Diagnostic Testing for Disorders of Thrombosis and Hemostasis

Linda Kidd, DVM, PhD, DACVIM
Western University College of Veterinary Medicine
Pomona, CA

Appropriate hemostasis requires a delicate homeostatic balance between fibrin clot formation and dissolution. Hemostasis is initiated after blood vessel damage to stop bleeding and during inflammatory states to facilitate innate and adaptive immune defense mechanisms. Imbalances in this complex system resulting in thrombosis or inadequate hemostasis can occur due to acquired and inherited disorders. The purpose of this session is to review diagnostic testing for common disorders of secondary hemostasis and thrombosis. For a review on diagnostic testing related to disorders of primary hemostasis please see the accompanying proceedings entitled "A clinical approach to disorders of primary hemostasis."

Understanding hemostasis is necessary in order to prevent and treat bleeding diatheses and thrombotic disease. For a review on normal hemostasis and fibrin clot dissolution, please see the accompanying proceedings entitled "What you need to know about the cell based model of coagulation." Clinical signs can help the clinician determine if a patient with a bleeding diatheses is suffering from a disorder of secondary hemostasis. Generally speaking, clinical signs of disorders of primary hemostasis include evidence of "superficial bleeding". Bleeding from mucosal surfaces such as the nasal mucosa (epistaxis), petechiation and ecchymosis of the skin and mucosal surfaces such as the gums and vulva are evidence of a disorder of primary hemostasis. This is in contrast to disorders of secondary hemostasis or coagulation that usually present with evidence of "deep bleeding." Hemarthrosis, bleeding into the peritoneal cavity, lungs, and mediastinum may be observed in patients with disorders of secondary hemostasis. However, clinical presentation doesn't always provide a clue as to whether a bleeding disorder is due to a defect in primary or secondary hemostasis. For example, bleeding in to the gastrointestinal tract or the urinary bladder and bruising or ecchymosis can be associated with disorders of primary or secondary hemostasis and dogs with coagulopathies can present with epistaxis.

Diagnostic testing for disorders of hemostasis includes evaluating a basic coagulation panel, which usually includes platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT). Diagnostic considerations regarding platelet count are discussed in the proceedings entitled "A clinical approach to disorders of primary hemostasis." The principles behind PT and aPTT are that patient plasma is added to a reaction mixture that includes either a contact activator (aPTT) or thromboplastin (PT) and calcium. The time to fibrin formation is measured. Therefore the PT detects deficiencies in the extrinsic and common pathway while the aPTT measures deficiencies in the intrinsic and common pathway.

Common disorders of secondary hemostasis include hepatic failure with decreased coagulation factor synthesis (all but factor VIIII are produced by the liver), hepatic cholestasis severe enough to interfere with vitamin K absorption, Vitamin K rodenticide toxicity, disseminated intravascular coagulation (DIC) and hemophilia.

Although the model of cell based coagulation more accurately reflects what occurs during hemostasis in vivo, when it comes to diagnostic testing for disorders of secondary hemostasis, division of secondary hemostasis using the "Y" model of the coagulation cascade is quite useful (Figure 1). This model features the extrinsic and intrinsic cascade. The structure of the Y model of coagulation makes it easy to memorize which factors are tested by measuring PT and aPTT. For example, mnemonics passed down to generations of veterinary students include the following; the extrinsic pathway is often memorized as "lucky 7 is all by himself", the intrinsic pathway by "it's not $12.00 but $11.98, and the common pathway by the "dollar bills" X,V,II and I. It is quite useful from a clinical standpoint to be familiar with this model in that PT and aPTT, test each "arm" of the cascade separately, with PT testing the extrinsic and common pathway and aPTT testing the intrinsic and common pathway. Looking at the pattern of prolongation of PT and/or aPTT in the context of the model can help clinicians localize and narrow differential diagnoses. For example, a pattern of marked prolongation of the aPTT and normal PT in a young dog presenting with hemarthrosis would lead the clinician to strongly suspect hemophilia A or B (Factor VIII or IX deficiency) rather than rodenticide toxicity. Marked prolongation of PT with normal a in a dog with compatible history would suggest early rodenticide toxicity because factor VII has the shortest half life of all the vitamin K dependent coagulation factors.

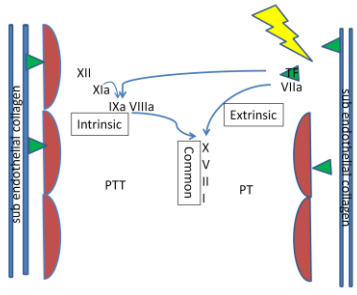

Figure 1. The relationship of the Y coagulation cascade model and diagnostic testing

DIC is technically a disorder of primary and secondary hemostasis as thrombocytopenia, thrombocytopathia, and vasculitis may occur in addition to consumptive coagulopathy and/or a hypercoagulable state. A very thorough review on the laboratory diagnosis of DIC in dogs and cats has recently been published.[2] Historically diagnosis of DIC has been based on clinical findings of an underlying disease process associated with DIC, and at least two of the following; thrombocytopenia, prolonged PT or aPTT, hypofibrinogenemia, low antithrombin levels, increased FDP or D dimers and evidence of schistocytes, keratocytes or acanthocytes. Unfortunately none of these tests is sensitive or specific for the diagnosis of DIC. Scoring models are being developed in hopes of standardizing the diagnosis of DIC so that diagnostic criteria can be used to assess and predict outcome. Testing using thromboelastography have also been investigated as a tool to detect DIC when dogs are in a hypercoagulable state, and which dogs are at risk for thrombosis, however the clinical utility of this testing modality remains to be seen.

Common sites of thrombosis in dogs include pulmonary thromboembolism (PTE), splenic vein thrombosis, caudal vena cava thrombosis, and aortic thrombosis. Mechanisms of thrombosis and diseases associated with thrombus formation are reviewed in the accompanying proceedings "What's new in the pathophysiology of thrombus formation in patients with predisposing underlying disease."

Observation of clinical signs and imaging usually alert the clinician to the occurrence of thrombosis associated with underlying disease processes in these patients. For example acute onset of dyspnea in a patient with IMHA likely signals PTE. Thoracic radiographic findings associated with PTE can include regionally hypovascular areas or pulmonary infiltrates. Thoracic radiographs may also be normal. Echocardiography can support the diagnosis of PTE. Angiography, ventilation perfusion scanning, and spiral CT with angiography may be utilized. However the diagnosis of PTE is often made on the basis of clinical signs, blood gas analysis, thoracic radiographs a complete coagulation panel, and an awareness of underlying predisposing underlying disease. Similarly, hindlimb paresis and weak femoral pulses may signal the development of aortic thrombosis in a dog with protein losing nephropathy. Ultrasound is quite useful for the detection of aortic, splenic, caudal vena cava thrombosis.

Tests of coagulation may support the clinical suspicion that thrombosis has occurred or a hypercoagulable state is present. Hyperfibrinogenemia and decreased AT suggest hypercogulability is present, whereas decreased fibrinogen, and prolongation of PT and aPTT suggests a consumptive coagulopathy and hypocoagulability. Elevations in FDP's and D dimers suggest breakdown of a fibrin clot and activation of fibrinolysis.

Unfortunately, reliable predictors of patients at risk of thrombosis have not been established. Recent studies investigating thromboelastography as a predictor of thrombosis in failed to show that a hypercoagulable tracing helps in predicting thrombosis although further studies are needed. Further studies using novel markers of a prothrombotic state that may be clinically useful as predictors of thrombosis are needed.

References

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