Physiology of haemostasis

James Sira
Lorna Eyre

Abstract

Haemostasis is a complex and sophisticated process that requires the interplay of multiple physiological pathways. Cellular and molecular mechanisms interact to seal damaged blood vessels with localized clot formation preventing significant bleeding. Once vascular integrity is restored, clot breakdown occurs and normal haemostasis is reinstated. Thrombohaemorrhagic imbalance may occur in the perioperative period or during critical illness, leading to an increased risk of thrombosis, bleeding or in some instances both. Therefore an understanding of the normal physiological processes is important for the anaesthetist as: (i) it allows us to identify targets for the therapeutic modulation of bleeding and thrombosis; (ii) many commonly encountered medications alter the normal haemostatic pathways and it is important to recognize their effects; and (iii) it enables enhanced understanding of the dynamic tests of haemostasis and clotting.

Keywords Blood coagulation; blood platelets; endothelium; glycocalyx; haemostasis; thromboelastography; vascular

Royal College of Anaesthetists CPD Matrix: 1A01, 2A05

Learning objectives

After reading this article, you should be able to:

- define haemostasis and identify the key components
- explain the role of platelets and their mechanism in haemostasis
- describe the principle of the cell-based model of coagulation
- identify the parameters used in thromboelastography

Haemostasis (from the Greek: aima, blood + stasis, halting) is defined as the arrest of bleeding and requires the rapid interaction of a number of closely regulated processes. These culminate in the production of a localized clot at the site of vessel injury usually over the course of seconds to minutes. Disruption of the vascular endothelium triggers this interplay of physiological processes, which include formation of an initial platelet plug (primary haemostasis), activation of coagulation to form a fibrin mesh (secondary haemostasis), fibrinolysis and vessel repair.

Vascular endothelium

The vascular endothelium has traditionally been described as a fine cellular monolayer lining the circulatory system, which together with the basement membrane forms the intima. It is now accepted that a sugar–protein glycocalyx is also an integral part of all healthy vascular endothelium. The glycocalyx can be considered as a complex gel that is produced by and coats the endothelium. It occupies a critical position between flowing blood and the endothelial cells. Glycoproteins and proteoglycans form the bulk of the glycocalyx, and it is the former that act as adhesion molecules contributing to the coagulation, fibrinolytic and haemostatic systems.

Under normal circumstances blood components pass unhindered through the circulatory system. The vascular barrier provides a non-thrombogenic surface due to the production of platelet inhibitors, coagulation inhibitors and fibrinolysis activators (Table 1). One of the most important substances produced is heparin sulphate that acts as a cofactor for the activation of antithrombin and thrombomodulin, both of which inhibit coagulation.[1]

In contrast, the subendothelial layer is highly thrombogenic and contains collagen, von Willebrand factor (VWF) and other proteins such as laminin, thrombospondin and vitronectin that are involved in platelet adhesion.[2] When the vascular endothelial layer is interrupted, for example, by trauma or inflammation, VWF is released, collagen is exposed and tissue factor (TF) is expressed on the surface of endothelial cells. This switch to a prothrombotic and proinflammatory state sees the endothelium orchestrate vasoconstriction, platelet and leucocyte activation and adhesion, promotion of thrombin formation, coagulation and fibrin deposition at the vascular wall.

Examples of vascular endothelial antithrombotic mediators

Mediator	Action
Prostacyclin Nitric oxide ADPase	Inhibition platelet activation
Thrombomodulin Heparin sulphate Tissue factor pathway inhibitor	Inhibition of coagulation
Tissue-plasminogen activator	Modulation of fibrinolysis

Examples of vascular endothelial pro-thrombotic mechanisms

Mediator	Action
Tissue factor	Released following endothelial damage
Von Willebrand factor	Platelet adhesion and aggregation
Plasminogen activator inhibitor-1	Inhibits fibrinolysis

Table 1

James Sira *MBChB BSc (Hons) FRCA is a Specialist Registrar at St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK. Conflicts of interest: none declared.*

Lorna Eyre *BSc (Hons) FRCA DICM is a Consultant in Critical Care and Anaesthesia at St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK. Conflicts of interest: none declared.*

The endothelium is also responsible for triggering and regulating fibrinolysis through the synthesis of tissue-type plasminogen activator and its inhibitor plasminogen activator inhibitor PAI-1.[3] These mechanisms constitute the initial step towards vascular repair.

Platelets

Platelets play a pivotal role in primary haemostasis and alongside the vessel wall and adhesive proteins, lead to the formation of an initial 'platelet plug'. There are normally between 150 and 400 billion platelets per litre of blood in a healthy adult, produced by megakaryocytes in the bone marrow. Their lifespan ranges from 8 to 14 days.[4] At the site of vessel injury, platelets recognize disruption of endothelial cells lining the blood vessels and the exposed underlying fibrous matrix. They subsequently form a core of thrombi through a process of adhesion, activation, secretion of the contents of intracellular storage organelles, and aggregation detailed below (Figure 1). In addition, activated platelets express phospholipids which promote localized coagulation and generation of thrombin and fibrin.

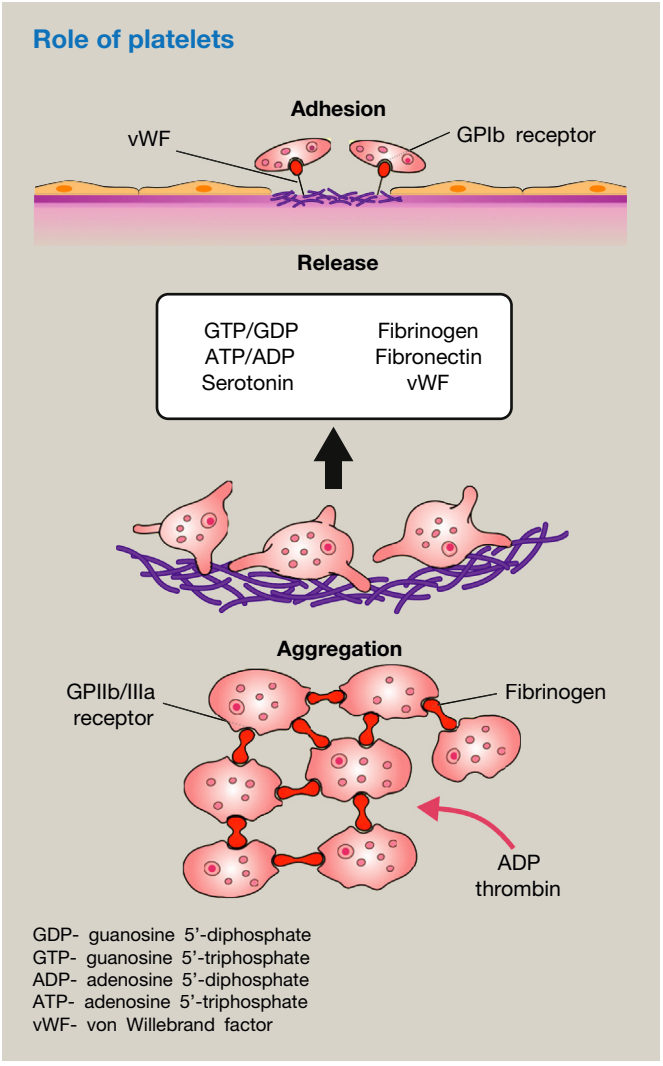

Figure 1

Adhesion

Platelets initially bind to collagen exposed by damage to the endothelium via glycoprotein (GP) receptor complexes. Of these, GP1b/V/IX and GPVI expressed on their surface are the most important. They initiate platelet aggregation and thrombus formation by primary interactions with von Willebrand factor and collagen,[4] respectively, and are also involved in coagulation and leucocyte engagement.

Cell adhesion ligands such as VWF and thrombospondin act as a bridge strengthening the association between platelet surface receptors and endothelial collagen. In the case of VWF it specifically binds to the GPIb component of the GP1b/V/IX glycoprotein complex[5] and in addition contributes significantly to platelet–platelet interactions. These tethering glycoproteins on the surface of platelets bring about the firm binding of a platelet monolayer to the exposed collagen.

Activation

As platelets adhere to the subendothelial components of the damaged vascular endothelium, activation occurs from a number of stimuli including some produced by the platelet itself. One of the major downstream consequences of ligand engagement of GPIb/GPVI by VWF/collagen is the secretion of platelet dense granule contents, ADP and thromboxane A2 (TxA2). These induce G-protein receptor mediated secondary platelet activation and amplify signals leading ultimately to activation of the platelet specific integrin, glycoprotein GPIIb-IIIa.[4] It is worth noting that the final pathway for all agonists is the activation of the GPIIb–IIIa integrin which serves as the main receptor for platelet adhesion and aggregation.[5]

Other stimuli for activation include collagen and thrombin. Thrombin is a particularly effective activator of platelets. It forms following exposure of tissue factor (TF) to plasma coagulation factors and appears on cellular surfaces including those of platelets. Activation of platelets results in a change in shape from discoid to spherical increasing platelet–platelet interactions, it also results in an increase in granule secretion and platelet aggregation.

Secretion

After adhesion, degranulation from both types of platelet storage granules (A-granules and dense bodies) occurs. The release of calcium is of particular importance in the activation of platelet surface phospholipids that then provide a surface for the assembly of various coagulation factors. A-granules contain platelet-specific proteins such as platelet-derived growth factor, chemokines, adhesive molecules and coagulation proteins such as factor V and protein S. Dense bodies contain non-metabolic adenines (e.g. ADP, GTP), divalent cations (Mg^{2+}, Ca^{2+}) and serotonin.

Aggregation

Aggregation leads to the formation of a haemostatic thrombus. TxA2 produced by activated platelets along with ADP enlarge this platelet aggregate in an attempt to seal off any vascular injury. Following platelet activation, the integrin GPIIb/IIIa undergoes a conformational change rendering it capable of binding various extracellular ligands including fibrinogen and VWF. In addition to this GPIIb/IIIa is also capable of interacting with the