

Heat related illnesses

Review of an ongoing challenge

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ABSTRACT

يعد تغير المناخ أكبر تحديات الطبيعة، حيث يسبب موجات حر شديدة. تتطلب تأثيرات موجات الحرارة وارتفاع متوسط درجة الحرارة على الأمراض المرتبطة بالحرارة مراجعة لاستراتيجيات الوقاية والعلاج الحالية لتوجيه البحوث المستقبلية. تتفاوت الأمراض المرتبطة بالحرارة من أعراض بسيطة إلى ما يهدد الحياة. على الرغم من فهم الفيزيولوجيا المرضية للأمراض المرتبطة بالحرارة، فإن التدخلات الدوائية محدودة والوقاية هي أفضل الاستراتيجيات. هناك ندرة في الدراسات الوبائية التي تستعرض تأثير التدخلات الدوائية على الوفيات. ولا تزال هناك حاجة لتحديد المكونات الرئيسية الحرجة بخلاف المشكلات النهائية، والتي يمكن استهدافها لتقليل مؤشر الأمراض المرتبطة بالحرارة.

Climate change is the most challenging natural calamity of chronic nature that presents intense episodes of heat waves, and events. Effects of heat waves and increasing average temperature on heat-related illnesses (HRI) demand a review of existing preventive and treatment strategies to direct future research. Heat-related illnesses are presented as minor to severe life-threatening conditions. Despite the understanding of the pathophysiology of HRI, pharmacological interventions are limited. Prevention is the best strategy against HRI. There is a dearth of epidemiological studies that reviewed the effect of pharmacological interventions on mortality, and there remains a need to identify critical key components other than inflammatory modulators, which can be targeted to decrease HRI.

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Exposure to heat in amounts exceeding the compensatory mechanisms of thermoregulation leads to physiological insult to the body and heat-related illnesses (HRI), either acute or delayed. Heat-related illnesses range from a mild form, like in edema, cramps, or syncope, to severe conditions such as heat exhaustion, syncope, and strokes with or without multi-organ failure.¹ A 1°C rise in temperature from 20°C to 21°C increases the number of patients with HRI by 11%.² The mortality rate also increases proportionally with an increase in temperature and duration of heat exposure.³

Arguably, the most significant global health threat of the 21st century, global climate change, is presenting an essential challenge to public health.⁴ Mean surface air temperature has been constantly increasing in the past 100 years, with summer temperature increasing at a rate of 0.6°C/century.⁵ Extreme climate events are predicted to increase in intensity, frequency, duration, and number leading to detrimental health effects across a variety of geographical regions. Mortality due to HRI surpassed the combined impact of earthquakes, tornadoes, floods, and hurricanes.⁶ An HRI incidence of approximately 70,000/year in Europe and 1,300/year in the United States has been reported. The heat wave of 2003 in France resulted in 14,800 deaths.⁷ Heat-related illnesses are preventable and can be managed effectively; however, the number of morbidities and mortalities associated with heat exposure are increasing with time. Considering global warming and extreme climate events, there are needs to assess the preventative techniques, diagnostic criteria, and treatment strategies. Here, we review the literature to decipher the pathophysiology of HRI along with preventive measures and treatment options.

PubMed, ScienceDirect, and Scopus were searched from 1990 to 2019 with the following keywords: Heat Related Illness, Heat Stroke, Heat Exhaustion, Heat Edema, Heat Rash, Heat Cramps, Heat Syncope, and Heat Tetany. Full-length articles related to the pathophysiology of HRI, preventive measures, and treatment strategies were selected and reviewed.

Physiology of thermoregulation. Autonomous regulation of homeostatic mechanisms to maintain the core body temperature is a vital function of the brain for life. The preoptic nucleus of the anterior hypothalamus (POAH) is the central temperature sensor in the central nervous system (CNS). Preoptic nucleus of the anterior hypothalamus regulates core body temperature at 37°C by sending excitatory and inhibitory signals to different brain regions in response to hypo- or hyperthermic conditions.⁸ Vasodilation and evaporation following sweat gland activation are core components of thermoregulation in hyperthermia. Skin blood flow can increase from a baseline of 250 mL/min to 6-8 L/min.⁹

Moreover, various regulatory mechanisms, such as conduction (direct heat transfer between 2 surfaces), convection (heat transfer from solid/liquid to moving liquid or air), radiation (heat transfer by electromagnetic waves), and evaporation (heat dissipation by evaporation of liquid), help maintain core body temperature at 37°C in healthy subjects.¹⁰ The critical thermal maximum for humans is 41.6°C to 42°C.¹¹ An increase in core body temperature leads to an acute response, resulting in the production of heat shock proteins and coordinated action involving endothelial cells, leukocytes, and epithelial cells.¹² Heat shock proteins protect the body against damage via a multitude of processes, mainly by inhibiting endotoxin leakage in the intestine by maintaining the integrity of the epithelial barrier. Failure of regulatory mechanisms (uncompensated phase) leads to the denaturation of proteins, subsequently. Severe systemic inflammatory responses manifest into organ failure (most commonly the brain and liver), circulatory failure, hypoxia, and increase in metabolic demand in response to heat exposure.¹³

Heat-related illnesses

Minor disorders. Heat edema. Lack of acclimatization to a hot environment can result in transient peripheral vascular dilation, leading to a cutaneous modality, heat edema. An increase in salt in the body due to fluid loss can increase the risk of heat edema. The movement of muscles affected by edema, such as elevation of feet/legs, can help transport fluid back into the circulation.¹⁴

Heat cramps. Excessive perspiration along with little or no fluid/electrolyte compensation leading to sodium imbalance results in intermittent and involuntary muscle spasms usually in the calves, arms, and abdominal wall. Electrolyte imbalance can occur due to profuse sweating during exercise or strenuous activity in a hot environment. Heat cramps are usually accompanied by tachycardia and elevated body temperature. Sodium replacement can help manage heat cramps.¹⁵

Heat syncope. Orthostatic dizziness due to a low blood supply to the brain in case of excessive blood circulation in the skin is known as heat syncope. In a hot environment, peripheral dilation is the initial strategy to dissipate heat by increased blood flow to the skin, which can result in low blood pressure and, thus, decreased perfusion to the brain. Low blood supply to the brain and dehydration can lead to heat syncope.¹⁶

Heat tetany. Hyperventilation followed by carpopedal spasm and paresthesia is related to a short period of stress in a hot environment. Treatment includes reassurance, slowing the breathing, and moving the subject to a cooler area.¹⁷

Heat rash. Heat rash, prickly heat, miliaria, or lichen tropicus is a dermatologic condition due to blockage of sweat glands by the stratum corneum. As sweat production is not inhibited in response to such blockage, it leads to rupture of ducts and inflammatory reaction leading to chronic pruritic dermatitis. Symptomatic treatment of rash, such as cooling the skin and applying calamine lotions to relieve itching, is adopted unless infection prevails due to the chronic cycle of inflammation, which can be treated with antibiotics.

Mild conditions. Heat exhaustion. The most common type of HRI is heat exhaustion, presenting with a myriad of symptoms such as fatigue, malaise, hypotension, anorexia, vomiting, anxiety, nausea, irritability, fainting, and circulatory collapse.¹⁸ The core body temperature in heat exhaustion is 38°C to 40°C. The treatment of heat exhaustion is to remove the patient from the hot environment to a cooler area and minimizing clothes to facilitate heat loss. Then, if the patient has fluid depletion, oral or intravenous fluid replacement of 1 L/h is started.¹⁴ Moreover, serum sodium, potassium, phosphate, calcium, and magnesium concentrations should be maintained.

Severe conditions. Heat stroke (HS). Heat stroke is a potentially life-threatening acute syndrome characterized, traditionally, by a core body temperature >40.6°C and neurologic dysfunction.¹⁹ Considering the pathophysiology of thermoregulation, HS is characterized by hyperthermia, leading to encephalopathy and multiorgan failure via a cascade of inflammatory modulators.²⁰ Despite aggressive treatment strategies, HS often presents as a fatal condition. Patients who recover from HS often sustain permanent damage to the CNS or other organs. There are 2 main categories of HS: classic and exertional. Classic HS is characterized by the effect of an extrinsic environment and affects immunocompromised individuals such as young children and the elderly population.²¹ Exertional HS is

a result of an increase in the body temperature due to strenuous workout in a hot environment and excessive heat production but failure to dissipate excessive heat.²² Table 1 shows the intrinsic and extrinsic risk factors associated with exertional HS. Exertional HS usually affects athletes and healthy working individuals.

Risk factors for classical HS include those affecting the immune system such as diseases, dermatologic conditions, infection, endocrine disorders, cardiovascular disease, obesity, dehydration, pulmonary disease, neurologic disease, psychiatric illness, and history of HRI. Drugs that predispose an individual to HS include beta-blockers, diuretics, calcium channel blockers, laxatives, anticholinergic drugs, salicylates, thyroid agonists, benzotropine, trifluoperazine, ephedra, certain diet pills, butyrophenones, alpha-agonists, inhaled anesthetics, monoamine oxidase inhibitors, and sympathomimetic medications.²¹ Moreover, low socioeconomic conditions and drug use has also been associated with classic HS incidence.

Pathophysiology of heat stroke. Heat stroke is a result of an uncompensated phase of thermoregulation, also known as thermoregulatory failure. An increase in body temperature due to strenuous workout or hot environment leads to peripheral vasodilation, resulting in hypovolemia and reduced cardiac output. Reduced cardiac output along with dehydration due to profuse sweating leads to decrease central venous pressure, which results in decreased heat dissipation from body surface, culminating in a further increase in core body temperature.⁹ This increase in core body temperature is accompanied by blood shift from the mesenteric circulation to cutaneous areas, leading to endotoxin leakage due to cellular damage and acidosis, a consequence of increase anaerobic metabolism.²⁴ Poor hepatic portal circulation in an uncompensated phase of thermoregulation cannot tackle the endotoxins, leading to excessive production of inflammatory modulators.²⁴ This process is followed by cytokine-induced production of vasoactive factors leading to circulatory failure.¹² Increased interleukin (IL)-1 α , IL-1 β , IL-6, soluble IL-6 receptor, IL-8, IL-10, IL-12, interferon- γ , and tumor necrosis factor- α concentrations are commonly observed at the time of HS. High levels of cytokines have been linked to HRI morbidity and mortality. These combined processes culminate in a decrease in CNS blood supply and increase in intracranial pressure, followed by compromised blood-brain barrier and increase in circulatory pyrogens. A state of imbalance of cellular potassium, sodium, and calcium transport along with depletion of cellular energy, leading to

Table 1 - Intrinsic and extrinsic risk factors associated with exertional heat stroke (HS).⁵

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|--|--|
| <i>Intrinsic factors</i> | |
| Lack of heat acclimatization | |
| Current febrile illness | |
| Skin disorders: anhidrosis, sunburn, psoriasis, etc. | |
| Dehydration | |
| Medications/supplements (e.g., diuretics, antihistamines, central nervous system stimulants, antidepressants) | |
| Sleep deprivation | |
| Recent alcohol use | |
| Low physical fitness | |
| Overweight/obesity | |
| Cardiovascular disorders (namely, hypertension, peripheral vascular disease) | |
| Malignant hyperthermia susceptibility | |
| <i>Extrinsic factors</i> | |
| Hot, humid environment (especially wet-bulb globe temperature >28°C) | |
| Exercise intensity | |
| Inappropriate work-to-rest ratios | |
| Heavy equipment/clothing | |
| Lack of education and awareness among athletes, coaches, and medical staff | |
| Lack of emergency plans to identify and treat exertional HS | |
| Lack of proper infrastructure (heat acclimatization period, access to fluids, preventative cooling strategies, and so forth) | |

cellular damage, follows. Thermoregulatory failure leads to the development of severe complications associated with HS, such as encephalopathy, myocardial injury, disseminated intravascular coagulation, blood clots in the stomach and small intestine, rhabdomyolysis, hepatocellular injury and failure, acute respiratory distress syndrome, cytoplasmic protein clumping in the spleen, acute renal failure, intestinal ischemia, pancreatic injury, and multiple organ dysfunction.¹²

Determinants of HRI mortality and morbidity.

Age and ageing. Negative changes in the thermoregulatory system have been associated with an increase in age, making the elderly population more prone to heat effects. Heat dissipation from the body surface in a hot environment requires an increase in cardiac output; however, old age has been associated with a decrease in cardiac output.²⁶ Moreover, debilitation and medication use also contribute to HRI morbidity and mortality in patients with old age. Epidemiological studies have shown that the risk of HRI mortality increases with increasing age >50 years. Likewise, children also have poor thermoregulation and are more prone to HRI. Increase surface-to-body mass ratio and slow sweat response are other contributing factors toward increased HRI incidence in children. However, increased mortality rate in children due to heat waves was not depicted in episode analyses.⁷

Gender. The negative impact of heat waves and heat is greater in women in all age groups. Many European studies showed that women are more prone to HRI mortality in heat waves than men. However, men are at higher risk of mortality due to HS as more men work in a hot environment.²⁷ Therefore, there may be contributing physiological factors in these differences, but social factors mainly contribute to this gender-biased effect on HRI mortality.²⁸

Pathophysiological factors and drugs. Alongside age and gender, several diseases, such as depression, cardiovascular disease, diabetes, and CNS-related disorders, increase the patient's risk to heat effects.^{29,30} The cardiovascular system plays a crucial role in heat dissipation, and HRI and hot environment contribute additional burden to the system. In many cases, mortality due to heat has not been associated with classic symptoms of HS or heat stress, depicting the underlying role of pathological conditions in heat effects.

Moreover, certain drugs increase the incidence of HRI as they interfere with thermoregulation. Anticholinergic drugs inhibit sweating and can increase the risk during exercise and in an extremely hot environment. Antipsychotic drugs, such as phenothiazines, affect the central thermoregulatory machinery and also act as anticholinergic agents. The antidopaminergic effect of antipsychotic drugs, such as thioxanthenes, can elevate the set point of 37°C in the thermoregulatory center, leading to impaired regulation. Therefore, during a heat wave and extreme heat events, the population with psychotic disorders and using antipsychotic drugs should be addressed especially as they are at higher risk, similar to children and patients with old age.³¹

Socioeconomic status. Socioeconomic status has been considered as a risk factor in European studies.⁷ Socioeconomic factors also affect the housing condition and air conditioning. Top-floor housing and brick houses have been associated with HRI mortality,^{32,33} while air conditioning has been shown as a protective factor against heat wave mortality in US studies.³⁴

Preventive strategies

Short-term strategies. Heat health warning systems. The heat health system is characterized by the initiation of acute public health intervention related to heat in response to meteorological forecasts.³⁵ Public health interventions in such a system require early identification of vulnerable population, such as old age population, children, and patients with specific diseases,

making them prone to heat effects. Such interventions include the opening of air conditioning centers, public awareness sessions, phone calls and visits to vulnerable individuals, and website bulletin. A positive effect of these interventions on HRI mortality has been documented.³⁶

Air conditioning. Increased use of air conditioning in the USA have been associated with lower or no HRI mortality.³⁷ Moreover, in Chicago, during the heat wave of 1995, the positive effect of air conditioning in reducing HRI mortality was documented as air conditioning in the working environment decreases the mortality rate by 70%.³⁴ Air conditioning also presents a benefit of air filtering; however, air conditioning can increase the temperature in the environment due to gas emission.

Albedo. Albedo is the most prominent factor associated with heat intensity in the heat island effect.³⁸ Increasing canopy cover, roof vegetation, planting, and installation of green roofs are some of the long-term strategies that can be adapted to decrease HRI. Greenhouse gas emission reduction and improved building ventilation also affect ambient temperature.³⁹

Treatment strategies

In severe HRI, a rapid reduction in core temperature along with supportive care is required. Most treatment elements are empiric, starting with the Airway, Breathing, and Circulation approach.

Cooling methodologies are adapted according to the body's response to heat stress. In exertional HS, the most effective cooling method is complete immersion of the body below the neck in cold water. However, the efficacy of immersion in classical HS has not been documented. Immersion in ice water is more effective than immersion in cold water. However, cold water immersion can lead to vasoconstriction and reduced heat dissipation and may lead to shivering. Body massage can be adopted to overcome vasoconstriction, and benzodiazepine is used to overcome shivering. When immersion is not practical due to poor patient tolerance and associated diarrhea and vomiting and in patients with comorbid conditions such as cardiovascular disease, tepid water is used for spray along with the use of a fan for evaporation. Massaging the neck, groin, and axilla with ice is another cooling strategy.⁴⁰ Blood pressure regulation is highly compromised in response to an increase in body temperature mainly due to cutaneous vasodilation: decreased cardiac output and a shift toward cutaneous flow result in reduction in central venous pressure (CVP). However, the magnitude of heat stress and reduction in CVP are not directly proportional, and

marked individual differences are observed. Tolerance to a hypotensive challenge in response to heat stress also varies from individual to individual. In response to exertional HS, both elevation and reduction in CVP have been observed.⁴¹

Moreover, patients with exertional HS do not usually have hypovolemia; therefore, there is a need to monitor fluid resuscitation by bedside ultrasonography.⁴² However, studies did not adequately discuss real-time monitoring guidelines of fluid resuscitation to prevent complications of rapid rehydration. Blood pressure, CVP, creatine phosphokinase (CPK) level, and urine output can be monitored to prevent pulmonary edema due to rehydration. Clinical studies are required to establish guidelines for fluid resuscitation in patients with elevated CVP. Moreover, decreased cardiac output also needs to be treated to prevent end-organ damage due to decreased blood supply. In decreased cardiac output and low CVP, which may lead to end-organ damage, inotropes are used to increase cardiac output in emergency care. However, the use of inotropes especially in the population at risks, such as patients with a history of cardiovascular disease and old age population, should be preferred, taking into consideration the effect of inotropes on peripheral circulation related to heat dissipation. Heat-induced cardiomyopathies need to be addressed by administration of vasoactive drugs, which mainly affect cardiac output by activating calcium channels. However, calcium transport has also been associated with muscle contraction and needs to be addressed to reduce muscle contraction-induced heat production. Clinical studies are required to monitor the effect of inotropes on muscle contraction-induced heat production and muscle relaxants, such as dantrolene, on cardiac output in patients with HS to establish guidelines for the use of positive and negative inotropes in the golden hour of emergency care.

Dantrolene attenuates calcium transport from the sarcoplasmic reticulum to the cytosol, inhibiting calcium and acting as a muscle relaxant. Dantrolene is used as a muscle relaxant to decrease the heat generated by muscle contraction.⁴³ The use of dantrolene in HS is a debatable point in several studies. Dantrolene side effects, such as drowsiness and diarrhea, are associated only with long-term use. However, in classical HS, dantrolene has not been shown to decrease cooling time, while, in the exercise model, dantrolene affected the cooling time and rate significantly. Therefore, dantrolene can be a drug of choice in exertional heat shock and when there is evidence of muscle rigidity-induced by either heat shock or shivering during cooling. However, dantrolene cannot be used as a single modality to treat any kind

of HRI but can be used with conventional methods if there is evidence of muscle spasm and contractions. There is no evidence of positive effects of dantrolene on cardiovascular attributes of patients with heat shock.⁴⁴ A previous diagnosis of malignant hyperthermia favors the use of dantrolene in heat shock. Larger trials and clinical studies are required to establish the diagnostic criteria and guidelines for the use of dantrolene in patients with heat shock besides the previous diagnosis of any disease. Moreover, animal models of exercise and clinical heat shock should be used to manifest the role of dantrolene in long-term cooling to determine its role in severe cases where conventional methods of cooling fail.

Hypotension can be treated by providing intravenous fluid in 500 mL aliquots along with continuous assessment to avoid aggressive volume expansion.⁴⁰ Creatine phosphokinase levels >5 times the upper limit of normal are linked to muscle breakdown. Efforts are aimed to normalize CPK levels to avoid end-organ damage in exertional and classical HS. Normal saline is administered once CPK levels are higher than normal.¹⁰

As HRIs range from minor conditions such as heat edema to life-threatening conditions such as HS, treatment strategies are adopted according to the nature of the illness. For minor to mild conditions where individuals present with elevated core temperature and dehydration but do not have any systemic complications such as nervous system dysfunction, subjects are treated in a cold environment and provided with oral hydration. A solution with high osmolality and slow gastric emptying are used to decrease core body temperature.

Anticytokine, anti-endotoxin, or anticoagulation therapies; anti-endotoxin antibodies; ibuprofen; platelet-activating factor receptor antagonists; and anti-tumor necrosis factor monoclonal antibodies have not shown any benefit in HRI mortality.⁴⁵

In conclusion, heat waves and heat events are increasing in frequency, and so does the incidence of HRI. Increase in the average temperature also contributes to HRI incidence. Heat related illnesses ranges from minor to serious life-threatening conditions, which present a grave challenge to the intervention of preventive and treatment strategies. Epidemiological studies lack effective cooling strategies and pharmaceutical interventions. The best cooling strategy is immersion. However, larger trials and clinical studies are required to establish guidelines for fluid resuscitation and use of inotropic agents and muscle relaxants. Guidelines for real-time monitoring of associated attributes, such as CVP, hypervolemia, and muscle spasm, in response to cooling are also not established. There is a need for

research related to the intervention of pharmaceutical agents for the treatment of exertional and classical HS with comorbidities such as renal dysfunction and cardiomyopathy. Since the average temperature is increasing, clinical studies are required to establish the effect of several drugs on the risk of HRI in order to mark the population at risk.

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