Hypercoagulable States
What the Oral Surgeon Needs to Know

Robert Bona, MD*

KEYWORDS

• Thrombophilia • Hypercoagulable • Factor V Leiden • Protein C • Protein S

KEY POINTS

- Factor V Leiden and prothrombin G20210A gene mutations are relatively common inherited thrombophilic abnormalities in the Caucasian population conferring the individual with a small increase risk for venous thrombosis.
- Antithrombin, protein C, and protein S deficiency are less common abnormalities that confer the individual with a significantly higher risk for venous thrombosis.
- The development of phospholipid antibodies is an autoimmune condition that predisposes the individual to arterial thrombosis, venous thrombosis, and/or pregnancy loss.
- Cancer is a common cause of thrombophilia.
- Long-term anticoagulation is often considered in these individuals; but treatment should be individualized, balancing the risk of thrombosis with the risk of bleeding with anticoagulant drugs.

NORMAL HEMOSTASIS

Normal clotting of the blood relies on several component parts, including functional platelets, intact endothelium, and normal coagulation proteins to name the most obvious elements. Physiologic clot formation in response to injury is limited by several anticoagulant proteins/factors. In the same way, abnormal clotting (thrombosis) is also prevented by the presence of these same factors. Although a deficiency of a procoagulant clotting protein (factor VIII) can lead to a bleeding disorder, a deficiency of or abnormality of these anticoagulant factors can lead to a hypercoagulable or thrombophilic condition.[1,2]

MAJOR ANTICOAGULANT MECHANISMS OF BLOOD

Endothelial Cell

The endothelium serves several important functions in the prevention of clot extension outside the direct area of injury and prevention of thrombosis.[3]

- First and foremost, the endothelial cells serve as a barrier between the flowing blood and the underlying stroma (collagen) and cells. Collagen is able to engage von Willebrand factor in the blood and begin the process of platelet adhesion, and subendothelial cells (smooth muscle cells, pericytes, fibroblasts) express tissue factor on their surface. Tissue factor interaction with factor VIIa in the blood will result in the rapid initiation of the coagulation cascade and fibrin deposition.
- Secondly, the endothelium synthesizes and secretes products that impair platelet aggregation. These products include the arachidonic acid metabolite, prostacyclin (PGI_2), and CD39, which is an ADPase. This enzyme degrades ADP to AMP and then adenosine, thereby neutralizing the potent proaggregation effect of ADP on circulating platelets.

Disclosures: None.
Frank H. Netter School of Medicine, Quinnipiac University, 275 Mount Carmel Avenue, MNH 307L, Hamden, CT 06518-1908, USA
* Corresponding author. North Haven Campus, 370 Bassett Road, MNH 307L, North Haven, CT 06473
E-mail address: robert.bona@quinnipiac.edu

Oral Maxillofacial Surg Clin N Am 28 (2016) 491–495
http://dx.doi.org/10.1016/j.coms.2016.06.002
1042-3699/16/$ – see front matter

- The production of glycosaminoglycans and expression of those compounds on the surface of endothelial cells: These complex proteoglycans enhance that action of antithrombin (AT) (see later discussion) as a potent inhibitor of the serine proteases in the coagulation reactions.
- Expression of thrombomodulin and the protein C (PC) receptor: The interaction of these receptors with their ligands results in the conversion of the zymogen PC to its active enzymatic form (activated PC) (see later discussion).
- Tissue factor pathway inhibitor (TFPI): TFPI is an inhibitor of the tissue factor pathway of coagulation. It initially binds to activated factor X (Xa) and the complex binds to the tissue factor-VII complex, thereby inhibiting the activity of the tissue factor.
- Fibrinolytic proteins: The endothelium can synthesize and secrete both profibrinolytic and antifibrinolytic proteins (tissue plasminogen activator and plasminogen activator inhibitor, respectively).

Circulating Proteins

Antithrombin

AT (previously known as AT-III) is a member of the serine protease inhibitor family of proteins. It is synthesized in the liver and circulates in the blood. It has a reactive center that interacts with active serine residue of the coagulation protein (serine enzyme). Once the enzyme cleaves the reactive center, a complex is formed (AT plus coagulation enzyme), which is cleared from the circulation (Fig. 1). Heparin binding to AT increases the availability of the reactive site allowing for a significantly enhanced activity. The endothelial cell–expressed glycosaminoglycans act in this fashion. The serine proteases that are inactivated in this way are primarily IIa (thrombin), factor Xa, and factor IXa.

Protein C/Protein S

PC and protein S (PS) are both vitamin K–dependent proteins synthesized by the liver and posttranslationally modified by the carboxylation of the gamma carbon on the glutamic acid residues on the amino acid terminus of the proteins. PC is a zymogen and requires activation to its active form by limited proteolysis. This activation occurs by the enzyme thrombin, which is brought into close proximity to the necessary cleavage site on PC by binding to the endothelial receptor, thrombomodulin.[4] The activation of PC is optimized by the precise expression of thrombomodulin and the endothelial cell PC receptor (EPCR). When thrombin binds to thrombomodulin and PC binds to its receptor (EPCR), the bound thrombin is able to catalyze the conversion of PC to activated PC (APC). APC along with its cofactor, PS, is able to proteolyze and inactivate coagulation factors Va and VIIIa (Fig. 2). This inactivation occurs optimally on endothelial cell surfaces. Notably, PS exists in 2 forms in the blood, approximately 40% free in the circulation and approximately 60% bound to the complement binding protein, C4b-binding protein. It is only the free PS that can serve as the cofactor for APC activity.

HYPERCOAGULABLE CONDITIONS (SELECTED)

- Inherited
  - AT deficiency
  - PC deficiency

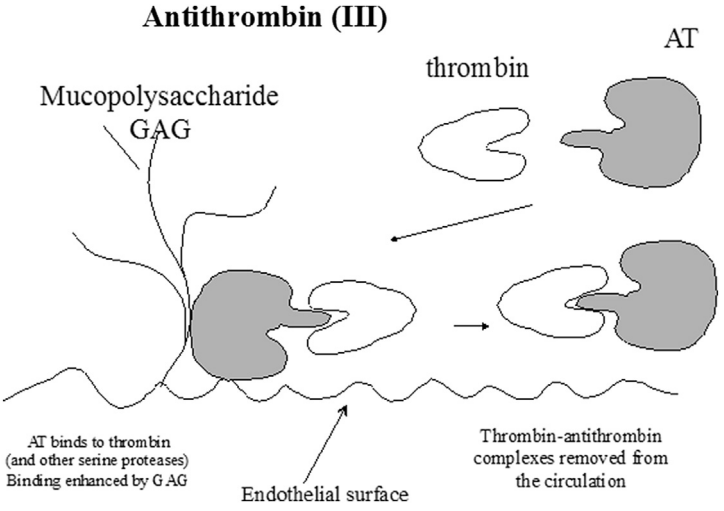

Fig. 1. Mechanism of action of AT. GAG, glycosaminoglycan.