Heatstroke in small animal medicine: a clinical practice review

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Abstract

Objective: To review the pathophysiology, diagnosis, current treatment, and prognosis of heatstroke.

Etiology: Heatstroke can be a life-threatening condition occurring because of an imbalance of heat dissipation and production. Certain factors may predispose some animals to heatstroke. The pathophysiology and sequelae of heatstroke share similarities with that of sepsis; thus, multiple organ dysfunction often ensues. The pathophysiological derangements that occur with heatstroke result from a complex series of events associated with direct cytotoxicity of heat and initiation of the acute-phase response by endotoxin, inflammatory cytokines, and chemokines. Activation of endothelial cells, coagulation factors, and fibrinolysis (with ensuing microvascular thrombosis) leads to hypoxia and organ dysfunction. Heat shock proteins produced secondary to sudden heating act as protein chaperones or molecular guardians to provide protection against future heatstroke and may be implicated as a possible genetic component of heatstroke.

Diagnosis: A history of recent exercise or being confined in a hot and/or humid environment, combined with clinical signs such as body temperature above 40°C (104°F), panting, tachycardia, hyperemia, dry mucous membranes, and depression to prostration is consistent with a diagnosis of heatstroke. A complete blood count performed during the initial examination of dogs with suspected heatstroke often includes nucleated red blood cells.

Therapy: The mainstays for treating heatstroke include rapid evaporative cooling, volume replacement to provide cardiovascular support, and management of secondary complications.

Prognosis: The prognosis is multifactorial. There is a significant negative correlation between comatose mental status, decreased temperature, and hypoglycemia with mortality.

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Introduction

Heatstroke is a life-threatening condition resulting from extreme hyperthermia. Heatstroke occurs when the body's ability to dissipate heat generated by metabolism, exercise, and/or environmental conditions is overwhelmed.[1] It is characterized by a core body temperature above 40°C (104°F), central nervous system dysfunction (e.g., delirium, convulsions, or coma), and varying degrees of organ dysfunction.[2–7] Heatstroke is recognized more often in the summer months, espe-

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cially in the southern United States where humidity is high. It is frequently reported in dogs and rarely reported in cats.[1,8] Although the core temperature above which heatstroke occurs in dogs has not been defined, temperatures as low as 41°C (105.8°F) may cause permanent brain damage.[8] Temperatures above 43°C (109.4°F) cause severe organ damage and markedly increased mortality.[1] When temperatures of 49–50°C (120.2–122°F) are reached and sustained for 5 minutes or less, all cellular structures are destroyed and cellular necrosis occurs.[7,9] In the last decade there has been only one heatstroke study, a retrospective study, in veterinary medicine. As such, some of the information within this article has been derived from human medicine.[10] Although the pathophysiology of heatstroke is not clearly defined in human medicine either, recent literature in that arena has helped to improve our understanding of this process and may offer new insights for

the treatment and prognosis of heatstroke in animals.[11,12] This article uses both human and veterinary literature to review the pathophysiology, prognosis, and treatment of heatstroke.

Pathogenesis

The imbalance between heat generation and dissipation is impacted by thermoregulation, acclimatization, acute-phase response (APR), production of heat shock proteins (HSPs), and a patient's predisposing factors.[7]

Thermoregulation
The hypothalamus, via thermoregulation, maintains an almost constant core body temperature under varying environmental conditions through the balance of heat dissipation and heat production.[1,7,13] Heat is produced from metabolism (endogenous source) and gained from the environment (exogenous source).[1,7] Heat is dissipated by 4 mechanisms: conduction, convection, radiation, and evaporation. Conduction occurs when the body is in contact with a cooler surface, thereby allowing heat to be transferred from the patient to that surface (e.g., placing a hyperthermic animal on a cold steel table). Convection is the transference of heat from the body as air passes over it, as is seen with a fan or with wind. Radiation is the natural process of the body releasing heat into the environment. Evaporation is the endothermic process of a fluid changing to a vapor. As the environmental temperature increases above $32\,^\circ$C ($89.6\,^\circ$F), evaporation becomes the most important mechanism for dissipating body heat.[1,8] In humans, evaporative cooling occurs through perspiration. Although perspiration occurs in dogs and cats via the footpads, it is an ineffective method of heat dissipation in these animals. Dogs and cats dissipate heat through evaporation by panting, which brings large quantities of air in contact with the mucosal surfaces of the nose and mouth.[1,2,7,8]

Blood temperature elevations of less than $1\,^\circ$C ($1.8\,^\circ$F) activate the peripheral and hypothalamic heat receptors, which then activate the hypothalamic thermoregulatory center. Efferent responses from this center, such as constriction of renal and splanchnic blood vessels and cutaneous vasodilation, cause increased delivery of blood to the body surface.[7,13] Sympathetic nervous and renin–angiotensin–aldosterone (RAA) system activation, cathecholamines, and endothelin may mediate these effects of the thermoregulatory center.[14] Neurogenic signals from the hypothalamus to the panting center are part of the initial compensatory mechanism in dogs.[1,8] Tachycardia and increases in cardiac output and minute ventilation also occur.[7] Dehydration can impair thermoregulation by decreasing evaporative heat loss because less water is available for the respiratory system and by decreasing heat dissipation through radiation and convection because of decreased blood flow to the periphery.

Acclimatization
Acclimatization is the physiologic process that allows the body to adapt to environmental or climatic changes. In animals this process is partially completed over 10 to 20 days, but 60 days are usually required for full acclimatization.[13] During conditions of increasing environmental temperatures, water is conserved in greater quantities through the action of aldosterone and antidiuretic hormone. Other compensatory mechanisms include tachycardia and increased cardiac output which enhance cardiovascular performance, activation of the RAA system, salt conservation, increased glomerular filtration rate, plasma volume expansion, and an increase in the ability to resist exertional rhabdomyolysis.[7] When humans are fully acclimatized, the volume of sweat produced can increase from 1.5 to 4.0 L/hr, and the sodium content of the sweat can decrease dramatically, from 65 to 5 mEq/L.[2] Without these adaptive mechanisms, hypovolemia and dehydration occur and lead to vasoconstriction and decreased cardiac output. Eventually, vasoconstriction and decreased cardiac output (secondary to ongoing heat dissipation) result in decreased tissue perfusion and tissue hypoxia that can lead to complications such as hemorrhagic diarrhea, disseminated intravascular coagulation (DIC), arrhythmias, and renal failure. Renal failure is a common sequela of heatstroke because severe dehydration, hypotension, hypoxia, rhabdomyolysis that causes myoglobinurina, direct thermal damage, acidosis, and DIC all contribute to glomerular damage and tubular necrosis.[15]

Acute Phase Response
The APR is a systemic coordinated reaction that is activated by inflammation, protects against tissue injury, and promotes repair. In humans, stimuli that activate the APR include bacterial infection (viral to a lesser degree), trauma (including surgical), neoplasia, burns, strenuous exercise, heatstroke, and various immune-mediated states. The APR is initiated and modified by cytokines and cytokine modulators, which mediate fever, leukocytosis, acute-phase protein synthesis, muscle catabolism, hypothalamic–pituitary–adrenal axis stimulation, and leukocyte and endothelial cell activation. Anemia is seen because of decreased production of and decreased responsiveness to erythropoietin. Metabolic changes such as proteolysis, osteoporosis, and changes in lipid metabolism may also occur. Interleukin 6, produced in response to heat stress, is the major acute-

Table 1: Predisposing factors that decrease heat dissipation

Predisposing factor	Mechanism of action
Exogenous	
Lack of acclimatization	Decreased neurohormonal responses
Confinement and/or poor ventilation	Decreased conduction, convection, radiation, and evaporation
Increased humidity	Decreased evaporative heat loss
Water deprivation	Decreased blood volume that leads to decreased cutaneous vasodilation and cooling
Furosemide	Fluid losses that lead to hypovolemia
	Electrolyte losses that lead to altered electrical activity
Negative inotropic drugs (β-blockers)	Impair cardiac contractility
Phenothiazines	Hypohidrosis (in humans)
	Altered autonomic function
Endogenous	
Brachycephalic anatomy	Inadequate ventilatory capacity
Laryngeal paralysis	Inadequate ventilatory capacity
Obesity	The insulating effect of fat leads to decreased heat dissipation and decreased ventilation
Cardiovascular disease	Decreased cardiac output
Neurological/neuromuscular	Altered thermoregulatory function
	Decreased ventilatory capacity
Age (geriatric)	As extrapolated from humans, poor acclimatization, compromised cardiovascular response, and deficient voluntary control
Hair coat and color	Darker coats absorb more heat
	Thicker coats decrease radiation and convection

phase protein inducer, and can regulate the response by controlling the levels of the inflammatory cytokines, and also stimulates hepatic production of antioxidants and acute-phase proteins that are anti-inflammatory. The APR can be protective or destructive, inflammatory or anti-inflammatory, or a combination since the mediators may act differently depending on the nature of the insult, the course of the process in which they intervene, or the combined effects of the different mediators. The systemic inflammatory response syndrome, sepsis, septic shock, and stress response are all varying degrees of the APR. An exaggerated and inflammatory APR is involved in the development of heatstroke.[7,16]

Heat Shock Proteins

HSPs enhance the ability of enzymes to function during heat extremes.[17] HSPs are produced by nearly all cells in response to sudden increases of temperature and other stressors and act as 'protein chaperones' or 'molecular guardians' that induce a state of cellular tolerance to help maintain intracellular function and structural protein integrity.[7,18–21] HSPs facilitate protein repair, regulate and offer protection against apoptosis, may help maintain the antioxidant pool and protect against oxidative stress, and decrease activation of nuclear factor-κB (a proinflammatory transcription factor).[18] In addition to providing protection during hyperthermia, they are also protective during arterial hypotension and cerebral ischemia.[22] HSPs regulate the baroreceptor reflex response during severe heat stress,

confer cardiovascular protection by abating hypotension and bradycardia, and prevent irreversible protein denaturation.[7] The elucidation of the role of HSPs has led to speculation of a genetic predisposition to the development of heatstroke.[7] Aging, lack of acclimatization, and certain genetic polymorphisms are factors associated with decreased HSP levels and may predispose patients to heatstroke.[7] If heatstroke is proven to have a genetic component, it may be possible to identify humans and animals at risk and provide them with prophylactic treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to induce up-regulation of HSPs; therefore, they maybe useful in the prophylaxis of heatstroke.[7]

Predisposing factors

Predisposing factors for the development of heatstroke can be either endogenous or exogenous and can affect either the ability to dissipate heat or produce heat.[8] Table 1 presents predisposing factors that affect heat dissipation and Table 2 presents predisposing factors and substances that affect heat production.[2,8,15]

Pathophysiology

Heatstroke is classified as either classic (exposure to a high environmental temperature) or exertional (from strenuous exercise).[1–3,5,7,8] Classic heatstroke is seen in dogs that are housed outdoors and deprived of shade and water. Exertional heatstroke is seen in dogs prior to

Table 2: Predisposing factors and substances that increase heat production

Exogenous	Endogenous
Amphetamines	Exercise
Metaldehyde	Pyrexia (febrile disease)
Macadamia nuts	Hormonal hyperthermia (hyperthyroid)
Organophosphates	Seizures
Halothane	Eclampsia

acclimatization and during forced exercise in humid and/or hot environmental conditions.[1,8] Heatstroke can also arise from a combination of classic and exertional conditions, as is seen with a dog frantically trying to escape from an overheated car.

Bouchama et al. proposed an alternative definition of heatstroke as, 'a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates.'[7] This definition highlights the similarity between the pathophysiology of sepsis and heatstroke.[4,11,23–25] Multiple organ dysfunction (MOD) is the most serious complication of heat stroke and may include circulatory collapse, encephalopathy, acute renal failure, DIC, rhabdomyolysis, myocardial injury, hepatic failure, intestinal ischemia or infarction, acute respiratory distress syndrome (ARDS), and endothelial dysfunction.[4,14,15]

The pathophysiological derangements that occur with heatstroke result from a complex series of events that are associated with the direct cytotoxicity of heat and the acute physiological alterations associated with hyperthermia. These derangements include increased metabolic demand, circulatory shock, hypoxia, endotoxemia, the release and activation of cytokines and chemokines, endothelial cell activation and/or damage, the activation of coagulation and fibrinolysis, and the activation and amplification of inflammation.[4,6–8,11,12,14]

Direct cytotoxicity

Direct cytotoxicity from heat occurs in various tissues and is dependent on the critical thermal maximum, a term that applies to the attempt to quantify the level and duration of heating necessary to initiate tissue injury.[7] In primates, temperatures of 42–43°C (107.6–109.4°F) and possibly those as low as 39–40°C (102.2–104.0°F) are reported to damage the gut wall and allow endotoxin (otherwise known as lipopolysaccharide) to enter the circulation.[26] In cultured mammalian cells and experimental animal models, apoptosis in the liver, spleen, thymus, lymph nodes, and the small intestinal mucosa has been observed within a few minutes after exposure to temperatures ranging from 41.5 to 42.0°C (106.7–107.6°F).[27,28] At temperatures of 43°C (109.4°F) and higher, oxidative phosphorylation is uncoupled and critical enzymes are denatured. In humans with cancer who are undergoing hyperthermia therapy, the coagulation and fibrinolytic systems are often activated during treatment, suggesting that heat may activate coagulation and fibrinolysis as well.[6,29] Autopsy findings of humans who have died from heatstroke reveal ultrastructural endothelial damage, widespread microthrombi, and necrosis and/or hemorrhage into various organs (primarily the lung, brain, kidney, liver, and gut).[14] Similar necropsy findings have been reported for dogs that have died from heatstroke.[10]

Cardiovascular effects

Because of renal and splanchnic vasoconstriction and cutaneous dilation, patients with heatstroke initially have increased cardiac output and decreased systemic vascular resistance.[7,14,30] This response is a protective attempt to shift circulation from the body core to the periphery, thus preventing an increase in the core body temperature. As heatstroke progresses, the splanchnic vasculature dilates, and this dilation, combined with the cutaneous vasodilation, leads to venous pooling, a decrease in circulating plasma volume with resultant decrease in cardiac output, and failure of heat dissipation mechanisms.[1]

Coagulation abnormalities

Coagulation abnormalities are common in heatstroke and often lead to hemorrhagic diathesis and widespread microthrombosis as a result of DIC.[6,10,31] During heatstroke, coagulation and fibrinolysis occur early and are sustained as evidenced by elevations of thrombin-antithrombin, plasmin-antiplasmin, and D-dimer; decreased protein C and platelet counts; and prolonged prothrombin time (PT).[6] In a review of canine heatstroke, prolongation of partial thromboplastin time and PT and decreases in platelet counts were noted.[10] These findings may be attributed to direct thermal injury of the endothelium, activation of the extrinsic (tissue factor) coagulation pathway, and monocyte/macrophage activation.[6] Sustained coagulation can lead to widespread microthrombosis and hemorrhagic diathesis. The excess fibrin leads to MOD and hemorrhage develops as the coagulation factors are consumed. Additionally, thrombin, factor VIIa, and factor Xa are proinflammatory and activate endothelial cells, platelets, and leukocytes.[32]

Diagnosis

The patient's history may include recent exercise or being confined in a hot and/or humid environment. At

presentation, the animal may be hyper-, normo-, or hypothermic. In dogs, wide ranges of rectal temperatures (<37.7°C [99.9°F] to >41.5°C [106.7°F]) have been documented at presentation.[10] Other clinical signs of heatstroke may include profound depression, prostration, panting, tachycardia, hyperemia, dry mucous membranes, rapid to nonexistent capillary refill time (CRT), and/or hyperdynamic to weak femoral pulses (with or without pulse deficits).[1,31] The presence of pulse deficits is indicative of cardiac arrhythmias. Neurologic abnormalities may include ataxia, cortical blindness, seizures, and coma.[31] Other clinical signs may include petechiations and echymoses on the mucous membranes, ear pinnae, or on the skin after clipping hair for the placement of an intravenous (IV) catheter.[31] Bloody diarrhea may be present or may develop during the course of therapy. Clinical laboratory findings may include elevations of the hematocrit, total solids, alanine aminotransferase, bilirubin, blood urea nitrogen, creatinine, and creatine kinase. In one canine study, hypoglycemia was common at presentation, and refractory hypoglycemia was associated with increased mortality.[10] Increased mortality was also associated with increasing creatinine levels despite fluid therapy.[10] In a study evaluating the peripheral blood smears of 25 human patients with heatstroke, atypical neutrophils (mainly hypersegmentation) and spherocytes were noted in 23 of 25 patients.[33] In a retrospective study of dogs with heatstroke, nucleated red blood cells (NRBC) were noted in 58% of dogs in which a complete blood count was performed.[10] In that study, it was speculated that damage to the bone marrow, due to direct heat, may have resulted in the premature release of NRBCs.[10]

Therapy

As with all emergency patients, the airway, breathing, and circulation (ABCs) should be rapidly assessed. Hypoxemia can be associated with hypoventilation, as the result of upper airway obstruction, brachiocephalic syndrome, laryngeal paralysis, obesity, and/or aspiration pneumonia. Pulmonary edema, resultant from ARDS or intrapulmonary hemorrhage due to DIC, are also important possible causes of hypoxemia that develop as a result of heatstroke and need to be considered before and during therapeutic intervention. Oxygen administration, sedation, intubation, and ventilation may be required.[1,2,8,31]

The mainstays for treating heatstroke include rapid evaporative cooling, volume replacement to optimize cardiovascular support, and management of secondary complications (e.g., shock, hypoglycemia, DIC, ARDS, and renal failure).[1,7,31] Rapid transfer of heat from the core to the skin and from the skin to the external

environment is necessary for effective heat dissipation.[7] Spraying the animal with cool water and placing it in front of a fan is a very efficient cooling method that utilizes evaporation, conduction, and convection.[1,7,31] Ice water baths should not be administered because they inhibit radiation cooling by causing intense cutaneous vasoconstriction, which shunts blood away from the skin, and causes capillary sludging that delays cooling of the core and can promote DIC.[1,31,34] Ice also causes shivering that increases heat production, and contact with ice causes extreme discomfort to patients and discomfort to medical attendees, and makes performing routine monitoring and cardiopulmonary resuscitation difficult.[1,31,34] Although gastric lavage, peritoneal lavage, and cold water enemas have been advocated, they are not practical, are labor intensive, can interfere with monitoring, and may lead to overshoot hypothermia.[3,31] To prevent rebound hypothermia and shivering, active cooling should be stopped when the core body temperature is between 39.7 and 40°C (103.5–104°F).[1,31]

Room temperature crystalloid fluids should be administered IV to assist with cooling and to maximize volume expansion. Volume expansion improves blood flow, which improves peripheral heat dissipation through radiation. Individual patient needs should be evaluated when considering the type, rate, and amount of fluids to administer. Most patients with heatstroke are hemoconcentrated and hypovolemic. Baseline parameters should include heart rate, pulse rate and quality, mucous membrane color and CRT, arterial blood pressure, urine output, lactate concentration, packed cell volume, and total solids. Central venous pressure is useful as a guide to adequate volume replacement in animals with normal cardiac function; however, complications such as hemorrhage from the site of catheter placement or pulmonary embolism may develop when used in coagulopathic patients.[1,31] Serial evaluations of perfusion parameters (mucous membrane color, extremity temperature, urine output, and lactate concentration) are essential. Lactate is a marker of tissue hypoxia and serial evaluation is useful when monitoring the response to therapy.[35,36] A recent study of humans with sepsis demonstrated that lactate clearance was associated with resolving global tissue hypoxia and was also associated with a decreased mortality rate.[36]

Colloids, such as dextrans and hydroxyethyl starch, are often needed to expand and maintain the intravascular volume, especially in the hypoalbuminemic patient. The hemoglobin-based oxygen carrier, polymerized bovine hemoglobin glutamer-200,[a] may be beneficial because of its colloidal and oxygen-carrying properties; however, recent studies have raised ques-

tions as to how it works at the microvascular level and the possible toxicities associated with its use.[31,37,38] If a hypocoagulable state is suspected, fresh frozen plasma (FFP) may be beneficial after the initial resuscitation period and during DIC because of the early activation of coagulation and fibrinolysis.[1,6,31] Decreased levels of protein C and antithrombin have been documented in patients with heatstroke.[6] Recombinant activated protein C, available as drotrecogin alfa (activated),[b] has been shown to reduce mortality in human patients with sepsis and its anti-inflammatory and anticoagulation effects may be beneficial in treating patients with heatstroke; however, its use in veterinary medicine is likely to be cost-prohibitive.[7] In the past, heparin, in addition to FFP, was recommended for treating DIC.[1,31] Recently, heparin therapy has been called into question because heparin has been shown to inhibit the effects of heparan sulfate at the microvascular level and to decrease the anti-inflammatory effects of antithrombin.[39] In septic human patients, an increased risk of hemorrhage when high doses of antithrombin III were administered was noted with concurrent administration of heparin.[40]

Mannitol is an osmotic diuretic that expands the intravascular volume, decreases blood viscosity, improves renal function, improves cerebral microcirculation, decreases intracranial pressure (ICP), and is a reactive oxygen species (ROS) scavenger.[15,41] The administration of mannitol (0.5–1.0 g/kg IV slowly over 15–20 minutes) may be indicated if the patient has neurological abnormalities or decreased urine production.[10,31] Its use is contraindicated in conditions with hyperosmolality (e.g., hypernatremia, ethylene glycol or salicylate toxicosis), active hemorrhage, pulmonary edema, vasculitis, dehydration, overhydration, and anuric renal failure.[42,43]

Hypertonic saline solution, commonly used as a 7.2–7.5% saline solution, improves cardiac contractility as well as coronary, microvascular, and regional cerebral blood flow.[44,45] It also decreases endothelial swelling, microvascular permeability, ICP, tumor necrosis factor (TNF) levels, and neutrophil/endothelial cell interactions.[44,45] In rats, when hypertonic saline (3%) is administered before or at the onset of heatstroke, time to death is delayed and improvements in arterial blood pressure, local cerebral blood flow, and oxygenation occur along with reductions in intracranial hypertension and cerebral neuronal damage.[46] Contraindications to the use of hypertonic saline solutions are dehydration, hyperosmolality, volume overload, ventricular arrhythmias, and uncontrolled hemorrhage.[47] Further studies are needed to determine the mechanisms for these changes and if these benefits are also observed when hypertonic saline is administered after the onset of heatstroke.

In the treatment of patients with heatstroke, lidocaine (2%) may be beneficial to ameliorate the damage from ROS (2 mg/kg as an IV bolus, followed by 66 µg/kg/min IV as a constant-rate infusion [CRI]) and to suppress cardiac arrhythmias (2–4 mg/kg IV until arrhythmias resolve, then 50–80 µg/kg/min IV as a CRI).[31,48] Dogs that develop ventricular cardiac arrhythmias after heatstroke have a higher mortality rate than those that do not develop arrhythmias.[10] Experimental studies in rats with heatstroke show that glutamate and ROS formation are elevated.[4,46,49,50] Lidocaine decreases the release of intracellular calcium and glutamate in the neuronal tissue of the brain, and by doing so, decreases the production of ROS. Lidocaine also scavenges ROS, decreases leukocyte activation and adhesion, reduces cytokine release from macrophages and polymorphonuclear neutrophils, and decreases endothelial dysfunction.[48] Electrocardiography (ECG) should be performed to evaluate the presence and frequency of arrhythmias. To monitor the progression or resolution of these arrhythmias, repeated intermittent or continuous ECG (direct or telemetric) should be performed.

If hypoglycemia is initially present or occurs during the course of treatment for heatstroke, dextrose should be administered as a bolus (0.5 g/kg diluted with crystalloids to make a 25% solution for IV administration), and then as an IV infusion (2.5–5% dextrose in crystalloids).[31] Glucose levels should be checked at initial presentation and then monitored frequently for the first several hours.[10] Drobatz et al. found a significant difference in the glucose concentrations between survivors and nonsurvivors of heat stroke, with 4 of 15 nonsurvivors having decreased blood glucose concentrations despite having received treatment with a 25% dextrose solution.[10]

Historically, NSAIDs have not been recommended for reducing the temperature of patients with heatstroke because of the belief that the hyperthermia of heatstroke was not mediated by the hypothalamus.[3,31] Recently, pyrogenic cytokines have been shown to be elevated in humans with heatstroke and despite removal from hot environmental temperatures and active cooling, some of these patients remain hyperthermic.[12] Since NSAIDs have the ability to lower the body temperature via the hypothalamus, there may be a subset of heatstroke victims who could benefit from treatment with NSAIDs. NSAIDs induce up-regulation of HSPs, which provide cellular protection during times of heat stress.[7] Therefore, NSAIDs may be indicated as prophylaxis during heatwaves.[7] Transcription and translation of HSP by mammalian cells are induced via the activation of heat shock factors by dexamethasone, salicylate, and NSAIDs. Despite the potential positive effects, the known negative effects of NSAIDs (i.e., inhibition of

Table 3: Heat index†: temperature (°F) versus relative humidity (%)

Temperature (°F)	Relative humidity (%)					
	90	80	70	60	50	40
90	121	113	105			
95		133	122	113	105	
100			142	129	118	109
105				148	133	121
110						135

Heat index	Heat disorder seen in humans
105–130°F	Heatstroke possible
> 130°F	Heatstroke highly likely with continued exposure

The heat index is the combined effect of heat and humidity to arrive at a temperature that the body feels. The heat index can increase up to 15°F by exposure to direct sunlight; however, this chart is based on shady, light wind conditions. The legend shows the possible effects humans may experience during exposure to the associated environmental conditions. This information may be used as a guide for what may be seen in dogs exposed to similar conditions.

As extrapolated from the National Weather Service web page on December 16, 2004, http://www.crh.noaa.gov/pub/heat.htm.

†The heat index is determined by reading down the column for temperature and across the row for relative humidity.

platelet function, and inhibition of renal and gastrointestinal prostaglandins) outweigh the benefits and, at this time, their use cannot be recommended.[3,31]

Prognosis

In animals with heatstroke, the prognosis is multifactorial and is impacted by the duration of exposure, the highest degree of core body temperature, pre-existing conditions, the development of secondary complications, and the rapidity of treatment.[1,31] Unfavorable prognostic indicators include coma or hypothermia (rectal temperature less than 37.7°C [99.8°F]) at presentation, progressive neurologic deterioration, persistent hypoglycemia, worsening of azotemia or oliguria despite adequate fluid resuscitation, evidence of DIC, refractory hypotension, elevated total bilirubin, ventricular arrhythmias, persistent hypoproteinemia, labored respiration, and pulmonary edema.[31] In dogs, blood glucose concentration was significantly lower in nonsurvivors, and a persistent hypoglycemia, despite treatment with 25% dextrose, was associated with increased mortality in one study.[10] In animals that died, death usually occurred within 24 hours of presentation, and all dogs that were alive 48 hours after presentation survived.[10]

Conclusion

Heatstroke is a complex disorder that involves the production of inflammatory mediators (cytokines and chemokines) that initiate and modulate the APR and activate the endothelium leading to coagulation and fibrinolysis. The events seen in heatstroke are very similar to those seen in sepsis and can lead to death due to MOD. The new definition of heatstroke proposed by Bouchama; 'a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multi-organ dysfunction in which encephalopathy predominates,' incorporates the pathophysiology of heatstroke as it is currently understood.[7] HSP may help protect against heatstroke and may indicate a genetic component for the development of heatstroke. With the continued elucidation of the events that lead to heatstroke and the underlying pathophysiology, new modalities for the treatment or prevention of heatstroke may be developed.

Educating the public and clients about the dangers of exercising and confining pets in environments conducive to heatstroke is necessary for heatstroke prevention.[1,2] Preconditioning pets (i.e., exercising regularly and starting out slowly in warm and humid weather until acclimatization occurs), checking the heat index (Table 3) before exercising during hot months, exercising during cooler periods of the day, and providing adequate access to water, shade, and ventilation are essential for the prevention of heatstroke.[1,2,31]

Acknowledgment

Footnotes

[a] Oxyglobin®, Biopure Corporation, Cambridge, MA.
[b] Xigris®; Eli Lilly and Company, Indianapolis, IN.

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