Preoperative assessment of coagulation and bleeding risk

Introduction

Intraoperative bleeding and coagulopathy increases morbidity and mortality after surgery. As well as the risk of bleeding, the risk of thrombosis must also be managed, for this is a major risk to patients undergoing surgery.

Coagulation management begins preoperatively with assessment of the patient's risk, to identify those at high risk of bleeding and also those at risk of thrombosis. Both laboratory and point of care tests of coagulation can be used to monitor the coagulation system.

Excessive bleeding intraoperatively is often treated with blood transfusion, to restore the haemoglobin concentration and maintain oxygen delivery to the tissues. Both anaemia and blood transfusion have been independently shown to increase morbidity and mortality in surgical patients (Shander et al, 2011).

This article will discuss the coagulation system and tests of coagulation, including point of care monitoring. The second part of the article (p. C76) will outline treatment strategies for managing coagulation.

Preoperative assessment

The patient's past medical history, particularly that of bleeding and previous surgical complications or challenges, a family history of bleeding disorders and a drug history, including antiplatelet agents and anticoagulants, is very useful. Some advocate the use of a standardized bleeding questionnaire in all patients to stratify this risk. In patients with a negative history, it is not necessary to perform a routine coagulation screen. Liaison with a haematologist is recommended for patients with known haemostatic derangements, including anticoagulant drug therapies, presenting for surgery.

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The coagulation system

Coagulation refers to the processes that cause the blood to clot. This forms part of haemostasis, whereby bleeding from damaged vessels is stopped. The trauma of surgery requires adequate haemostasis to prevent intraoperative and postoperative haemorrhage. The coagulation cascade is a complex system of pro- and anticoagulant factors.

Haemostasis

Traditionally coagulation was thought to consist of an intrinsic and extrinsic pathway whereby a cascading activation of serine proteases (the coagulation factor enzymes) and cofactors led to the creation of a stable fibrin clot (*Figure 1*). This theory has been replaced with a single, cell-based model of coagulation occurring in three stages (*Figure 2*): initiation, amplifi-

Figure 1. The classical coagulation cascade with the intrinsic and extrinsic pathway. Ca++ = calcium.

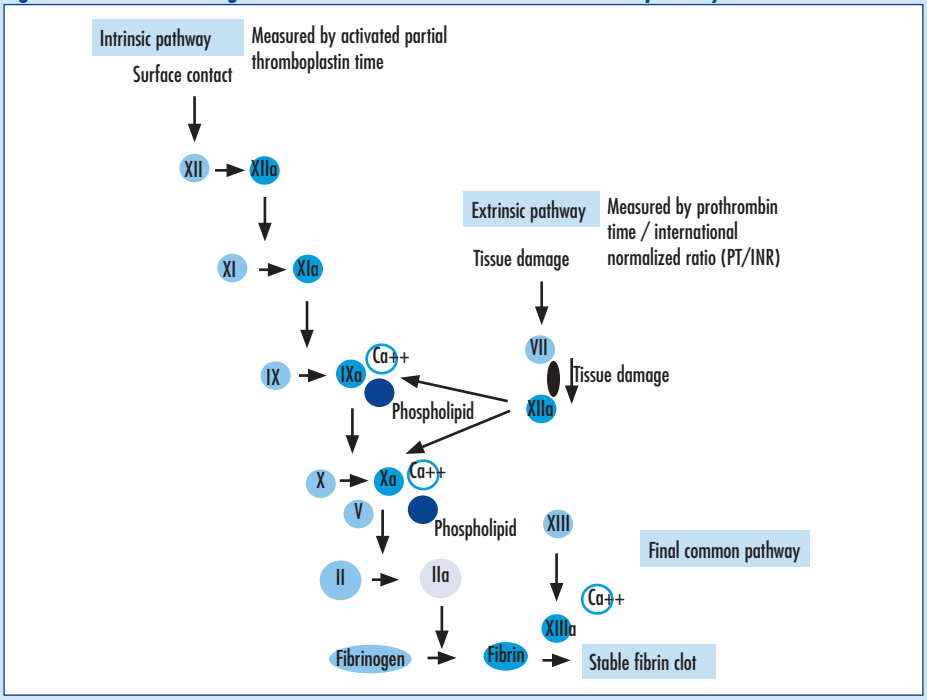
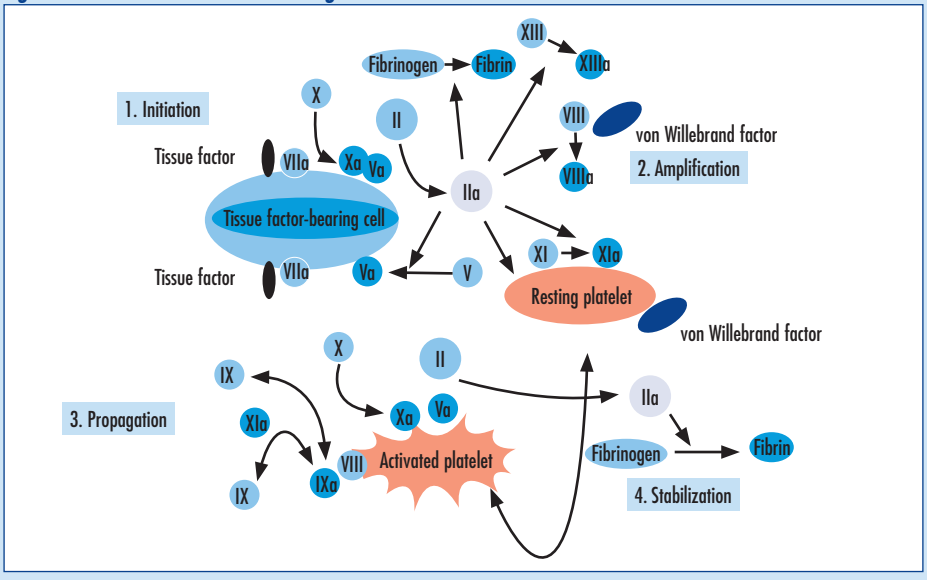


Figure 2. The cell-based model of coagulation.



cation and propagation (Hoffman and Monroe, 2001). Haemostasis is triggered by damage to the vascular endothelium that lines blood vessels, as a result of trauma (including surgery) or inflammatory disease states. A prothrombotic state is then initiated to stop bleeding from the vessel, including local vasoconstriction, platelet and leucocyte activation and adhesion, thrombin generation and fibrin deposition, plugging the disrupted vascular endothelium.

Tissue factor is a protein expressed on fibroblasts and damaged or stimulated cells, including the endothelium. Cells bearing tissue factor initiate coagulation by binding and activating circulating clotting factors. Glycoprotein receptor complexes on the surface of platelets bind to the damaged endothelium. Coagulation is amplified as more platelets adhere to the endothelium, accumulate activated clotting factors on their surface and become activated. Coagulation is then propagated by the generation of the haemostatic protein thrombin (factor IIa), in a 'thrombin burst' that polymerizes fibrinogen (factor I) into fibrin, forming a plug at the vessel wall.

Subsequently fibrinolysis is triggered as the endothelium is repaired, regulating the clot's production and breakdown.

Tests of coagulation

Conventional coagulation tests include activated partial thromboplastin time, prothrombin time and international normalized ratio (*Table 1*). These tests were developed based upon the classical intrinsic and extrinsic pathways of coagulation. Besides clot formation, clot stability is important, and is governed by factor XIII and the activity of the fibrinolytic system. Importantly, prothrombin time or activated partial thromboplastin time results do not reflect the activity of factor XIII or fibrinolysis. Point of care tests give rapid results upon which to base intraoperative coagulation management. Viscoelastic tests of coagulation such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) analyse whole blood to give a complete assessment of haemostasis from clot formation to fibrinolysis.

Point of care tests of coagulation

Activated clotting time

The activated clotting time is used to monitor the effect of unfractionated heparin, usually during cardiopulmonary bypass, but also for heparinized patients undergoing vascular surgery or haemofiltration. Fresh whole blood is added to an activator of coagulation, via the intrinsic pathway. The normal reference range is between 70 and 180 seconds. In cardiopulmonary bypass, heparin is usually given to maintain an activated clotting time >400 s to prevent clotting within the bypass circuit.

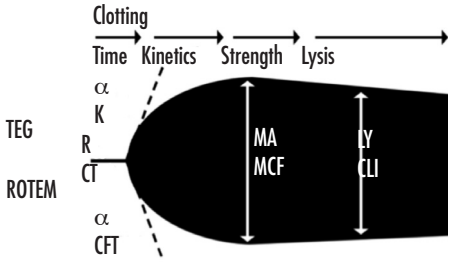
Viscoelastic tests: thromboelastography and rotational thromboelastometry

These tests allow a global assessment of coagulation using whole blood. The use of point of care test-based coagulation and transfusion management algorithms intra-

Table 1. Conventional tests of coagulation

Test	Method	Measurement	Normal range	Prolonged by
PT or PT–INR	The time for fibrin strand formation when platelet-poor plasma is added to calcium and thromboplastin (tissue factor and phospholipid). The INR is the ratio of the test PT sample compared to a normal PT (patient PT / control PT), used because of variability between laboratory reagents and instruments	Extrinsic and common coagulation pathways, prothrombin (factor II), fibrinogen (factor I), factors V, VII and X	PT: 13–15 seconds, INR: 0.9–1.2	Factor II, V, VII, X deficiency, vitamin K deficiency or inhibition (e.g. warfarin), fibrinogen deficiency, high concentration heparin, direct thrombin inhibitors (e.g. lepirudin), dilutional coagulopathy
APTT	APTT reagent contains phospholipid but no tissue factor. Platelet-poor plasma is added to reagent and a contact activator (e.g. silica or ellagic acid), before calcium is added to initiate clotting. The APTT is the time taken for a fibrin clot to form once the calcium is added	Intrinsic and common coagulation pathways, fibrinogen, factors II, V, VIII, IX, XI, XII. Does not test VII and XIII	27–35 seconds	Factor VIII, IX, XI, XII deficiency, lupus anticoagulant, acquired clotting factor inhibitors, vitamin K deficiency, liver disease, direct thrombin inhibitors, disseminated intravascular coagulation, dilutional coagulopathy, unfractionated heparin, novel oral anticoagulants (rivaroxaban, apixaban, dabigatran)
Thrombin time	Measures the conversion of fibrinogen to fibrin after the addition of thrombin (which cleaves fibrinogen) to platelet-poor plasma, comparing the rate of clot formation to that of normal pooled plasma	Functional fibrinogen levels (qualitative or quantitative deficiency)	13–15 seconds	Dysfibrinogenaemia, disseminated intravascular coagulation, liver disease, malignancy, unfractionated heparin, elevated fibrin degradation products (e.g. disseminated intravascular coagulation), paraproteinaemia, hypoalbuminaemia
Fibrinogen	Fibrinogen can be measured by several assays, including the commonly used Clauss assay, based upon the time for fibrin clot formation, allowing the fibrinogen concentration to be calculated against a calibration curve of reference plasma with known concentrations of fibrinogen	Fibrinogen concentration	1.5–5.0 g/litre	
Factor assays	Specific factor assays can be requested in the light of an abnormal screening test	Individual factors selected including prothrombin (II), VII and X	Dependant upon selected test	

APTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time



	TEG	ROTEM	Description
Clotting time	R (reaction time) (min)	CT (clotting time)	Relates to concentration of soluble clotting factors in the plasma, the period of initial fibrin formation (time to reach 2 mm amplitude on the tracing)
Clot kinetics	K (K value) (min)	CFT (clot formation time)	Measure the kinetics of clot formation, measures the speed to reach a specific level of clot strength (period for amplitude to increase from 2 to 20 mm)
	∝ angle (angle in degrees) (°)	∝	Measures the rate of clot formation, reflects rate of fibrin build up and cross-linking (angle between a tangent to the tracing at 2 mm amplitude and the horizontal midline)
Clot strength	MA (maximum amplitude) (mm)	MCF (maximum clot firmness)	Represents the ultimate strength of the clot (platelets and fibrin), maximum dynamic properties of fibrin and platelet bonding via GPIIb/IIIa receptors (greatest vertical width of tracing)
Clot stability	LY30 (lysis at 30 minutes as a ratio of MA)	CLI (clot lysis index)	Relates to clot stability and lysis, measures the rate of amplitude reduction from MA at 30 minutes (in per cent)

Figure 3. Parameters and traces of thromboelastography (TEG) and rotational thromboelastometry (ROTEM).

operatively reduce transfusion requirements (Görlinger et al, 2012).

Thromboelastography and rotational thromboelastometry assess haemostatic function from clot formation and strengthening, then retraction and fibrinolysis. Whole blood is added to a cuvette, into which a pin is suspended, connected to a detector. The cup is rotated around the pin (thromboelastography) or the pin rotated in the cup (rotational thromboelastometry). As the blood clots, fibrin strands form between the cup and pin, altering the rotation and forming characteristic traces as this is transmitted to the detector (*Figures 3* and *4*). Native tests use whole blood alone, or activators (e.g. kaolin, tissue factor) can be added to accelerate the coagulation process. Heparinase can be added to reverse the action of heparin to assess haemostasis in heparinized patients. Functional fibrinogen concentration can be measured using a platelet inhibitor (abciximab for thromboelastography or cytochalasin D in the fibrinogen test using rotational thromboelastometry – FIBTEM).

Platelet tests

Platelet count is part of the routine full blood count, with normal range 150–400x10^9/litre. However, patients with a normal quantitative platelet count can suffer with functional disorders of adhesion, activation or action, either as a result of disease or antiplatelet drugs. Increasingly patients presenting for surgery are required to continue their antiplatelet drugs (for example those with drug-eluting coronary stents) or to minimize this interruption to avoid the risk of perioperative thrombosis. There is also marked individual variability in response to antiplatelet drugs – 30% of patients have no platelet inhibition from clopidogrel and the time for offset of effects is not always predictable.

Platelet function can be assessed by a variety of tests including light transmission aggregometry, flow cytometery and impedance aggregometry.

The Platelet Function Analyser-100 (PFA-100) measures platelets occluding an aperture in a membrane, under similar shear conditions to in-vivo flow. As platelets are activated, attach and aggregate, the aperture is plugged, and the time taken to occlude the aperture reflects the platelet function.

The multiple platelet function analyser (Multiplate) is a whole blood assay that has five channels containing agonists (e.g. adenosine diphosphate or adrenaline) that stimulate platelet aggregation (*Figures 5* and *6*). Adenosine diphosphate activates

Figure 4. Thromboelastography (TEG) traces in differing clinical scenarios. K = K value (kinetics); LY30 = lysis at 30 minutes; MA = maximum amplitude; R = reaction time.

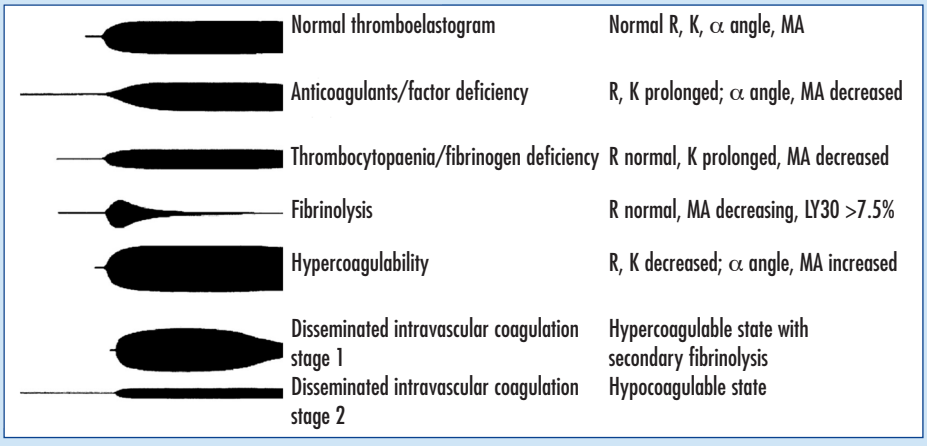
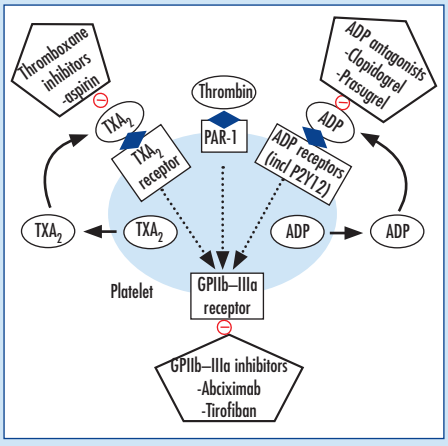


Figure 5. Platelet receptors. ADP = adenosine diphosphate; GP = glycoprotein; PAR-1 = protease-activated receptor-1; TXA_2 = thromboxane A_2.



adenosine diphosphate and GPIIb/IIIa receptors, and is added to measure the effect of its inhibitors (e.g. clopidogrel, prasugrel and abciximab). Arachidonic acid allows the assessment of the effect of aspirin (a thromboxane A_2 inhibitor) and GPIIb/IIIa inhibitors (e.g. abciximab). The inhibition by antiplatelet agents of the different activation pathways can then be measured. This is useful in patients on dual antiplatelet agents to determine when it is safe to proceed to surgery without an increased bleeding risk.

Standard thromboelastography or rotational thromboelastometry cannot be used to assess antiplatelet drugs. Platelet mapping assays use the thromboelastograph to measure the reduction in maximum amplitude (MA) caused by antiplatelet therapy, and report the percentage inhibition and percentage aggregation of platelets. The inhibiting effect of different types of antiplatelet agents, including thromboxane A_2 inhibitors (e.g. aspirin) and adenosine diphosphate inhibitors (e.g. clopidogrel and prasugrel), are measured using arachidonic acid or adenosine diphosphate agonists to create an adjusted MA that is compared to the patient's baseline. A result of less than 30% platelet inhibition is associated with an increased risk of in stent thrombosis, but it can be assumed that there is no increased risk of bleeding at this level of inhibition (*Figure 7*).

Figure 6. Platelet function tests. ADP = adenosine diphosphate; AU = aggregation units; MA = maximum amplitude.

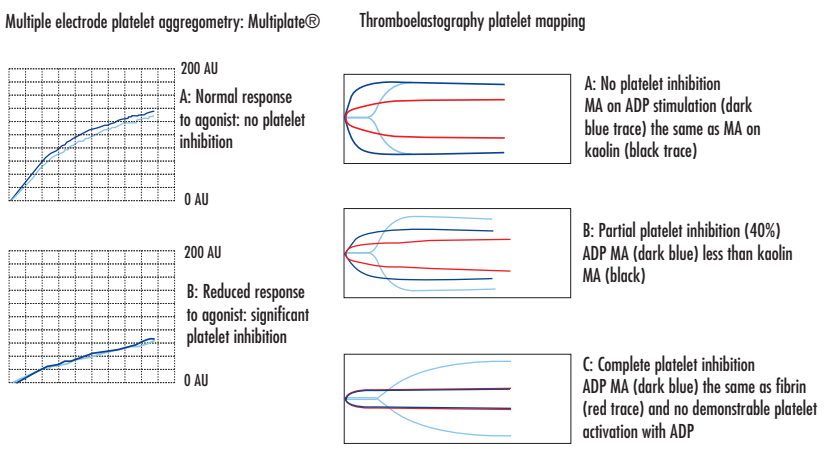
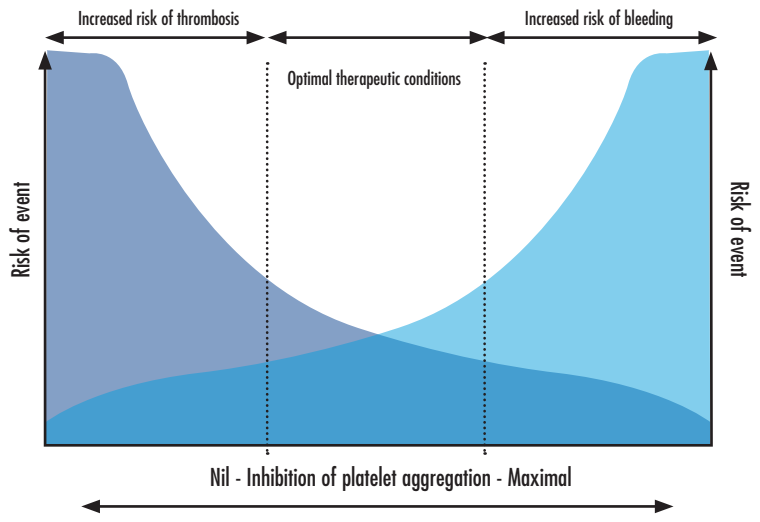


Figure 7. Platelet inhibition and risk of bleeding and thrombosis.



KEY POINTS

- Preoperative assessment of a patient for bleeding risk is paramount to be prepared for coagulopathy and haemorrhage.
- Haemostasis is now described by a cell-based model of coagulation focused upon tissue factor-bearing cells and their interaction with circulating platelets and clotting factors to form a stable fibrin clot.
- Conventional tests of coagulation measure the classical intrinsic and extrinsic pathways of the coagulation cascade, but do not monitor the activity of factor XIII and fibrinolysis.
- Viscoelastic tests (e.g. TEG or ROTEM) allow a rapid, global assessment of coagulation from clot formation to breakdown.
- Qualitative platelet defects, including the degree of inhibition from antiplatelet drugs, can be monitored using platelet function tests to determine the risk of bleeding or thrombosis.

Conclusions

Preoperative assessment of patients allows the identification of those patients at risk of bleeding. This is particularly important in the case of patients taking anticoagulant or antiplatelet medications. Additionally the risk of thrombosis must be assessed when stopping these. A perioperative plan should be made on an individual patient basis depending upon surgical and patient factors, and liaison with a haematologist made for those at a high risk of bleeding. BJHM

Conflict of interest: none.

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