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Concentration of D-dimers in healthy cats and sick cats with and without disseminated intravascular coagulation (DIC)

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The objective of this prospective study was to measure concentrations of D-dimers in 48 cats with various diseases and in 20 healthy cats to evaluate the sensitivity and specificity for D-dimers to diagnose disseminated intravascular coagulation (DIC). The cats were classified as having DIC if an underlying disease and at least three of the following criteria were present: thrombocytopenia, prolonged activated partial thromboplastin time, prothrombin time or thrombin time, schistocytes and/or a reduced antithrombin activity. D-dimer concentrations were measured using a semi-quantitative latex agglutination (LA) test (Accuclot D-Dimer, Sigma Diagnostics). The D-dimer test was positive for 8/12 cats with DIC and for 16/36 sick cats without DIC. D-dimers were negative for all healthy control cats. The comparison of the sick cats with DIC and those without DIC revealed a specificity and sensitivity of the D-dimer test of 56% and 67%; a comparison of the results for healthy cats and cats with DIC revealed a specificity and sensitivity of 100% and 67%, respectively. The D-dimer LA test is only of limited value for the diagnosis of DIC in cats.

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Disseminated intravascular coagulation (DIC) is an acquired syndrome characterised by excessive activation and loss of regulation of coagulation, with subsequent deposition of fibrin throughout the microvasculature.[1] This syndrome occurs due to various underlying diseases and is not related to a particular site.[2] DIC constitutes a dynamic phenomenon in which marked changes in the patient's status and in the results of the coagulation tests occur rapidly and repeatedly during the course of treatment.[3] The International Society of Thrombosis and Haemostasis (ISTH) has proposed a scoring system for human patients with DIC which includes global coagulation parameters and molecular markers.[2] Stokol and Brooks indicated that the development of a DIC scoring system for cats, based on routine test results, seems worthwhile.[1]

D-dimer concentrations have been considered an important criterion for the diagnosis of DIC in humans.[4] D-dimer antigens are released during the breakdown of cross-linked fibrin and their presence in plasma indirectly implies activity of thrombin, clotting factor XIII, plasmin, and thus formation of insoluble fibrin in the vascular system. In human medicine, D-dimer measurements are used for diagnostics of thromboses, early detection of gestational problems and cardiac disorders, prognosis of neoplastic diseases, or DIC.[5–9] An increase in D-dimer concentrations had a high sensitivity (85%) and specificity (97%) for DIC diagnostics in humans.[5] However, D-dimer concentrations may be detected in conjunction with several other conditions, therefore, DIC can only be diagnosed with a combination of coagulation tests.[10] In dogs, increased concentrations of D-dimers were detected in patients with thromboembolic events, hepatopathy, neoplastic, cardiac, or renal disorders, after surgical intervention, and in dogs with haemorrhage. Moreover, D-dimers were also increased in dogs suffering from DIC.[11–14]

In contrast to research relating to humans and dogs, only a few studies are available on DIC diagnostics in cats.[15–17] Occasionally, D-dimer concentrations in cats suffering from various diseases have been reported.[17] However, it is unclear to what extent the determination of D-dimer concentrations can contribute to a diagnosis of DIC in cats. Therefore the objective of this study was to measure D-dimers in sick cats suffering from DIC and in those without DIC as well as in

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healthy cats. Moreover, sensitivity and specificity of D-dimer testing should be established by a comparison of the sick cats with and without DIC and by a comparison of cats with DIC and healthy cats.

Material and methods

Probands

In a prospective study, a coagulation profile of 48 cats suffering from various diseases was established between June 2004 and August 2005. Twenty healthy cats were used as a control group.

Study design

For each cat, a case history was taken and a clinical examination was performed. Blood was taken from the V cephalica antebrachii, V femoralis, or V jugularis. The initial 1–2 ml of blood was put in lithium-heparin tubes for clinical chemistry (Konelab 30i, Thermo Electron GmbH, Dreieich, Germany). Subsequent millilitres of blood were put in ethylenediaminetetraacetic acid (EDTA) tubes for haematological evaluation (Cell-Dyn 3500, Abbott, Wiesbaden, Germany) and in 3.13% sodium citrate tubes for coagulation testing, respectively. Great care was taken to complete the examination of the blood samples, especially the counting of platelets, within 30 min. For all cats, the platelets were counted microscopically using Thrombo Plus-tubes (Sarstedt, Nümbrecht, Germany) and a Neubauer counting chamber. Schistocytes were counted on a blood smear (Pappenheim stain) using the method of Weiss.[18] The average schistocyte count was graded according to the following scheme: 1–2 schistocytes (1+), 3–8 schistocytes (2+), 9–20 schistocytes (3+), >20 schistocytes (4+) per oil immersion field. Directly after the blood withdrawal, the citrated blood was centrifuged, examined at once or portioned and stored at −50°C. The coagulation profile included the activated partial thromboplastin time (aPTT; Pathromtin SL, Dade Behring, Marburg, Germany), prothrombin time (PT; Hepato Quick, Diagnostica Stago, Asnieres, France), thrombin time (TT; Thrombin Reagent, Diagnostica Stago, Asnieres, France), and antithrombin (AT) activity (Technochrom AT modular, Technoclone GmbH, Vienna, Austria). The D-dimer concentrations were determined using a semi-quantitative latex agglutination (LA) test (Accuclot D-Dimer; Sigma Diagnostics, St Louis, USA). This test contains murine monoclonal antibodies against human D-dimers. Concentrations of D-dimers below 250 ng/ml or above 250 ng/ml were considered negative or positive, respectively. The concentrations were determined with undiluted plasma as well as with plasma at dilutions of 1:2, 1:4, and 1:8.

For a diagnosis of DIC, the cat had to suffer from a predisposing disease and to meet at least three of the following criteria: thrombocytopenia, prolonged aPTT, PT or TT, reduced AT activity and/or presence of schistocytes.[15–17] In 9/48 cats, these parameters were also established on day 2 after hospitalisation. A cat was considered suffering from DIC if the DIC criteria were met at least once (on day 1 or day 2). Depending on the underlying disease, numerous additional diagnostic examinations, such as radiography, ultrasonography, and various laboratory and cytological or pathohistological examinations were performed.

Statistics

The data were evaluated using the statistical software SPSS 12.0 for Windows in cooperation with the Institute for Biometrics and Data Processing of the Free University of Berlin. The specificity of the D-dimer test corresponded to the percentage of negative test results among the sick cats, which did not meet the criteria for DIC. The sensitivity corresponded to the percentage of positive test results for sick cats, which met the DIC criteria. In addition, sensitivity and specificity were established by comparing healthy cats and those suffering from DIC. The non-parametric *U*-test according to Mann and Whitney was used to determine significant differences of D-dimer concentrations among sick cats that met the criteria for DIC and those that did not.

Results

Control cats

The 20 healthy control cats were European shorthair cats; their age ranged from 1 to 11 years (median 3). Seven cats were female, two were female-spayed; 10 cats were male, one was male-castrated. They were presented for removal of a bone implant (four), for spaying or castrating (six) and for blood donation (10). All haematological, clinical–chemical and coagulation parameters were within the reference range. All of the cats had negative D-dimer test results.

Cats suffering from various diseases

The 48 sick cats included 36 domestic shorthair cats, four Maine Coon cats, three Persians, three British Shorthair cats, one Carthusian, and one Norwegian Forest Cat. Twenty-five cats were male, 17 of them neutered; 33 cats were female, 13 of them spayed. Their age ranged from 1 to 18 years (median 6.5 years). They suffered from bacterial infections ($n = 15$), viral infections (four), sterile inflammatory diseases (five), neoplasias (12), trauma (five), hypertrophic cardiomyopathy (HCMP) (three), or various diseases (four).

Twelve of 48 sick cats (25%) met the criteria for DIC (Table 1). Abnormalities of their coagulation profile included thrombocytopenia (10/12), prolonged PT (10/12), aPTT (9/12), or TT (9/12), or reduced AT activity (3/12). In five cats blood smear evaluation revealed schistocytes. Seven of these 12 cats suspicious for DIC died or were euthanased, respectively. In four cats a post mortem examination could be performed (approximately 24 h after euthanasia or death). In one cat with feline infectious peritonitis (FIP) the characteristic

Table 1. Diseases, coagulation parameters, schistocytes and D-dimer concentrations in 12 cats with DIC (printed bold = abnormal parameters)

Disease	Platelets (G/l)	PT (s)	aPTT (s)	TT (s)	AT (%)	Schistocytes	D-dimer (ng/ml)
FIP	**129**	**38.3**	**28.0**	**34.0**	98	**2+**	**500–1000**
FIP	**100**	**29.3**	23.4	10.1	**74**	**2+**	**500–1000**
Panleukopenia	**165**	**31.4**	18.0	**21.0**	106	**3+**	<250
Pyothorax	**123**	**28.1**	**41.2**	**28.1**	88	0	<250
Pneumonia	**130**	**30.6**	**37.9**	**24.2**	108	0	**250–500**
Pneumonia	398	**33.1**	23.8	**23.1**	**60**	0	**500–1000**
Pneumonia	**55**	24.0	**27.1**	**25.5**	82	0	<250
Peritonitis	**128**	**36.0**	**41.0**	16.0	80	0	**500–1000**
Lymphadenitis	400	**41.5**	**28.6**	**24.7**	96	**2+**	**1000–2000**
Pancreatitis	**125**	**28.6**	**41.8**	19.0	**79**	0	<250
Nephritis	**99**	**32.8**	**40.1**	**21.6**	82	**1+**	**500–1000**
DKA	**125**	23.3	**29.7**	**22.9**	108	0	**250–500**
Reference ranges	176–499	20.6–27.8	17.0–26.7	10.0–20.0	80–113		<250

FIP = Feline Infectious Peritonitis, DKA = Diabetic ketoacidosis, PT = prothrombin time, aPTT = activated thromboplastin time, TT = thrombin time, AT = antithrombin.

diffuse granulomatous inflammation especially in the liver, gastrointestinal tract, lung and pancreas was detected. Another cat had a sepsis, pneumonia, purulent pleuritis, chronic interstitial nephritis and a HCMP. Another cat revealed signs for septic shock with liver necrosis, congestion of the lung and fibrinous peritonitis. The post mortem examination of the fourth cat revealed an interstitial nephritis, additionally lung oedema, chronic liver congestion with hepatitis, cardiomyopathy, uraemic gastritis and hyperplasia of the parathyroid gland were detected. In three cats the owner declined autopsy, they had pneumonia (two) and FIP. Another five cats suspicious for DIC survived due to intensive supportive therapy, they suffered from pyothorax, panleukopenia, lymphadenitis, pancreatitis, and diabetic ketoacidosis (DKA). One of these cats received a fresh whole blood transfusion.[19]

Two of the cats where DIC was suspected had D-dimer concentrations of 250–500 ng/ml, five had concentrations of 500–1000 ng/ml, and one cat had concentrations of 1000–2000 ng/ml. Four of 12 cats with DIC had negative D-dimer results.

Thirty-six of 48 cats did not meet the criteria for DIC. Of these 36 cats, 12 had thrombocytopenia; four, 11, and five had a prolonged PT, aPTT, and TT, respectively; in one cat the AT activity was reduced; 10 cats had schistocytes (1+ to 2+). In 9/36 cats none of the tests were abnormal, seven cats had one abnormal test result, and 20 cats had two. The pathohistological examination of three of these 36 cats did not indicate a DIC.

Sixteen of 36 cats suffering from various diseases had positive D-dimer test results. Five of 36 cats had D-dimer concentrations between 250 and 500 ng/ml. In three of these cats (suffering from cholangiohepatitis (one), aseptic fat necrosis (one), lymphoma (one)), the other coagulation parameters were in the normal range; one cat with HCMP displayed thrombocytopenia; another cat with a tumour had thrombocytopenia and a reduced AT activity. Eleven of 36 cats had D-dimer concentrations of 500–1000 ng/ml. In one of these cats (adenocarcinoma) no abnormal coagulation parameters or schistocytes were present; in four cats (fever of unknown origin (one), trauma (two), cholangiohepatitis (one)) a thrombocytopenia (one), schistocytes (two), or a prolonged aPTT (one) was detected. In six cats (FIP (one), septic peritonitis (one), pancreatitis (two), pyothorax (one), HCMP(one)) two parameters were abnormal (prolonged TT/schistocytes (two), prolonged aPTT/schistocytes (one), prolonged aPTT/TT (two), or prolonged PT/schistocytes (one)).

The 20 cats that tested negative for D-dimers suffered from the following diseases: pyothorax (one), pyometra (one), abscess (one), cholangiohepatitis (one), aseptic fat necrosis (one), lymphoma (five), other neoplasias (four), trauma (three), HCMP (one), fever of unknown origin (one), immune-mediated haemolytic anemia (IMHA) (one). Eleven cats displayed thrombocytopenia, nine, three, and two cats had a prolongation of aPTT, PT, or TT, respectively, and one cat had an increased AT activity. Four cats displayed schistocytes.

Specificity and sensitivity of the D-dimer test

A specificity of 56% and a sensitivity of 67% of the D-dimer LA test were found when cats suffering from DIC ($n = 12$) were compared to cats suffering from various diseases ($n = 36$). The differences of D-dimer concentrations among these groups were not significant ($P = 0.146$). The D-dimer test had a specificity of 100% and a sensitivity of 67% when healthy cats ($n = 20$) and cats suffering from DIC ($n = 12$) were compared. There was no correlation between the number of abnormal coagulation parameters and a positive or negative D-dimer test result ($P = 0.248$).

Discussion

DIC was suspected in 12/48 sick cats examined in this study, as these cats met at least three criteria for a diagnosis of DIC (thrombocytopenia, prolonged aPTT, PT, TT, reduced AT activity, or schistocytes).[15–17] Eight of 12 cats suffering from DIC had positive D-dimer test results using a semi-quantitative LA test containing murine monoclonal antibodies against human D-dimers. In another study, where an immunoturbidimetric D-dimer assay was used, D-dimer was measurable in only 3/7 cats with DIC. One cat with DIC had necropsy-confirmed renal hilar venous thrombosis but the D-dimer test result was negative. The authors suggested that the mouse anti-human monoclonal antibody used in this assay did not consistently cross-react with feline D-dimer.[17] In a study of human patients with DIC 5/33 patients had a negative D-dimer test using a LA test. These five patients tested positive for D-dimers using an immunoblot test method.[5] It still has to be evaluated which test method is suited best for cats.

None of the healthy cats had positive D-dimer results. In another study, 5/30 healthy cats displayed increased D-dimer concentrations, which were detected by LA.[20] As small amounts of fibrinogen are catabolised constantly in the body, it has been reported that low concentrations of D-dimers may be detectable in healthy humans and dogs.[11,21,22]

In our study, a specificity of 56% and a sensitivity of 67% of the D-dimer LA test were found for distinction of cats diagnosed with DIC and cats suffering from various diseases. When comparing healthy cats and cats suffering from DIC the results were considerably better (specificity 100%, sensitivity 67%). Similarly, the LA D-dimer assay was 100% sensitive in 20 dogs with DIC and 97% specific for healthy dogs.[11] In another study in which healthy dogs were compared to dogs with DIC the D-dimer LA test had a specificity of 90% and a sensitivity of 87%.[12] The authors noted that various D-dimer tests were useful in differentiating healthy dogs from dogs with DIC, acute thromboembolic diseases, or haemorrhage. However, this high specificity could be attributed to the comparison of affected dogs with a healthy population.

Thirty-six of 48 cats in our study suffered from various diseases without meeting the criteria for DIC. Fifty-six per cent of these 36 cats had negative D-dimer test results. Fourteen per cent and 30% of these cats had D-dimer concentrations of 250−500 ng/ml and 500−1000 ng/ml, respectively. In another study, 8/36 sick cats without DIC but with 0−3 altered coagulation parameters displayed increased concentrations of D-dimers.[17]

Positive D-dimer tests in cats without DIC might be due to local thrombi formation. Whether cats are more susceptible to local thrombi formation than other species is unknown. However, feline platelets are stimulated by much lower concentrations of aggregation inductors such as collagen, adenosine diphosphate, or thrombin than those of dogs.[23] In another study, thrombelastograms of 25 healthy cats were evaluated to establish reference ranges. Compared to dogs, normal cats favour a hypercoagulable state: cats had a significantly shorter reaction (R) and thrombus formation time (K) and a higher maximum amplitude (MA) and coagulation index (CI) than dogs.[24]

Cats with and without DIC suffering from FIP, pyothorax, septic peritonitis and pancreatitis, or aseptic fat necrosis had positive D-dimer test results. Several of these cats suffered from SIRS or sepsis and both diseases can trigger DIC in humans, dogs, and cats.[14,16,25,26] Humans and dogs suffering from SIRS or sepsis and DIC displayed increased D-dimer concentrations.[14,26,27] There is no information on D-dimer concentrations in cats suffering from systemic inflammatory response syndrome (SIRS) or sepsis in the literature.

Cats suffering from cholangiohepatitis had either positive or negative D-dimer test results. In another study, cats with cholangiohepatitis had also high D-dimer concentrations. Liver failure may cause increased D-dimer concentrations because of decreased hepatic clearance of the D-dimers.[17] In a canine study, 9/12 dogs suffering from hepatopathy displayed significantly higher D-dimer concentrations than 30 healthy dogs.[13] Hepatic disease may be associated with thromboemboly, coagulopathies, or haemorrhage from vascular damage or destruction.

In our study, 3/12 cats with neoplastic diseases had positive D-dimer test results. In another study high D-dimer concentrations were measured in a cat suffering from pericardial sarcoma and a mast cell tumour of the spleen.[17] In a study of dogs suffering from different neoplasias, 9/16 and 7/16 dogs had negative or positive D-dimer test results, respectively.[13] Tumours which activate the coagulation system to a higher degree behave biologically more aggressive and increased marker levels may have a prognostic impact.[9]

DIC has been described in cats, dogs, and humans after traumatic events.[3,16,28,29] Two cats with trauma had positive D-dimer test results, however, both cats did not meet the criteria for DIC.

Two of three cats of our study with HCMP had positive D-dimer test results. Decreased blood flow or stasis which are associated with cardiac diseases, could promote the development of thrombi by impaired clearance of activated coagulation factors and an enhancement of platelet endothelial interactions.[20] In another study, 3/20 cats displaying HCMP had increased D-dimer concentrations. Median D-dimer concentrations were not different between the HCMP and the healthy group.[30] In cats displaying thrombus formation in the aorta secondary to cardiac diseases, 50% (8/16) had positive D-dimer results.[20] The number of positive D-dimer test results in cats suffering from thrombosis is relatively low as compared to a study on 19 dogs suffering from thrombosis, 17 of which had positive D-dimers.[12] Possible explanations for this observation are that cats may rapidly clear D-dimers or that a localised thrombus (in the aorta) may not result in high systemic

D-dimer concentrations, particularly with concurrent diminished blood flow beyond the occlusion site.[20]

A major limitation of the study is the fact that there is no standardised scoring system for DIC in cats like in human medicine and that it is difficult to prove the presence or absence of DIC in our patients. Moreover coagulation parameters were measured in most cats only once and DIC might have been missed due to its dynamic character. Wada et al detected an increase in D-dimer concentrations a few days prior to a clinical DIC in humans.[31] The criteria that we used to diagnose DIC were based on earlier studies.[15–17] Only in 4/12 cats suspicious for DIC an autopsy could be performed. However, the pathohistological examination is not a gold standard to confirm DIC either, because the post mortem dissolution of microthrombi may occur within several hours and the absence of microthrombi is no exclusion criteria for DIC. Further studies are needed to develop universally accepted diagnostic criteria for DIC in cats. Other limitations of our study are the low number of feline patients examined and the lack of specific antibodies against feline D-dimers.

Increased D-dimer concentrations may indicate organ damage and/or a coagulopathy. The semi-quantitative LA test is only of limited value for the diagnosis of DIC in cats.

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