Research and Reviews

Pathophysiology of Heat Illness: Thermoregulation, risk factors, and indicators of aggravation

Yasufumi MIYAKE[*1]

Abstract

The core body temperature of humans is strictly maintained at approximately 37.5°C by 4 mechanisms: radiation, convection, conduction, and vaporization. The prevention of heat illness requires maintaining physical factors as well as avoiding unfavorable environmental factors. Physical factors include sufficient intravascular volume and cardiac function to move internal heat accumulation to the body surface, while unfavorable environmental factors include high temperature and humidity, strong sun exposure, calm air, and excessive exercise. Because of their decreased sensitivity to high temperatures and humidity, elderly people tend to neglect cooling the environment, drinking fluid, and avoiding heat. Because their internal fluid volume is already decreased and their cardiac function is reduced, the elderly are more likely to experience heat illness than younger people. As a result, the classic heat illness observed among the elderly tends to be of high severity at the time of hospital visit, and it is associated with a poor prognosis. Multiple organ failure including circulatory failure is the main cause of death in heat illness during the acute phase, and patients often die within the first 2 days of hospital admission. Disseminated intravascular coagulation and impaired functioning of the central nervous system, liver, and kidneys characterize severe heat illness; these characteristics are particularly important for determining severity classification and as prognostic factors.

Key words Heat illness, Pathophysiology, Multiple organ failure, Disseminated intravascular coagulation (DIC)
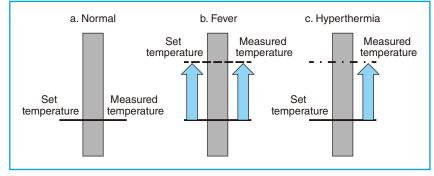
Introduction

The intense summer heat waves of the past few years in Japan have led to increased risk of death among the Japanese people due to the increased incidence of heat illness. Therefore, it is very important to understand the pathologic condition of heat illness and its risk factors, and to be familiar with its preventative measures, emergency care, and treatment. In this report, we outline the process that leads to heat illness, the differential diagnosis to distinguish between fever and heat illness, the pathologic condition of multi-organ failure in heat illness, and the importance of disseminated intravascular coagulation (DIC) as a result of heat illness.

Body Temperature Control[1]

In the human body, a considerable amount of heat is produced from muscles during exercise, and heat is constantly being produced by the various metabolic activities necessary to maintain homeostasis. The core temperature (also called deep body temperature) is strictly maintained at close to 37.5°C; this is the optimal temperature for efficient enzymatic activity for maintaining life.

The heat produced inside the body is transferred to the blood and carried by the bloodstream to the network of capillaries that lie immediately underneath the skin throughout the body. At the body surface, the blood is cooled by the environmental air temperature. The cooled blood flows

*1 Professor, Emergency and Critical Medicine, Showa University School of Medicine, Tokyo, Japan (ymiyake-nsu@umin.ac.jp).

Fig. 1 Thermoregulation in the body
Under normal conditions, the body temperature setting and the actual body temperature are the same (a). With fever, the body temperature elevates because the body temperature setting is elevated (b: internally controlled hyperthermia). In hyperthermia caused by heat illness (c), in contrast, the body attempts to maintain the regular body temperature, but the cooling mechanisms fail and the actual body temperature increases.

back to the deep body, and thereby prevents the elevation of body temperature. Sweat is created in large quantities in the sweat glands from the blood (plasma) that flows in the capillaries, and its evaporation at the epidermis takes away the vaporization heat.

In addition, 3 other mechanisms prevent the body temperature from increasing: radiation, convection, and conduction. Radiation at the body surface dissipates heat into the surrounding air. Convection removes heat when wind (or an ascending current of air) disturbs the insulating zone of air surrounding the body, and improves the radiation effect by ensuring that cold air is always touching the body surface. Conduction transfers heat to a fluid (e.g., cold water) or solid (e.g., an ice pillow or gel pack) that the body is touching. Drinking cold water yields the same conductive effect during the process of being warmed to 37°C in the body and excreted as urine or sweat.

Fever and Hyperthermia

The body temperature is regulated by the hypothalamus to about 37°C, but this temperature setting is reset when a person develops fever due to an infectious disease. When pathogens or viruses invade the body, the body fights the infection by releasing endogenous pyrogens (various cytokines and prostaglandins, thromboxane, etc. that elevate body temperature), inhibiting the growth of pathogens, promoting the produc-

tion of antibodies, and activating enzymes that fight infection. It is characteristic of fever that the elevation of the body temperature setting is carried out internally, and that this precedes other defensive mechanisms.

In contrast, when the body temperature is elevated by external causes, such as environmental factors, the elevation of body temperature occurs even though the body temperature setting remains at 37°C. This occurs when physiological thermoregulation mechanisms cannot keep up with the increasing body temperature (**Fig. 1**).

Mechanisms Leading to Hyperthermia and Risk Factors for Heat Illness

The ability to suppress body temperature elevation is greatly influenced by external environmental factors. These factors affect how efficiently extra heat can be released from the body. They include the environmental temperature, humidity, radiant heat, wind strength, sunlight, and clothing. When indoors, air-conditioning and/or fans can help to regulate body temperature; when outdoors, staying in the shade, wearing a hat, and wearing breathable and quick-drying clothing can have a cooling effect. The danger of heat illness increases when a person does not feel uncomfortable in such an environment (due to aging or mental illness) or cannot escape from such an environment (e.g., patients who are bedridden or cannot move due to injury or stroke, those who must work in hot environment to meet a deadline, and

Table 1 Comparison of non-exertional (classical) heat illness and exertional heat illness

	Exertional heat illness	Non-exertional (classical) heat illness
Age	Early to middle aged	Elderly
Gender difference	Predominantly males	No gender difference
Scene	Outdoors, under a hot sun	Indoor (incidence increases greatly during a heat wave)
Time to onset	Sudden onset within a few hours	Gradual deterioration over days
Muscular exercise	Some	None
Underlying disease	None (healthy)	Yes (heart disease, diabetes, stroke sequelae, mental illness, dementia, etc.)
Prognosis	Good	Poor

those who are otherwise motivated to stay in unfavorable environment such as those playing/ watching competitive sports).

The second factor affecting the efficiency of heat exchange is cardiac function. The heart circulates the blood, which carries the accumulated heat within the body. The blood flow, which moves the heated blood to the body surface and cooled blood back to the heart, is produced by the contractility of the heart; that is, the heart acts as a pump. When a patient with chronic heart failure or angina is in an extremely hot environment for an extended period of time, the heart cannot adequately pump blood to the body surface to dissipate heat, resulting in the internal accumulation of heat. Cardiac disease is a risk factor for heat illness for this very reason. The same is true for patients with hypertension who are prescribed oral medication to suppress heart function. In patients with hypertension, blood pressure is lowered by suppressing the pumping function of the heart, which in turn reduces heat exchange efficiency and therefore increases the risk of heat illness.

Additionally, the blood volume itself, namely the intravascular volume, is another important factor. In the advanced stages of internal water deficit (dehydration), the volume of the blood carrying heat is reduced, which lowers the efficiency of heat transport and increases the risk of heat retention. Advanced dehydration also increases the viscosity of the blood, producing more resistance to circulation, which increases the burden on the heart.

In some patients with hypertension or heart failure, diuretics may be prescribed. Diuretics

act to lower blood pressure by promoting the renal excretion of water and salt to reduce intravascular volume. As a result, the volume of the blood (the key heat carrier) is reduced, and the risk of heat illness rises. Similarly, patients under salt or water restriction face the same risk. People who refrain from drinking water during the late evening in order to avoid the inconvenience of going to a bathroom in the night tend to become dehydrated; and this may have an effect on thermoregulation and the risk of heat illness. Nonetheless, the issue of water intake needs to be balanced with the requirements of each patient's existing conditions, and therefore patients are advised not to make their own decisions, but rather to consult their primary physician regarding adjustments to water intake during the summer.

Consecutive extremely hot days and nights can reduce people's stamina, especially that of the elderly. Such heat can also reduce the appetite and gradually lead to dehydration. As a result, an increasing number of elderly people are diagnosed with heat illness after a few consecutive days of extreme heat. **Table 1** shows the differences between the exertional heat illness that occurs in healthy people during physical labor and the non-exertional (classic) heat illness that occurs in the elderly after a series of hot days.

Pathophysiology of Heat Illness and Multiple Organ Failure

The true pathophysiology of heat illness is centered on the organ impairment caused by the fever itself and the ischemia caused by reduced blood flow to organs.
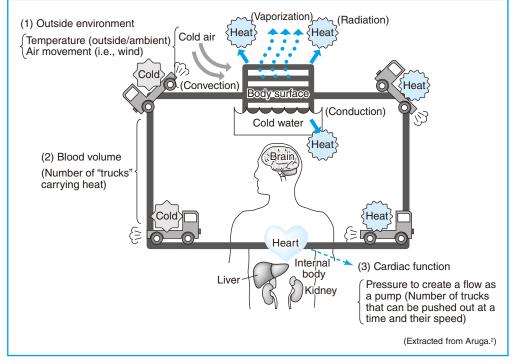
Fig. 2 Regulation of the human body temperature, and the 3 elements that can cause heat illness

The efficiency of heat radiation is reduced when the ambient temperature rises. Furthermore, sweat does not dry as well in a humid environment, reducing the efficiency of heat loss through evaporation, and there is no effect of convection in calm air. The result of these effects is that the body surface temperature rises. When this situation continues for a long time, the dehydration caused by sweating progresses and, when combined with blood being retained at the dilated peripheral blood vessels, blood volume decreases. Increased viscosity of the blood further increases the burden on the heart. The heart rate and contractility increase to augment the reduced blood volume in the body. However, in such situations, the heart itself is exposed to higher temperatures, and the blood flow to the cardiac muscles is already reduced, which further increases the burden on the heart. When heat release from the body core is impeded, and the bodily functions that maintain body temperature fail, body temperature starts to climb, causing heat illness (**Fig. 2**).[2]

Enzyme denaturation begins when body temperature reaches 40°C at the cellular level; when it reaches 41°C, decreases in mitochondrial function disturbs oxidative phosphorylation (intracellular energy production), leading to organ impairment. The reactions in various organs during heat illness are summarized in **Table 2**. In mild cases, muscles and the digestive tract become the focus of impairment; however, as heat illness advances, the central nervous system, circulatory organs, liver, kidney, and the coagulation system also sustain damage. Once the barrier function of the intestinal mucosa is impaired by heat and decreased blood flow, intestinal bacteria and their toxins pass through the intestinal wall, enter the portal vein blood flow, and circulate throughout the body via the liver. Consequently, the main symptoms that a patient will develop include fever, shock, and multiple organ failure, which are similar to the symptoms of sepsis (**Fig. 3**).[3]

Characteristics of DIC Caused by Heat Illness

The Acute DIC Diagnostic Criteria have been adopted to diagnose DIC in Class III heat illness.[4] Hypercytokinemia caused by bacterial translocation, which itself results from the hyperpermeability of the intestinal mucosa as described

Table 2 Reactions of each vital organ/system affected by heat illness

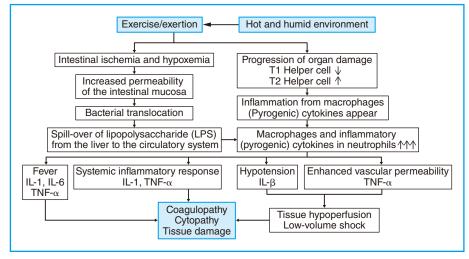|	
Circulatory system	Elevated heart rate, increased cardiac output (3 L/min per 1°C increase of deep body temperature), peripheral vasodilatation (normal blood flow is 0.2 L/min, but can rise to 8 L/min at the maximum), intravascular dehydration (normal sweat volume is 0.5 L/day, but can reach up to 15 L/day at the maximum). If a person has existing impaired cardiac function, there is a risk of developing acute heart failure due to the added burden on the heart.
Central nervous system	Cerebral ischemia and cerebral edema (hyperthermia itself, or secondary effect due to vascular endothelial damage and circulatory failure by elevated glutamine and high cytokine levels). The nerve cells of the cerebellum and cerebral cortex are particularly vulnerable to heat.
Digestive tract	In addition to the common symptoms of diarrhea and vomiting, exercise and hyperthermia can increase the permeability of the intestinal mucosa, causing systemic sepsis from the digestive tract via the portal vein and liver. Gastrointestinal hemorrhage may also be observed.
Pulmonary edema	Progression to acute respiratory distress syndrome (ARDS) due to hyperventilation and pulmonary vasodilation and hyperpermeability due to hyperpnea and cytokines.
Acute renal failure	Due to circulatory impairment, dehydration, and rhabdomyolysis.
Hepatic impairment	Hepatocellular impairment by fever, ischemia, and hypercytokinemia from the intestinal tract.
Hemorrhagic diathesis	DIC and microthrombus in various organs including the central nervous system.
Other reactions	Electrolyte abnormality (low potassium, low phosphorus, low magnesium), hypoglycemia, metabolic acidosis, and vicarious respiratory alkalosis.

Fig. 3 Pathology leading to heat illness when combined with hypercytokinemia

above, is thought to be important in the development of DIC,[5] and there have been reports of increased levels of procalcitonin in severe cases.[6] Therefore, the onset of DIC in heat illness develops under pathologic conditions similar to those of systemic inflammatory response syndrome (SIRS) as well as sepsis, severe trauma, exten-

sive burns, and acute pancreatitis, which were encountered in emergency and intensive cares. At present, it is widely believed that the Acute DIC Diagnostic Criteria of the Japanese Association for Acute Medicine (JAAM) are most appropriate for clinical use.
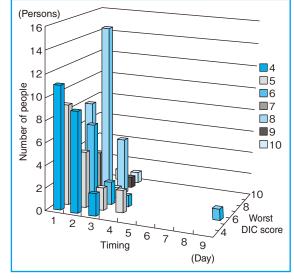
The Heatstroke STUDY-2010 (HsS2010),[7]

Fig. 4 The day of illness on which Class III patients showed their highest DIC score

Table 3 Re-classification of organ damage among Class III heat illness patients from the HsS2010 data

Severity classification	Number of patients	%
I	334	
II	204	
III (1)	84	
III (2)	737	
III (1)(2)	287	
III (Not applicable)	10	
Total (without DIC)	1,656	93.9
III (3)	1	
III (1)(3)	2	
III (2)(3)	6	
III (1)(2)(3)	99	
Total (with DIC)	108	6.1
Total	1,764	100.0

Impaired organ in Class III heat illness: (1) central nervous system; (2) liver and/or kidney; and, (3) DIC.

conducted by the heat illness committee of JAAM (chair: Dr. Yasufumi Miyake), is the most recent national survey on heat illness, and includes data from 1,780 cases. When the data of the HsS2010 were analyzed, there were 108 cases that met the acute diagnostic criteria for DIC (DIC score ≥4), including 2 cases of Class I and 4 cases of Class II. In an analysis of only the Class III heat illness cases, 74 patients were discharged from the hospital alive, whereas 22 patients died (23%) (excluding those with missing information). Of those 96 cases, there were 7 cases (7%) in which patients temporarily recovered but died of a cause other than DIC, whereas in 11 cases, the patients' condition steadily deteriorated and died of DIC (11%). Elderly people aged 50–80 years more frequently developed DIC, most likely because this age group is more prone to experience non-exertional heat illness (onset of heat illness in everyday situations).

Figure 4 illustrates the distribution of the worst (highest) DIC scores according to the day of illness after being admitted. Patients whose worst DIC score was 4 or 5 were already in that condition on the day of admission. Those whose worst DIC score was in the range of 6–8 most commonly experienced that condition on the second day of hospitalization. Those patients whose worst score was 9 or 10 most often reached that condition on the third day of hospitalization.[8]

Some patients with high DIC scores continued to deteriorate and died without recovering; this influenced the distribution pattern.

Kanda et al.[9] reclassified the case severity based on the diagnostic criteria of Class I through III using the same HsS2010 data, and found that single organ impairment is extremely rare in Class III heat illness: the majority of DIC occurs with multiple organ impairment (**Table 3**). They also found that the prognosis for DIC with the impairment of 2 or more organs is particularly poor.[9] These findings indicate that the prognosis of Class III heat illness differs substantially based on the number and type of organs impaired, and the prognosis becomes particularly poor when heat illness is accompanied by DIC. It may be possible to provide more accurate prognoses in the future by further sub-classifying Class III cases based on the number of impaired organs (i.e., III-1 refers to patients with single organ impairment or those without DIC onset, whereas III-2 refers to those with DIC and 2 or more impaired organs).

Conclusion

Heat illness is a preventable disease. However,

people who are driven to work long hours in an unfavorable environment by the fear of losing their job, those who spend extensive periods of time watching or participating in competitive sport, and elderly people living alone, are at risk of more severe symptoms and delayed diagnosis: this can result in death in the most severe cases. The classic treatment for heat illness is body cooling, but recently the option of cooling the blood itself has emerged (e.g., cooling the blood in a collecting column during the blood purification process, or circulating cold water in a balloon positioned by the central vein). Treatment should be comprehensive, including body temperature management using all available cooling methods along with respiratory, circulatory, hepatic, and renal function support, as well as the transfusion of blood platelets or fresh frozen plasma and administration of AT-III as needed. Protein C has been reported to be effective for heat illness in an animal model,[10] which suggests that the administration of thrombomodulin, which has anti-DIC and anti-inflammatory actions, may be effective.

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