Abstract

Hypercoagulation disorders, or thrombophilia, can be as critical as hypocoagulation disorders. Recognizing the signs and understanding the common conditions associated with hypercoagulation are essential to providing appropriate care for these patients, which is often the difference between life and death.
Hypercoagulable States: Recognizing Thrombophilia

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Thrombophilia is a predisposition for inappropriate thrombus (clot) formation. When a thrombus forms within a blood vessel, a process called thrombosis, it can block the flow of blood and prevent appropriate tissue perfusion. Patients with thrombophilia may experience longer hospital stays and higher mortality rates due to the comorbidities of clot formation.

A thrombus can be difficult to detect prior to the sudden onset of neurologic and respiratory signs, which can quickly become fatal. Those signs may be the result of a thromboembolism, which occurs when a piece of the thrombus breaks off and travels in the blood vessel before lodging in an organ, potentially the brain or lungs; this thromboembolus can cause extreme organ damage and failure.

Thrombosis is recognized as a leading cause of death in critically ill humans. Increasingly, it is being recognized as a major contributor to death in veterinary patients as well. Thus, recognizing veterinary patients at risk for thrombus formation is extremely important so that prevention and treatment options can be started as soon as possible.

PATHOPHYSIOLOGY OF COAGULATION
The cell-based model of coagulation describes the formation of thrombi in vivo. In the initiation

Take-Home Points

- Thrombophilia is an imbalance in the hemostatic system that can lead to clot formation.
- Irregularities in Virchow’s triad illustrate the mechanisms that predispose a patient to thrombophilia: endothelial injury, hypercoagulability, and circulatory stasis.
- Thrombophilia is difficult to diagnose and may not be recognized until necropsy.
- Many critical conditions are associated with thrombophilia: sepsis, systemic inflammatory response syndrome, immune-mediated hemolytic anemia, hyperadrenocorticism, and cardiac disease.
phase, a thrombus begins to form within the vascular space when the endothelial layer of the vasculature is injured. Normally, endothelial cells serve as a barrier between circulating platelets and prothrombotic factors, such as von Willebrand factor and tissue factor (TF) cells. With injury, the subendothelial matrix is exposed to those prothrombotic factors, leading to thrombin production on the surface of TF cells.\(^3\)

During the amplification phase, thrombin binds to surface receptors on platelets, causing changes to the platelets’ surfaces. The platelets stretch from round to elongated with multiple projections, increasing their surface area.\(^3\) This process is known as platelet activation, which causes adenosine diphosphate release, which promotes platelet aggregation and recruitment.\(^1\)

The final phase of the cell-based model of coagulation is propagation. In that phase, thrombin cleaves fibrinogen, resulting in the formation of fibrin. Fibrin threads wind around the initial platelet plug to create a grid of fibers, similar to a spider web, that trap platelets and blood cells at the injury site. That grid is a thrombus. To begin repairs, the platelets begin to shrink and the thrombus tightens, pulling the vessel walls together.\(^1,3\)

Hemostasis is the delicate balance that limits bleeding at an injury site and maintains normal circulation within the rest of the body.\(^2\) Because thrombi can inhibit blood flow and prevent tissue perfusion, fibrinolysis, an antithrombotic process that breaks down fibrin, helps maintain healthy circulation. During coagulation, large amounts of thrombin produce the fibrin clot and simultaneously inhibit fibrinolysis until the clot has been stabilized. Then, thrombin production decreases, and fibrinolysis takes over.\(^1,3\) As the clot breaks down, the patency of the vessel is restored. That process occurs in hemostasis. Hypercoagulability signals that the balance has been tipped toward coagulation.

**VIRCHOW’S TRIAD**

Irregularities in Virchow’s triad (FIGURE 1) are major contributors to thrombophilia. Virchow’s triad illustrates 3 components that contribute to prothrombotic conditions: endothelial injury, hypercoagulability, and circulatory stasis.\(^1,4\) Patients commonly exhibit more than 1 of these components, which greatly increases their risk for thrombus formation.\(^1,2,4\)

**Endothelial Injury**

As previously mentioned, endothelial injury starts the process of coagulation by tipping toward a prothrombotic state. In a healthy patient, platelet aggregation does not put the patient at risk for thrombophilia. Platelet aggregation antagonists, including prostacyclin and nitric oxide, are released simultaneously to prevent excess thrombus formation.\(^1\) However, an imbalance can lead to platelet hyperaggregability, a prothrombotic state.

**Hypercoagulability**

Many conditions can contribute to hypercoagulability (e.g., platelet hyperaggregability, decreased anticoagulant factors, increased procoagulant factors, decreased fibrinolysis).\(^1\) In healthy animals, endogenous anticoagulants are activated at the same time as procoagulants, ensuring that coagulation remains localized and within normal limits.

Many medical conditions are associated with hypercoagulable states, most commonly hyperadrenocorticism, immune-mediated hemolytic anemia (IMHA), glomerular disease, and heart disease. Inflammatory conditions with increased production of proinflammatory cytokines also put patients at increased risk for thrombosis.\(^1,2\)

**Circulatory Stasis**

Circulatory stasis refers to altered movement of blood
through the venous system caused by changes in cardiovascular function or reduced movement, most often resulting from illness or injury. The reduced blood flow and increased blood viscosity put the animal at risk for thrombosis.\textsuperscript{1,2,4}

**DIAGNOSIS AND TESTING**

Diagnosing thrombophilia is a challenge.\textsuperscript{5} Patients with chronic conditions, such as those previously listed, may seem healthy. Clinical signs can be vague, more often imperceptible, until a patient exhibits extreme distress. The location of the thrombus may determine whether the patient exhibits dyspnea or neurologic signs or may be non–weight bearing.\textsuperscript{2,4} Patients may be painful or anxious, which can exacerbate respiratory distress (FIGURE 2). Unfortunately, thrombophilic patients are often not identified until a hypercoagulable event.

To determine whether a patient is thrombophilic, at least 1 of the following 3 things must be identified: increased procoagulants (coagulation factors or thrombin), decreased anticoagulants (antithrombin), or decreased fibrinolysis.\textsuperscript{6}

Traditional coagulation tests, such as those for prothrombin time and partial thromboplastin time, are the most accurate tests for detecting hypocoagulable states, but they do not reliably identify hypercoagulability.\textsuperscript{3}

Viscoelastic testing in the form of thromboelastography and rotational thromboelastometry is extremely helpful for identifying hypercoagulability. By directly testing the clot, thromboelastography and rotational thromboelastometry can assess platelets, coagulation factors, and fibrinolysis. They can even go so far as to evaluate the time it takes to initiate fibrin cross-linking, the rate of clot formation, the rate of fibrinolysis, and the strength of the clot. Accelerated fibrin formation, delayed fibrinolysis, and strong clots indicate hypercoagulability.\textsuperscript{6} However, viscoelastic testing is not readily available due to the size and cost of required equipment. Until recently, this equipment was mainly found in university hospitals. Now, point-of-care versions of thromboelastography, known as viscoelastic coagulation monitors, are available (FIGURES 3 AND 4). These are smaller, less expensive, and available at many specialty clinics.

Other tests used to identify thrombophilia are considered indirect tests. D-dimers are proteins that are released when fibrin breaks down; measuring D-dimer levels is a specific assessment of fibrinolysis. However, 1 study found some canine patients with normal D-dimer levels to be at risk for thrombosis,\textsuperscript{7} indicating that this test may not be a reliable indicator of thrombophilia.

Antithrombin is an endogenous anticoagulant that is synthesized in the liver and found in plasma.\textsuperscript{6} It binds with numerous coagulation factors (IIa, IXa, Xla, and XIIa) to inactivate them.\textsuperscript{1} Any decrease in antithrombin will predispose a patient to hypercoagulability. Patients may have antithrombin deficiencies resulting from a condition such as disseminated intravascular coagulation (DIC) or protein-losing nephropathy.

**FIGURE 1.** Virchow’s triad

**FIGURE 2.** A dog in respiratory distress resulting from a suspected pulmonary thromboembolism.
Testing antithrombin levels is not always possible, is expensive, and must be performed by an outside laboratory. Awaiting results is often not an option for a patient experiencing a thrombotic event.

ASSOCIATED CONDITIONS

Many conditions serve as risk factors for thrombophilia (TABLE 1). Recognizing that a patient may be at risk for a thrombotic event can help guide diagnosis and treatment.

Inflammatory Conditions

Coagulation activation is a central theme in many inflammatory conditions such as sepsis, systemic inflammatory response syndrome (SIRS), and DIC. Inflammation and coagulation are intertwined in a potentially devastating cycle of continual activation. Hypercoagulation leads to an inflammatory response, which causes hypercoagulation; the cycle continues.

Sepsis is the body’s inflammatory response to infection, which may lead to SIRS. An inflammatory response compromises endothelial cells, which increases the production of procoagulant molecules and causes a decrease in anticoagulant molecules. Those conditions elicit coagulation and may cause hypercoagulability. DIC is a secondary condition presumed to be initiated by SIRS. Initially, DIC is characterized by the creation of microthrombi. Exhausting procoagulant factors and hyperactivating anticoagulant factors, the animal quickly moves from a hypercoagulable to hypocoagulable state.

Hyperadrenocorticism

Hyperadrenocorticism, also called Cushing’s disease, is often caused by a benign tumor on the pituitary gland. The tumor causes overproduction of adrenocorticotropic hormone, which clinically leads to polyuria, polydipsia, and polyphagia as well as a classically potbellied appearance with a poor hair coat. One study found thrombosis to be 4 times more likely in patients with hyperadrenocorticism than in healthy patients. Although the exact mechanism of this predisposition is unknown, low antithrombin leading to an overproduction of thrombin has been reported for dogs with hyperadrenocorticism. In addition, medications used to treat hyperadrenocorticism, such as desmopressin, have been linked to increased levels of prothrombotic factors.

Immune-Mediated Hemolytic Anemia

IMHA is marked by alloantibodies against an animal's own red blood cells, which cause hemolysis. Up to 70% of dogs with IMHA die from thromboembolic events, making it the leading cause of death in these patients. Although the cause is not fully understood and appears to be multifactorial, postmortem studies have shown widespread fibrin creation in dogs with IMHA.
# Protein-Losing Nephropathy

PLN is signified by damage to the glomerulus in the kidney, which allows protein to be excreted in the urine. Antithrombin is a small plasma protein that is often lost through urination when there is glomerular damage. Excreting antithrombin can cause an imbalance in the procoagulant and anticoagulant molecules that favors coagulation. The mechanisms of hypercoagulability with PLN are not fully understood, but platelet hyperaggregability has been identified in patients with PLN. Studies have found a thrombus, either pre- or postmortem, in up to 25% of patients with PLN.

# Neoplasia

TF, a procoagulant that helps activate factor VII and platelets, has been identified in malignant tumors. TF is suspected to play a role in angiogenesis (development of blood vessels) in tumors, which then shed TF microparticles, leading to thrombi creation.

# Cardiac Disease

Arterial thromboembolism is the embolization of a thrombus within a peripheral artery and affects dogs and cats but is more common in cats (known as feline arterial thromboembolism [FATE]) (FIGURE 5). FATE is associated with left atrial enlargement, although many cats are asymptomatic for cardiac disease before the embolism. Enlargement of the left atrium alters blood flow and endothelial injury may occur, which, as shown by Virchow’s triad, increases the patient’s risk for thrombosis. The clot often lodges in the distal aorta, where it branches off into the iliac arteries, cutting off circulation in both hind limbs. Sometimes called a “saddle thrombus,” this thrombus can lead to decreased tissue perfusion, pain, and an inability to bear weight or move the affected limb or limbs.

Thrombosis secondary to cardiac disease is uncommon in dogs, but it occasionally affects dogs with atrial fibrillation or dilated cardiomyopathies.

# MANAGEMENT

The objectives of managing thrombophilic animals include treating the underlying condition (if possible), inhibiting new thrombus formation, and lysing existing thrombi.

Managing the underlying condition is difficult. Stabilization may be necessary before any diagnostics can be performed. Painful patients should be given analgesia, and patients in respiratory distress or with...
In case of emergency, hypoxia should be given oxygen supplementation. For patients with an ailment that predisposes them to thrombosis, antithrombotic drugs should be considered.

Medications can be used to inhibit thrombus formation. Antiplatelet drugs, as their categorical name implies, inhibit platelet aggregation. Aspirin is a cyclooxygenase (COX) inhibitor that binds to platelets’ COX and prevents the generation of thromboxane, a platelet agonist. Clopidogrel, a drug typically well tolerated by cats with FATE, inhibits platelet aggregation. Anticoagulants such as heparin are used for their ability to bind with antithrombin. Notably, heparin should be used with caution due to the variability in patient response.

Fibrinolytics, such as recombinant tissue plasminogen activator, are used to dissolve existing thrombi; they work by activating plasminogen, which makes plasmin. Plasmin degrades fibrin and causes clot lysis. Fibrinolytics are to be used with caution as they may lead to extreme hemorrhage and reperfusion injury. The benefits of using fibrinolytics must be weighed against the potential for serious complications.

**Prognosis**

Unfortunately, the prognosis for patients with thrombophilia is guarded to grave. This prognosis is based on the ability to treat the underlying condition in a timely manner, which may not be possible, and the patient’s response to treatment. The client’s ability to dedicate the time and finances needed to care for these patients with follow-up veterinary care for medications and monitoring diagnostics also plays a large role in the patient’s long-term outlook.

**Summary**

Hypercoagulable states represent an imbalance between prothrombotic and antithrombotic mechanisms that predispose a patient to clot formation. Knowledge of the conditions associated with hypercoagulable risk factors helps ensure patients receive timely, necessary treatment. Antithrombotic and thrombolytic therapy may be needed.

**References**


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Melissa is a licensed veterinary technician who earned her VTS credential in emergency and critical care in 2018. Melissa has worked in multiple areas of veterinary medicine, including emergency, intensive care, and critical care. Currently, Melissa is the northeast regional manager of learning and development manager for United Veterinary Care and owns her own veterinary nurse consulting business. Melissa has spoken at both national and international conferences and is a RECOVER CPR-certified instructor. Her work has been shared in multiple veterinary publications and she has been featured in videos for Vet Candy.