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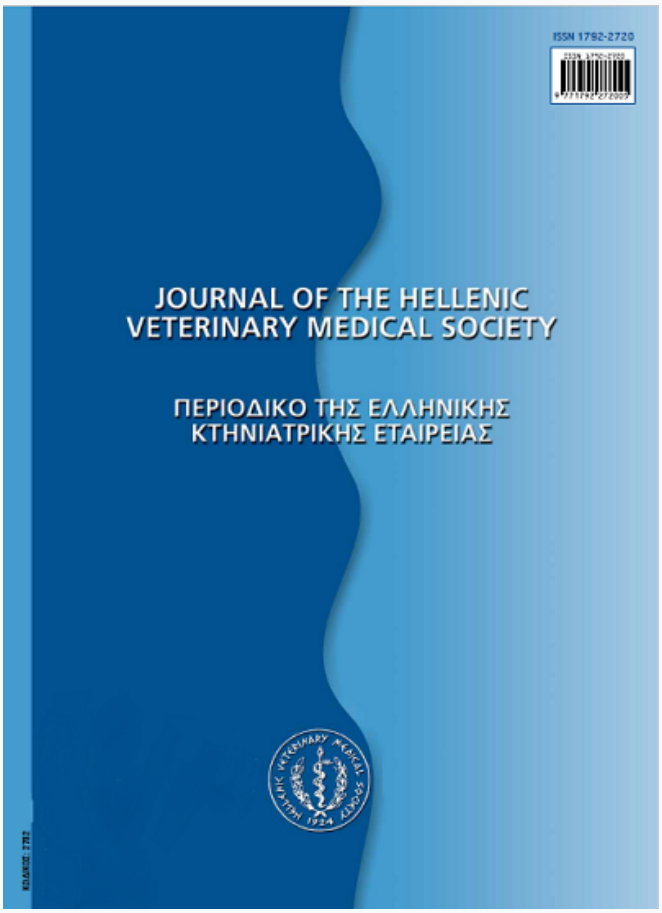

Τα Δ-διμερή ως διαγνωστικό μέσο θρομβοεμβολικών διαταραχών στο σκύλο

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Review article
Ανασκόπηση

D-dimer as a diagnostic tool for canine thromboembolic disorders

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Τα Δ-διμερή ως διαγνωστικό μέσο θρομβοεμβολικών διαταραχών στο σκύλο

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ABSTRACT. D-dimers are small protein fragments present in the blood after a blood clot is degraded by plasmin. During the fibrin(ogen) degradation, a number of products are produced called fibrin(ogen) degradation products (FDPs). D-dimers are part of the FDPs, formed as a result of plasmin activity on cross-linked fibrin. Thus, D-dimers indicate the activity of both trombin and plasmin and are specific markers for fibrinolysis. D-dimer measurement is widely used in the diagnostic work-up of human patients as the most sensitive test to diagnose pulmonary thromboembolism (PTE) and disseminated intravascular coagulation (DIC) and it is, also, considered essential in the evaluation of antithrombotic therapy. During the last decade, there was considerable research regarding the potential utility of D-dimer in veterinary medicine, particularly in canine and equine species. In dogs, D-dimer plasma concentrations can be used to rapidly detect the thrombotic complications and DIC associated with many systemic diseases (high quantitative D-dimer levels). The symptoms of PTE are subtle and the confirmation of diagnosis with routine hematological tests can be difficult, thus jeopardizing the patient's survival. Several techniques have been employed for the detection of D-dimer; the immunoenzymatic assay (ELISA), the immuno-turbidimetric assay and several latex agglutination assays are more commonly used.

Keywords: D-dimers, dog, DIC, thromboembolism

ΠΕΡΙΛΗΨΗ. Τα δ-διμερή είναι προϊόντα αποδόμησης του ινώδους (FDPs) που παράγονται με την επίδραση της πλασμίνης στα πολυμερή του ινώδους. Αποτελούν έτσι δείκτες της δραστηριότητας της θρομβίνης και της πλασμίνης και, επομένως, της ινωδόλυσης. Ειδικότερα, τα δ-διμερή είναι ένα από τα προϊόντα αποδόμησης των πολυμερών του ινώδους που έχουν υποστεί διασταυρούμενη ανασύνδεση. Κατά τη δευτερογενή, ενδογενή ή εξωγενή αιμόσταση, ενεργοποιείται ο παράγοντας Χ της πήξης του αίματος. Μέσω αυτού γίνεται η μετατροπή του παράγοντα ΙΙ σε ΙΙα, ο οποίος με τη σειρά του συμμετέχει στη μετατροπή του ινωδογόνου σε μονομερή του ινώδους (τα οποία πολυμερίζονται) και του παράγοντα XIII σε XIIIα. Ο παράγοντας XIIIα προκαλεί διασταυρούμενη σύνδεση των μονομερών του ινώδους, δημιουργώντας μεγαλύτερες και ισχυρότερες ίνες ινώδους. Κατά την ινωδόλυση, στη συνέχεια, δημιουργούνται τα FDPs, ένα από τα οποία είναι και τα δ-διμερή, που προέρχονται αποκλειστικά από τα διασταυρούμενα μονομερή του ινώδους, συνδέοντας έτσι την ανίχνευσή τους με ενεργή πήξη – ινωδόλυση. Τα δ-διμερή έχουν μεγαλύτερη ευαισθησία στη διάγνωση του Συνδρόμου Διάσπαρτης Ενδοαγγειακής Πήξης

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(ΣΔΕΠ) σε σύγκριση με τα FDPs, καθώς ανιχνεύουν τόσο την ύπαρξη πρόσφατα σχηματισμένου θρόμβου, όσο και την ταυτόχρονη αποδόμησή του. Στην Ιατρική, η ποσοτική ανίχνευση των δ-διμερών χρησιμοποιείται κυρίως για την έγκαιρη διάγνωση της θρομβοεμβολής και του ΣΔΕΠ, καθώς και στην αξιολόγηση της αντιθρομβωτικής θεραπείας. Αντίστοιχες παθολογικές καταστάσεις έχουν διαπιστωθεί και στο σκύλο, στη διερεύνηση των οποίων θα μπορούσε ενδεχομένως να συμβάλει ο προσδιορισμός των δ-διμερών. Η διάγνωση του ΣΔΕΠ στο στάδιο της υπερπηκτικότητας είναι δύσκολη επειδή τα συμπτώματα δεν είναι ειδικά, γεγονός που καθυστερεί την έναρξη της αντιθρομβωτικής θεραπείας, με επακόλουθο την αυξημένη θνησιμότητα. Στο σκύλο, η μέτρηση των δ-διμερών φαίνεται ότι μπορεί να συμβάλει ουσιαστικά στη διάγνωση της θρομβοεμβολής και του ΣΔΕΠ, επειδή η συγκέντρωσή τους αυξάνει σημαντικά και στις δύο αυτές παθολογικές καταστάσεις. Για τον προσδιορισμό των δ-διμερών στο αίμα του σκύλου χρησιμοποιείται η μεθοδολογία που εφαρμοζόταν αρχικά στον άνθρωπο και, συγκεκριμένα, η ανοσοενζυμική μέθοδος ELISA, η ανοσοφωταύγεια και η συγκόλληση. Οι μέθοδοι αυτοί έχουν αξιολογηθεί ως προς την ευαισθησία και την ειδικότητά τους στο σκύλο.

Λέξεις ευρετηρίασης: δ-διμερή, σκύλος, Σύνδρομο Διάχυτης Ενδοαγγειακής Πήξης, θρομβοεμβολή

INTRODUCTION

Hemostatic abnormalities are commonly reported in veterinary medicine (Feldman 1999). As a rule, an hemostatic abnormality occurs with excessive bleeding; occasionally, abnormal hemostatic mechanisms can, also, cause thromboembolism (TE) (Allison and Meinkoth 2007). Even though disseminated intravascular coagulation (DIC) is considered to be a relatively common syndrome in dogs, the diagnosis of fulminant DIC is difficult to be confirmed by the traditional hemostatic profile. D-dimer concentration may permit early diagnosis and more precise classification of coagulopathies in some species (Monreal 2003). The purpose of this article is to review the use of D-dimer as a diagnostic tool in canine internal medicine.

AN OVERVIEW OF HEMOSTASIS AND ITS COMMON ABNORMALITIES

Hemostasis is a highly controlled balance between coagulation and fibrinolysis. The mechanisms of coagulation and fibrinolysis are briefly presented in figures 1 and 2. Hemostasis depends on the integrity of blood vessels, platelet counts and function, coagulation factors, fibrinolytic factors, as well as coagulation inhibitors. Disruption of any of these components may result in hemorrhage or thrombosis. Primary hemostatic defects are characterized by the presence of superficial cutaneous and mucosal bleeding and they are usually caused by thrombocytopenia, while liver disease and rodenticide poisoning leading to vitamin K deficiency are the leading causes of secondary hemostatic defects (Couto 2003). DIC is a complex syndrome in which excessive intravascular coagulation leads to multiple-organ microthrombosis and paradoxical bleeding caused by the inactivation or excessive consumption of platelets and clotting factors secondary to enhanced fibrinolysis.

Thrombosis is the formation of thrombi within the vascular system. Thrombi are formed when the normal balance between prothrombotic and anti-thrombotic factors shift to favour thrombosis. Clinical signs depend on the underlying disease and location of the lesion (Stockham and Scott 2002). Pulmonary thromboembolism (PTE) is a significant, under-diagnosed complication in small animals.

DIAGNOSTIC SIGNIFICANCE OF D-DIMER VS FIBRIN DEGRADATION PRODUCTS

D-dimer is a specific product of the plasmin mediated lysis of cross-linked fibrin (Stokol 2003, Ware et al. 2007, Hackner 2009a, Hackner 2009b). The activation of the coagulation cascade may follow the intrinsic and/or the extrinsic pathway. No matter which pathway is activated, factor X is converted to factor Xa. In the presence of Ca^{2+}, Factor Xa and factor Va form the prothrombinase complex, which converts prothrombin (factor II) to thrombin (factor IIa). Thrombin converts factor XIII to factor XIIIa and it, also, cleaves fibrinopeptides A and B from the central E region of fibrinogen to form fibrin monomers, which in contrast to fibrinogen can polymerize to form protofibrils. Factor XIIIa cross-links adjacent D regions of different fibrin monomers to form stable cross-linked fibrin protofibrils and thus a stable thrombus.

The Fibrin degradation products (FDPs) are generated when plasmin cleaves fibrin and fibrinogen at specific sites to form several fibrin and fibrinogen fragments. In contrast, plasmin-mediated degradation of cross-linked fibrin produces a different set of FDPs

because of the covalent bonds formed by factor XIIIa between adjacent D regions (D-dimers) (Stockham and Scott 2002).

D-dimer formation is briefly depicted in figures 3 and 4. It is illustrated that D-dimer detection requires activation of both thrombin and plasmin; thrombin to produce fibrin from fibrinogen and to activate factor XIII to produce the cross-links and plasmin for fibrinolysis of the cross-linked fibrin, exposing the neoepitopes created by the cross-linking process. Therefore, D-dimer assay is a diagnostic tool with higher specificity in thromboembolic disorders.

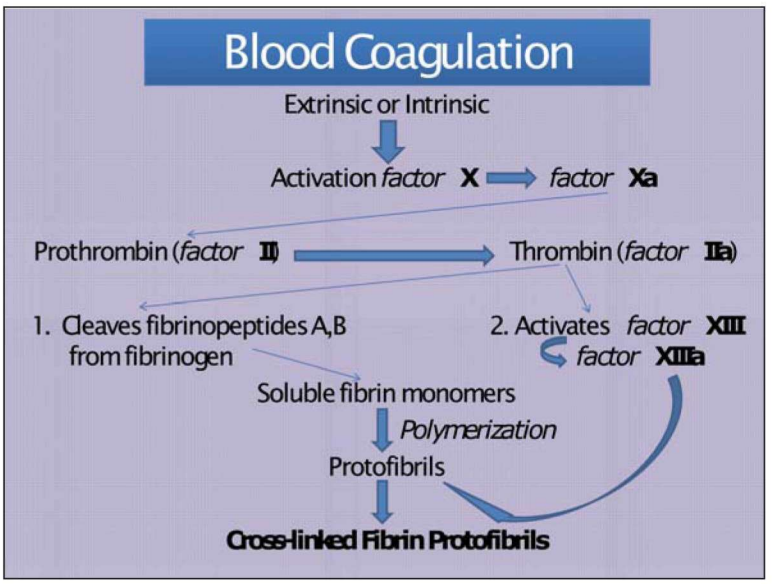

Figure 1. Schematic presentation of coagulation

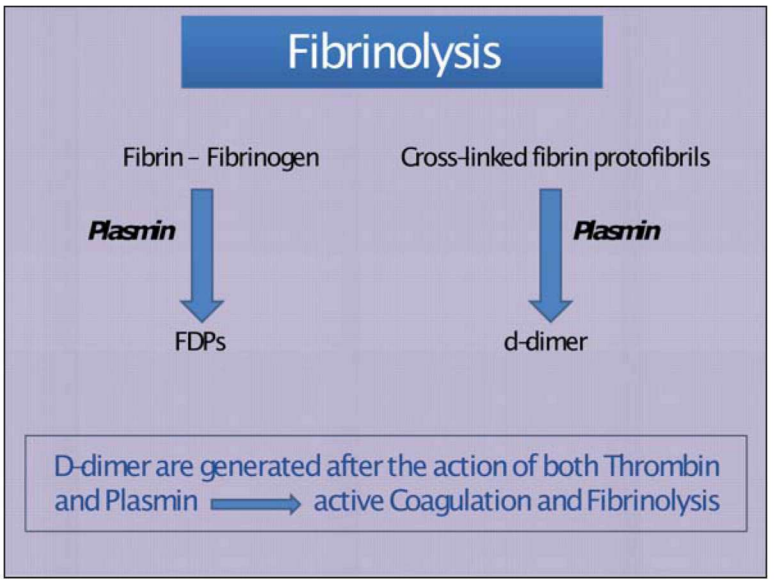

Figure 2. Schematic presentation of fibrinolysis

D-DIMER IN HUMAN MEDICINE

The clinical value of D-dimer assays has been the objective of numerous studies in human medicine (Righini et al. 2008, Adamet al. 2009). In practice, D-dimer assays have been validated in the exclusion of deep vein thrombosis and/or pulmonary embolism in certain patient populations, since this cannot be achieved on clinical grounds alone. Deep-vein thrombosis can be confidently ruled out in a patient with low risk for deep-vein thrombosis and a negative D-dimer test. Ultrasound testing can be safely omitted in such patients (Wells et al. 2003). Due to its high negative predictive value (>92%), D-dimer measurement has been used to predict the risk of thrombosis recurrence and to individualize anticoagulant therapy (Righini and Perrier 2008).

Measurements of D-dimer may, also, be used along with other tests to help diagnose DIC. DIC is a complex hemostatic abnormality arising from a variety of underlying conditions, including surgical procedures, septic shock, poisonous snake bites, liver disease and postpartum disorders. With DIC, clotting factors are activated and then used up throughout the body, resulting in extensive vascular microthrombosis, while, at the same time, the patient appears vulnerable to excessive bleeding. D-dimer levels may be used to monitor the effectiveness of DIC treatment. A sensitive, immunoturbidimetric D-dimer assay, which was validated and clinically evaluated, was found to provide excellent sensitivity and negative predictive value for the diagnosis of DIC (Lehman et al. 2004).

D-DIMER IN VETERINARY MEDICINE

In veterinary medicine, most of the publications on D-dimer refer to companion animals and equines rather than livestock. However, an increase in D-dimer has been reported in ***cattle*** with left abomasal displacement (Sobiech et al. 2008). There is evidence that cattle with abomasal displacement have hemostatic dysfunction and that DIC is a significant risk factor for mortality (Irmak and Turgut 2005).

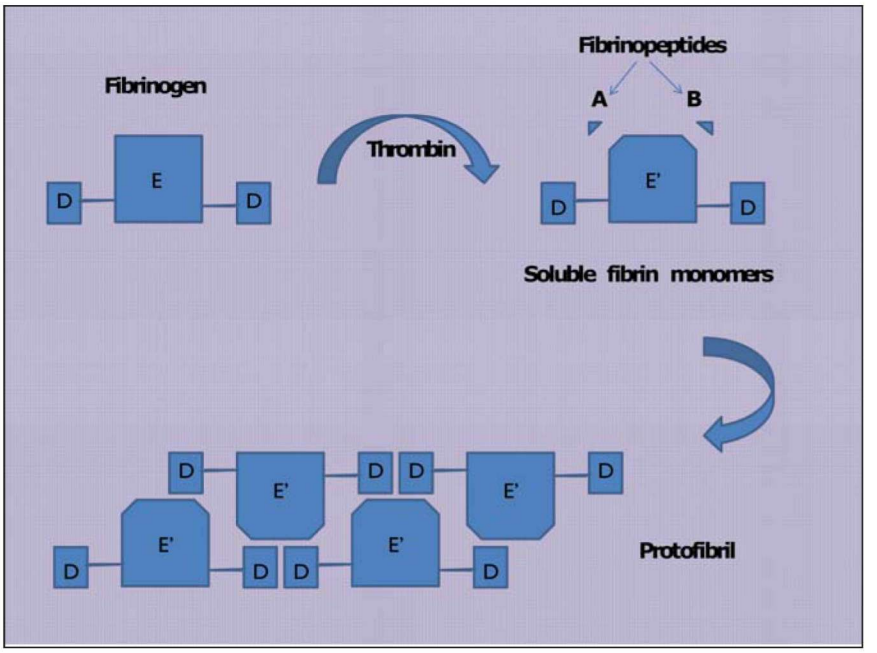

Figure 3. Schematic presentation of d-dimer formation

The fibrinogen molecule is represented with a central (E) and two satellite (D) parts. Fibrinopeptide A and B are cleaved from the E-part resulting to the formation of fibrin monomers, which then polymerize to form a large molecule.

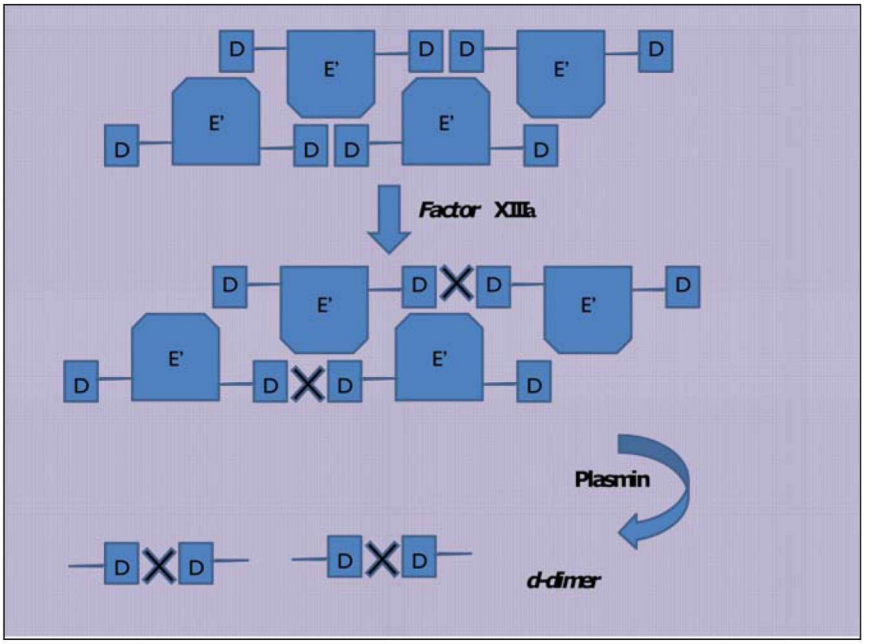

Figure 4.
Soluble fibrin polymer is converted to cross-linked fibrin by factor XIIIa. These cross-links form a very strong bond between the D-domains, thus producing neoepitopes in fibrin that become exposed after plasmin digestion of fibrin. This new molecule that derives from two D-domains of adjacent cross-linked fibrils, represents a D-dimer molecule.

Regarding the use of D-dimer in ***equine*** medicine, a previously validated D-dimer assay was found to improve the prognostic ability in colic cases that are usually accompanied by DIC. Furthermore, it was found that healthy horses have detectable concentrations of serum FDPs and D-dimer and a high D-dimer concentration supports the diagnosis of DIC, while FDPs were not useful for the diagnosis of DIC in this species (Sandholm et al. 1995, Stokol et al. 2005). In another study (Armengou et al. 2008) on the plasma D-dimer concentration in sick newborn foals, it was found that increased values are significantly associated with sepsis. Due to the marked hypercoagulation and hyperfibrinolysis that occurs in septic neonates, the inclusion of D-dimer assay in the minimal database of critical newborn foals during their hospitalization is well justified. However, based on the results of this study, the relationship between D-dimer concentration

and DIC needs further assessment.

An immunoturbidimetric D-dimer assay for DIC in ***cats*** was validated and its diagnostic utility was assessed (Brazzell and Borjesson 2007). Although thromboembolism is a well-known complication of feline cardiomyopathy, D-dimer concentrations in cats with cardiomyopathy were not significantly different compared to healthy cats. Other D-dimer assays, potentially more efficient, should be evaluated in cats. Moreover, feline plasma may contain a substance that interferes with the specific assay. This has been observed with human neutrophil elastase that degrades D-dimers (Bach-Gansmo et al. 1996).

D-DIMER AS A DIAGNOSTIC TOOL IN COMMON HYPERCOAGULABLE STATES IN DOGS

D-dimer indicates the activation of both thrombin and plasmin (thus being specific for fibrinolysis) and it can be an important tool in detecting TE and DIC in dogs. D-dimer concentrations are increased in several other disorders, such as immune-mediated hemolytic anemia (IMHA), surgical procedures, cancer, liver disease, heart failure, renal failure and internal hemorrhage (Stokol 2003).

PTE is probably underdiagnosed in veterinary patients due to technical limitations and the subtle, nonspecific clinical signs. The fact that thrombi dissolve fast makes their identification difficult during post-mortem examination. PTE could mimic other clinical disorders, such as pneumonia, pulmonary edema, lung cancer and pleural effusions and, furthermore, it occurs almost exclusively secondary to one or more underlying conditions. Any suspicion of PTE should prompt a thorough investigation for these conditions (Hackner 2009b). Most dogs with PTE present simultaneously protein loss nephropathies or neoplasia, suggesting that these disorders could be associated with a higher risk of developing PTE (Nelson and Andreasen 2003). Even though a diagnosis of PTE in human medicine is made with the simultaneous evaluation of several laboratory tests, high values of D-dimer increase significantly the possibility of PTE (Tick et al. 2008). Similarly, in a canine study, the healthy control dogs had D-dimer values less than 250 ng/mL, whereas dogs with PTE had values over 2.000 ng/mL and a prediction specificity of 98.5%. For D-dimer values between 1.000 and 2.000 ng/mL, the specificity was 94% (Nelson and Andreasen 2003).

Sepsis seems to have an effect in D-dimer concentration. De Laforcade et al (2003), in a study using similar assay for measuring D-dimer in dogs with naturally occurring sepsis, found that dogs with sepsis have a significantly higher D-dimer value compared to healthy controls. Four out of 20 septic dogs had values higher than 2.000 ng/mL. One dog had TE and 5 dogs had DIC (de Laforcade et al. 2003). Unfortunately, there was no reference to whether these dogs were among the ones with the highest values, a fact that would amplify the results from Nelson and Andreasen (2003).

Dogs with congestive heart failure (Tarnow et al. 2007) and immune-mediated hemolytic anaemia (Scott-Moncrieff et al. 2001) were presented with increased D-dimer values. In another study, dogs with malignant tumors had, also, higher D-dimer values compared to dogs with benign tumors (Kristensen et al. 2008).

DIC is the most serious acquired thromboembolic and hemorrhagic disorder affecting dogs. It is always a consequence of other diseases, including sepsis, neoplasia and immune-mediated hemolytic anaemia (Stokol 2003). A final diagnosis is not possible based on a single diagnostic examination, whereas the combination of clinical evaluation and laboratory tests will confirm it. The use of D-dimer assays for early DIC recognition has proven to be significant (Caldin et al. 2000, Stokol et al. 2000). Besides, D-dimer value is quite higher in dogs that died of DIC in contrast to those who survived (Wiinberg et al. 2008). The presence of high plasma D-dimer value is compatible with activated fibrinolysis usually in favour of DIC (Brooks 2006).

D-dimers have a half life of approximately 5 hours, thus their detection is useful in active or recent fibrinolysis (Hackner 2009a, Hackner 2009b). In a study by Marsh et al. (1994), D-dimers appeared in the blood of healthy dogs within an hour of thrombus induction, their concentration peaked 4 hours later and remained elevated even after 24 hours. Similar results were presented in another study in which D-dimer concentration was significantly elevated within 30 minutes, 1, 2, 4 and 24 hours, respectively, after experimental induction of PTE (Ben et al. 2007).

METHODS FOR D-DIMER DETERMINATION

Several techniques are currently available for D-dimer measurement, using monoclonal antibodies raised against the D-dimer epitope. Among these methods,

those based on the enzyme-linked immunosorbent assay (ELISA) and agglutination (latex agglutination or immune-turbidimetric assay) are the most commonly used (Caldin et al. 2000, Stokol et al. 2005, Boutet et al. 2009).

ELISA methods were initially developed for research purposes before the latex agglutination assays. Several technological advances in assay format and instrumentation led to ELISA-based assays that have increased sensitivity and are capable of detecting elevated D-dimer antigen associated with a variety of clinical disorders in human medicine (Perrier et al. 1997). Various D-dimer tests that use monoclonal antibodies to human D-dimer have been validated for use in veterinary medicine. However, the only commercially available ELISA D-dimer test that has been studied in veterinary medicine (Griffin et al. 2003) is no longer marketed by its manufacturer (Stokol 2003).

Latex agglutination tests are qualitative tests, quick and easy to perform, inexpensive and not requiring specialized equipment (Nelson and Andreasen 2003). A sensitivity of 100% with a specificity of 97% has been reported (Stokol et al. 2000). An immunometric "Point-of-Care" test has been used in healthy dogs (Wiinberg et al. 2007), dogs with chronic congestive heart failure (Tarnow et al. 2007) and in clinically ill dogs with and without TE/DIC (Dewhurst et al. 2008). In the latter study, D-dimer test was found to be an easy to use test, which could aid in a first opinion practice.

Immunorurbidimetric assays use antibody-coated beads that react with D-dimer, producing changes in sample turbidity, which are read by an automated analyzer. They are quantitative, sensitive, readily automated and less prone to technical error than latex agglutination tests (Stokol 2003). The immuno-turbidimetric technique was found to be reliable and accurate, since it conforms to the current standard of precision, linearity and accuracy. However, the clinical specificity and sensitivity of the above method was not assessed (Caldin et al. 2000). In a comparative study (Boutet et al. 2009) between the latex agglutination test and the immunoturbidimetric assay, in which both tests were based on the same monoclonal antibody, the immunoturbidimetric assay had good concordance with the latex-agglutination test, but it, also, offers the advantage of speed and eventual automation.

Citrate is a commonly used anticoagulant to collect samples for routine coagulation tests (Allison and Meinkoth 2007). Both citrate and EDTA tubes have been used for collection of blood samples for D-dimer. However, citrate tubes are preferable, since storage for 2 hours significantly affected values for EDTA-treated plasma samples (Ceron et al. 2008).

Regarding the stability of D-dimer in canine plasma, it has been reported that storage of plasma for 2 days at room temperature does not have any significant effect on most of the hemostatic parameters of canine plasma including D-dimer (Furlanello et al. 2006). Furthermore, hemolysis had no significant effect on D-dimer concentration when samples were stored refrigerated or frozen or even in room temperature, if samples were measured within 24 hours. D-dimer was stable in non-hemolysed samples stored at -20° C for up to 1 month after collection (Stokol et al. 2000, Boutet et al. 2009).

CONCLUSION

D-dimer evaluation for the diagnosis of PT and DIC in dogs has shown a promising diagnostic potential. Although the predictive value of a positive result seems to be limited, recent studies support the use of D-dimer tests always in conjunction with the widely used tests for coagulation in the appropriate clinical context. Furthermore, due to the high negative predictive value, they can be used in the diagnosis and the monitoring of antithrombotic therapy. Further method development and validation of species specific D-dimer assay will play a critical role in the reliability of results. Finally, interpretation of results based on clinical evidence will improve diagnosis and, ultimately, clinical decisions. ■

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