In June 2021, western Canada experienced an unprecedented heat wave, setting dozens of weather records, including a new all-time Canadian temperature record of 49.6°C in the village of Lytton, British Columbia. This heat wave led to an almost fourfold spike in sudden deaths, as well as significant increases in emergency calls and hospital visits, putting a strain on the Canadian healthcare system. Preliminary reports from the British Columbia Coroner’s Service suggest that the majority of the reported deaths were in elderly individuals.

Temperatures are on the rise worldwide, with the mean global temperature 0.9°C hotter in the first 2 decades of the 21st century compared to that from 1850-1900. In Canada, the rate of temperature rise is approximately twice the global rate. In fact, from 1948 to 2020, annual average temperatures in Canada increased by 1.8°C. As temperatures rise, the frequency, severity, and duration of heat waves rise in parallel. Although humans are able to adapt to gradual increases in mean temperatures over time, heat waves, defined as prolonged periods of higher-than-normal temperatures, put an increased strain on the cardiovascular system. This strain may be further exacerbated by air pollution, concurrent wildfires or smog. In countries such as Canada, where people and healthcare systems are not acclimatized to extreme heat, patients with underlying cardiovascular disease and other chronic diseases are at heightened risk of developing heat stroke and its complications. Box 1 illustrates a clinical case that may be encountered during a heat wave. This review summarizes the current knowledge on the interaction between cardiovascular disease and heat stroke (Fig. 1).

**Definitions**

Heat stroke is a syndrome of hyperthermia (usually a body temperature of > 40.5°C) secondary to extreme environmental heat exposure, with associated central nervous system dysfunction, with manifestations that can range from confusion to seizure to coma. Classic (non-exertional) heat stroke typically affects older individuals and those with underlying chronic diseases that impair the body’s ability to dissipate heat. Conversely, exertional heat stroke typically affects younger individuals, most commonly athletes, outdoor workers, and military personnel, whose production of heat due to exertion overwhelms the body’s ability to dissipate it. The incidence of classic heat stroke tends to spike during heat waves, whereas exertional heat stroke occurs sporadically at any time of year. This review focuses on classic heat stroke, as it is more closely associated with cardiovascular function.

**Pathophysiology of Heat Stroke**

Heat stroke results from an imbalance in heat production and heat dissipation. When thermal homeostasis is...
impaired cardiovascular function have a limited ability to increase stroke volume, cardiac output, and blood flow to the skin, increasing the risk of heat stroke. In turn, these patients, whose cardiac condition is already compromised, are susceptible to cardiovascular complications of heat stroke, including arrhythmias, myocardial ischemia, heart failure, shock, and sudden death. Indeed, the majority of excess deaths during heat waves are cardiovascular in origin, highlighting the impact the cardiovascular system has on the development of heat stroke, and vice versa. This review summarizes the current understanding of the interaction between the cardiovascular system and heat stroke, including the pathophysiology, cardiovascular complications, and treatment.

Maintained, heat production is dictated by the body’s metabolic rate, and heat dissipation is achieved through 4 major mechanisms—evaporation of sweat, convection, conduction, and radiation. The latter 3 mechanisms are achieved through passive transfer of heat from the skin to the environment, and they are regulated through cardiac output and cutaneous vascular tone. As core temperature rises, sweat production and cardiac output increase and blood flow is diverted to the skin through cutaneous vasodilation and visceral vasoconstriction.

Under an extreme environmental heat load, heat production increases through an increased metabolic rate, but the ability to dissipate heat decreases, due to a lower temperature gradient between the body and the environment. Indeed, as the environmental temperature exceeds the core body temperature, mechanisms of conduction, convection, and radiation act in reverse, with heat transferring from the environment to the body. Humid conditions can further exacerbate this heat imbalance, impairing the ability of sweat to evaporate. As heat production exceeds heat dissipation, the core body temperature rises. Cutaneous blood vessels maximally dilate, and fluid is lost through tachypnea, sweat production, and cutaneous blood flow. The resulting vasodilatory and hypovolemic state requires increased cardiac output to maintain mean arterial pressure; as this compensatory measure fails, circulatory collapse ensues, leading to a further rise in core body temperature.

On a molecular level, the body’s initial adaptive response to a rise in core body temperature is a cytokine cascade, including release of heat-shock proteins, to protect against cellular damage; however, prolonged/extreme hyperthermia results in a deleterious systemic inflammatory response due to heat-related cellular damage and possibly increased gastrointestinal permeability to endotoxins. This inflammatory response further exacerbates an already hypovolemic and distributive state, resulting in multiorgan dysfunction and death (Table 1).

Impact of the Cardiovascular System on Heat Stroke

Individuals with cardiovascular dysfunction, particularly the elderly, are unable to sufficiently augment cardiac output and increase cutaneous blood flow, and thus they have a heightened risk of developing heat stroke. Indeed, in a meta-analysis of heat stroke patients, underlying cardiovascular disease significantly increased the risk of death by almost 2.5 times.

The hypovolemia and decreased systemic vascular resistance caused by a thermal load require an increase in cardiac output to maintain blood pressure, organ perfusion, and thermal homeostasis. In healthy individuals subjected to a thermal stress, cardiac output increases, cutaneous vessels dilate, and splanchnic vessels constrict, resulting in maintenance of blood pressure and increased cutaneous blood flow. In contrast, older individuals have an attenuated ability to increase cardiac output, which is largely driven by an increase in heart rate, as opposed to stroke volume. Older individuals also have impaired cutaneous vasodilation, as a result of atherosclerotic disease and stiff vasculature that is less responsive to nitric oxide. Individuals with underlying ventricular dysfunction or stenotic valvular lesions are also unable to sufficiently augment cardiac output, increasing the risk of heat stroke and circulatory collapse. For example, in patients with mitral stenosis subjected to a thermal stress, hemodynamic studies demonstrate an impaired ability to increase cardiac output and stroke volume, and a significant increase in the pulmonary wedge pressure.

Box 1. Illustrative case problem

During a heat wave in western Canada with temperatures > 40°C for 5 consecutive days, a 74-year-old man living alone was taken to a hospital by ambulance after being found in his home with an altered level of consciousness. His past medical history included hypertension, type 2 diabetes mellitus, heart failure with preserved ejection fraction, and mild cognitive impairment. His rectal temperature was 41°C, heart rate 126 beats per minute, blood pressure 94/56 mm Hg, respiratory rate 28, and oxygen saturation 92% while breathing room air. His Glasgow coma scale (GCS) score was 6. An initial electrocardiogram demonstrated atrial fibrillation with rapid ventricular response, and 1 mm of ST-segment depressions in the inferior leads. His initial troponin I level was elevated at 1.344 ng/L.
Impact of Cardiac Medications on Heat Stroke

A number of commonly prescribed cardiac medications increase the risk of heat stroke. Beta-blockers and non-dihydropyridine calcium-channel blockers impair the ability to increase cardiac output in response to thermal stress. Diuretics exacerbate the hypovolemic state of heat stroke and increase the risk of electrolyte disturbances. Renin–angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) increase the risk of acute kidney injury associated with heat stroke. Oral hypoglycemic agents (metformin, sulfonylureas, sodium-glucose co-transporter 2 [SGLT2] inhibitors) can also have deleterious effects in the setting of dehydration.

Although salicylates are recognized as anti-pyretic medications in the management of fever, this is accomplished through modulation of the hypothalamic temperature set point. Unlike fever, hyperthermia in heat stroke is not caused by hypothalamic dysfunction, and thus antipyretics, such as aspirin, have no benefit, and in fact, can worsen associated coagulopathy and liver dysfunction.15

Impact of Heat Stroke on the Cardiovascular System

Heat stroke increases the stress on the heart dramatically. In patients with underlying cardiovascular disease, the heart’s ability to meet the heat-dissipation needs of the body can be overwhelmed, resulting in a number of cardiac complications (Table 2).

Table 1. Noncardiac manifestations of heat stroke

| Organ system | Manifestations in heat stroke                  |
|--------------|-----------------------------------------------|
| Central nervous | Confusion, seizure, coma                      |
| Respiratory | Cardiogenic or noncardiogenic pulmonary edema, ARDS |
| Hepatic | Liver-enzyme elevation, acute liver failure |
| Renal | Acute kidney injury, acid–base disturbances, electrolyte disturbances |
| Hematologic | DIC                                           |
| Musculoskeletal | Rhabdomyolysis                               |

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

Figure 1. The cardiovascular system and heat stroke.

Arrhythmias

One of the earliest and most common cardiac manifestations of heat stroke is sinus tachycardia,16,17 likely in response to volume depletion and adrenergic stimulation. Sinus tachycardia is also a key mechanism for heat dissipation through cardiac output augmentation. Other tachyarrhythmias, including atrial fibrillation and supraventricular tachycardia, are also common, and although they may be driven by the same underlying mechanisms as sinus tachycardia, they have deleterious effects on cardiac output. In the most severe cases, heat stroke can lead to ventricular tachyarrhythmias and cardiac arrest.18 Conduction disturbances, including PR prolongation, intraventricular conduction delay, and right and left bundle branch blocks can also occur, potentially as a result of rate-related aberrant conduction. QT prolongation is common, and may be associated with underlying electrolyte disturbances.

Myocardial injury/ischemia

Up to 50% of patients with heat stroke have ST-segment deviations. Although some of these changes are nonspecific,
Heart failure

Heat stroke can also cause heart failure, which may be a result of ischemia and supply—demand mismatch, as well as stress-induced cardiomyopathy,22 from the high adrenergic state of heat stroke. In healthy individuals, a thermal load results in a hyperdynamic left ventricle. For the majority of patients who experience circulatory collapse, it is related to distributive/hypovolemic shock, with a low systemic vascular resistance and high cardiac index; however, a minority of patients develop a hypodynamic state, with a reduced cardiac index and increased systemic vascular resistance, particularly those with pre-existing cardiovascular disease who are exposed to a heat wave for a prolonged period of time.10,23,24 Those with a hypodynamic state have an increased mortality rate.23

Sudden death

Heat waves result in increased incidence of sudden death, which often occurs before patients arrive in the hospital. The majority of deaths during heat waves are not directly attributable to heat, but rather to underlying cardiovascular dysfunction. In fact, during the 1995 Chicago heat wave, an average of 241 excess deaths occurred per day, 94% of which were attributed to an underlying cardiovascular cause.25

Treatment

Rapid cooling to a target temperature of < 39°C is paramount for management of heat stroke, and such treatment should be delayed only if cardiopulmonary resuscitation is required.7,26,27 Patients presenting with coma or shock often also require intubation and mechanical ventilation for airway protection. Cooling can be achieved through a number of approaches, including cold water immersion, infusion of cold intravenous fluids, application of ice packs, and fanning. Theoretically, use of extracorporeal membrane oxygenation (ECMO) provides benefit, albeit no robust evidence supports its use. Cooling alone can rapidly reverse coma and other organ dysfunction associated with heat stroke, but serial biochemical monitoring of cardiac, hematologic, renal, and hepatic function is still warranted.

Cardiac evaluation, including continuous telemetry, echocardiography, and invasive hemodynamic monitoring also may be utilized. A mean arterial pressure of > 65 mm Hg should be maintained, and this may require vasopressor support in addition to intravenous fluid resuscitation. In patients with heart failure, inotropic support can also be considered. No pharmacologic therapy has proven benefit in management of heat stroke; however, nonessential medications that may exacerbate heat stroke, such as diuretics, renin—angiotensin system inhibitors, and sodium—glucose co-transporter 2 (SGLT2) inhibitors should be withheld if there are no contraindications to doing so.

No evidence is available to guide management of patients with evidence of myocardial injury in the setting of heat stroke. Investigation and intervention in patients with evidence of myocardial ischemia should be based on a patient’s underlying cardiac risk factors, ischemic symptoms, electrocardiographic changes, and troponin kinetics, with recognition that supply-demand mismatch (as opposed to acute plaque rupture) is the predominant pathophysiologic mechanism underlying myocardial injury in this population.
Prevention

During heat waves, at-risk patients should be advised of strategies to mitigate the risk of heat stroke. Wearing light clothing and keeping well-hydrated is advised. When the ambient temperature surpasses the core body temperature, fanning is ineffective, as it simply recirculates hot air. When combined with a cool shower or bath, however, fanning is more effective. If air conditioning is not available in residences, malls, grocery stores, and hotels are alternative locations where people can find refuge from heat waves. Several Canadian provinces have established cooling centres that are activated during heat waves. Several Canadian provinces, such as Saudi Arabia. Medications that may exacerbate heat stroke can be proactively withheld during severe heat waves, especially in vulnerable patients who may not be able to adhere to other preventive measures. Family members, neighbours, and community members should be encouraged to check on at-risk individuals frequently. Please see Box 2 for a conclusion to the illustrative case presented in Box 1.

Conclusion

Heat stroke is a life-threatening but reversible condition. An intact cardiovascular system is critical for maintenance of thermal homeostasis, and underlying cardiovascular disease, particularly in the elderly, increases risk. Heat stroke results in multiorgan dysfunction, and its cardiovascular complications include arrhythmias, conduction disturbances, myocardial ischemia/injury, and at extremes, heart failure, circulatory collapse, and death. Cooling and supportive care are paramount in management of heat stroke.

Current understanding of the relationship between heat stroke and the cardiovascular system is subject to several limitations, particularly the relative infrequency of major heat waves, and the small and/or retrospective nature of the studies available. As heat waves increase in frequency, further areas of study should explore the efficacy of preventive measures and the role of coronary angiography in patients who have myocardial injury.

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