Compendium

Heatstroke: Thermoregulation, Pathophysiology, and Predisposing Factors

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Abstract: *Heatstroke is a common veterinary emergency that, depending on the severity of injury, can progress to a life-threatening condition. Heatstroke can be classic (nonexertional) or exertional. Classic heatstroke develops when the body is exposed to high external temperatures, whereas exertional heatstroke is caused by strenuous exercise. Thermoregulation is the intrinsic ability of the body to maintain core body temperature within normal limits through an intricate balance of heat conservation and heat dissipation. Severe disease ensues when persistent hyperthermia causes injury to the body for which these mechanisms can no longer adequately compensate. The first stages of heatstroke are characterized by initial thermoregulation, acute phase response, and activation of heat shock proteins. The organ systems most commonly affected during heatstroke are the gastrointestinal tract and the coagulation, renal, cardiac, pulmonary, and central nervous systems.*

For more information, please see the companion article, "Heatstroke: Clinical Signs, Diagnosis, Treatment, and Prognosis."

Heat-related illnesses are prevalent in human and veterinary medicine. Over a 9-year period, one study estimated that 55,000 human cases of heat-related illness were treated in emergency departments in the United States.[1] The Hebrew University Veterinary Teaching Hospital in Rehovot, Israel, reported 40 cases of heatstroke in canine patients between 2005 and 2006.[2] During summer months, all emergency-room cases should be evaluated closely for clinical signs of heatstroke. To limit the incidence of heat-related illnesses, exposure to heat should be minimized for high-risk populations with predisposing risk factors.

Heat-related illnesses are categorized based on clinical signs and the body temperature of the patient. These illnesses range from mild to severe based on the length of heat exposure and whether the patient has any underlying predisposing factors. Heat stress is the mildest form of heat-related illness, and heatstroke is the most severe (**TABLE 1**). Numerous definitions have been proposed to describe the intricate disease process of heatstroke. In humans, the classic definition is a severe illness characterized by a core temperature >104°F (>40°C) and central nervous system abnormalities; however, a more thorough definition of heatstroke in humans has been proposed: "A form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multi-organ dysfunction in which encephalopathy predominates."[3] A similar syndrome has been described in veterinary patients.[4]

There are two types of heatstroke. Nonexertional, or classic, heatstroke is caused by exposure to high external temperatures and is seen commonly in veterinary medicine. Exertional heatstroke is associated with strenuous exercise. The development of

Table 1. Categories of Heat-Related Illness

Severity	Heat-Related Illness	Core Temperature	Clinical Signs/ Definition
Mild	Heat stress[17]	Normal	Discomfort and physiologic strain
	Heat cramps[7]	Normal	Muscle cramps (identifiable limp or reluctance to walk) secondary to water and sodium depletion
	Heat exhaustion	Normal to slightly increased (<40° C) or decreased	Weakness, anxiety, and fainting
Severe	Heatstroke[3]	Increased (>40° C)	Central nervous system and cardiovascular depression

heatstroke is multifactorial and strongly influenced by environmental temperature, humidity, and current medical status of the patient.

Physiologic Response to Heat Stress

During an episode of heat stress, systemic and cellular compensatory mechanisms are activated to reduce the risk of hyperthermia. The main mechanisms are thermoregulation, acclimatization, acute phase response, and induction of heat shock proteins.

Thermoregulation

The anterior portion of the hypothalamus, known as the *preoptic area*, is the main organ responsible for thermoregulation.[3–6] Changes in body (blood) or ambient temperature are detected by peripheral thermoreceptors, located in the skin and mucous membranes, and central thermoreceptors, located within internal structures, such as the spinal cord and abdominal visceral organs.[6] Stimulation of these thermoreceptors leads to peripheral vasodilation and central vasoconstriction, effectively shunting heated core blood to the skin to facilitate heat dissipation (**FIGURE 1**).[3,6]

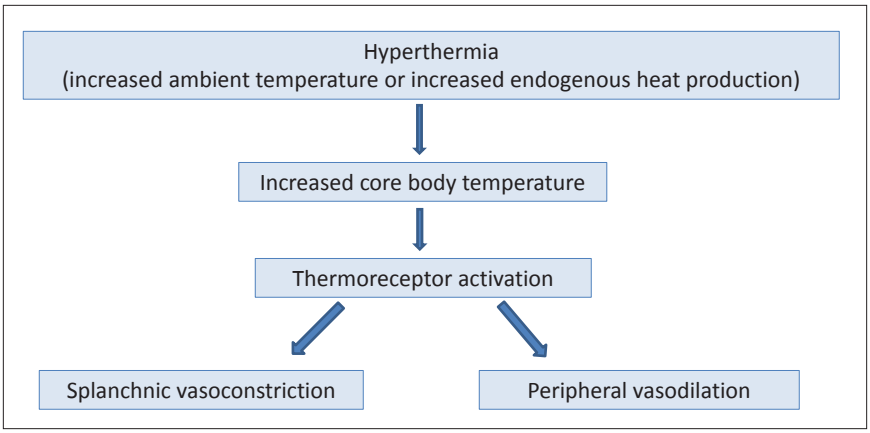

Figure 1. Initial compensatory stages of thermoregulation.

The body relies on four main mechanisms to achieve heat dissipation. *Conduction* takes place when the body comes in contact with a cooler object and heat is transferred from the patient to the object.[4] *Radiation* is the natural process of the body releasing heat into the environment. *Convection* is the transfer of heat to surrounding cooler air as it passes over the patient. The fourth mechanism, *evaporation*, takes place when a fluid changes into a vapor. Evaporation is achieved through perspiration in humans and panting in some veterinary patients (e.g., dogs, cats).[3–5,7,8] Radiation and convection account for 70% of the total body heat loss in dogs and cats when environmental temperatures are below skin temperatures.[9] With increasing environmental temperatures, these mechanisms become inefficient, and the body must rely on evaporation to maintain normothermia. Evaporation can also become ineffective when relative humidity is increased.

Acclimatization

Humans and animals can adapt to hyperthermia caused by high external temperatures or strenuous exercise through the process of acclimatization. Acclimatization consists of several mechanisms, including increased cardiac output and activation of the renin-angiotensin-aldosterone system. These changes result in conservation of sodium by the sweat glands and kidneys, increased glomerular filtration rate, and, in humans, the capacity to secrete sweat.[3,4] Salt conservation increases water reabsorption through the kidneys, which subsequently increases circulating volume and maintains hydration. Cardiac output has been shown to increase up to 50% in the initial phases of heatstroke in human patients.[10] These mechanisms are highly developed in elite athletes, including racing greyhounds and marathon runners, to increase their ability to resist rhabdomyolysis.[3,4] In animals, partial acclimatization to environmental and climatic changes takes 10 to 20 days, and full acclimatization takes up to 60 days.[4]

Acute Phase Response

In addition to the hypothalamus-driven reaction, the canine body initiates an acute phase response similar to that documented in humans with bacterial infections, trauma, neoplasia, burns, strenuous exercise, heatstroke, or immune-mediated diseases.[4] This response, which is a coordinated cellular reaction activated by inflammation, protects against tissue injury and promotes repair.[4] It involves an intricate balance of increases in proinflammatory and antiinflammatory cytokines. Cytokines centrally mediate several actions within the body, including fever production, leukocytosis, accelerated synthesis of acute phase proteins, muscle catabolism, hypothalamic-pituitary-adrenal axis stimulation, and leukocyte and endothelial cell activation.[3] Interleukin (IL)-1-β is one of the first proinflammatory mediators present in the early stages of heat stress.[3,11] IL-1-β enhances monocyte cytotoxicity and increases the production of other proinflammatory mediators, such as IL-6 and tumor necrosis factor-α (TNF-α).[12] IL-6 is involved in the stimulation of acute phase protein production, which inhibits the generation of reactive oxygen species and the release of proteolytic enzymes from activated leukocytes.[3] IL-10 is the main antiinflammatory cytokine involved in the acute phase response. IL-10 limits the hyperinflammatory response through downregulation of T cells and is released in states of acute stress to counteract the activation of the neuroendocrine axis in the central nervous system (**FIGURE 2**).[13] A similar inflammatory cascade is seen in patients with systemic inflammatory response syndrome (SIRS) and sepsis.

Heat Shock Proteins

Nearly all cells have an innate thermoregulatory compensatory mechanism for acute episodes of hyperthermia: when they are exposed to high temperatures, they produce heat shock proteins.[3,14] These proteins act as "molecular guardians," providing a protective tolerance to hyperthermia by maintaining intracellular function and structural protein integrity.[3,15] Experimental studies have

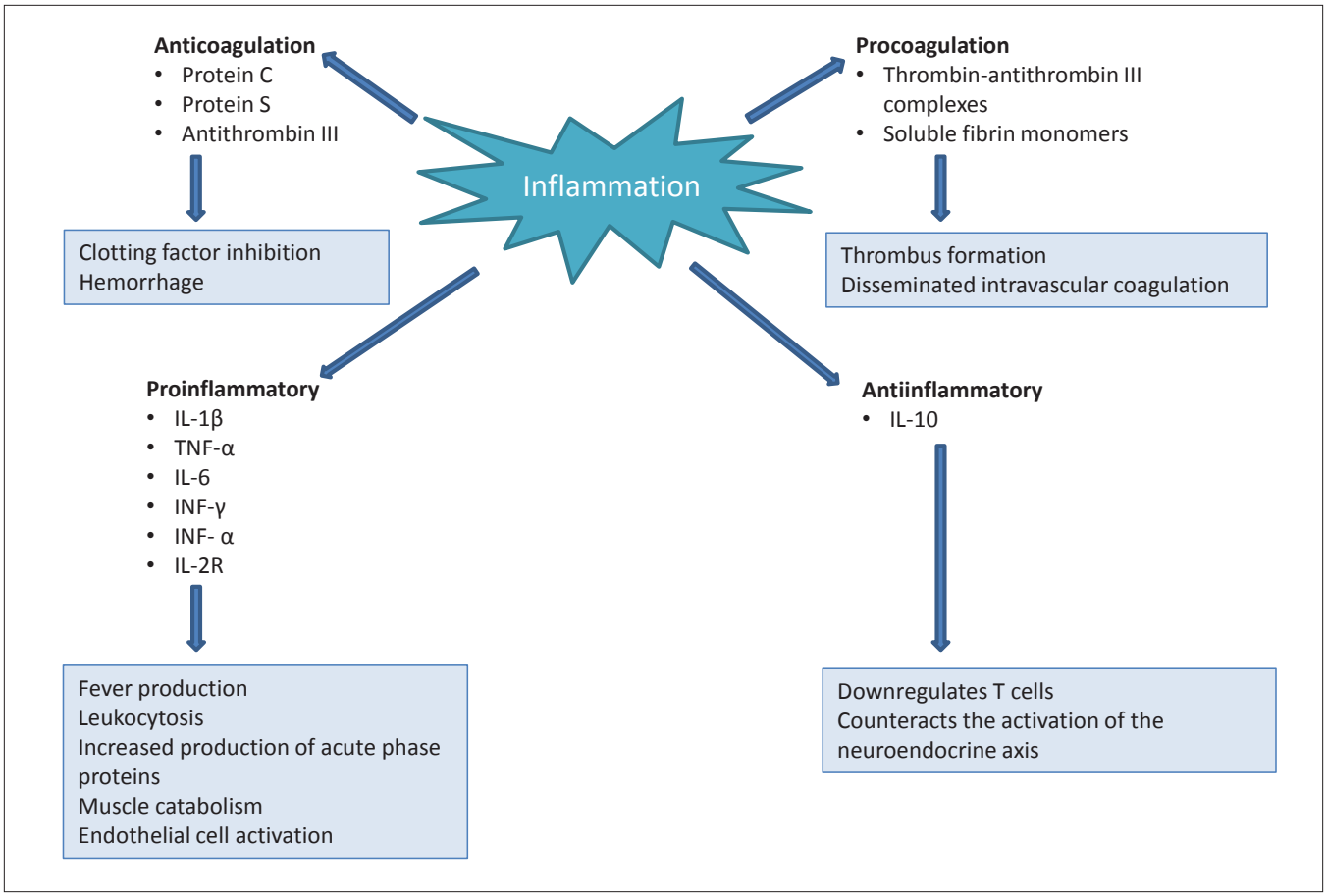

Figure 2. Acute phase response. *IL* = interleukin, *INF* = interferon, *TNF* = tumor necrosis factor.

shown that induction of heat shock proteins reduces production of excessive proinflammatory cytokines.[15] As a result, the severity of heatstroke-induced arterial hypotension, cerebral ischemia, and cerebral neuronal damage was reduced in these studies.[16] Although effective, cellular protective mechanisms are limited and, when overwhelmed or impaired, contribute to the progression of heatstroke.[16]

Pathophysiology

Predisposition

Exogenous and endogenous factors can predispose a patient to the development of heat-related illness. Predisposing factors can impair the ability to dissipate heat and/or cause increased heat production (**BOX 1**).[8]

Exogenous factors include lack of acclimatization, confinement to an area with limited ventilation or shade, elevated environmental humidity, water deprivation, and administration of specific medications.[4,8] In veterinary patients, exposure to high external temperatures in vehicles is common. In <40 minutes, the temperature in an automobile can reach 145°F (62.7°C) during the summer months, even in a light-colored vehicle with the windows partly opened.[17] Medications that affect the body's ability to respond to temperature changes include loop diuretics, β-blockers, and phenothiazines.[7,8]

Endogenous predisposing factors are underlying medical conditions and physical traits that impair the ability to dissipate heat. Known underlying medical conditions in humans include obesity, cardiovascular abnormalities, neurologic or neuromuscular diseases, and laryngeal paralysis. Obesity can limit heat dissipation by inhibiting cutaneous vasodilation.[8,18] In a recent retrospective study, obese veterinary patients with heatstroke were reported to have an increased likelihood of death.[19]

Age can also serve as a predisposing factor. Elderly human patients are thought to be at a higher risk for heatstroke because of their reduced ability to sweat, impaired acclimatization, deficient voluntary control (e.g., impaired physical mobility), compromised cardiovascular response, and need for drug therapies that may affect the body's ability to thermoregulate.[8,20] Similar impairments may be present in aging veterinary patients, although no studies have been reported. The most common physical attributes that affect heat dissipation in veterinary patients include a thick, dark haircoat and congenital or acquired anatomic upper airway abnormalities, as seen in brachycephalic breeds or patients with laryngeal paralysis. A thick, dark haircoat decreases heat dissipation by adding layers of insulation and limiting effective cutaneous vasodilation.[8] Brachycephalic veterinary patients can have decreased nasal turbinate surface area for evaporative cooling. Structural

Box 1. Predisposing Factors for Heatstroke

Endogenous
- Obesity
- Cardiovascular disease/abnormalities
- Neurologic or neuromuscular disease
- Thick haircoat
- Upper airway abnormalities (brachycephalic breeds and/or laryngeal paralysis)

Exogenous
- Lack of acclimatization
- Confinement with limited ventilation or shade
- Water deprivation
- Medications: Loop diuretics, β-blockers, and phenothiazines

abnormalities, such as stenotic nares and an elongated soft palate, can create partial upper airway obstruction, further impairing heat dissipation through panting.[8] As a result, hyperthermia is a common sequela to brachycephalic upper airway crisis.

Affected Organ Systems

Although the body has effective mechanisms to defend cells from thermal injury, there is an individual point for each patient at which the body can no longer compensate and severe heatstroke ensues. Injury to multiple organ systems can be seen in cases of heatstroke. Organ systems commonly affected are the gastrointestinal tract and the coagulation, renal, cardiac, pulmonary, and central nervous systems.

Exposure to extreme temperatures that cause direct tissue damage is called *direct cytotoxicity*.[4] The result of direct cytotoxicity varies with tissue type and depends on the tissue's critical thermal maximum. The critical thermal maximum attempts to quantify the level and duration of heat necessary to initiate tissue injury.[3] At extreme body temperatures of 120.2° to 122°F (49° to 50°C), necrosis destroys all cellular structures in less than 5 minutes.[3,21] As the body continues to be exposed to high temperatures, additional proinflammatory cytokines are produced, perpetuating the inflammatory state and cellular injury. These cytokines are markers of SIRS and, if allowed to persist, contribute to the development of multiple organ failure.

Gastrointestinal Tract

Damage to the gastrointestinal tract is caused in part by direct cytotoxicity and in part by prolonged splanchnic vasoconstriction and hypoperfusion, which happen early during the compensatory stages of heatstroke.[3] In animal models of heat stress, prolonged periods of splanchnic vasoconstriction and hypoperfusion lead to intestinal and hepatocellular hypoxia.[3] Hypoxia causes the generation of highly reactive oxygen and nitrogen species that accelerate mucosal injury and results in hyperpermeability of the intestinal mucosa.[3] Increased mucosal permeability predisposes the patient to gastrointestinal bacterial translocation, mainly of resident gram-negative bacterial endotoxin.[22] In experimental studies of heat stress in veterinary species, radiolabeled endotoxin was not only identified in systemic circulation, but also increased with increasing body temperature.[3,23,24] The resultant endotoxemia and bacteremia perpetuate the acute phase response and increase production of inflammatory cytokines, contributing to cardiovascular instability and the development of sepsis. Septic shock can result as TNF-αand IL-6 induce endothelial cell activation and the release of endothelial vasoactive factors, such as nitric oxide and endothelins, leading to hypotension.[3,23–26]

Coagulation System

Direct cytotoxicity results in endothelial damage, marked by an increase in plasma markers of endothelial activation: von Willebrand factor antigen, intracellular adhesion molecule-1, and endothelin.[27] Subsequent platelet and leukocyte adherence to areas of endothelial damage further contributes to the proinflammatory state.[8] Endothelial damage activates the coagulation cascade in the early stages of heatstroke through the release of thromboplastin and factor XII.[27,28] Procoagulation predominates because levels of thrombin–antithrombin III complexes and soluble fibrin monomers increase while levels of anticoagulation factors, such as protein C, protein S, and antithrombin III, decrease.[3,8] The fibrinolytic pathway is activated by increased levels of plasmin-antiplasmin complexes and D-dimers and decreased concentrations of plasminogen, predisposing heatstroke patients to developing disseminated intravascular coagulation (DIC).[19,27,29] The incidence of DIC was confirmed in >48% of cases in two recent canine studies involving heatstroke.[19,30]

Renal System

Acute kidney injury was noted in 33% of canine heatstroke patients.[19] In heatstroke patients, acute kidney injury results from direct cytotoxicity, ischemic injury from vasoconstriction during initial compensatory phases, hypovolemia, and vascular insults.[8,22,29,31] Histologic evaluation of kidneys from canine heatstroke patients suggests that these mechanisms of injury lead to moderate to severe interstitial and glomerular congestion, interstitial hemorrhage, and mild to severe tubular degeneration with necrosis.[30] Further renal injury can develop from excess myoglobin filtration secondary to massive rhabdomyolysis.[8,29]

Cardiovascular System

Initially, the cardiovascular system is vital to the body's thermoregulatory process as cardiac output, peripheral vasodilation, and central vasoconstriction increase. As the disease process progresses, these compensatory mechanisms fail, and distributive shock results from the decreased systemic vascular resistance caused by central vasodilation and venous pooling. Cardiac myocytes are susceptible to direct cytotoxicity, resulting in fragmentation of the myocardium and loss of myofibrillar striations.[8,32] These

Key Facts

- The body uses four mechanisms to dissipate heat: convection, conduction, evaporation, and radiation. Radiation and convection account for 70% of total body heat loss in dogs and cats.[9]
- In veterinary patients, exposure to high external temperatures within vehicles is a common scenario. In less than 40 minutes, the temperature in an automobile can reach 62.7C° (145°F) during the summer months, even in a light-colored vehicle with the windows partly opened.[17]
- Endogenous or exogenous predisposing factors can increase an animal's risk of progressing to a more severe form of heat-related illness.

structural changes lead to myocardial conduction defects and ventricular arrhythmias.[8] Histologic evaluation of hearts from canine heatstroke patients showed the presence of epicardial, endocardial, and myocardial hemorrhage.[30]

Pulmonary System

The pulmonary system can suffer from direct cytotoxicity. Direct thermal injury to the pulmonary endothelium results in vasculitis and may progress to acute lung injury or acute respiratory distress syndrome (ARDS). Histologic evaluation of lungs from canine heatstroke patients revealed that all dogs had mild to severe diffuse pulmonary edema and hyperemia.[30] ARDS was a common finding in one human heatstroke study.[33] These changes impair respiratory function and further decrease heat dissipation, contributing to the exacerbation of hyperthermia.

Central Nervous System

The central nervous system is extremely sensitive to hyperthermia. Direct cytotoxicity causes neuronal injury and cell death.[8] Cerebral edema, hemorrhage, and mild to moderate neuronal necrosis were noted on necropsy in canine heatstroke patients.[30] Dopamine, serotonin, and many of the proinflammatory cytokines (IL-1, TNF-α, and IL-6) that are elevated during heatstroke are thought to be mediators for cerebral edema and decreases in cerebral perfusion.[34] These underlying cerebral changes are responsible for the neurologic derangements that many heatstroke patients develop.

Summary

The body relies on thermoregulation to maintain a core body temperature that preserves normal cellular function. This process involves an intricate balance between heat dissipation and conservation. Thermoregulation is achieved through evaporation, radiation, convection, and conduction. Temperature changes are sensed by thermoreceptors and appropriate compensatory processes are initiated, including the acute phase response and activation of heat shock proteins. If heat stress is left unchecked, protective mechanisms fail, leading to organ injury. Cellular structures can be damaged through acute cardiovascular changes or direct cytotoxicity. As organ systems are injured, a chain reaction is started, leading to further damage. Organ systems commonly affected in heatstroke patients include the gastrointestinal tract and the coagulation, renal, cardiovascular, pulmonary, and central nervous systems.

References

1. Nelson NG, Collins CL, Comstock RD, et al. Exertional heat-related injuries treated in emergency departments in the U.S., 1997-2006. *Am J Prev Med* 2011;40:54-60.
2. Aroch I, Segev G, Loeb E, et al. Peripheral nucleated red blood cells as a prognostic indicator in heatstroke in dogs. *J Vet Intern Med* 2009;23:544-551.
3. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med* 2002;346:1978-1988.
4. Johnson S, McMicheal M, White G. Heatstroke in Small Animal Medicine: A clinical practice review. *Journal of Veterinary Emergency and Critical Care* 2006;16:112-119.
5. Holloway S. Heat Stroke in Dogs. *Compend Contin Educ Pract Vet* 1992;14:1598-1604.
6. Guyton A, Hall J. Body Temperature, Temperature Regulation and Fever. *Textbook of Medical Physiology*. 11th ed. Philadelphia, PA: Elsevier Saunders, 2006;889-901.
7. Wexler RK. Evaluation and treatment of heat-related illnesses. *Am Fam Physician* 2002;65:2307-2314.
8. Flourney W WJ, Macintire D. Heatstroke in Dogs: Pathophysiology and Predisposing Factors. *Compendium* 2003;25:410-422.
9. Lewis S. Effects of heat on canine and feline. *ISU Vet* 1976;38:117-121.
10. Brothers RM, Bhella PS, Shibata S, et al. Cardiac systolic and diastolic function during whole body heat stress. *Am J Physiol Heart Circ Physiol* 2009;296:H1150-1156.
11. Lu KC, Wang JY, Lin SH, et al. Role of circulating cytokines and chemokines in exertional heatstroke. *Crit Care Med* 2004;32:399-403.
12. Bouchama A, al-Sedairy S, Siddiqui S, et al. Elevated pyrogenic cytokines in heatstroke. *Chest* 1993;104:1498-1502.
13. Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy--review of a new approach. *Pharmacol Rev* 2003;55:241-269.
14. Polla BS, Bachelet M, Elia G, et al. Stress proteins in inflammation. *Ann N Y Acad Sci* 1998;851:75-85.
15. Christians ES, Yan LJ, Benjamin IJ. Heat shock factor 1 and heat shock proteins: critical partners in protection against acute cell injury. *Crit Care Med* 2002;30:S43-S50.
16. Yang YL, Lin MT. Heat shock protein expression protects against cerebral ischemia and monoamine overload in rat heatstroke. *Am J Physiol* 1999;276:H1961-1967.
17. Jardine DS. Heat illness and heat stroke. *Pediatr Rev* 2007;28:249-258.
18. Durkot MJ, Francesconi RP, Hubbard RW. Effect of age, weight, and metabolic rate on endurance, hyperthermia, and heatstroke mortality in a small animal model. *Aviat Space Environ Med* 1986;57:974-979.
19. Bruchim Y, Klement E, Saragusty J, et al. Heat stroke in dogs: A retrospective study of 54 cases (1999-2004) and analysis of risk factors for death. *J Vet Intern Med* 2006;20:38-46.
20. Sprung CL. Hemodynamic alterations of heat stroke in the elderly. *Chest* 1979;75:362-366.
21. Buckley IK. A light and electron microscopic study of thermally injured cultured cells. *Lab Invest* 1972;26:201-209.
22. Gaffin SL, Hubbard R. Pathophysiology of Heat Stroke. Virginia: Office of the Surgeon General, United States Army, 2001.
23. Gathiram P, Wells MT, Brock-Utne JG, et al. Antilipopolysaccharide improves survival in primates subjected to heat stroke. *Circ Shock* 1987;23:157-164.
24. Gathiram P, Wells MT, Raidoo D, et al. Portal and systemic plasma lipopolysaccharide concentrations in heat-stressed primates. *Circ Shock* 1988;25:223-230.
25. Bouchama A, Hammami MM. Endothelin-1 in heatstroke. *J Appl Physiol* 1995;79:1391.
26. Sakurada S, Hales JR. A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. *J Appl Physiol* 1998;84:207-214.
27. Bouchama A, Hammami MM, Haq A, et al. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med* 1996;24:1173-1178.
28. Bouchama A, Bridey F, Hammami MM, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost* 1996;76:909-915.
29. Johnson K. Pathophysiology of Heat Stroke. *Compendium for Continuing Education for Practicitioners* 1982;16:141-145.
30. Bruchim Y, Loeb E, Saragusty J, et al. Pathological findings in dogs with fatal heatstroke. *J Comp Pathol* 2009;140:97-104.

31. Drobatz KJ, Macintire DK. Heat-induced illness in dogs: 42 cases (1976-1993). *J Am Vet Med Assoc* 1996;209:1894-1899.
32. Hanneman GD, Higgins EA, Price GT, et al. Transient and permanent effects of hyperthermia in dogs: a study of a simulated air transport environmental stress. *Am J Vet Res* 1977;38:955-958.
33. el-Kassimi FA, Al-Mashhadani S, Abdullah AK, et al. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. Chest 1986; 90:571-574.
34. Lin MT. Heatstroke-induced cerebral ischemia and neuronal damage. Involvement of cytokines and monoamines. *Ann N Y Acad Sci* 1997;813:572-580.

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1. Which form of heat-related illness is considered mild and is defined as perceived discomfort associated with exposure to a hot environment?
- **a.** heat stress
- **b.** heat exhaustion
- **c.** heat cramps
- **d.** heatstroke

2. Where are peripheral thermoreceptors located?
- **a.** skin and mucous membranes
- **b.** spinal cord
- **c.** spleen
- **d.** heart

3. Which mechanism of heat dissipation is characterized by heat being transferred from the patient to a cooler object?
- **a.** convection
- **b.** radiation
- **c.** conduction
- **d.** evaporation

4. _____ is an antiinflammatory cytokine that plays a role during the acute phase response.
- **a.** IL-6
- **b.** TNF-α
- **c.** IL-1-β
- **d.** IL-10

5. _____ has been found to be an exogenous predisposing factor in heatstroke.
- **a.** Obesity
- **b.** Age
- **c.** Water deprivation
- **d.** Cardiovascular disease

6. How does obesity serve as a predisposing factor?
- **a.** It limits cutaneous vasodilation.
- **b.** It limits central vasoconstriction.
- **c.** It creates a higher core body temperature at rest.
- **d.** It leads to decreased mobility.

7. Which structural abnormality may contribute to impaired heat dissipation in dogs?
- **a.** decreased nasal turbinate surface area
- **b.** stenotic nares
- **c.** elongated soft palate
- **d.** all of the above

8. Direct cytotoxicity is cell death caused by
- **a.** chemical exposure.
- **b.** direct crushing injury of cells
- **c.** exposure to extreme temperatures causing cellular damage
- **d.** the efficacy of an antibiotic

9. Dopamine and serotonin are thought to be mediators for _____ in heatstroke patients.
- **a.** cellular dehydration
- **b.** cellular excitability
- **c.** cerebral edema
- **d.** vasoconstriction

10. Exposure for less than 5 minutes at what temperature can cause cellular destruction from necrosis?
- **a.** 110°F
- **b.** 115°F
- **c.** 108°F
- **d.** 120°F