The normal haemostatic system

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The haemostatic system is a critical and closely controlled component of the body's defence system, which provides haemostasis where and when required, in adequate but not excessive amounts. Thrombosis is haemostasis in the wrong place and the wrong time. The haemostatic system closely interacts with other components of the host defence system, including adrenergically mediated acute stress responses, cytokine-initiated inflammation, and healing and immune functions. Our view of the haemostatic system has changed radically — from a series of interacting humoral factors to an integrated cell-based system.[1] In view of the increasing range of focused therapies that modulate haemostasis, it is important to understand the structure and function of the system.

Basis of the haemostatic system

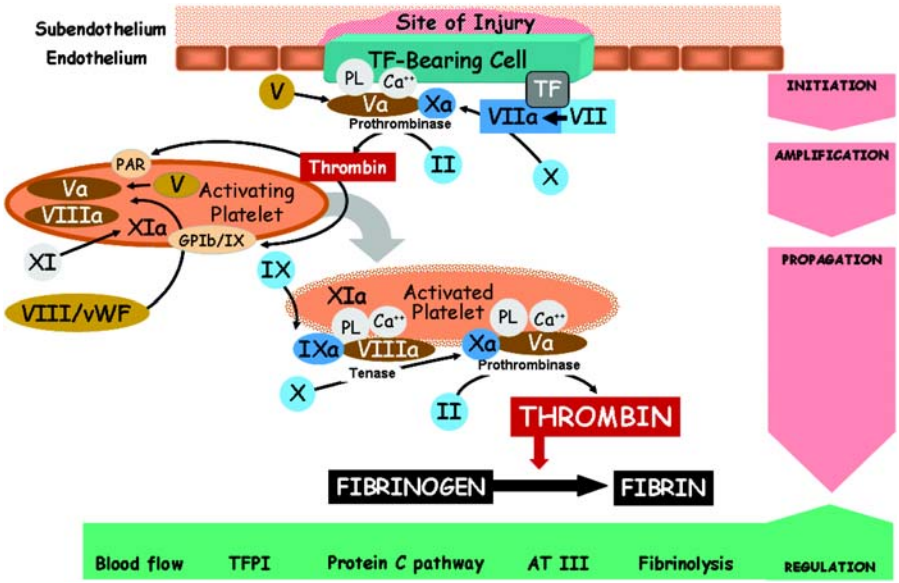
The triad of vascular constriction, platelet plugging and fibrin clot initiation forms haemostatic plugs that provide a framework for haemostasis (Figure 1) and set the scene for healing. Thrombin is the potent proteolytic enzyme of the coagulation sequence that converts fibrinogen to soluble fibrin monomers, which subsequently polymerise to form the fibrin clot. Ironically, thrombin also initiates regulation of the system, especially via the thrombomodulinñprotein C system. Fibrinogen is the bulk protein of the coagulation system, and fibrin is the end-product of a cascade of proteolytic activity. In this cascade, precursor coagulation proteins are activated with the aid of cofactors to become potent proteolytic enzymes, which activate precursors further down the coagulation "amplifier". The polymerised fibrin is modified by factor XIII to form a stable fibrin clot. Thrombin is initially generated in small amounts in relationship to tissue factor-bearing cells, and the process is subsequently transferred to the activated platelet surface, where amplification occurs.

After injury, vascular constriction and, depending on the extent of blood loss, systemic hypotension, minimise bleeding and allow time for haemostasis to begin. Controlled or "tolerated" hypotension is now accepted as an important aspect of managing critical haemorrhage. Vascular constriction is further accentuated by vasoconstrictors released in association with platelet-plug formation. Vascular endothelial cells play an active part by producing substances that act at the membrane surface or interact with platelets and the coagulation system (eg, prostacyclin, antithrombin III, plasminogen activator, von Willebrand factor, thrombomodulin, heparin cofactor II, and nitric oxide).

Following the initial vascular reactions, successful haemostasis depends on adequately functioning platelets, coagulation cascade, and less understood contributions from red cells and leukocytes. The coagulation system is triggered via the extrinsic pathway, by which damaged tissues expose tissue factor (TF).[2] The latter is a membrane-bound protein present in cells surrounding the vascular bed. Factor VII and VIIa (1% circulates normally in the blood) are bound to TF, leading to activation of factor X. Activated factor X (factor Xa) interacts with cofactor Va to form prothrombinase complexes, with the generation of a small amount of thrombin on the cell surface. Factor IX is also activated by the TF–VIIa complex, but plays a limited role in the initiation phase of coagulation, diffusing to platelets that have adhered near the site of the TF-bearing cells, binding to a specific platelet surface receptor and interacting with factor VIIIa leading to activation of factor X directly on the platelet surface. The concept of intrinsic and extrinsic systems of haemostasis is of historical significance, but is now accepted as an artificial division, although it still has value in performing and assessing laboratory investigations of haemostasis.

Von Willebrand factor (vWF) is a multimeric glycoprotein that plays a central role in haemostasis by mediating adhesion of platelets to the exposed subendothelium and linking the primary vascular and platelet phase of haemostasis with coagulation. It does this by acting as the carrier protein for coagulant factor VIII, which dissociates from vWF to form a complex on the activated platelet surface with factor IXa (tenase complex), to activate factor X. VWF is further released from Weibel–Palade bodies in nearby endothelial cells and platelet α-granules. Platelets interact with vWF via surface glycoprotein (GP) Ib–IX–V complexes, slowing their motion along the subendothelium and thus facilitating receptor interaction leading the platelets to bind to collagen. Adhesion to collagen is facilitated by the GPIa–IIa receptor. GPIIb–IIIa can then bind vWF, fibrinogen, fibronectin, vitronectin and thrombospondin, providing further important sites of anchorage for the spreading platelet. The initiation phase of platelet plug formation leads to the development of a platelet monolayer over the injured subendothelium. With the concomitant activation of the coagulation cascade, there is local generation of thrombin. Thrombin is a potent platelet agonist via the protease activated receptor (PAR), producing a haemostatic plug.

Figure 1. Mechanisms of haemostastis



Key: *Roman numerals represent coagulation factors. a = activated. AT III = antithrombin III. GP = glycoprotein. PAR = protease activated receptor. PL = phospholipid. TF = tissue factor. TFPI = tissue factor pathway inhibitor. vWF = von Willebrand factor.*

Further extension occurs by platelet recruitment by platelet agonists, such as thrombin and mediators, ADP and thromboxane A2 released directly from platelets. P-selectin is expressed during activation and also plays a role in platelet-to-platelet cohesion.

Parallel to and within the coagulation system are complex feedback mechanisms that ensure fine tuning and protection against inappropriate and excessive activation. There are several inhibitory proteins, including antithrombin III, thrombomodulin, protein C and protein S, and TF pathway inhibitor, as well as the fibrinolytic system, which are important in controlling the degree and site of fibrin formation. Thrombin itself acts as either a procoagulant or anticoagulant depending on context. Perturbations in this complex defence system can produce a wide range of clinical disorders from excessive arterial or venous thrombosis, microvascular obstruction and atheroma, to haemostatic failure.

Coagulopathy in shock and haemorrhage

There have been interesting new insights into the nature of the initial coagulopathy in patients with hypovolaemic shock and/or hypoxia, in whom it appears to be a mechanism for ensuring fluidity of the blood at times of hypoperfusion, shock, hypoxia or transient cessation of the circulation. Early coagulopathy in trauma victims appears restricted to those who have had tissue hypoperfusion, and is not associated with significant consumption of coagulation factors.[3] The mechanism relates to activation of the protein C anticoagulant system and fibrinolysis.

There is also more attention to the importance of adequate fibrinogen levels. The precursor components of the coagulation cascade need to fall to very low levels before there are serious impacts on haemostatic function. However, this is not the case with fibrinogen, the bulk protein of the system, which must be present at adequate levels for sufficient, stable clot formation.[4] There is now closer attention to maintaining adequate levels of fibrinogen when coagulopathy develops.[5]

Brief mention should be made of recombinant activated coagulation factor VII (rFVIIa, NovoSeven [Novo Nordisk]), as it is being widely used off label, and there is controversy about its benefits and risks. rFVIIa is effective for the prevention or treatment of bleeding in patients with inhibitors to factors VIII and IX. Current insights into haemostatic mechanisms have resulted in a better understanding of the central role that factor VII/VIIa has in the localisation and initiation of haemostasis. Consequently, this has led to the wider use of rFVIIa as a "panhaemostatic" agent. There are numerous case reports and series published on the use of rFVIIa in critical life-threatening haemorrhage.[6] In many cases, control of critical bleeding is possible with surgical haemostasis and blood product replacement to support the underlying coagulopathy. Patients with uncontrolled critical bleeding and coagulopathy, despite large transfusions and surgical intervention have significant mortality rates, and most case reports and case series have described the use of rFVIIa in these type of salvage clinical situations. However, there is increasing interest in the early use of rFVIIa, especially in high-risk cardiac surgery cases and trauma.

Assessing haemostatic function[7]

There may be clinical features suggesting local or generalised failure of the haemostatic system. Clinical history is important, especially with respect to previous bleeding problems, family history, comorbid medical conditions and medications. The nature of surgery or an invasive intervention may have haemostatic issues that need specific consid-

eration. Tests of whole blood clotting time and clot observation do not generally have a role in assessing haemostasis. However, in emergency settings, while waiting for laboratory results, observation of blood collected into a glass tube and maintained at 37° C, for clot formation, size, retraction and possible lysis provides crude information of a possible coagulopathy. The thromboelastogram (TEG) is a more accurate and controlled procedure for global assessment of the haemostatic system at the bedside, but requires close attention to technique and quality control. A full blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level and D-dimer ± thrombin clotting time (TCT) provide a broad screen for most clinically significant haemostatic disorders. Further specific tests of haemostasis may be performed (eg, mixing studies, factor assays, platelet function tests and test of fibrinolytic function). In broad terms, the PT tests integrity of the extrinsic system, the APTT tests the intrinsic system, and the TCT tests fibrinogen conversion. The D-dimer assay measures the breakdown products from lysis of fibrin. The haemostatic system optimally functions at 37° C, and laboratory coagulation tests are performed at that temperature. Hypothermia may severely impair a patientís systemic and local haemostasis, despite the system being structurally intact, and laboratory tests giving results in the reference range.

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