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The relationship between proinflammatory mediators and heat stress induced rhabdomyolysis in exercising marines

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Heat illness has a severe impact on the readiness of a military combat unit by reducing availability and performance of the warrior. In spite of command and company level education on heat illness prevention, there are still episodes of heat-related injury. During one 1998 recruit training cycle at a major East Coast command, 54 of the 1866 students were treated for some degree of heat illness. Although not numerically significant, one incident may have a poor outcome for both recruit and command. Of importance is that these data are reported from one site, one training cycle, and only one service.

Physical exertion in a hot environment can result in symptoms of heat illness that span a continuum that begins with prickly heat [1] and moves through heat edema and syncope [2], heat cramps, heat exhaustion, heat tetany [1], and finally reaches heat stroke [1–3]. Add to this dehydration, which is an important risk factor for occurrence of heat related illnesses when it reaches more than 3% of body weight. When fluids are not ingested before physical activity, the chance for a heat-related illness is higher (Table 1) [4]. It should be noted that thermoregulation is maintained in all heat illnesses except heat stroke, which has a 10% mortality rate despite therapeutic intervention [5].

Heat stroke is identified by (1) inability to lose core heat as internal temperature rises in excess of 41°C, (2) central nervous system disturbances that include stupor and coma, and (3) inability to sweat [6,7]. Cell membrane destruction occurs when internal temperature exceeds 42°C and is evidenced by release of enzymes associated with rhabdomyolysis, including creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and asparate aminotransferase (AST) [3,8]. AST is most sensitive to skeletal muscle cell injury and is a strong predictor of mortality [9].

With destruction of cell membrane, heat shock protein 70 (HSP70) appears in peripheral blood samples. Although much is still unknown about heat shock proteins, what is known is that HSP70 ensures that proteins translocate to where they are needed, fold for protection, and degrade when they have been denatured [10,11], all occurring in response to cell stress. Also activated in response to cell stress, and demonstrating heightened activity with HSP70 release, are proinflammatory cytokines. Three proinflammatory cytokines with enhanced expression to HSP70 are interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF). All of these substances are released from monocytes, and all have been isolated in plasma of heat-injured subjects [3,12,13]. These proinflammatory cytokines, which are both pyrogenic (fever producing) and proteolytic (protein destroying), may enhance exercise-induced temperature elevations above 40°C and increase severity of rhabdomyolysis.

It is also known that proinflammatory cytokines induce the synthesis and release of C-reactive protein from the liver [13]. The induction of liver proteins

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Table 1
Heat illnesses

Type	Symptoms/lab values	Causative factor
Prickly heat [1]	Red, vesicular rash	Plugged sweat glands causing inflammation.
Heat edema [2]	Swelling in dependent areas	Peripheral vasodilation from heat with orthostatic pooling.
Heat cramps [1]	Painful spasms of skeletal muscles of the arms, legs, and abdomen. Labs show hyponatremia, hypochloremia, and low urine sodium.	Fluid replacement with inadequate salt.
Heat syncope [2]	Dizziness, fainting	Inadequate cool down after exercise in hot, humid environment.
Heat exhaustion [1]	Flushed face, hyperventilation, loss of coordination, core temp 38–40°C, confusion, profuse sweating, thirst, malaise, weakness, frontal headache, dizziness, visual disturbances, tachycardia, nausea, vomiting, chills, hypoxia	Inadequate heat loss to heat generation.
Heat tetany [1]	Rigors, unresponsive, tachypnea, tachycardia	Respiratory alkalosis and lack of heat dissipation.

From Phillips R. Proinflammatory effects of heat stress in exercising marines. Grant submission. TriService Nursing Research Program, 2000; with permission.

signals an “acute phase response,” which is initiated by the overwhelming muscle cell injury of rhabdomyolysis. The response appears clinically as (1) fever, (2) changes in circulating levels of trace metals, (3) activation of hepatic proteins, and (4) an increase in circulating leukocyte count (WBC) [14]. Increases in circulating WBCs augment the available pool of monocytes for transcription, synthesis, and release of cytokines. Any level of C-reactive protein indicates an inflammatory response, and in the presence of exercise, induced temperature elevation suggests that not only has a loss of thermoregulatory control and development of rhabdomyolysis occurred but activation of the acute phase response has also occurred.

Literature review

Body temperature regulation

Set point range is the term used to describe the concept of “normal” body temperature. Normal body temperature is maintained within a narrow internal range, varying 0.5 °C to 1.5°C over a 24-hour period, despite wide fluctuations in environmental temperature [15]. This set point temperature is not measurable, although it indicates the point where thermal response to heat gain or loss is not required. Temperature regulates in the region of the preoptic area of the hypothalamus, and it is here that incoming thermal signals from central and peripheral receptors integrate and are compared to set point range. When compared temperature is lower than set point range, vasoconstriction and shivering activate. When the temperature is above set point range, vasodilatation and sweating bring about evaporation [16].

Skin blood flow is the major controller of temperature regulation. Apical skin areas, such as hands, feet, ears, and nose, have vasomotor control only by noradrenergic vasoconstrictor nerves. These nerves respond to increased release of norepinephrine. Raising levels of norepinephrine cause the smooth muscle of the vessel wall to constrict, reducing blood flow and increasing insulation. When heat gain is the goal, active vasoconstriction achieves that goal; however, there is no active vasodilator mechanism in the hands, feet, ears, or nose to cause vessels to dilate. The only mechanism to allow vasodilation is downregulation of norepinephrine release. Therefore, when heat dissipation is the goal, the inability of apical skin to actively vasodilate impedes the body’s ability to reduce insulation and transfer heat to the environment. This increases internal heat load and builds thermal stress. The vasomotor response is different in the nonapical skin areas. These areas are located in the remaining portion of skin, such as the arms, legs, and trunk, and have active vasoconstrictor and vasodilator response during periods of heat stress [17]. The vasodilator activity, mediated by a cholinergic nerve co-transmitter, [18] increases skin blood flow and allows for more efficient reduction of body heat [19].

Heat generation during exercise

Exercising muscle metabolizes fats and carbohydrates for energy. As chemical energy is converted to work, it liberates 25% of its heat to drive the body's chemical furnace. This liberation of heat leaves 75% of the generated heat at the muscle, raising exercising muscle temperature 3 to 4°C in 3 to 6 minutes [20,21]. This initial rise in internal body temperature is related to the intensity of muscle work [22], and the sudden increase in internal heat load triggers a rapid increase in cardiac output to counter redistribution of blood flow to the exercising muscles and meet rising metabolic demands. This demand includes increasing blood flow to the subcutaneous fat stores to mobilize metabolites for energy [2]. The increase in skin blood flow can reach levels in excess of 8 L/min in an attempt to reduce heat by convection, conduction, and radiation (Table 2). After 30 to 40 minutes of sustained performance, temperature plateaus as production of heat matches dissipation. It should be noted that the redistribution of circulating volume to the periphery decreases core volume and reduces central venous return, resulting in an eventual decrease in stroke volume, central venous pressure, and eventually mean arterial pressure [23]. The decrease in mean arterial pressure can lead to circulatory collapse and sudden loss of consciousness during the exertional activity.

Exercise in a hot, humid environment elevates skin temperature rapidly by radiation. The increase in skin temperature narrows the skin to core temperature gradient and challenges the cardiovascular system to maintain adequate blood flow to exercising muscle while maintaining elevated skin blood flow for heat dissipation. The *critical upper limit* in temperature is the point where the cardiovascular system can no longer maintain this elevated workload [21]. When this limit is exceeded, thermoregulation fails, cardiovascular collapse occurs, and the individual succumbs to heat stroke.

Heat dissipation during exercise

In a neutral environment and under normal basal conditions, little or no sweat is secreted so evaporation does not occur [24]. Vaporization of liquid on average accounts for loss of 19% of body heat and occurs from the respiratory tract based on humidity [25]. During exercise, an effort to maintain thermal balance occurs through sensible and insensible methods. Sensible losses occur through conduction, convection, and radiation of heat out to the environment. Insensible loss by evaporation is contingent on the humidity of the environment.

The ability to sweat is physiologically linked to heat dissipation during exercise. The volume of sweat output depends on (1) skin temperature, (2) ambient temperature, and (3) sweat capacity [26]. Sweat capacity depends on (1) size of the individual, (2) level of fitness, and (3) degree of acclimatization to heat [27]. For example, well-trained marathon athletes produce heat at a rate of 565 kcal/m^2 per hour of exercise [28]. One gram of evaporated sweat dissipates 0.58 kcal of body heat [29]. During a marathon, fluid intake is required to sweat if the individual is to continue heat dissipation. As sweat rates increase with duration of exercise, fluid loss can approach 6% to 10% of body mass. This hypovolemia results in less production of sweat [29] and a building of internal heat load [21]; however, a reduction of as little as 1% in body water [30] impairs thermoregulatory ability during exercise. A loss of 3% of total body weight is predictive of a heat illness [4].

Table 2
Biophysics of heat transfer

Physical heat transfer mechanism	Description of heat transfer
Conduction	Heat transfer by use of nonmoving objects. This may be via solid objects or still air. (Examples: Tissue to tissue transfer of heat occurs within the body. Skin will conduct heat to clothing.)
Convection	Heat transfer is by gas or liquid. Transfer of heat by circulating blood keeps internal organ temperatures in close approximation. (Example: Skin blood flow during vasodilatation increases heat transfer.)
Radiation	Heat transfer between bodies without motion of conduction. (Example: Heat will radiate from warm to cool on a gradient.)
Evaporation	Liquid transforms to vapor by use of thermal energy at the skin surface. (Example: Sweat that dries on the skin rather that drops off the skin.)

From Phillips R. Thermoregulatory and inflammatory mechanisms of shivering after cardiopulmonary bypass in cardiac surgery patients. Unpublished dissertation, University of Texas Health Science Center at San Antonio. 1999; with permission.

Biochemical effect of failure to dissipate heat

Leukocytes

Increased distribution of peripheral leukocytes (WBC) has been found in heat injured patients admitted with rectal temperatures in excess of 40.1°C [31]. When heat injured patients were compared to normal controls, the heat injured patients had a significantly higher level of leukocytes and lymphocyte subtypes than the control subjects. In addition, a significant positive correlation was found between absolute lymphocyte number and degree of hyperthermia. These laboratory results support the premise that heat illness augments the available cells for IL-6 synthesis.

Enzymes

When striated muscle destruction occurs, it releases the enzymes CPK, LDH, and AST into circulating peripheral blood. Severity of the release indicates the extent of muscle cell damage. Several studies [26,32,33] evaluated serum enzyme activity in exercised, heat stressed individuals. The most commonly assayed enzymes were CPK and LDH. Bood samples taken immediately after heat stress demonstrated elevated CPK and LDH, values that remained elevated 6 and 24-hours after exposure. Peak CPK greater than 10,000 U/L was an indicator for development of acute renal failure [30]. Muscle cell wall destruction not only releases enzymes but also myoglobin, which spills into urine when the level reaches 15 to 20 mg% [34,35]. Myoglobinuria is the causative factor of acute tubular necrosis in 24% to 33% of rhabdomyolysis induced renal failure cases [30].

Endotoxin

During severe heat stress and exhaustive exercise, the gastrointestinal wall becomes ischemic from an inadequate blood supply. Add to this elevated catecholamine levels, hypovolemia, hypoxemia, acidic pH of gut contents, and hyperthermia and the necessary dynamics for translocation of endotoxin from the lumen of the intestines into the portal circulation exist. Endotoxin is a known pyrogenic substance, and release of this pyrogen into the central circulation sets into motion the hypothalamic drive to increase body temperature [2]. In addition, endotoxin release signals the need for WBC subtypes to synthesize and release chemical mediators of inflammation, known as cytokines, also potent pyrogens.

Proinflammatory cytokines

The presence of significant enzyme release as a result of muscle cell damage triggers an increase in WBC subtypes and an increase in transcription, synthesis, and release of cytokines. The larger the amount of necrotic tissue, the greater the enzyme release and, it is hypothesized by this author, the greater the release of IL-6 and HSP70.

During the 1993 pilgrimage to Mecca, the role of IL-6 in heatstroke was elucidated [36]. Twenty-five consecutive heatstroke patients, plus 14 heat-stressed and 13 normal control subjects, provided whole blood samples for serum IL-6 assay. Not surprisingly, normal controls had no detectable IL-6; however, mean IL-6 was detectable and significantly higher in patients diagnosed with heat stroke than in patients diagnosed with heat stress.

Leukocytosis, with significant changes in absolute number and percentage of IL-1, IL-6, and TNF-α, is associated with heat exhaustion and heat stroke and has been found in the peripheral blood of heat illness patients [24]. An additional source of IL-6 may be the presence of circulating HSP70, a stress protein that experiences up-regulation of its expression when cell stress occurs [37].

HSP70

Another stimulus for IL-6 transcription is the presence of the stress proteins of the HSP70 family. Asea and associates [12] demonstrated in cell cultures, that in the presence of HSP70, there is an up-regulation of proinflammatory cytokines from human monocytes. Heat shock proteins and their regulatory partners, heat shock transcription factors, are genetic programs written to provide a cellular response to stressful conditions. These proteins are classified by molecular weight into “families” and play a key role in the regulation of anticipated cell death; however, HSP70 provides a strong inhibitory signal against normal cell death in the face of a cell stressor [10]. This inhibitory signal is due to HSP70 being an essential component for cellular recovery, survival, and homeostasis [38]. It is expected that HSP70 be present in the peripheral blood of heat stressed subjects.

Implications for military nursing research

Little is known about how cytokine levels interact with degree of heat illness and severity of rhabdomyolysis as determined by enzyme levels, and to what extent the inflammatory process and HSP70 are triggered has not been elucidated. In addition, it is not clear to what degree preexercise hydration, fitness level, and anthropometric characteristics influence these variables. Also of interest is how cooling measures used for heat-related illnesses affect activation of vasomotor and shivering activity, further

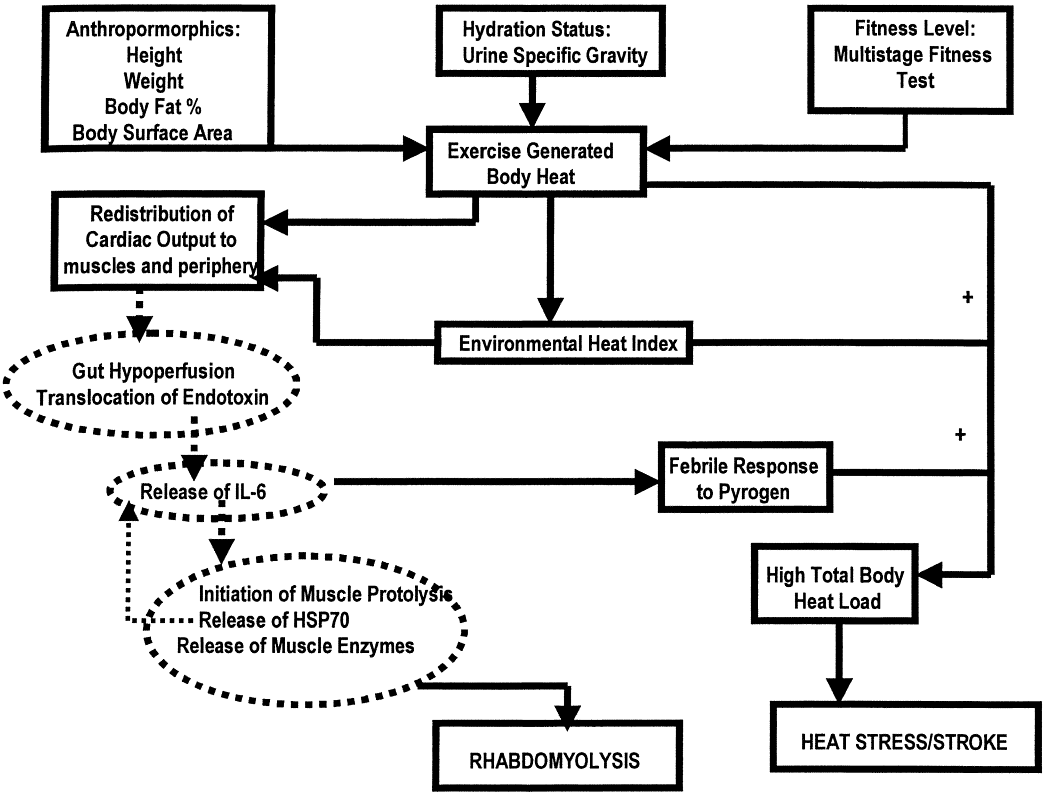

Fig. 1. Physiologic framework for proinflammatory effects of heat stress in exercising marines. The solid lines represent physiologic relationships already know and dotted lines indicate relationships tested by this study. (*From* Phillips R. Proinflammatory effects of heat stress in exercising marines. Grant submission. TriServices Nursing Research Program, 2000; with permission.)

challenging a weakened thermoregulatory system and prolonging activity of already proteolytic muscles.

Therefore, a study was designed to address differences between (1) preexercise hydration, (2) fitness, (3) anthropometric variables, (4) HSP70 release, (5) endotoxin translocation, (6) cytokine presence, and the (7) severity of rhabdomyolysis in subjects who do and do not experience a degree of heat illness. A second purpose of the planned study is to identify existence and strength of relationships between preexercise hydration, fitness, and anthropometrics and occurrence and severity of a heat illness and HSP70 release and endotoxin translocation with cytokine presence and severity of rhabdomyolysis. It is the central hypothesis of this study that IL-6 is released in response to endotoxin and that the severity of this IL-6 release will affect the extent of rhabdomyolysis experienced by exercising marines after an episode of heat. It is also expected that the preexercise variables will have an effect on the release of IL-6. Finally, subjects requiring rapid cooling for a heat illness will be assessed for onset, severity, and duration of vasomotor activity and shivering to identify effect on rhabdomyolysis, cardiovascular, and oxygenation parameters (Fig. 1). Shivering severity and duration will be monitored using the shivering severity instrument (Table 3) [39,40]. The specific aims of the study are outlined in Table 4.

This study will provide insight into how hydration status, obesity, age, fitness level, and environmental

Table 3
Shivering severity score

Shivering score	Muscle group involvement
0	No evidence of shivering
1	Masseter muscle tension
2	Neck and chest fasciculation
3	Abdominal muscle involvement
4	Extremity involvement

From Phillips R: Shivering severity instrument reliability and validity assessment. Unpublished manuscript, 1998.

Table 4
Specific aims "proinflammatory effects of heat stress in exercising marines"

Purpose	Specific aim
1. To describe differences between subjects who do or do not experience a heat illness.	Aim 1. Describe pre-exercise anthropormorphics, hydration, fitness, enzymes, proinflammatory mediators, HSP70, endotoxin, enzymes, and WBC differentials. Aim 2. Compare anthropormorphics, hydration, fitness, enzymes, proinflammatory mediators, HSP70, endotoxin, enzymes, and WBC differentials between those with and without a heat illness.
2. Identify existence and strength of relationships between mediators of inflammation and severity of rhabdomyolysis.	Aim 1. Determine relationship between anthropormorphics, hydration, fitness, enzymes, proinflammatory mediators, HSP70, endotoxin, enzymes, and WBC differentials and severity of heat illness. Aim 2. Identify relationships in the course of hydration, enzymes, proinflammatory mediators, HSP70, endotoxin, enzymes, and WBC differentials over the 72 hours after heat injury.
3. Identify effects of mechanisms of warming on proinflammatory mediator response and severity of rhabdomyolysis.	Aim 1. Determine differences in temperatures, thermal gradients, cardiovascular parameters, oxygenation status, proinflammatory indicators, and severity of rhabdomyolysis between shivering and nonshivering subjects. Aim 2. Identify relationships between temperatures, thermal gradients, cardiovascular parameters, oxygenation status, proinflammatory indicators, and severity of rhabdomyolysis with severity of shivering.

From Phillips R. Proinflammatory effects of heat stress in exercising marines. Grant submission, TriService Nursing Research Program, 2000; with permission.

factors predispose an individual to onset and severity of a heat illness episode; however, the ability to predict the severity of heat illness remains unclear. Previous research has been conducted to describe the development of a heat illness [1–3]. These studies, however, lack the realities of military life. This previous research was conducted using voluntary subjects tested in environmentally controlled laboratory settings where they are not exposed to high levels of sleep deprivation, anxiety from a new training life style and living arrangements, and exposure to new levels of physical, emotional and mental endurance. Thus they yield results not generalizable to military training protocols. The three main stressors, sleep deprivation, anxiety, and increasing expectations, are usually eliminated in controlled studies. Therefore, this study will provide new knowledge of differences between warriors in desert warfare training who do or do not experience heat illness while performing the same physical activity. The study also provides an opportunity to compare anthropomorphics, hydration (urine specific gravity) [41], fitness, thermal data (mean skin temperature as described by Teichner—see box)[42], biochemical values (CBC, CPK, LDH, AST, C-reactive protein, IL-6, endotoxin, and HSP70), and onset and severity of heat illness between subjects exposed to the same environmental thermal stress.

Teichner's mean skin temperature formula [42]

$$\begin{aligned} TSK_M = {} & 0.149(\text{cheek}) + 0.186(\text{chest}) \\ & + 0.107(\text{arm}) + 0.186(\text{back}) \\ & + 0.186(\text{thigh}) + 0.186(\text{calf}) \end{aligned}$$

Additional contributions from this study include results of laboratory values reported during a heat illness that have never before had baseline values available from the same individual for comparison and have never been compared with values obtained from individuals experiencing the same physical and thermal challenge without development of a heat illness. Delineation of these variables may provide insight into the biochemical makeup of physiologic responses to heat and physical exertion. Only then can data-driven decisions about prevention and intervention be made.

The goal of this study will provide direction for future work with heat illness in our active duty population. Our mission is to keep the fighting force ready to fight. This includes being ready for the hot deserts of the Middle East or the flight deck of an aircraft carrier. As our motto states, "Navy Medicine, Steaming to Assist."

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