

Editorial

Heat stroke: what goes on at vascular level?

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Heat stroke is the most calamitous consequence of environmental heat stress affecting every age group that can be traced back to more than 2000 years. It can be defined as a form of hyperthermia associated with a systemic inflammatory response leading to multiorgan dysfunction syndrome in which encephalopathy predominates. Based on its etiology, heat stroke can be divided into classic (resulting from exposure to high environmental temperatures) (called classic or non-exertional heat stroke) or exertional heat stroke (from strenuous exercise).¹ In 2015 a severe heat wave struck southern Pakistan with temperatures as high as 49°C (120°F) claiming lives of at least 2000 people from dehydration and heat stroke, mostly in the province Sindh and its capital Karachi.² This letter focuses on the underlying mechanism and triggering factors which lead to the presentation of heat stroke. Human body has a well-developed thermoregulatory mechanism which tends to maintain its core temperature by the production of heat shock proteins during episodes of stress including extreme heat, cold, and even infections. Progression to heat stroke from heat stress results from a thermoregulatory failure, exaggeration of acute phase response and mutations in the expression of heat shock proteins. These factors independently or collectively promote the development of heat stroke.¹ In patients with heat stroke, plasma levels of inflammatory cytokines (tumor necrosis factor α [TNF- α], interleukin [IL]-1 β , and interferon- γ) and anti-inflammatory cytokines (IL-6, soluble TNF receptors p55 and p75, and IL-10) are seen elevated and no suppression is seen on cooling of the body to a normal temperature. It is important to know that the severity of heat stroke correlates with the levels of IL-6 and TNF receptors. The incidence of infection is also increased in such patients. Increased levels of TNF- α and

IL-1 due to systemic and local production is associated with high intracranial pressure, decreased cerebral blood flow and severe neuronal injury.¹

Endothelial-cell injury and diffuse microvascular thrombosis are prominently seen in patients with heat stroke. Activation of coagulation and fibrinolysis is also an early and constant feature in heat stroke. Onset of heat stroke corresponds to the activation of coagulation marked by the presence of thrombin-antithrombin III complexes, soluble fibrin monomers and decreased levels of protein C, protein S and antithrombin III. As evident by the increased levels of plasmin- α 2-antiplasmin complexes and D-dimers and decreased levels of plasminogen, fibrinolysis is also profoundly activated. Cooling of the body temperature attenuated fibrinolysis but has no effect on coagulation activation. Hyperthermia promotes a prothrombin state, augments vascular permeability and enhances cell-surface expression of adhesion molecules. Plasma levels of von Willebrand factor antigen, endothelin, thrombomodulin, metabolites of nitric oxide, soluble E-selectin, and intercellular adhesion molecule 1 are seen elevated.¹ At an organic level, Heat stress induces active cutaneous vasodilatation and splanchnic vasoconstriction which deviates the heated blood from the center to the periphery, here the heat is dissipated to the environment. Heat stress also stimulates metabolism and steadily reduces splanchnic blood flow (i.e. intestine and liver). This in conjunction, may result in splanchnic hypoperfusion and leads to the generation of cellular hypoxia, compromised cellular energy production, derangements in intracellular Ca²⁺ (Ca²⁺) homeostasis. This change in Ca²⁺ increases the production of mitochondrial reactive oxygen species and nitrogen species which promotes circulatory and

intestinal barrier dysfunction, which in turn may increase the translocation of gut contents into the splanchnic circulation.^{1,3} Increased concentration of lipopolysaccharide in the blood can trigger the systemic inflammatory response which eventually result in sepsis i.e. heat sepsis. The dual pathway model of heat stroke suggests that heat stroke is triggered by two independent pathways consecutively along the core temperature progression of $>40^{\circ}\text{C}$. The first pathway called the “heat sepsis” pathway is due to endotoxemia, systemic inflammation and sepsis and is triggered by core temperature (T_c) $<42^{\circ}\text{C}$. The second pathway, known as the heat toxicity pathway, is due to the thermolytic effect of heat and is triggered at $T_c >42^{\circ}\text{C}$.⁴

One of the deadliest consequences of heat stroke is its effects on central nervous system which occur because of electrolyte and hemodynamic disturbances. Usual consequence is the loss of consciousness or transient however, in some cases the brain damage could be permanent. The chances of irreversibility, however, depend on various variables including a delay in receiving medical management, prior neurological deficit, and degree of hyperthermia.⁵ According to a study in rural India, the mortality rate was 33% higher during extreme heat days.⁶ Since, Pakistan is geographically related to India, we can estimate the risk of heat strokes in the area. The pathophysiology of heat stroke has multiorgan manifestation, most concerning being its effects on central nervous system. Therefore, practice of preventive measures and early resuscitation might be the key to decrease heat related mortality nationwide.

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