Clinical aspects of coagulation

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Abstract
Anaesthetists are often confronted with complex clinical scenarios, including coagulopathies. Knowledge and understanding of the coagulation cascade, pathways of haemostasis and common inherited and acquired disease are essential for clinical decision making. An overview of clinical aspects of coagulation, with the most recent therapeutic and monitoring strategies, is presented. Brief discussions on disseminated intravascular coagulopathy (DIC), heparin induced thrombocytopenia (HIT), thrombelastography and recombinant factor VIIa are included.

Keywords coagulopathy; DIC; HIT syndrome; recombinant factor VIIa; thrombelastography

Haemostasis is a complex physiological process resulting in the cessation of bleeding at the site of damaged blood vessels. It consists of three components: endothelial wall and blood vessels; platelets; and plasma-clotting factors. The initial reaction of active vasoconstriction and release of endothelium mediators is followed by platelet adhesion, activation and induction of plasma proteins. The activated serine proteins lead to the formation of insoluble fibrin, which finally forms a haemostatic plug.

Blood fluidity is maintained by the balanced activity of pro- and anticoagulation enzymes (Figure 1), and disruption of this equilibrium leads to thrombosis or bleeding.

Genetic or acquired deficiency of blood-clotting factors, their inhibition or activation by drugs or pathological processes, and the influence of massive fluid transfusion alter the process of blood clotting. The pathological state known as coagulopathy is associated either with excessive haemorrhage or tendency for hypercoagulation (Table 1).

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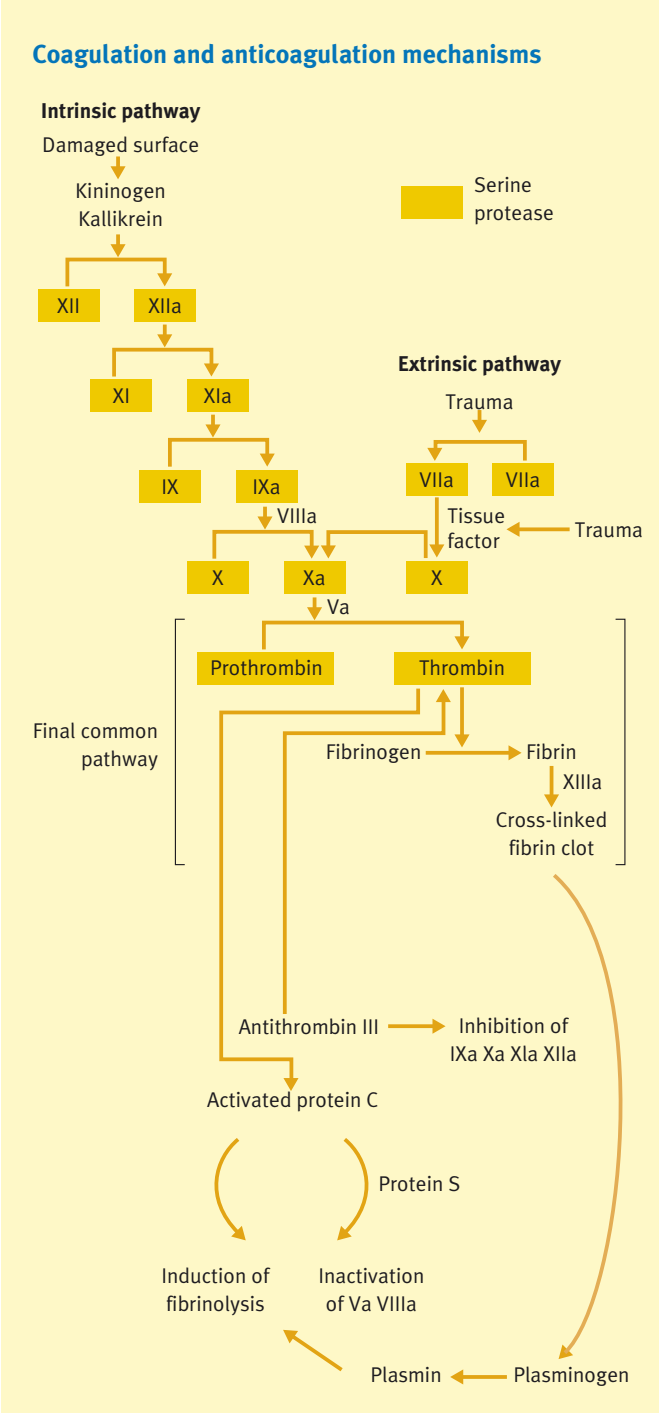

Figure 1

Primary haemostasis and platelets

Primary haemostasis is usually initiated within 20 seconds of damage to the blood vessel wall and endothelial cells, and results in an initial platelet plug at the site of injury. Platelets are anuclear cellular fragments, derived from bone marrow megakaryocytes. They contain alpha and dense granules, and express various membrane glycoproteins (membrane receptors vital for platelet adhesion and activation).

Inherited and acquired coagulation disorders

Genetic

Bleeding disorders

- Haemophilia A, B, C
- von Willebrand disease
- Factors II, V, VII, X deficiency (common pathway proteins)
- Factor XIII and fibrinogen deficiency

Hypercoagulable diseases

- Antithrombin III deficiency
- Protein C and S deficiency

Acquired

Prohaemorrhagic

- Liver diseases
- Drugs: vitamin K deficiency, warfarin, heparin
- Haemodilution and massive transfusion
- Disseminated intravascular coagulation
- Hyperfibrinolysis
- Venom-induced coagulopathy

Prothrombotic

- Heparin-induced thrombocytopenia
- Antiphospholipid antibody syndrome ('lupus anticoagulant')
- Microvascular thrombosis: thrombotic microangiopathy, coumarin-induced skin necrosis

Table 1

The alpha granules contain von Willebrand factor (vWF), platelet-derived growth factor, coagulation factors V and VII and fibrinogen. The dense granules contain ADP, ATP and serotonin. The contents of these granules are released on platelet activation.

Primary haemostasis is initiated when platelets adhere to collagen fibres exposed in the damaged vascular endothelium via the receptor glycoprotein Ia/IIA. This adherence is facilitated by vWF, which forms cross-links with the platelet-receptor glycoprotein Ib/IX/V and the collagen fibrils. Platelet activation follows and the granules are discharged, activating other platelets and white blood cells, potentiated by the metabolism of membrane phospholipids to thromboxane A_2. The platelets undergo a change of shape that exposes phospholipids needed for the coagulation factors in secondary haemostasis. The glycoprotein IIb/IIIa is expressed by activated platelets and fibrinogen links adjacent platelets by interacting with this receptor.

Inherited coagulation disorders

Bleeding diathesis

Haemophilia A is a genetic blood disorder characterized by factor VIII deficiency. It is inherited as X-linked recessive, with an incidence of 1:6000 in the male population. Patients with factor VIII activity less than 1% have severe disease, presenting with spontaneous haemorrhages mainly into the deep tissues and joints. Those with moderate disease have activity level of 1–5% and those with mild 6–50%. Laboratory tests show a typically prolonged activated partial prothrombin time (APTT).

Fresh frozen plasma, purified plasma concentrate, monoclonal antibody purified factors VIII and IX, and recombinant factor VIIa and IX are all used in the treatment of the disease. Viral contamination was a major risk of blood-product transfusion, when many haemophiliac sufferers were infected with HIV. Perioperative management of patients with moderate and severe disease aims at increasing factor VIII activity to 100% for major surgery and to 50% for minor surgery. These activities are maintained for at least 2–7 days after surgery.

Haemophilia B (Christmas disease) is caused by deficiency of factor IX. The inheritance, clinical presentation and treatment are similar to haemophilia A but the incidence is 1:30,000.

von Willebrand disease is an autosomally inherited bleeding diathesis (incidence > 1:10,000), which often goes undiagnosed. Megakaryocytes and endothelial cells stored in the endothelium synthesize vWF, which has an important role in activating, transporting and stabilizing factor VIII. These two factors facilitate platelet activation, adhesion and their further recruitment. Inherited deficiency characteristically presents with mucosal haemorrhages. Blood products are seldom necessary for treatment, and the amount of vWF may be increased to a sufficient level only with desmopressin in the preoperative period.

Factor XI deficiency (haemophilia C or Rosenthal syndrome) is an autosomal recessive inherited disorder, most common in Ashkenazi Jews. Bleeding occurs after trauma or surgery. The protective recommended factor XI levels are 45% for major surgery and 30% for minor surgery.

Factors II, V, VII, X, XIII and fibrinogen deficiency are rare autosomally inherited coagulopathies. Patients present with variable clinical severity, depending on the degree of gene expression, and are treated with replacement therapy.

Hypercoagulable diseases

Antithrombin III (ATIII), protein C and S deficiencies: antithrombin is the most potent inhibitor of coagulation, inactivating serine proteases by forming stable complexes (Figure 1). Genetic defects in production of these proteins results in a procoagulation state, clinically presenting with pulmonary embolism, superficial and deep venous, cerebral vein and mesenteric thrombosis. These states are aggravated by surgery, trauma or oral contraceptive. Anaesthetic implications are related to heparin and warfarin treatment in the perioperative period.

Acquired coagulopathies

Haemorrhagic disorders

Liver diseases: all clotting factors, with exception of factor VIII, which is partially produced by the endothelial cells, are synthesized in the liver. Liver diseases commonly present with bleeding diathesis. All coagulation screening tests could be abnormal (Table 2). Substitution therapy with fresh frozen plasma, cryoprecipitate, vitamin K and plasma concentrates is considered and often given under haematological guidelines.

Vitamin K is a fat-soluble vitamin required for the synthesis of factors II, VII, IX and X, and proteins C and S. Inadequate diet, malabsorption syndrome, antibiotic therapy, billiary, gastrointestinal