The Use of Plasma D-Dimer Assays to Detect Thromboembolic Disease in the Dog

Thrombi that form in the arterial or venous system commonly cause significant morbidity and mortality in human and veterinary patients. Greater than 60% of patients with thromboembolic disease die from this disorder. Procedures for early detection of excessive clot formation are not well defined. Traditional diagnostic methods of contrast angiography, nuclear scintigraphy, and laboratory assays of coagulation can be inconclusive or insensitive in diagnosing thromboembolic disease. Of the laboratory markers, D-dimer has shown clinical utility in early embolism detection for human beings. In pathologic conditions, plasmin cleaves fibrinogen to yield fragments X,Y,D, and E that are further cleaved to [fibrin(ogen) degradation products (FDPs)] consisting of fragments E and D. Additionally, fibrin polymers are cleaved to produce X oligomers that are further cleaved by plasmin to produce D-dimers. In contrast to the general end product of fibrin degradation (FDPs), the measurement of D-dimer concentrations is indicative of active coagulation (thrombin generation), fibrinolysis (plasmin generation), and D-dimer clearance. Even though veterinary laboratories are performing D-dimer assays, the reference intervals for clinically healthy dogs, clinically ill dogs without thromboembolic disease, and dogs with known thromboembolic disease are just now being established. Other studies examining D-dimer and FDP testing in dogs with disseminated intravascular coagulation (DIC) compared to healthy dogs found that D-dimers were positive in dogs with fulminate or hemorrhagic DIC. Also, sensitivity, specificity, and predictive values are unknown and often laboratories only report positive or negative results. We found that a positive result without a reported D-dimer concentration is very nonspecific.

We have established D-dimer reference intervals in clinically healthy dogs; D-dimer concentrations in a population of clinically ill dogs without thromboembolic disease; and D-dimer concentrations in a population of dogs known to have thromboembolic disease. D-dimer determinations are performed in duplicate using a latex agglutination with plasma. Semi-quantitative D-dimer concentrations (<250, 250-500, 500-1000, 1000-2000, and >2000 ng/ml) are determined using undiluted and diluted plasma at 1:2, 1:4, 1:8.

We found plasma D-dimer concentrations in healthy dogs were <250 ng/ml (classified as negative). D-dimer concentrations in a population of clinically ill dogs without thromboembolic complications were: Neoplasia: <250 ng/ml = 58%; >250 – 2000 ng/ml = 42%; Heart failure: <250 ng/ml = 86%, 500 – 1000 ng/ml = 14%; Liver disease: <250 ng/ml = 30%, >250 – 2000 ng/ml = 70%; Renal failure: <250 ng/ml = 50%, 250 – 500 ng/ml = 50%; Post-operative: <250 ng/ml = 70%; >250 – 1000 ng/ml = 30%. (Table 1) Dogs with D-dimers = 1000 – 2000 ng/ml had hemoperitoneum or thromboembolic disease (Table 1). All dogs with thromboembolic disease had strong positive D-dimer concentrations: 1000 – 2000 ng/ml, n = 6; and >2000 ng/ml, n = 3. (Table 1) None of the thromboembolic disease dogs had concurrent elevated FDPs.

Even though these results are preliminary and cases are still being accumulated, a positive D-dimer test does not appear to be specific for pathologic thromboembolic disease. This is similar to findings in human beings where D-dimers were elevated in a number of diseases that can be associated with fibrinolysis. In human beings, specificity for deep vein thrombosis and pulmonary thromboembolism is reported as 35%-71%. In dogs, D-dimer concentrations >2000 ng/ml were consistent with thromboembolic disease, and have continued to be so in more recently evaluated cases. In the absence of a fibrin forming condition, such as hemoperitoneum, titers >1000 ng/ml also indicated a predisposition to thromboembolic disease. FDPs were not abnormal in any group; therefore, FDPs may be an insensitive indicator of thromboembolism that has not progressed yet to DIC.

Sample submission: The sample needed is plasma. Blood is collected into citrate tubes, the tubes centrifuged, and the plasma removed within 30 minutes. Plasma may be sent on ice packs or frozen and sent to the laboratory for analysis. Plasma from heparin or EDTA tubes may be used, but has not been validated in our laboratory for dogs.

More information is at http://vetmed.iastate.edu/vpath/diagnostic-services/clinical-pathology

Table 1. D-dimer results in normal, clinically ill, and thromboembolic (TE) groups.

D-dimer ng/dl	<250	250-500	500-1000	1000-2000	>2000
Normal	30				
Neoplasia	7	1	2	2*	
Heart failure	6		1		
Liver disease	3	3	3	1*	
Renal failure	2	2			
Post-surgery	7	1	2		
TE				6	3

*Indicates history of hemoabdomen.

From: Andreasen CB, Nelson OL. The use of a plasma D-dimer assay to detect thromboembolic disease in the dog. Proceedings of the X International Symposium of Veterinary Laboratory Diagnosticians. July 2001. Salsomaggiore, Italy. Pp. 217-218.