Thrombi form when one or more of the following mechanisms are present: blood stasis, endothelial cell activation or damage, platelet activation, activation of the coagulation cascade, inhibition of fibrinolysis, and deficiencies or abnormalities in anticoagulant proteins. Blood stasis alters blood flow, decreases the clearance of activated clotting factors, and promotes clot formation, especially when tissue injury is present. Damage to the endothelium of blood vessels, commonly seen with cardiomyopathy, presents reactive substances to the circulating blood, thereby promoting platelet adhesion and aggregation and triggering a thrombotic process.

Hypercoagulability refers to a qualitative and quantitative change in hemostasis. Decreased levels of antithrombin, proteins C and S, plasminogen, and tissue plasminogen activator (TPA); increased levels of plasminogen activator inhibitor 1 (PAI-1); and increased platelet aggregation have been implicated in hypercoagulability.

In the cell-based model of coagulation, the coagulation cascade is initiated by tissue factor (TF; FIGURE 1). TF is a transmembrane protein released from fibroblasts when vessels are injured. Cytokines, endotoxins, and other inflammatory mediators may induce TF synthesis. TF binds with factor VII to form the TF-FVIIa complex. This complex activates factors IX and X, eventually producing thrombin and factor Va. Thrombin then activates factor XI (leading to production of factor IXa from factor IX), factor V, and factor VIII. Activated factor IX (factor IXa), activated factor VIII (factor VIIIa), and calcium ions form the prothrombinase complex, which binds to phosphatidylserine on platelets, amplifying the production of factor X and thereby generating production of large amounts of thrombin (via factor Xa and prothrombin).

In addition to activating factors in the coagulation cascade, thrombin cleaves fibrinogen to fibrin and inhibits fibrinolysis, allowing fibrin to stabilize the platelet plug. Thrombin also binds to thrombomodulin on endothelial cells. The resulting complex activates protein C. Activated protein C and protein S inhibit the activation of factor V and factor VIII, decreasing the production of thrombin, which reduces fibrin formation, allowing fibrinolysis.

Fibrinolysis is initiated when plasminogen is activated to plasmin and is accomplished by the release of TPA from endothelial cells. Fibrinolysis is needed to restore patency to vessels after hemorrhage has been controlled with a hemostatic plug. Plasmin breaks down fibrin and fibrinogen to fibrin degradation products. When cross-linked fibrin is lysed by plasmin, small segments are formed that can be measured with the dimerized plasmin fragment D (D-dimer) test.

Pathophysiology

Pulmonary thromboembolism (PTE) occurs when venous thrombi produced in large, deep veins travel through the right side of the heart and lodge in the pulmonary arterial bed. The caudal lung lobes are more likely to be involved because they receive most of the right ventricular output. Consequences of PTE include hypoxemia, bronchoconstriction, ventilation-perfusion (V-Q) mismatch, and hyperventilation. With time, further complications arise, such as atelectasis, pulmonary edema, and pleural effusion. Hemodynamic complications from PTE depend on the extent to which the pulmonary vasculature is occluded and the amount of preexisting cardiac and pulmonary compromise. If the reserve capacity of the pulmonary vasculature is exceeded, pulmonary vascular resistance increases, causing increases in right ventricular afterload and ventricular oxygen demand. If the oxygen supply is insufficient, hypoxemia may develop.
Pulmonary Thromboembolism

exceeded, ischemia, arrhythmias, or right ventricular failure may follow. Decreased cardiac output is a secondary complication of PTE caused by the obstruction of pulmonary blood flow, which decreases pulmonary venous return.

**Predisposing Factors**

PTE is associated with many diseases in dogs and cats, such as immune-mediated hemolytic anemia, nephrotic syndrome, hyperadrenocorticism, neoplasia, pancreatitis, and sepsis (BOX 1). Hyperadrenocorticism leads to thrombus formation from an increase in factors V, VIII, IX, and X; fibrinogen; and plasminogen, as well as a decrease in antithrombin from hypertension-induced urinary loss. Obesity and hypercholesterolemia seen with hyperadrenocorticism may also contribute to thrombus formation. Nephrotic syndrome leads to multiple hemostatic abnormalities such as decreased antithrombin levels and hypoalbuminemia from urinary loss and endothelial damage from hypercholesterolemia. Elevated cholesterol levels alter platelet surface membranes, thereby increasing platelet aggregability. Hypoalbuminemia from urinary loss increases thromboxane production and results in increased platelet sensitivity. Although low antithrombin levels are also seen with protein-losing enteropathy, gastrointestinal diseases associated with protein loss typically do not involve thromboembolic risk because procoagulant and anticoagulant factors are lost in proportion to antithrombin.

During pancreatitis, active proteolytic enzymes enter the vascular space. Normally, these enzymes are bound by free α-macroglobulins and cleared from the plasma by the reticuloendothelial system. When α-macroglobulins are no longer available, due to excessive levels of proteolytic enzymes, the active proteases activate the coagulation and fibrinolytic systems. Sepsis may lead to thrombosis by causing endothelial damage and activating factor XII and platelets. Sepsis may also inhibit fibrinolysis by consuming antithrombin and reducing plasmin activity. Placement of an intravenous catheter is an additional risk factor discovered in studies done in 1990 and 1999 (77% and 80%, respectively, of dogs with PTE). Intravenous catheters and the infusion of nonisotonic solutions may cause endothelial damage that may lead to PTE. Immune-mediated hemolytic anemia leads to a prothrombotic state by exposing the erythrocyte membrane. An accompanying increase in acute-phase proteins leads to a deficiency in fibrinolysis.

In diabetes mellitus, decreased production of prostacyclin and increased production of thromboxane cause platelet hyperaggregability. Neoplasia can also cause hypercoagulability. A procoagulant factor that activates factor X has been found in tumors and has been shown to inhibit the fibrinolytic system in people.

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**Figure 1. The clotting cascade.** TF = tissue factor, TPA = tissue plasminogen activator, UPA = urokinase-like plasminogen activator.
**Box 1. Diseases Associated With Pulmonary Thromboembolism**

- Heartworm disease
- Neoplasia
- Immune-mediated hemolytic anemia
- Sepsis
- Hyperadrenocorticism
- Diabetes mellitus
- Pancreatitis
- Systemic inflammatory response syndrome
- Cardiomyopathy
- Protein-losing nephropathy
- Nephrotic syndrome
- Disseminated intravascular coagulation
- Vasculitis
- Polycythemia

**Diagnosis**

Diagnosing PTE is difficult. The clinical signs typically include tachypnea, dyspnea, and hypoxemia, none of which is pathognomonic for PTE. If PTE is suspected, the initial assessment should include thoracic radiography, abdominal ultrasonography, arterial blood gas analysis, a blood chemistry profile, heartworm testing, a complete blood count, and urinalysis. If the results of these tests fail to identify an underlying disease process, then further diagnostics should be performed, such as echocardiography, prothrombin time/partial thromboplastin time, D-dimer measurement, and testing for hypercoagulability. Testing for hypercoagulability includes thromboelastography and measuring antithrombin and fibrinogen levels. Advanced imaging that may aid in the diagnosis of PTE includes V-Q scans, spiral computed tomography (CT), and pulmonary angiography.

**Radiography**

Thoracic radiographs should be taken; however, they are often normal. Radiographic abnormalities that have been associated with PTE include pleural effusion, regional oligemia, alveolar infiltrates, cardiomegaly, hyperlucent lung regions, and enlargement of the main pulmonary artery. Regional oligemia represents reduced vascular filling distal to the thrombotic occlusion and appears as areas of increased radiolucency. In studies, 9% to 27% of dogs and 7% of cats with PTE had normal radiographs.

**Arterial Blood Gas Analysis**

Because PTE results in hypoxemia from V-Q mismatch, arterial blood gas analysis may be an important diagnostic tool. In one study, arterial blood gas analysis revealed that 80% of dogs with PTE were hypoxic and all dogs had increased alveolar-arterial oxygen gradients on room air. Arterial PaO₂ may be low or normal because of hyperventilation. Administration of oxygen corrects hypoxemia caused by V-Q mismatch, alveolar hypoventilation, or diffusion impairment by increasing PaO₂. In patients with PTE, the response to oxygen depends on the degree of vascular obstruction. When >50% of the surface area of the circulatory bed is obstructed, intrapulmonary shunting occurs, leading to venous admixture of blood and decreased oxygen responsiveness.

**Echocardiography**

Echocardiography may be useful in evaluating patients suspected of having a PTE. The echocardiogram rarely shows a right-sided thrombus or a thrombus in the main pulmonary artery, but it may show changes suggestive of pulmonary hypertension or PTE, such as dilation of the pulmonary trunk and right-sided chambers. However, a normal echocardiogram does not rule out PTE.

**D-dimer Measurement**

D-dimer is produced from the degradation of cross-linked fibrin, which is specific to active coagulation and fibrinolysis. Measurement of D-dimer has been useful for the detection of early embolism. A 2003 study determined that D-dimer concentrations >500 ng/mL were 100% sensitive for predicting thromboembolic disease, but the specificity was 70%. When the D-dimer concentration was >1000 ng/mL, the sensitivity was 80% and the specificity was 94%; when the concentration was >2000 ng/mL, the sensitivity was 35% and the specificity was 98.5%. The sensitivity of D-dimer in the diagnosis of PTE is more important than the specificity, as false negatives can have fatal consequences.

**Testing for Hypercoagulability**

Identification of a hypercoagulable state does not confirm or predict PTE but simply indicates potential risk. Thromboelastography (TEG) may be used as an overall assessment of hypercoagulability. TEG assesses the hemostatic function in whole blood by evaluating the interaction between the cellular and plasma components involved in clot formation and fibrinolysis. Specifically, TEG evaluates all steps of hemostasis, including initiation, amplification, propagation, and fibrinolysis, including the interaction of platelets with proteins of the coagulation cascade. Hyperfibrinogenemena may indicate a hypercoagulable state, but most patients with PTE do not have elevated fibrinogen levels. Antithrombin levels may be assessed because a deficiency of antithrombin has been correlated with an increased risk of thrombosis. Antithrombin levels 50% to 75% of normal result in a moderate risk of thromboembolism, while levels <50% result in a severe risk. However, normal antithrombin levels do not rule out a hypercoagulable state.

**Advanced Imaging**

Pulmonary angiography, V-Q scans, or postmortem findings can provide a definitive diagnosis of PTE. Pulmonary angiography may reveal a filling defect if thromboemboli completely occlude a vessel. If angiography is going to be used, it should be performed as soon as possible because thromboemboli in dogs may dissolve quickly. Dogs or cats undergoing pulmonary angiography should first be evaluated for pulmonary hypertension because dogs or cats with severe pulmonary hypertension may die acutely following injection of the contrast media into the pulmonary circulation.
In pulmonary angiography, iodinated contrast medium is injected into the pulmonary artery. The pulmonary vasculature is then visualized using radiology or fluoroscopy. Intraluminal filling defects, abrupt termination of pulmonary arteries, or the complete absence of pulmonary branches are diagnostic for PTE. Findings supportive of PTE include asymmetric blood flow, tortuous pulmonary arteries, abrupt tapering of pulmonary vessels, and a regional loss of vascularity. These signs are referred to as Hampton hump and the Westermark sign in human medicine.

Pulmonary angiography requires general anesthesia, is invasive, and poses a significant risk to the patient. Nonselective angiography is easier and safer for the patient. General anesthesia is not usually required, and the contrast medium is injected into the right side of the heart or jugular vein. However, this study may be more difficult to interpret due to dilution of the contrast medium by venous blood and superimposition of vascular structures.

V-Q scans using radioisotopes may be used to diagnose PTE, but access to this type of testing is limited. Perfusion scans are noninvasive and are performed by injecting radiolabeled albumin intravenously. If the scan is normal, then PTE cannot be ruled out. If the perfusion scan is abnormal, a ventilation scan should be performed. Unfortunately, any disease causing hypoventilation may cause an area of hypoperfusion on the study. Abnormal perfusion scans are seen with regional perfusion deficits such as those in pulmonary parenchymal disease, chronic obstructive pulmonary disease, or bronchoconstriction. To diagnose PTE, an area that has hypoperfusion without hypoventilation has to be identified.

Spiral CT is often used in the diagnosis of embolism in humans because, unlike V-Q scans, it allows direct visualization of the thrombi. Studies in humans have shown CT to have a sensitivity and specificity between 70% and 100%. However, a normal CT scan cannot be used to rule out a PTE with the same degree of certainty that a V-Q scan can.

Treatment
Pulmonary thromboemboli usually begin to dissolve without treatment within hours of formation and may completely dissolve in days. However, a prothrombotic tendency persists, so pulmonary thromboemboli continue to form. The goals of treatment are reversal of the prothrombotic state and correction of the hemodynamic and pulmonary changes responsible for morbidity and mortality. Treatment of PTE usually consists of supportive care, administration of oxygen, and anticoagulant therapy (TABLE 1 and TABLE 2). Resolution of the underlying disease process should always be the primary goal.

**Antiplatelet Therapy**
Antiplatelet drugs such as aspirin and clopidogrel inhibit platelet aggregation. Aspirin is commonly used in veterinary medicine for this role. It is a cyclooxygenase (COX) inhibitor that prevents the formation of prostaglandins such as thromboxane A2 and prostacyclin. Thromboxane A2 is produced by platelets and induces platelet aggregation. Prostacyclin is produced by vascular

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**Table 1. Dosing Recommendations for Antiplatelet, Anticoagulant, and Thrombolytic Therapy for Dogs**

<table>
<thead>
<tr>
<th>Antiplatelet Therapy</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.5 mg/kg PO q24h</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.5 mg/kg PO q24h</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulant Therapy</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>IV bolus: 80–100 U/kg</td>
</tr>
<tr>
<td></td>
<td>CRI: 18 U/kg/h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombolytic Therapy</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Loading dose: 5200–18,000 U/kg over 30 min 1 to 3 times</td>
</tr>
<tr>
<td>Tissue plasminogen activator (TPA)</td>
<td>1 mg/kg IV over 15 to 20 min q60–180 min until improvement, then repeat as needed</td>
</tr>
</tbody>
</table>

**Table 2. Dosing Recommendations for Antiplatelet, Anticoagulant, and Thrombolytic Therapy for Cats**

<table>
<thead>
<tr>
<th>Antiplatelet Therapy</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>5 mg/cat q3d</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>18.75 mg/cat PO q24h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulant Therapy</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Loading dose: 100 U/kg IV</td>
</tr>
<tr>
<td></td>
<td>CRI: 10–30 U/kg/h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombolytic Therapy</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Loading dose: 90,000 U over 20–30 min</td>
</tr>
<tr>
<td>Tissue plasminogen activator (TPA)</td>
<td>0.25–1.0 mg/kg/h for a total dose of 1–10 mg/kg</td>
</tr>
</tbody>
</table>

**aPTT** = activated partial thromboplastin time, **CRI** = constant-rate infusion.
endothelium, inhibits platelet aggregation, and is derived from COX-1 and COX-2. Aspirin is about 50 times more potent at inhibiting COX-1 than COX-2. Ultra-low-dose aspirin is used with the goal of inhibiting thromboxane A2 production without affecting prostacyclin production. The antiplatelet effects of aspirin are irreversible and rapid, and the gastrointestinal effects are dose related. A study done in dogs with immune-mediated hemolytic anemia indicated that ultra-low-dose aspirin (0.5 mg/kg PO q24h) might be effective at inhibiting platelet aggregation.14

Clopidogrel is a thienopyridine that selectively inhibits ADP-induced platelet aggregation.17 This medication has no effect on COX, suggesting that it may work synergistically with aspirin. The onset of action may take up to 2 days, and a steady state is reached in 5 to 7 days; like aspirin, the effect of clopidogrel on platelets is irreversible.14

**Anticoagulant Therapy**

Heparin and warfarin do not dissolve existing thrombi; they are used to prevent the formation of new thrombi. Heparin activates antithrombin and accelerates the neutralization of activated factor X and thrombin, whereas warfarin inhibits synthesis of vitamin K–dependent clotting factors (II [prothrombin], VII, X, XI). Studies19 have shown that the dose of heparin required to prevent thrombus formation prolonged the activated partial thromboplastin time (aPTT) to 1.5 to 2 times normal; therefore, the goal of heparin therapy is to achieve this aPTT. These studies also found that when the aPTT was <1.5 times normal, the risk of thromboembolism recurrence increased.10 Warfarin can be given orally to achieve an aPTT of 1.5 to 2 times normal, but 2 to 7 days of therapy may be needed to reach this goal. Only factor VII and protein C are significantly affected when warfarin therapy is first started; thus, thrombosis is still possible. Administering heparin can counteract the risk for thrombosis early in warfarin therapy. Baseline clotting times should be evaluated before starting heparin treatment and again 6 hours later. The dose of heparin should be adjusted accordingly to prolong the aPTT to 1.5 to 2 times normal. Clotting times should then be assessed daily until the aPTT has stabilized within the 1.5 to 2 times normal range, which can take up to 5 days.

In its Sixth Consensus Conference on Antithrombotic Therapy, the American College of Chest Physicians recommends an intravenous bolus of heparin followed by a constant-rate infusion to prevent thrombosis in humans with PTE.16 For dogs, an intravenous bolus of 80 to 100 U/kg is given, followed by a constant-rate infusion of 18 U/kg/h.14 For cats, an intravenous bolus of 100 U/kg is given, followed by a constant-rate infusion of 10 to 30 U/kg/h.14 Studies in humans16 have shown no increase in major bleeding when this protocol is used compared with subcutaneous administration. For acute PTE, subcutaneous administration of heparin is not recommended because it may take significantly longer to reach the target aPTT range. It is also important to remember that antithrombin is required for heparin to work, so patients with documented or suspected antithrombin deficiency should be given a plasma transfusion.14

Hemorrhage can be a serious complication of heparin therapy. Protamine sulfate, a heparin antagonist, may be given if bleeding cannot be controlled after heparin therapy has been discontinued. Heparin therapy should be tapered over several days to prevent rebound hypercoagulation after cessation of therapy.19 Hemorrhage is also a potential complication of warfarin therapy and may be treated with plasma or vitamin K₃. However, if vitamin K₃ is used, further treatment with warfarin is contraindicated for several weeks.

**Thrombolytic Agents**

Thrombolytic agents convert inactive plasminogen to active plasmin. Plasmin is a proteolytic enzyme that stimulates fibrin breakdown. Thrombolytic agents include streptokinase, urokinase, TPA, single-chain urokinase-type plasminogen activator, and anisoylated plasminogen-streptokinase activator complex.

Streptokinase is a first-generation thrombolytic agent that acts by binding to plasminogen and converting it to plasmin. It has no direct fibrin-binding properties, and it causes degradation of circulating fibrinogen, leading to an accumulation of fibrinogen degradation products. Coagulation factors V and VIII and prothrombin are also degraded by streptokinase, leading to the potential for massive bleeding. Streptokinase interrupts newly forming fibrin networks by substituting for fibrinogen in the process of fibrin polymerization. The half-life of streptokinase is 30 minutes, and the depletion of fibrinogen increases coagulation times for up to 24 hours after administration.18

Urokinase is another first-generation thrombolytic agent. It is found in urine and produced from fetal kidney cells. Urokinase directly converts plasminogen to plasmin.20 Common formulations include a combination of high-molecular-weight urokinase and a small amount of low-molecular-weight urokinase. The high-molecular-weight urokinase is converted to fibrin-specific low-molecular-weight urokinase in the blood. Low-molecular-weight urokinase has an affinity for lysine plasminogen, which accumulates within thrombi.18 The half-life of urokinase is 16 minutes, and thrombolytic activity stops rapidly when the infusion is stopped. In humans, urokinase is recommended only for acute myocardial infarction and PTE.18

TPA is a second-generation thrombolytic agent. Its mechanism of action involves the formation of a complex between fibrin, TPA, and plasminogen.13 TPA has a high affinity for fibrin because of a fibrin binding site, preferentially activating thrombus-associated plasminogen.13 When TPA is used for thrombolysis, the risks of proteolysis and excessive bleeding increase.13 In cats, the administration of TPA at a rate of 0.25 to 1 mg/kg/h for a total dose of 1 to 10 mg/kg was associated with resolution of the primary thrombus on angiography. Forty-three percent of cats survived treatment and were walking within 48 hours; however, 50% of cats died during therapy due to ischemia-reperfusion injury.18 Some success was seen in a few dogs when TPA given as a bolus injection was used together with heparin.14 Bolus injections of 1 mg/kg were given over 15 to 20 minutes every 60 to 180 minutes until there was evidence of improvement and then repeated as needed. At this
dose, no major hemorrhage was seen, and minor hemorrhage was controlled by temporarily stopping the administration.14

Further study is needed to evaluate the efficacy of thrombolytics in veterinary medicine.

Conclusions
Diagnosis of PTE can be difficult, primarily because the clinical signs may resemble those of many different diseases and the tests required for a definitive diagnosis are invasive and specialized. Because the mortality rate for PTE is significant and veterinary experience with thrombolytics is limited, the focus should be on prevention. Knowing which diseases increase risk and how they affect the Virchow triad can help direct treatment. Patient survival depends on rapid diagnosis and instituting appropriate therapy without delays.

References
1. Heparin accelerates the neutralization of clotting factor
   a. VIIIa.
   b. IXa.
   c. Xa.
   d. XIa.

2. Protein-losing enteropathy does not typically lead to PTE because
   a. antithrombin is not lost.
   b. only larger procoagulant factors are lost.
   c. procoagulant and anticoagulant factors are lost in proportion to antithrombin.
   d. only smaller anticoagulant factors are lost.

3. Which change(s) is/are involved in thrombus formation resulting from hyperadrenocorticism?
   a. increased plasminogen, fibrinogen, and factors V, VIII, IX, and X; decreased antithrombin
   b. decreased factors VIII, IX, and X
   c. increased antithrombin
   d. decreased plasminogen, fibrinogen, and factors VII and VIII

4. Testing for hypercoagulability should include
   a. thromboelastography and measuring antithrombin and fibrinogen levels.
   b. D-dimer and fibrinogen levels.
   c. arterial blood gas analysis.
   d. a complete blood count.

5. Which statement(s) about aspirin is/are true?
   a. It only inhibits COX-1.
   b. It inhibits COX-1 and COX-2.
   c. Its effects on platelets are rapid and irreversible.
   d. b and c

6. Which statement about streptokinase is false?
   a. It acts by binding to plasminogen, converting it to plasmin.
   b. It substitutes for fibrinogen in fibrin polymerization.
   c. It binds directly to fibrin.
   d. It degrades prothrombin and coagulation factors V and VIII.

7. Which statement about TPA is true?
   a. It is a first-generation thrombolytic agent.
   b. It has a high affinity for fibrin because of a fibrin binding site, preferentially activating thrombus-associated plasminogen.
   c. It binds directly to plasminogen.
   d. When it is used for thrombolysis, the risks of proteolysis and hemorrhage do not increase.

8. PTE is seen with pancreatitis because
   a. active proteolytic enzymes gain access to the vascular space.
   b. α2-macroglobulins that normally bind proteolytic enzymes are no longer available.
   c. active proteolytic enzymes activate the coagulation and fibrinolytic systems.
   d. all of the above

9. Increased production of ________ and decreased production of ________ lead to PTE in diabetes mellitus.
   a. prostacyclin; thromboxane
   b. thromboxane; prostacyclin
   c. prostacyclin; acute phase proteins
   d. thromboxane; clotting factors

10. Sepsis leads to thrombosis by causing endothelial damage and activation of factor
    a. VIII.
    b. IX.
    c. X.
    d. XII.