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REVIEW ARTICLE

Heat stroke: implications for critical care and anaesthesia

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Heat-related illnesses, such as heat stroke, are relatively uncommon in temperate climates. Much of the clinical experience comes from Saudi Arabia (where there is an annual pilgrimage to Mecca) and the military. Case reports and review articles are not commonly seen in anaesthesia-related journals. The intention of this article is to review the available literature on heat stroke and to discuss its relationship with other hyperthermic syndromes, such as malignant hyperthermia.

Heat stroke

Heat stroke is a medical emergency characterized by a high body temperature, altered mental status and, in classical heat stroke, hot, dry flushed skin.[16] It was first recognized by the Romans in 24 BC. But it took until 1946 for it to be shown that heat stroke could lead to multi-organ damage with haemorrhage and necrosis in the lungs, heart, liver, kidneys, brain and gut.[8] Even in the new millennium, we are not much further on in understanding the mechanisms that take a person from a hyperthermic insult through to multi-organ failure and death. There has been no real decrease in mortality from this disease, which is variably quoted as 10–50%, in the last 50 years.[8]

Definitions

There are several heat-related illnesses. These may take the form of heat syncope, heat cramps, heat exhaustion and heat stroke, the latter being the most severe.[9]

Heat syncope is fainting due to peripheral vasodilatation secondary to high ambient temperature.

Heat cramp refers to muscular cramping occurring during exercise in heat, which is related to salt deficiency and is usually benign. However, there has been a case reported of a young man with post-exercise muscle cramping who subsequently fulfilled the laboratory diagnostic criteria for susceptibility to malignant hyperthermia.[32]

Heat exhaustion occurs when the individual becomes dehydrated and weak. Nausea and vomiting occur frequently. Excessive sweating leads to a loss of predominantly water or salt. Salt-depletion heat exhaustion usually occurs when unacclimatized personnel exercise and replace only water losses. Water-depletion heat exhaustion is usually seen in acclimatized personnel who have inadequate water intake during exposure to extreme heat. Whatever the mechanism, the individual collapses from dehydration, salt depletion and hypovolaemia. The core temperature may or may not be raised and tissue damage does not occur.[9 14 35]

Heat stroke occurs when the core body temperature rises against a failing thermoregulatory system.[9 16] The core temperature necessary for the condition to be classified as heat stroke varies but is quoted by most authors as a rectal temperature exceeding 40.6°C.[35] As some cooling may take place before reaching hospital, it is probably wise not to adhere to this definition too strictly.[1 14]

Heat stroke may be divided into exertional and non-exertional (classical) heat stroke.[35] Exertional heat stroke, as its name suggests, occurs in previously healthy young people exercising, usually in hot and humid climates, probably without being acclimatized. Classical heat stroke occurs during extreme heat waves, the elderly being particularly vulnerable.[13 35]

Table 1 Risk factors predisposing to the development of exertional heat stroke (after Dickinson)

Risk factor[15]	**Examples**
Obesity	
Current upper respiratory infection or febrile illness	
Recent alcohol consumption	
Dehydrating illness	Diarrhoea, vomiting
Lack of sleep, food or water	
Skin diseases	Anhidrosis, psoriasis, miliaria
Conditions increasing heat production	Thyrotoxicosis
Lack of acclimatization	
Lack of physical fitness	
Drugs	Anticholinergics (atropine, co-phenotrope)
	Diuretics
	Phenothiazines
	Tricyclic antidepressants
	Antihistamines, cold remedies
	Anti-parkinsonian drugs
	Beta-blockers
	Amphetamines, Ecstasy
Previous heat stroke	
Age	
Protective clothing	

Some authors view heat exhaustion and heat stroke as different degrees of severity of a spectrum of disordered thermoregulation.[14] Other authors consider these two illnesses as separate entities with different aetiology, biochemistry and predisposing factors.[25]

Thermoregulation

It is important for humans to maintain body temperature within a small range to avoid cellular and enzymatic dysfunction. In humans, this range is usually of the order of 36.5–37.5°C, even in the face of adverse environmental temperatures. This thermoregulation is under the control of the autonomic nervous system, which integrates afferent input and efferent responses. Central control resides in the hypothalamus, where mean body temperature is determined from peripheral and central structures and compared with a 'set point'. The efferent response is both autonomic (sweating and vasodilatation) and behavioural.[11] There is some distinction made between exertional and classical heat stroke at this point; failure of thermoregulation (lack of sweating) may be more important in classical heat stroke and less so in exertional heat stroke, when there may be persistent sweating.[28]

Risk factors

The environment

If heat gain is to be avoided, heat must be lost through convection, conduction, radiation and evaporation of sweat. In practice, the last is the most important mechanism. 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 in allowing evaporation of sweat and convection of heat. As air temperature approaches body temperature, the effectiveness of this mechanism is lost.[9]

The military report three measures of environmental temperature load. Dry bulb temperature (DBT) is measured by placing a thermometer in the shade, and this represents true air temperature. A thermometer with its bulb enclosed in a wet wick measures wet bulb temperature (WBT). This can be used in the open air or shielded in a box, and measures the ability of the environment to cool by evaporation. The difference between these two measurements is proportional to the prevailing humidity (WBT<DBT until 100% humidity, when WBT=DBT). Globe temperature (GT) is measured by a thermometer placed in a globe and exposed to radiant heat. The military use the 'wet bulb globe temperature index' (WBGT), which has been modified to: 0.7 WBT+0.1 DBT+0.2 GT, and this is used to guide restrictions on training in the heat.[9 10]

Cases of classical heat stroke occur in response to sustained environmental heat, but this is not necessarily the case in exertional heat stroke.[13] Cases have been reported in rather more temperate climates. Giercksky and colleagues describe the case of a 31-yr-old male who developed heat stroke after running 5 km at 21°C in Norway, and who subsequently developed severe liver failure.[18] Boersma and colleagues describe the fatal case of a previously healthy 20-yr-old male who developed heat stroke after mountain-biking for 3 h in 26°C heat in a forest in the Netherlands. He died of a cerebral haemorrhage secondary to disseminated intravascular coagulation (DIC).[7]

Activities

Vigorous exercise is a risk factor in the development of exertional heat stroke. This is a particular problem for military personnel, for whom training and combat may involve the wearing of protective clothing, which does not lend itself to aiding heat loss. Other groups at risk include fun runners and those taking part in other vigorous sporting activities, such as mountaineering. Those at occupational risk include foundry workers, boilermen and firemen.[14]

Sex

Women seem curiously protected from exertional heat stroke despite their increasing participation in sports and occupations that require a degree of physical fitness. Exertional rhabdomyolysis is also rare in women. It appears that the body temperature at which thermoregulatory reflexes are activated is lower in women than in men. Thus women appear to store less heat than men for a given workload. It is not known whether this is an effect of oestrogen or simply that men are capable of generating more heat because of larger muscle bulk.[28]

Other factors

Other factors predisposing to heat stroke[10 15] are listed in Table 1.

Clinical features

Heat stroke is a systemic disorder and victims can therefore display a variety of symptoms and signs concordant with multi-organ dysfunction.[4] The two cardinal features, however, are raised body temperature and neurological dysfunction. There is some debate about whether the clinical features of classical heat stroke are different from those of exertional heat stroke. A large observational study by Dematte and colleagues followed the course of 58 patients admitted to the intensive care unit after the 1995 Chicago heat wave.[13] They showed system dysfunction similar to that already reported in exertional heat stroke. This is in contrast with other reports.[8]

Cardiovascular features

The cardiovascular system is commonly compromised in heat stoke. This is important because it may limit the effectiveness of heat loss mechanisms. Tachyarrhythmias and hypotension are frequently described.[13] Hypotension may result from translocation of blood from the central circulation to the periphery in an attempt to lose heat,[28] or it may result from the increased production of nitric oxide observed in heat stroke victims.[4 25]

A study of Doppler and echocardiographic findings in patients with classical heat stroke and heat exhaustion was published recently by Shahid and colleagues.[35] They demonstrated a circulation that was hyperdynamic with tachycardia, resulting in high cardiac output. They also demonstrated that hypovolaemia was more pronounced in heat stroke victims. Interestingly, signs of peripheral vasoconstriction were observed more often in patients with heat stroke. Heat exhaustion patients were more likely to demonstrate peripheral vasodilatation. Whether this reflects changes in the circulation as a result of cooling or reflects progression of the disease is unclear. This supports other authors' findings of the two different types of circulatory abnormalities seen in exertional heat stroke: a hyperdynamic group, as described above, and a hypodynamic group with reduced cardiac output, elevated peripheral vascular resistance and variable pulmonary resistance.[15]

Akhtar and colleagues undertook analysis of electrocardiographic changes during heat stroke, and they appear to be common.[1] All components of the ECG can be affected, including rhythm disturbances, conduction defects, prolongation of the Q–T interval and ST segment changes. Rhythm disturbances, including sinus tachycardia, atrial fibrillation and supraventricular tachycardia, have been reported. These may settle with cooling or require cardioversion. Conduction defects described include right bundle branch block and intraventricular conduction defects, which tend to persist for at least 24 h. Prolongation of the Q–T interval is the most commonly observed ECG finding, and may be related to hypocalcaemia, hypokalaemia or hypomagnesaemia. ST segment changes may be seen in localized leads, suggesting myocardial ischaemia in the territory of a particular coronary artery—in one study,[1] 21% of patients showed these changes. It is easy to imagine how this could progress to myocardial dysfunction/infarction. Dematte and colleagues demonstrated one patient with reversible myocardial depression and normal coronary arteries. Other patients have not been so lucky—transmural myocardial infarction was reported by Knochel in 1961 in the presence of normal coronary arteries[28] and Shahid and colleagues describe one patient who showed marked global hypokinesia on echocardiography.[35] This patient then suffered an asystolic arrest and died.

Neurological features

Neurological dysfunction is a cardinal feature of heat stroke.[4] Patients may present with neurological impairment of varying degrees and duration, including delirium, lethargy, coma and seizures.[13] Neurological damage is presumably attributable to metabolic disarray, cerebral oedema or ischaemia.[7]

These deficits are common to both classical and exertional heat stroke, although the latter are said to have more transient symptoms.[31] The central nervous system is particularly vulnerable to heat, the cerebellum being the most susceptible.[2 15] A case of exertional heat stroke-induced cerebellar atrophy in a 45-yr-old man has been described.[2] In this case, early computed tomography (CT) imaging of the brain was normal, and moderate cerebellar atrophy was first noticed on magnetic resonance imaging (MRI) 10 weeks after the hyperthermic insult (Fig. 1). This proved to be progressive during the subsequent year—it was clearly not transient. Other cases of neurological insult have been described, including a 20-yr-old male who died as a result of an intracerebral haemorrhage. He developed a mild coagulopathy secondary to exertional heat stroke.[7] Rarer still, McNamee and colleagues reported possibly the first case of central pontine myelinolysis in a patient with classical heat stroke during the 1995 Chicago heat wave.[31] Guillain–Barré syndrome has also been reported; in this case anticholinergic agents had been prescribed to reduce sweating in a 28-yr-old drug addict withdrawing from opiates.[33]

These cases illustrate that neurological injury may not necessarily be transient. In one series, 24% of patients had no neurological impairment and 43% had minimal impairment, but 33% had moderate to severe impairment of neurological function at discharge from hospital.[13] Some authors speculate that this neurological injury may be related to hypernatraemic cerebral damage.[5]

Features of acid–base disturbance and plasma composition changes

The changes are well described in exertional heat stroke.[28] Lactic acidosis may occur even as a normal response to severe exertion, but lactate is rapidly cleared by the liver and converted to glucose. In heat stroke the patient is shocked, this mechanism is less efficient, and restoration of

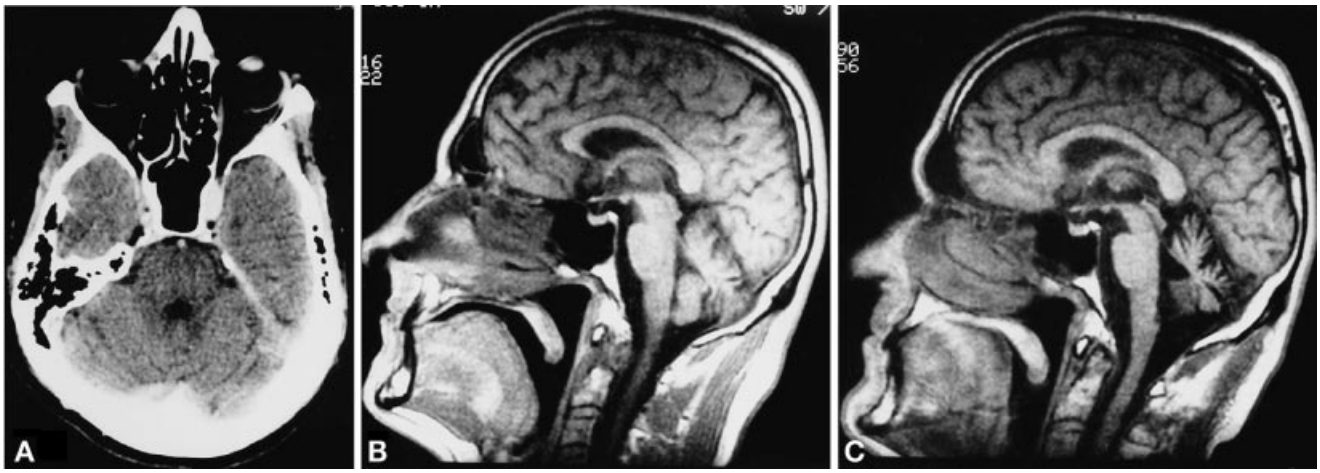

Fig 1 (A) Normal CT of the superior cerebellum 2 weeks after heat stroke. (B and C) Sagittal T_1-weighted MRI 10 weeks (B) and 11 months (C) later. There is generalized cerebellar atrophy in C. Reproduced with permission from Reference 2.

the circulating volume may lead to worsening lactic acidosis as skeletal muscle is reperfused. The body compensates with acute respiratory alkalosis secondary to increased respiratory effort. This may in itself lead to heat-induced tetany. After several hours, the situation changes from a mixed picture of acidosis and alkalosis to predominant metabolic acidosis because of sustained tissue damage. The patient may develop rhabdomyolysis. Injured cells leak phosphate, which reacts with extracellular calcium. This process leads to hyperphosphataemia and hypocalcaemia.

Hypokalaemia is commonly seen early, and this may be a direct catecholamine effect or may occur secondary to heat-induced hyperventilation, leading to respiratory alkalosis. Hypokalaemia may also be related to sweat losses and renal wasting resulting from the physiological hyperaldosteronism induced by training in the heat. Within hours, the situation can be reversed. Sustained hyperthermia, hypoxia and hypoperfusion lead to failure of the Mg^{2+}-dependent Na^+/K^+-ATPase pump, leading to cellular leak of K^+. Hyperkalaemia is made worse by hypocalcaemia and acute renal failure. ECG monitoring remains the most useful tool in determining the timing of intervention. Acute hypophosphataemia is also observed and is probably related to the increased glucose phosphorylation seen in alkalotic conditions. Hyperuricaemia develops secondarily to release of purines from the injured muscle. Excretion of uric acid is also reduced in the presence of lactic acidaemia.

It is hard to believe that similar processes, albeit less striking ones, do not occur in classical heat stroke. Indeed, Dematte and colleagues reported acid–base abnormalities in 45% of their patients.[13] The picture was of mixed non-anion gap metabolic acidosis/respiratory alkalosis *vs* mixed positive anion gap metabolic acidosis/respiratory alkalosis, and 60% of their patients required mechanical ventilation: 10% went on to develop acute respiratory distress syndrome.

Renal features

Renal dysfunction is well documented in exertional heat stroke and the incidence of acute renal failure is approximately 30%.[28] The cause is usually multifactorial, including direct thermal injury, the pre-renal insults of volume depletion, and renal hypoperfusion, rhabdomyolysis and disseminated intravascular coagulation.[13] The literature is inconsistent as to how common renal dysfunction is in classical heat stroke. In one series, 53% of patients with classical heat stroke developed moderate to severe renal insufficiency, and 19% of this subset died.[13] In these patients, although creatine kinase levels were elevated to levels below those seen in exertional heat stroke, elevation of this enzyme did occur despite a lack of history of exercise.

Gastrointestinal features

Abnormal liver function tests may be seen. Mild elevations in aspartate aminotransferase (AST), lactate dehydrogenase (LD) and total bilirubin have been described. Concentrations of AST, alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GT), LD and total bilirubin increased over time, with peaks on the third day after the heat insult.[13]

The course may be more severe in exertional heat stroke. Liver damage is almost always seen and is probably related to direct thermal injury and hypoxia secondary to splanchnic redistribution.[18 34] Fulminant liver failure, however, is rare. There have been three reports of severe liver failure; two of the three patients required liver transplantation. Both patients who were transplanted died, one at 41 days and the other at 11 months, from chronic rejection.[34] The third patient, a 31-yr-old male, developed heat stroke after running 5 km in 21°C heat. He progressed to severe liver failure and a biopsy on day 5 showed extensive liver cell necrosis. He was referred for consideration of liver

Table 2 Summary of initial management

1	ABC. Check airway and breathing. Correct airway and breathing problems as a matter of urgency. Seek evidence of shock/hypovolaemia and resuscitate accordingly with crystalloid/colloid or both. Assess level of consciousness
2	Check rectal temperature and institute cooling methods as available
3	Examine to exclude alternative diagnoses
4	Arrange laboratory tests (Table 4)
5	Be alert for complications (metabolic complications and evidence of organ failure)

Table 3 Minimal monitoring for severe cases of heat stroke

Continuous monitoring of core temperature (rectal or tympanic)
Pulse, blood pressure and respiration
Urine output (catheterize if necessary)
Arterial oxygen saturation by pulse oximetry
Twelve-lead electrocardiogram and continuous monitoring
Glasgow Coma Scale

Table 4 Laboratory investigations in heat stroke

1	Full blood count and blood film
2	Serum electrolytes, urea, creatinine and blood glucose
3	Serum calcium and phosphate
4	Serum osmolarity
5	Liver function tests, including enzymes
6	Muscle enzymes, especially creatine kinase
7	Arterial blood gases
8	Clotting screen
9	Urine for protein, casts, myoglobin and osmolarity

transplantation but recovered completely with conservative treatment.[18]

Haematological features

Exertional heat stroke is usually associated with haemorrhagic complications.[28] These may be petechial haemorrhages and ecchymoses, which may represent direct thermal injury or may be related to the development of DIC. Again, the literature is inconsistent regarding the development of DIC in classical heat stroke. In Dematte's series, 45% of patients had laboratory evidence of DIC.[13] It is important to remember that this consumption coagulopathy may be further compounded by hepatocellular damage.

Immunological features

The pathophysiology of heat stroke has many similarities with the sepsis syndrome.[8 16] When blood is redistributed from the splanchnic circulation to the periphery in an attempt to lose heat and supply skeletal muscle, there is a risk of gut ischaemia.[13] This facilitates the absorption of bacterial endotoxins.[28] Inflammatory mediators, which appear in the circulation in response to endotoxaemia, are soluble tumour necrosis factor, interleukins 1, 2, 6 and 8, platelet-activating factor, vasoactive amines and arachidonic acid metabolites.[22 28] Their targets are widespread throughout the body; this, combined with direct thermal injury, accounts for the multiple organ dysfunction seen in heat stroke.[28] Blood purification therapy (continuous venovenous haemofiltration and plasma exchange) may have a role in the treatment of heat stroke.[27] The removal of proinflammatory cytokines during blood purification may improve survival.

Sublethal thermal injury results in the synthesis of heat shock proteins. These may protect the cell from further thermogenic injury and may also play a role in heat acclimatization.[28]

Muscle features

Although rhabdomyolysis is not always a feature of heat stroke, it is a serious complication that makes other complications, such as renal failure, more likely. It is not clear from the literature whether the terms 'rhabdomyolysis' and 'exertional heat stroke' can be used interchangeably. They do not necessarily refer to the same thing. Rhabdomyolysis can be a feature in several disorders—notably, it underlies disorders of skeletal muscle (mitochondrial disorder, glycolytic disorder, lipid metabolic disorder and inflammatory myopathy).[26] It may also be caused by prolonged immobility and trauma, leading to compartment syndromes. In the context of the military, exercise and heat stroke are the commonest causes of rhabdomyolysis.[26]

Treatment options

Management of these severely ill patients starts with adherence to the basic resuscitative guidelines of 'airway, breathing and circulation' (ABC in Table 2). At best, the patient is conscious, has a falling body temperature, is well hydrated and has no complications. The most severely affected patients have a fluctuating conscious level with a rising body temperature and circulatory shock.[15] The patient should be monitored adequately (Table 3) and appropriate investigations undertaken (Table 4). How well you can cool the patient and subsequently manage them depends upon the facilities available—suffering from classical heat stroke in a first-world country with its attendant medical facilities is very different from suffering from exertional heat stroke in the middle of war.

Rapid cooling is desirable, and it has been shown that decreasing the body temperature below 38.9°C within 30 min of presentation improves survival.[13] Various methods exist to promote heat loss from the body, including cold/ice-water immersion, promotion of evaporative heat loss and the use of body-cooling units. There is controversy about which of these techniques is the most effective in promoting rapid heat loss. Critics of immersion point out that it is uncomfortable for the patient, may interfere with resuscitative measures, and may induce shivering and cutaneous vasoconstriction, which in itself is counterproductive.[19 36] Proponents of cold/ice-water cooling argue that cooling takes place more rapidly than with evaporative methods because of the greater thermal gradient between a hot core and a cool periphery. It is also available in hospitals without requiring specialist equipment and is suitable for both classical heat stroke and exertional heat

stroke victims.[17] Body-cooling units, such as those described by Weiner and Khogali in 1980, rely upon accelerating evaporative losses and are said to be two to three times more effective than ice-water immersion.[40] Patients are sprayed with finely atomized water mixed with warm air, keeping the wetted skin at a temperature of 32–33°C. They concluded that warm air spraying with good air circulation and a temperature at the body surface of 30–35°C during spraying, cooled hyperpyrexial patients more rapidly and comfortably than other methods (such as lying on mattresses filled with cold water or cold water immersion). 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.[36] Cold intravenous fluids, gastric lavage, enemas, intraperitoneal dialysis and extracorporeal circulation are other routes of heat exchange.[1]

Prognostic indicators

As with other groups of critically ill patients, there is no one marker that predicts outcome.

Temperature

Decreasing the core body temperature below 38.9°C within 30 min of presentation improves survival.[13] However, tissue injury can continue to develop after cooling to normal body temperature in approximately 25% of patients, suggesting that activation of mediators (e.g. endotoxin, cytokines, injured endothelium, activated coagulation factors) plays a role in this disease.[8]

Cardiovascular features

As already described, heat stroke patients may present with either a hyperdynamic or a hypodynamic circulation. Patients in the latter group present with circulatory failure and have a poorer outcome.[3]

Biochemical markers

Alzeer and colleagues describe the changes seen in CK, LD, AST and ALT concentrations in 26 heat stroke victims compared with 10 controls.[3] Concentrations of these serum enzymes were significantly higher at the time of admission in the non-surviving group and the severely ill group than in those who had a quick recovery. The enzyme with the highest prognostic accuracy for survival *vs* death was total LD, followed by CK, AST and ALT. In patients who survived, enzyme concentrations tended to decline after 24 h. The use of these enzymes was tested statistically against temperature, anion gap and serum potassium concentrations and was found to give better results.

Disability at discharge

An in-hospital mortality rate of 21% in classical heat stroke patients has been reported.[13] Most surviving patients recover nearly normal renal, haematological and respiratory function. One-third of patients at discharge have moderate to severe functional impairment, which may be prolonged. The degree of functional disability correlated highly with 1-yr survival. At 1 yr, a further 28% of patients had died.

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.

Relationship between exertional heat stroke and malignant hyperthermia

Malignant hyperthermia is a rare pharmacogenetic disorder inherited in an autosomal dominant fashion. It is typically triggered in susceptible individuals by exposure to potent inhalational anaesthetic agents and succinylcholine. Impaired sarcoplasmic function leads to a rising intracellular calcium concentration, resulting in sustained muscular contraction and a hypermetabolic state. The cellular abnormality appears to be heterogeneous, but the change that is implicated most frequently is a defect in the ryanodine receptor protein (the sarcoplasmic reticulum Ca^{2+} release channel). Other candidates include defects in the dihydropyridine receptor (T tubule voltage sensor) and other proteins involved in excitation contraction coupling. The clinical picture[24] is one of rising end-tidal carbon dioxide concentration, tachypnoea, tachycardia, pyrexia, muscle rigidity and occasional cyanosis. This progresses to rhabdomyolysis with hyperkalaemia and elevated creatine kinase concentrations. Multi-organ failure and DIC can ensue.[32]

This clinical picture bears many similarities to heat stroke. Indeed, there have been several reports of patients with exertional heat stroke who subsequently fulfilled the laboratory diagnostic criteria for susceptibility to malignant hyperthermia.[21 23 29] Hackl and colleagues report two cases of exertional heat stroke in military recruits.[21] Both patients were referred for testing for susceptibility to malignant hyperthermia: one patient fulfilled these criteria and one did not. Kochling and colleagues and Hopkins and colleagues report similar cases.[23 29] Ogletree and colleagues report the case of a young man with intermittent post-exercise muscle cramping and subsequent positive testing for malignant hyperthermia contracture.[32] More recently, Wappler and colleagues reported a series of 12 patients with exercise-induced rhabdomyolysis who were screened for malignant hyperthermia. Ten of these patients had positive contracture testing and one result was equivocal.[38] Bendahan and colleagues comment on a large series (26) of individuals with exertional heat stroke who had abnormal muscle contracture tests. Muscle energetics analysis performed by ^{31}P magnetic resonance spectroscopy 6 months after their initial presentation revealed several metabolic abnormalities. The authors speculate that these defects in muscle metabolism may indicate abnormalities in the calcium

release channel of the sarcoplasmic reticulum and that this may manifest itself in an abnormal contracture test result.[6]

Other authors have looked at this connection from the opposite angle by studying exercise responses in patients known to be susceptible to malignant hyperthermia.[12 20 38] In the study by Green and colleagues, the malignant hyperthermia-susceptible (MHS) patients displayed the same thermoregulatory, plasma catecholamine and metabolic responses as the control subjects.[20] Campbell and colleagues, however, showed that central temperature increased more in the MHS subjects than in the controls and peripheral temperature increased in both groups with exercise but had delayed onset in the MHS group.[12] The authors speculate that this resulted from the delayed peripheral vasodilatation that normally accompanies high-intensity exercise. They also demonstrated greater increases in free fatty acid and cortisol concentrations in MHS subjects and higher concentrations of lactate during early exercise in these subjects. The conclusions of this paper were that the pattern of temperature change in MHS subjects was evidence of an abnormality of heat dissipation, and that this, together with the increase in free fatty acids, could indicate an abnormality in sympathetic activity in this group of patients. The patients of Wappler and colleagues showed higher values for heart rate, creatine kinase, temperature, lactate and potassium after exercise compared with controls or values quoted for previous MHS individuals.[39] However, the authors conceded that the experimental protocols, study populations and measurements made during exercise were not standardized in these different papers, so conclusions are difficult to draw.

Most recently, Tobin and colleagues reported the case of a 12-yr-old boy who had a previous suspected malignant hyperthermia reaction whilst being anaesthetized for manipulation of a fractured humerus.[37] Eight months later he died as a result of exercise-induced hyperpyrexia after playing a game of football. Unfortunately, he had not undergone muscle biopsy contracture testing before his death, but DNA analysis in both the child and his father revealed a mutation in the skeletal muscle ryanodine receptor gene, which has been associated previously with malignant hyperthermia.

These case reports demonstrate that there is some overlap, although rare, between exertional heat stroke and malignant hyperthermia. It is also possible that the abnormality predisposing to exertional heat stroke may be inherited, as in the case reports of Hopkins and colleagues and Tobin and colleagues.[23 37] Certainly, it is recommended that malignant hyperthermia is excluded in patients who have had episodes of exertional heat stroke.[23 39] It has also been suggested that contracture testing should be extended to anyone with exercise-related symptoms, such as severe muscle cramping, fever and soaking sweats, and also to their families.[32]

Dantrolene therapy has an established role in the management of malignant hyperthermia. The role of dantrolene in the treatment of heat stroke, either classical or exertional, remains unclear. It has been speculated that heat stroke victims may have an underlying skeletal muscle abnormality. Although distinct from malignant hyperthermia, it may involve a similar common pathway: deregulation of control of the myoplasmic calcium concentration.[23] Hsu and colleagues report the results of muscle biopsy samples taken in 37 military recruits with exertional heat stroke.[26] An increased percentage of type II muscle fibres was found in these patients (the vastus lateralis was sampled). Nearly 60% of these had a preponderance of type II muscle fibres compared with controls. It is not known whether this was a pathological response or hereditary. They also found that recruits with predominance of type II fibres tended to have a poorer endurance capacity under a treadmill load test. The authors speculate that the above factors may have contributed to their susceptibility to exertional heat stroke and rhabdomyolysis. Did these recruits have a genetic predisposition to the development of exertional heat stroke? These findings certainly support the recent work published by Bendahan and colleagues.[6]

Despite the intriguing idea of muscle dysfunction linking exertional heat stroke and malignant hyperthermia, results of treating patients with dantrolene have been disappointing. Dantrolene has been used in the treatment of both classical and exertional heat stroke.[8 30] At the present time, there is not enough evidence to recommend that this drug should be used routinely in the treatment of heat stroke.

Conclusions

Heat stroke is a rare disorder with significant morbidity and mortality. It is likely that, in the case of exertional heat stroke, there is a degree of overlap with malignant hyperthermia. All individuals who have a history of exertional heat stroke or allied symptoms should be screened for malignant hyperthermia susceptibility. Similarly, it is likely that there is at least a subset of individuals with susceptibility to malignant hyperthermia who are possibly at risk of exertional heat stroke.

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