Haemostasis

Steven K Austin

Abstract

Haemostasis involves an explosive reaction, designed to curtail blood loss, restore vascular integrity, provide a barrier to infection and ultimately preserve life. Haemostatic balance is maintained through four key components – vascular endothelium, platelets, coagulation pathway and fibrinolysis. Any imbalance in this tightly regulated process can result in thrombotic or haemorrhagic conditions with associated morbidity and mortality.

Keywords Anticoagulant pathways; coagulation; endothelium; fibrinolysis; haemostasis; platelets

Key points

- The four principal elements essential for functional haemostasis are endothelium, platelets, coagulation factors and their regulators, and the process of fibrinolysis
- Primary haemostasis refers to the role of platelets recognizing injury and interacting with the endothelium and components of the subendothelium to cause an initial arrest of bleeding
- Secondary haemostasis refers to the coagulation process that leads to fibrin formation
- Fibrinolysis and natural anticoagulants aim to limit and remodel a thrombus, and ultimately regulate the control of haemostasis to restore and maintain the delicate haemostatic balance

Introduction

Haemostasis is an essential protective mechanism that depends on a balance between procoagulant and anticoagulant processes. Rapid transformation of blood from its fluid state into a localized thrombus at the site of tissue damage is controlled by an intricate interplay of four key components – vascular endothelium, platelets, the coagulation pathway and fibrinolysis; each is discussed in turn.

Endothelium

The role of the endothelium is multifaceted. It acts primarily as a physical barrier separating haemostatic blood components from reactive subendothelial structures. It modulates vascular tone and permeability. In addition, endothelial cells produce inhibitors of coagulation and platelet aggregation (Figure 1). Expression of specific proteins (thrombomodulin) and mucopolysaccharides (heparan sulphate, dermatan sulphate) promote an anticoagulant effect by accelerating the action of circulating natural anticoagulants. Platelet aggregation is inhibited by endogenous synthesis of ectoenzymes, which degrade adenosine diphosphate (ADP; a platelet agonist), and production of prostacyclin and nitric oxide. Finally, the endothelium modulates fibrinolysis by producing activators and inhibitors of clot lysis.

Tissue damage disrupts the integrity of the endothelial basement membrane, exposing the underlying extracellular matrix and prothrombotic haemostatic factors, including collagen, von Willebrand factor (VWF), fibronectin (promotes platelet adhesion) and tissue factor (TF). Additionally, antithrombotic endothelial properties are lost when stimulated by thrombin, shear stress, oxidants, endotoxin or cytokines interleukin-1, tumour necrosis factor and interferon-γ. Activated endothelial cells express TF, which initiates the coagulation pathway, impairs fibrinolysis by secreting plasminogen activator inhibitor (PAI-1) and reduces surface expression of the anticoagulant, thrombomodulin. Furthermore, stimulated endothelial cell attract leucocytes by synthesizing chemokines and expressing intracellular adhesion molecules (leucocyte integrins).

These procoagulant events are themselves regulated, limiting intravascular extension of the thrombus. Proposed mechanisms include the negative charge of intact endothelium (repels platelets), adjacent prostacyclin release (inhibits platelet activation), heparan inhibition of thrombin, thrombomodulin enhancement of thrombin anticoagulant effects, and secretion of tissue plasminogen activator (tPA), which can initiate fibrinolysis.

The extent to which each property (metabolic, structural) of the endothelium dictates the fine balance between procoagulant and anticoagulant phenotype varies, and led to the concept of vascular bed-specific haemostasis. Responsible mechanisms include growth factors, cytokines, mechanical forces, circulating lipoproteins, coagulation factors and components of extracellular matrix. Hence the prevalence of pathological thrombosis varies at different vascular sites, and may be associated with different acquired factors or disease states.

Platelets

The circulating platelet is an anuclear discoid cell produced from megakaryocytes.[1] It functions as a vehicle for transporting regulatory factors, prothrombotic proteins, growth factors and other molecules inside platelet granules to the endothelium. The platelet membrane functions as a template for promotion/acceleration of haemostasis and wound healing. Platelets circulate close to the endothelium, facilitating rapid recognition disruption or injury. A reduction in the number of platelets results in a bleeding tendency. The normal platelet count is $150–450 \times 10^9$/litre; at $<80 \times 10^9$/litre, haemostasis may be impaired. The risk of bleeding correlates with the severity of platelet reduction.

The process of platelet plug formation is called primary haemostasis, as opposed to the secondary events of the procoagulant system. Primary haemostasis consists of platelet adhesion,

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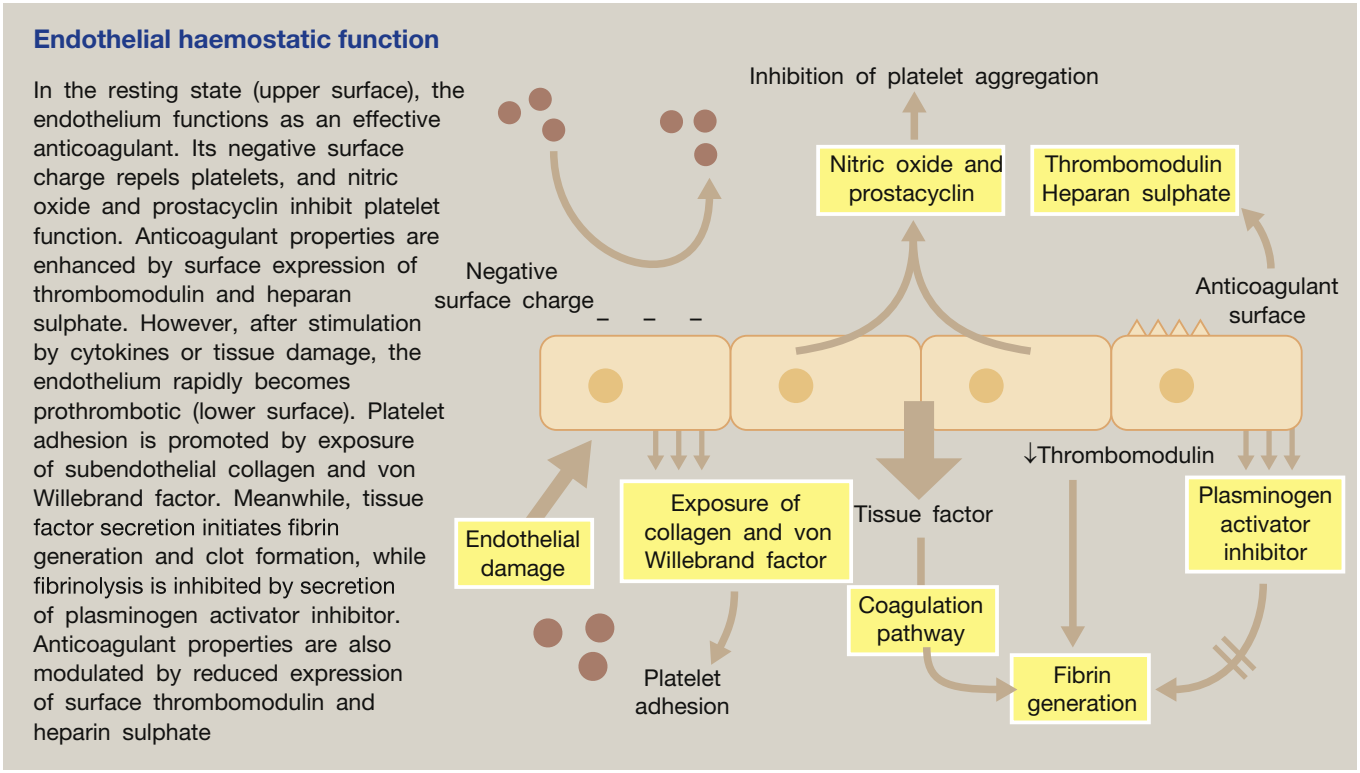

Figure 1

activation and aggregation, a seamless dynamic interaction between the endothelium, plasma proteins and platelets.

Adhesion: blood flow is normally laminar, faster at the centre than the edge, creating a shear effect. Shear force is greatest at the endothelium. Platelets are displaced to the mural plasma zone and exposed to maximal vessel wall shearing forces. Under such high shear, platelets contact the endothelium briefly, 'rolling' along the endothelial surface. This interaction can occur with both intact (activated) and disrupted endothelium, slowing platelet velocity and encouraging more substantial tethering to the vessel wall. Platelet tethering to exposed thrombogenic surfaces occurs when the platelet surface glycoprotein Ibα (GPIbα) binds to VWF. VWF is a large, multimeric adhesive protein synthesized by the endothelium and secreted into the plasma and subendothelial matrix.

VWF binds to collagen (and possibly other subendothelial components), intact endothelium precludes any interaction between VWF and platelets. In areas of vascular injury exposed to high shear forces, subendothelial VWF is exposed, whereas (more importantly) circulating plasma VWF is immobilized after contact with subendothelial elements. This causes VWF to undergo a conformational change, exposing binding sites for GPIbα on the platelet membrane, which ultimately initiates the platelet response to vascular injury. Simply put, VWF acts as a bridge between platelets and subendothelial connective tissue, probably the initial step that tethers platelets to areas of damage. However, this initial attachment is not stable, and a concomitant high dissociation rate allows platelets to continue rolling slowly along the endothelium. Meanwhile, platelet activation begins, and a second platelet surface glycoprotein, GPIIb-IIIa receptor, undergoes conformational change; this allows synergistic binding between GPIIb-IIIa and fibrinogen, leading to firmer, permanent adhesion. GPIIb-IIIa can also bind with VWF, and other adhesive proteins (fibronectin, vitronectin), which may play a more important role at low shear rates, when they can substitute for the action of VWF. Adhesion is also aided by interaction of collagen with GPIa-IIa.

Activation: platelets become activated as they adhere stepwise to endothelial cells (or a variety of other surfaces). This also results in endothelial cell activation and the expression/secretion of chemokines. Activation results in a marked structural change, the platelets becoming spherical with protuberant pseudopodia. Platelet granules centralize secondary to activation of the cytoskeletal contractile apparatus, and secretion follows. Subsequent contraction of these microfibrils may cause clot retraction and promote platelet plug formation. Exposure of negatively charged platelet phospholipids and receptors for specific plasma clotting factors, particularly activated factor V derived from platelet α-granules, provide a procoagulant surface for assembly of the enzyme–co-factor complexes of the coagulation pathway.

Platelet activation is caused by binding of various agonists (e.g. thrombin, thromboxane A2, ADP, collagen, arachidonic acid) to specific receptors.[2] Signal transduction is mediated by G proteins and intracellular cyclic adenosine monophosphate (cAMP); increased cAMP concentrations inhibit platelet adhesion, aggregation and release. Following platelet activation, adenylate cyclase activity is reduced, decreasing cAMP concentrations and increasing mobilization of calcium. Many calcium-

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