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EDITORIAL

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Heatstroke: a new look at an ancient disease

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Heatstroke was first described by a Roman in 24 B. C. when an expedition into Arabia Felix, led by Aelius Gallus, was decimated by an illness which was ". . . unlike any of the common complaints, but attacked the head and caused it to become parched, killing forthwith most of those who were attacked . . ." [1]. The relationship between high ambient temperature, hyperthermia and the clinical manifestations of heatstroke was not established until the middle of the nineteenth century [2]. A major advance in understanding the pathophysiology of heatstroke was made by Malamud et al. in 1946, who showed that heatstroke led to multiple-organ damage with haemorrhage and necrosis in the lungs, heart, liver, kidneys, brain, and gut [3]. Almost 50 years later, the cascade of events from exposure to heat to hyperthermia, multiple-organ damage and death is still not fully understood [4–7]. Consequently, there has been no real decrease in the mortality rate (10–50%) or incidence of permanent neurological damage (7–14%), despite improvements in cooling methods and care of patients [4–10].

Heatstroke afflicts very many people in hot climates. In Makkah during the 1987 Moslem pilgrimage, 2000 cases were reported and 1000 victims died [8]. In the temperate climates of Europe and the USA, many cases have been reported during heatwaves [4–6, 9, 10].

The clinical diagnosis of heatstroke is strongly suggested when hyperthermia is associated with neurological abnormalities after exposure to high ambient temperature [4–6, 11]. Rectal temperature is usually higher than 42 °C and the neurological abnormalities may consist of restlessness, delirium, coma or seizures [4–6, 11]. Muscle rigidity and profuse sweating are generally absent in classic (non-exertional) heatstroke [11]. Clinical signs of shock, with a haemodynamic profile typical of sepsis, are present in about 25% of patients [11, 12].

Respiratory alkalosis with metabolic acidosis is the predominant acid-base disorder; hypoxaemia is common [4, 6, 11]. Hyperglycaemia and hypophosphataemia are the most striking biochemical abnormalities [11, 13]. Creatine kinase activity is moderately increased, with no overt rhabdomyolysis [6, 11, 13]. This contrasts with exertional heatstroke where hyperkalaemia, hyperphosphataemia and renal failure predominate and hypocalcaemia may occur [4]. The haematological findings are usually leucocytosis, normal haematocrit values, and a normal or low platelet count [14].

The treatment of heatstroke is cooling [4–6, 11, 15]. Heat is dissipated either by conduction (immersion in iced water) [4–6], or by evaporation (repeated wetting of the skin while fanning the patient) [11, 15]; the latter is recommended [11, 15]. No pharmacological agents has been found to be beneficial in the treatment of heatstroke [4, 11]. Despite cooling, about 25% of patients experience failure of one or more organ-systems [4, 11].

What is the mechanism of hyperthermia in heatstroke? Body temperature is controlled by the hypothalamus maintaining a balance between production and dissipation of heat [16]. Heatstroke occurs when excess heat is produced (exertional heatstroke) or when high ambient temperature and humidity interfere with the dissipation of heat (classic heatstroke) [4–6, 16]. Other factors that interfere with the dissipation of heat, including a limited cardiovascular reserve, obesity and anti-cholinergic drugs, may increase susceptibility to heatstroke [4–6, 16, 17].

There is ever-increasing albeit indirect evidence to suggest that central thermoregulatory mechanisms may be involved in classic heatstroke [18–20]. The concentration of circulating endotoxins and pyrogenic cytokines TNF-α,

IL-1, IL-6 and IFN-γ is elevated in heatstroke patients [19, 20]; this can cause increased production of hypothalamic arachidonic acid metabolites, thereby raising the hypothalamic set-point [16]. The plasma and urine concentrations of taurine, an amino acid involved in central thermoregulation, are also elevated in heatstroke patients [21].

What is the mechanism of tissue injury and organ damage? The clinical and metabolic consequences of heatstroke, which include shock, disseminated intravascular coagulation, lung injury, lactic acidosis and hyperglycaemia, are very similar to those of the sepsis syndrome [4–6, 11, 22]. Whereas tissue injury was formerly attributed to hyperthermia itself, it has recently been observed that normal volunteers heated passively and cancer patients treated with whole-body hyperthermia can endure a rectal temperature of 41–42 °C with no, or minimal, tissue injury [23, 24]. Heatstroke can occur when the rectal temperature increases to only 40 °C [5, 11]; moreover, tissue injury continues to develop after cooling to normal body temperature in 25% of heatstroke patients [3, 4, 6, 11]. These observations led to the speculation that certain mediators are implicated in the pathogenesis of organ damage [3, 7, 18–20]. Several putative mediators, including endotoxin [7, 8, 19], cytokines [19, 20], activated coagulation components [22, 25–27], and activated or injured endothelium [28–31], have been studied.

Circulating endotoxins have been identified in heatstroke patients [19] and in primate models of heatstroke [18]. In a study by Gathiram et al. [32], primates treated with anti-endotoxin antibodies before being heat-stressed to a rectal temperature of 43.5 °C survived to the end of the study, but most of the placebo-treated animals died. The animals that died had a significantly elevated plasma lipopolysaccharid concentration. This suggests that endotoxin at least partially mediates the tissue injury associated with hyperthermia.

Endotoxin stimulates the production and/or release of various mediators, particularly TNF-α [33]. As expected, the concentration of circulating TNF-α was found to be elevated in all plasma samples from 17 patients with heatstroke [19]. IL-1, IL-6 and IFN-γ concentrations were also elevated [20]. Further, there was a significant correlation between the plasma IL-6 concentration and the severity of heatstroke [20]. These findings suggest that cytokines have a pathogenic role in heatstroke. However, this needs to be confirmed by studies showing improved survival when the biological activity of each specific cytokine is neutralised.

Widespread microthrombi and ultrastructural evidence of endothelial cell injury are prominent histological findings during autopsy of heatstroke victims [28, 29]. Activation of the coagulation factors, and elevation of D-dimer and factor VIII antigen concentrations in the blood of heatstroke patients have been reported [26–28, 31]. Furthermore, the plasma concentrations of endothelin and circulating intercellular adhesion molecule-1 (c-ICAM-1), known to be partly released by activated or injured endothelial cells, are increased [30]. The role of coagulation and endothelial cell activation or injury in the pathological manifestations of heatstroke is worth further study.

Heatstroke is a continuing challenge for clinicians confronted with this devastating disease. It is hoped that, as more is learned about the cascade of events from exposure to heat to hyperthermia, multiple-organ failure and death, an improved strategy for the management of heatstroke patients will be developed.

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