Canine Heatstroke

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INTRODUCTION

Hyperthermia can be a pyrogenic or a non-pyrogenic elevation of body temperature above the normal hypothalamic set point (1, 2, 3). Non-pyrogenic hyperthermia occurs when heat dissipating mechanisms cannot adequately compensate for heat production, or when these are impaired (2, 3, 4). More than 70% of the total body heat loss in dogs is dissipated through radiation and convection from body surfaces (3, 4, 5). As the environmental temperature increases, approaching body temperature, evaporation, primarily through panting, becomes more important in maintaining normothermia. Heatstroke (HS) is a severe illness characterized by core temperatures >41˚C (105.8˚F) and central nervous system (CNS) dysfunction. It results from exposure to a hot and humid environment (classical HS) or due to strenuous physical exercise (exertional HS) (1-5). The result is cutaneous and splanchnic vasodilatation with consequent venous blood pooling. Such accumulation of blood in these organs is a major contributor to the hypovolemic shock and the consequent intestinal ischemia, hypoxia and hyperpermeability that many HS patients develop in the course of the disease (5-7). This results in inflammatory cytokines and reactive oxygen and nitrogen species generation by the injured tissue that may lead to further mucosal injury with consequent necrosis and increased intestinal permeability with subsequent leak of endotoxins into the bloodstream (7, 8). The intestinal mucosal damage is probably associated with the characteristic gelatinous and bloody diarrhea, frequently observed in canine HS patients (6, 9).

Cytokine production, endotoxemia and endothelial injury may lead to increased vascular permeability and the consequent edema, a mechanism similar to that described in sepsis (7, 8, 10, 11). This may ultimately result in activation of the coagulation cascade, which may culminate to disseminated intravascular coagulation (DIC), systemic inflammatory response syndrome (SIRS) and possibly to multiorgan dysfunction (MOD) (7, 8, 10, 11).

Several factors are associated with the risk of developing HS. These include obesity, breed (brachiocephalic, Golden and Labrador retrievers), body weight (>15kg), high environmental temperature and humidity, acclimation and fitness (5, 6, 9, 12). Of these factors, only two adaptive mechanisms are directly invoked to combat heat stress: heat acclimation and the rapid heat shock response (12). Heat acclimation induces adaptive physiological and behavioral changes that improve the individual's ability to cope with extreme environmental heat (12). Acclimation is a time dependent process leading to a dynamic expansion of the body temperature regulatory range due to left and right shifts in the temperature threshold for heat dissipation and thermal injury, respectively (13). The heat shock response is a rapid molecular cytoprotective mechanism that involves production of heat shock proteins (HSP). When subjected to sublethal heat stress, the body enhances HSP transcription and synthesis to increase HSP72 cellular reserve, thus providing cytoprotection when subjected to additional stress (12, 13, 14).

The most common clinical signs in canine HS include collapse, tachypnea, bleeding (e.g. petechiae, hematemesis, hematochezia), shock, disorientation/stupor, seizures and semi-coma/coma (6, 9). Although the definition of HS is based on hyperthermia, it is important to remember that patients can be hyper-, normo- or hypothermic on presentation, particularly if cooling measures were initiated by the owners. Furthermore, in a retrospective study of canine heat

related illness, hypothermia upon admission was a poor prognostic indicator (9). Therefore, HS should not be disregarded in a patient with normal or low core temperature if the history reveals recent exercise or confinement in a hot and humid environment, cooling by the owner and clinical and/or clinicopathological findings compatible with HS (4, 6, 9).

The most common hematological findings in canine HS are thrombocytopenia, increased packed cell volume (PCV) and hemoglobin concentration (6, 9). Nucleated red blood cells (nRBC), are present in most of the dogs with HS and in very high numbers (10-120 per 100 WBC), is a highly significant risk factor for mortality. In a recent study, we have observed maximum level of nRBC upon admission with a gradual decline over the first 36 hours from the insult (13). This phenomenon was attributed to thermal lesions within the bone marrow, leading to blood-bone marrow barrier injury and subsequent release of nRBC to the peripheral circulation. Examination of the bone marrow in a recent study that evaluated post mortem changes in 11 dogs with HS failed to reveal microscopic disruption of its architecture, suggesting that if the blood-bone marrow barrier was indeed injured, light microscopy may not be a sensitive enough tool to detect such subtle lesions (16). An alternative hypothesis might be that the bone marrow release of nRBC to the peripheral circulation in canine HS is mediated via the actions of cytokines produced during SIRS. Both hypotheses warrant further investigation (7, 8, 16).

The most commonly observed serum biochemistry abnormalities in HS upon admission include increased serum activities of creatine kinase, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (6, 9, 17, 18). Additional abnormalities included hypoglycemia and increased serum creatinine concentration (6, 9). Hypoglycemia can result from increased utilization or decreased production as a result of hepatic failure or sepsis (4).

The major complications reported in canine HS are DIC, acute renal failure, CNS abnormalities and cardiac arrhythmias (6, 9). The pathophysiology of DIC involves the release of tissue thromboplastin and factor XII by injured endothelium, which activates the coagulation and complement cascades, inducing SIRS and widespread coagulation (19, 20). As DIC may appear hours to days after the initial hyperthermic insult, dogs with HS should be monitored for coagulation abnormalities and clinical signs of DIC at least during the first 24 hours post insult (6, 9).

Azotemia is a common finding in HS (3, 8). It results from prerenal and renal mechanisms, such as severe hemoconcentration and direct renal tissue damage leading to tubular necrosis, a frequent finding at necropsy of dogs with HS (16). This probably occurs as a result of a direct renal thermal injury, dehydration, hypoxia, endotoxemia, release of cytokines and vasoactive mediators and microthrombosis associated with DIC (3, 6, 19, 20).

Severe hyperthermia may lead to cerebral hypoperfusion, neuronal necrosis, direct vascular damage, cerebral edema, hemorrhage and multifocal vascular thrombosis with tissue infarction that may lead to CNS abnormalities and death (6, 16, 21). However, it should be noted that other physiological factors such as respiratory alkalosis, shock and hypoglycemia also play a major role in these neurological abnormalities (21).

Thermal and biochemical injury to pulmonary endothelium may lead to non-cardiogenic pulmonary edema, also known as acute respiratory distress syndrome (ARDS). Histopathologic lung lesions in dogs after HS include pulmonary infarcts, marked alveolar hemorrhage or edema (16).

A few extra-cardiac mechanisms were proposed as contributing processes to the development of cardiac arrhythmias. These included myocardial hypoperfusion, lactic acidosis and electrolyte imbalance and possibly direct thermal injury. A recent study of post mortem findings in 11 dogs with HS showed mild to severe subendocardial, myocardial and epicardial hemorrhages and hyperemia in all dogs (16). These findings suggest that DIC has a pivotal role in the pathogenesis of the reported cardiac arrhythmias. Antiarrhythmic therapy should be considered, however, only if the patient has related clinical signs.

The lesions of HS are related to the primary thermal insult, however, secondary deterioration occurs due to dehydration, shock and a poor perfusion. Thus, early diagnosis and intervention are crucial to the prevention of further cerebral and renal deterioration and exacerbation of coagulation abnormalities. In a study on 54 dogs with HS we have showed that time lag from insult to admission (>1.5 hrs) was a crucial factor in survival (6).

TREATMENT OPTIONS

Cooling - It is highly recommended that the owner will initiate whole body cooling even before admission. During

cooling, temperature should be monitored every 5 minutes to avoid hypothermia. Cooling should be terminated when body temperature has reached 39.5˚C. Cooling does not result in suppression of the inflammatory response.

Fluid Therapy

Crystalloids - Most canine HS victims suffer from dehydration, hemoconcentration and hypovolemic-distributive shock. Therefore aggressive fluid treatment is called for. Initial dose of 30-50 ml/kg/hr in a bolus and then perfusion should be constantly assessed by monitoring physiological parameters including: heart rate, mucous membrane color, CRT, pulse quality and blood pressure, and based on that more fluid should be added. When blood pressure and perfusion cannot be restored, colloids (Hetastarch, Dextran) and vasopressure agents (dopamine, debutamine, vasopressin) should be used.

Dextrose in hypoglycemic dogs as a single bolus (1ml/kg of 50% dextrose with maximum of 10 ml) and then in CRI, with close monitoring of the glucose level is recommended. Caution should be taken to avoid a rapid increase of glucose level which may lead to cerebral edema.

Respiratory support - all dogs with HS will benefit from oxygen therapy. In cases in which laryngeal edema is severe, intubation is recommended. In the most severe cases, positive pressure ventilation is required.

Mannitol (0.5-2 g/kg in bolus over 15 minutes) to reduce intracranial pressure is controversial since it is contraindicated in cases with cerebral hemorrhage, but will be beneficial to reduce intracranial pressure in cases in which cerebral edema play a major role in the appearance of the neurological signs.

Valium (diazepam) in cases in where seizures are present. Other reasons for seizures such as hypoglycemia should be eliminated before initiating such treatment.

Antimicrobial treatment - broad spectrum antibiotics should be used to combat sepsis as a result of gut bacterial translocation. Ampicillin 25 mg/kg TID and metronidazole 15 mg/kg BID might be a good combination. Gastric protectants should be added, to prevent further gastric damage.

Diuretics - if urine output remains insufficient despite adequate fluid replacement and mean arterial blood pressure is >60 mm Hg, a combination of dopamine 3µg/kg/min, furosamide 1mg/kg/hr and mannitol 1mg/kg/min can be used in CRI, with additional boluses of furosamide or mannitol.

The treatment of the hemostatic abnormalities in DIC is based on stabilization of the coagulation system with concurrent prevention of thrombosis. Fresh frozen plasma is given initially at a dose of 10ml/kg and additional volumes are

Table: Risk factors for mortality in 54 dogs with naturally occurring heat stroke (6).

Variable	RF[1] present		RF[1] not present		RR[2]	Exact $CI_{95\%}$[3]	P
	n	Number of deaths (%)	n	Number of deaths (%)			
Timelag >90 min	34	21 (62)	15	4 (27)	2.32	1.08-5.90	0.032
Cooling by owners before admission	26	10 (39)	28	17 (61)	0.63	0.35-1.12	0.173
Obesity	11	9 (82)	36	15 (42)	1.96	1.11-3.21	0.040
Coma/semicoma upon admission	22	15 (68)	20	8 (41)	1.71	0.95-3.32	0.060
Seizures during illness	19	14 (74)	35	13 (37)	2.00	1.17-3.37	0.020
Prothrombin time >18 sec upon admission	8	7 (88)	39	18 (46)	1.90	1.05-2.94	0.050
aPTT[4] >30 sec upon admission	14	13 (93)	33	12 (36)	2.55	1.57-4.28	<0.001
Thrombocytopenia[5] during illness	42	19 (45)	8	3 (37)	0.83	0.28-1.80	1.000
Creatinine >1.5 mg/dl at 24 hrs from admission	20	15 (75)	17	4 (24)	3.19	1.41-8.39	0.003
Glucose < 47 mg/dl upon admission	12	10 (83)	12	5 (42)	2.00	1.01-5.27	0.03
Presence of DIC[6]	28	19 (68)	26	8 (31)	2.21	1.22-4.31	0.013
Presence of Acute renal failure	18	14 (78)	36	13 (36)	2.15	1.28-3.64	0.008
Presence of DIC[3] + acute renal failure	12	11 (92)	21	6 (29)	3.21	1.63-7.01	0.001
Presence of environmental heat stroke	20	10 (50)	34	17 (50)	1.00	0.55-1.72	1.000
Presence of exertional heat stroke	34	17 (50)	20	10 (50)	1.00	0.58-1.82	1.000

[1] Risk factor; [2] Relative risk; [3] 95% confidence interval; [4] aPTT- activated partial thromboplastin time;
[5] Platelet count < 150x103/µm; [6] Disseminated intravascular coagulation.

based on the PT and aPTT levels. Low molecular heparin (2U/kg BID S.C.) treatment should be initiated only when antithrombin levels are adequate, since its presence is required for heparin to exhibit its beneficial effects.

Monitoring for 24 hrs from insult includes constant monitoring of vital signs: temperature, femoral pulse and capillary refill time to asses perfusion, hydration and shock status of the patient. In addition: PCV/TS, PT and aPTT, antithrombin, CBC, glucose, lactate, blood gas (arterial or venous), blood pressure, and urine output should be monitored. The mental status of the patient should be evaluated frequently and continuous ECG monitoring is recommended as arrhythmias may appear during the first 24 h after the insult had occurred.

The reported mortality rate in canine HS is 50% despite appropriate treatment. The most significant reported risk factors to death in canine HS are DIC, ARF, semi-coma / coma, seizures and hypoglycemia (3, 4) (Table).

CONCLUSIONS

In conclusion, HS in dogs is a life-threatening condition, resulting in serious secondary complications, such as DIC, ARF and ARDS, and a high mortality rate despite appropriate treatment. Early admission along with whole body cooling by the owners and caregivers are important for survival. The diagnosis of canine HS should not rely exclusively on hyperthermia upon admission or presence of neurological abnormalities, but should be based on the combination of the history, clinical signs and laboratory results. Treatment and monitoring should be intensive and prolonged, since complications can have a delayed onset, and present serious risk factors for mortality.

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