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Hemostatic Changes in Dogs with Naturally Occurring Sepsis

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Sepsis is a frequent source of morbidity and mortality in critically ill patients. The goal of this case control study was to measure hemostatic changes in dogs with naturally occurring sepsis. Blood was collected within 24 hours of admission from 20 dogs that fulfilled the criteria for sepsis. Sepsis was defined as histologic or microbiological confirmation of infection and 2 or more of the following criteria: hypo- or hyperthermia, tachycardia, tachypnea, or leukopenia, leukocytosis, or >3% bands. Culture and sensitivities were performed on appropriate samples from all septic dogs. Twenty-eight control dogs were enrolled on the basis of normal results of physical examination, CBC, serum biochemistry, and coagulation profile. Plasma samples were analyzed for prothrombin time (PT), partial thromboplastin time (PTT), fibrin(ogen) degradation products (FDP), D-dimer (DD) concentrations, antithrombin (AT) activity, and protein C (PC) activity. Data were compared between groups by chi-square or independent *t*-tests. PC ($P < .001$) and AT ($P < .001$) activities were significantly lower in dogs with sepsis compared to controls. Dogs with sepsis had significantly higher PT ($P = .007$), PTT ($P = .005$), D-dimer ($P = .005$), and FDP ($P = .001$) compared to controls. Platelet counts were not significantly different between groups. Ten of the 20 septic dogs (50%) died, but no association was identified between any of the measured variables and outcome. These findings are consistent with previous studies in animals with experimentally induced disease and in clinical studies of humans. On the basis of these results, further investigation of the role of AT and PC in canine sepsis is warranted.

Key words: Antithrombin; Dogs; Hemostasis; Infection; Protein C.

Sepsis is a systemic response to infection that is associated with substantial morbidity and mortality in both humans and animals. Common naturally occurring conditions that predispose dogs to sepsis include peritonitis, pancreatitis, pneumonia, pyometra, prostatitis, and wound infections. Despite therapy with surgery, antibiotics, and cardiovascular support, the mortality for both humans and dogs with sepsis remains high.[1–4] Studies of dogs with sepsis have reported 20–68% survival.[5–8] Clinical studies in people and experimental models of sepsis continue to define the hemostatic and inflammatory changes that ultimately lead to disseminated intravascular coagulation (DIC), multiorgan dysfunction, and death.[9–12] Sepsis also is a common clinical entity in dogs. However, the hemostatic and inflammatory changes associated with naturally occurring sepsis in dogs have not been defined.

Sepsis is associated with the development of a procoagulant state. The release of inflammatory cytokines and expression of tissue factor results in stimulation of the coagulation cascade, down-regulation of the fibrinolytic system, and reduction in endogenous anticoagulants.[9,13,14] Antithrombin (AT) and protein C (PC) are the 2 most important endogenous anticoagulants that regulate the occurrence of thrombosis. Studies have documented changes in AT and PC in septic human patients.[15–23] In addition to decreased AT concentrations in these patients, initial AT concentrations have been shown to predict mortality.[9,10,16,18,24] Activation and ultimate consumption of PC also have been documented in sepsis.[18–21,23] In a canine model of DIC, PC concentrations decreased after injection of endotoxin.[25] Reduced PC activity has been correlated with mortality in human patients with sepsis,[9,16,21–23,26] and a recent clinical trial has revealed that administration of recombinant human activated PC reduced mortality in human patients with severe sepsis.[27]

Several veterinary studies have examined these fibrinolytic and anticoagulant proteins in naturally occurring disease states such as DIC,[28] nephrotic syndrome,[29] and severe gastrointestinal disease associated with canine parvovirus.[30] In a study of horses describing changes in hemostatic and fibrinolytic indices in septic foals, PC and AT were significantly lower in septic foals compared to healthy controls. No relationship was found between survival and hemostatic abnormalities, but a trend was noted for increased mortality in foals with reduced PC activity.[31] In a study of canine parvoviral enteritis, affected dogs had decreased AT activity and thromboelastograph findings supportive of hypercoagulability.[30] It is likely that PC and AT are altered in dogs with naturally occurring sepsis as they are in human septic patients. Early identification of affected dogs ultimately could help direct therapeutic measures or predict outcome. The purpose of the present study was to determine whether concentrations of PC and AT are altered in septic dogs compared to healthy controls.

Materials and Methods

All dogs admitted to the Intensive Care Unit of the Tufts University Foster Hospital for Small Animals between September 2000 and December 2001 that fulfilled the criteria for sepsis within 24 h of admission were considered eligible for the study. All dogs that received anticoagulant therapy or blood products before blood sampling were excluded from the study. Animals were classified as septic if histologic or microbiological confirmation of infection was available and if 2 of the following criteria were met: hypo- or hyperthermia (<37.8°C or >39.4°C), tachycardia (heart rate >140 bpm), tachypnea (respiratory rate >20 breaths/min), and leukopenia (<6,000 cells/μL), leukocytosis (>16,000 cells/μL), or >3% bands.[32] Aerobic or anaerobic bac-

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Table 1. Distribution of septic foci in dogs with sepsis.

System	%	Disease
Abdominal	35	Intestinal perforation with septic peritonitis (n = 4)
		Necrotizing pancreatitis with septic peritonitis (n = 1)
		Traumatic splenic infarct and necrosis with septic peritonitis (n = 1)
		Ulcerated intestinal mass with septic peritonitis (n = 1)
Reproductive	25	Pyometra (n = 4)
		Retained fetus with bacterial metritis (n = 1)
Respiratory	20	Pneumonia (n = 3)
		Pyothorax (n = 1)
Urinary	10	Ulcerative cystitis (n = 1)
		Transitional cell carcinoma with necrosis and cystitis (n = 1)
Other	10	Septic arthritis (n = 1)
		Muscle ischemia with abscessation (n = 1)

terial cultures and sensitivities were performed on appropriate samples from all septic dogs. Dogs that fulfilled the criteria for sepsis were subdivided into 2 groups for the purpose of analysis: dogs that had DIC and those that did not. Dogs were considered to have DIC if thrombocytopenia was present (<179,000 cells/μL) and if at least 2 of the following criteria were met: at least 25% prolongation in prothrombin time (PT) or partial thromboplastin time (PTT), reduced AT activity, abnormally high fibrin(ogen) degradation products (FDP) concentration, or evidence of red blood cell fragmentation (eg, schistocytes, acanthocytes).[33] The selection of healthy control dogs was based on normal physical examination and lack of abnormalities on a CBC, serum biochemistry, PT, and PTT. The study protocol was approved by the Tufts University Institutional Animal Care and Use Committee.

After written owner consent, jugular venipuncture was performed and 13 mL of whole blood was obtained from each dog. Serum and whole blood anticoagulated with ethylenediaminetetraacetic acid (EDTA) were used for serum biochemistry profile and CBC, respectively. Citrated plasma (1 part 3.8% citrate: 9 parts blood) samples were collected for PT, PTT, FDP, and D-dimer (DD) concentrations and for AT and PC activities. Blood for CBC, serum biochemistry, platelet count, PT, and PTT immediately were submitted to the clinical laboratory of Tufts University School of Veterinary Medicine for analysis. Remaining blood was centrifuged within 30 minutes of collection and separated, and plasma was stored frozen at −70°C until analysis. Every 2 months, citrated plasma samples were batched and sent to Cornell University Diagnostic Laboratory where assays for PC, AT, DD, and FDP were performed.

PC and AT activities were measured by functional chromogenic assays. PC activity was measured by colorimetry with a commercial chromogenic substrate kit.[a] In this assay system, PC in test plasma is activated by a snake venom derivative, and the amidolytic activity of the activated PC is detected by its cleavage of a synthetic chromogenic substrate.[34] The reference range for PC activity in dogs by this method (75–135%) was determined by assay of plasma from 30 clinically healthy dogs (18 female, 12 male; 6 months to 10 years of age). We found dilutional agreement and a dynamic linear range of the assay from 0 to 100% plasma PC activity. The intra-assay and interassay coefficients of variation (n = 12 determinations) for this assay were 2.9 and 6.9%, respectively. With the use of this assay, the PC activities of 6 dogs having hemorrhagic diatheses caused by vitamin K deficiency after anticoagulant rodenticide ingestion all were <5% (range, 0–4%), and activities of dogs congenitally deficient in Factors VII, VIII, and IX all were within reference range. Antithrombin activity was measured by use of a colorimetric method and chromogenic substrate kit as described previously.[30,35,b] The standard curve for determination of patient and control dog PC and AT activities was derived from serial dilutions of a pooled, normal canine reference plasma (prepared from 15 normal healthy dogs) having an assigned value of 100% activity. DD[c] and FDP[d] concentrations were measured according to manufacturers' directions in semiquantitative latex agglutination assays as described previously.[33,36]

PC, AT, DD, FDP, CBC, and serum biochemistry data were analyzed by independent *t*-tests. Pearson correlation analysis was used to test for correlations between these parameters. Comparisons of PC, AT, DD, and FDP were made between septic dogs with DIC and without DIC and between dogs that survived to hospital discharge and dogs that died by independent *t*-tests. $P < 0.05$ was considered significant. Data were analyzed by commercial statistical software.[e]

Results

Twenty dogs with sepsis and 28 control dogs were enrolled in the study. Eighteen of the 20 dogs in the septic group were purebred with Labrador Retrievers (n = 3), German Shepherd dogs (n = 3), and Golden Retrievers (n = 2) represented most frequently. There were 16 female dogs and 4 male dogs in the septic group, which differed significantly from normal dogs, of which 14 were female and 14 were male ($P = .03$). There was no difference in age between the 2 groups (mean 6.02 ± 3.98 years for septic dogs versus 7.45 ± 3.69 years for normal dogs, $P = .15$). Heart rate was significantly higher in septic dogs than in controls (158.5 bpm ± 37.3 for septic dogs versus 102.8 bpm ± 15.1 for controls; $P < .001$). Similarly, septic dogs had higher respiratory rates compared to control dogs (60 breaths/min, range 24–100, for septic dogs versus 20 breaths/min, range 12–32, for control dogs; $P < .001$). Rectal temperature and white blood cell count did not differ between groups. The mean rectal temperature for septic dogs was 39.2°C ± 1.5 versus 38.5°C ± 0.4 for controls ($P = .111$), and the median white blood cell count for septic dogs was 13,350 cells/μL (range 900–70,300) compared to 7,600 cells/μL (range 4,900–10,400) for controls ($P = .288$).

The distribution of septic foci is summarized in Table 1. The most common sources included abdominal (n = 7; 35%), reproductive (n = 5; 25%), respiratory (n = 4; 20%), and urinary (n = 2; 10%). Other sources included septic arthritis (n = 1) and muscle ischemia secondary to an arterial thromboembolism (n = 1).

Five of the 20 septic dogs (25%) fulfilled the criteria for DIC. Two dogs had an abdominal source of sepsis (1 dog with a perforated intestinal foreign body and another with necrotizing pancreatitis), 2 dogs had pyometra, and 1 dog

Table 2. Aerobic and anaerobic culture results listed according to body system in 20 dogs with sepsis. The number of dogs affected with each organism is listed in parentheses.

	No. of Dogs	Gram Positive	Gram Negative	Anaerobic
Abdominal	7	Coag neg staph (1) *Enterococcus* (2) β-hemolytic strep (1)	*E. coli* (6) *Klebsiella* (1)	
Reproductive	5	Group G strep (1) *Enterococcus* (2) β-hemolytic strep (2)	*E. coli* (3) *Klebsiella* (1)	
Respiratory	4	β-hemolytic strep (2)	*E. coli* (2)	*Fusobacterium* (1) *Clostridium* (1)
Urinary	2	β-hemolytic strep (1)	*E. coli* (1) *Acinetobacter* (1)	
Septic arthritis	1	β-hemolytic strep (1)		
Muscle	1	β-hemolytic strep (1)	*E. coli* (1) *Enterobacter* (1)	

had a retained necrotic fetus. Three of these dogs survived to hospital discharge, and 2 dogs died during hospitalization.

Positive culture results were obtained from all dogs with sepsis. Aerobic culture and sensitivities were performed on all 20 septic dogs and were positive in 19 dogs (Table 2). The only dog that had a negative aerobic culture result grew an anaerobic organism. Thirteen of the 20 septic dogs (65%) had anaerobic cultures performed, of which 1 was positive in a dog with pyothorax. Of the 19 dogs with aerobic infections, 7 dogs (37%) had pure gram-negative infections, 5 dogs (26%) had pure gram-positive infections, and 7 dogs (37%) had mixed gram-positive and gram-negative infections. Nine of the 20 septic dogs (45%) had multiple organisms isolated. The most common organism isolated was *Escherichia coli* (13 of 20 dogs; 65%). *Streptococcus* was isolated in 8 dogs (β-hemolytic streptococcus, n = 7; Group G streptococcus, n = 1). *Enterococcus* spp. was isolated in 4 dogs.

Results of hemostatic indices are summarized in Table 3. Both PC ($P < .001$) and AT ($P < .001$) activities were significantly lower in septic dogs compared to control dogs (Fig 1). The activities of PC and AT were significantly correlated ($r = .81$, $P < .001$; Fig 2). Septic dogs also had significantly higher FDP ($P < .001$) and DD concentrations ($P = .005$), as well as a longer PT ($P = .005$) and PTT ($P = .007$) compared to control dogs. Platelet counts were not significantly different between groups ($P = .123$). Of the 20 dogs with sepsis, 15 had a high FDP concentration (75%), and 3 of the dogs with high FDP concentration met the criteria for DIC (20%). All 20 septic dogs had low AT activity. Of the 5 dogs that met the criteria for DIC, 2 dogs had prolonged PT and PTT, 2 dogs had normal PT and PTT, and 1 dog had prolonged PTT only. No difference was found in any of the measured variables in dogs with and without DIC. No correlation was found between PC and the type of infection (mixed, pure gram-positive, or pure gram-negative).

Additional information from serum biochemistry results is summarized in Table 4. Mean serum albumin concentration was significantly lower in septic dogs compared to control dogs ($P < .001$), whereas alkaline phosphatase activity ($P < .001$) and total bilirubin ($P = .008$) concentration were significantly higher in septic dogs. No differences in blood glucose ($P = .873$), urea nitrogen ($P = .191$), or creatinine ($P = .901$) concentrations were identified between the 2 groups.

Ten of the 20 dogs (50%) with sepsis died. No relationship was identified between any of the measured variables and outcome.

Table 3. Hemostatic indices of normal dogs and dogs with sepsis (mean ± SD or total number of dogs in each category).

	Septic	Control	*P*
PT (seconds)	7.47 ± 1.59	5.9 ± 0.43	.005
PTT (seconds)	14.04 ± 4.35	10.42 ± 0.64	.007
Platelet count (cells/μL)	210,842 ± 128,166	262,750 ± 73,710	.123
FDP (μg/mL)			<.001
<5	0	15	
5–20	5	11	
>20	15	2	
D-dimer (ng/mL)			.005
<250	3	18	
250–500	7	5	
500–1,000	5	5	
1,000–2,000	1	0	
>2,000	4	0	

PT, prothrombin time; PTT, partial thromboplastin time; FDP, fibrin(ogen) degradation products.

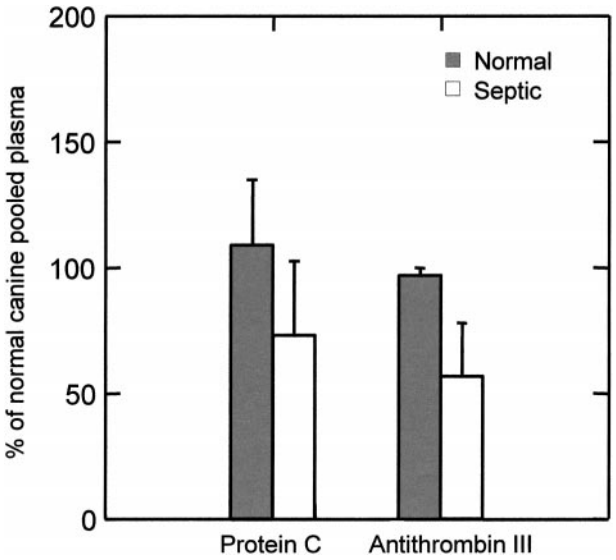

Fig 1. Protein C (shaded bars) and antithrombin (open bars) activities in normal dogs (n = 28) and in dogs with naturally occurring sepsis (n = 20) (mean ± SD).

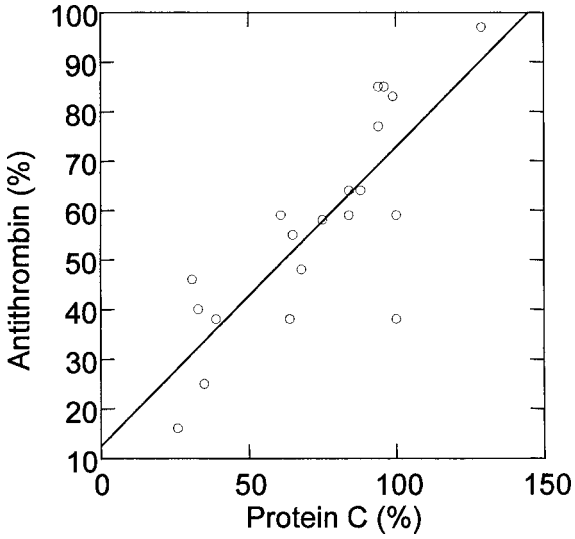

Fig 2. Correlation between protein C and antithrombin in dogs with sepsis (n = 20). Individual dogs are represented by open circles (r = .81, $P < .001$).

Discussion

The results of this study are consistent with previous studies in which the activity of circulating anticoagulant proteins was shown to be decreased in both experimentally induced animal models of sepsis[25] and in clinical studies involving humans with severe sepsis.[15–22] The results of this study demonstrated reduced activity of endogenous anticoagulants in dogs with sepsis and suggests an imbalance of hemostasis with a tendency toward a procoagulant state in affected dogs. The risk of thrombosis is thought to be moderate with AT activity between 50 and 75% and extreme when AT activity falls below 50%.[37] Fifteen out of 20 septic dogs (75%) in this study had AT activity below 75%, and 7 affected dogs (35%) had AT activity below 50%.

No correlation was found between PC or AT activity and survival in the septic dogs. In a study involving only 20 dogs, any statements regarding survival must be made with caution. In 1 study of 48 human patients with sepsis who had serial measurements of anticoagulant proteins, nonsurvivors had lower activities of PC and AT, but neither of these variables was significantly different between groups at admission.[16] The results of the current study document reduced PC and AT activities in dogs with naturally occurring sepsis within 24 hours of admission, but serial measurements of PC and AT would be needed to evaluate the effect of these factors on duration of hospitalization and outcome.

It is difficult to select a uniform patient population in the study of naturally occurring sepsis. The definition of sepsis used in this study is based on evidence of a systemic inflammatory response along with documented infection. In human patients, specific definitions for sepsis, septic shock, and severe sepsis have been established to categorize patients according to the severity of the inflammatory response and to facilitate comparisons among studies.[38] Severity of illness is uniformly assessed in human patients by means of an established scoring system.[39] Such a classification system has not been established for dogs with sepsis, and evaluation of severity of illness still is largely subjective. Although the reduced PC and AT activities documented in this study of dogs with sepsis were significant, defining a subcategory of severe sepsis in dogs would allow more uniform selection of clinical cases, and could highlight important changes that occur in dogs that are most severely affected.

Both FDP and DD concentrations were significantly higher in dogs with sepsis compared to controls, indicating the presence of fibrinolysis. Increased activity of the fibri-

Table 4. Biochemical profile results of normal dogs and dogs with sepsis. Normally distributed data (albumin, glucose) are reported as mean ± SD. Transformed data (alkaline phosphatase, total bilirubin, urea nitrogen, and creatinine) are reported as median (range).

	Septic	Control	P
Albumin (g/dL)	2.5 ± 0.8	3.6 ± 0.2	<.001
Glucose (mg/dL)	97.1 ± 35.9	98.4 ± 11.2	.873
Alkaline phosphatase (U/L)	205 (56–854)	62 (21–282)	.001
Total bilirubin (mg/dL)	0.18 (0.10–1.39)	0.10 (0.10–0.25)	.008
Urea nitrogen (mg/dL)	24 (8–161)	18 (12–158)	.191
Creatinine (mg/dL)	0.9 (0.5–3.4)	1.0 (0.8–1.4)	.901

nolytic system has been associated with DIC. Serial measurements of these markers of fibrinolysis would be helpful to understand the role of fibrinolysis in sepsis in dogs and to evaluate trends as they relate to morbidity and mortality.

No differences in white blood cell or platelet counts were observed between dogs with sepsis and healthy controls. This finding differs from a previous report in which white blood cell count was higher and platelet count lower in septic dogs compared to healthy controls.[32] In the current study, blood samples were drawn at admission and were not uniformly repeated throughout hospitalization. Serial blood sampling beginning at admission and continuing regularly throughout hospitalization would allow documentation of changes in hemostatic indices that occur over time.

The low concentrations of albumin and abnormally high concentrations of alkaline phosphatase and total bilirubin observed in the current study are consistent with findings of previous studies of dogs with sepsis.[5] Hypoalbuminemia might be due to decreased hepatic production, increased capillary permeability, malnutrition, or sequestration. High alkaline phosphatase activity might be due to cholestatic changes that occur during sepsis, and changes in serum total bilirubin concentrations might reflect severe hepatic dysfunction or accompanying hemolysis. Increased total bilirubin concentrations have been documented in a canine model of chronic peritonitis.[40] Additional studies are needed to determine whether changes in these parameters correlate with the severity of disease.

Data from this study showed a reduction in the activity of endogenous anticoagulant proteins in dogs with naturally occurring sepsis, and analysis revealed a significant correlation between PC and AT activity. Additional studies that define the hemostatic and biochemical changes that occur over time are warranted to achieve a better understanding of sepsis and to identify those dogs that are most severely affected.

Footnotes

[a] STAchrom Protein C, American Bioproducts, Parsippany, NJ
[b] STAchrom ATIII, American Bioproducts, Parsippany, NJ
[c] Accuclot D-dimer, Sigma Diagnostics, St Louis, MO
[d] Spli-Prest, Diagnostica Stago, Parsippany NJ
[e] Systat 9.0.1 for Windows, SPSS, Chicago, IL

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