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REVIEW ARTICLE

HEAT EXHAUSTION AND EXERTIONAL HEATSTROKE

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INTRODUCTION

Heat illness is a major cause of preventable morbidity worldwide, especially in regions characterized by high ambient temperatures. The major heat-related illnesses, heat exhaustion and heatstroke, involve varying degrees of thermoregulatory failure that occur when individuals are exposed to elevated temperatures. Heat exhaustion is characterized by moderately increased body temperature (101-102 degrees F), paleness, dizziness, nausea, vomiting, as result of excessive heat and dehydration. It may rapidly progress to heatstroke when the body's thermoregulatory mechanisms become overwhelmed. Heat stroke is defined as a core body temperature in excess of 40.5°C (105°F) with associated central nervous system dysfunction in the extreme environmental heat [1]. Exertional heat stroke generally occurs in healthy individuals who engage in heavy exercise during heat waves when air temperatures exceed 102.5°F (39.2°C) for 3 or more consecutive days. In classic exertional heat stroke, rate of heat production exceed to the capacity of the body to dissipate heat and the arterial carbon dioxide tension is often less than 20 mm Hg [2]. Patients with nonexertional heat stroke usually have respiratory alkalosis. In contrast, those with exertional heat stroke nearly always have both respiratory alkalosis and lactic acidosis [2]. It occurs in younger patients who are unable to avoid extreme environmental conditions. Typical patients are athletes, military cadets and soldiers during basic training [3]. In both cases, thermoregulatory mechanisms fail if the stress becomes too great, which results in accelerated hyperthermia. Heat stroke is associated with a systemic inflammatory response, which leads to end-organ damage with involvement of the CNS and end-organ dysfunction [4].

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INCIDENCE

Heat exhaustion and exertional heatstroke affect our athletes and soldiers during training in extreme hot climate (personal observation) but data regarding incidence in Pakistan is lacking. Risk of developing the exertional heat stroke is related directly to peak temperature, duration of exposure and acclimatization period. Heat waves increase the mortality rate. The European summer heat wave of 2003 was exceptionally harsh in both duration and intensity. In France alone, the number of heat-related deaths reached 14,800 by August 20 [5]. In an epidemiologic study during heat waves in urban areas in the United States, the incidence of heat stroke varied from 17.6 to 26.5 cases per 100,000 populations [6]. Most people affected by classic heat stroke are very young or elderly [7]. In Saudi Arabia, the incidence varies seasonally, from 22 to 250 cases per 100,000 populations [8].

PATHOPHYSIOLOGY

To understand the pathophysiology of heat exhaustion and exertional heat stroke, the systemic and cellular responses to heat stress must be appreciated. All heat illnesses exist along a continuum and share similar elements. In exertional heat stroke, the root cause is rate of heat gain exceeding the ability of the body to dissipate heat during exercise in hot weather [2].

Heat stroke results from thermoregulatory failure coupled with an exaggerated acute-phase response in the body. In this disorder, the multiorgan injury results from a complex interplay among the

cytotoxic effect of the heat, inflammatory and coagulation responses [8]. Heat stress induces thermoregulatory failure, exaggeration of the acute-phase response, and alteration in the expression of heat-shock proteins which may contribute to the development of heat stroke [9]. Active cutaneous vasodilatation and splanchnic vasoconstriction permit the shift of heated blood from the central organs to the periphery, from which heat is then dissipated to the environment. Physical manifestations in heat stroke may include vasodilation in skin, tachypnea, rales due to noncardiogenic pulmonary edema, excessive bleeding due to disseminated intravascular coagulation and evidence of neurologic dysfunction such as altered mentation or seizures [10].

The cutaneous vasodilatation may also lead to splanchnic hypoperfusion and ischemia, resulting in increased production of reactive oxygen and nitrogen species, which may in turn induce intestinal mucosal injury and hyperpermeability [10]. Endotoxins may then leak into the circulation and enhance the acute-phase response, leading to increased production of pyrogenic cytokines and nitric oxide. Both cytokines and nitric oxide can interfere with thermoregulation and precipitate hyperthermia, hypotension, and heat stroke (figure) [11].

THERMOREGULATION

Human body gains temperature from the environment and heat produced by the body itself. This overall heat load must be dissipated to maintain a body temperature of 37°C, a process called thermoregulation [11]. A rise in the temperature of the blood by less than 1°C activates peripheral and the hypothalamic thermoregulatory center. The efferent response from this center increases the delivery of heated blood to the surface of the body [12]. Active sympathetic cutaneous vasodilatation then increases blood flow in the skin by up to 8 liters per minute [13].

In exertional heat stroke, heat production from muscles may increase by 15 times the resting rate. Core temperatures measured after long distance races have been found to be as high as 105.8°F (40.6°C) in conscious athletes and 109.4°F (43°C) in those who have collapsed [14]. An increase in the blood temperature also initiates sweating. Evaporation is the principal mechanism of heat loss in a hot environment, but this becomes ineffective above a relative humidity of 75 percent [1]. If the air surrounding the surface of the body is not saturated with water, sweat will vaporize and cool the body surface [15,16]. As blood is shunted from the central circulation to the muscles and skin to facilitate heat dissipation, visceral perfusion is reduced, particularly in the intestines and kidneys [17].

ACUTE-PHASE RESPONSE

The acute-phase response to heat stress is a coordinated reaction that involves endothelial cells, leukocytes, and epithelial cells. These cells protect against tissue injury and promotes repair [18]. Interleukin-1 was the first known mediator of the systemic inflammation induced by strenuous exercise [19]. A variety of cytokines are now known to be produced in response to endogenous or environmental heat (table-1). The plasma levels of inflammatory cytokines (tumor necrosis factor a [TNF-a], interleukin-1b, and inter-feron-g) and anti-inflammatory cytokines (interleukin-6, soluble TNF receptors p55 and p75, and interleu-kin-10) are elevated in persons with heat stroke; cool-ing of the body to a normal temperature does not result in the suppression of these factors [20-24].

The interleukin-6 produced during heat stress modulates local and systemic acute inflammatory responses by controlling the levels of inflammatory cytokines [25,26]. The systemic progression of the inflammatory response is secondary and involves other cells, such as monocytes [27]. An imbalance between inflammatory and anti-inflammatory cytokines may result in either inflammation-associated injury or refractory immunosup-pression. A similar sequence of events has been shown to occur in sepsis [28].

HEAT-SHOCK RESPONSE

Nearly all cells respond to sudden heating by producing heat-shock proteins or stress proteins. Expression of heat-shock proteins is controlled primarily at the level of gene transcription. During heat stress, one or more heat-shock transcription factors bind to the heat-shock element, resulting in an increased rate of transcription of heat-shock proteins. Increased levels of heat-shock proteins in a cell induce a transient state of tolerance to a second, otherwise lethal, stage of heat stress, allowing the cell to survive [29-31].

Acclimatization

Acclimatization to heat takes days to weeks and allows a person to safely be active at temperatures that would have previously been dangerous. Successive increments in the level of work performed in a hot environment result in adaptations that eventually allow a person to work safely at levels of heat [11]. This adaptive mechanism includes earlier onset of sweating, increased sweat volume, more dilute sweat, enhanced cardiovascular performance, activation of the renin-angiotensin-aldosterone axis, salt conservation with expansion of plasma volume, increased glomerular filtration rate, and the ability to resist rhabdomyolysis [32]. This response enhances tolerance of heat and cellular protection against heat stress. Although excessive expression of the heat-shock proteins blocks essential cellular processes, partial up-regulation of these proteins may prove beneficial, particularly as a preventive measure during a heat wave.

DIAGNOSTIC EVALUATION

The diagnosis of exertional heat stroke is based upon a careful history and physical examination. Heat exhaustion is characterized by nonspecific symptoms such as malaise, headache, and nausea. It can progress to heatstroke, a much more serious illness involving central nervous system dysfunction such as delirium and coma if not properly diagnosed in time. The patients may present in advance stage with complications such as rhabdomyolysis, hepatic failure, arrhythmias, disseminated intravascular coagulation, renal or hepatic failure, hypoglycemia, rhabdomyolysis, and seizures [33,34].

Physical findings in heat stroke may include cutaneous vasodilation, tachypnea, rales due to noncardiogenic pulmonary edema, excessive bleeding due to disseminated intravascular coagulation and evidence of neurologic dysfunction such as altered mentation or seizures. The skin may be moist or dry, depending upon underlying medical conditions, the speed with which the heat stroke developed, and hydration status. Rectal temperature should be determined in all patients. Not all victims of heat stroke should be assumed to be volume-depleted [35]. The full differential diagnosis of hyperthermia should be considered in each patient (table-2).

LAB DIAGNOSIS

Laboratory studies should include Complete blood count, coagulation profile, serum electrolytes, urea, Creatinine and liver enzymes estimation. CBC, Prothrombin time (PT), activated partial thromboplastin time (PTT), and fibrinogen tests may provide evidence of hemoconcentration, a leukocytosis as high as 30,000 to 40,000/mm^3 and disseminated intravascular coagulation [8]. Urine specific gravity typically is increased. Proteinuria, hematuria, myoglobinuria, or granular casts provide evidence of acute renal failure or rhabdomyolysis. Evaluate for uremia and hyperkalemia by serum urea and electrolytes. Hepatic transaminases concentrations are elevated almost universally in heatstroke. Reconsider the diagnosis of heatstroke if aspartate aminotransferase and alanine aminotransferase levels are within the reference ranges. Hypoglycemia may occur because of increased use of glucose or hepatic damage leading to impaired gluconeogenesis. The CK level is elevated in rhabdomyolysis, especially in exertional heatstroke and may be associated with its complications (eg,

Table-1: Effects of heat stress and heat stroke on circulating cytokines and cytokine receptors growth factors.

Cytokine or factor	Heat stress		Heat stroke		Reference
	Exercise induced	Environmental	Classic	Exertional	
Tumour necrosis factor α	Increased or unchanged	Unchanged	Increased or unchanged	Increased	Bouchama et al.[20], Chang. [21]
Interleukin 1-ß	Increased or unchanged	NA	Increased or unchanged	Increased	Chang.[21], Bouchama et al [22]
Interleukin -6	Increased	Increased	Increased	Increased	Chang.[21], Bouchama et al. [22]
Interleukin -10	Increased	Increased	Increased	NA	Bouchama et al.[23]
Soluble tumor necrosis factor receptors (p55 P75)	Increased	Increased or unchanged	Increased	NA	Hammami et al. [24]

hypocalcemia, hyperphosphatemia, myoglobinuria and acute renal failure) [12]. Arterial blood gases (ABGs) measurements are useful to evaluate acid-base status, pulmonary function, and tissue oxygenation. Exertional heat stroke cases may have both respiratory alkalosis and lactic acidosis [36].

The chest radiograph may demonstrate pulmonary edema, while the electrocardiogram may reveal dysrhythmias, conduction disturbances, nonspecific ST-T wave changes, or heat-related myocardial ischemia or infarction [37,38].

MANAGEMENT

Management of heat exhaustion and stroke require ensuring adequate cooling, airway, breathing and circulation. Central venous pressure monitoring is useful for assessing volume status and determining the need for fluid resuscitation [38]. Cooling measures is considered the treatment of choice because it is effective, noninvasive and easily performed. Immersing the patient in ice water is the most effective method of rapid cooling [18, 38].

Heat Exhaustion

- Treat heat exhaustion with rest, removal from hot environment and correction of dehydration and electrolyte abnormalities.
- Patients may be cooled gently with ice packs applied to the neck, groin and axillae.

Table-2: Differential diagnosis of heat stroke

Environmental exposure	Hypothalamic stroke
Sepsis	Status epilepticus
Encephalitis	Cerebral hemorrhage
Brain abscess	Neuroleptics malignant syndrome
Meningitis	Sedative-hypnotic withdrawal
Typhoid fever	Sympathoninetic toxicity
Thyroid storm	Anticholinergic toxicity

- For mild cases, oral rehydration with 0.1% isotonic sodium chloride solution usually is adequate.
- The water deficit is best corrected slowly (one half of the total water depletion replaced in the first 3-6 h, with the remainder replaced over the next 6-9 h).
- Monitor vital signs, including orthostatics and urine output, to guide fluid replacement.
- Heat exhaustion should correct in 2-3 hours, slower resolution or failure to resolve should initiate consideration of other causes of elevated temperature or transfer to hospital.

Heatstroke

- Institute aggressive cooling measures as rapidly as possible to minimize end-organ damage. An ideal goal is to drop the patient's core temperature by 0.2°C/min. The endpoint core temperature is around 38°C to avoid overshoot.

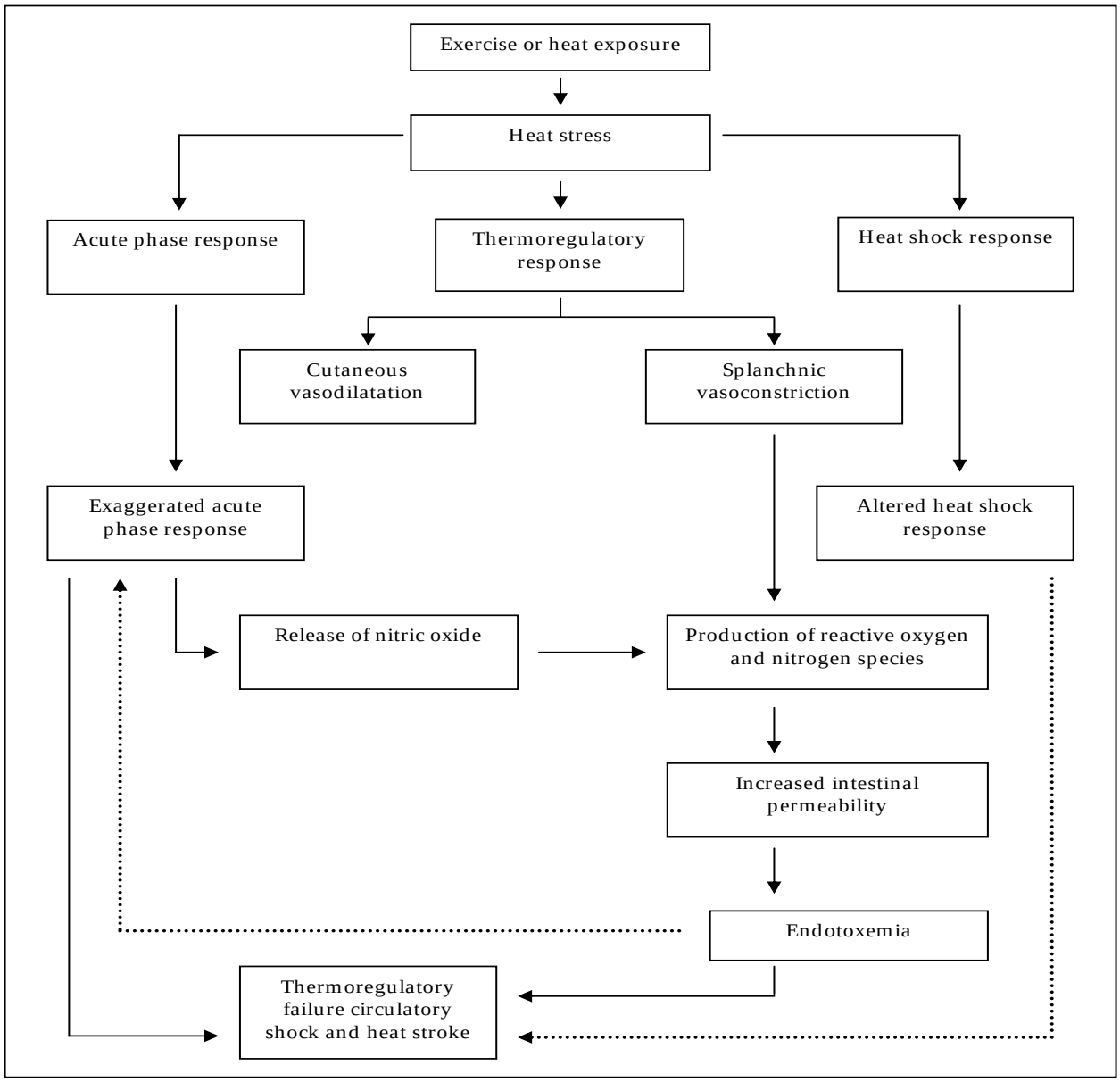

Figure: The sequence of events in the progression of heat stress to heat stroke[11].

- Evaporative cooling is safe, effective, easily accomplished and well tolerated.
- Ice water or slush immersion is an alternative cooling method. Although ice water or slush immersion is effective at rapidly lowering body temperature.
- Other modalities with anecdotal success include internal cooling methods, such as ice water gastric lavage and ice water rectal lavage, as well as invasive techniques such as ice water peritoneal and thoracic lavage, and cardiopulmonary bypass. Gastric or bladder lavage likely adds very little to the effect of evaporative cooling when performed properly and the former additionally carries the risk of aspiration [3, 34].

MEDICATION

No drugs significantly reduce core temperature in patients with heat illness. In contrast to patients with fever who develop elevated temperatures because of an elevated hypothalamic set point, hyperthermic patients

do not benefit from antipyretic therapy. Salicylates can worsen coagulopathies and acetaminophen in large doses can worsen hepatic damage. The mainstay of therapy involves rapid cooling and rehydration [40,41]. Muscle relaxants and neuroleptics have been used in the past to treat complications of heat illness, shivering, and seizure prophylaxis, but clinical trials are lacking.

Neuroleptics

These agents have been used to suppress shivering during rapid cooling. Chlorpromazine (Thorazine)-Antidopaminergic drug that blocks postsynaptic mesolimbic dopamine receptors, has anticholinergic effects, can depress reticular activating system, blocks alpha-adrenergic receptors and depresses release of hypophyseal and hypothalamic hormones. Used to suppress shivering during treatment, thereby minimizing endogenous heat production.

Benzodiazepines

Patients may have seizures from hyperthermia, requiring benzodiazepines. These agents are used to treat seizures.

Prevention

- Exertional heat stroke can be prevented in young athletes and soldiers by creating awareness, taking precautions and proper acclimatization in hot weather.
- Acclimatization typically requires 60 minutes per day of exercise in hot conditions for at least 1 week. Gradually increase exercise intensity and duration, especially athletes.
- Heat response plans should be prepared for high risk group people and can be activated in the event of extremes of temperature. Identify susceptible populations and at risk behaviors during training and sports.
- Reschedule strenuous physical activities for cooler periods of the day.
- Drink 400-500 mL of cool fluids before exercising and 200-300 mL at frequent intervals during exercise.
- Monitor body weight before and after exercise.
    - Weight loss of more than 7% of body weight represents severe water depletion. Cease exercise and rehydrate to normal weight.
    - Weight loss of 5-6% of body weight represents moderate water depletion. Hydrate to normal weight and proceed with light workouts.
    - Weight loss of 2-3% body weight represents mild water depletion. Dehydrate to normal body weight before engaging in further exercise.
- Wear light, loose-fitting, and light-colored clothing.
- Bath or shower in tepid water.
- Use air conditioning, fans, and adequate ventilation in extreme weather.
- Soldiers and athletes should not exercise in temperature extremes with concurrent illness.

CONCLUSION

The threat of heat related illness is increasing because of global warming in temperate climates. The exertional heatstroke is serious disorder among athletes and soldiers during training in extreme hot climate due to thermoregulatory failure leading to very high body temperature and multiple organs injuries including central nervous system dysfunction. Prompt recognition and immediate cooling through full-body ice-water immersion are crucial. The importance of adequate hydration and the proper precaution during exercise in hot summer season should be given priority in Pakistan.

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