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Pathological Findings in Dogs with Fatal Heatstroke

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Summary

Eleven dogs with fatal heatstroke were examined grossly and histopathologically *post mortem*. All showed multi-organ haemorrhagic diathesis with coagulative necrosis. Hypaeremia and diffuse oedema were observed in the skin (eight dogs), lungs (11), brain (11) and bone marrow (one). Congestion of the splenic pulp (10 dogs) and hepatic sinusoids (nine) was also noted. Necrosis was observed in the mucosa of the small intestine (seven dogs), large intestine (eight), renal tubular epithelium (nine), hepatic parenchyma (eight) and brain neural tissue (four). The results showed that naturally occurring, fatal canine heatstroke induces acute multiple organ lesions affecting most body systems, and suggest that the more prevalent lesions include haemorrhagic diathesis, microthrombosis and coagulative necrosis. These are probable sequels of hyperthermia-induced disseminated intravascular coagulation and systemic inflammatory response syndrome, which lead to multi-organ dysfunction and death.

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Keywords: canine; disseminated intravascular coagulation; haemorragic diathesis and acute renal failure; hyperthermia

Introduction

Heatstroke is a life-threatening syndrome seen in human beings, dogs and other species. It occurs particularly under hot and humid conditions, when heat production exceeds heat dissipation (Coris *et al*., 2004; Bruchim *et al*., 2006) It may result from exposure to environmental heat stress (classic heatstroke) or to strenuous physical exercise (exertional heatstroke) and is characterized by body core temperatures of >40°C in man and >41°C in the dog, and by central nervous system (CNS) dysfunction (Shapiro and Seidman, 1990; Drobatz and Macintire, 1996; Eshel *et al*, 2001; Bouchama and Knochel, 2002; Flournoy *et al*, 2003; Bosak, 2004; Johnson *et al*., 2006).

During hyperthermia, endotoxaemia and activation of the coagulation cascade may culminate in disseminated intravascular coagulation (DIC) and multi-organ dysfunction (MOD), the organs most commonly affected being the brain, kidney, liver, heart and skeletal muscle (Chao *et al*., 1981; Johnson, 1982; Bouchama *et al*, 1991, 1996; Ruslander, 1992; Hiss *et al*., 1994; Drobatz and Macintire, 1996; Hammami *et al*, 1997, 1998; Diehl *et al*, 2000; Bouchama and Knochel, 2002; Oglesbee *et al*, 2002; Flournoy *et al*, 2003; Bosak, 2004; Lu *et al*, 2004, Bruchim *et al*., 2006). The main post-mortem manifestations include (1) diffuse haemorrhagic diathesis, manifested by purpura, melena and bloody diarrhea, (2) pulmonary, renal and myocardial bleeding, and (3) CNS haemorrhages, which may result in death (Drobatz and Macintire, 1996; Bosak, 2004; Bruchim *et al*, 2006). Acute tubular necrosis, icterus and pancreatitis have also been reported (Bruchim *et al*, 2006). Several reports have described the post-mortem changes in dogs with experimentally produced hyperthermia, (Shapiro *et al*. ,1973; Oglesbee *et al*, 1999, 2002; Diehl *et al*., 2000), but descriptions of such changes in natural cases are limited (Eshel *et al*, 2001; Bosak, 2004).

The purpose of the present report is to describe the gross and microscopical changes seen *post mortem* in 11 dogs with naturally occurring fatal heatstroke.

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Materials and Methods

Cases

The dogs selected for this study (Table 1) consisted of 11 previously healthy animals admitted to the Hebrew University Veterinary Teaching Hospital during the summer of 2005. The diagnosis of heatstroke was made on the basis of typical history (exposure to a hot humid environment or to strenuous activity, or both) and typical clinical signs (acute collapse, CNS dysfunction and tachypnoea). Eight dogs had been cooled by their owners, and at the time of admission 10 showed bloody diarrhoea. After admission to hospital, clinical laboratory tests were carried out (Table 1), DIC being diagnosed *ante mortem* in five animals. DIC was diagnosed on the basis of thrombocytopenia (<150,000/μl) and at least two of the following: prolongation (>25%) of the prothrombin time (PT) or activated partial thromboplastin time (aPTT), and clinical or post-mortem signs compatible with DIC (petechiae, ecchymoses, haematochezia, haematemesis, of haematuria). Death occurred either naturally (10 cases) or as the result of euthanasia (one case). The median hospitalization period was 12 h (range 2–24 h).

Procedures

The dogs were subjected to necropsy within 24 h of death. All organs were examined for gross lesions and, when such lesions were recorded, appropriate samples were obtained for histopathology. In addition, samples for histopathology were routinely obtained from the skin, lungs, heart, small and large intestine, liver, spleen, kidneys, brain and bone marrow. The tissues were fixed in 4% formalin and embedded in paraffin wax, and sections (3–4 μm) were stained with haematoxylin and eosin (HE).

Results

Pathological Findings

The small intestine (two dogs), liver (one dog) and the large intestine (one dog) were not examined, due to autolysis. The bone marrow was examined in eight dogs. Gross dermatological lesions, observed in eight of the 11 dogs, included multifocal petechiae and ecchymoses, combined with moderate to severe dermal hyperaemia and oedema; these changes were confirmed microscopically (Tables 2 and 3).

All dogs showed mild to severe diffuse pulmonary oedema and hyperaemia. The lungs were heavy, and large volumes of frothy exudate were present in the trachea and bronchi but not in the nasal cavity. Pleural blood-stained effusion was present in two dogs (Table 2). Microscopically, the lungs showed mild to severe diffuse interstitial hyperaemia and alveolar oedema, and multiple, diffuse, moderate to severe haemorrhages (Table 3). Mild to severe multifocal to coalescing subendocardial, myocardial and epicardial haemorrhages were observed in all dogs, both grossly (Fig. 1; Table 2) and microscopically (Table 3). Haemopericard was noted in three animals (Table 2).

Severe, diffuse haemorrhages were present on the visceral and parietal peritoneum, including the

Table 1
Details of 11 dogs with heatstroke, including clinical findings on admission to hospital

Dog no.	*Age (years)*	*Breed*	*Body weight (kg)*	*Type of heat-stroke*	*Interval (h) between heat insult and*		*Body temperature (°C)*	*Neurological status*	*Creatinine (mg/dl)**	*PT†/aPTT‡ (sec)*	*Platelets (10^9/litre)§*	*nRBC (10^3/μl)*
					admission	*death*						
1	3	Golden retriever	40	En	7	23.8	38.5	Coma	3.69	11.0/30.0	63	1.97
2	1	Shar-pei	15	Ex	2	26	37	Semicoma	1.84	11.6/26.2	203	0.74
3	8.5	Mixed	12	Ex	5	29	36.5	Stupor	0.93	13.0/70.0	148	1.51
4	9	Staffordshire bull terrier	15	Ex	6	30	37.3	Semicoma	2.08	21.0/34.0	187	5.47
5	4.4	Great Dane	60	En	4	6.4	37	Coma	NA	NA	56	3.87
6	6	Belgian malanios	43	En	1	13	41.5	Coma	1.74	9.4/17.9	24	0.62
7	5	Dogue de Bordeaux	57	Ex	6	18	37	Coma	0.9	13.8/24.4	231	0.85
8	3	Dogue de Bordeaux	55	Ex	1	7	NA	Stupor	0.5	NA	31	3.48
9	4	Dogue de Bordeaux	60	En	1	13	42.5	Coma	1.28	7.3/17.3	209	3.65
10	5	Mixed	NA	En	2	4.4	NA	Semicoma	1.1	9.2/21.4	116	3.13
11	0.6	Labrador retriever	30	Ex	6	10.8	40.1	Semicoma	2.08	10.3/27.7	377	11.14

PT, prothrombin time; aPIT, activated partial thromboplastin time; En, environmental; Ex, exertional; NA, not available.
*Reference interval: 0.5–1.5 mg/dl.
†Reference interval: 6.0–8.5.
‡Reference interval: 11.0–17.4.
§Reference interval: 150–500×10^9/litre.

Table 2
Gross pathological findings in 11 dogs with heastroke

Organ	*Lesions*	*Gross changes in dog no.*										
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Skin	Hyperaemia, oedema, haemorrhages	+ +	+ + +	0	+ +	+ +	0	+ +	+	+ + +	+ + +	0
Thorax	Pleural effusion	0	0	0	0	0	0	0	+ +	0	+	0
Lungs	Hyperaemia, oedema, haemorrhages	+	+	+ +	+ +	+ + +	+ +	+	+ +	+ +	+ +	+ +
Pericardium	Haemopericard	+	0	0	0	0	0	0	+ +	0	+	0
Heart	Epi- endo- and myocardial haemorrhages	+ + +	+ +	+	+ +	+ + +	+ +	+ + +	+ + +	+ +	+ +	+ +
Abdomen	Peritoneal effusion	0	+ +	0	0	0	0	+ +	0	NA	+ +	0
Mesentery/ peritoneum	Hyperaemia, haemorrhages	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +	+ +
Gastrointestinal tract	Hyperaemia, melena, haemorrhages	Aut	+ + +	Aut	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Spleen	Splenomegaly, congestion	+ +	+	+	+ +	0	+ +	+ +	+ +	+ +	+ + +	+
Kidney	Swelling, hyperaemia	0	+	+ +	0	+ +	+ +	+	+ + +	+ +	+	0
Urinary bladder	Hyperaemia, haemorrhages	+	0	0	+ + +	0	0	0	0	0	0	0
Liver	Hepatomegaly	+	+ +	+ +	+	+ +	+ +	+ +	+ + +	+ +	+ +	Aut
Brain	Oedema, hyperaemia, haemorrhages	+	0	+	+ + +	+ +	+ +	+ +	+	+ +	+	0
Bone marrow	Hyperaemia, oedema, haemorrhages	0	0	+ +	+ +	0	0	0	0	0	0	0

0, No change; +, mild change, + +, moderate changes; + + +, severe changes, Aut, not examined due to autolysis; NA, data not available.

mesentery, in all dogs, and in three animals a serosanguineous intraperitoneal effusion was noted. Severe "paint brush" haemorrhages were present in the serosal, muscular and submucosal layers throughout the gastrointestinal tract in all dogs (Fig. 2), and free blood was present in the small intestinal lumen of two dogs (Table 2). Microscopical lesions in the small intestine and colon of nine dogs consisted of

Table 3
Histopathological findings in 11 dogs with heatstroke

Organ	*Lesions*	*Histopathological changes in dog no.*										
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Skin	Hyperaemia, oedema, haemorrhages	+	+	0	+	+ +	0	+ +	+	+ +	+ +	0
Lungs	Hyperaemia, oedema, haemorrhages	+ +	+	+ +	+ + +	+ +	+ + +	+ + +	+ + +	+ + +	+ +	+ +
Heart	Epi-, endo-, and myocardial haemorrhages	+	+ +	+	+ + +	+ + +	+ +	+ + +	+ + + AS	+ + +	+	+
Small intestine	Transmural haemorrhages	Aut	+ + +	Aut	+ + +	+ + +	+ + +	+ + +	+ +	+ + +	0	+ + +
	Mucosal necrosis	Aut	+ + +	Aut	+	+ + +	+ +	+ + +	0	+ + +	0	+ + +
Large intestine	Transmural haemorrhages	+ + +	+ +	+ +	+ + +	+ + +	Aut	+ + +	+ +	+ + +	0	+ + +
	Mucosal necrosis	+ + +	+ +	0	+	+ + +	Aut	+ + +	+	+ + +	0	+ + +
Spleen	Red pulp congestion	+ + +	+ +	0	+ + +	+ +	+ + +	+ + +	+ +	+ + +	+ + +	+ + +
Kidney	Interstitial haemorrhages,	+ + +	+ +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +
	Tubular necrosis	+ +	0	MPG	+	+ +	+ +	+ +	+ + +	+ + +	+	+ +
Liver	Acute congestion,	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +	+ + +	+ + +	0	Aut
	Hepatocyte necrosis	0	+	+ +	+ +	+	0	+	+	+ +	0	Aut
Brain	Meningeal oedema, hyperaemia,	+ + +	+ +	+ +	+ + +	+ +	+	+ + +	+ + +	+ + +	+ +	+ +
	Neuronal necrosis	0	0	0	+ +	0	0	+ +	0	+	0	+
Bone marrow	Hyperemia, oedema, haemorrhages	0	0	0	0	0	0	0	0	0	+	0

0—No change; +, mild changes; + +, moderate changes; + + +, severe changes; Aut, not examined due to autolysis; AS, aortic stenosis; MPG, membranoproliferative glomerulonephritis.

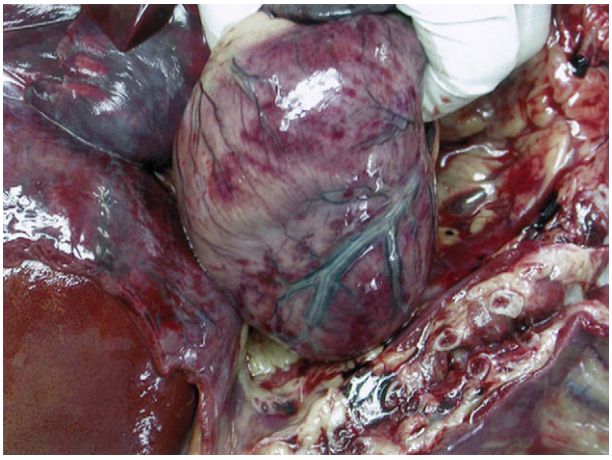


Fig. 1. Dog 8. Gross cardiac lesions, including severe multifocal subendocardial haemorrhages.

severe transmural congestion and haemorrhages, with marked separation of all layers in eight of them (Fig. 3; Table 3) and mild to severe necrosis of the small and large intestinal mucosal epithelium (seven and eight dogs, respectively). Moderate splenomegaly was present in all dogs, associated microscopically with moderate to severe splenic red pulp congestion (Tables 2 and 3). Hepatomegaly was also noted in all dogs, associated microscopically (in nine dogs) with acute, severe congestion (Tables 2 and 3). Dilated sinusoids compressed the adjacent hepatocytes, resulting in mild to moderate hepatic parenchymal necrosis (seven dogs; Table 3).

Renal abnormalities included mild to severe bilateral renal swelling in eight dogs and subcapsular haemorrhages in two (Table 2). Microscopically, all kidneys showed lesions, including moderate to severe interstitial and glomerular congestion, interstitial haemorrhages and mild to severe tubular degeneration and necrosis (Table 3; Fig. 4). Tubular necrosis was detected both in the proximal and the distal convoluted renal tubules. Urinary bladder mucosal haemorrhages were present in two dogs.

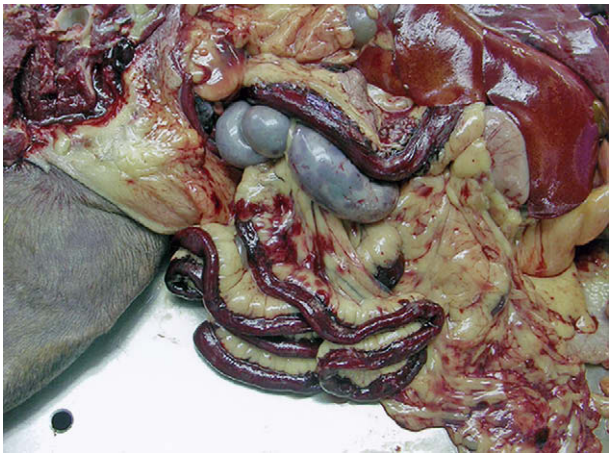


Fig. 2. Dog 8. Gross abdominal and small intestinal lesions, including severe serosal and mesenteric, multifocal to coalescing, haemorrhages, and generalized jaundice.

Grossly, meningeal and brain parenchymal hyperaemia and oedema were present in nine dogs (Fig. 5; Table 2). Brain samples for histology included cerebellum, medulla oblongata, brainstem, hippocampus and cerebral cortex. Histopathologically, the brain parenchyma and meninges showed mild to severe oedema and hyperaemia in all sampled areas (11 dogs) and acute, mild to moderate, neuronal necrosis was detected in the hippocampus (four dogs, Table 3). Moderate bone marrow hyperaemia and haemorrhages were observed grossly in one dog, and in one additional dog, mild bone marrow haemorrhages were noted microscopically.

In all affected organs, microscopical examination of the haemorrhagic lesions revealed mild to moderate fibrinoid thrombosis of the adjacent microvasculature. Additional findings, considered incidental, included subvalvular aortic stenosis, membranoproliferative glomerulonephritis, and mild histiocytic meningitis (one dog each).

Discussion

The most commonly observed lesions in this study of natural cases of canine heatstroke were hyperaemia, oedema, haemorrhages and necrosis in various organs. Similar observations were reported in other studies of canine heatstroke (Drobatz and Macintire, 1996; Bosak, 2004; Bruchim *et al*, 2006).

During strenuous exercise or hyperthermia, blood shifts from the mesenteric circulation to the working muscles and skin, to meet tissue oxygen demands and facilitate heat dissipation; this results in intestinal ischaemia, hypoxia and hyperpermeability (Hall *et al*., 1999, 2001). The marked changes observed in the gastrointestinal tract of all dogs examined illustrate its sensitivity to hyperthermia, shock and hypoperfusion, and are probably associated with the characteristic gelatinous and bloody diarrhoea often observed in canine heatstroke patients. The injured tissue generates highly reactive oxygen and nitrogen species and inflammatory cytokines; these aggravate intestinal mucosal injury, resulting in necrosis (Hall *et al*, 1994, 1999, 2001). Such factors, together with endotoxaemia, hypoperfusion, ischaemia and activated neutrophils, contribute to the diffuse endothelial lesions observed in various tissues, including the endocardium, epicardium, and pulmonary interstitial capillaries. Endothelial injury may lead to

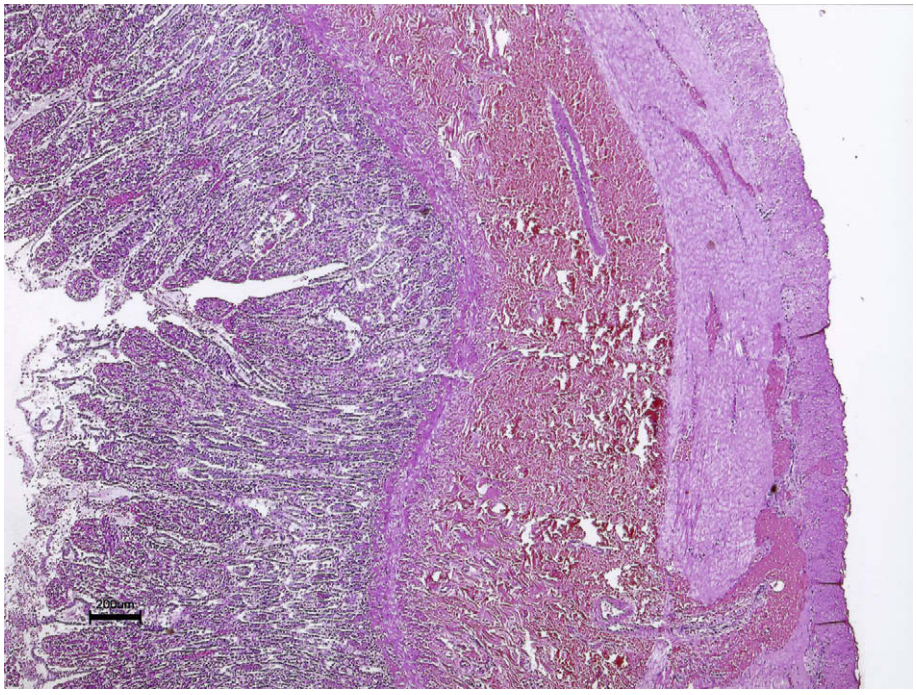


Fig 3. Dog 8. Microscopical small intestinal lesions, including severe multifocal to coalescing transmural haemorrhages and separation of the intestinal layers. HE. Bar 200 μm.

increased permeability and consequently to oedema, a mechanism similar to that described in sepsis (Russell, 2006). Endothelial injury may also result in tissue thromboplastin and factor XII release, with consequent activation of the coagulation and complement cascades. These in turn lead to systemic inflammatory response syndrome (SIRS) and widespread coagulation and bleeding, culminating in DIC (Bouchama *et al*., 1996; Bouchama and Knochel, 2002; Reiniker and Mann, 2002; Esmon, 2003; Bruchim *et al*., in press). Both the increased endothelial permeability and the DIC were probably mainly responsible for the pulmonary oedema, hyperaemia and haemorrhages present in the cases examined, resulting in acute respiratory distress syndrome (ARDS), followed by respiratory failure, as has often been observed in heatstroke (Abdullah and el-Kassimi, 1992; Flournoy *et al*, 2003; Bruchim *et al*, 2006).

DIC was diagnosed *ante mortem* in only five of the 11 cases. However, the invariable detection of diffuse, multiple haemorrhages and microthrombosis in all dogs at post-mortem examination suggests that DIC had occurred in all of them. Failure to diagnose DIC *ante mortem* may have been due to the short interval between admission and death or to the limited number of relevant factors (e.g., PT, aPTT, platelet count, and clinical signs of bleeding) taken into account. Additional clinicopathological factors (e.g., fibrin and fibrinogen degradation products, D-dimer, activated protein-C and antithrombin) might have improved ante-mortem diagnosis of DIC.

Time is of crucial importance in the treatment and prognosis of heatstroke patients (Bruchim *et al*, 2006). The median time lag between the heat insult and admission in the present study was only 4 h and, moreover, most dogs were cooled by the owners before presentation at the hospital. However, the median

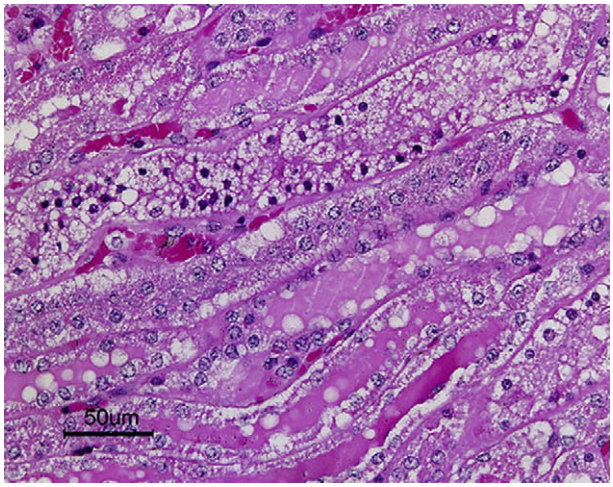


Fig. 4. Dog 8. Microscopical renal lesions, including various stages of degeneration and necrosis of the tubules. HE. Bar, 50 μm.

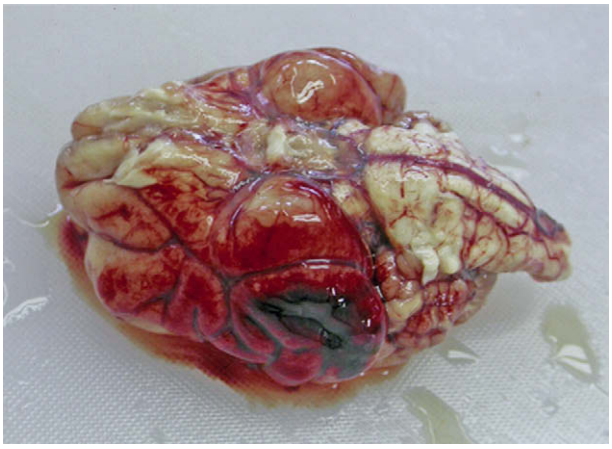


Fig. 5. Dog 4. Gross brain lesions, including focal extensive haemorrhage in the left hemisphere.

time interval between the heat insult and death was 13 h. Experimentally induced hyperthermia studies in monkeys showed that tissue injury progressed even after normothermia was regained (Eshel *et al.*, 2001). The relatively long interval (6.4–30 h) between heat insult and death in 10 of 11 dogs, may have accounted for the severity of the multiple organ lesions detected *post mortem* in these animals. In one animal (dog 10), a particularly short interval (4.4 h) was associated with relatively minor microscopical post-mortem lesions.

During the initial stages of hyperthermia, the cardiac output increases and vascular resistance decreases. Normally, low systemic vascular resistance results in peripheral vasoconstriction (Flournoy *et al.*, 2003). However, during extreme hyperthermia, such vasoconstriction is prevented by the hypothalamic sympathetic centre. This results in cutaneous and splanchnic vasodilatation, with consequent venous blood pooling (Wills *et al.*, 1976; Kregel *et al.*, 1988; Gagnon *et al.*, 1999). This mechanism was probably the main factor responsible for the splenic red pulp congestion, hepatic sinusoid congestion and periacinar necrosis noted in most dogs in this study. Such accumulation of blood in these organs is probably a major contributor to the hypovolaemia recorded in many heatstroke patients.

Direct renal thermal injury, hypoxia, hypovolaemia (with consequent reduced glomerular filtration), coagulative necrosis, endotoxaemia, and local and systemic release of cytokines and vasoactive mediators may contribute to the renal swelling, tubular degeneration and necrosis invariably observed (Lin *et al.*, 2003). A previous study (Bruchim *et al.*, 2006) showed that the serum creatinine concentration 24 h after admission and following aggressive fluid therapy was significantly associated with prognosis, while its concentration on admission was not. In the present study, most of the dogs did not survive long enough for the biochemical manifestations of renal failure to be detected. The renal lesions observed suggested that injury to the kidney is common in canine heatstroke, regardless of an apparently normal creatinine concentration on admission.

Cardiac arrhythmias are common in heatstroke (Drobatz and Macintire, 1996; Shahid *et al.*, 1999; Bruchim *et al.*, 2006; Mellor *et al.*, 2006). Possible contributory factors include myocardial hypoperfusion, lactic acidosis and electrolyte imbalance (Knight and Allen, 1997; Flournoy *et al.*, 2003) and direct thermal injury. In the present study, mild to severe subendocardial, myocardial and epicardial haemorrhages and hyperaemia were present in all the dogs. These findings suggest that DIC plays a role in the pathogenesis of cardiac arrhythmias. In a suspected case of naturally occurring canine exertional heatstroke, presence of myocardial damage was supported by an increased concentration of serum cardiac troponin I, a leakage biomarker of myocardial damage (Mellor *et al.*, 2006).

Heatstroke is characterized by two components, namely (1) elevated core temperature, and (2) CNS abnormalities and dysfunction (Bouchama and Knochel, 2002; Flournoy *et al.*, 2003; Bosak, 2004). All the dogs in the present study showed clinical CNS abnormalities on admission, and post-mortem examination revealed CNS lesions, including meningeal and brain oedema, severe hyperaemia and occasional neuronal necrosis. It should be noted that mild histiocytic meningitis, recorded in one dog, was probably a pre-existing lesion as it could not have developed in the short interval between heat insult and death.

The CNS lesions were probably not the main cause of death. This statement is supported by previous findings that (1) the canine brain is resistant to sublethal hyperthermia (Oglesbee *et al.*, 2002), and (2) cerebral derangement observed during and after experimentally induced hyperthermia in monkeys was reversible (Eshel and Safar, 2002). The post-mortem lesions found in the present study suggest that systemic haemodynamic deterioration and pulmonary changes are the main causes of death in canine heatstroke. Brain injury and diffuse oedema, if they affected the hypothalamic vasomotor centre, may have played a role in the pathogenesis of circulatory abnormalities.

Metarubricytosis has been reported frequently in canine heatstroke patients (Drobatz and Macintire, 1996; Bruchim *et al*, 2006) and attributed to thermal lesions within the bone marrow, leading to injury of the blood — bone marrow barrier and subsequent release of nucleated red blood cells (nRBC) into the

peripheral circulation (Drobatz and Macintire, 1996). Examination of the bone marrow in this study failed to reveal disruption of its architecture, suggesting that if injury of the blood — bone marrow barrier occurred, light microscopy may not have been sensitive enough to detect it. An alternative hypothesis is that the bone marrow nRBC release is mediated by cytokines produced during SIRS. Both of these hypotheses warrant further investigation.

The results of this study may aid pathologists in the diagnosis of heatstroke when the history is obscure and the disease course is unclear. Clinicians should bear in mind that DIC plays a major role in the pathogenesis of heatstroke and therefore multiple tests for its early diagnosis are warranted. Close monitoring of cardiac, pulmonary, renal and hepatic functions are necessary. Because impairment of renal function is often observed only several hours after the thermal insult, early therapeutic renal support is crucial in heatstroke treatment. Even when digestive system abnormalities are not apparent on admission, support for this system and preventive treatment for endotoxaemia are important. Splenic and hepatic blood pooling should be borne in mind in evaluating the haemodynamic status of the patient and prescribing treatment.

In conclusion, naturally occurring, fatal, canine heatstroke often induces acute multiple organ lesions affecting most body systems, and thus resembles sepsis in many ways. The exact sequence of events leading to these lesions has been only partly explored (Oglesbee *et al*., 1999, 2002; Diehl *et al*., 2000; Eshel *et al*., 2001; Eshel and Safar, 2002). These events result in increased endothelial permeability, oedema, DIC and SIRS, which probably lead to MOD. The similarity seen between the post-mortem manifestations of heatstroke and those described in other systemic syndromes (e.g., septic shock and gut reperfusion syndrome) support the notion that the pathogenesis of heatstroke includes hyperthermia-induced endotoxaemia, inflammatory response syndrome and sepsis. To verify this, further studies should include cytokine and endotoxin assays, as well as bacterial culture of the blood and internal organs.

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