Thrombosis, Hypercoagulable States, and Anticoagulants

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KEYWORDS

• Venous thromboembolism • Pulmonary embolism • Deep venous thrombosis
• Thrombophilia • Anticoagulation

KEY POINTS

- Thrombophilias are inherited or acquired derangements of secondary hemostasis that confer an increased risk of VTE.
- The most common inherited thrombophilias are factor V Leiden and the prothrombin gene mutation.
- The goal of the history and physical examination in a patient with suspected VTE is to determine the pretest probability of VTE, which should guide the decision of whether to pursue further work-up with D dimer or imaging.
- Testing for hypercoagulable disorders should be pursued only in patients with VTE who have an increased risk for an underlying hypercoagulable disorder.
- DOACs are the preferred medications for VTE treatment except in patients who are pregnant, have active cancer, antiphospholipid antibody syndrome, severe renal insufficiency, or prosthetic heart valves.

INTRODUCTION

Venous thrombemboli (VTE) are major causes of morbidity and mortality. The two most common types of VTE, deep venous thrombosis (DVT) and pulmonary embolism (PE), have an estimated incidence of 900,000 and mortality of 100,000 to 180,000 in the United States each year.[1,2] This article reviews the pathophysiology, diagnosis, and management of venous thromboembolic disease, with an emphasis on hypercoagulable states and direct oral anticoagulants (DOACs).

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PATHOPHYSIOLOGY

Venous thrombosis results from derangements of the hemostatic mechanism, which involves interactions between the vascular endothelium, platelets, and coagulation proteins. There are two components of hemostasis: primary hemostasis, which is initiated when endothelial injury results in exposure of subendothelial matrix components, triggering platelet adherence, activation, and aggregation; and secondary hemostasis, the coagulation cascade–dependent deposition of fibrin that forms a mesh that stabilizes the platelet plug. The coagulation cascade involves a series of proenzymes that are serially activated in a process that culminates in the formation of fibrin (**Fig. 1**). Predisposing factors to venous thrombosis are describe by Virchow's triad: (1) venous stasis, (2) hypercoagulability (inherited or acquired abnormality of secondary hemostasis), and (3) vascular injury.

There are several endogenous negative regulators of the coagulation cascade, including protein C, protein S, and antithrombin (AT) III. Thrombin converts protein C to activated protein C (APC). APC acts in concert with protein S to proteolytically inactivate factors Va and VIIIa, providing a negative feedback loop that limits thrombin production. AT III binds to and inactivates thrombin, factor Xa, and other clotting cascade proteases.

TYPES OF THROMBOSIS

DVT is clotting of blood in a deep vein, most commonly of the lower extremity. Lower extremity DVTs are classified as distal if the thrombi are confined to deep calf veins, and proximal if there is thrombosis in the popliteal or more proximal veins (femoral or iliac). Proximal DVTs are at higher risk of progression to PE than distal DVTs. Upper extremity DVT most commonly occurs as a result of endothelial trauma caused by placement of intravenous catheters.

Most commonly, a PE develops when a DVT detaches from its site of origin and travels through progressively larger veins, eventually reaching the right side of the heart and then lodging in the pulmonary artery or one of its branches.

DVT and PE are the most common venous thrombotic conditions and the most common presenting manifestations of hypercoagulable states. There are a variety of less common venous thrombotic presentations that occur with increased frequency in certain hypercoagulable states (**Tables 1** and **2**).

HYPERCOAGULABLE STATES

Inherited Thrombophilia

The most common cause of inherited thrombophilia is the factor V Leiden mutation, and the second most common cause is the prothrombin gene mutation (see **Table 1**). Together these account for about half of the inherited thrombophilias. The remainder is mostly caused by defects of AT, protein S, and protein C.

A single point mutation in the factor V gene results in the production of factor V Leiden, which is resistant to cleavage by protein C. Risk of thrombosis is increased in factor V Leiden heterozygotes, and is even higher in homozygotes (see **Table 1**). The most common clinical manifestation in patients with factor V Leiden is DVT with or without PE, but these patients are also at increased risk for other venous thromboses, such as cerebral, mesenteric, and portal vein. Testing for factor V Leiden is done either via genetic testing of peripheral blood to look for the causative mutation, or via functional APC resistance assays.