Abstract: Heatstroke (HS) is a serious medical emergency due to thermoregulatory failure, an amplified acute phase response and alteration in the expression of heat shock proteins, resulting from exposure to environmental heat (classical heatstroke) or strenuous physical exertion (exertional heatstroke). It is characterized by elevation of core temperature above 40°C and Central Nervous System (CNS) dysfunction that results in delirium, convulsions or coma. There is multiorgan injury due to complex inter-play between the cytotoxic effect of the heat and the inflammatory and coagulation responses of the host. It is often fatal and even has high rate of permanent neurological damage in the survivors.

It is predicted that due to global warming, the incidence of heat wave related disorders will become more prevalent. The recent high death toll in most countries and death of high profile athletes due to heat shock has also increased public awareness of the adverse effects of heat wave injuries. Treatment includes cooling by various techniques, rehydration and management of complications like seizures, Disseminated Intravascular Clotting (DIC), renal, hepatic and respiratory failure and rhabdomyolysis, etc. To provide immediate treatment, the use of mobile “heat stroke van” may be a useful concept. The earlier the management, the better the results in preventing mortality and morbidity.

Heatstroke can be prevented by simple measures like patient education, acclimatization, adequate salt and water intake and restriction and/or rescheduling of physical activity during the period of minimum humidity and temperature of the day.

INTRODUCTION

Heatstroke (HS) is of significant interest to the intensivist and military doctors all over the world. Military personnel, unacclimatized, debilitated and medically compromised individuals are prone to develop a spectrum of heat related disorders ranging from heat exhaustion to highly fatal HS. It is an important, treatable form of multiple organ dysfunction syndrome (MODS). The importance of knowledge about this entity in tropics needs no elaboration, and with increased global warming, the incidence of this often-fatal illness is rising even in temperate climates. Heat related illnesses are largely under-diagnosed group of diseases due to lack of proper definition and awareness amongst physicians and general population.¹

In the US itself, almost 7000 deaths were reported to be due to heat related illnesses in the period from 1979 to 1997.² In 2007 also several hundreds of cases of heat disorders were reported during the 30th Chicago Marathon, many of whom had to be hospitalized. The 2003 European heat wave killed about 15,000 people in France and 20,000 people in Italy. Maximum incidence of heat related illnesses with very high mortality is reported from Saudi Arabia with incidence as high as 45-1300/lakh of population.³ India faced the worst heat wave in 1998 when 2600 deaths were reported in a span of 10 weeks. Over 1000 people perished in 2002 due to heat wave when the temperature crossed 122°F, in 2003 heat wave 1600 died of which 1200 were reported from Andhra Pradesh. During the 2005 heat wave, primarily affecting Andhra Pradesh, Orissa and neighboring Bangladesh, mainly women, children and people below the poverty line, were taken ill. In the Armed Forces too heat related disorders are seen not uncommonly.
Heatstroke is defined as a form of hyperthermia with systemic inflammatory response and MODS in which encephalopathy predominates. The classical type is usually seen in extremes of age or in other predisposed individuals especially when an unacclimatized individual is exposed to excessive environmental temperature and humidity. Exertional heat-stroke (EHS) usually occurs sporadically and follows exertion involving excessive muscular activity. This can occur even in temperate climates, and cases have been reported in individuals exerting at temperature as low as 21°C. A combination of the two types is usually seen in clinical practice. Genetic susceptibility is increasingly being known to play a role in its causation and genes related to cytokines, heat shock proteins and coagulation proteins are implicated. Various risk factors predisposing to the development of HS are obesity, recent respiratory tract infection or other febrile illnesses, drugs (anticholinergics, diuretics, phenothiazines, antidepressants, antihistaminics and beta-blockers), alcohol consumption, dehydration, poor physical fitness, lack of acclimatization, exerting with tight-fitting clothes and history of HS in the past. The other important factors associated with heat wave related deaths and poor prognosis are humidity, being unable to care for oneself (specially the elderly bed-ridden patients), pre-existing psychiatric, cardiovascular and pulmonary illnesses. It is rare in females, probably due to a lower temperature at which the thermoregulatory reflexes are activated, effect of estrogens and lower muscle bulk.

PATHOGENESIS

Thermoregulation is a highly complex inbuilt mechanism to maintain a constant range of temperature which is essential for normal functioning of the internal milieu. Any abnormal increase in temperature is gauged by the hypothalamic thermoregulatory center resulting in a reflex cutaneous vasodilatation and augmenting the skin blood flow. Thermal sweating is also induced resulting in a loss of as much as 600 Kcal/hr by evaporation. Dehydration and salt depletion leads to impaired thermoregulation by decreasing the plasma volume and cardiac output (CO).

Acclimatization enhances cardiovascular performance and also involves activation of renin-angiotensin aldosterone axis, salt conservation by kidneys and sweat glands, an increase in glomerular filtration rate, and capacity to secrete sweat. Proper acclimatization also expands plasma volume and decreases the chances of exertional rhabdomyolysis. Repeated heat exposure can increase the capacity to lose heat by 20-fold. Acclimatization to heat takes days to weeks but even 10 days proper schedule can decrease detrimental effect of exertional heat stress and also has beneficial effect on the cognitive function.

The basic pathophysiological defect underlying HS is body’s inability to maintain normal thermoregulation. This leads to cellular injury due to excessive heat stress causing acute phase response akin to inflammatory reaction seen in sepsis. Heat shock proteins (HSPs) and cytokines play a major role in this chain of events.

Acute phase response is a cellular and humoral response almost similar to the one seen in sepsis syndrome. The endothelial cells and leukocytes are activated in response to heat stress and help in protecting against tissue injury, and accelerating repair. The released cytokines cause fever, leukocytosis and other acute phase responses. Cytokines like interleukin-6 also increase the hepatic synthesis of anti-inflammatory acute phase proteins which inhibit reactive oxygen species and release of proteolytic enzymes from activated leukocytes.

Heat Shock Response

Heat shock proteins or stress proteins are a group of complex molecules released as a cellular response to heat stress. Increased levels of heat stress proteins (HSPs) protect cells against damage by heat, ischemia, hypoxia, endotoxins and inflammatory cytokines. Increase in temperature causes gene transcription leading to increased synthesis of HSPs which act as
“molecular chaperones” to prevent irreversible denaturation of cellular proteins thus allowing the cells to survive. Interactions between HSPs and cytokines have received considerable attention in the literature during the last decade such that a complex pathway of interactions between cytokines, HSPs and endotoxin is thought to be occurring in vivo in the orchestration of the acute phase response to heat injury. Work is in progress for the potential therapeutic benefit of cytokine neutralization for mitigation of heat stroke morbidity and mortality based on the current understanding of their role in this syndrome.

Progression from fairly benign heat stress to often fatal heatstroke is attributed to the following factors:

Thermoregulatory Failure
Response to heat stress leads to considerable increase in CO (upto 20 lit/min), and shift of blood from core to periphery. Various factors like salt and fluid depletion, cardiac disease and cardio-depressant drugs prevent this increase in CO, and the patients can lapse into HS.

Hyperactive Acute Phase Response
Increase in peripheral blood flow leads to relative splanchnic (mainly hepatic, renal and intestinal) ischemia, which predisposes to mucosal injury and alteration in immune and barrier function of the intestines. The splanchnic ischemia also leads to increased production of reactive oxygen and nitrogen species which may induce intestinal mucosal injury and hyper-permeability. This leads to bacterial and other antigens gaining access to circulation contributing to stimulation of a systemic immune response. Cytokines and endothelial-derived factors like TNF-α, IL-1β, etc cause alteration of set-point for sweat activation and vascular tone leading to precipitation of hyperthermia and hypotension. Increase in cytokines in the central nervous system leads to increased intracranial pressure and reduced cerebral blood flow causing neuronal injury.

Altered Heat Shock Response and Coagulopathy
Heat shock response is protective in heat stress. Attenuation of heat shock response in HS confirms its protective value. Low levels of HSPs are known to occur in old and unacclimatized individuals, and constitutionally in certain genetic polymorphisms favoring early progression from heat stress to HS.

Vascular endothelial damage due to direct cytotoxic effects of heat and inflammatory and coagulation responses to HS leads to diffuse microvascular thrombosis demonstrated by increase in factors like thrombin-antithrombin complexes, fibrin monomers and fall in protein C, protein S and antithrombin. There is marked activation of fibrinolysis as is evident from increased levels of D-dimers, plasmin-α2 antiplasmin complexes and fall in plasminogen levels.

Malignant Hyperthermia (MH)
MH occurs in persons with genetic defects at one of several receptors controlling the release of sarcoplasmic calcium in skeletal muscle. When they are exposed to triggering agents, sudden increase in intracellular calcium results in a cascade of events, ultimately leading to the uncoupling of oxidative phosphorylation in the mitochondria with excess metabolic breakdown. Clinical symptoms of MH are the consequences of uncontrolled calcium release in skeletal muscle and the subsequent uncoupling of oxidative phosphorylation and excess cellular metabolism. Exaggerated jaw rigidity after succinylcholine and excess carbon dioxide production are often the earliest signs. As symptoms progress, skeletal muscle rigidity, tachycardia, cardiovascular
instability and hyperthermia develops. As with other causes of drug-related hyperthermia, consumptive coagulopathy, pulmonary edema, and cerebral edema can develop as potentially fatal complications. The main agents aggravating MH are inhalational volatile anesthetics like ether, halothane, enflurane, isoflurane, sevoflurane and desflurane and depolarizing muscle relaxants such as succinylcholine and decamethonium. Although MH is typically associated with anesthetics, people genetically susceptible to it may develop symptoms after excess exertion in warm environments. The clinical picture and most biochemical alterations are similar to HS. Various case reports, albeit rare, indicate a pathogenetic and clinical overlap between exertional heat stroke and MH and it is suggested that MH be excluded in patients with history of exertional heatstroke.

Clinical and Laboratory Parameters

HS is characterized by core temperature of more than 40°C and brain dysfunction which may vary from subtle confusion, abnormal behavior to coma. EHS occurs in previously healthy young people exercising, usually in hot and humid climates, probably without being acclimatized. Classical HS occurs during extreme heat waves, the elderly being particularly vulnerable. In appropriate clinical setting, patients present with increased body temperature and altered mentation, tachycardia, hyperventilation and occasionally hypotension. Body temperature may not be as high as defined specially when the patients report late. Hence, any patient with altered mentation during heat waves and after exertion should be suspected to have HS irrespective of his core temperature. The clinical features of EHS are shown in Table 1 and are compared with those of classical HS in Table 2.10 Cardiovascular alterations include hypotension, tachycardia, ST-T changes, prolonged QT interval, bundle branch blocks and myocardial infarction. Gastrointestinal manifestations are quite common and may comprise of severe diarrhea, jaundice and deranged liver function tests. The other important clinical features and complications of classical HS have been described in detail by Semenza, et al in their study of Chicago heat wave of 1995.1 Metabolic alterations are characterized by respiratory alkalosis in classical HS, and respiratory alkalosis with lactic acidosis is typically seen in EHS. EHS may be associated with rhabdomyolysis, hyperphosphatemia, hypocalcemia and hyperkalemia, and these findings are exaggerated after cooling once the normal circulatory state is restored. Jaundice is a frequent occurrence with transaminase levels peaking around day 3 of illness. Renal involvement is seen in almost 30% of EHS cases and is attributed to renal hypoperfusion, rhabdomyolysis and thermal insult.

Differential Diagnosis and Complications

HS needs to be differentiated from certain encephalopathies (which may pose a diagnostic problem in similar clinical and environmental settings) like falciparum malaria, viral/bacterial meningocencephalitis. Sepsis, thyroid storm, pheochromocytoma, diabetic ketoacidosis, gastroenteritis and pontine hemorrhage can also be confused with HS. Drug induced hyperthermia, neuroleptic malignant syndrome and MH should also be considered in differential diagnosis and a proper history should be obtained.

Complications of HS are similar to those seen in sepsis syndrome, i.e. MODS and encephalopathy. The other complications encountered are cerebral edema, seizures, rhabdomyolysis, acute renal failure, acute respiratory distress syndrome, myocardial, hepatocellular, pancreatic and intestinal injury/ischemia, electrolyte disturbance and hemorrhagic complications like disseminated intravascular coagulation with marked thrombocytopenia.

Treatment
The treatment is governed by certain basic principles of which the most important is immediate on-the-site cooling of the body. Simultaneous supportive measures for the malfunctioning organ systems and reversal of altered physiology help in saving the patient from this otherwise fatal condition.

**Cooling Methods**

Cooling measures of various kinds are in vogue to help dissipation of excess heat from core to skin and finally to the environment. Heat loss from the body is accelerated by all the three methods of heat transfer namely conduction, convection and radiation. Increase in temperature gradient between skin and environment by immersion in cold water increases heat loss by conduction, increase in gradient of water-vapor pressure between skin and environment increases heat loss by evaporation, and increase in velocity of air adjacent to skin (by blowing air) increases heat loss by convection. Application of ice or cold water induces cutaneous vasoconstriction and shivering which attenuate heat dissipation and produce heat respectively thus reducing the efficiency of cooling mechanisms. Vigorous massaging and tepid water spraying (40°C) or exposure to hot moving air at 45°C, alternately or simultaneously help in overcoming this problem. Internal cooling techniques like iced gastric and peritoneal lavage are infrequently used and carry the risk of water intoxication. Body-cooling units are specialized equipments where atomized water at 15°C is sprayed and air at 45°C is fanned. Aim of cooling techniques is to keep the rectal temperature <39.4°C and skin temperatures between 30-33°C. No studies are available that compare these cooling techniques, hence no evidence as to superiority of one over the other exists. If a body-cooling unit is not available, keeping patients “wet and windy” by tepid watering of the skin and promoting air movement with fans is equally acceptable. Some recent workers are again favoring cold water immersion as a treatment of choice for EHS mainly for young patients despite its earlier criticism. No drug has been proved helpful in specific management of heatstroke. Acetylcylisalic acid and acetaminophen have not been evaluated in standard trials and both are presently contraindicated as these can aggravate bleeding and hepatic injury respectively. Dentrolene sodium, a very effective antidote for MH, has not been found effective in other heat related disorders.

Cooling the patient to normal body temperatures may not reverse completely the chain of inflammatory cascade precipitated by heat stress though cooling the patient to <38.9°C within 30 min of presentation is known to improve survival.

**Hemodynamic Management**

Hypotension is associated with mortality rate of 33% compared to 10% in patients without it. The use of vasoactive agents in such patients in the first 24 hours resulted in higher incidence of deaths. The circulatory alteration and collapse in both, i.e. EHS and non exertional heatstroke were, for the most part, due to a form of distributive shock characterized by vasodilatation and relative or absolute hypovolumia. The initial hemodynamic management in both exertional and classical heatstroke should include fluid replacement (cold crystalloids) sufficient to restore blood pressure and tissue perfusion. Fluid resuscitation should be titrated to clinical endpoints of optimal heart rate, urine output and blood pressure and the patients who remain hypotensive after the initial fluid replacement and cooling should be considered for invasive hemodynamic monitoring. Presently, the therapeutic approach recommended for hemodynamic management of sepsis can also be applied for HS because of pathophysiological similarities between the two disorders.

Seizures are known to occur especially during cooling and should be managed on standard lines with benzodiazepines. Respiratory failure may require elective intubation and mechanical ventilation. One must look for arrhythmias, myocardial infarction or myocardial failure. Rhabdomyolysis should be treated with saline infusion, furosemide, mannitol and sodium
bicarbonate. Careful monitoring of serum calcium and potassium and prompt management of hyperkalemia may prevent life-threatening cardiac arrhythmia. Patients should also be observed for disseminated intravascular coagulation and hepatic failure.

HS is a relatively immunosuppressed state and chances of secondary infection exist. Patients with pre-existing infections in any form as observed in our study are more prone to HS during severe exertion. Aspiration pneumonia is a well-known complication and antibiotics should be used in all such patients. However, it should be remembered that raised body temperature, leukocytosis and other acute phase reactants are present as part of the HS pathogenesis, and may be misleading.

Residual brain damage, especially the cerebellar syndrome and spinal cord lesions with motor neuron loss may occur despite prompt treatment in about 20% of patients, and these patients with residual deficit continue to have high mortality even after discharge from the hospital as compared to those who recover completely.

**Prognosis**

Adverse prognostic factors in HS are delayed presentation and hypotension, hemodynamic instability, persistently high serum enzymes especially, LDH and transaminases, increased levels of cytokines like TNF-α, and residual neurological disabilities.

**CONCLUSION**

One must anticipate heatstroke in appropriate settings and have a high index of clinical suspicion. Public education regarding acclimatization, adequate water and salt intake, scheduling outdoor activity in cooler times of the day with low humidity and modifying levels of physical activity especially in hot surroundings is important. Education of at-risk population like elderly, cardiac patients and those on drugs like anticholinergics and beta-blockers is essential to decrease the morbidity and mortality due to HS during heat waves. Prompt, appropriate action with effective implementation of a community-wide disaster plan and education at all levels of medical care in conjunction with aggressive prehospital prevention and onsite management with prompt rescue plans will be needed to minimize the threat of heat related morbidity and mortality.

**REFERENCES**

Multiple Choice Questions

1. **Following categories of people are vulnerable to classical heatstroke on exposure to heat waves, except:**
   A. Unacclimatized soldiers
   B. Medically compromised individuals
   C. Extremes of ages
   D. Trained athletes

2. **Important risk factors predisposing to the development of exertional heatstroke are, except:**
   A. Dehydration
   B. Alcohol consumption
   C. Female sex
   D. Poor physical fitness

3. **One of the following statements is false regarding malignant hyperthermia:**
   A. It occurs in persons with genetic predisposition with defects in receptors controlling the release of sarcoplasmic calcium in skeletal muscles
   B. The main agents inciting malignant hyperthermia are use of calcium blockers
   C. It may occur due to excess exertion in warm environment even in persons with genetic predisposition
   D. The clinical picture and most biochemical alterations are similar to heart stroke

4. **Complications of heatstroke involve following, except:**
   A. Rhabdomyolysis
   B. Panhypopituitarism
   C. Thrombocytopenia
   D. DIC

5. **Prognosis of heatstroke depends on following factors, except:**
   A. Hypotension
   B. Persistently high serum enzymes, especially LDH and transaminases
   C. Low levels of cytokines
   D. Residual neurological disabilities

6. **Following statements in respect of heatstroke are true, except:**
   A. Heat shock proteins have no role in heatstroke
   B. Acclimatization enhances cardiovascular performance
   C. Excessive heat causes cellular injuries leading to acute phase response
   D. Global warming will increase the incidence of heatstroke