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The full details of the published version of the article are as follows:

TITLE: A review of hyperfibrinolysis in cats and dogs

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JOURNAL: Journal of Small Animal Practice

PUBLISHER: Wiley

PUBLICATION DATE: 13 October 2019

DOI: https://doi.org/10.1111/jsap.13068

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Title: A review of Hyperfibrinolysis in Dogs and Cats

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Hyperfibrinolysis

Abstract

The fibrinolytic system is activated concurrently with coagulation, it regulates haemostasis and prevents thrombosis by restricting clot formation to the area of vascular injury and dismantling the clot as healing occurs. Dysregulation of the fibrinolytic system resulting in hyperfibrinolysis may manifest as clinically significant haemorrhage. Hyperfibrinolysis occurs in both cats and dogs secondary to a variety of congenital and acquired disorders. It has been described in cats and dogs with conditions commonly encountered in primary care practice such as trauma, cavitary effusions, liver disease and *Angiostrongylus vasorum*. In addition, delayed haemorrhage reported in Greyhounds following trauma and routine surgical procedures has been attributed to a hyperfibrinolytic disorder that has yet to be characterised.

Diagnosis of hyperfibrinolysis is challenging, and until recently has relied on techniques that are not readily available outside of a referral hospital setting. With the recent development of point of care viscoelastic techniques, assessment of fibrinolysis is now possible within primary care practice. This will provide veterinary surgeons with the opportunity to target haemorrhage due to hyperfibrinolysis with antifibrinolytic drugs and reduce associated morbidity and mortality. The fibrinolytic system and the conditions associated with increased fibrinolytic activity in cats and dogs are the focus of this review article. In addition, laboratory and point of care techniques for assessing hyperfibrinolysis and antifibrinolytic treatment for patients with haemorrhage will be reviewed.

The Fibrinolytic System

Primary haemostasis is initiated following vascular injury and results in the formation of a haemostatic plug consisting of platelets, von Willebrand factor and exposed subendothelial collagen. This haemostatic plug provides a surface for secondary haemostasis, activation of coagulation factors, thrombin generation and fibrin formation (Smith, 2009). Fibrinolysis is activated concurrently with coagulation and restricts clot formation to the area of vascular injury via plasmin mediated lysis of fibrinogen and fibrin, in order to preserve vascular patency the fibrinolytic system dismantles the clot as healing occurs (Ekert and Muntz, 1972). Under physiological conditions fibrinolysis is controlled by co-factors, receptors and

inhibitors, which regulate haemostasis and prevent thrombosis (Figure 1). Dysregulation of the fibrinolytic system results in hypofibrinolysis or hyperfibrinolysis, which may manifest clinically as thrombosis or haemorrhage respectively. Investigation of the fibrinolytic system should be considered in patients with haemorrhage when surgical haemostasis has been achieved and investigations do not reveal a primary or secondary haemostatic disorder.

Activation of fibrinolysis

Plasmin is the primary fibrinolytic protease, it is converted from circulating inactive plasminogen by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPa). Direct injury or stimulation of vascular endothelial cells results in the release of tPA and factor XII activation following contact with negatively charged surfaces (Kooistra et al., 1994; Renné, 2012). Factor XIIa complexes with kininogen and pre-kallikrein to form bradykinin which potently induces more tPA release from endothelial cells (Brown et al., 1999). Plasmin cleaves fibrinogen and fibrin, resulting in the exposure of fibrin carboxyl terminal lysine residues which further enhance fibrinolysis by acting as binding sites for tPA and plasminogen (Ekert & Muntz, 1972; Cesarman-Maus & Hajjar, 2005). Lysis of fibrin results in the formation of soluble fibrin degradation products (FDP's) including D-dimers.

Inhibition and attenuation of fibrinolysis

The three main inhibitors of fibrinolysis are plasminogen activator inhibitor-1 (PAI-1), alpha-2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI), which are primarily produced by the liver (Saito et al., 1982; Eaton et al., 1991; Knittel et al., 1996). PAI-1 is the main inhibitor of tPA and uPA and therefore the most significant inhibitor of fibrinolysis (Loskutoff et al., 1989; van Meijer & Pannekoek, 1995). Alpha-2 antiplasmin inhibits fibrinolysis by forming a complex with active plasmin to neutralise its action and also by preventing absorption of plasminogen onto the fibrin clot. Alpha-2 antiplasmin also crosslinks fibrin and factor XIIIa which strengthens the fibrin clot and enhances its resistance to plasmin (Carpenter & Mathew, 2008). TAFI is activated by thrombin in a reaction that is catalysed by thrombomodulin (Bajzar et al., 1996; Bouma & Meijers, 2004). TAFI is a potent down-regulator of fibrinolysis; by removing carboxyl-terminal lysine groups from fibrin strands it prevents the

binding of plasminogen and tPA to the thrombus. TAFI decreases plasminogen activation, attenuates positive feedback from plasmin and at high concentrations also directly inhibits plasmin (Mosnier & Bouma, 2006; Foley et al., 2013). The anticoagulant, pro-fibrinolytic enzyme activated protein C neutralises PAI-1 and attenuates the production of TAFI (Sakata et al., 1986; Bajzar et al., 1996).

(Figure 1)

Hyperfibrinolytic Disorders

Hyperfibrinolytic disorders result in premature clot lysis and haemorrhage, which may be further exacerbated by the development of a consumptive coagulopathy if dysregulation of fibrinolysis persists (Hunt, 1996; Rizoli et al., 2011; Sigrist et al., 2018). In human and veterinary medicine, haemorrhage due to hyperfibrinolysis has been associated with both congenital and acquired disorders and can be classified as primary or secondary. Primary hyperfibrinolysis occurs due to quantitative or qualitative abnormalities of the proteins involved in the regulation of the fibrinolytic pathway (Kolev and Longstaff, 2016). Secondary hyperfibrinolysis describes hyperactivity of a normal fibrinolytic pathway, typically provoked by abnormal coagulation, or hyperfibrinolysis due to increased susceptibility of fibrin to lysis (Kolev and Longstaff, 2016). Although this method of classification requires further refinement, it clarifies the underlying pathophysiology of hyperfibrinolysis, contextualising its role within the systemic status of the patient, and may be helpful in guiding therapeutic interventions.

Laboratory Assessment of Fibrinolysis

Methods to measure the individual components of the fibrinolytic pathway are not readily available in practice, cost prohibitive and frequently lack validation for veterinary species. Elevated FDP and D-dimer concentrations indicate increased fibrinolytic activity, however they lack specificity and viscoelastic techniques are currently considered superior for assessing fibrinolysis (Spiel et al., 2006; Schöchl et al., 2009; Longstaff, 2018). It is important to note that even viscoelastic techniques are imperfect and may either fail to detect hyperfibrinolysis or conversely report hyperfibrinolysis in apparently healthy patients (Raza et al., 2013; Sigrist et al., 2018).

Fibrin/fibrinogen degradation products & D-dimers

FDPs are produced following plasmin-mediated lysis of fibrinogen and/or fibrin, thus elevated FDP's indicate increased fibrinolytic activity (Bick., 1982). Fibrinogen is present in the circulation regardless of whether or not clot formation has occurred, as such the presence of FDPs is not a specific marker of clot formation and lysis. D-dimers are a specific form of FDP produced following plasmin-mediated lysis of cross-linked fibrin, with elevations indicating that activation of coagulation and fibrinolysis has occurred (Elms et al., 1983; Greenberg et al., 1985). Point of care kits to assess FDP and D-dimer concentrations are available and have been evaluated for their utility in dogs and cats (Stokol et al., 1999; Griffin et al., 2003; Brazzell & Borjesson, 2007; Dewhurst et al., 2008; Bauer & Moritz, 2009; Tholen et al., 2009). Discordant FDP and D-dimer results, i.e. elevated FDPs alongside normal D-dimer concentration, are possible and have been attributed to primary hyperfibrinolysis and laboratory technique (Sato et al., 1995; Song et al., 1999; Zoia et al., 2017, 2018).

Elevated FDPs and D-dimers are supportive of, but not specific to, hyperfibrinolysis. Mildly elevated FDPs/D-dimers are documented during normal post-operative healing in dogs (Sobiech et al., 2011; Moldal et al., 2012; Shipov et al., 2018). Increased FDP's/D-dimers are also associated with pathological processes such as disseminated intravascular coagulation (DIC) or thromboembolic disease in which a regulated hyperfibrinolysis represents an initial protective mechanism (Stokol et al., 1999; Nelson & Andreasen, 2003; Stokol, 2003; Machida et al., 2010). Due to this lack of specificity FDPs/D-dimers should not be used to identify patients with hyperfibrinolysis who would benefit from antifibrinolytic therapy. Antifibrinolytic drugs are contraindicated in thromboembolic disease and rarely recommended in people with DIC, therefore the administration of antifibrinolytic drugs to patients based on elevated FDP's/D-dimers has the potential to cause harm. (Wada et al., 2010).

Viscoelastic techniques

Viscoelastic tests provide a global assessment of the coagulation system by detecting the change in blood viscosity as the different coagulation phases occur. Rotational thromboelastometry (ROTEM) and

thromboelastography (TEG) can be used to diagnose hypocoagulability, hypercoagulability, enhanced and reduced fibrinolysis (Kol and Borjesson, 2010; McMichael and Smith, 2011).

Samples for TEG and ROTEM are collected into 3.2% buffered sodium citrate and standardised sampling protocols advised (Flatland et al., 2014). Before testing, samples are recalcified and in-vitro coagulation is accelerated and preanalytical errors are reduced with the use of contact activators (Wiinberg et al., 2005, 2007; Bauer & Moritz, 2009). TEG activators used for the assessment of fibrinolysis include kaolin and kaolin combined with tissue factor (Rapid TEG). Tissue factor is utilised to activate the extrinsic pathway when assessing fibrinolysis using ROTEM. Results obtained using different activators are not directly comparable (Wiinberg et al., 2005, 2007; Bauer & Moritz, 2009).

Analysis is performed following a standardised 30 minute delay and within 2 hours of collection (Goggs et al., 2014). Whole blood is placed in a cup and warmed to 37^{o}C, a pin attached to a torsion wire is suspended within the cup. The torsion wire is connected to a mechanical-electrical transducer. TEG operates by moving the cup around the stationary pin in a gentle arc. ROTEM has an immobile cup and instead the pin slowly oscillates. Coagulation results in the formation of fibrin strands between the cup and the pin. Movement of the cup (TEG) or pin (ROTEM) creates different degrees of torsion according to blood viscosity, and as fibrinolysis occurs torsional forces are reduced. Changes in torsional forces on the pin are converted into electrical signals. Graphical and numerical information is created from electrical signals and presented as the thromboelastogram (ROTEM) or thromboelastograph (TEG). It is important to note that although thromboelastogram tracings for TEG and ROTEM appear similar they are not directly comparable.

Fibrinolysis is reported as the percentage reduction in clot strength at 30 and 60 minutes after maximal clot strength is achieved (TEG) and percentage lysis at 30 and 60 mins following initiation of clotting (ROTEM). In vitro fibrinolysis proceeds slowly due to an imbalance of anti-fibrinolytic and pro-fibrinolytic factors. Whole blood samples contain anti-fibrinolytic factors, such as alpha-2 antiplasmin, which circulate in plasma (Sabovic et al., 1989). Consequently in vitro fibrinolysis may not be detectable

within the testing timeframe or before sample dehydration occurs. Modification of TEG assays with recombinant tissue plasminogen activator (tPA) has been shown to accurately reflect the fibrinolytic potential of whole blood and aid detection of fibrinolytic dysfunction (Figure 2) (Kupesiz et al., 2010; Spodsberg et al., 2013; Fletcher et al., 2016; Yoo et al., 2016). The use of tPA in ROTEM to diagnose fibrinolytic dysfunction is not reported in the veterinary literature but is reported in people (Kuiper et al., 2016).

(Figure 2)

ROTEM offers four standard tracings, INTEM, EXTEM, APTEM, FIBTEM, which are interpreted together. EXTEM and APTEM are utilised for the detection of fibrinolytic disorders and contain tissue factor (TF) which activates the extrinsic pathway (Srivastava and Kelleher, 2013). Aprotinin is added to APTEM to inhibit fibrinolysis, increased clot lysis on EXTEM combined with a normal APTEM tracing indicates hyperfibrinolysis (Marly-Voquer et al., 2017).

Viscoelastometry is available in specialist hospitals, but currently is not routinely utilised in primary care practice. Portable handheld viscoelastic analysers are now available and have been recently validated in both canine and feline patients (Buriko & Silverstein, 2018; Jandrey et al., 2018). In the future, as our understanding of the utility and application of viscoelastic techniques develops alongside advances in technology, it is likely that viscoelastic techniques will be integrated into primary care practice. Practices utilising point of care viscoelastic devices will need to use established veterinary clinical pathology guidelines to determine reference intervals (Goggs et al., 2014).

Congenital Hyperfibrinolysis

Congenital hyperfibrinolysis occurs due to increased clot fragility and susceptibility to fibrinolysis (resulting from quantitative or qualitative factor issues), and/or a deficiency of fibrinolytic inhibitors. In people congenital hyperfibrinolysis is reported due to alpha-2 antiplasmin deficiency, PAI-1 deficiency, haemophilia, FXIII deficiency and dysfibrinogenaemia (Anwar & Miloszewski, 1999; Maino et al., 2008; Mehta & Shapiro, 2008; Kolev & Longstaff, 2016). Haemophilia A and B occur in both cats and dogs (Cotter et al., 1978; Brooks, 1999; Barr & McMichael, 2012). Reports of congenital FXIII deficiency and

fibrinogen disorders within the veterinary literature are extremely rare, alpha-2 antiplasmin and PAI-1 deficiency have not been reported (Kammermann et al., 1971; Cotter et al., 1978; Wilkerson et al., 2005; Chambers, 2013; Kong et al., 2014; Jolivet et al., 2017). Deficiency of the anti-fibrinolytic serpins alpha-2 antiplasmin and PAI-1 results in disinhibition of the fibrinolytic system and primary hyperfibrinolysis (Kolev & Longstaff, 2016; Franchini & Mannucci, 2018). Haemophilia, FXIII deficiency and dysfibrinogenaemia are coagulopathies which stimulate upregulation of the fibrinolytic system and secondary hyperfibrinolysis (Kolev & Longstaff, 2016; Franchini & Mannucci, 2018). A hyperfibrinolytic profile has been recognised in the Greyhound breed which likely represents an inherited coagulopathy (Lara-García et al., 2008).

Haemophilia

Haemophilia A (factor VIII deficiency) and B (factor IX deficiency) are sex linked inherited coagulopathies reported to occur in both dogs and cats (Littlewood, 1989; Barr & McMichael, 2012). Haemophilia C, due to factor XI deficiency, has also been reported in dogs and cats (Dodds & Kull, 1971; Knowler et al., 1994; Troxel et al., 2002). The critical role of factors VIII and FIX in coagulation is best illustrated by the cell based model of coagulation (Smith, 2009). In people with haemophilia haemorrhage occurs due to both defective coagulation and up-regulated fibrinolysis (Broze & Higuchi, 1996; Mosnier et al., 2001; Foley & Nesheim, 2009). A more intensely haemorrhagic phenotype has been reported in human haemophiliacs with hyperfibrinolysis (Grünewald et al., 2002).

Impaired thrombin production affects fibrin structure and cross-linking, impairs platelet accumulation and decreases TAFI activation (Wolberg & Campbell, 2008; Brummel-Ziedins et al., 2009; Foley & Nesheim, 2009). Haemophiliacs with impaired thrombin production form loose fibrin clots with high permeability constants that are susceptible to lysis (Bettigole et al., 1964; Sixma & Wester, 1977; Fraser et al., 2011). Thrombin activates FXIII which crosslinks fibrin monomers to stabilise clots, so decreased FXIIIa results in the formation of fragile clots susceptible to lysis (Lorand et al., 1981; Muszbek et al.,

196 1999). Finally, thrombin is required for activation of TAFI and insufficient TAFIa is associated with
197 premature clot lysis (Broze & Higuchi, 1996; Foley & Nesheim, 2009). Haemophiliac dogs treated with
198 low dose soluble thrombomodulin to increase TAFIa produced clots that were more resistant to
199 fibrinolysis (Foley et al., 2012).
200
201 The pathophysiology of haemophilia A and B in people and dogs is similar, to the extent that dogs are
202 used in research as a disease model to assess the efficacy of therapeutic interventions (Nichols et al.,
203 2010). Hyperfibrinolysis has not been reported in dogs and cats with haemophilia and further studies are
204 required to investigate the role of hyperfibrinolysis in cats and dogs with haemorrhage due to
205 haemophilia**.** The use of viscoelastic techniques to assess global coagulation is reported in haemophiliac
206 dogs (Othman et al., 2009; Aroch et al., 2015). However, in the study by Othman et al (2009) TEG
207 tracings were only recorded until maximum amplitude was reached and hyperfibrinolysis was not
208 assessed. The single case report by Aroch et al (2015) did not document hyperfibrinolysis on ROTEM in
209 a dog with Haemophilia A.
210
211 Recombinant factor VIII and IX replacement therapy is used for prophylaxis and treatment in people
212 with haemophilia. Studies have demonstrated a reduction of spontaneous bleeding episodes in
213 haemophiliac dogs treated prophylactically with both plasma derived, and recombinant human, factors
214 VIII and IX, however specific factor replacement therapy is not routinely available for veterinary patients
215 (Brinkhous et al., 1985, 1996, 2002; Russell et al., 2003) . The mainstay of treatment in cats and dogs with
216 haemophilia is blood product administration, during bleeding episodes or prior to planned surgical
217 procedures, in the form of cryoprecipitate (for haemophilia A), fresh frozen plasma, whole blood or
218 packed red blood cells (Aslanian et al., 2014). In the absence of effective haemorrhage prophylaxis
219 repeated blood product administration represents a considerable financial commitment for clients.
220 Antifibrinolytic therapy also forms part of haemorrhage prophylaxis and treatment in people with
221 haemophilia (Rizza, 1980; Ghosh, 2004; Hvas et al., 2007). Currently evidence does not exist to support
222 the use of antifibrinolytic therapy in veterinary patients with haemophilia. However, antifibrinolytic
223 therapy is unlikely to cause harm and could be considered for haemorrhage prophylaxis and treatment in

cats and dogs with severe haemophilia prior to considering euthanasia (Aroch et al., 2015; Kelmer et al., 2015).

Fibrinogen Disorders

Fibrinogen is cleaved to fibrin by thrombin and then fibrin monomers are polymerised to form the network of fibres essential for the foundation of a stable clot (Lord, 2011). Acquired quantitative and qualitative fibrinogen disorders occur rarely in people and are challenging to diagnose (Al-Mondhiry & Ehmann, 1994; de Moerloose et al., 2013). Fibrinogen disorders are typically asymptomatic with haemorrhage occurring following trauma or surgery (Moen & Lord 2006). Afibrinogenemia has been reported in a Bernese Mountain Dog, a Chihuahua and a Bichon Frise, while hypofibrinogenaemia has been reported in a German Short Haired Pointer (Kammermann et al., 1971; Wilkerson et al., 2005; Chambers, 2013). The treatment of choice for veterinary patients with haemorrhage secondary to fibrinogen disorders is cryoprecipitate or fresh frozen plasma to replenish fibrinogen. Thromboembolic complications are reported in people with congenital fibrinogen disorders, although the underlying pathophysiology is incompletely understood (Korte et al., 2017). As such the use of antifibrinolytic agents in cats and dogs with congenital fibrinogen disorders is not recommended.

FXIII deficiency

Factor XIII (also known as fibrin stabilising factor) contributes to clot stability by cross linking loose fibrin polymers, increasing tensile strength and reducing susceptibility to fibrinolysis (Anwar and Miloszewski, 1999). FXIII also crosslinks alpha-2-antiplasmin to fibrin which significantly decreases its susceptibility to lysis (Sakata & Aoki, 1980; Fraser et al., 2011). Thus, in the absence of FXIII, the fibrin meshwork is unstable and susceptible to lysis by plasmin (Board et al., 1993; Mosesson et al., 2008; Chapman et al., 2016). Congenital FXIII deficiency is rare in people and only one case report exists in the veterinary literature describing FXIII deficiency in a dog (Acharya et al., 2004; Kong et al., 2014). Treatment options are similar to those previously discussed for cats and dogs with haemophilia including the use of cryoprecipitate.

Breed Associated Hyperfibrinolysis: Greyhounds

Delayed haemorrhage is reported following trauma and surgery in greyhounds in the absence of primary or secondary coagulation derangement (Lara-García et al., 2008). The prevalence of delayed post-operative bleeding following routine gonadectomy in Greyhounds is reported to be as high as 26% (Lara-García et al., 2008) although it is possible that surgeon inexperience, combined with the thin skin and haircoat of the breed, contributed to an increased incidence of haemorrhage and enhanced detection of bruising in this study. Nonetheless, the reported prevalence of haemorrhage in Greyhounds following gonadectomy is significantly higher than the prevalence of 0-2% reported in other dog breeds (Berzon, 1979; Pollari et al., 1996; Burrow et al., 2005; Peeters & Kirpensteijn, 2011). Delayed haemorrhage is typically associated with the surgical site, however in some Greyhounds bleeding may progress to a generalised haemostatic disorder requiring intensive care and blood product administration (Marín et al., 2012a; Marín et al., 2012b; Lara-García et al., 2008).

When comparing Greyhounds who developed post-operative bleeding and those who did not, no significant difference in platelet count or function, PT, aPTT, fibrinogen, D-dimer, factor XIII and plasminogen concentration was found (Lara-García et al., 2008). However, alpha-2 antiplasmin and antithrombin levels were significantly reduced (although still within reference range) in the group of greyhounds with delayed post-operative bleeding (Lara-García et al., 2008). The absence of primary or secondary coagulation derangement combined with the delayed onset of bleeding suggest that enhanced fibrinolysis may be the primary mechanism behind post-operative bleeding in this breed (Lara-García et al., 2008). Furthermore the incidence of delayed post-operative haemorrhage is reduced in Greyhounds receiving peri-operative antifibrinolytic drugs (Marín et al., 2012).

Current research using viscoelastic techniques does not strongly support the clinical suspicion of hyperfibrinolysis as the cause of delayed haemorrhage in Greyhounds (Vilar et al., 2008; Shropshire 2018). This may be due to low viscoelastic test sensitivity to detect endogenous fibrinolytic activity, and it is also possible that results may be affected by the high haematocrit in this breed (Bochsen et al., 2011; Raza et al., 2013; Brooks et al., 201). The only standard TEG variables associated with delayed haemorrhage in Greyhounds are alpha angle and maximal amplitude, both of which are influenced by fibrin cross-linking

(Vilar et al., 2008). Hyperfibrinolysis was not detected by tissue factor activated tPA TEG in healthy Greyhounds (Shropshire 2018). However, to the authors' knowledge, kaolin and tissue factor assays or tPA TEG have not been utilised to assess coagulation and fibrinolysis in traumatised or post-surgical Greyhounds with delayed haemorrhage.

Management of haemorrhage in greyhounds following trauma or surgery should initially focus on ensuring appropriate surgical haemostasis has been achieved and ruling out a primary or secondary coagulopathy. To avoid misdiagnosis and inappropriate treatment, it is important not to immediately attribute unexplained haemorrhage in this breed to hyperfibrinolysis. In Greyhounds with haemorrhage suspected to be, at least in part, secondary to hyperfibrinolysis, treatment with antifibrinolytic drugs can be considered. The prophylactic use of antifibrinolytic drugs in Greyhounds undergoing surgery should be considered based prior history and risk-benefit analysis.

Acquired Hyperfibrinolysis

Acquired hyperfibrinolysis in people is associated with DIC, trauma, neoplasia, end stage liver cirrhosis and obstetric complications (Tallman & Kwaan, 1992; Hyman et al., 2011; Asakura, 2014; Leebeek & Rijken, 2015; Davenport & Brohi, 2016; Hibbs et al., 2018). Acquired primary hyperfibrinolysis associated with quantitative and/or qualitative abnormalities of proteins involved in regulation of the fibrinolytic pathway has been reported in cats and dogs with haemoperitoneum, cavitary effusions, acute traumatic coagulopathy and *Angiostrongylus vasorum* infection (Fletcher et al., 2016; Yoo et al., 2016; Muri et al., 2018; Sigrist et al., 2017, 2018; Zoia et al., 2018, 2017). Primary hyperfibrinolysis has been diagnosed in cats with haemorrhagic pleural and peritoneal effusion and following snake envenomation (Fuchs et al., 2017; Sigrist et al., 2018). Acquired secondary hyperfibrinolysis is described in dogs with DIC due to up-regulation of a normal fibrinolytic pathway (Vilar-Saavedra and Hosoya, 2011).

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is an acquired consumptive thrombo-haemorrhagic disorder. It occurs when an underlying disease results in the systemic activation of coagulation and

fibrinolysis. Diseases reported to incite DIC in cats and dogs are numerous and varied; systemic infection, inflammation and neoplasia are most commonly associated with DIC in veterinary patients (Feldman et al., 1981; Estrin et al., 2006.; Wiinberg et al., 2008). The clinical manifestations of DIC are influenced by the underlying aetiology, host response and co-morbid conditions (Bick et al., 1999). Depending on the ever-changing balance between pro-thrombotic and anticoagulant, antifibrinolytic and profibrinolytic factors the phenotype may be subclinical, thrombotic or hyperfibrinolytic (Asakura, 2014; Wada et al., 2014).

Thrombin generation in DIC is initiated when tissue factor expression by vascular endothelial cells, monocytes or neoplastic cells activates coagulation factors (Versteeg et al., 2013). Proinflammatory cytokines and chemokines propagate coagulation, impair physiological anticoagulant pathways and suppress fibrinolysis (Simmons & Pittet, 2015, Levi & van der Poll, 2017). Consumption and depletion of anticoagulant factors further sustains the hypercoagulable state (Feldman et al., 1981; Marder & Francis, 1987, Levi & Sivapalaratnam, 2018). Initially patients are hypercoagulable, however at this early stage microthrombi formation may not be clinically apparent and DIC is "non-overt" (Asakura, 2014; Wada et al., 2014). Continued formation and deposition of fibrin will eventually result in microcirculatory impairment and organ dysfunction. Furthermore, the increased utilisation and depletion of platelets ultimately results in a clinically apparent or "overt" consumptive coagulopathy (Asakura, 2014; Wada et al., 2014). This systemic activation of coagulation typically results in concurrent complementary activation of the fibrinolytic pathway.

Thrombosis predominates in patients with DIC when the fibrinolytic response to systemic coagulation is inadequate or impaired. Organ dysfunction is common and haemorrhage is infrequently observed (Estrin et al., 2006; Wiinberg et al., 2008). Severe impairment of the fibrinolytic system is observed in patients with endotoxaemia or sepsis when shutdown of fibrinolysis occurs secondary to increased endothelial release of PAI-1 (Sawdey et al., 1989; Madoiwa et al., 2006; Levi et al., 2009; Wada et al., 2014). In patients with a prothrombotic DIC phenotype it is the development of a consumptive coagulopathy rather than imbalanced hyperfibrinolysis that results in clinical signs of haemorrhage. This phenotype is

also referred to as suppressed-fibrinolytic-type DIC (Asakura, 2014). Administration of antifibrinolytic agents to prothrombotic patients with impaired fibrinolysis has the potential to cause harm. As such, current treatment guidelines do not recommend the routine use of antifibrinolytic agents in people with DIC (Levi et al., 2009; Wada et al., 2014).

Occasionally life-threatening haemorrhage is reported to occur in people with a hyperfibrinolytic DIC phenotype, also referred to as enhanced-fibrinolytic DIC where increased profibrinolytic factors are present (Asakura, 2014). Hyperfibrinolysis results in rapid dissolution of microthrombi and therefore organ dysfunction due to microcirculatory impairment is uncommon (Asakura et al., 2001). Enhanced fibrinolytic DIC leading to significant haemorrhage has been associated with acute promyelocytic leukaemia, aortic aneurysm, prostatic carcinoma and amyloidosis in people (Tallman & Kwaan, 1992; Adam et al., 2004; Takahashi et al., 2008; Prokopchuk-Gauk & Brose, 2015). DIC and hyperfibrinolysis is reported in dogs with metastatic mammary carcinoma and increased circulating levels of uPA occur in dogs with metastatic disease (Mischke et al., 1998; Ramos et al., 2017). Hypocoagulation and hyperfibrinolysis have also been documented in a dog with DIC secondary to metastatic haemangiosarcoma using TF activated TEG (Vilar-Saavedra and Hosoya, 2011). Further studies are required to interrogate the role of hyperfibrinolysis induced haemorrhage in cats and dogs with DIC.

Disseminated intravascular coagulation is associated with a poor prognosis in cats and dogs (Estrin et al., 2006). The dynamic nature of DIC makes optimising therapeutic interventions challenging. Point of care thromboelastometry has been utilised to diagnose, guide and monitor treatment of haemorrhage in people with a hyperfibrinolytic DIC phenotype (Velez and Friedman, 2011). In the future, point of care viscoelastic techniques may provide the opportunity to interrogate the contribution of hyperfibrinolysis to haemorrhage observed in cats and dogs with DIC. Current therapy recommendations for haemorrhage associated with DIC includes blood product administration to replenish oxygen carrying capacity, platelets, coagulation factors and inhibitors (Papageorgiou et al., 2018). The introduction of antifibrinolytic agents to the therapeutic protocol of cats and dogs with documented enhanced-

363 fibrinolytic DIC has the potential to be blood product sparing in addition to reducing morbidity and
364 mortality.
365
366 **Cavitary Effusions**
367 Haemorrhagic fluid aspirated from the pericardial, pleural or peritoneal cavity will not clot and the
368 absence of clot formation is utilised clinically to confirm that inadvertent sampling from the heart or
369 vasculature has not occurred (Murphy & Warman, 2007). The primary mechanism behind the formation
370 of this anti-coagulant environment relates to the fibrinolytic activity of mesothelial cells lining the
371 pericardium, pleural space and peritoneum (Mutsaers & Wilkosz, 2007). Their fibrinolytic activity is
372 achieved primarily through the secretion of tPA and uPA, which cleaves plasminogen found in
373 pericardial, pleural and peritoneal fluid (Idell et al., 1992; Ivarsson et al., 1998). Mesothelial cells can
374 further enhance anticoagulation by increasing local expression of protein C (Iakhiaev and Idell, 2006).
375 Severe injury to the pleura and peritoneum i.e. due to surgical trauma, sepsis, ischaemia and neoplasia,
376 activates coagulation and suppresses fibrinolysis. The formation of fibrous adhesions is a common
377 sequelae to pleural and peritoneal disease when fibrinolysis is suppressed (Mutsaers & Wilkosz, 2007;
378 Stommel et al., 2014).
379
380 Systemic hyperfibrinolysis secondary to cavitary effusion is thought to occur due to resorption of
381 hyperfibrinolytic fluid from the lymphatic circulation and subsequent return to the systemic circulation
382 via the thoracic duct (Mutsaers et al., 2015). Elevated FDP and D-dimer concentrations consistent with
383 increased fibrinolytic activity have been documented in 40% of dogs with pleural effusion and 50% with
384 peritoneal effusion secondary to a variety of causes. In both studies primary hyperfibrinolysis due to lysis
385 of fibrinogen was diagnosed, and increased lysis of fibrin excluded, based on discordant FDP and D-
386 dimer concentrations (Zoia et al., 2017, 2018). This method of diagnosis is problematic as the sensitivity
387 and specificity of utilising discordant FDPs and D-dimers to diagnose primary hyperfibrinolysis is
388 unknown and causes of discordant results other than primary hyperfibrinolysis are also possible (Sato,
389 Takahashi and Shibata, 1995; Song et al., 1999). Thromboelastometry has been utilised to diagnose
390 hyperfibrinolysis in dogs with spontaneous haemoperitoneum which occurred secondary to neoplasia in

96% of patients, D-dimers were also found to be increased in this group (Fletcher et al., 2016). It is likely that rupture of neoplastic lesions resulting in activation of coagulation, fibrin formation and concurrent increased fibrinolytic activity contributed to the reported increase in FDP and D-dimer concentration.

Cavitary effusions occur secondary to a number of diseases such as liver failure, congestive heart failure, neoplasia, sepsis and pancreatitis, all of which have been associated with DIC (Fletcher et al., 2016; Zoia et al., 2017, 2018). Elevated FDP and D-dimer concentrations occur in patients with DIC due to concurrent activation of the fibrinolytic system (Levi et al., 2009). Administration of antifibrinolytic drugs to patients with DIC is not recommended, therefore due to the risk of misdiagnosis causing harm, discordant FDP and D-dimer concentrations should not be used to diagnose primary hyperfibrinolysis as a cause of haemorrhage in patients with cavitary effusions (Wada et al., 2014; Levi et al., 2009). Prospective studies using viscoelastic techniques are required to interrogate the extent to which primary hyperfibrinolysis contributes to haemorrhage in cats and dogs with cavitary effusions and whether this represents a novel therapeutic target.

Hepatic failure

The liver is an essential organ in coagulation as it is the primary source of most coagulation factors and fibrinolytic proteins, it is also responsible for their clearance (Mammen, 1992; Kavanagh et al., 2011). Coagulation changes associated with liver disease are dynamic and multifactorial, both haemorrhage and thrombosis are reported with liver disease (Mammen, 1992; Rogers et al., 2008; Kavanagh et al., 2011; Dircks et al., 2012; Respess et al., 2012; Kelley et al., 2015). Haemorrhage can occur due to thrombocytopaenia, thrombocytopathia, decreased concentrations of procoagulant factors (factors I, II, V, VII, XIII), dysfibrinogenaemia and hypofibrinogenaemia (Willis, 1989; Dunayer & Gwaltney-Brant, 2006; Botsch et al., 2009; Poldervaart et al., 2009; Prins et al., 2010). Thrombosis may occur due to decreased concentration of antithrombin and protein C, increased vWF and increased FVIII (Lisciandro et al., 1998; Kummeling et al., 2006; Toulza et al., 2006; Dereszynski et al., 2008; Prins et al., 2010). Furthermore, DIC occurs in cats and dogs with liver disease and may contribute to a consumptive coagulopathy (Lisciandro et al., 1998; Peterson et al 1998.; Prins et al., 2010).

Dysfunction of the fibrinolytic system is also reported in people and dogs with liver disease and may result in hypofibrinolysis or hyperfibrinolysis, the latter of which can produce a consumptive coagulopathy (Pernambuco et al., 1993; Kelley et al., 2015; Leebeek & Rijken, 2015). Hypocoagulation and hyperfibrinolysis is documented in people and veterinary patients with liver disease and is associated with disease severity (Kelley et al., 2015; Fry et al., 2017). Dogs with acute liver disease trend towards hypocoagulability and hyperfibrinolysis as functional impairment occurs (Kelley et al., 2015). Hyperfibrinolysis can occur due to decreased hepatic production of anti-fibrinolytic proteins such as alpha-2-antiplasmin (Williams, 1989). Decreased hepatic clearance of plasminogen activators and plasmin also contributes to a hyperfibrinolytic state (Leebeek and Rijken, 2015). In addition, ascites is a negative prognostic indicator that is often associated with severe liver disease in cats and dogs and may result in systemic primary hyperfibrinolysis (Wright et al., 1999; Raffan et al., 2009).

Whether or not hyperfibrinolysis contributes to haemorrhage in dogs and cats with liver disease and would represent a new therapeutic target has not yet been studied. As such, empiric use of antifibrinolytic agents to treat haemorrhage in patients with liver disease cannot be advised. In this group of patients, it is prudent to consider assessment of coagulation prior to surgical interventions such as feeding tube placement and liver biopsies, assessment of fibrinolysis can also be considered, particularly if unexplained haemorrhage is occurring. In cats and dogs with hepatic impairment and reduced capacity to produce coagulation factors, hyperfibrinolysis has the potential to contribute to the rapid development of a consumptive coagulopathy. Further research is needed to establish if viscoelastic techniques could help to identify hyperfibrinolysis in cats and dogs with liver disease and guide antifibrinolytic therapy, alongside coagulation factor replacement and vitamin K, in patients with active haemorrhage or planned surgical procedures.

Lungworm Infection (*Angiostrongylus vasorum*)

Angiostrongylus vasorum infection is associated with clinical signs of coagulopathy, verminous pneumonia, pulmonary hypertension, neurological deficits, polyuria and polydipsia attributed to hypercalcaemia and

gastrointestinal signs (Chapman et al., 2004; Esteves et al., 2004; Nicolle et al., 2006; Wessmann et al., 2006; Traversa et al., 2008; Koch & Willesen, 2009; Helm et al., 2010) Haemorrhage in dogs with *A.vasorum* has been associated with von Willebrand factor deficiency, immune mediated thrombocytopaenia, consumptive coagulopathy secondary to DIC, vascular injury and more recently hyperfibrinolysis (Schelling et al., 1986; Caruso & Prestwood, 1988; Cury & Lima, 1996; Ramsey et al., 1996; Gould & McInnes, 1999; Cury et al., 2002; Garosi et al., 2005; Whitley et al., 2005; Ganter & Hofer, 2008; Adamantos et al., 2015; Sigrist et al., 2017).

Decreased fibrinogen concentration and hyperfibrinolysis using ROTEM has been reported in 67% of dogs with *A.vasorum* infection and haemorrhage (Sigrist et al., 2017). Treatment with fresh frozen plasma and tranexamic acid resulted in improvement or resolution of hypocoagulability and hyperfibrinolysis on ROTEM with all dogs treated surviving to discharge (Sigrist et al., 2017). The authors excluded DIC as a cause of hyperfibrinolysis based on the low fibrinogen concentration and fact that previous studies have reported haemorrhage in dogs with normal coagulation profiles and platelet count. More recently tPA modified TEG has been used to diagnose hyperfibrinolysis and guide successful treatment with tranexamic acid in a dog with *A.vasorum* infection (Cole et al., 2018).

The pathophysiology of hyperfibrinolysis in patients infected by *A. vasorum* is incompletely understood. It is likely that adult nematodes interact with the intravascular environment to optimise survival by augmenting the host immune response and modulating haemostasis. Mechanical and biochemical trauma caused by adult *A.vasorum* nematodes and their metabolites may also induce tPA release from the vascular endothelium within the heart and pulmonary vasculature (Sigrist et al., 2017). It is yet to be determined whether *A.vasorum* directly enhances plasmin production and fibrinolysis as is reported in *Dirofilaria immitis* infection (González-Miguel et al., 2012; González-Miguel et al., 2013).

It is important to note that hyperfibrinolysis is not the only possible cause of haemorrhage in dogs with *A.vasorum* (Schelling et al., 1986; Caruso & Prestwood, 1988; Cury & Lima, 1996; Ramsey et al., 1996; Gould & McInnes, 1999; Cury et al., 2002; Garosi et al., 2005; Whitley et al., 2005; Ganter & Hofer, 2008;

Adamantos et al., 2015). Hypercoagulability has also been documented in dogs with *A.vasorum* infection and therefore the prophylactic use of antifibrinolytic agents is not advised in dogs without clinical signs of haemorrhage (Adamantos et al., 2015). However, in dogs with haemorrhage due to *A.vasorum* infection the use of ROTEM and tPA TEG can be used to diagnose hypocoagulability, hyperfibrinolysis and guide therapy with fresh frozen plasma and antifibrinolytic drugs (Sigrist et al., 2017; Cole et al., 2018). When possible viscoelastic techniques should be incorporated into assessment of coagulation status in dogs with haemorrhage due to *A.vasorum*. If viscoelastic techniques are not available then the use of antifibrinolytic agents could be considered alongside blood products in coagulopathic dogs diagnosed with *A.vasorum* and clinical signs of haemorrhage.

Acute Traumatic Coagulopathy

Trauma-induced coagulopathy (TIC) is a term used to describe the spectrum of coagulation changes which occur following severe injury (Hess et al., 2008). There are multiple phenotypes of trauma induced coagulopathy and the clinical manifestation is influenced primarily by thrombin production, platelet function and fibrinolysis (Moore et al., 2015; Shenkman et al., 2017). The accumulation of catecholamines and metabolites post injury, the extent of endothelial activation and the host immune response also effect the phenotype of TIC (Johansson et al., 2012; Cohen et al., 2009; Johansson et al., 2017).

Early haemorrhage following trauma is a phenotype of TIC associated with the combined effects of acute traumatic coagulopathy (ATC) and resuscitation-associated coagulopathy (Cohen et al., 2013). Acute traumatic coagulopathy is an endogenous coagulopathy that occurs in the immediate minutes following trauma prior to, or independent of, resuscitation attempts (Brohi, 2003; MacLeod et al., 2003). Hypocoagulability and hyperfibrinolysis are the hallmarks of ATC, which is reported to occur in up to 25% of severely traumatised people and is associated with a 4-fold increased risk of mortality and massive transfusion requirement (Brohi, 2003; MacLeod et al., 2003; Eastridge et al., 2006; Hess et al., 2008). Whether or not ATC is actually a form of DIC with an enhanced-fibrinolytic profile is fiercely contested, as the formation of thrombi and the consumptive coagulopathy which characterise DIC are not observed immediately following trauma (Johansson et al., 2012; Palmer & Martin, 2014; Dobson et al., 2015). Resuscitation-associated coagulopathy occurs secondary to haemodilution with large fluid volumes, the

administration of colloids, massive transfusion and prolonged surgery which contribute to the development of acidaemia and hypothermia (Cohen, 2012; Fries et al., 2005; Martini et al., 2005).

Three distinct fibrinolytic phenotypes are reported in people with acute traumatic coagulopathy; hyperfibrinolysis, physiological fibrinolysis and shutdown of fibrinolysis (Moore et al., 2014). Hyperfibrinolysis, as seen in ATC, occurs when trauma and hypoperfusion (shock) result in endothelial cell activation and glycocalyx dysfunction, platelet dysfunction, increased systemic tPA and activation of protein C (Cohen et al., 2012; Johansson et al., 2012; Wohlauer et al., 2012; Chapman et al., 2016; Greven et al, 2018). APC was initially thought to be the primary driver of hyperfibrinolysis in ATC through inhibition of PAI-1, however this has recently been called into question. It is now thought that massive release of tPA from the vascular endothelium following trauma is the primary mechanism behind ATC (Chapman et al., 2016). Increased circulating concentrations of tPA cause saturation of its inhibitor PAI-1 and fibrinolysis proceeds uninhibited as antifibrinolytic mechanisms are overwhelmed (Chapman et al., 2016). Fibrinolytic shutdown is reported in up to 60% of severely traumatised people and is associated with thrombosis and organ dysfunction (Moore et al., 2014). Hypercoagulability has been reported in 1 dog and cat following trauma (Gottlieb et al., 2017). The pathophysiology of fibrinolytic shutdown is incompletely understood, however increased circulating PAI-1 and inadequate tPA release in response to injury are proposed mechanisms (Chapman et al., 2016).

Haemostatic derangement is reported in cats and dogs following trauma (Mischke, 2005; Simpson et al., 2009; Abelson et al., 2013; Holowaychuk et al., 2014; Yoo et al., 2016; Gottlieb et al., 2017; Muri et al., 2018; Sigrist et al., 2017, 2018). However, evidence to support the existence of ATC characterised by hypocoagulation and hyperfibrinolysis is currently limited. Two separate case reports have documented hypocoagulation and hyperfibrinolysis using ROTEM and tPA challenged TEG in dogs with severe polytrauma (Yoo et al., 2016; Muri et al., 2018). Both dogs received antifibrinolytic drugs which resulted in the resolution of hyperfibrinolysis on ROTEM/TEG and haemorrhage control. Hyperfibrinolysis has also recently been documented in cats following trauma (Sigrist et al., 2018). ATC is likely to be challenging to diagnose in veterinary patients due to the fact that it is a dynamic coagulopathy. There is

typically a delay between the traumatic episode and presentation to centres where fibrinolysis can be assessed (generally referral hospitals). It is possible that by the time fibrinolysis can be assessed the hyperfibrinolytic phase has resolved or that the most severely traumatised animals may have succumbed to their injuries.

There is great interest in the use of tranexamic acid in veterinary trauma patients due to the results of the human CRASH-2 and MATTER trials (Morrison et al., 2012; Roberts et al., 2013). These landmark trials found that empiric administration of tranexamic acid to trauma patients with haemorrhagic shock was associated with increased survival. However, CRASH-2 also reported that mortality was increased in a subset of patients when tranexamic acid was administered empirically 3-8hrs post trauma. Major haemorrhage protocols used by human trauma centres advocate restrictive crystalloid administration, empiric use of tranexamic acid within the first 3hrs post trauma and resuscitation using a 1:1:1 ratio of fresh frozen plasma, packed red blood cells and platelets (Holcomb et al., 2015).

Empiric use of antifibrinolytic drugs has the potential to cause harm in hypercoagulable traumatised cats and dogs with shutdown of fibrinolysis. Viscoelastic techniques can be utilised to diagnose ATC and guide therapy in traumatised animals, however given the dynamic nature of TIC and ATC point of care assessment is advised (Holowaychuk et al., 2014; Yoo et al., 2016; Muri et al., 2018;). The coagulation status of the patient may change rapidly and increased lag time between sampling and interpretation of results could result in misdiagnosis and inappropriate treatment. Further studies are needed, however the use of antifibrinolytic drugs in traumatised cats and dogs who are bleeding and have laboratory evidence of hyperfibrinolysis is unlikely to cause harm and may be of benefit (Yoo et al., 2016; Muri et al., 2018). Furthermore, implementing balanced resuscitation using blood products, restricting crystalloid administration and performing damage control surgery in line with current recommendations in human medicine should be considered (Rossaint et al., 2016).

Treatment of Hyperfibrinolytic disorders

Antifibrinolytic agents are frequently used in people to treat severe haemorrhage associated with congenital and acquired disorders of coagulation, menorrhoea, post-partum haemorrhage, neoplasia, gastrointestinal and urogenital haemorrhage, surgical haemorrhage and trauma (Mannucci, 1998). The antifibrinolytic agents most commonly used in human and veterinary medicine are Epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA). Aprotinin administration is described in the human literature but was removed from the global market in 2008 due to safety concerns. In veterinary medicine the Chinese herb Yunnan Baiyao has also been anecdotally used for haemostasis, however robust evidence does not currently support its efficacy (Egger et al., 2016; Frederick et al., 2017; Lee et al., 2017).

Tranexamic acid and aminocaproic acid are lysine analogues, they exert their mechanism of action by competitively binding C-terminal lysine sites on plasminogen. As a result of lysine analogue binding plasminogen is prevented from binding fibrin and plasmin formation is inhibited (Figure 3).

The recommended dose of EACA for dogs with active haemorrhage is a loading dose of 50-100mg/kg IV followed by 15mg/kg administered q8hrs until haemorrhage has resolved (Hopper, 2006). In dogs 100mg/kg is associated with increased clot strength in comparison to lower dosages with no adverse effects reported (Brown et al., 2016). Rapid administration may cause hypotension and gastrointestinal signs, weakness, myonecrosis, myoglobinuria and rhabdomyolysis are dose dependent adverse reactions reported in human patients following EACA administration (Borchers, 2014). To the authors' knowledge there is no literature available regarding the use of EACA in cats.

Tranexamic acid is up to 10 times more potent than EACA and its antifibrinolytic activity is superior and more sustained (Verstraete, 1985; McCormack, 2012). There is no consensus regarding optimal dosing, currently the recommended dose of TXA for dogs with active haemorrhage is 15mg/kg slow IV administered q8hrs until haemorrhage has resolved (Hopper, 2006; Osekavage et al 2018). Tranexamic acid is associated with few adverse events, although vomiting has been reported in dogs and seems to be associated with higher doses (20 mg/kg IV) or rapid bolus administration (Kelmer et al., 2013; Kakiuchi et al., 2014; Kelmer et al., 2015). It should therefore be used with caution in patients with

586 contraindications for vomiting, such as raised intra-ocular or intra-cranial pressure and obtunded patients
587 vulnerable to aspiration. Tranexamic acid has been associated with seizure activity in people secondary to
588 inhibition of gamma-aminobutyric acid type A receptors and glycine receptors, both of which are major
589 inhibitory neurotransmitters (Lin and Xiaoyi, 2016). Evidence to guide the use of tranexamic acid in cats
590 is currently not available.
591
592 In people the incidence of thromboembolism associated with administration of antifibrinolytic agents is
593 reported to be low (Ker et al., 2015; Nicolau-Raducu et al., 2016, Juhl et al., 2018) but this has not been
594 established in cats and dogs. Empiric use of these drugs is therefore not recommended in patients with
595 pro-thrombotic conditions. Caution is also advised in the use of antifibrinolytic agents in cats and dogs
596 with renal haemorrhage due to the risk of clot formation causing intra-renal and ureteric obstruction
597 (Stark, 1965; Vujkovac & Sabovic, 2006). Both TXA and EACA are primarily excreted by the kidneys and
598 in people with renal impairment TXA administration is associated with seizures (Montes et al., 2012).
599 Although guidelines do not exist for TXA and EACA use in veterinary patients with renal impairment a
600 reduction in dose in line with human medical recommendations is advised (Andersson et al., 1978; Jerath
601 et al., 2018).

602 **Summary**

603 Hyperfibrinolysis occurs in both cats and dogs secondary to a variety of congenital and acquired
604 disorders. It has been described in cats and dogs with conditions commonly encountered in primary care
605 practice such as trauma, cavitary effusions, liver disease and *A.vasorum*. In addition, delayed haemorrhage
606 attributed to hyperfibrinolysis is reported in Greyhounds following trauma and routine surgical
607 procedures. Clinically significant haemorrhage can occur as the consequence of hyperfibrinolysis and has
608 the potential to increase morbidity and mortality. Viscoelastic techniques provide a global assessment of
609 coagulation and are considered superior for assessing the fibrinolytic systemic. Currently assessment of
610 fibrinolysis using viscoelastic techniques is limited to specialist hospitals or laboratories with ROTEM and
611 TEG, however this is changing with the recent development of point of care viscoelastic analysers. In the
612 future it is likely that consideration and interrogation of the fibrinolytic system will become routine in the

management of coagulopathic cats and dogs in primary care practice. The authors hope that lives will be saved as our ability to recognise, diagnose and treat haemorrhage due to hyperfibrinolysis improves.

Words: 5,916 (excluding references)

No conflict of interest has been declared.

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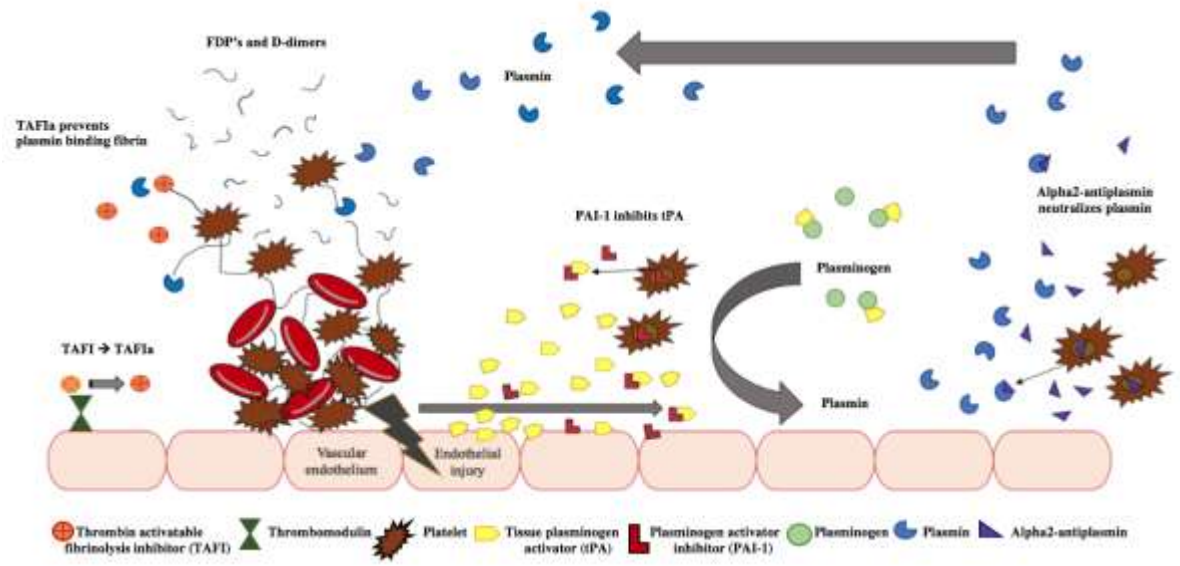
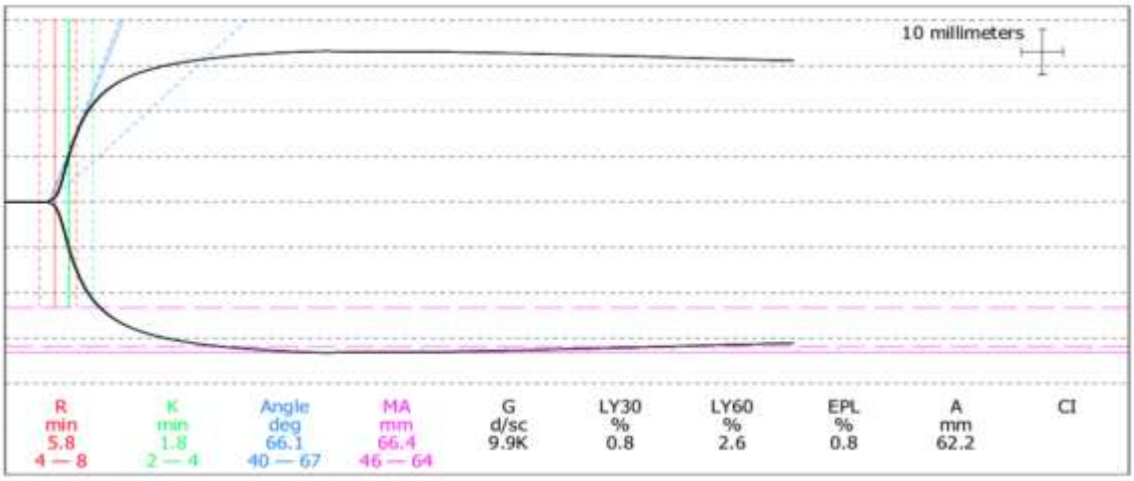
Figure 1. The Fibrinolytic System

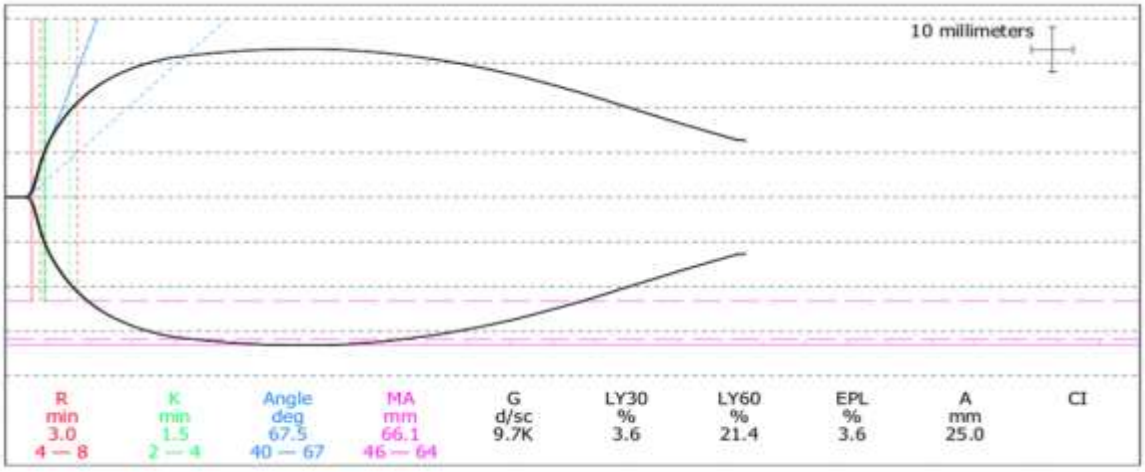


The fibrinolytic system is activated concurrently with coagulation following vascular injury. Tissue plasminogen activator (tPA) released from vascular endothelial cells binds and activates plasminogen to plasmin. Following activation of plasminogen the tPA/plasmin complex binds lysine residues on fibrin. Plasmin cleaves fibrin resulting in the formation of fibrin degradation products/D-dimers. The fibrinolytic system is regulated and inhibited primarily by plasminogen activator inhibitor-1 (PAI-1), alpha-2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI). PAI-1 is the main inhibitor of tPA and uPA and therefore the most significant inhibitor of fibrinolysis. Alpha-2 antiplasmin inhibits fibrinolysis by forming a complex with active plasmin to neutralise its action and also by preventing absorption of plasminogen onto the fibrin clot. TAFIa is a potent down-regulator of fibrinolysis; by removing carboxyl-terminal lysine groups from fibrin strands it prevents the binding of plasminogen and tPA to the thrombus.

Figure 2. TEG tracing with enhanced fibrinolysis following the addition of tPA (50 IU/ml) to citrated whole blood from a critically ill Greyhound.



Standard TEG tracing without evidence of fibrinolysis



Modified TEG tracing with evidence of fibrinolysis following addition of tPA (50IU/ml)

Figure 3. a) Plasminogen is activated to plasmin by uPA or tPA on the surface of fibrin, resulting in fibrinolysis and the production of fibrin degradation products. (b) Anti-fibrinolytic drugs bind to plasminogen C-terminal lysine sites and inhibit activation of plasminogen to plasmin on the surface of fibrin