

Compendium

Hypercoagulability in Dogs: Pathophysiology

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Abstract: The risk of hypercoagulability is increased when the hemostatic balance between procoagulant and anticoagulant mechanisms is shifted in favor of coagulation. Hypercoagulability is an increasingly recognized contributor to the deleterious manifestations of veterinary disease. The basis for thrombus formation in many acquired diseases is being investigated and more clearly defined. A thorough understanding of the hemostatic system and knowledge of disorders that lead to hypercoagulable states are critical to a logical therapeutic approach.

A companion article on the treatment of hypercoagulability will be published in the May 2012 issue of Compendium.

Hypercoagulable conditions are acquired disorders that predispose animals to thromboembolic disease. Thrombosis is the formation of a clot (thrombus) inside a blood vessel that obstructs the flow of blood through the circulatory system. Thrombosis is one of the leading causes of death in critically ill people despite the use of prophylactic anticoagulant therapy,¹ and it is increasingly recognized as a cause of morbidity and mortality in veterinary medicine. In a series of 47 dogs with pulmonary thromboembolism confirmed at necropsy,² cardiac disease, neoplasia, hyperadrenocorticism, disseminated intravascular coagulation (DIC), and sepsis were the underlying diseases identified most frequently, and 64% of the dogs had multiple concurrent disease processes that may have contributed to development of thromboembolism.

As the understanding of hemostasis evolves, the ability to identify patients at risk for thrombosis becomes increasingly important so that preventive measures and appropriate therapy can be instituted. This article reviews the pathophysiology of hypercoagulability and the major acquired abnormalities that are associated with thromboembolism in dogs. A companion article reviews the available therapies for hypercoagulability.

Pathophysiology of Hypercoagulability

Under normal hemostatic conditions, the relationship between the coagulation cascade and mechanisms designed to regulate coagulation is complex. Coagulation is the result of activation of proteases that ultimately generate a thrombus and cross-linked fibrin at a site of vascular injury. Natural anticoagulants such as protein C, protein S, antithrombin, and fibrinolytic enzymes play an important part in dampening the coagulation response and

ensuring that thrombin formation and fibrin deposition occur only when necessary. The traditional separation of hemostasis into the intrinsic, extrinsic, and common pathways has been modernized. It is now accepted that these pathways are intimately linked with inflammation and that the extrinsic pathway is the most important initiator of in vivo coagulation.³ The current view of hemostasis emphasizes that anticoagulant, fibrinolytic, and antifibrinolytic mechanisms are of equal importance in coagulation.

The concept presented by Rudolph Virchow in the mid 1800s is fundamental to the understanding of thromboembolism. Virchow described the triad of endothelial damage, abnormal blood flow, and a change in the systemic balance of procoagulant and anticoagulant factors in the pathogenesis of thromboembolism (**FIGURE 1**). Endothelial damage and vascular stasis are prothrombotic. Changes in systemic coagulation factors involve platelet hyperaggregability, excessive activation or decreased removal of coagulation factors, deficiencies of anticoagulants, or defective fibrinolysis.⁴

Under normal circumstances, mechanisms involving antithrombin, protein C,

Key Facts

- Rudolph Virchow described three conditions that contribute to pathologic thrombus formation: blood stasis, endothelial damage, and hemostatic imbalance favoring procoagulant factors (hypercoagulability).
- Knowledge of how platelet aggregation, antithrombin, protein C, and the fibrinolytic system function is critical to understanding factors that contribute to hypercoagulability.
- Mechanisms that contribute to hypercoagulability have been identified in a number of veterinary disorders and often result in a prothrombotic tendency.

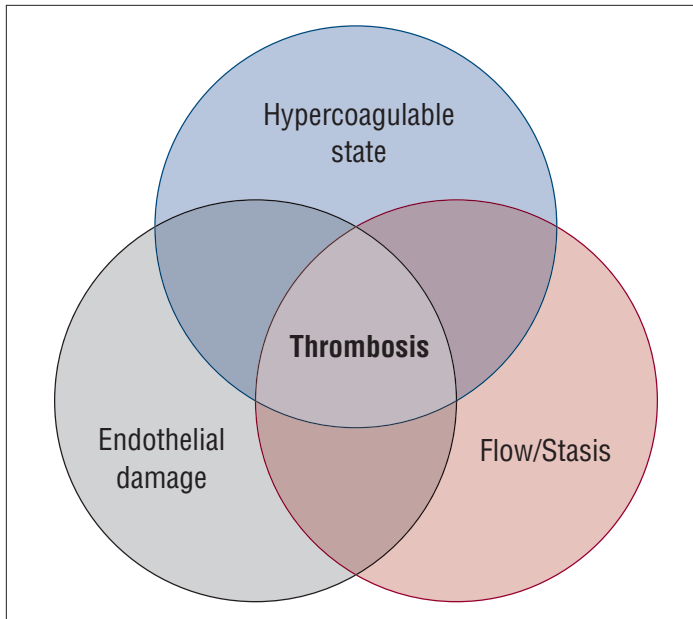


Figure 1. The Virchow triad.

and the fibrinolytic system operate to keep blood in a fluid state in the vasculature and to prevent excessive clot formation. When these systems fail or are not dominant, coagulation is favored. Understanding how acquired conditions can lead to hypercoagulability requires a thorough understanding of these systems.

Platelet Hyperaggregability

Vascular injury triggers platelet activation and initiates the coagulation cascade, which results in a localized platelet–fibrin clot at the site of injury. Platelet activation results in the release of adenosine diphosphate (ADP), which further assists in platelet activation and recruitment. The platelet fibrinogen receptor glycoprotein IIb/IIIa (GPIIb/IIIa) becomes activated and cross-links fibrinogen into a stable clot.⁵

Although thrombocytosis does not favor thrombus formation, platelet hyperaggregability does.^{4,6} The interaction between platelets and the vascular endothelium helps control platelet aggregation. Platelets adhere to exposed subendothelial collagen after vascular injury. Adhered platelets release substances that aid in aggregation, including ADP, catecholamines, and serotonin.⁶ Intact endothelium releases inhibitors of platelet aggregation, such as prostacyclin and nitric oxide. Any disruption in this interaction can potentiate thrombosis.⁶

Antithrombin

The anticoagulant antithrombin, an α_2 -globulin, is synthesized by the liver and found in plasma and, to a lesser extent, on the surface of endothelial cells and platelets.⁷ The plasma half-life of antithrombin in healthy dogs is 1.7 days.⁸ In the absence of heparin, antithrombin slowly forms inactive complexes by irreversibly binding with activated forms of factors IIa, IXa, Xa, XIa, and XIIa. In the presence of heparin, rates of factor neutralization are increased.⁹

Antithrombin deficiency predisposes a patient to thrombosis.¹⁰ The risk of thrombosis in patients with antithrombin deficiencies is moderate when antithrombin activity is between 50% and 75% of normal and marked when antithrombin activity is <50% of normal.⁹ In veterinary medicine, antithrombin deficiencies are primarily due to increased loss or consumption of antithrombin.

A major cause of antithrombin deficiency in animals is glomerular disease, which permits selective loss of low-molecular-weight proteins. Results of studies in dogs with severe protein-losing glomerulonephropathies have confirmed that thrombosis is secondary to a hypercoagulable state generated partially by antithrombin deficiency.¹¹ Additionally, protein-losing enteropathies (PLE) are characterized by excessive nonselective loss of plasma proteins from the gastrointestinal tract, which results in antithrombin deficiency.¹² Corticosteroid administration, which is a mainstay of treatment of PLE, may also be involved in the development of a hypercoagulable state (see Hyperadrenocorticism).

In DIC, antithrombin deficiency is the result of antithrombin consumption. High rates of activated serine protease generation in DIC cause a rapid decrease in antithrombin activity as the antithrombin serine protease complexes form and are cleared by the liver.

Protein C and Protein S

Protein C and its cofactor protein S, which are vitamin K–dependent plasma proteins synthesized by the liver and endothelial cells, are natural anticoagulants. Activated protein C binds with protein S and inactivates factors Va and VIIIa, which are both major propagators of coagulation.¹³ The protein C anticoagulant pathway results in enhanced thrombin inactivation and has direct antiinflammatory activity.¹³ Activated protein C also increases local fibrinolytic activity via activation of plasminogen activator inhibitor.⁴ Decreased levels and defective synthesis of protein C or S result in increased levels of activated clotting factors and decreased fibrinolytic function.¹⁴

Fibrinolysis

The end result of the coagulation cascade is formation of a stable fibrin clot to achieve hemostasis. Dissolution of clots by fibrinolysis is essential. Plasmin, which is formed when plasminogen is cleaved by plasminogen activators, acts as the major fibrinolytic enzyme. Plasmin breaks down fibrinogen and fibrin to lyse the clot, which yields fibrin degradation products.¹³ Tissue plasminogen activator (TPA) and urokinase are physiologic plasminogen activators and are inhibited by plasminogen activator inhibitor type 1 (PAI-1). Hypercoagulability caused by hypofibrinolysis can be secondary to decreases in plasminogen, TPA, or urokinase or increases in PAI-1.⁴

Conditions Leading to Hypercoagulability

Many diseases are associated with hypercoagulability (TABLE 1). It is important to recognize these diseases and identify patients in which appropriate antithrombotic therapy should be administered. Disorders known to predispose animals to a hypercoagulable state include protein-losing nephropathies and PLE, immune-mediated hemolytic anemia (IMHA), diabetes mellitus, hypercortisolism,

necrotizing pancreatitis, sepsis, parvoviral enteritis, dirofilariasis, neoplasia, and cardiac disease.¹⁵ Below, we review concepts of hypercoagulability in some of the most clinically relevant disease states.

Hyperadrenocorticism

Thromboembolic disease is one of the most serious complications associated with hyperadrenocorticism in dogs. Although the exact etiology is unknown, multiple mechanisms are suspected. Low antithrombin activity with concomitant increase in thrombin-antithrombin complexes (TATs) has been reported in dogs with hyperadrenocorticism, which suggests that consumption rather than loss is the basis of antithrombin deficiency in these patients.¹⁶ Antithrombin binds irreversibly to thrombin, and stable TATs can be measured in plasma as evidence of thrombin generation, which is compatible with a hypercoagulable state.¹⁶ Embolic tendency may be related to hyperadrenocorticism-induced hypertension leading to antithrombin loss, which contributes to a hypercoagulable state. Decreased plasma levels of antithrombin correlate with severity of hypertension and proteinuria.¹⁶ Additionally, high concentrations of circulating coagulation factors have been documented in patients with hyperadrenocorticism.^{16,17} In a study of 56 dogs with naturally occurring hyperadrenocorticism,¹⁷ concentrations of procoagulation factors II, V, VII, IX, X, and XII; fibrinogen; and plasminogen were found to be significantly increased. An increased fibrinogen concentration increases the thromboembolic risk by increasing blood viscosity, promoting platelet aggregation, and increasing the rate of fibrin generation.¹⁸ An increased hematocrit and prolonged periods of recumbency are additional factors that predispose these patients to thromboembolism via an increase in vascular stasis.²

Diabetes Mellitus

Hemostatic abnormalities in diabetes mellitus result in hypercoagulability. Multiple mechanisms contribute to these abnormalities, including nonenzymatic glycosylation of receptors, increased oxidative stress to platelets, and decreased heparan sulfate levels.^{19,20} Glycosylation of GPIIb/IIIa complex, the platelet receptor for fibrinogen, may account for increased platelet aggregation.¹⁹ Oxidative stress is associated with decreased platelet life span²⁰ and increased platelet adhesiveness.²⁰ Platelets in diabetic patients show an increased tendency to adhere to the endothelium, which has also been associated with oxidative stress and may be partly due to decreased levels of endothelial heparan sulfate.²⁰

Additional mechanisms have been identified as contributing to the hypercoagulable state of diabetic patients. Increased blood viscosity and decreased red blood cell deformity alter blood flow.²¹ Hyperglycemia is responsible for most of the coagulation abnormalities in patients with diabetes mellitus because it affects thrombus formation, thrombus inhibition, fibrinolysis, and platelet and endothelial functions.²¹ Hyperglycemia is associated with thrombin activation, hyperfibrinogenemia, and increased concentrations of factors VII, VIII, X, XI, and XII and von Willebrand factor.²¹ Lastly, activities of protein C, protein S, and antithrombin are decreased in diabetic patients.²¹

Table 1. Known Etiologic Factors for Thrombotic Events^{a,b}

Disease Category	Disease
Endocrine	<ul style="list-style-type: none"> • Hypercortisolism (hyperadrenocorticism and iatrogenic corticosteroid administration) • Diabetes mellitus
Immune-mediated	<ul style="list-style-type: none"> • Immune-mediated hemolytic anemia • Lymphocytic enteritis (protein-losing enteropathy)
Renal	Protein-losing nephropathy
Inflammatory/infectious	<ul style="list-style-type: none"> • Pancreatitis • Sepsis • Parvoviral enteritis • Dirofilariasis
Neoplasia	<ul style="list-style-type: none"> • Acute leukemias • Solid tumors
Cardiac	<ul style="list-style-type: none"> • Infective endocarditis • Heartworm disease

^aCommon diseases selected for review of proposed or known mechanisms of hypercoagulability.

^bHackner SG, Schaer BD. Thrombotic disorders. In: Weiss DJ, Wardrop KJ. *Schalm's Veterinary Hematology*. 6th ed. Ames, IA: Wiley-Blackwell; 2010:668-678.

Immune-Mediated Hemolytic Anemia

As many as 50% of dogs with IMHA have coagulation abnormalities consistent with hypercoagulability.²² High concentrations of fibrinogen, soluble fibrin, and D-dimer are evidence of excess thrombin substrate and unopposed systemic action of thrombin on fibrinogen to generate cross-linked fibrin.²³ Concomitant low antithrombin activity is an additional indication of hemostatic imbalance favoring fibrin deposition.²³ Results of studies of IMHA in dogs also indicate an increase in the proportion of activated platelets in circulation.²⁴ Effects of cytokines released from damaged red blood cells and endothelium in dogs with IMHA may be the underlying cause of many of these abnormalities.²²

Glomerular Disease

In dogs with protein-losing nephropathies, the incidence of thrombotic disease is as high as 25%.²⁵ Multiple mechanisms have been proposed for the prothrombotic state of glomerular disease. Platelet hyperaggregability may have a role.²⁶ Hypercholesterolemia and hypoalbuminemia, which accompany proteinuria in nephrotic syndrome, may be responsible for platelet hyperaggregability.²⁷ Increased fibrinogen concentration, inhibition of the fibrinolytic system, and altered concentrations of natural anticoagulants such as antithrombin and protein C also may contribute to the prothrombotic state.^{26,28} Immune complex deposition in glomerulonephritis and amyloid deposition in amyloidosis result in increased permeability of glomerular capillaries to plasma proteins. Antithrombin is a small plasma protein (65,000 daltons) and is lost

via the urine when glomeruli are damaged.^{9,26,28} Most procoagulant proteins are larger and are not lost in the urine. The imbalance of procoagulant and anticoagulant molecules resulting from the loss of antithrombin favors thrombosis. Although protein C has a low molecular weight, it is not easily lost into the urine because of its considerable negative charge.²⁸ However, loss of cofactor protein S in the urine may result in a loss of protein C function that could contribute to a prothrombotic state.^{28,29}

Pancreatitis

The link between inflammation and coagulation is well defined. Inflammation promotes coagulation by leading to intravascular tissue factor expression and down-regulation of fibrinolytic and protein C anticoagulant pathways.³⁰ Cytokine influence (mainly of tumor necrosis factor and interleukin-1) causes increased production of fibrinolytic inhibitors PAI-1, α_2 -antiplasmin, and thrombin-activated fibrinolytic factor.³¹ Any disease involving a systemic inflammatory response, such as sepsis, severe pancreatitis, infectious disease, or heatstroke, has the potential to inhibit fibrinolysis, which contributes to a hypercoagulable state.

Neoplasia

The mechanisms by which the coagulation system is activated in some patients with cancer include increased platelet activation, increased expression of thromboplastin, and decreased coagulation factor clearance.³² Thromboplastin (tissue factor) is found within normal cells, and when it is exposed by cell injury, it facilitates the activation of factor VII.³² There is evidence that thromboplastin activity is increased in malignant cells.³³ Endothelial damage and alterations in hemodynamic flow contribute to the hypercoagulable state.

Cardiac Disease

Based on the fundamentals of the Virchow triad, the formation of thrombi associated with cardiac disease suggests that endothelial damage and vascular stasis are primarily responsible. The classic clinical picture of thrombosis associated with cardiac disease is a cat with aortic thromboembolism. Human patients with congestive heart failure (CHF) have high plasma markers of thrombin activity, fibrinolytic activity, and platelet activation.³⁴ Vascular abnormalities, increased coagulability, and impaired blood flow are well-recognized factors associated with thrombosis in people with cardiac disease. Little is known regarding venous and arterial thromboembolism in dogs with CHF, although the prevalence of thromboembolism in these dogs is rare. It has been demonstrated that dogs with CHF have high concentrations of plasma fibrinogen, D-dimers, and TAT and low activities of protein C and antithrombin, which suggest a hypercoagulable or prothrombotic state analogous to the clinical situation in people with CHF.³⁴

Conclusion

Hypercoagulability describes an imbalance of normal mechanisms involving clot formation or clot lysis that results in a tendency to favor clot formation. Increased attention is being given to

thromboembolism that is associated with naturally occurring disease. By understanding factors that predispose animals to thrombosis and associated disease conditions, we can further define how thrombi form in some of these disease states. While hypercoagulability represents a risk for thromboembolism, the actual incidence is unknown and unpredictable. The risk for thromboembolism appears to be increased in patients with severe manifestations of certain diseases and concurrent hypercoagulable states and is compounded by other factors that promote thrombosis, such as blood stasis and endothelial damage.

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- Which condition is not included in the Virchow triad of factors that contribute to thrombus formation?
 - platelet instability
 - abnormal blood flow
 - endothelial damage
 - a hypercoagulable state
- _____ do(es) not cause thrombus formation.
 - Platelet hyperaggregability
 - Decreased fibrinolysis
 - Thrombocytosis
 - Defective anticoagulants
- Which statement is false with regard to platelet aggregation?
 - Platelets release ADP and serotonin to aid in aggregation.
 - Prostacyclin released from the endothelium opposes aggregation.
 - Nitric oxide released from platelets leads to recruitment of additional platelets.
 - Increased platelet aggregation favors hypercoagulability.
- Protein C is a natural anticoagulant that works via all of the following mechanisms except
 - inactivation of factors Va and VIIIa.
 - inactivation of factors II, VII, IX, and X.
 - direct antiinflammatory activity.
 - increase in local fibrinolytic activity via activation of plasminogen activator inhibitor.
- Thrombosis as a result of hypofibrinolysis may occur secondary to a/an _____ in the _____ level.
 - decrease; plasminogen
 - increase; TPA
 - increase; urokinase
 - decrease; PAI-1
- An antithrombin deficiency of _____ has been associated with a moderate risk of hypercoagulability.
 - 50% to 75%
 - 60% to 85%
 - 70% to 95%
 - 80% to 100%
- Antithrombin deficiency does not contribute to hypercoagulability in
 - hyperadrenocorticism.
 - glomerulonephritis.
 - diabetes mellitus.
 - pancreatitis.
- _____ does not lead to a hypercoagulable state.
 - Hyperadrenocorticism
 - Hypercalcemia
 - Protein-losing nephropathy
 - Pancreatitis
- _____ is/are not a suspected cause of hypercoagulability in dogs with hyperadrenocorticism.
 - Decreased antithrombin activity
 - High levels of circulating procoagulation factors
 - Increased concentrations of protein C and protein S
 - Increased fibrinogen concentration
- _____ is not suspected to contribute to the hypercoagulable state of renal disease.
 - Platelet hyperaggregability
 - Inhibition of the fibrinolytic system
 - Antithrombin deficiency
 - Increased production of coagulation factors