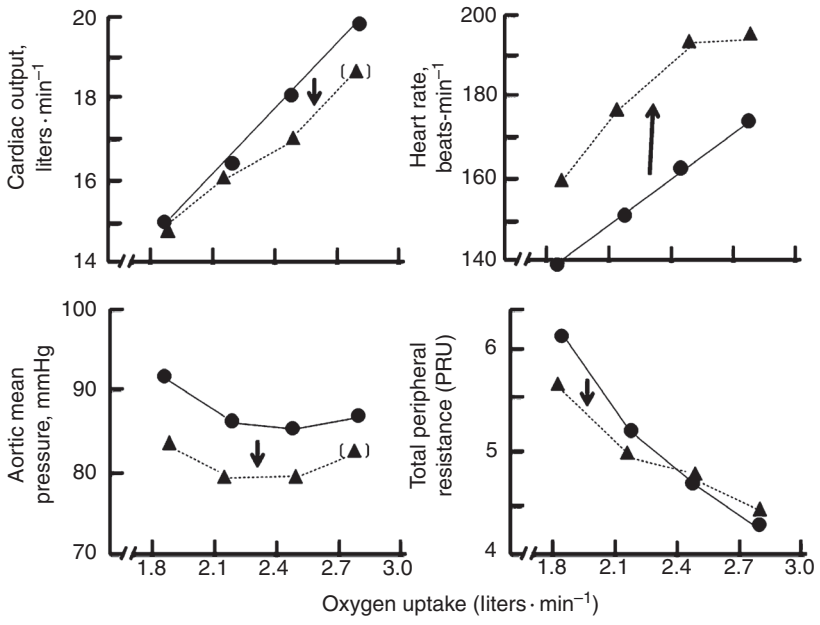

Figure 10 The impact of graded exercise intensity on cardiovascular responses during hot (triangle) and temperate (circle) conditions. Reprinted (with permission) from Rowell (338).

To help support blood pressure and cardiac output demands during exercise-heat stress, blood is redirected from the viscera (splanchnic and renal) to skin and active skeletal muscle (339). The visceral blood flow reductions are graded to the exercise intensity, and the effects of exercise and heat are additive (339). These visceral blood flow reductions are mediated by increased sympathetic activity, thermal receptor stimulation and other mechanisms (250). Secondary to reduced visceral blood flow, blood can be mobilized from the compliant splanchnic beds to help maintain cardiac filling during exercise heat stress.

The severe cardiovascular demands imposed by heat stress can lead to syncope and orthostatic intolerance during rest and exercise (4, 201). Hyperthermia and dehydration are often associated and both can modify cardiac filling, blood pressure, and baroreflex regulation, which contribute to orthostatic intolerance (67, 91, 92, 93, 427). In addition, hyperthermia can reduce local venoarteriolar responses (45) and possibly reduce cerebral vascular conduction (428) and accompanying cerebral perfusion during orthostatic challenge. Similarly, heat stress and dehydration might mediate increased cerebral vascular resistance and contribute to reduced CBF during an orthostatic challenge (62, 428). However, one study reports that cerebral autoregulation was not impaired by passive heat stress (46). Therefore, it is unclear if cerebral vascular resistance changes contribute to the orthostatic intolerance associated with heat stress and dehydration.

Aerobic Exercise Performance

Heat stress

It has long been appreciated that heat strain degrades endurance performance (e.g., marching in the desert) and the hotter the ambient temperatures, the shorter the distance marched before fatigue (4). More recently, Ely et al. (111) quantified the impact of hot weather on marathon race performance. Figure 11 shows that finishing times were progressively slowed with increased WBGT over a range of 5 to 25°C, which represents the conditions associated with low to high risk of exertional heat illness during marathon races (Table 1). Moreover, the data indicate that slower runners suffered a greater decrement in finishing time than faster runners.

To better understand the physiological impact of heat on exercise performance, numerous laboratory experiments have been performed. These experiments have included measurement of (i) $\dot{V}O_2max$; (ii) time to exhaustion (TTE) (constant work-rate); and/or (iii) time trial (TT) tests (self-paced) which measure either the total power output completed during a defined period or the time to complete a specific total power output. Unlike $\dot{V}O_2max$, TTE and TT tests are performed at submaximal exercise intensities. It is well established that heat stress degrades maximal-intensity exercise or $\dot{V}O_2max$ (13, 145, 205, 296, 322, 342, 361, 429). Figure 12 shows that heat stress lowers $\dot{V}O_2max$ regardless of heat acclimatization

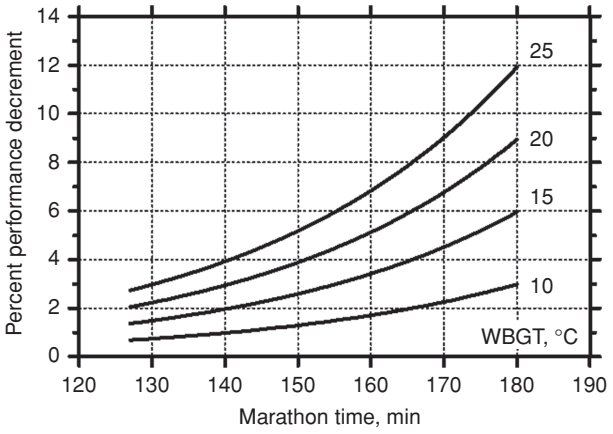

Figure 11 Nomogram examining the potential performance decrement (*y*-axis) based on projected marathon finishing time (*x*-axis) with increasing Wet Bulb Globe Temperature. Reprinted (with permission) from Ely et al. (111).

status across a broad range of aerobic fitness levels (361). The $\dot{V}O_2max$ reductions are proportionate to the skin temperature (from 32° to 38°C) elevation (13) and are likely mediated by an inability to achieve maximal cardiac output (343).

Collectively, TTE and TT studies demonstrate that heat stress degrades aerobic exercise performance (128, 243, 403). Galloway and Maughan (128) conducted one of the first studies to systematically compare the effects of graded heat stress on TTE (70% $\dot{V}O_2max$) performance. Using an ambient temperature range of 4 to 31°C (with 70% relative humidity), TTE was ~42 min shorter (44%) in the warm-humid (31°C) environment relative to the study of optimum environment (11°C). At the point of exhaustion, subject core temperatures

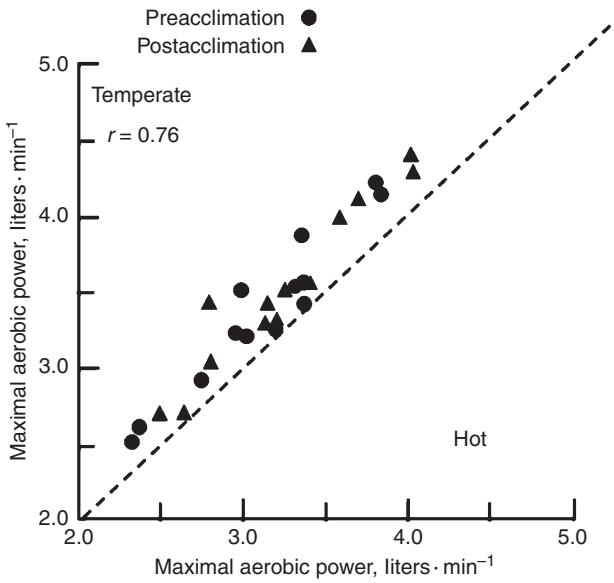

Figure 12 Maximum aerobic power values for the pre- and postacclimation tests in both environments. Reprinted (with permission) from Sawka et al. (361).

(~40°C vs. 39.5°C), skin temperatures (35°C vs. 25°C), and heart rates (~175 vs. 165 bpm) were higher in the warm-humid than optimum environment. Similarly, MacDougal et al. (243) observed that TTE (70% $\dot{V}O_2$max) was ~42 min shorter (47%) when mean skin temperature was increased to ~35 from ~29°C (hyperthermia and "normal") by employing a water perfused suit. At exhaustion, core temperature (~39.5°C) and heart rate (~180 bpm) responses were similar in the "normal" and hyperthermic conditions. Tatterson and colleagues (403) reported that TT (30 min) performance was degraded by ~6% in a warm-humid environment (skin temperatures were 33°C vs. 27°C); at completion, core temperature and heart rate were ~39.3°C and ~195 bpm, respectively. Periard and colleagues (320) reported that TT (40 km) performance was degraded by ~13% (mean power output) in a hot-humid environment; at completion, skin temperatures (36°C vs. 28°C), core temperature (39.8 vs. 38.9°C), and heart rate (187 vs. 180 bpm) were higher in the warm-humid compared to temperate trials. In all of these above studies, exercise performance was degraded and subjects incurred high core and skin temperatures and high cardiovascular stress in the hot environment.

The physiological mechanism(s) primarily responsible for degrading TTE and TT performance (submaximal intensity) in the heat remains a vigorously debated question (69, 76, 295). It is well recognized that depending on the exercise-heat stress condition (duration, intensity, hydration status, and environment), cardiovascular strain (338), glycogen depletion (114), perceptual discomfort (58, 313), and central nervous system dysfunction (297) might contribute. Cardiovascular strain was traditionally considered the primary mechanism degrading submaximal-intensity performance in the heat (338), however, since compromised skeletal and/or brain blood flow are not typically observed, except with extreme stress, alternative explanations were sought (147, 295).

During the past 15 years, the scientific literature has been dominated by the notion that high core (brain) temperature is the primary mechanism [via central nervous system (CNS) dysfunction] responsible for the degraded (submaximal intensity) aerobic performances that accompany heat stress (151, 290, 299). The high core temperature argument is based on the assumption that a "critical" core temperature threshold of ~40°C represents a safety-brake for catastrophic hyperthermia or represents the physiologic precipice for a downward trend in performance (292, 294). Nielsen and colleagues (290) first proposed that "high core temperature per se and not circulatory failure" is the critical factor for exhaustion during exercise-heat stress. In their initial study, TTE (60% $\dot{V}O_2$max) performance was determined for 9 to 12 consecutive days (heat acclimation) in a hot-dry environment. Heat acclimation increased TTE (48 to 80 min) over the test days, but fatigue consistently coincided with the attainment of a core temperature approximating 40°C and skin temperature of ~37°C. In a subsequent experiment, Gonzalez-Alonso (151) manipulated initial body temperatures prior to a TTE (60% $\dot{V}O_2$max) in a hot-dry environment by precooling, no-precooling and preheating the subjects. It was again observed that exhaustion coincided with the attainment of a core temperature of ~40°C. However, it also co-existed with elevated skin temperature (~37°C) and heart rates (~196 bpm) near age-predicted maximum. In additional experiments, TTE (66% $\dot{V}O_2$max) performance was determined while wearing a water perfused suit to manipulate the rate of heat storage (151). Perfusing warm (vs. temperate) water increased skin temperature (35.6 vs. 38.4°C) and shortened TTE (56 vs. 31 min), but subjects again stopped exercising at core temperatures near ~40°C. Therefore, the studies used to support the high core temperature argument for limiting aerobic exercise performance (151, 290, 299) have all induced high core temperatures but also with higher skin temperatures in heat stress compared to the control trial.

No study, to date, has demonstrated that high core temperature alone (without coexisting high skin temperature) will degrade aerobic performance. In contrast, there is strong evidence that high skin temperatures (>35°C) alone (accompanied by modest core temperature levels) can degrade aerobic performance and facilitate early fatigue during exercise-heat stress. One study employed CHS (within the prescriptive zone, see Figure 2) to induce similar, but modest, core temperature elevations with a higher skin temperature during heat stress. Ely and colleagues (109) determined TT (preceded by 30 min @50% $\dot{V}O_2$max) performance in two environmental (40 and 20°C) conditions; the core temperatures were similar (~38.2°C) and well below the proposed "critical core temperature"; but the environments produced modest (31°C) or high (36°C) skin temperatures. In their experiment, TT performance was degraded by 17% when high-mean skin temperature was present. In both trials, heart rates near age-predicted maximum were achieved. These findings are consistent with other studies where UCHS produced high skin temperatures (~36-37°C), large cardiovascular drift, and premature fatigue; with physical exhaustion routinely (~50% of cases) occurring at relatively low (<38.5°C) core temperatures (271, 363). Together, these studies suggest that high skin temperature, and associated cardiovascular strain, can be the primary mechanism mediating degraded TT and TTE performance during heat stress.

There are reasons to suspect that core temperature of ~40°C is not critical or an indicator that fatigue is imminent. First, aerobic performance studies supporting the "critical core temperature hypothesis" are all confounded by the co-existence of high skin temperatures and substantial cardiovascular strain. As discussed above, aerobic performance is degraded if skin temperature is high (36°C), despite a modest (<38.5°C) core temperature (109, 271, 363). Also, it has been shown that during short (8 km) or long (21 km) competitive races, running performance (velocity) is preserved despite attainment of core temperature ≥40°C when mean skin temperature is relatively low (26-30°C) (110, 221). Second, studies characterizing the physiological responses of distance runners during races have reported core temperatures well in excess of 40°C (even > 41°C), without apparent sequelae

(57, 249, 333). It is also known that the minimal lethal body temperature for humans is ~42°C (56) and human CNS cells can tolerate blood temperatures in excess of 41°C without harm (103). Third, animal and tissue studies provide little support for a "critical" core temperature and—"it does not make sense that 40 to 41°C should indicate that the brain is sensitive to a significantly lower level of temperature than the 42 to 45°C often quoted for other tissues" (157).

Direct evidence that hyperthermia degrades CNS function comes from associations between a "critical" core temperature and altered brain wave (EEG), motor-neural output, and sensory changes consistent with fatigue (291, 297, 299). However, EEG alterations may (291, 298) or may not (328) be the consequence of reductions in brain blood flow, which ultimately represents a cardiovascular mediated (as skin temperatures were high) mechanism (148, 300). The effects of heat stress on degrading neuromuscular function are progressive (408) and as much as half of the neuromuscular fatigue effects attributed to a hot brain may be explained by hot muscles (409). It is not possible to determine if the remaining loss of efferent motor cortical output is the result of an unwilling or incapable participant, but the same exercise task in the heat is generally perceived as more difficult (elevated relative perceived exertion) and uncomfortable (elevated thermal discomfort) than in temperate conditions (127, 314).

Cheuvront and colleagues (76) have recently proposed that degraded aerobic performance (TTE, TT) during heat stress might be better explained by the reduced $\dot{V}O_2max$ and associated increased relative exercise (%$\dot{V}O_2max$) intensity. A large $\dot{V}O_2max$ is a prerequisite for success in sports where aerobic endurance is required (22, 97, 193), and $\dot{V}O_2max$ decreases incrementally with step-wise increases (ambient temperature from 25 to 45°C and mean skin temperature from 31.7 to 38.4°C) in heat stress (13). When $\dot{V}O_2max$ is decreased by heat stress, the resultant increased %$\dot{V}O_2max$ during constant-rate exercise (TTE) would be more difficult to sustain (earlier fatigue) or would require a slowing of self-paced exercise (TT) to achieve a similar sensation of effort (76). There are several reasons why the conscious sense of effort would be higher during exercise-heat stress. An increased %$\dot{V}O_2max$ induces greater cardiopulmonary stress (heart rate and respiration) and associated elevated perceived exertion (313) and the warmer/wetter skin induces elevated thermal discomfort (127, 143, 314). Thus, the earlier fatigue or slowing of pace during heat stress might be better explained by physiological mechanisms (reduced cardiac reserve and $\dot{V}O_2max$) increasing perceived exertion and thermal discomfort to induce associated behavioral changes toward sensory optimum (58, 76). The "critical" core temperature theory proposes that high brain temperature deteriorates CNS function and the drive to exercise (297), the "relative exercise intensity" theory proposes that high skin temperature degrades cardiac reserve and $\dot{V}O_2max$ to increase % $\dot{V}O_2max$ and sensation of effort (e.g., perceptual exertion and thermal discomfort) to induce slowing of self-paced work (76). The relative exercise intensity theory does not discount any potential contribution of deteriorated CNS function (from either high CNS or muscle temperatures) but emphasizes the physiological contributions of high skin temperature and reduced cardiovascular reserve acting through behavioral adjustments (76).

Hypohydration

During exercise-heat stress, sweat output often exceeds water intake producing a body water deficit or hypohydration (dehydration). The water deficit reduces both intracellular and extracellular volume. Since sweat is hypotonic to plasma, exercise-heat stress-mediated hypohydration induces a plasma hypertonicity and hypovolemia that are proportionate to the water deficit (74, 181, 362). Hypohydration increases heat storage (357, 362) and reduces one's ability to tolerate exercise-heat strain (363). The increased heat storage is mediated by reduced sweating rate and reduced skin blood flow for a given core temperature (117, 119, 269, 362). The reduced ability to tolerate exercise-heat strain when hypohydrated is likely due to an inability to sustain the required cardiac output (146, 149, 198, 272) and reduced skeletal muscle blood flow (146).

Adolph (4) clearly illustrated that water restriction markedly reduced a Soldier's ability to complete an exercise task in a hot outdoor environment. Buskirk and colleagues (53) were the first to demonstrate that hypohydration (−6% body mass) degraded $\dot{V}O_2max$ (0.2 liters·min^{-1}) in a temperate environment. Craig and Cummings (90) subsequently demonstrated that hypohydration (−2% to −4% body mass) degrades $\dot{V}O_2max$ (10-22%) in a hot environment and speculated that water deficits might have greater adverse effects on performance in hot than temperate conditions. There is now considerable substantiation that hypohydration predictably degrades $\dot{V}O_2max$ (296), TTE (90, 215, 323, 419), and TT (24, 198) performance in warm and hot environments.

The physiological and performance penalties that accompany water deficits in warm weather are lessened in cooler weather. When Cheuvront et al. (71) had subjects perform cycle ergometer exercise for 30 min at constant intensity (~50% $\dot{V}O_2max$) followed by TT (total work completed in 30 min) in temperate and cold environments, hypohydration (−3% body mass) reduced the total work completed by 8% in the temperate and by 3% in the cold environment. Kenefick and colleagues (198) further characterized the interaction between weather and hypohydration by having subjects perform cycle ergometer exercise for 30 min at constant intensity (50% $\dot{V}O_2max$) followed by a TT (total work completed in 15 min) in 10, 20, 30, and 40°C environments when euhydrated and hypohydrated (−4% body mass). In these experiments, CHS conditions were employed so core temperature was relatively constant but mean skin temperature increased with ambient temperature. It was observed that TT performance was more-or-less preserved despite hypohydration in the cool condition, but became progressively compromised at warmer air temperatures. Figure 13 presents the percent decrement TT performance from euhydration at each skin temperature. Beyond

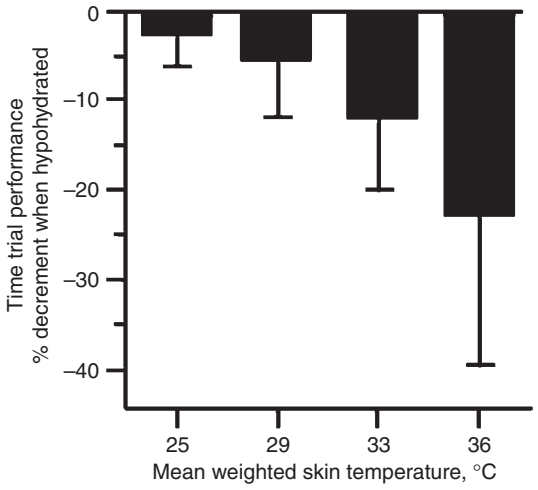

Figure 13 The percent decrement in time trial performance from euhydration at each skin temperature. Reprinted (with permission) from Kenefick et al. (198).

skin temperatures of 29°C, TT performance was degraded by ~1.6% for each additional 1°C increase in mean skin temperature. Clearly, the warmer the environment, the greater the TT performance decrement for a given hypohydration level.

Heat Acclimation and Acquired Thermal Tolerance

Heat acclimation adaptations

Heat acclimation develops following exposure to controlled experimental conditions, whereas heat acclimatization is produced in the naturally occurring environment. Heat acclimation induces biological adjustments that reduce the negative effects of heat stress (359, 424). Heat acclimation develops through repeated heat exposures that are sufficiently stressful to elevate both core (16) and skin temperatures (329) and provoke profuse sweating. The magnitude of biological adaptations induced by heat acclimation depends largely on the intensity, duration, frequency, and number of heat exposures (359, 424). Heat acclimatization is specific to the environment (hot/dry vs. hot/wet) and physical activity level, however, heat acclimatization to a desert or jungle climate can markedly improve exercise capabilities in the other hot environment (359, 424).

Heat acclimation usually requires a minimum daily heat exposure of about 2 h (can be broken into two 1-h exposures) combined with aerobic exercise (359, 424). The physiological strain induced by the same exercise-heat stress condition decreases with each day of heat acclimation. The four "classic" markers of heat acclimation are lower heart rate and core temperature, higher sweat rate and improved aerobic exercise capacity during heat stress. During the initial exercise-heat exposure, physiological strain is high, as manifested by elevated core temperature and heart rate. Most of the improvements in heart rate, core temperature and sweat rate are achieved through the first two weeks of daily exercise in a hot climate. The heart rate reduction develops most rapidly in 4 to 5 days. After 7 days, the reduction in heart rate is virtually complete. The thermoregulatory benefits from heat acclimation are generally thought to be complete after 10 to 14 days of exposure (359, 424), however, improvements in physiological tolerance may take longer (355). Heat acclimation is transient and gradually disappears if not maintained by continued repeated heat exposure.

Aerobic training programs in temperate environments can reduce physiological strain and improve exercise capabilities in the heat, but such training programs provide nominal benefits compared to heat acclimation (12). Figure 14 compares the benefits of an aerobic training program with a heat acclimation program on reducing physiological strain and improving performance during exercise-heat stress (82). After

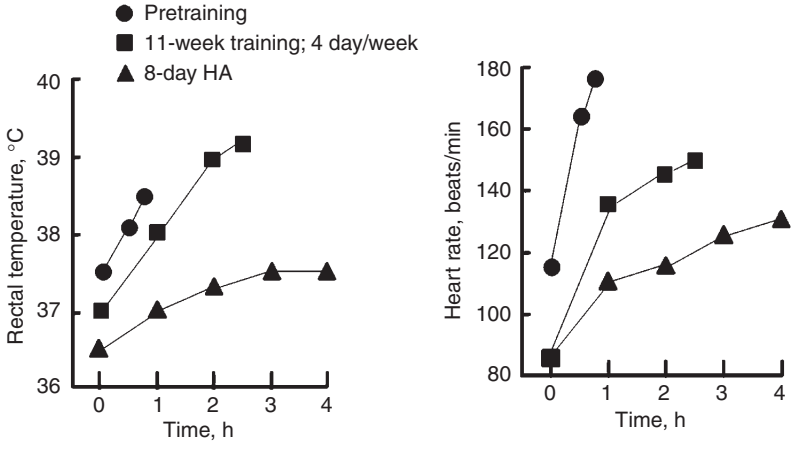

Figure 14 A comparison of the benefits from an aerobic training program with a heat acclimation program on reducing physiological strain and improving performance during exercise-heat stress. Reprinted (with permission) from Sawka and Young (360). Original data adapted (with permission) from Cohen and Gisolfi (82).

Table 4 Summary of Functional Outcomes (Top) and Biological Adaptations (Bottom) Associated with Acclimation

Thermal comfort	Improved	Maximal aerobic power	Increased
		Submax. aerobic performance	Improved
Core temperature	Reduced	Thirst	Improved
Rest (temperate)		Electrolyte losses	Reduced
Exercise		Total body water	Increased
Sweating	Improved	Plasma volume	Increased
Earlier onset		Cardiac output	Better sustained
Higher rate		Heart rate	Lowered
Skin temperature	Reduced	Stroke volume	Increased
Skin blood flow	Improved	Blood pressure	Better defended
Earlier onset		Myocardial compliance	Increased
Higher rate (tropic)		Myocardial efficiency	Increased
Muscle glycogen	Spared	Cardio-protection	Improved
Lactate threshold	Increased	Heat shock proteins	Increased
Muscle and plasma lactate	Lowered	Acquired thermal tolerance	Increased
Skeletal muscle force generation	Increased	Whole-body metabolic rate	Lower

completing an initial (pretraining) exercise heat test (attempting 4 h at ~35% maximal aerobic power in hot, dry conditions), the subjects completed the training program (1 h a day and 4 times per week for 11 weeks in temperate conditions) before repeating the exercise-heat test. Next, the subjects completed a heat acclimation program (attempting 4 h per day at ~35% maximal aerobic power for 8 days) followed by the exercise-heat test. The exercise training slightly reduced physiological strain and improved exercise duration, but these improvements were modest compared to the large improvements demonstrated with heat acclimation.

The biological adaptation and functional outcomes of heat acclimation have been reviewed extensively (173, 359, 424). Table 4 provides a summary of the functional outcomes and biological adaptations of heat acclimatization (acclimation if produced in controlled experimental setting or acclimatization is produced in naturally occurring environment, but acclimation will be used in this article). The functional outcomes of heat acclimation are improved thermal comfort (144), submaximal aerobic exercise performance (240), and maximal aerobic power (240) during heat stress. These improvements are achieved by integrated thermoregulatory, fluid-electrolyte, metabolic, cardiovascular, and acquired thermal tolerance adaptations. Thermoregulatory adaptations are demonstrated by reduced core temperatures at rest (52) and during exercise (107), lowered skin temperatures (240), improved sweating (283), and improved skin blood flow (330). Fluid-electrolyte adaptations are demonstrated by improved fluid balance (106), reduced sweat electrolyte losses (7), increased total body water and extracellular (plasma) volume (319). Metabolic adaptations are demonstrated by lowered whole-body metabolic rate (356), lowered lactate threshold (240), reduced muscle lactate (435), muscle glycogen sparing (115) and increased skeletal muscle force generation (208). Cardiovascular adaptations are demonstrated by increased stroke volume and cardiac output (290), improved cardiac efficiency and ventricular compliance (233), improved cardiac pressure generation (83), and improved cardioprotection (172). Improved acquired thermal tolerance is partially mediated by increased heat shock protein (HSP) basal levels (434) and altered HSP expression patterns (253).

Heat acclimation and aerobic exercise performance in hot and temperate environments

The impact of heat acclimation on $\dot{V}O_2max$ has not been extensively studied. Sawka and colleagues (361) found that heat acclimation (9 days in 49°C for 120 min at 45% $\dot{V}O_2max$) increased $\dot{V}O_2max$ by ~4% in both a hot (49°C) and temperate (21°C) environment, however, there was no control group. Heat acclimation effects on submaximal aerobic performance in the heat are quite dramatic (82, 107, 240, 290), such that heat-acclimatized subjects can easily complete tasks in the heat that were difficult or impossible before heat acclimation. To date, most studies have employed TTE tests to access the effectiveness of heat acclimation on improving heat tolerance (82, 107, 290).

Lorenzo and colleagues (240) conducted the most extensive study regarding heat acclimation (10 days in 40°C for 100 min at ~50% $\dot{V}O_2max$) on exercise performance and included a control group that completed 10 days of identical exercise in a temperate-cool environment (240). Figure 15 provides the impact of heat acclimation (experimental group) and control exposure (temperate-cool environment) on $\dot{V}O_2max$, TT performance (5 min at 50% $\dot{V}O_2max$ then total work completed in 60 min), and lactate threshold (incremental cycle ergometer protocol after preheating in water bath) conducted in hot (38°C) and temperate-cool (13°C) environments (240). No differences were found for the control group. Heat acclimation increased $\dot{V}O_2max$ by 8% in hot and by 5% in temperate-cool environments. In addition, heat acclimation increased TT performance by 8% in hot and by 6% in temperate-cool environments. Thus the TT performance improvements were proportionate to the $\dot{V}O_2max$ improvements in both environments, again suggesting that relative intensity has an important impact on exercise performance in the heat. The improved aerobic performance was associated with

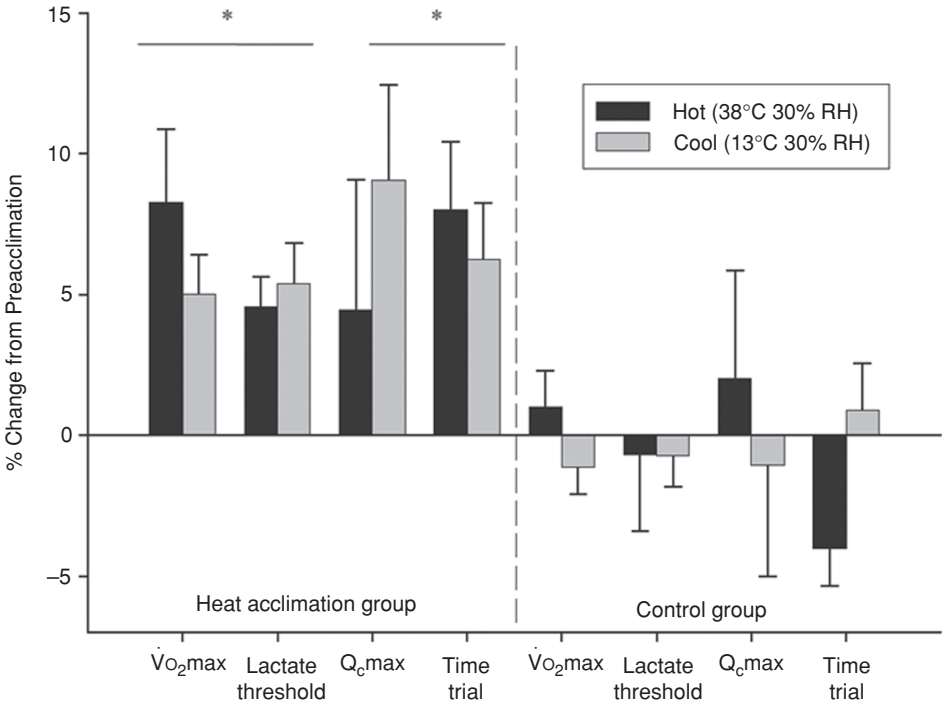

Figure 15 Cardiorespiratory and performance changes as a percent change from the preacclimation trials in both environmental conditions. Reprinted (with permission) from Lorenzo et al. (240). *$P < .05$ vs. the preacclimation trials in both environments.

increased maximal cardiac output, increased lactate threshold, plasma volume expansion, lower skin temperatures, and increased core-to-skin gradient after heat acclimation (240). The finding that heat acclimation improves exercise capabilities in temperate-cool environments was novel and will likely stimulate future research studies.

Acquired thermal tolerance and molecular adaptations

Individuals and animals repeatedly exposed to the hyperthermia of exercise can become more resistant to exertional heat injury (EHI) and stroke. This is because of the heat acclimation adaptations and cellular adaptations that induce acquired thermal tolerance. Acquired thermal tolerance is the acquired resistance of cells exposed to mild, sublethal temperature elevations to survive subsequent more severe temperature elevations which would have been previously lethal (261, 422). Acquired thermal tolerance and heat acclimation are complementary; as acclimation reduces heat strain and acquired thermal tolerance increases survivability to a given heat load (173). Kregel (213) has reviewed the association of acquired thermal tolerance among cells, tissues and animals, and more research has been conducted on cell and tissue models (213, 422). However, rodents with fully developed acquired thermal tolerance can survive ~60% more heat load than what would have been initially lethal (122).

Cellular abnormalities associated with severe heat stress include protein denaturation, translational inhibition, ribosomal biogenesis arrest, and cytoskeletal damage, all of which are reduced by acquired thermal tolerance (261, 422, 423). These cellular abnormalities from severe heat stress can result in net outcomes that depend on the cell type and magnitude of hyperthermia which range from minimal apparent changes, to survival and adaptation, to apoptosis, and under extreme conditions, necrosis. These responses likely occur on a continuum rather than as sharply demarcated processes. Recent evidence suggests that measurable changes in the activity of heat-responsive transcription factor heat shock factor 1 (HSF1) can occur even with the relatively mild febrile-range hyperthermia (386, 413).

Mammalian cells have two fundamental classes of responses to hyperthermia: The first class of responses is a change in the activity of extant proteins and other molecules. Examples include activation of stress kinases and changes in protein-protein interactions that lead to activation of transcription factors such as HSF1. The second class of responses includes changes in protein expression that includes *de novo* expression of some proteins, increased expression of others, and decreased expression of yet others. Historically, the proteins showing altered expression (typically increased) after a marked, but sublethal hyperthermia have been termed HSP (136, 422). The physiological signals that induce HSP expression and redistribution include other stressors such as hypoxia, energy depletion, nitrosative/oxidative stress (ROS/NOS) and acidosis which are common to exercise-heat stress (213).

Acquired thermal tolerance is often associated with increased expression (261) and redistribution of HSPs within

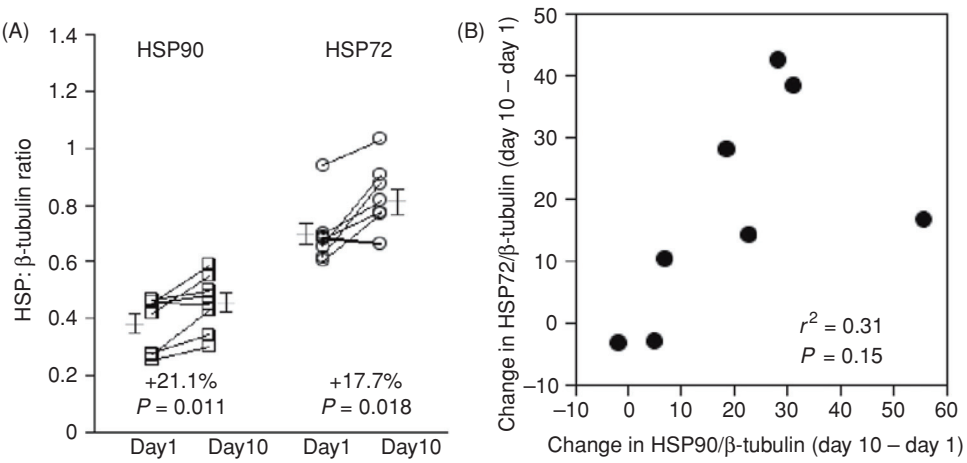

Figure 16 (A) Comparison of baseline heat shock protein (HSP) values between day 1 and day 10 of heat acclimation (HA). (B) Quantification of Western blot analysis in densitometry units representing ratio of HSP:β-tubulin. Values are means and standard deviation with correlation between post-HA (day 10 vs. day 1) increase in HSP72 and HSP90 expression. Reprinted (with permission) from McClung et al. (253).

the cell (423), although acquired thermal tolerance can be induced in the absence of HSP expression [see Kregel (213)]. HSPs are grouped into families by molecular mass (136, 213, 422) and each has a variety of cellular locations and functions that include processing of stress-denatured proteins, management of protein fragments, maintenance of structural proteins, and chaperone of proteins across cell membranes. For example, HSP 27 (sometimes referred to as sHSP), resides in the cytosol and nucleus and has antiapoptotic and microfilament stabilization functions. The HSP 70 family (HSP 72, 73, 75, and 78) resides in the cytosol and nucleus (HSP 72 and 73), endoplasmic reticulum (HSP 78), and mitochondria (HSP 75) and has molecular chaperone (HSP 73, 75, and 78), cytoprotective (HSP 72) and antiapoptotic (HSP 73) functions (213). In addition, HSPs can modulate inflammatory cytokine production and protect animals from endotoxin exposure (276) which should protect against the systemic inflammatory response syndrome (SIRS) associated with heat stroke (229).

The HSP responses increase within several hours of heat exposure and last for several days after exposure. After an initial heat exposure, mRNA levels peak within an hour, and subsequent HSP synthesis depends upon both the severity and cumulative heat stress (246). In addition to heat stress, endotoxin translocation from the gut might mediate HSP expression (368,369). Both heat exposure and high-intensity aerobic exercise elicit HSP synthesis; however, the combination of exercise and heat exposure elicits a greater HSP response than either stressor independently (380). In humans, baseline HSP 72 and HSP 90 levels in peripheral blood mononuclear cells (PBMC) are increased after 6 to 10 days of heat acclimation (253, 434). Figure 16 presents the baseline HSP 90 and HSP 72 responses on subjects completing a 10-day exercise-heat acclimation. HSP90 and HSP72 increased by ~18% and ~21%, respectively, and were significantly correlated with each other (253). Furthermore, PBMC cells obtained from heat acclimated individuals exhibited greater blunting of the HSP response (compared to unacclimated) to heat shock (43°C for 1 h) and this blunted response was directly related to the degree of physiological heat acclimation (lower core temperature) (253). A recent animal study confirmed that heat acclimation increased baseline HSP 72 and HSP 90 levels in lung, heart, spleen, liver, and brain and blunted the heat shock response of HSP 72 (349). In addition, HSP 72 induction might be dependent upon adaptability of the immune system in addition to the thermal challenge (306).

The adaptive responses to heat stress may also confer acquired cross-tolerance, that is, protection against unrelated stressors, such as ischemia-reperfusion injury, hypoxia, and traumatic brain injury (171). The mechanisms mediating acquired cross-tolerance are believed to involve multiple pathways that confer cytoprotection and maintenance of DNA and chromatin integrity, upstream epigenetic information as well as metabolic adaptations (407). Cytoprotection is mediated through increases in HSP's, as well as antiapoptotic and antioxidative pathways. Heat acclimation also induces hypoxic inducible factor 1α and its targeted metabolic pathways (glycolytic enzymes, glucose transporters, erythropoietin) conferring protection against closed head injury, hypoxia, and ischemia-reperfusion injury (407). Detailed gene and protein expression studies have not been completed following human heat acclimation, but exercise and heat shock similarly affect stress response genes such as stress kinase (123), growth and transcription factors, and inflammatory and immune response genes (369, 388).

Water and Minerals

Water and mineral needs

Daily water balance depends on the net difference between water gain and water loss. Water gain occurs from consumption of liquids, the water in food, and water produced during

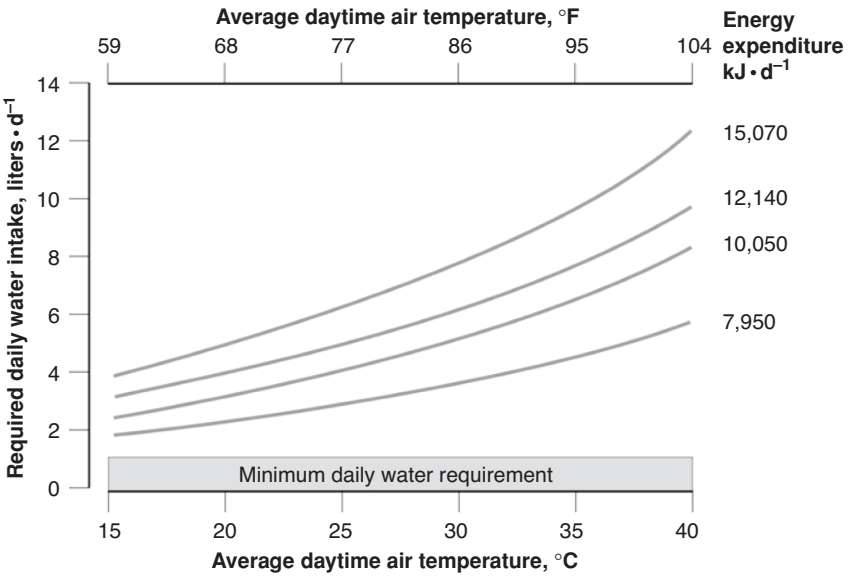

Figure 17 Predictions of daily water requirements as function of daily energy expenditure and air temperature. Figure adapted (with permission) from Institute of Medicine (181).

cellular respiration. Water is lost via ventilation, fecal and urine production, and secretion of sweat. The quantity of water lost in the expired air is proportionate to the ventilatory volume and modified by the humidity of the ambient air (260). Of important note, the volume of metabolic water produced during cellular metabolism (~0.13 g·kcal^{-1}) approximates that lost via ventilation (~0.12 g·kcal^{-1}) (85, 260). As a consequence, these two pathways produce water turnover and a net loss of body mass, with little or no effect on net water balance. Gastrointestinal tract losses tend to be negligible (~100-200 ml·day^{-1}), with the exception that certain illnesses, such as diarrhea, can lead to loss of large amounts of fluid and electrolytes. Water losses in urine approximate 1 to 2 liters/day, but can be larger or smaller depending on daily fluid consumption and activity (181, 325). Minimum outputs of ~20 ml·h^{-1} and maximal volumes of ~1000 ml·h^{-1} are possible (181). The ability to vary urine output represents the primary means to regulate net body water balance across a broad range of fluid intake volumes and losses.

Humans maintain net water balance (loss = gain) remarkably well day to day, as thirst and hunger drives coupled with ad libitum access to food offset daily water losses. Studies examining day-to-day variability of water status indicate that water balance typically varies only 0.2% to 0.7% (3, 73). It is recognized, however, that after significant body water deficits like those associated with physical exercise or heat stress, many hours of rehydration and electrolyte consumption may be needed to reestablish body water balance (378). Fluid needs are met from beverages and food sources. For adults in the United States, total water intake is typically ~28% from foods, ~28% from drinking water, and ~44% from other beverages (181). The average self-reported intake (mean and 95% CI) for men and women is 3.5 (2.0-5.6) and 3.0 (1.7-4.8) liters·day^{-1}, respectively (181). Studies of preformed water turnover in men and women are slightly more modest, with turnover rates of 3.0 and 2.5 liters·day^{-1}, respectively (325). With water turnover rates of ~3 liters·day^{-1}, approximately 5% to 10% of body water is turned over daily (325).

Physical activity alone or combined with environmental heat stress can substantially increase water daily requirements. As mentioned, a person's sweat rate increases as a function of exercise intensity and warm conditions amplify the sweating response associated with exercise. As an example, it is not unusual for distance runners to have sweating rates of approximately 0.7 to 1.0 liters/h (Table 2). The imposition of warm weather and/or clothing can increase those sweating rates by 50% to 100%. Depending upon the duration of activity and heat stress exposure, sweat losses will vary and thus impact daily water requirements. Figure 17 depicts generalized modeling approximations for daily water requirements based upon calculated sweating rates as a function of daily energy expenditure (activity level) and air temperature (181). This prediction model indicates that daily water requirements can increase 2- to 6-fold from baseline by simple manipulation of either energy expenditure or ambient temperature.

Sweat is composed of primarily water and modest amounts of solute. Sodium is the mineral element secreted in greatest abundance, followed by chloride, potassium, calcium, and magnesium (47, 87, 264, 377, 416). Sweat sodium concentration values in the range of 20 to 50 mM are frequently cited in the literature, but values vary considerably both within and between individuals (7, 47, 87, 264, 317, 377, 416). Sweat potassium concentration averages 5 mM (typical range 4-7 mM), whereas calcium and magnesium levels are typically in the range of 0.5 to 1.5 mM and 0.1 to

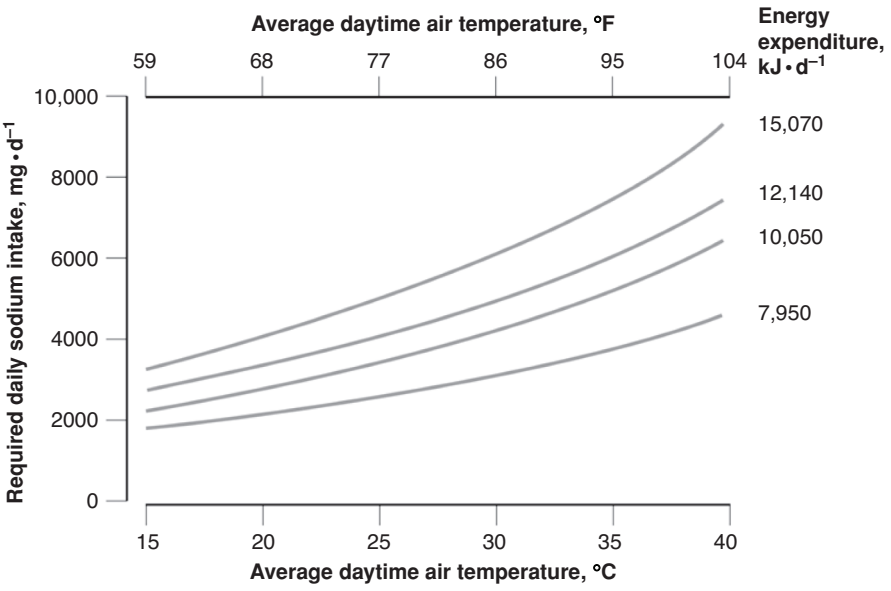

Figure 18 Predictions of daily sodium requirements as function of daily energy expenditure and air temperature. Figure adapted (with permission) from Institute of Medicine (181).

0.2 mM, respectively (23, 80, 86, 174, 175, 264, 377). Neither sex, maturation nor aging seem to have marked effects on sweat mineral concentrations (257, 275). The sweat glands reabsorb sodium by active transport, but the ability to reabsorb sweat sodium does not increase proportionally with the sweating rate. As a result, the concentration of sweat sodium increases as sweating rate increases (7, 87). Heat acclimation improves the ability to reabsorb sodium, thus heat acclimated persons have lower sweat sodium concentrations (>50% reduction) for any given sweating rate (7, 99), but considerable between-subject variability persists.

Figure 18 depicts generalized modeling approximations for daily sodium requirements for a range of daily energy expenditures (activity level) and air temperatures (181). It is apparent that the sweat losses accompanying physical activity and warm weather conditions can increase dietary sodium requirements. It is important to note, however, that this analysis assumed a heat acclimated state and relatively dilute sweat sodium concentrations (25 mM or about 0.6 g·liter^{-1}). If the model assumed higher sweat sodium concentrations, daily needs would be even higher for any given energy expenditure and weather combination. Fortunately, decreases in sodium stores are usually corrected at meal times consequent to a greater salt appetite and the additional food consumed to restore energy balance (181). Therefore, sodium supplementation is generally not necessary or is achievable by salting food to taste. There are situations, however, where combinations of physical activity and/or ambient temperatures produce persistent sweating and unless meals are consumed during the activity, considerable salt deficit can accrue. Under such conditions, consideration should be given to replacing the sodium on-the-go; for example, with the use of a sports drink. (See the *Hyponatremia* section.)

Water deficits

It is sometimes difficult to match fluid consumption with sweat losses so water losses of 2% to 6% of typical body mass have frequently been observed (353). Although this is more common in hot environments, similar deficits are observed in cold climates when working in heavy clothing (302). The mismatch between intakes and losses is due to physiological and behavioral factors. When body water deficits (hypohydration) occur from unreplaced sweat losses, a hypertonic hypovolemia generally results. Plasma volume decreases and plasma osmotic pressure increases in proportion to the decrease in total body water. Plasma volume decreases because it provides the fluid for sweat, and osmolality increases because sweat is ordinarily hypotonic relative to plasma. Resting plasma osmolality increases in a linear manner from about 290 mmol·kg^{-1} when euhydrated by ~1.5 mmol·kg^{-1} for each 1% decrease in TBW (181). The increase in osmotic pressure is primarily due to increased plasma sodium and chloride with no consistent effect on potassium concentrations (105, 214, 268, 370).

Hypohydration increases the core temperature and heart rate responses to exercise, and increases the perception of effort to perform physical exercise (149, 266). Water deficits of as little as 1% of body weight can elicit measurable effects (108). In warm weather, core temperature typically increases an additional 0.1 to 0.2°C for every percent body weight lost due to unmet water needs, whereas heart rate increases an additional 3 to 5 bpm (149, 181, 266, 347). In cooler weather, hypohydration induces a more modest impact on core temperature and heart rate (71, 200, 289, 357). Altering the timing of fluid ingestion (e.g., more frequent or drinking a bolus early or late into an exercise bout) does not appear to modify the relationships between hydration state and the

physiological modifications to the exercise response (267). The magnitude of the penalty will effectively negate the core temperature and cardiovascular advantages conferred by high aerobic fitness and heat acclimation (59, 351, 357).

The added thermal and cardiovascular burden accompanying water deficits are produced by regulated changes in the thermoregulatory control system. Hypohydration increases the threshold core temperature for skin vasodilatation (150, 280) and the commencement of sweating (269), and reduces the sensitivity of each to changes in core temperature (150, 269). Both the singular and combined effects of plasma hyperosmolality and hypovolemia have been implicated for mediating these thermoregulatory adjustments (118, 119, 401, 402).

As discussed earlier, a physiological consequence of hypohydration is degraded endurance exercise performance and likely sports performance. For example, McGregor et al. (254) reported that semi-professional soccer players hypohydrated in excess of 2% of initial body mass were less able to sprint during latter stages of a variable-intensity running protocol meant to simulate match play and required more time to complete an embedded soccer dribbling task. Hypohydration appears to have little or no effect on muscular strength (113, 155) or anaerobic performance (72, 183) but sometimes has been reported to reduce small muscle endurance (30, 274) and tolerance to repeated bouts of high-intensity work (194). Hypohydration in excess of 2% to 3% body mass is, however, associated with deterioration in the ability to execute sport specific skills (20, 96, 101). For example, Baker et al. (20), reported that basketball players attempted fewer shots and were less able to make shots linked with movement (e.g., lay-up) when hypohydrated by 3% of body mass and shooting was further impaired at a 4% deficit. While the mechanism(s) remain unresolved, it may be linked to changes in vestibular function and/or vestibular sensitivity as consequence of water deficit (135, 231).

Hyponatremia

Dilution of plasma sodium will induce movement of water from the extracellular fluid into intracellular spaces and cause cell swelling. If it occurs rapidly and is of sufficient magnitude, this fluid shift can congest the lungs, swell the brain, and alter CNS function (17). The clinical signs and symptoms associated with hyponatremia include confusion, disorientation, mental obtundation, headache, nausea, vomiting, aphasia, incoordination, and muscle weakness. Complications of severe and rapidly evolving hyponatremia include seizures, coma, pulmonary edema, and cardiorespiratory arrest.

Hyponatremia is relevant to the discussion of exercise and heat stress as it has developed in otherwise healthy individuals participating in marathon and ultramarathon competition (81, 95, 168, 391), military training (132, 304), and recreational activities (18). Smaller participants appear to be at most risk (8, 81) and in athletic events, it has been more frequently observed in females and slower competitors (8, 95). A common feature has been prolonged sustained exercise (typically >5-h duration) where sweating was the primary means of heat dissipation and aggressive fluid replacement was implemented to prevent hypohydration.

Over the past 10 to 15 years, there has been considerable confusion regarding the causes of exercise-associated hyponatremia; probably because there are multiple factors that could contribute to sodium dilution during prolonged exercise (273). There is general agreement, however, that exercise-associated hyponatremia primarily arises from persistent overdrinking of fluids relative to sweating rate and the inability to excrete the relative fluid excess either during or in the initial recovery period (293, 337, 365, 415). It has also been established empirically and via derivation that plasma sodium can be predicted from the mass balance of water, sodium, and potassium as $Na^+_{plasma} = 1.03\ (Na^+_{exchangeable} + K^+_{exchangeable})/TBW - 23.8$ (105, 288). When this relationship is applied to exercise and used to predict sodium responses to exercise and varying fluid replacement strategies, the result is predicted values that reproduce what has been observed in observational studies (265); indicative that the plasma sodium responses observed during exercise can be modeled by the mass balance of water, sodium, and potassium.

To address the plausible contributing factors in the etiology of exercise-associated hyponatremia, Montain et al. (265) modeled the body water and plasma sodium responses to a variety of exercise intensities, hydration strategies for individuals with differing body mass and fatness. Since hyponatremia is more common in long-duration activities and slower competitors, a slow running time (8.5 $km \cdot h^{-1}$) was modeled. Figure 19 predicts the percent change in body mass over time for three drinking rates, as well as the expected plasma sodium concentration if sweat sodium was relatively dilute, moderate, or salty. The slowest drinking rate (400 $ml \cdot h^{-1}$) over the duration of the modeled period (12 h) predicts an elevated plasma sodium level well above that of asymptomatic hyponatremia (135 $mEq \cdot liter^{-1}$). However, this drinking rate results in a 2% level of hypohydration by 5 h (yellow zone), and 4% by 11 h, the latter being a level of fluid loss that would substantially degrade performance (red zone). The fastest drinking rate in the simulation (800 $ml \cdot h^{-1}$) is well in excess of sweating rate and produces an accumulation of body mass over time and this fluid intake pattern is predicted to result in asymptomatic hyponatremia within 5 to 6 h of activity and symptomatic hyponatremia (sodium <130 $mEq \cdot liter^{-1}$; red zone) by 10 h if the sweat is relatively dilute; 2.5 and 5 h, respectively, if the sweat is relatively salty. The intermediate drinking rate is predicted to produce hyponatremia not because the rate of fluid intake exceeds sweating rate, but because of progressive salt deficit. The latter prediction is consistent with observational (305, 391) evidence suggesting that in ultramarathon activities, fluid replacement with water or other electrolyte-poor beverages (relative to sweat sodium concentrations) can lead to dilution of plasma sodium below 130 $mEq \cdot liter^{-1}$ without overdrinking relative to sweating rate. Consumption of an electrolyte-supplemented drink is predicted to substantially delay or prevent this outcome (265), consistent with the

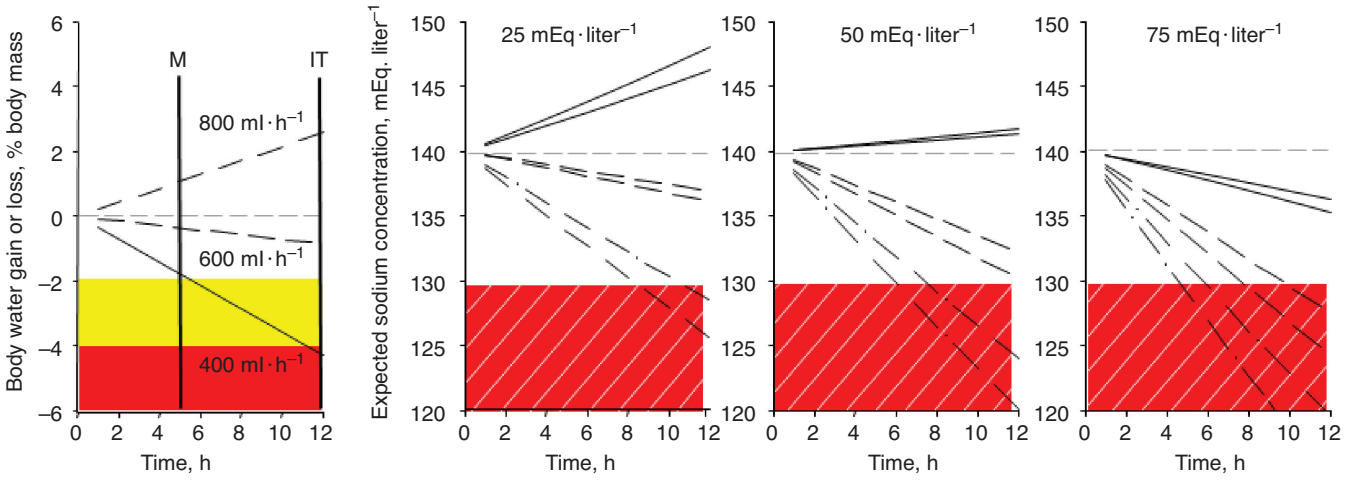

Figure 19 Predicted body mass loss (due to water deficit; left panel) for two 70-kg people of different body composition, running at 8.5 km·h^{-1} in temperate weather (18°C), and drinking water at three rates [400 ml·h^{-1} (solid line), 600 ml·h^{-1} (broken line), 800 ml·h^{-1} (broken dotted line)]. The yellow-shaded areas indicate when water loss would be sufficient to modestly degrade performance, and when water loss would substantially degrade performance (red). Also predicted are plasma sodium concentrations for three rates sweat sodium loss. Two lines sharing the same line style are the predicted outcomes for people of two different body compositions; with total body water accounting for 50% and 63% (leaner) of body mass. The hatched shaded areas denote the presence of hyponatremia (plasma sodium concentration <130 mEq·liter^{-1}) into the range where symptoms develop.

observation that sodium intake is predictive of the magnitude of plasma sodium change that develops during an ironman triathlon (311). The principal lesson from this illustration is that overdrinking, both in its absolute (volume related) and relative forms (relative to sodium loss), is the mechanism that leads to exercise-associated hyponatremia. As such, prevention strategies should focus on not drinking in excess of sweating rate, and to include salt-containing fluids or foods when participating in exercise events that produce multiple hours of continuous or near-continuous sweating.

Hydration assessment

Human hydration assessment is a key component for prevention and proper treatment of fluid and electrolyte imbalances (79, 247, 309). The efficacy of the available assessment indices depends critically upon the nature of body fluid losses. In many clinical and most sports medicine situations, a hypertonic-hypovolemia is produced as consequence of the loss of hypotonic body fluids (79, 247, 352). The rise in extracellular tonicity is a hallmark clinical feature that provides diagnostic distinction from isotonic or hypotonic hypovolemia (116, 247). Hypotonic fluid losses, in turn, modulate renal function, and urine composition in accordance with the body water and mineral deficit (88, 332, 381), thus providing the fundamental framework for using blood (osmolality, sodium, and fluid regulatory hormones) and urine (osmolality, specific gravity, and color) as principle body fluid hydration assessment measures. However, as illustrated in Figure 18 when substantial solute (electrolyte) is lost consequent to profuse sweating during prolonged exercise, an isotonic or hypotonic-hypovolemia can result.

Plasma osmolality has been the single-criterion hydration assessment measure in large-scale fluid-needs-assessment surveys (181), but is not practical for rapid assessment or use in field situations. There are other methods available, but each has its own limitations, whether it is a methodological limitation or poor sensitivity. Large-population heterogeneity explains, in part, why many of the existing hydration status markers lack diagnostic sensitivity from a single measurement (74). Change measures can improve diagnostic accuracy, but their usefulness depends on the homogeneity of measures taken on the same person if day-to-day monitoring is desired (74). More acute change measures (over hours) require a valid baseline and control over confounding variables. Table 5 provides definable thresholds (74) which can be used as a guide to detect hypohydration from hypertonic-hypovolemia. The current advice is that hydration can be considered adequate when any two assessment outcomes are consistent with euhydration (Table 5) (79, 352). Values that occur between euhydration and hypohydration represent typical human variation (212) in homeostatic set points due to biology, as well as social (diet) and environmental (exercise, climate) influences.

Heat Illness

Serious exertional heat illnesses

During the past three decades, exertional heat illness hospitalizations have increased markedly in civilian and military communities (63, 285). Heat exhaustion, heat injury, and heat stroke are terms used to describe a plurality of serious heat illnesses (431). Heat exhaustion is defined as a mild to moderate illness characterized by inability to sustain cardiac output

Table 5 Biomarkers of Hydration Status

Measure	Euhydration	Population reference interval	Dehydration
TBW, liters	<1%	N/A	≥3%
Plasma osmolality, mmol·kg^{-1}	<290	285-300	≥297
Urine-specific gravity, units	<1.02	1.010-1.03	≥1.025
Urine osmolality, mmol·kg^{-1}	<700	300-900	≥831
Urine color, units	<4	N/A	≥5.5
Body weight[a], kg	<1%	N/A	≥2%

[a]Potentially confounded by changes in body composition during very prolonged assessment periods.
Compiled from [Sawka et al. (352); Cheuvront and Sawka (79); Kratz et al. (212); and Cheuvront et al. (74)].

with moderate (>38.5°C) to high (>40°C) body temperature resulting from strenuous exercise and environmental heat exposure and is frequently accompanied by hot skin and dehydration (431). Heat injury is defined as a moderate to severe illness characterized by organ (e.g., liver and renal) and tissue (e.g., gut and muscle) injury associated with high body temperature resulting from strenuous exercise and environmental heat exposure, with body temperatures that usually, but not always, are more than 40°C (431).

Heat stroke is defined as a severe illness characterized by profound central nervous system dysfunction, organ (e.g., liver and renal), and tissue (e.g., gut and muscle) injury with high body temperatures resulting from strenuous exercise and environmental heat exposure (431). Heat stroke is often categorized as "classic" or "exertional," with the former observed primarily in otherwise sick and compromised individuals and the latter observed primarily in apparently healthy and physically fit individuals (431). Heat stroke victims have profound neuropsychiatric impairments that develop early. Heat stroke can be complicated by liver damage, rhabdomyolysis, disseminated intravascular coagulation (DIC), water and electrolyte imbalances, and renal failure (431).

Risk factors for exertional heat illness include lack of heat acclimatization, low physical fitness, dehydration, high body mass index, underlying health conditions, and certain medications (431). Serious exertional heat illness, however, can occur in low-risk persons who are practicing sound heat mitigation procedures. Figure 20 presents the percentage of Marine recruits suffering exertional heat stroke relative to their risk category (131). Note that ~50% of the cases were low or medium risk indicating that fitness, leanness and heat acclimation provided insufficient protection. Exertional heat stroke often occurs under conditions that the victim has been exposed to many times before or while others are concurrently being exposed to the same condition without incident. This suggests that these victims were inherently more vulnerable that day and/or some unique event triggered the heat stroke. It is suspected that some victims of exertional heat stroke were sick the previous day (130). Exertional heat stroke often occurs very early during an exercise bout suggesting that the victim began the exercise in a compromised state on that particular day (61, 112, 375). The common observation of rapid development of hyperthermia suggests that fever from a preexisting illness or inflammation may augment the normal

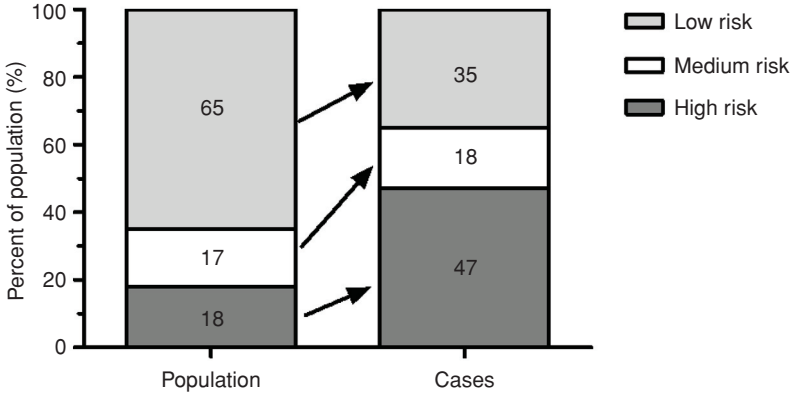

Figure 20 Distribution of relative risk among male Marine Corps recruits and distribution of exertional heat stroke at Parris Island, SC, for years 1988 to 1992. High risk = body mass index (BMI) ≥22 kg·m^{-2}, 1.5 mi run time ≥12 min; medium risk = BMI ≥26 kg·m^{-2}, 1.5 mi run time <12 min or BMI <22 kg·m^{-2}, 1.5 mi run time ≥12 min; low risk = BMI <26 kg·m^{-2}, 1.5 mi run time <12 min. Adapted (with permission) from Gardner et al. (131).

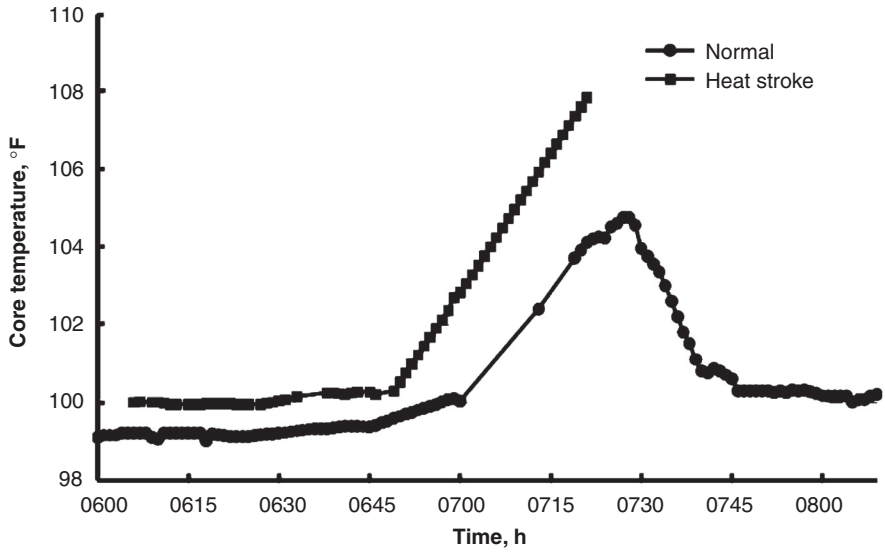

Figure 21 Core temperature of a male Marine Corp recruit during normal physical training and when incurring exertional heat stroke, conducted on two different days. Note the rapid development of hyperthermia on the day of heat stroke despite performing the same activity as the day that heat stroke was not observed. Wenger et al. (unpublished data).

hyperthermic response to exercise. Figure 21 shows the core temperature profile of a Marine recruit during a normal physical training run and during the development of exertional heat stroke (Wenger, unpublished data). Note the rapid development of hyperthermia on the day of the heat stroke, despite performing the same activity previously when heat stroke did not ensue.

This raises the question as to the mechanism(s) responsible for the rapid and profound increase in core temperature on the heat stroke day. Fever and inflammatory responses from gut ischemia and endotoxin release (218, 219) or prior skeletal muscle injury (270) may adversely influence thermoregulation and mediate augmented hyperthermia. It has been previously discussed that stressful exercise and heat stress can markedly reduce gut blood flow (339), which was associated with increased small intestine permeability in rats (218) and accentuated by dehydration (219) during exercise-heat stress in humans. Gut underperfusion and ischemia will result in endotoxin release from the small intestine with consequent inflammatory and coagulation responses that are associated with heat stroke (36). The resultant ischemia promotes nitrosative and oxidative stress, which compromises tight junctions of the gut epithelial membrane and causes them to become "leaky;" as a result, gram-negative and gram-positive bacteria that are normally confined to the gut lumen are able to freely cross the membrane barrier (100, 158, 217, 218).

The rapid rise in body temperature may be mediated by neuronal pathways of thermogenesis that are stimulated in the liver following pathogen exposure. The liver reticuloendothelial system (RES) comprises monocytes, macrophages, and Kupffer cells that detect bacterial pathogens (e.g., endotoxin released from small intestine) and stimulate the complement cascade for rapid, local production of prostaglandin E_2 (PGE_2, an endogenous trigger of fever) (31). PGE_2 binds to receptors on local vagal (afferent) neurons, which project to the preoptic area of the hypothalamus to alter heat loss and heat production pathways to generate fever (31). Although an effective mechanism of thermoregulatory control under infectious and inflammatory states, the rapid generation of neuronal fever during exercise-heat stress augments the hyperthermia of exercise to rapidly induce very high core temperatures.

Systemic inflammatory response syndrome

Figure 22 provides the progression of pathophysiological events that mediate the SIRS to gut endotoxin leakage. Heat stroke sequelae are thought to be a consequence of a SIRS that ensues following heat-induced damage to the gut and other organs (36). The thermoregulatory, hypermetabolic, immune, and organ function disturbances that comprise the SIRS often lead to multiorgan dysfunction, shock, and death. As discussed, reduced gut perfusion and the release of bacterial endotoxin is a key pathophysiologic event for initiation of the SIRS.

Figure 23 provides micrographs of sloughing and histological damage to the epithelial gut membranes that facilitates endotoxin leakage into the systemic circulation (218). The "gut-liver axis" functions as the final defense against intestinal endotoxin translocation into the systemic circulation, but decrements in liver function during exercise-heat stress may compromise this protective mechanism. Under homeostatic conditions, a small amount of endotoxin enters the portal blood and through antigen sampling helps to maintain the liver RES in a primed state. During conditions of prolonged reductions in liver blood flow, the clearance function of this organ is compromised and can result in the development of

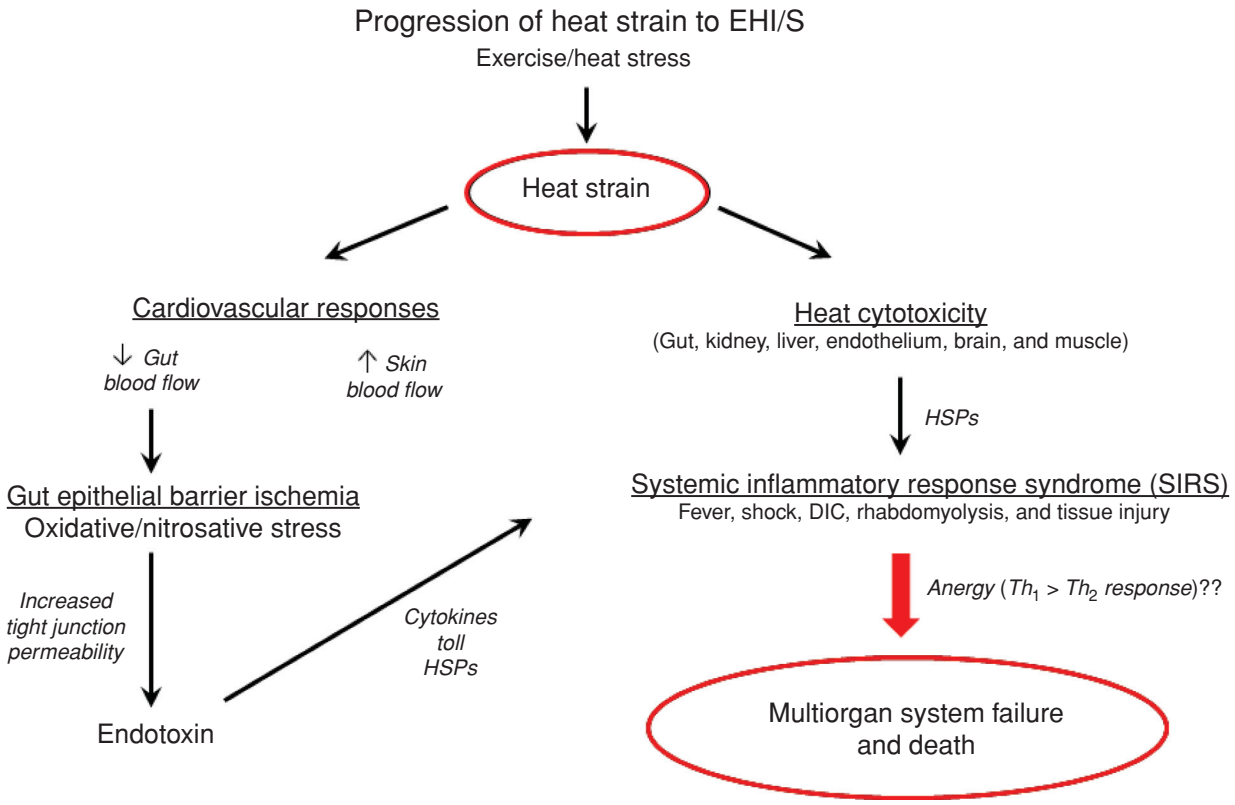

Figure 22 Summary of exertional heat stroke pathophysiological responses that culminate in multiorgan system failure. During exercise heat stress, there is an increase in cutaneous blood flow and decrease in splanchnic blood flow. Gut epithelial membrane ischemia induces oxidative and nitrosative stress that increases tight junction permeability and allows endotoxin to leak into the systemic and portal circulation. Toll-like receptors (e.g., TLR4) detect pattern-associated molecular patterns (PAMPs) on the cell membrane of endotoxin and stimulate pro- and anti-inflammatory cytokine production. Heat is toxic to several organs and stimulates the secretion of heat shock proteins (HSPs) that interact with cytokines and other proteins to mediate the systemic inflammatory response syndrome of the host. A shift of the cytokine milieu from anti-inflammatory (Th2) to a pro-inflammatory (Th1) balance (a process known as anergy) is thought to mediate many of the adverse consequences of the heat stroke syndrome that lead to multiorgan system failure and death.

a septic state. Experimental and clinical studies have shown decreased splanchnic blood flow at temperatures of ~40°C and compromised liver function at temperatures of ~41 to 42°C (40, 65, 204).

Several lines of evidence support the hypothesis that endotoxin is the initiating stimulus for the heat-induced SIRS. First, increased portal or systemic endotoxin levels are observed in heat stroke patients and animal models. An 18-year old football player collapsed from exertional heat stroke (core temperature ~40.6°C) and remained hospitalized for 4 days with extensive liver damage that was thought to be the cause of endotoxemia at the time of death (153). In heat stroke patients, endotoxin was detected at ~42.1°C and remained elevated despite cooling whereas circulating endotoxin was detected at rectal temperatures exceeding 41.5°C in a nonhuman primate model of heat stress (37, 133). Second, stimulation of the liver RES rendered rats endotoxin-tolerant and protected against heat stroke mortality (104). Third, antibiotic therapy has shown protection against heat stroke in several species. In dogs treated with antibiotics to reduce gut flora levels, 18-h survival rates were increased more than 3-fold, as long as the treatment was provided prior to heat exposure (55). Anti-lipopolysaccharide (LPS) hyperimmune serum reversed heat stroke mortality of primates and returned plasma LPS levels to baseline, but was ineffective at the highest body temperature of 43.8°C, suggesting that extreme hyperthermia can cause irreversible organ damage and death (134).

Thermoregulatory responses after heat stroke

Hypothermia and recurrent hyperthermia are core temperature responses often observed in patients and experimental animal models during heat stroke recovery (226, 245, 375). Hypothermia is not a universal heat stroke recovery response in humans, but has been anecdotally observed following aggressive cooling treatment. Patients may show a rapid undershoot of body temperature to less than 37°C following cooling therapy, which has been traditionally regarded as a dysregulated response due to compromised thermoregulatory control following heat-induced damage to the POAH (see earlier discussion which considers the POAH as the main thermoregulation control site) (245). However, despite evidence of

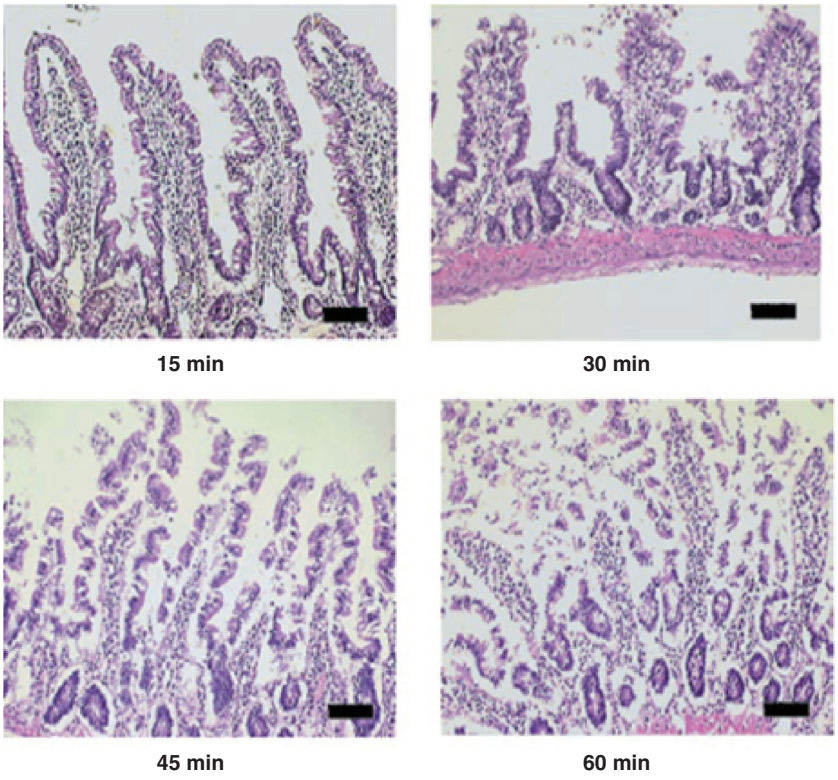

Figure 23 Representative light micrographs of histological damage (hematoxylin and eosin stain) to inverted rat small-intestinal sac tissue exposed to 41.5 to 42°C over a 60-min time course. Villi appear normal at 15 min compared with the initial sloughing of epithelia from the villous tips at 30 min of exposure. At 45 min, there is significant lifting of villi epithelial linings at the top and sides, which is completed denuded by 60 min of exposure. Bars represent 100 μM. $N = 2$ to 4 rats per time point. Reprinted (with permission) from Lambert et al. (218).

extensive damage to a number of CNS regions (e.g., cerebral cortex, cerebellum, and cerebral ventricles) there is scant clinical or experimental evidence to support the widespread belief that the POAH is damaged in response to heat stress or the SIRS (137, 163, 228, 245). A clinical study of 125 fatal military exertional heat stroke cases failed to detect histological damage to the POAH despite the occurrence of hypothermia, recurrent hyperthermia, cerebral edema, degeneration of the Purkinje cells of the cerebellum and extensive histological damage to peripheral organs, including the spleen, liver, and kidney (245, 375). Shibolet et al. (375) reported fever within 3 days of exertional heat stroke collapse, which was associated with petechial hemorrhages of the ventricle walls and hypothalamus (exact region not specified) in the most severe cases. Interestingly, mild cases also presented with fever, but histological damage to the POAH was not reported (375). More recent studies have used computer tomography (CT) scans and magnetic resonance imaging (MRI) to assess CNS abnormalities in exertional heat stroke victims. Severe CNS dysfunction (e.g., coma) correlated with cerebral edema that presented as a loss of gray-white matter discrimination, which was the only notable abnormality (400). Neurological impairments in heat stroke patients are likely a consequence of increased intracranial pressure (ICP) from reduced CBF, cerebral ischemia, and possibly intracranial hemorrhage (294). The Purkinje cells of the cerebellum appear to be particularly sensitive to heat injury with the progression of cerebellar atrophy readily apparent in MRI images of exertional heat stroke victims that experienced ataxia or other functional impairments (6, 255) (Fig. 24). Despite the emergence of sensitive technologies for clinical assessments, damage to the POAH region has not been documented in exertional heat stroke victims that present with these common CNS and neurological abnormalities.

In experimental animals, hypothermia is a natural heat stroke recovery response that occurs in the absence of cooling treatments and is thought to be a regulated response that is important for survival (Table 6). Small rodents, such as mice and rats display more than 1.0°C hypothermia following heat stroke collapse and the depth and duration of this response is directly related to heat severity (227). Furthermore, exposure to warm ambient temperatures that prevent this response causes increased intestinal damage and mortality (227, 426). If a similar relationship exists between heat severity and hypothermic characteristics for humans, this could have important implications for the timing of clinical treatment strategies.

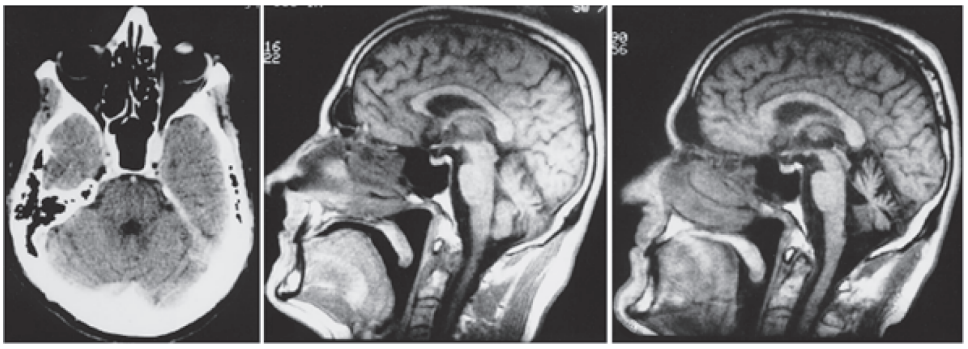

Figure 24 Computer tomography (CT) scans of a 45-year-old man that collapsed from exertional heat stroke on a hot summer day. He was unconscious and hyperthermic (42°C) with convulsion at the time of hospital admission. The patient remained unconscious for 5 days. (A) Normal CT scan of the cerebellum 2 weeks following collapse (B) and (C). Progression of cerebellar atrophy from 10 weeks (B) to 11 months (C). Note that hypothalamic damage was not reported in this patient. Reprinted (with permission) from Albukrek et al. (6).

The low incidence of hypothermia in heat stroke cases may be due to body scaling issues (significantly smaller surface area to body mass ratio compared to small rodents) or clinical interventions that have masked the response. Based on the Q_{10} effect, hypothermia is thought to minimize energy demands and reduce the generation of harmful reactive oxygen species that would otherwise cause tissue damage in response to heat stress. This suggests that cooling of heat stroke patients to a hypothermic level (i.e., core temperature <37°C) may be beneficial for the prevention of tissue injury. Further support for this contention is provided by the use of induced hypothermia, in which core temperature is physically decreased using cooling blankets or other methods, as a protective measure for treatment of cardiac arrest (184), traumatic brain injury (178), and stroke (98, 248). Small rodents often develop regulated hypothermia in response to extreme environmental insults, such as dehydration, food restriction, and hypoxia and recent data suggest that this is also a survival strategy for heat stroke recovery (51, 180, 211). In mice, hypothermia immediately following heat stroke collapse was associated with ~35% decrease in metabolic heat production and the behavioral selection of microclimates that precisely regulated the depth and duration of the core temperature decrease; importantly, these responses occurred in the absence of histological damage to the POAH (228) (Fig. 24).

The most common thermoregulatory response observed during heat stroke recovery is recurrent hyperthermia (227, 245, 256, 375). The appearance of hyperthermia during the initial hours following heat stroke collapse (often referred to as rebound hyperthermia) is typically regarded as a compensatory peripheral vasoconstriction response to cooling of the skin surface with ice packs; conversely, protracted episodes are regarded as disturbances in CNS thermoregulatory control related to POAH damage (245). Similar to the discussion of hypothermia control, there is scant evidence to support the hypothesis that recurrent hyperthermia is due to a lack of thermoregulatory control since patients and animal models that display this core temperature response do not exhibit POAH damage (228, 245, 375). Rather, recurrent hyperthermia appears to be a true fever response that, under certain heat stroke conditions, may be important for recovery. In mice, hyperthermia was observed within ~24 to 36 h following heat stroke collapse and associated with ~20% increase in metabolic heat production and increased plasma levels of

Table 6 Magnitude of Hypothermia in Animal Models During Heat Stroke Recovery

Species	Maximum T_c	Recovery T_a	Hypothermia	Authors
Cat	NS	NS	33.5, 35.0°C	Adolph (5)
Guinea Pig	NS	NS	37°C	Adolph (5)
	IPH; 43.9°C	21-23°C	T_h; 34°C	Romanovsky and Blatteis (335)
Mouse	42°C	10°C; 25°C	32°C	Wright (433)
	38.7-41.9°C	24°C	29-35°C	Wilkinson et al. (426)
	42.4, 42.7, 43.0°C	25°C	29-31°C	Leon et al. (227)
Rat	41.5-42.8°C	Heat pad 39-40°C	35-36°C	Lord et al. (239)
Salamander	33.7°C	Thermal gradient	10°C below controls	Hutchison and Murphy (179)

Abbreviations: IPH, intraperitoneal heating; T_a, ambient temperature; T_c, core temperature; T_h, hypothalamic temperature; NS, not specified. Adapted from Leon (225).

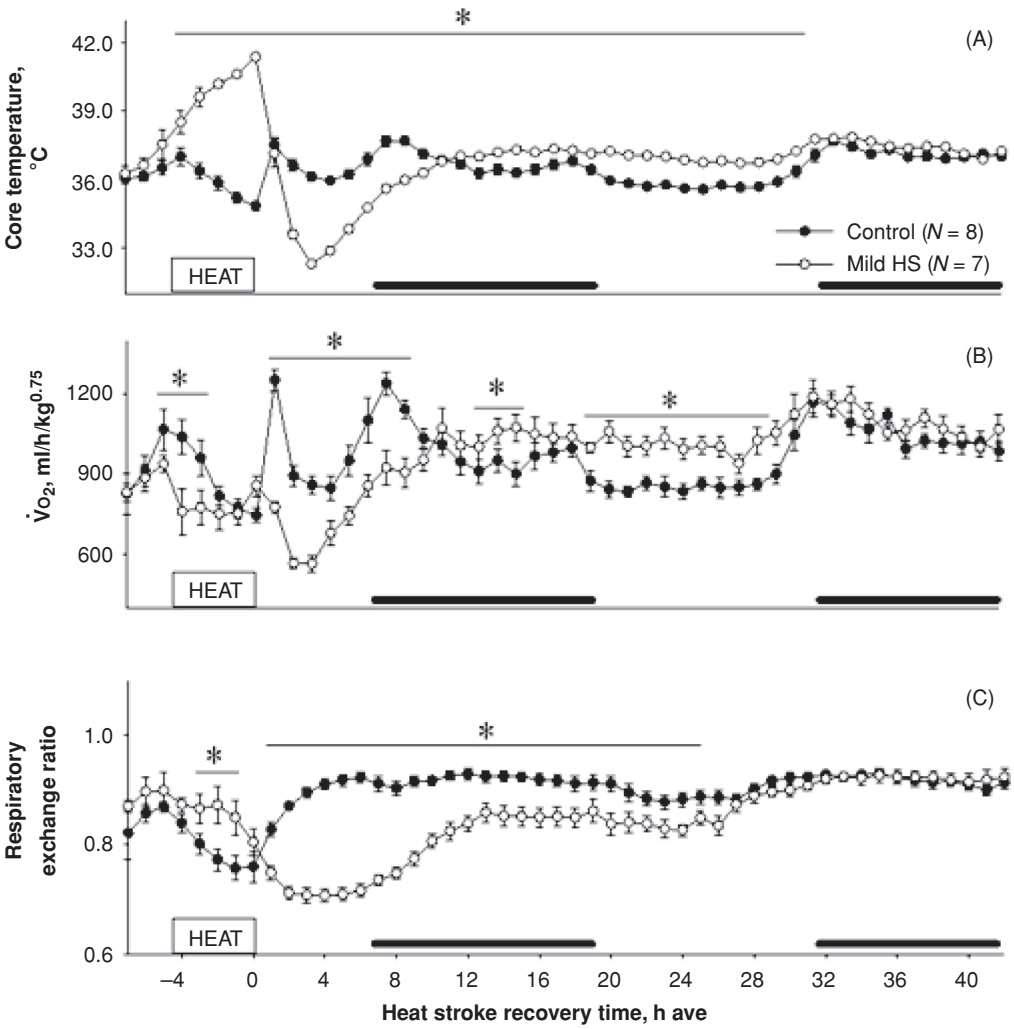

Figure 25 Time course of core temperature (A; °C; radiotelemetry), metabolic rate (B; oxygen consumption, $\dot{V}o_2$), and respiratory exchange ratio (C; RER) of control and mild heat stroke mice during heat stroke and recovery in an indirect calorimeter. Time 0 represents the start of recovery following heat stroke collapse. Note that mice developed hypothermia immediately following collapse that was preceded by ~35% reduction in $\dot{V}o_2$. Despite reliance on fatty acid oxidation (RER~0.7) during hypothermia, mice developed fever (~1°C), which was associated with ~20% increase in $\dot{V}o_2$ from 20 to 32 h of recovery. Note that hypothermia and fever were observed in heat-stroked mice in the absence of histological damage (hematoxylin and eosin) to the preoptic area of the hypothalamus. Data are 1-h averages. Black horizontal bars indicate lights-off periods. *represents significant difference between heat stroke and control animals at $P < 0.05$. Reprinted (with permission) from Leon et al. (228).

the pro-inflammatory cytokine IL-6 (a known fever inducer) (226, 227, 228) (Fig. 25).

The failure to recover from regulated hypothermia and develop fever within ~24 to 36 h of severe heat stroke collapse was associated with increased mortality, suggesting that fever is important for survival under extreme conditions (227, 228). Cytokines are important regulators of body temperature during infection and inflammation and may regulate fever during heat stroke recovery in response to the SIRS (226). Fever induced by an intraperitoneal injection of LPS (the cell wall component of gram-negative bacteria) in rats is also associated with ~15% to 20% increase in metabolic heat production and elevated pro-inflammatory cytokine (IL-1 and IL-6) levels (49, 50, 160). Interestingly, hyperthermia observed during recovery in exertional heat stroke patients was rapidly re-established following clinical cooling (245). This is reminiscent of Liebermeister's experimental observations of the highly regulated nature of fever when it was shown that febrile rats actively re-established an elevation in body temperature following experimental warming or cooling of the POAH (235).

It is important to note that while fever is typically regarded as an adaptive response to infection and inflammation, there are heat stroke recovery conditions in which a regulated increase in core temperature is associated with poor outcome. An amateur long-distance runner was hospitalized for 10 days

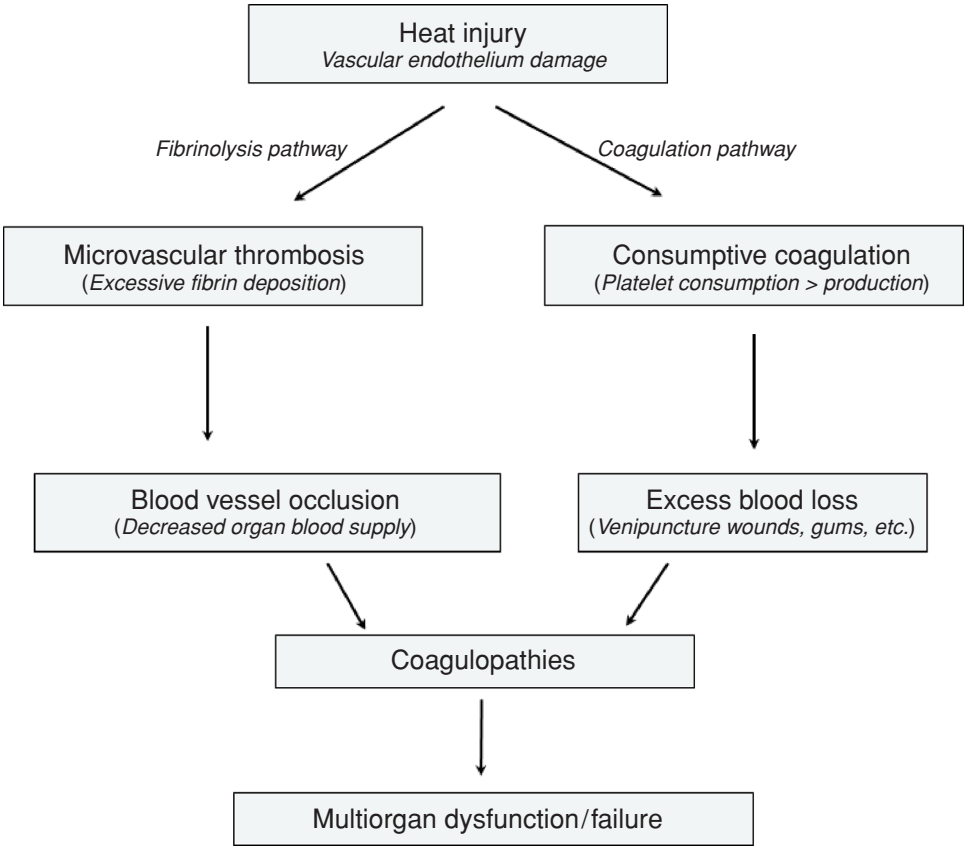

Figure 26 Mechanisms of disseminated intravascular coagulation (DIC). Heat injury to the vascular endothelium initiates the coagulation and fibrinolysis pathways. Excess fibrin deposition may lead to vascular thrombosis in the arterioles and capillaries and lead to occlusion of the blood supply to the 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 and gums). The combined effects of vessel occlusion and excess blood loss result in coagulopathies leading to multiorgan dysfunction. Reprinted (with permission) from Leon and Helwig (229).

after collapsing from exertional heat stroke during a 6-mile foot race (256). Moderate fever (>38°C) was evident during the first 4 days of hospitalization, but on the 10th day the patient experienced convulsions and a rapid increase of body temperature to 41°C and rapid cooling and aspirin were ineffective in reducing body temperature and the patient died (256). The potent antipyretic actions of classic nonsteroidal anti-inflammatory drugs (NSAIDs, such as aspirin) are attributed primarily to cyclooxygenase inhibition and reduced production of PGE_2, which is an important trigger for fever. The inability of aspirin to inhibit the rapid rise in body temperature in the long-distance runner suggests that the hyperthermia was not a true fever, but rather a pathologic response to increased metabolic heat production induced by convulsions. Therefore, it is important to recognize that there is an optimal body temperature range above which the protective effects of fever are no longer realized due to the toxic effect(s) of high body temperature on cell viability (206). It is also important to note that the use of antipyretic drugs is contraindicated for the treatment of heat stroke due to the potential toxic effects of these drugs on the liver as its use has been associated with the need for liver transplantation in some patients (137, 163, 164, 346, 417).

Coagulopathies

DIC is a common complication of heat stroke that may present as microvascular thrombosis or consumptive coagulation (Fig. 26). Microvascular thrombosis is characterized by fibrin deposition and/or platelet aggregation that occludes arterioles and capillaries and often leads to multiorgan system dysfunction (232). Consumptive coagulation is a result of rapid consumption of platelets and coagulation proteins, which exceeds the rate at which they are produced to cause prolonged bleeding from venipuncture sites and other areas (e.g., gums) (14, 21).

Coagulation is initiated in response to severe heat stress and inflammatory activation of the vascular endothelium (34, 36, 277). Heat (43-44°C) directly activates platelet aggregation *in vitro*, which is irreversible with cooling (125, 425). In cancer patients treated with whole body hyperthermia (WBH; 41.8°C for 2 h), platelet concentrations were decreased from the time of maximum body temperature through 18 h of

recovery (396). Endotoxin and cytokines are inflammatory mediators that activate leukocytes and endothelial cells to amplify the coagulation cascade and participate in the progression of DIC. Tissue factor (TF) is a cell-surface receptor expressed by monocytes and vascular endothelial cells that initiates the coagulation cascade. The expression of TF is regulated by endotoxin and reciprocally modulated by pro- and anti-inflammatory cytokines. For example, tumor necrosis factor (TNF), IL-1α, IL-1β, IL-6, IL-8, leukemia inhibitory factor, interferon-gamma (IFNγ), and monocyte chemoattractant protein-1 stimulate TF whereas transforming growth factor (TGF)-β, IL-4, IL-10, and IL-13 inhibit its expression (167, 286, 324, 366). The clinical manifestation of coagulopathies includes conjunctival, skin, pulmonary, and CNS hemorrhages, the latter of which may manifest as severe neurological impairment.

Immune responses

Exertional heat stroke can induce immune dysfunction, observed as disturbances in the distribution of several peripheral lymphocyte subpopulations. At the onset of exertional heat illness, suppressor, natural killer (NK), and total lymphocyte counts were significantly elevated, whereas the helper-to-suppressor ratio was significantly attenuated (104). Through 24 h of recovery, mitogen (phytohemagglutinin) stimulation of T-lymphocyte subsets was significantly attenuated in exertional heat illness patients compared to controls that exercised without collapse (104). It is often difficult to dissociate the effects of exercise and hyperthermia on cell immune dynamics since these stressors stimulate common immune cell disturbances. In a baboon model, increases in lymphocytes and T suppressor-cytotoxic cells were directly correlated with hyperthermia severity (38). Leukocytosis was observed from 3 to 12 h following moderate heat stroke with significant leucopenia evident at the onset of severe heat stroke, which correlated with increased IL-6 production (38). Proposed mechanisms mediating alterations in cell types include changes in regional blood flow, catecholamine and cortisol release in response to heat stress as well as direct effects of exercise, cytokines, and endotoxin (32, 104).

The SIRS is initiated by the innate and adaptive immune systems, which interact with one another to sense the presence of invading pathogens (or other exogenous substances) and orchestrate an immunological response. The innate immune system comprises monocytes, macrophages, and neutrophils that use receptors on their cell surface to recognize pattern-associated molecular patterns (PAMPs) on the cell surface of endotoxin and other invading pathogens (185). Toll-like receptors (TLRs) are a class of pattern recognition receptors that have been widely studied in the immune response to infection (262, 414). TLR4 is the principal receptor for LPS that stimulates gene transcription factors, such as NF-κB to increase the synthesis of a variety of immune modulators in response to endotoxin. Cellular necrosis is associated with the release of damage-associated molecular patterns (DAMPs) that activate the innate immune response to initiate the SIRS. Mitochondrial DNA (mtDNA) is released into the circulation from injured organs and tissues (e.g., liver and skeletal muscle) and functions as an endogenous DAMP (with a structure similar to bacterial DNA) that activates TLR9 and initiates the migration of neutrophils into the organs. Neutrophil migration and degranulation is hypothesized to mediate organ injury in a number of inflammatory states, including sepsis. In rats, intravenous injection of mtDNA DAMPs (MTDs) equivalent to 5% of the rat's liver induced a marked inflammatory response characterized by neutrophil influx into the liver, oxidant injury to the lung, and increased production of the pro-inflammatory cytokines IL-6 and TNFα in the lung (436). Similarly, intraperitoneal injection of MTDs that mimicked $\sim$10% necrosis of the liver in mice was effective in initiating neutrophilic peritonitis. In patients, plasma mtDNA was significantly elevated 24 h following traumatic injury compared to controls (436). mtDNA is thought to represent only a subset of endogenous DAMPs involved in initiation of the SIRS and progression of organ damage following cellular injury.

Cytokines

Cytokines are intercellular messengers released by macrophages, T and B cells, endothelial cells, and astrocytes that exhibit pleiotropic, redundant actions in a variety of disease and injury states (29, 68, 196). Cytokine-inducing stimuli include bacterial and viral infection (102, 316), psychological stress (244, 307), heat stress (33, 38, 54, 165, 226, 236), WBH (287), and exercise (60, 263, 397). Elevations in pro- and anti-inflammatory cytokines are often detected in the circulation of heat stroke patients and animal models, but there is limited information regarding how the cytokine "milieu" fluctuates throughout progression of heat exposure and recovery (33, 37, 242, 287, 389). Pro-inflammatory cytokines have been strongly implicated as adverse mediators of heat stroke morbidity/mortality, but these conclusions are based primarily on correlative data, which do not reveal the actions of these proteins in the SIRS or multiorgan dysfunction syndrome.

There are several lines of evidence that link cytokines with symptoms of the heat-induced SIRS. These include the induction of heat stroke symptoms by cytokine injection in experimental animal models, the association of increased circulating cytokine levels with heat stroke morbidity/mortality, and the effectiveness of cytokine neutralization in altering heat stroke mortality in animal models. Peripheral injection of IL-1β, IL-2, IL-6, IL-10, TNFα, and platelet-activating factor into experimental animals replicates the pathophysiological responses observed in exertional heat stroke, including hyperthermia, hypothermia, DIC, and death (222, 223, 308, 310, 367, 411). More direct evidence for a role of cytokines in the heat-induced SIRS is evident from clinical and experimental studies that correlate 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, IFNγ, TNFα, and sTNFR concentrations are observed at the time of heat stroke collapse or shortly after cooling (33, 37, 38, 159, 162, 226, 389). In some cases, only 30% to 40% of heat stroke patients show increased concentration of a particular cytokine (e.g., IL-1β and IL-10) (33, 35), whereas other cytokines, such as IL-6, are often significantly elevated in 100% of a patient cohort (33). Sustainment of high IL-6 levels during cooling correlates with heat stroke severity, organ damage, and death, whereas high circulating IL-8 levels are implicated in leukocyte activation and coagulation (35, 177). Bouchama et al. (33) showed increased serum IFNγ levels in more than 50% of exertional heat stroke patients prior to cooling therapy. Whereas IL-6 levels tended to be highest in nonsurvivors, IFNγ levels did not correlate as strongly with heat stroke morbidity/mortality in individuals that were otherwise healthy (33). In military recruits with EHI/stroke, plasma levels of IFNγ were elevated concomitantly with IL-1β, IL-6, TNFα, IL-2 receptor (IL-2R), and IL-8 (242). High IFN-inducible gene expression and IFNγ levels are clinical measures of viral or intracellular bacterial infection that are evident in EHI patients with preexisting infections (389). A recent mouse model of passive heat stroke examined 11 cytokines (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p40, IL-12p70, IFNγ, macrophage inflammatory protein 1α, and TNFα) and detected time-dependent changes in only four of those proteins. Whereas IL-12p40 was elevated at the time of heat stroke collapse (core temperature = 42.7°C), the strongest cytokine response was observed at the depth of hypothermia (core temperature ~29°C) when IL-1β, IL-6, and IL-10 were significantly elevated compared to controls (226). High-IL-6 levels were also detected 24 h following collapse when mice displayed ~1°C fever (226, 228).

The ability (or inability) to detect elevated circulating levels of cytokines may not accurately reflect their physiological actions, since many of these proteins have tissular or paracrine actions that are not understood. Furthermore, the presence of soluble cytokine receptors may mask detection of a cytokine or alter its cellular action(s) since these receptors are known to function as agonists or antagonists of cytokine actions (2, 207, 364). The sIL-6R potentiates endogenous IL-6 effects by a process known as "transignaling" in which the receptor integrates into the membrane of cells that otherwise do not possess that receptor (207) (Fig. 27).

In rats, the intracerebroventricular (icv) injection of sIL-6R augmented and prolonged the effect of IL-6 on fever and motor activity (364). Reciprocal changes between IL-6 and the sIL-6R have been observed from the time of clinical admission to postcooling in heat stroke patients, but the manner in which these protein interactions altered heat stroke outcome was not determined (159). Interestingly, elevated circulating levels of soluble cytokine receptors are often observed despite an inability to detect circulating levels of the cytokine. In a small cohort of heat stroke patients, circulating TNFα and β levels were undetectable at the time of clinical admission, but sTNFR concentrations were significantly elevated in survivors compared to nonsurvivors (159). Since the sTNFR acts as an antagonist of endogenous TNF actions, this cytokine has been implicated as an adverse mediator of heat stroke outcome, although heat stroke studies conducted in cytokine knockout mice have failed to support this hypothesis (159, 224). Rather, recent cytokine neutralization studies in IL-6 and TNF double-receptor (TNFR) knockout mice (mice that cannot produce IL-6 or generate a cellular signal to TNF) suggest that IL-6 and TNF have basal (permissive) actions that are critical for survival (224). That is, IL-6 and TNFR knockout mice showed higher mortality rates than their wild-type controls following heat stroke collapse (224).

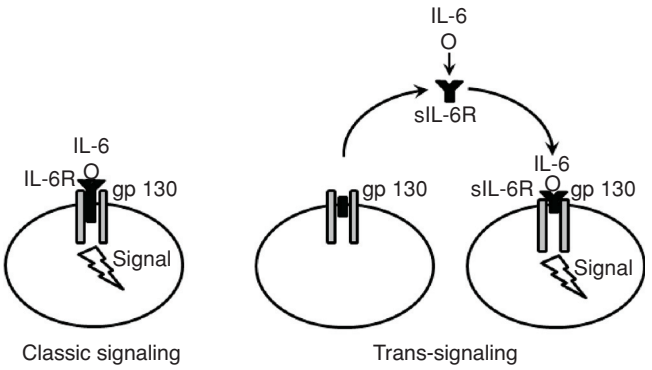

Figure 27 IL-6 receptor signaling pathways. Classic signaling involves IL-6 binding to the membrane-bound IL-6 receptor (IL-6R), which stimulates an interaction between the IL-6:IL-6R complex and the membrane-bound gp130 to initiate intracellular signaling. Transignaling occurs when the extracellular domain of the membrane-bound IL-6R is proteolytically cleaved to generate the soluble IL-6R (sIL-6R) that binds IL-6. The IL-6:sIL-6R complex can stimulate cells that only express gp130 (i.e., do not normally possess the transmembrane IL-6R) to transmit an intracellular signal. Cells that express gp130 only would not be able to respond to IL-6 in the absence of the sIL-6R. Reprinted (with permission) from Leon and Kenefick (230).

There are several aspects of these knockout studies that warrant consideration regarding the role of IL-6 and TNF in the heat stroke syndrome. First, IL-6 knockout mice succumbed to heat stroke at hypothermia depth, which corresponded to the time at which maximal circulating levels of IL-6 (226) and the sIL-6R (LR Leon, unpublished observation) were detected in wild-type mice (225, 226). Thus, IL-6 appears to have protective actions that are mediated at or near this time of recovery. Second, TNFα was undetectable in the circulation of wild-type mice through 24 h of recovery, yet TNFR knockout mice succumbed to heat stroke. These data indicate that TNF has compartmentalized actions that are not reflected by elevations in the circulating levels of this protein (225). Interestingly, recent findings in our laboratory indicate that the sTNFR60 and sTNFR80 are elevated in the circulation of wild-type mice at hypothermia depth and 24 h of recovery, which provides some insight into the time course of cellular actions of TNF (LR Leon, unpublished observation). Third, fever was evident in IL-6 and TNFR knockout survivors

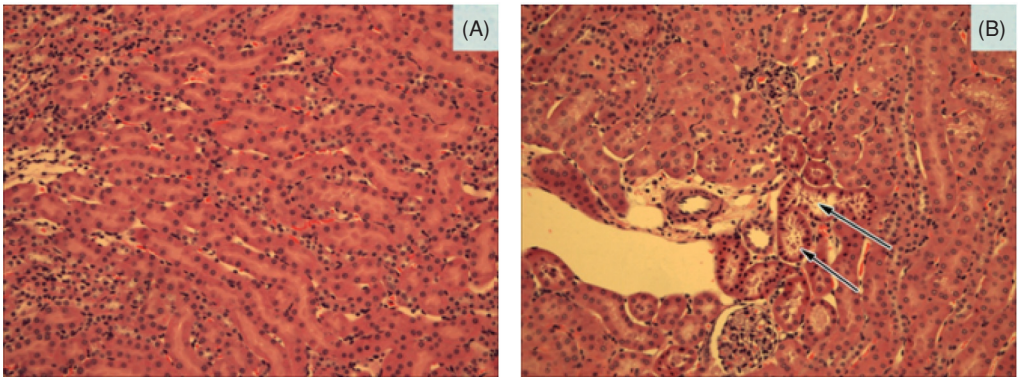

Figure 28 Representative photomicrographs of histological damage (hematoxylin and eosin; 200×) to the kidney of a normothermic (A) and passively heat-stroked mouse (core temperature = 42.7°C). (B) Arrows indicate identified tissue lesions which included renal tubular necrosis in the straight tubules of the kidney lower cortex. This was observed as shrunken, acidophilic, and fragmented epithelial cells with pyknotic nuclei. Renal damage was first detected at the time of heat stroke collapse with progressively greater damage from hypothermia to 24 h of recovery (time of fever). Reprinted (with permission) from Leon et al. (226).

suggesting redundancy in the regulation of this response as well as the potential importance of this regulated elevation in core temperature for recovery (225). To-date, these are the only studies to examine cytokine-soluble receptor interactions and the effect of cytokine neutralization on heat stroke outcome. Although future studies using traditional methods of cytokine inhibition/neutralization are important to verify the findings from gene knockout mice, current findings suggest that correlation studies have misinterpreted the role of endogenous cytokines in the heat stroke syndrome and these proteins may perform currently unidentified functions that are critical for survival.

Multiorgan system dysfunction syndrome

Multiorgan system failure is the ultimate cause of heat stroke mortality that results from a complex interplay between heat cytotoxicity, coagulation, and inflammatory responses. The pathophysiology of heat stroke is thought to be a consequence of the SIRS that ensues following heat-induced damage to the gut and other organs. A variety of noninfectious and infectious clinical conditions are associated with a SIRS and similar physiological mechanisms are thought to mediate the pathogenesis of these conditions. Provided below is an overview of the responses that comprise the heat-induced SIRS and current understanding of the pathophysiologic mechanisms that mediate the adverse events of this syndrome.

The severity of exertional heat stroke is primarily related to the extent of damage to the brain, kidney, and liver, which may be a consequence of heat toxicity alone or in combination with the exaggerated reactions that comprise the SIRS. CNS dysfunction is a hallmark of heat stroke that is dominant early in the disorder as patients often exhibit serious mental status changes (e.g., severe confusion, delirium, combativeness, and coma) at the time of collapse or clinical presentation. Brain hyperthermia is a consequence of whole-body hyperthermia inducing an increase in cerebral metabolic rate, and a reduction in CBF (294). Whereas increased blood brain barrier permeability facilitates protein and pathogen leakage from the systemic circulation into the brain, neurological impairments are thought to be a consequence of increased ICP and autonomic dysfunction that culminates in cerebral ischemia or hemorrhage (294). The most conspicuous histological damage to the CNS includes progressive degeneration of neurons in the cerebellum and cerebral cortex with congestion and edema in the region of the cerebral ventricles (245, 375). To-date, there are no clinical or experimental studies that report structural damage to the POAH following heat stroke (228, 245, 375, 400).

Renal failure is a common finding in heat stroke patients with protein clumping in tubular epithelial cells in response to heat injury, sympathoadrenal and cytokine activation, rhabdomyolysis, or DIC (65, 153, 204, 242) (Fig. 28). Renal failure is a potential mechanism for increased plasma cytokine concentrations, as cytokine clearance is a reported function of this organ (159). In patients that survive more than 24 h, severe hypotension, dehydration, blood urea nitrogen (BUN) and oliguria are associated with tubular necrosis or inter-tubular edema of the kidney (245).

Liver damage often does not peak until ~24 to 48 h following heat stroke, but may require weeks or months to resolve (28, 225, 245, 345). For example, liver damage consisting of centrilobular degeneration and necrosis with parenchymal damage was only evident in military exertional heat stroke patients that survived more than 30 h (245). Primary hepatic dysfunction is a consequence of direct heat injury as well as reduced perfusion in response to high skin blood flow for heat dissipation. In volunteers subjected to exercise-heat stress, temperature of the hepatic venous blood was ~1.5°C warmer than core body temperature suggesting that hyperpyrexia of the portal blood may predispose to cellular injury of the liver. Splanchnic hypoxia increases liver lactate concentrations and causes an outflux of glucose that presents as hyperglycemia (34, 226, 341). An alteration in

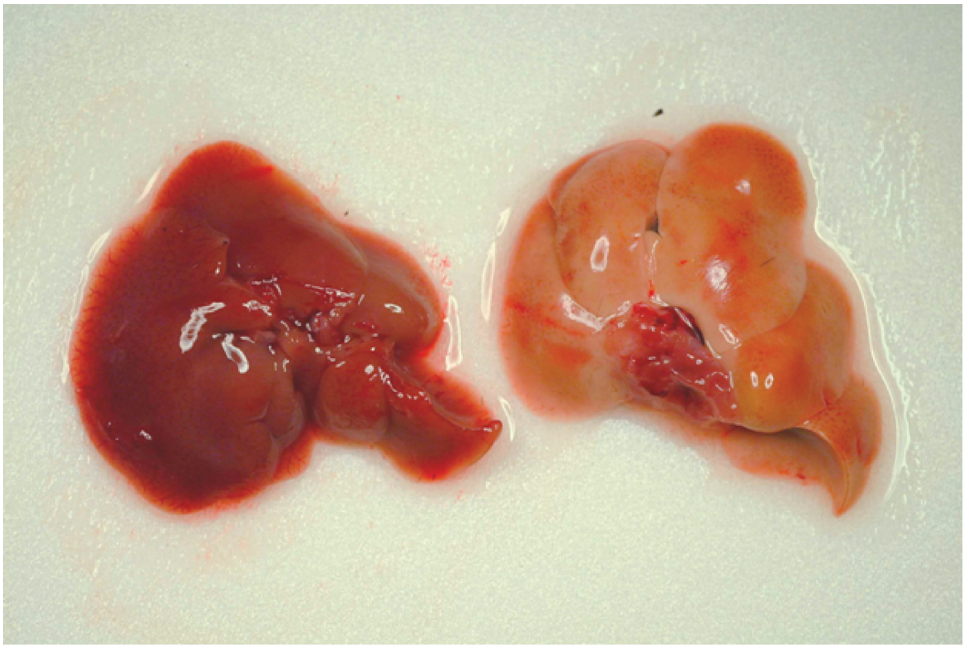

Figure 29 Fatty liver change observed in a heat-stroked mice (right) ~72 h following heat stroke collapse (core temperature = 42.7°C). Liver from a nonheated control (left) and heat stroke nonsurvivor (right) are shown. Reprinted (with permission) from Leon (225).

phosphoenolpyruvate carboxykinase, a key regulatory enzyme of the hepatic gluconeogenic pathway following heat injury to the liver has been proposed as a mechanism of hypoglycemia, although this has never been experimentally verified (312). The enhanced breakdown of fat or an inability of the mitochondria to utilize fat is manifest as fatty-liver changes (65, 225) (Fig. 29). Unfortunately, many heat stroke patients require liver transplantation and the use of NSAIDs, such as acetaminophen has been associated with hepatic failure (137, 163, 164, 346, 417).

Exertional rhabdomyolysis is often associated with exertional heat stroke and may occur in the absence of mental status changes or severe hyperthermia (130, 303). Rhabdomyolysis is a common form of exertional skeletal muscle injury that is caused by the leakage of muscle cell contents into the circulation or extracellular fluid. Muscle apoptosis is a consequence of decreased ATP levels as intracellular calcium concentrations increase in response to muscle metabolic heat production. Myoglobin released from damaged muscle cells is filtered and metabolized by the kidneys, but protein will begin to appear in the urine as the renal threshold for filtration of myoglobin is exceeded (124). Myoglobin is toxic to the kidney nephrons and causes overproduction of uric acid, which precipitates in the kidney tubules to cause acute renal failure, coagulopathy and death if not rapidly detected and treated (19, 124, 238, 315, 420).

Serum enzyme levels may be insensitive biomarkers of organ damage from exertional heat stroke (11, 28). Common clinical biomarkers measured in the serum of heat stroke patients include creatine phosphokinase (CPK), BUN, aspartate aminotransferase (AST; also known as SGOT), alanine aminotransferase (ALT; also known as SGPT), lactate dehydrogenase (LD) and bilirubin. These biomarkers are released by a variety of tissues and many are altered by heat injury as well as exhaustive exercise so they lose their sensitivity or specificity as biomarkers of organ damage from heat stroke (139, 156, 373). Using a rat model, Hubbard et al. (176) showed that serum CPK, SGOT, and SGPT levels were differentially elevated by exercise alone, hyperthermia alone, or the combination of these factors (Table 7).

Accurate diagnosis of organ damage requires assessment of the level and pattern of enzyme release rather than just a pure quantitative measurement (176). Although organ biopsy is considered the "gold standard" for determination of the degree, type, localization, and dynamics of histological damage to peripheral organs (e.g., liver), this procedure is not feasible in many field and clinical settings (27). Therefore, attempts have been made to establish a scoring system for stratification of the severity of organ damage and outcome based on a combination of serum enzyme levels and physiological parameters (9). Serum levels of AST and LD provided better differentiation between severely ill heat stroke patients and quick recovery groups than body temperature, anion gap, or serum potassium in a cohort of patients suffering from heat stroke during the annual pilgrimage to Mecca (9). However, recent findings from a rat heat stroke model suggest that common clinical biomarkers may lack specificity and sensitivity to detect the type and extent of organ damage and the time course of the recovery of organ function (229). Leon and Helwig demonstrated in rats that core temperature, motor activity, plasma BUN, AST, and ALT levels normalized within 10 days of heat stroke collapse despite a persistence of histological

Table 7 Elevations in Serum Enzyme Activity of Rats After Exercise and/or Hyperthermia

Conditions	N	% Fatalities in 24 h	T_c max, °C	Work done	Enzyme activity poststress. IU·l^{-1} 30-min CPK	24-h CPK	24-h SGPT	24-h SGOT
Group 1 Run to exh at 5°C	13	0	38.2 ± 1.1	81 ± 33	2818 ± 1718	236 ± 210	125 ± 81	637 ± 376
Group2 Run to exh at 20, 26, or 30°C	57	42 (n = 24)	41.5[a] ± 1.0	38[a] ± 18	1776 ± 1931 (n = 55)	303 ± 187 (n = 34)	1029[a] ± 1570 (n = 36)	2457[a] ± 3694 (n = 32)
Group 3 Heat at 41.5°C	81	31 (n = 25)	42.2[a] ± 0.4		245[a] ± 195 (n = 80)	268 ± 470 (n = 60)	1828 ± 3396 (n = 67)	3678 ± 5382 (n = 64)
Group 4 Control	20	0	37.1 ± 0.5		154 ± 76	172 ± 135	26 ± 6	89 ± 24 (n = 15)

Values are means ± SD; n, no of rats. All control values significantly different ($P < 0.05$) from experimental except in 24-h CPK, creatine phosphokinase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase. Samples taken at 30 min include potential fatalities.
[a]$P < 0.05$ between means ± SD and one above it.
Adapted from Hubbard et al. (176).

damage in the kidney and liver, respectively (229) (Fig. 30). These data are consistent with a study showing normal plasma SGOT, SGPT, and bilirubin levels in a runner within 60 days of exertional heat stroke collapse despite persistence of liver damage through 12 months of recovery (28).

Some heat stroke patients are released following several days or weeks of hospitalization and treatment, but continue to experience organ dysfunction during the ensuing years of recovery. The clinical responses (hyperthermia, hypotension, CNS dysfunction, and DIC) occurring during progression or shortly after heat stroke are clinically recognized and treated. However, those occurring during the months and years following hospitalization are underreported and the mechanisms responsible for long-term decrements in organ function remain poorly understood. A recent epidemiological study of EHI/stroke patients suggests a ~40% increased mortality risk from heart, kidney, and liver failure within 30 years of hospitalization (418). It seems possible that long-term kidney or liver failure in exertional heat stroke patients may be a result of a failure to detect residual organ damage that might precipitate organ failure many years after apparent recovery.

Gene Expression and Exertional Heat Injury

Gene expression responses to heat shock

Studies of isolated mammalian cells (both as primary isolates and as cultured cell lines) have consistently demonstrated an extensive gene expression response to severe heat stress (388). Experimentally, this typically involves exposing cells to a rise in temperature above normal culture conditions by 5 to 6°C for at least 30 to 45 min (heat shock), followed by a return to normothermic conditions for a period of up to several hours (237, 384, 385, 387). Microarray studies of both normal human cells (PBMCs) (385) and human cells in culture [human hepatocellular carcinoma cell line (HepG2)] (387) have shown that heat shock produces an extensive change in the gene expression profile at the level of mRNA, involving at least dozens of genes, and includes elements of every major biochemical pathway known. These changes also include a significant decrease in gene expression. The extent of the response changes over time; the number of genes whose expression is altered is greater after a period of recovery under normothermic conditions than occurs immediately after severe hyperthermic exposure (387). This is likely due, at least in part, to the fact that severe heat stress has an inhibitory effect on transcription and translation (237); indeed, cells have evolved specialized adaptations that allow for increased expression of some genes even under temperatures that are usually non-permissive. For example, some HSPs lack introns, which makes it possible to express them without the need for RNA splicing (237).

Gene expression responses to exertional heat injury

In addition to showing extensive responses to *in vitro* heat shock, PBMCs demonstrate time-dependent changes in their gene expression profile after EHI (389). In an observational study conducted on Marine Corps Recruits undergoing basic training, PBMCs were obtained from four individuals who presented to the Branch Medical Clinic with maximal core temperatures ranging from 39.3 to 42.5°C with clinical evidence of EHI (elevation of one or more of the following serum enzymes: CK, liver transaminases, or LD). All four subjects had evidence of a prodromal viral-like illness, which is generally considered a risk factor for EHI, and one had findings suspicious for pneumonia. All received IV hydration and underwent active cooling on ice sheets per local protocol. Blood samples were obtained upon presentation, 2 to 3 h after active cooling had been completed, and at a follow-up 1 to 2 days later. Controls were three age-matched recruits who were also undergoing basic training but who did not develop EHI. RNA was isolated from PBMCs and expression profiles were analyzed using DNA microarrays. Because of small sample volumes and low RNA yields, pooling of samples was required.

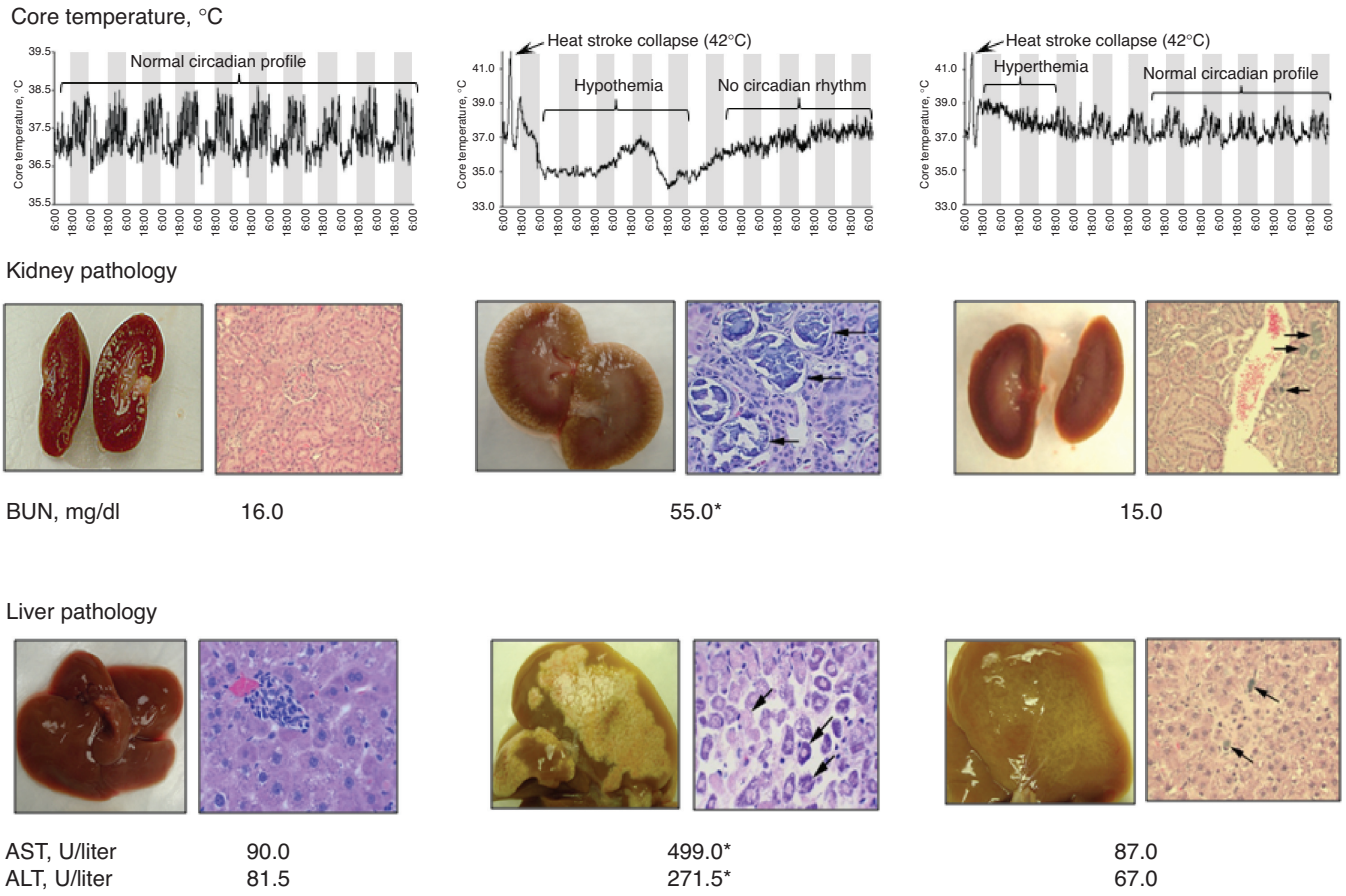

Figure 30 Representative data showing that common clinical measures do not always accurately reflect the presence of peripheral organ damage. Core temperature (radiotelemetry; ±0.1°C) of male Fischer 344 rats was recorded at 1-min intervals during 10 days of heat stroke recovery. On day 10, circulating levels of blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were compared with gross morphology and histological damage (hematoxylin and eosin) to the kidney and liver. Representative core temperature tracings (top row), kidney pathology and BUN levels (middle row), and liver pathology, AST and ALT levels (bottom row) from one control (left panel) and two heat stroke rats (middle and right panel; core temperature = 42.0°C) are shown. Left panel: Nonheated control 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 panel: Following heat stroke collapse, profound hypothermia (~34-35°C) was observed through 5 days of recovery and then the animal re-warmed 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 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 panel: Following heat stroke collapse, hyperthermia (~39°C) was observed through day 3 and then the animal 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 presence of organ damage in this animal. These data demonstrate that traditional clinical biomarkers of organ function lack specificity and sensitivity to detect damage in all animals following heat stroke collapse. Gray shading in core temperature graphs represents 12-h lights-off, active period. *Indicates values elevated above control. Adapted (with permission) from Leon and Helwig (229).

Despite these limitations, the results of this study showed that PBMCs isolated from individuals who had experienced EHI underwent a time-dependent series of gene expression changes that included a significant heat shock response. Indeed, the broadest HSP response was seen at presentation, where 25 HSPs were identified as showing significant increases in expression, as compared to 19 showing increased expression after cooling and only 8 at the follow-up visit. However, HSPs constituted only a portion of the response; in total, 144 sequences showed increased expression relative to controls at presentation, 237 after cooling, and 179 after recovery. As might be expected, the overlap between the actual sequences increased after EHI and those that had been found in a previous study (385) to be increased after heat shock was greatest at presentation and smallest at the time of follow-up. Likewise, there was substantial overlap between the sequences which showed decreased expression after EHI and those which had previously been identified as decreased after an *in vitro* heat shock (11-18%). The microarray data thus support the concept that the gene expression response

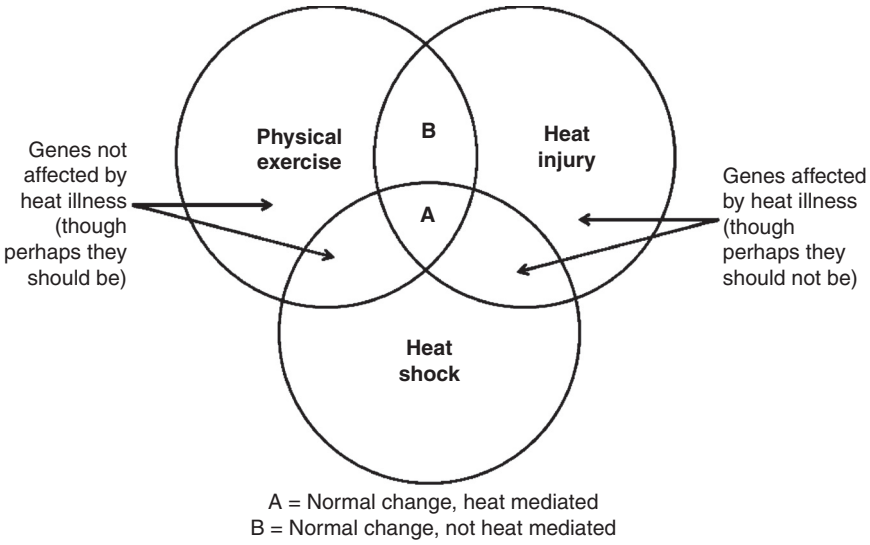

Figure 31 Interpretation of Venn diagram for gene expression experiments.

to EHI shares some, but not all, features with the *in vitro* response to heat shock, such as changes in expression of HSPs.

Interestingly, and in contrast to the *in vitro* findings, at least one-fourth of the 36 most highly increased sequences (defined as those which showed a statistically significant increase of 5-fold or more over control expression) were genes which are known to be IFN inducible. The significance of this finding is unclear, but several different interpretations are possible. It may be that prodromal viral illness induces a series of molecular changes, reflected in the increase in IFN-inducible genes that render a subject more susceptible to EHI. Alternatively, these genes may play a mechanistic role in EHI. A third possibility is that these gene expression changes are an artifact of the small-sample size. However, it is interesting to note that Bouchama et al. (33), in a case series report of heat stroke victims in Saudi Arabia, found that half of 10 patients in whom IFNγ was measured had elevated levels of circulating IFNγ that diminished after treatment. Additionally, *in vitro* work with transformed murine endothelial cells (1) has shown that pretreatment of these cells with IFNγ alters cellular fate after heat shock from survival to death by apoptosis. It thus seems at least plausible that IFN-induced gene expression may play a role in the pathogenesis of EHI, either as a marker of susceptibility or perhaps in a mechanistic role. Future work will be required to explore this idea.

Comparison of gene expression responses to heat shock, physical exercise, and exertional heat injury

The observation that IFN genes are expressed by PBMCs after EHI and following *in vitro* heat shock generated the hypothesis that IFN-inducible genes might play a role in EHI. However, as EHI by definition includes not just exposure to heat, but also to the effects of physical exercise, a more complete analysis is needed regarding the effects of both isolated heat stress *in vivo* (perhaps by warming subjects passively in a hot tub) as well as to exercise *in vivo* under conditions that prevent substantial warming. By comparing genes affected by EHI to those affected by normal exercise and passive heating, it should in principle be possible to identify shared elements of all three conditions as well as those that are specific to each condition and thus potentially likely to represent signature responses with pathophysiological implications (Fig. 31).

Microarray platforms allow for rudimentary comparisons between experiments performed by different investigators (388). Sonna and colleagues (388) used this approach to compare gene expressions between three different studies that used Affymetrix (Santa Clara, CA, USA) microarray platforms to describe PBMC responses to: (i) *In vitro* heat shock (385), (ii) physical exercise (84), and (iii) EHI (389). A graphical representation of some of the genes identified by this comparison is presented in Figure 32.

This comparative analysis made it possible to classify gene expression responses to physical exercise and EHI into biologically plausible categories with mechanistic implications. As shown in Figure 32, some of the gene expression changes (such as increases in expression of HSPs and other stress-responsive genes such as early growth response protein 1) accompanying exertion might be accounted for simply by the rise in temperature that occurs during exercise, as evidenced by the observation that PBMCs exposed to heat shock *in vitro* also increased expression of the same genes. Likewise, the observation that some HSPs (such as HSPA6) are affected by heat shock and EHI but not by physical exercise suggests the possibility that they may play a role in responses to severe heat stresses that are either not required under less stressful conditions or simply performed by other HSPs.

The comparative analysis (illustrated in Figure 32) identified IFN-inducible gene expression as a phenomenon

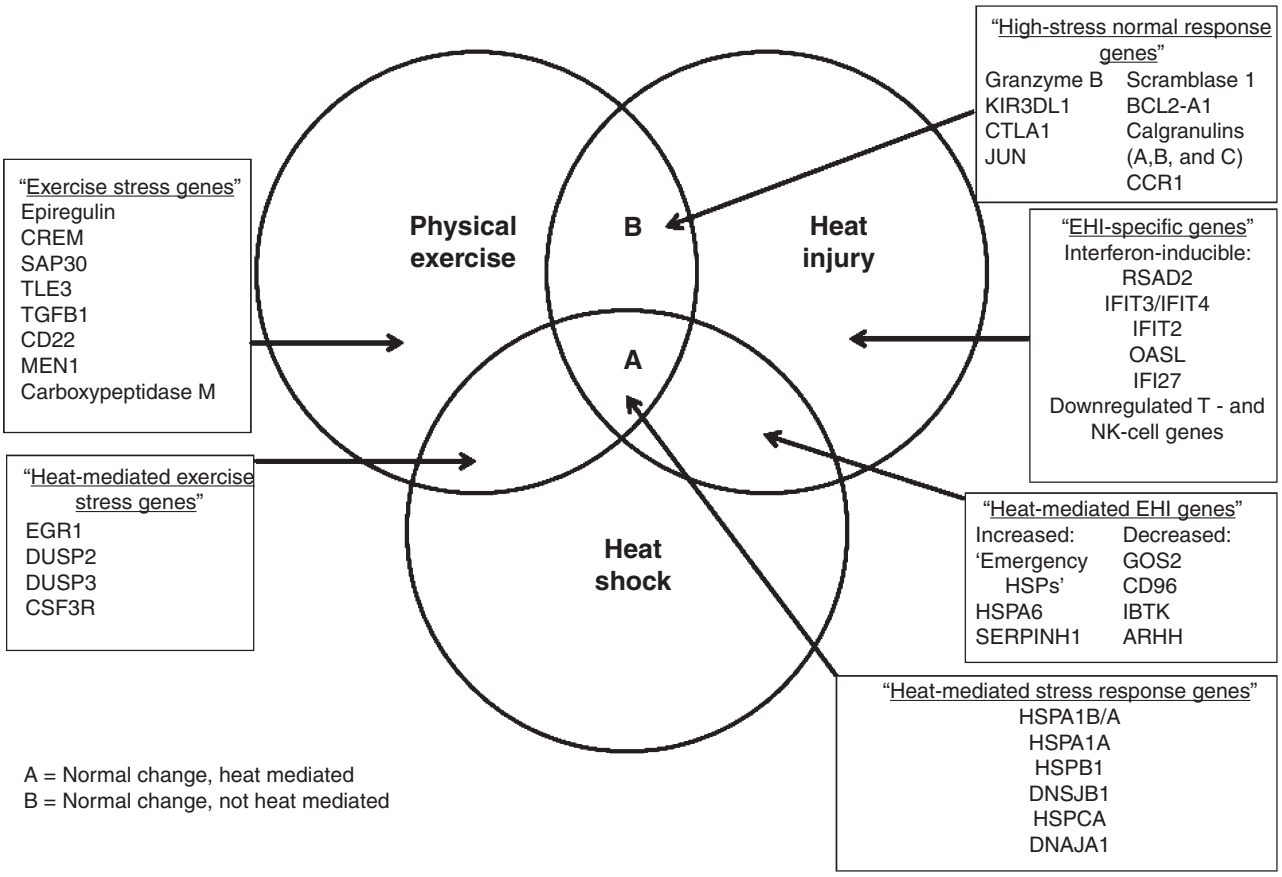

Figure 32 Gene expression responses to physical exercise, heat injury, and heat shock.

observed in EHI but not under conditions of physical exercise or as part of an *in vitro* heat shock response. Interestingly, this analysis also revealed that EHI is characterized by decreased expression of a substantial number of genes that are typically expressed on NK^- cells and on activated and cytotoxic T cells. Because PBMCs represent a mixed cell population, a simple explanation for this observation could be that EHI produces a selective dropout of circulating NK^- and activated/cytotoxic T-cell subpopulations. Flow cytometry studies will be required to determine whether these decreases in gene expression are due to changes in the distribution of PBMC subtypes during EHI or due to repression of gene expression within cells.

The observation that IFN-induced gene expression is a feature of EHI that differentiates it from the physiological effects of physical exercise is consistent with other reports that physical exercise does not normally produce increases in circulating IFNα and IFNγ. In one study (398), 16 elite runners showed no significant differences in levels of circulating IFNα and IFNγ after running a marathon, though marked elevations of IL-6 and IL-1 were detected (399). Likewise, microarray studies of individuals undergoing physical exercise have not reported increases in mRNA sequences encoding IFNα or IFNγ (84, 437). Additional review of the EHI study data (388) identified a gene sequence corresponding to IFNγ that was significantly and strongly increased in EHI but that had been excluded from the reported list of affected genes because of the strict post hoc filter criteria used in the original report. While not conclusive, these observations are consistent with the hypothesis that IFNs might play a role in the pathophysiology of some cases of human EHI. This hypothesis, however, requires validation in a larger, follow-up cohort of individuals suffering from EHI.

"Multiple-hit" hypothesis

Few would doubt that a single overwhelming exposure to heat stress during exertion can trigger EHI. Epidemiological data have raised the possibility that, for some individuals, EHI may also occur as the result of a "multiple-hit" process. Several studies have identified subjects who developed EHI at ambient temperatures and exercise intensities that would normally be considered compensable (112, 130, 195), Moreover, individuals with EHI commonly report feeling ill in the days leading up to the acute illness (112, 375), and frequently report prior day exposure to heat (195).

The gene expression findings discussed above suggest a hypothetical mechanism that might help explain why EHI appears to be the result of a "multiple-hit" process for some. It may be that an antecedent pro-inflammatory exposure

(induced, perhaps, by a subclinical heat injury or a viral illness) that causes increases in IFN levels can increase subsequent susceptibility to EHI. This initial exposure might act to augment the hyperthermia of exercise, perhaps deactivate molecular protective mechanisms mediating acquired thermal tolerance, and make tissues more susceptible to injury for a given heat stress, or perhaps interfere with compensatory mechanisms necessary to prevent overheating. As discussed above, IFNs (particularly IFNγ) are candidate mediators worthy of additional study.

Conclusion

This review expanded upon past *Handbook of Physiology* articles in *Comprehensive Physiology* which provided detailed historical reviews of human thermoregulation and heat acclimation, cardiovascular, and endocrine adjustments to heat stress and heat stroke. This review highlights significant scientific advances during the past decade regarding aerobic exercise performance in the heat, fluid-electrolyte needs during exercise-heat stress, molecular adaptations to exercise-heat stress, and pathophysiologic events associated with exertional heat illness. We have described new insights into why aerobic exercise performance is degraded by heat stress. We have described recent advances on the benefits of heat acclimation/acquired thermal tolerance on not only improving exercise capabilities but inducing protection from heat stroke and other dissimilar stressors. We have described why heat stroke should be viewed as a SIRS that mediates end-organ damage which possibly has long-term health consequences. Of major note is our questioning of several "traditional" concepts regarding the importance of core temperature as the key mediator of exercise performance degradation or the induction of heat stroke.

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