



FDP and D-dimer testing – Use and interpretation

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Introduction:

Thromboembolic disease (TE), where thrombi form in the arterial or venous system, is a cause of significant morbidity and mortality in dogs and cats in a number of disease states. Mortality rates from TE are very high making early recognition important, however testing methods for early detection of excessive clot formation in veterinary patients are lacking. Standard diagnostic methods such as measurement of platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), antithrombin III levels (ATIII) and fibrin degradation products (FPDs) can be insensitive and lack specificity in diagnosing thromboembolic disease. More advanced testing can be used to increase sensitivity for early diagnosis, including, ultrasonography, magnetic resonance imaging, contrast angiography and nuclear scintigraphy. However, the majority of these modalities require referral to a specialty center, may be difficult to perform in an unstable patient, are expensive, and not 100% diagnostic.

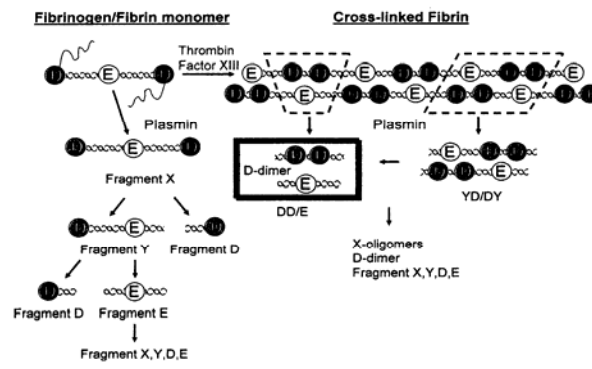
Physiology:

In humans, elevations in PT and aPTT, and reductions in platelet count either alone or in combination have a reasonable degree of sensitivity (85-90%) for the diagnosis of advanced thromboembolic disease or overt disseminated intravascular coagulation (DIC), however specificity is less than 50%. Several reasons exist for the poor specificity of the test. Multiple diseases cause elevations of PT and aPTT not associated with DIC including: anticoagulant rodenticide intoxication, severe acute or chronic hepatic disease, vitamin K malabsorption, anticoagulant administration, and congenital clotting factor deficiencies. Many other diseases without concomitant DIC can be associated with low platelet numbers including primary and secondary causes of immune mediated thrombocytopenia and bone marrow suppressive disorders including infectious disease, neoplasia or drugs. Factors that may lead to false elevations of PT and aPTT levels include poor venipuncture technique, inappropriate blood to anticoagulant ratio, and sample handling problems including prolonged time to run the assay.

Anti-thrombin III is the main inhibitor of coagulation. Significant reduction in serum levels from consumption have been shown to be a very sensitive assay for DIC but

specificity is less than 50%. ATIII measurement has also been shown to be prognostic, with progressively lower levels below 70% predictive of increasing mortality rates.

Measurement of FDPs has been the primary test used in canine patients along with standard coagulation assays to detect DIC, but the sensitivity and specificity are variable. Sensitivity and specificity of FDP measurement for DIC has been reported in various studies to be between 75-85% and 67-75% respectively. No studies have looked at the diagnostic utility of FDP for TE diagnosis in dogs or cats. In the human, FDPs are not sensitive or specific for TE.



Pathophysiology:

In early TE typically PT, aPTT and platelet counts can be normal or near normal with significant clot formation. In contrast even with early clot formation there is usually significant clot lysis occurring. FDPs are byproducts of fibrinogen and fibrin degradation and as such may be present without active clot production. D-dimer is also a fibrin degradation product but is only produced by lysis of crossed linked fibrin strands and therefore is only present with active clot lysis. Of the laboratory markers used in humans, only D-dimer has shown clinical utility in early thromboembolism detection. The FDP assay is a polyclonal assay while D-dimer is a monoclonal assay which may increase specificity. Recently, D-dimer measurement has been validated in the dog and cat using readily available human latex agglutination assays and studies have been performed to assess sensitivity and specificity in the diagnosis of early thromboembolic disease as well as DIC, a few which will be described below. D-dimer values are measured in ng/ml in the latex agglutination based assays and are typically reported as < 250 ng/ml which is considered negative, 250-500, >500-1,000, >1,000-2,000, and > 2,000. FDPs are reported as < 5 ug/ml which is considered negative, 5-20 or a value of > 20.

Clinical studies:

A study of 20 dogs with confirmed DIC compared sensitivity and specificity of D-dimer and FDP tests for diagnosis. The study reported a statistically similar sensitivity for FDP and D-dimer (85-100%) but D-dimer had a higher specificity at 100% compared to 90%

for FDPs. The conclusion was that the D-dimer test could be substituted for FDP test for diagnosis of DIC.

D-dimer was evaluated in a study of 323 dogs admitted to a veterinary teaching hospital that had standard coagulation assays performed. The study found that D-dimer was significantly higher in sick vs. healthy dogs. Forty six percent of sick dogs had a D-dimer > 25% above the reference range. Twenty five of the dogs were found to have DIC based on the presence of 3 of the following lab abnormalities: PT or aPTT elevation of > 25% above the reference range, or a platelet count or ATIII level > 25% below the reference range. D-dimer levels were elevated in 23/25 dogs with DIC. Using a cut-off of > 1,000, the sensitivity of D-dimer for diagnosing DIC was 76% and specificity was 77%. The negative predictive value of a D-dimer concentration < 1,000 was 96%.

Another study evaluated 12 healthy dogs, 18 dogs with DIC, 23 dogs with thromboembolic disease (19 acute, 4 chronic) and 18 dogs with intracavitary hemorrhage with no concomitant DIC or TE. Inclusion criteria for the DIC group was based on the presence of a disease commonly associated with DIC and at least 2 of the following lab abnormalities: times for PT, aPTT or both that were more than 25% prolonged, thrombocytopenia (<150,000 cell/uL), AT level < 70%, and presence of schistocytes. The diagnosis of TE was based on the presence of an underlying disorder associated with TE (protein losing nephropathy, IMHA, sepsis, neoplasia, naturally occurring hyperadrenocorticism or steroid usage for > 7 days), and evidence of a thrombus on ultrasound, CT scan or during necropsy. Duration of clinical signs < 3 days was considered acute TE and > 2 weeks for chronic. The D-dimer was negative in all healthy dogs. All dogs with DIC were strongly positive for D-dimer and 15/18 dogs were FDP positive (2 at a low level and 13 at a high level). In dogs with acute TE 17/19 were strongly positive for D-dimer, however in chronic TE, D-dimer was positive in only 2/4 dogs and 1/4 was FDP positive. D-dimer was positive in 15/18 dogs and FDPs were positive in 13/17 dogs with intra-cavitary hemorrhage. The D-dimer values were significantly lower in the intra-cavitary hemorrhage group than in dogs with either DIC or TE.

Another study compared D-dimer values of 30 healthy dogs, 67 clinically ill dogs without TE and 20 dogs with TE. The clinically ill dogs were categorized into the following groups: 1) neoplasia; 2) congestive heart failure; 3) liver disease; 4) renal failure; and 5) post operative procedures (none with recognized TE). Twenty of the clinically ill dogs had evidence of TE. D-dimer concentration ranges as follows:

D-dimer ng/ml	<250	250-500	500-1000	1000-2000	>2000
Clinically normal	30				
Neoplasia	9	1	4	1*	1*
Heart failure	8		1		
Liver disease	4	4	4	1*	
Renal failure	5	2	1		
Post surgery	11	3	6		
TE			4	9	7

* indicates history of hemoabdomen.

D-dimer concentrations were highest in dogs with TE; next highest was the hepatic disease group. Only these 2 groups had median D-dimer concentrations markedly different from clinically healthy dogs. The sensitivity of D-dimer concentrations >500 ng/mL for predicting TE was 100%; however, the specificity of D-dimer for TE at that concentration was 70%. The specificity of D-dimer concentrations >1,000 ng/mL to predict TE was 94% (sensitivity, 80%), and the specificity of D-dimer concentrations >2,000 ng/mL was 98.5% (sensitivity, 36%). FDPs were not high in any TE patient; and thus they may be an insensitive indicator of thromboembolism.

D-dimer has recently been evaluated in cats using a quantitative latex agglutination assay and a reference interval was established. It has been found that D-dimer concentrations in cats were not highly specific or sensitive. This finding also was true for ATIII levels that were concurrently examined in the same study. Further evaluation is needed.

Conclusions:

D-dimer alone is a strong indicator of TE or DIC at levels >1,000 ng/ml if concurrent intracavitary hemorrhage is not present. With levels > 500 ng/ml suspicion for TE should be high when concurrent disorders typically associated with TE are present.

Intracavitary hemorrhage is often associated with high D-dimer and FDP levels making diagnosis of TE or DIC difficult in those cases.

D-dimer is not 100% specific, therefore an elevated D-dimer is not always diagnostic for either DIC or TE. The underlying disease process, clinical signs and other lab data must be used to substantiate a diagnosis.

A D-dimer of < 1,000 ng/ml is highly predictive for the lack of DIC or acute TE.

With chronic TE there is a 50% false negative rate for D-dimer, therefore other diagnostic tests should be considered before lack of TE is diagnosed.

FDP levels are not routinely elevated in cases of TE and therefore have a low sensitivity for those disorders. In addition moderate to marked increases can be seen in a variety of disorders where TE or DIC do not exist.

A D-dimer > 1,000 ng/ml in the presence of thrombocytopenia, > 25% elevation aPTT or PTT, or an ATIII level < 70% is strongly suspicious of DIC.

The sensitivity and specificity of D-dimer is equal to or greater than that of FDPs and can be used in place of FDPs to assess for the presence of DIC.

The use of D-dimer for diagnosis of TE or DIC in cats is questionable and needs further investigation.

Recommendations:

Consider D-dimer measurement in addition to the minimum data base in diseases with a high incidence of TE or DIC including: immune mediated hemolytic anemia, pancreatitis, peritonitis, sepsis, parvoviral enteritis, hepatic and splenic neoplasia, hepatic disease, heat stroke and GDV. If positive a coagulation panel should also be obtained.