



Heat Stroke

BR Bansode

Physician and Cardiologist, Dr. Babasaheb Ambedkar Hospital, Central Railway, Mumbai 400 027.

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Increasing evidence shows that atmospheric carbon dioxide levels are rising and are causing global warming.¹ According to some predictions heat-related mortality will increase drastically as global warming develops. Air conditioning can allow people to continue to work effectively in hot weather and may become necessary to prevent mortality, but it uses a large amount of energy, which in turn accelerates global warming. Simpler measures like regular meals, drinking enough water will normally prevent dehydration in elderly and other vulnerable people during heat stress. Also an open window, fans, air coolers, light and loose fitting clothing and avoidance of unnecessary exertion can prevent heat stress.

There are several heat related illnesses, like heat syncope, heat cramps, heat exhaustion heat stroke, hyperthermia and multiorgan dysfunction syndrome.

Romans in 24 BC recognized heat stroke as hot, dry flushed skin.² In 1946 it was shown that heat stroke leads to multiorgan damage with hemorrhage and necrosis in the lung, heart, liver, kidneys, brain and gut.³ Heat stroke is a medical emergency characterized by high core body temperature (40°C) with central nervous system dysfunction like confusion, delirium, convulsion and coma. In spite of effective and aggressive treatment of heat stroke it is often fatal and survivors may sustain permanent neurological damage.

Over last decade researches have shown that heat stroke results from thermoregulatory failure with exaggerated acute phase response with altered expression of heat shock proteins ensuring multiorgan injury resulting from a complex interplay among the cytotoxic effect of heat and the inflammatory and coagulation responses of host.^{5,8,10}

Heat Wave: Three or more consecutive days during which the air temperature is > 32.2°C

Heat Stress: Perceived discomfort and physiological strain associated with exposure to a hot environment, especially during physical work.

Heat Stroke: Severe illness characterized by a core temperature > 40°C and central nervous system abnormalities such as delirium, convulsions, or coma resulting from exposure to environmental heat (classic heat stroke) or strenuous physical exercise (exertional heat stroke)

Heat exhaustion: Mild-to-moderate illness due to water or salt depletion that results from exposure to high environmental heat or strenuous physical exercise; signs and symptoms include

intense thirst, weakness, discomfort, anxiety, dizziness, fainting, and headache; core temperature may be normal, below normal, or slightly elevated (>37°C but < 40°C).

Hyperthermia: A rise in body temperature above the hypothalamic set point when heat-dissipating mechanisms are impaired (by drugs or disease) or overwhelmed by external (environmental or induced) or internal (metabolic) heat.

Multiorgan-dysfunction syndrome: Continuum of changes that occur in more than one organ system after an insult such as trauma, sepsis, or heat stroke

HEAT STROKE

Heat stroke is defined clinically as a core body temperature that rises above 40°C and is accompanied by hot, dry skin and CNS abnormalities like delirium, convulsions or coma. Heat stroke is of two types, classical heat stroke and exertional heat stroke. Classical heatstroke results from exposure to high environmental temperature, the elderly people are more vulnerable. Exertional heat stroke occurs in previously healthy young people, exercising usually in hot and humid climate, without being acclimatized.

Abderrezak Bouchama et al proposed an alternate definition of heat stroke based on their research work and understanding, that "Heat stroke is a form of hyperthermia associated with systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates".

Incidence of heat stroke in United State varies from 17.6 to 26.5 cases / 100,000 population.¹¹ In Saudi Arabia, incidence of heatstroke varies seasonally from 22 to 250 cases / 100,000 populations,¹² while the incidence of heat exhaustion ranges from 450 to 1800 cases / 100,000 populations. It is unknown why mild illness develops in response to heat exhaustion in some people while in others it progresses to heat stroke and multiorgan dysfunction. Some genetic factors may determine the susceptibility to heat stroke. Candidate's susceptibility gene includes those that encode cytokines, coagulation proteins and heat shock proteins involved in the adaptation to heat stress.^{6,10}

Pathogenesis of heat strokes

Risk Factors

The environment

Body gains heat from environment and produced by metabolism. This heat gain must be lost through convection, conduction,

Effect of Heat Stress and Heat Stroke on Circulating Cytokines, Cytokine Receptors, Growth Factors, and Chemokines

Cytokine or Factor	Heat Stress			Heat Stroke	
	Exercise Induced	Environmental	Therapeutic	Classic	Exertional
Interleukin-1 β	Increased or unchanged	NA	Increased	Increased or unchanged	Increased
Interleukin-6	Increased	Increased	Increased	Increased	Increased
Interleukin-8	Increased	NA	Increased	NA	NA
Interleukin-10	Increased	Increased	Increased	Increased	NA
Interleukin-12	Increased or unchanged	NA	Unchanged	NA	NA
Interleukin-1-receptor antagonist	Increased	NA	NA	NA	NA
Soluble interleukin-2-receptor	Increased	NA	NA	Increased	NA
Soluble interleukin-6-receptor	NA	Increased	NA	Decreased	NA
Soluble TNF receptors (p55&p75)	Increased	Increased or unchanged	Increased	Increased	NA
Interferon- γ	Increased or unchanged	NA	Unchanged	Increased	NA
Interferon- α	Increased or unchanged	NA	Unchanged	NA	NA

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radiation and evaporation of sweat. The effectiveness of sweating in cooling the body is dependent on both the environmental temperature and the humidity. Low humidity and air movements are important for evaporation of sweat. As air temperature reaches body temperature the effectiveness of this mechanism is lost,⁵ the classical heat strokes occur in response to rising or sustained environmental heat, but it is not necessary in exertional heat stroke,⁶ so heat gain should be avoided.

Activities

Vigorous exercise in humid climate is a risk factor in development of exertional heat stroke. This is seen in military personnel, marathon runners, mountaineers, foundry workers and fireman.

Sex

Women seem to be protected from exertional heat stroke. Exertional rhabdomyolysis is also rare in women. It was attributed to body temperature at which thermoregulatory reflexes are activated is lower in women than in men. It is not known whether this is an effect of estrogens or simply that men are capable of generating more heat because of larger muscle bulk.

Other Factors

Obesity, febrile illness, alcohol consumption, dehydration from any illness, conditions which increase heat like thyrotoxicosis and drugs like anticholinergic, diuretics, phenothiazines, antihistaminics, tricyclic antidepressant, beta blockers and amphetamine.

Thermoregulation

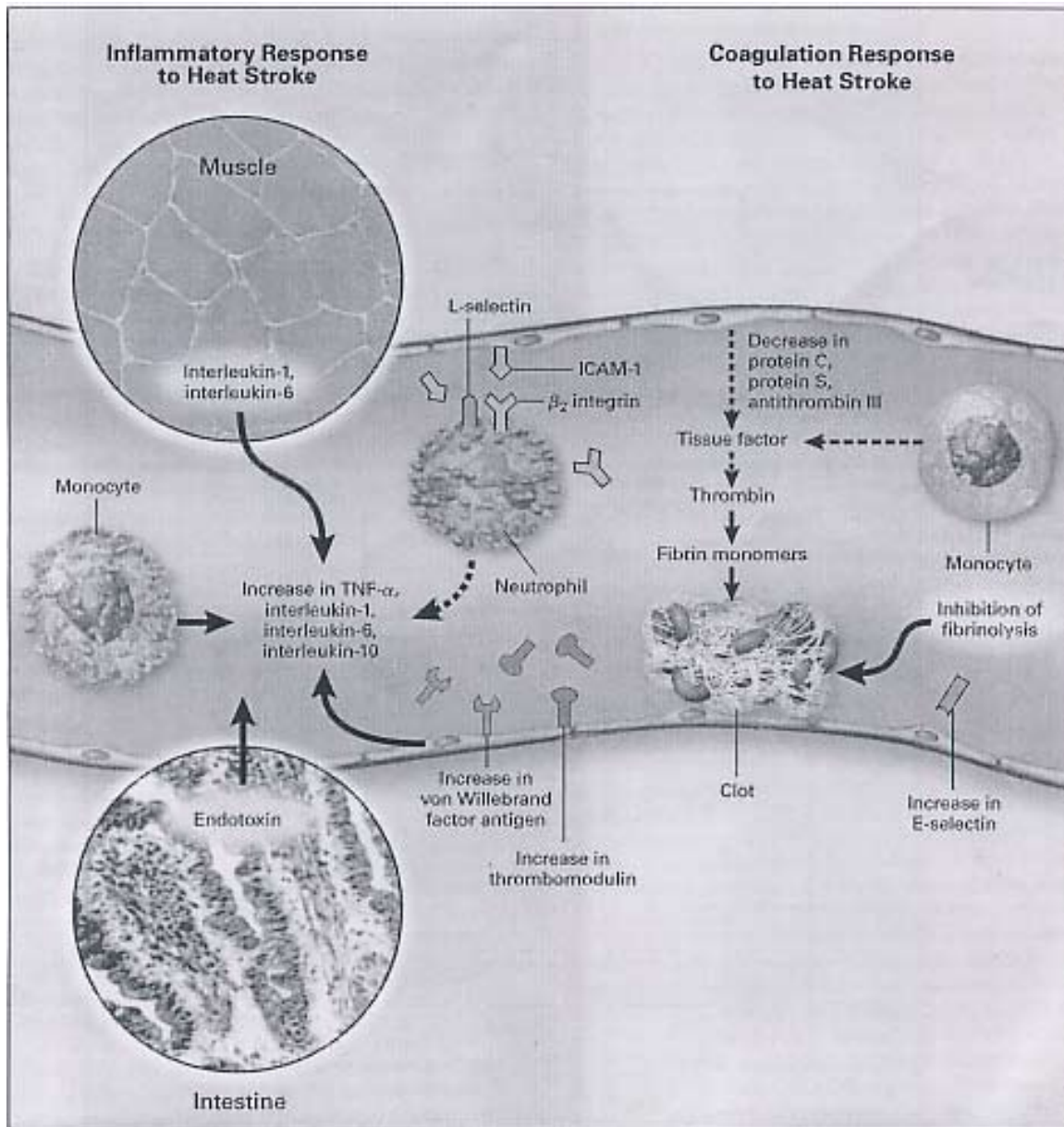
Thermoregulation is a process by which human body temperature is maintained within a narrow range 36.5 to 37.5°C to avoid cellular and enzymatic dysfunction even in extreme conditions of environment. It is under control of autonomic

nervous system, which integrates afferent input and efferent responses. Hypothalamus has central control where mean body temperature is determined from peripheral and central structures and compared with a "set point". With rise in blood temperature efferent response from this center increases delivery of heated blood to the surface of the body. Active sympathetic cutaneous vasodilatation then increases blood flow to the skin about 8 liters / min.³⁰ An increase in blood temperature also initiates thermal sweating.^{14,15} If the air surrounding the surface of the body is not saturated with water, sweat will vaporize and cool the body surface. A rise in blood temperature also increases heart rate, cardiac output, and minute ventilation.^{4,13,14} As blood shunted from central circulation to the muscles and skin to facilitate heat dissipation, visceral perfusion is reduced particularly in intestines and kidneys.¹³ Loss of sodium and water by sweating is substantial, which may amount to 2 liters or more per hour must be balanced by generous salt supplementation to facilitate thermoregulation.¹⁷ Dehydration and salt depletion impair thermoregulation.¹⁷ Successive increments in level of work performed in a hot environment result in adaptation that eventually allows a person to work safely at levels of heat that were previously intolerable or life-threatening. This process of acclimatization to heat takes several weeks and involves enhancement of cardiovascular performance. An increase in the conservation of salt by sweat glands and kidneys expands the plasma volume, which in turn increases the glomerular filtration rate and the ability to resist exertional rhabdomyolysis.

Acute reaction to heat stress

The acute reaction to heat stress is a coordinated reaction that involves endothelial cells leukocytes and epithelial cells, which protects against tissue injury and promotes repair. Interleukin-1 was the first known mediator of systemic inflammation induced by strenuous exercise.¹⁹ A variety of cytokines are now known

Possible Path physiological Mechanisms of Heat Stroke



Hyperthermia due to passive heat exposure or to exercise may facilitate the leakage of endotoxin from the intestine to the systemic circulation as well as the moment of interleukin-1 or interleukin-6 proteins from the muscles to the systemic circulation. The result is excessive activation of leukocytes and endothelial cells, manifested by the release of proinflammatory and anti-inflammatory cytokines (TNF- α , interleukin-1, interleukin-6, and interleukin-10), up-regulation of cell-surface adhesion molecules, and shedding of soluble cell-surface adhesion molecules (E-selectin, L-selectin, and intercellular adhesion molecule 1 (ICMA-1), as well as activation of coagulation (with decreased levels of protein-C and S and antithrombin-III) and inhibition of fibrinolysis. The inflammatory and coagulation responses to heat stroke, together with direct cytotoxic effects of heat, result in injury to the vascular endothelium and micro-thrombosis. The solid arrows indicate pathways for which there is clinical or experimental evidence, and the broken arrows indicate putative pathways.

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to be produced in response to endogenous or environmental heat.^{9,20-22}

Cytokines mediate fever, leukocytosis increases synthesis of acute phase proteins, muscle catabolism, stimulations of the hypothalamic pituitary-adrenal axis and activate WBC and endothelial cells.^{9,22} Interleukin-6 produced during heat stress

modulates local and systemic acute inflammatory responses by controlling the level of inflammatory cytokines.²⁴ It also stimulates hepatic production of anti-inflammatory acute phase proteins which inhibit the production of reactive oxygen species and release of proteolytic enzymes from activated leukocytes.^{18,22} Other acute phase proteins stimulate endothelial cell adhesion,

proliferation, and angiogenesis, thus contribute to responsible repair and healing.¹⁸ Monocytes are responsible for systemic progression of inflammation as seen in sepsis.

Stress Proteins

In response to sudden heating all cells react and produce heat shock proteins or stress proteins.²⁵ Increased level of these stress proteins in a cell induces a transient state of tolerance to a second, otherwise lethal stage of heat stress, allowing the cell to survive.^{10,25} Heat shock proteins protects from heat stress by preventing their irreversible denaturation²⁵ and by acting as central regulators of the baroreceptor - reflex response during severe heat stress, abating hypotension, bradycardia and conferring cardio vascular protection.⁷

Cardiovascular adaptation to acute heat stress is normally observed as an increase in cardiac output up to 20 liters/min and shift of heated blood from core-circulation to peripheral circulation.¹³ This adaptation fails when salt and water reduces or in cardiovascular diseases. When drug therapy interferes with cardiovascular functions, heat stress can progress to heat stroke.⁴

During strenuous exercises or hyperthermia blood shifts from mesenteric circulation to working muscles and skin, leading to ischaemia of gut and intestinal hyperpermeability.^{13,26,27} So in humans after strenuous exercises there is high concentration of endotoxin, inflammatory cytokines and acute phase proteins in the blood.^{9,28,29} These pyrogenic cytokines and endothelial derived factors can interfere with thermoregulation by raising the set point at which sweating is activated and alter vascular tone in splanchnic circulation, which precipitates hypotension, hyperthermia and heat stroke. Increased level of heat shock protein protects the cells from injury due to heat, ischemia, hypoxia, endotoxin and inflammatory cytokines. While low levels of heat shock protein are found in patients who progress to heat stroke.^{10,30,31}

Pathophysiology

Effect of heat

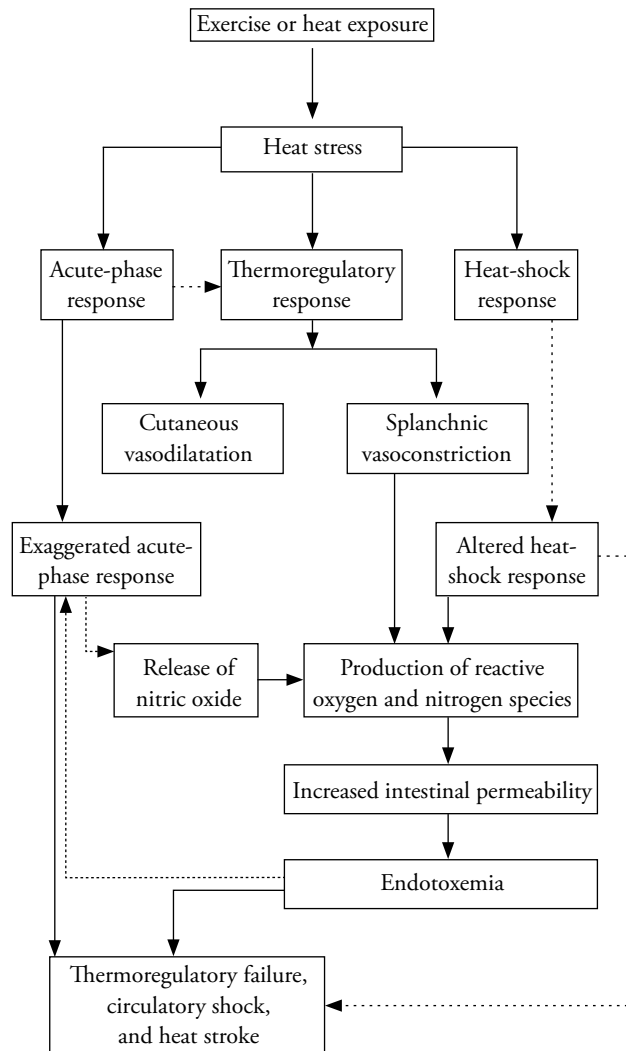
Heat directly induces tissue injury. The severity depends on high temperature and duration of exposure to heat.^{32,33} At extreme temperatures (49 °C to 50 °C) all cellular structures are destroyed and cellular necrosis occur in less than 5 mins.³² At lower temperatures cell death is largely due to apoptosis.

Cytokines

Plasma level of inflammatory cytokines (i.e. TNF- α , interleukine-1 β and interferon- γ) & the anti-inflammatory cytokines (interleukine-6, interleukine-10, soluble TNF receptor p55 and p75) are elevated in the patients suffering from heat stroke.³⁴⁻³⁷ Cooling of the body to a normal temperature does not result in the suppression of these factors. The levels of interleukin-6 and TNF receptor correlate with severity of heat strokes.^{36,38}

So imbalance between inflammatory and anti-inflammatory cytokines may result in inflammation associated injury or refractory immunosuppression. But research has not proved this yet.

The Sequence of Events in the Progression of Heat Stress to Heat Stroke



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Coagulation Abnormality

Microvascular thrombosis and endothelial cell injury are predominant features of heat stroke. In heat stroke activation of coagulation cascade is early than fibrinolysis and seen with appearance of thrombin, antithrombin III complexes and soluble fibrin monomers and low levels of protein C protein S and antithrombin III. While activation of fibrinolysis is also shown with increased level of plasmin α_2 -antiplasmin complexes and D dimmers and low levels of plasminogen. When the core body temperature normalize with treatment, fibrinolysis inhibits but not activated coagulation abnormalities which is seen in sepsis.³⁸

Clinical Features

Heat stroke is systemic disorder and patients show two cardinal features hyperthermia and central nervous system dysfunction. The clinical features of classical heat stroke and exertional heat stroke may be same but the populations affected are the elderly and young. Brain damage may be mild to severe (delirium-coma) and during cooling therapy convulsions may occur. Patients

in both the group have shown tachycardia, hyperventilation and hypotension. Initially patients with heat stroke show low potassium and phosphate but later due to hemoconcentration level of calcium and proteins are high. In exertional heat stroke rhabdomyolysis, high phosphate, calcium and potassium are observed even after body temperatures lowers with therapy. Multiorgan dysfunctions syndrome is serious complication of heat stroke.⁸

Lab Investigations

- Complete hemogram
- Serum biochemistry including RFT, LFT
- ABG analysis
- Muscle enzyme (creatin kinase)
- Coagulation profile
- Urine examination

Management

Basic aim of therapy in heat stroke is cooling the body temperature and support to organ dysfunction.

Cooling

Rapid cooling therapy brings core temperature to below 38.9°C within 30 minutes and improves survival.⁶

Cold water / ice water application rapidly lowers the temperature but it triggers cutaneous vasoconstriction and patients may have shivering and convulsions. To avoid this vigorous massage and spraying tepid water with fans can help to lower the temperature. Sometimes dantrolene sodium therapy is useful for lowering body temperature; CNS abnormalities may improve with rapid cooling. But residual brain damage may persist and is associated with high mortality. Cooling units, cooling blankets and cold IV fluids, intragastric lavage, enemas, IPD are other route of heat exchange.

In patients with heat stroke normalizing body temperature may not prevent or reduce inflammation, coagulation abnormalities and multiorgan dysfunction. So therapy with anti-inflammatory, immunomodulators and corticosteroids will improve survival. Coagulation and fibrinolysis are frequently activated during heat stroke and may lead to disseminated intravascular coagulation.^{8,39} Replacement therapy with recombinant activated protein C, which attenuates both the coagulation and the inflammation, reduces mortality in patients with severe sepsis and may be useful in those with heat stroke as well.^{39,40} A logical goal for the next generation of immunomodulators is selective pharmacological induction of the expression of heat-shock proteins.

Prevention

Heat stroke is a preventable illness and through knowledge of the disorders can help to reduce mortality and morbidity. The classical heat stroke is predominant in very young or elderly persons with chronic mental disorders or cardiopulmonary diseases and those receiving medication that interfere with salt and water balance such as diuretics, anticholinergic agents and tranquilizers that impair sweating. Exertional heat stroke is commonly seen in manual laborers, military personnel, football player, and long distance runners. To prevent these types of heat stroke people can acclimatize themselves to heat and plan outdoor activity

during cooler time of the day, reduce their level of physical work, drink additional water and consume salty foods. In football player's modification should be done for practice, avoidance of dehydration and salt depletion, which have been found to be effective means of preventing heat strokes.

SUMMARY

It is clear that heat stroke is a devastating disease with significant morbidity and mortality attached to it. Certainly, classical heat stroke is inherently preventable. Exertional heat stroke may not necessarily be so.

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