Hypercoagulability in Dogs: Treatment

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Abstract: Hypercoagulability is a state in which the hemostatic balance shifts toward excessive platelet activation and fibrin deposition, leading to thrombosis. Although a definitive diagnosis is often difficult to make, identifying patients at risk for thromboembolism is critical. By identifying these patients and understanding mechanisms that contribute to hypercoagulability, clinicians can select protocols that aid in thrombus prevention. Several therapeutic options exist, including antiplatelet, anticoagulant, and fibrinolytic drugs.

Hypercoagulable states include various acquired clinical disorders characterized by an increased risk for thromboembolism. Thrombosis is the formation of a clot or thrombus inside a blood vessel that obstructs the flow of blood through the circulatory system. Thromboembolism is the obstruction of a blood vessel by a thrombus carried by the blood from the site of origin to a distal site.

Thrombosis is one of the leading causes of death in critically ill people despite the use of prophylactic anticoagulant therapy. Additionally, canine thromboembolic disease is an important clinical disorder of veterinary medicine that requires a treatment plan to address the acute ischemic crisis as well as the underlying disease. 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 available therapies for hypercoagulability. A companion article reviews the pathophysiology of hypercoagulability and the major acquired abnormalities that are associated with thromboembolism in dogs.

Treatment

When hypercoagulability is diagnosed or suspected, therapy to prevent clot extension and recurrence is indicated. In experimental conditions, thromboemboli begin to dissolve without treatment within hours of formation. However, in naturally occurring disease, a prothrombotic tendency may persist. Medical treatment of thromboembolic diseases consists of inhibition of new thrombus formation by use of antiplatelet drugs, anticoagulants, and vitamin K antagonists and dissolution of existing thrombi with thrombolytic drugs (FIGURE 1).

Information regarding blood flow and thrombus consistency is important in making appropriate therapeutic decisions. Thrombosis may occur in arteries or veins. The mechanisms of thrombus formation and risk factors involved vary between these two locations. Because of the high blood pressure and blood flow in arteries, blood stasis and patient immobilization do not significantly affect the risk for thrombus formation in these vessels, and hypercoagulability of blood has a relatively minor role. Instead, the high shear conditions present in most arteries result in a greater proportion of platelets in arterial thrombi. Strategies to inhibit arterial thrombogenesis therefore focus mainly on anti-platelet drugs. In venous thrombosis, on the other hand, blood stasis and patient immobilization are important risk factors, as are prothrombotic abnormalities. Venous thrombi form under low shear forces and tend to contain lower numbers of platelets. Early venous thrombi are platelet rich, but as they mature, they extrude platelets. Strategies to limit venous thrombogenesis focus mainly on anticoagulants, although antiplatelet drugs also are employed.

Antiplatelet Drugs

Antiplatelet drugs function to inhibit platelet aggregation and adhesion. There are three classes: cyclo-oxygenase inhibitors, adenosine diphosphate (ADP) receptor antagonists, and glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists.

Aspirin, a cyclo-oxygenase inhibitor, is a standard antiplatelet drug. It irreversibly inactivates platelet cyclo-oxygenase, thereby inhibiting metabolism of arachidonic acid and subsequent generation of thromboxane A₂. Thromboxane is

Key Facts

- A definitive diagnosis of hypercoagulability is often impossible to make, and empirical therapy may be necessary to reduce the risk of recurrent thrombosis.
- The risk for thromboembolism appears cumulative. Multiple conditions associated with hypercoagulability as well as factors leading to blood stasis or endothelial damage may occur in the same patient.
- Identification of at-risk patients is important to instituting appropriate therapies to prevent thrombus formation, propagation, and recurrence.
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Clotting cascade.

**Intrinsic Pathway**
- XII → Xilla
- XI → Xa
- IX → Xa
- VIII

**Extrinsic Pathway**
- Sepsis
- Infection
- Trauma

**Common Pathway**
- Prothrombin / II
- IIa / Thrombin
- Va

**Fibrinolytic Pathway**
- Plasmin → Plasminogen

**Anticoagulants**

**Endogenous Anticoagulants**

<table>
<thead>
<tr>
<th>Vitamin K-Dependent Coagulation Factors</th>
<th>Factor</th>
<th>Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

**Exogenous Anticoagulants**

- UFH
- LMWH
- Warfarin
- APC
- PC
- PS
- TM
- APC
- SK
- UK
- rPA
- TNH
- tPA
- UFH
- UK

**Unfractionated Heparin**

The anticoagulant activity of unfractionated heparin is due to its high affinity for antithrombin. Once bound with unfractionated heparin, antithrombin undergoes a conformational change that potentiates the inhibition of thrombin and activated factor X (Xa). Heparin anticoagulation is monitored using the activated partial thromboplastin time (aPTT), which evaluates the intrinsic and common coagulation pathways. The goal of anticoagulant therapy is to maintain a therapeutic range of 1.5 to 2.5 times either the patient's baseline aPTT (if available) or the upper limit of the reference interval for aPTT.

The primary limitation of unfractionated heparin is its molecular heterogeneity (molecular weight: 3000 to 35,000 daltons), which results in an anticoagulant response that varies widely among patients. Binding of unfractionated heparin to plasma proteins, platelets, and endothelial cells and the variability of plasma concentrations of heparin-binding proteins in patients with thromboembolic disease contribute to the unpredictable anticoagulant response. Antithrombin levels are reduced with unfractionated heparin use, and to avoid rebound hypercoagulability with cessation...
of therapy, it is important to taper therapy over several days. Concurrent anticoagulation via platelet function inhibition (e.g., aspirin administration) has been demonstrated to reduce the risk of rebound hypercoagulability in people.

Low-Molecular-Weight Heparins
LMWH are manufactured from unfractionated heparin with a uniform molecular weight of approximately 5000 daltons. Although LMWH also exert anticoagulant effects by binding with and catalyzing the activity of antithrombin, their molecular weight allows binding with antithrombin exclusively. By not binding with thrombin, LMWH have less influence on the common coagulation pathway than unfractionated heparin; this explains the lack of increase in aPTT in patients treated with LMWH. In people, treatment with LMWH elicits a more predictable anticoagulant response than does treatment with unfractionated heparin because of the better bioavailability, a longer half-life, and dose-independent clearance of LMWH. Alteration of platelet aggregation is a concern with the use of LMWH in people; however, it has not been found to be a problem in dogs.

Warfarin
Warfarin prevents the activation of the vitamin K–dependent coagulation factors II, VII, IX, and X and proteins C and S. Warfarin inhibits vitamin K epoxide reductase activity in the liver, thereby preventing the regeneration of vitamin K from the epoxide. The onset of action is 2 to 3 days. Rapid inhibition of proteins C and S results in a transient period of hypercoagulability; therefore, heparin should be started concurrently with warfarin for 3 to 5 days to prevent thrombosis. Warfarin therapy is adjusted based on the International Normalized Ratio (INR), which is considered to be superior to the prothrombin time. The INR was developed by the World Health Organization to address wide variations in the thromboplastins used for various prothrombin time (PT) tests between laboratories. It can be calculated by the formula (Patient PT/Control PT)\(^{ISI}\), with ISI being a value specific to the thromboplastin in each PT test. Maintenance of the INR between 2.0 and 3.0 minimizes the risk of hemorrhage without limiting the effectiveness of warfarin therapy. Close monitoring is necessary with warfarin therapy because the anticoagulant effect varies between patients and the most common complication is life-threatening hemorrhage.

Fibrinolytics
Thrombolytic therapy is aimed at lysis of existing thromboemboli. The potential benefits must be balanced against the risk of hemorrhage, which, in people, has been reported to be three times higher in patients treated with fibrinolytics than in patients managed with heparin alone. Traditional fibrinolytics include streptokinase, urokinase, and recombinant tissue plasminogen activator (r-tPA). Streptokinase is produced by β-hemolytic streptococci. Urokinase is a protease that is produced by the kidneys and is naturally found in urine. Streptokinase and urokinase exert fibrinolytic effects by forming complexes with plasminogen, which promotes the formation of plasmin and results in a lytic state. The r-tPA products activate plasminogen to form plasmin, which degrades fibrin and results in clot lysis. The r-tPA products activate bound plasminogen more rapidly than they activate freely circulating plasminogen; thus, they are described as clot-specific agents. Researchers in a 1996 canine study described the successful use of streptokinase in four patients with naturally occurring aortic thromboembolism (ATE). A 1998 case report described the successful use of r-tPA for dissolution of a distal aortic thrombus in a dog. Despite successful clot lysis, one major complication of thrombolytic therapy is life-threatening hemorrhage.

Although much of the documentation of reperfusion injury is from studies of feline ATE, the significance of this complication must not be overlooked. The authors of a 1988 review of r-tPA use in cats with naturally occurring ATE reported mortality rates as high as 50% and attributed these deaths to reperfusion hyperkalemia during clot lysis.

Conclusion
Hypercoagulability describes an imbalance of normal mechanisms involving clot formation or clot lysis that results in a tendency to favor clot formation. In recent years, increased attention has been given to thromboembolism associated with naturally occurring disease. Much of what is understood in animals is extrapolated from human literature. Treatment is typically reserved for patients with documented emboli. Prophylactic therapy also should be considered in patients with risk factors for thromboembolic disease.

### Table 1. Known Etiologic Factors for Thrombotic Events

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Hypercortisolism (hyperadrenocorticism and iatrogenic corticosteroid administration)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Immune-mediated</td>
<td>Immune-mediated hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic enteritis (protein-losing enteropathy)</td>
</tr>
<tr>
<td>Renal</td>
<td>Protein-losing nephropathy</td>
</tr>
<tr>
<td>Inflammatory/infectious</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Paroviral enteritis</td>
</tr>
<tr>
<td></td>
<td>Dirofilariasis</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Acute leukemias</td>
</tr>
<tr>
<td></td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td></td>
<td>Heartworm disease</td>
</tr>
</tbody>
</table>

*Common diseases selected for review of proposed or known mechanisms of hypercoagulability.

Aspirin, heparin, and warfarin have been the mainstays of antithrombotic therapy in veterinary medicine. Pharmacologic thrombolysis also may be a therapeutic option, although it is not as widely used in animals. Anticoagulant and fibrinolytic therapy must be tailored to maximize anticoagulant intensity while minimizing hemorrhagic risks.

References
1. Which statement regarding venous thrombi is false?
   a. Prothrombotic conditions are risk factors for formation of venous thrombi.
   b. Mature venous thrombi contain lower numbers of platelets than arterial thrombi.
   c. Blood stasis is a risk factor for formation of venous thrombi.
   d. As venous thrombi mature, platelets adhere to them, enhancing propagation.

2. Which statement regarding arterial thrombi is true?
   a. Strategies to inhibit arterial thrombogenesis focus mainly on antiplatelet drugs.
   b. Prothrombotic conditions are significant risk factors for formation of arterial thrombi.
   c. Blood stasis is a major risk factor for formation of arterial thrombi.
   d. Arterial thrombi contain lower numbers of platelets than venous thrombi.

3. Which of the following statements regarding antiplatelet drugs is true?
   a. Aspirin reversibly binds to and inhibits cyclo-oxygenase.
   b. GPIIb/IIIa receptor antagonists are oral drugs that enhance platelet aggregation.
   c. Clopidogrel is an ADP receptor antagonist that inhibits platelet recruitment.
   d. Aspirin therapy increases production of thromboxane A₂—enhancing platelet aggregation.

4. Heparin enhances the activity of which anticoagulant?
   a. protein C
   b. protein S
   c. tPA
   d. antithrombin

5. Which statement regarding unfractionated heparin or LMWH is true?
   a. LMWH bind primarily to activated factor X.
   b. Unfractionated heparin binds to activated factor X and factor II (thrombin).
   c. The primary mechanism of action of unfractionated heparin is to enhance the activity of plasminogen.
   d. The advantages of LMWH, compared with unfractionated heparin, are better bioavailability, a longer half-life, and dose-independent clearance.

6. Which of the following is a recognized limitation of unfractionated heparin use?
   a. high cost
   b. unpredictable anticoagulant response
   c. inhibition of thrombin and activated factor X
   d. prolongation of the aPTT

7. Which is not a characteristic of LMWH?
   a. molecular weight of 5000 daltons
   b. does not bind to thrombin
   c. improved bioavailability over unfractionated heparin
   d. causes a predictable prolongation of the aPTT

8. Which statement regarding warfarin therapy is false?
   a. Warfarin prevents activation of vitamin K–dependent factors II, VII, IX, and X.
   b. Warfarin prevents the activation of proteins C and S.
   c. Warfarin therapy must be closely monitored to prevent hemorrhage.
   d. Warfarin enhances the activity of antithrombin.

9. ______ requires close monitoring to prevent hemorrhagic complications associated with its use.
   a. Warfarin
   b. Clopidogrel
   c. Aspirin
   d. LMWH

10. Which statement regarding fibrinolytic therapy is false?
    a. Reperfusion injury is a potential complication of fibrinolytic therapy.
    b. Fibrinolytic therapy is aimed at lysis of existing thrombo-emboli.
    c. Fibrinolytic therapy is not associated with an increased risk of hemorrhage.
    d. Fibrinolytics activate plasminogen to form plasmin, which results in a lytic state.