Management of coagulation during cardiopulmonary bypass

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Coagulation in cardiac surgery

During normal haemostasis, a platelet plug forms at the site of vessel injury. This is stabilized by fibrin produced from enzymatic reactions of coagulation factors. These reactions can only proceed at a sufficient rate on the phospholipid surface of activated platelets. This requirement for platelet phospholipid, plus a series of inhibitors, and the fibrinolytic system restrict clot production to the site of injury. Historically, coagulation was considered as two separate pathways of factors, denoted by Roman numerals, arranged in cascades. The 'intrinsic' (contact activation) and 'extrinsic' (tissue factor) pathways join to form a common pathway at factor Xa that activates thrombin, which in turn converts fibrinogen to fibrin. Although not an accurate representation of *in vivo* coagulation, this scheme remains useful when trying to understand laboratory tests. The prothrombin time (PT) is a test of the extrinsic pathway. The activated partial thromboplastin time (APTT) is a test of the intrinsic pathway.

Modern understanding is that i*n vivo* haemostasis begins with tissue factor (TF) and circulating factor VII.[1] A network of reactions is triggered with platelets playing a central role, rather than a unidirectional enzyme cascade. TF is a transmembrane glycoprotein expressed on cells outside the bloodstream. Coagulation is initiated when TF becomes exposed at the site of vessel injury, binds and activates circulating factor VII. The resulting TF–VIIa complex activates factors X and IX. Activated factor X (Xa) then binds cofactor V. This TF–Xa/Va complex cleaves prothrombin to thrombin. Thrombin is an important enzyme in coagulation as it cleaves fibrinogen to fibrin and activates platelets, factor XI, and cofactors V and VIII. Thrombin also activates control mechanisms such as the inhibitor protein C and the fibrinolytic enzyme plasmin. The small amount of thrombin produced thus far is not sufficient to produce a fibrin clot. Amplification of thrombin production is achieved by accelerating enzyme reactions on the platelet surface. Platelets are activated and localized via receptors for substances such as collagen and thrombin. They release procoagulant factors and change shape, exposing negatively charged membrane phospholipid. Factors IXa, Xa, and XIa also have negatively charged sites that attach to platelet phospholipid via calcium ions acting as a sandwich-like buffer. XIa activates IX, an additional source of IXa to that derived by TF–VIIa. Two key enzyme–cofactor complexes form on the platelet surface. IXa joins with its cofactor VIIIa to form a 'tenase' complex that activates X. Similarly, a 'prothrombinase' complex is formed by Xa and Va. The combination of enzyme, cofactor, calcium, and phospholipid surface increase the speed of these reactions many thousand-fold. This produces an explosive increase in thrombin production sufficient to produce fibrin.[2] Platelets become linked together in this platelet-fibrin clot via their fibrin-receptor glycoprotein IIbIIIa (GpIIbIIIa).

Coagulation overlaps with inflammatory pathways; for example, activated platelets release inflammatory cytokines and thrombin activates monocytes. Coagulation can activate the inflammatory system and vice versa. This becomes relevant with extreme activation of either system, such as in systemic inflammation.

During CPB for OHS, heparin is required to prevent blood clotting within the CPB circuit.[3] By facilitating the action of antithrombin III, heparin inhibits thrombin. Despite heparin anticoagulation, some activation of coagulation still occurs and increases with the duration of CPB. Contact activation occurs on foreign surfaces within the bypass circuit. In addition, there is exposure of blood to air and TF in the wound and recirculation of this blood via cardiotomy suction. Thrombin bound to fibrin deposited on surfaces within the CPB circuit is resistant to inhibition by heparin–antithrombin III. Consumption of clotting factors and platelets follows their activation by thrombin. Thrombin-induced fibrinolysis by plasmin not only lyses fibrin clot, but plasmin also degrades platelet surface receptors such as GpIIbIIIa.

Key points

Coagulation and inflammatory pathways are triggered by contact of blood with the cardiopulmonary bypass (CPB) circuit and surgical wound during open heart surgery.

Heparin remains the standard anticoagulant for CPB; despite inconsistent relationships between coagulation tests, thrombin inhibition, and plasma concentrations.

Activated clotting time is the standard test of coagulation during CPB.

Thromboelastography is a point of care coagulation test that gives rapid, qualitative information about coagulation factors, platelets, and fibrinolysis.

Following protamine reversal of heparin, failure to re-establish normal haemostasis can occur and may result in postoperative bleeding.

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Activation of inflammatory cells such as monocytes may impair haemostasis via their expression of TF. Endothelial cells become activated by various agonists including thrombin and cytokines. They, in turn, can release inflammatory mediators and coagulation factors. Hypothermia of less than 35°C slows coagulation enzyme kinetics, impairs platelet function, and delays heparin elimination. Other contributors to CPB-related coagulopathy include haemodilution, pre-operative platelet inhibitors, heparin itself, and protamine.[4,5]

Postoperative bleeding is a common complication of cardiac surgery but a surgical cause is only found in 50% of re-explorations.[5] Empiric transfusion of blood products is often inappropriate, carries the risk of adverse effects, and has been associated with an increase in wound infection. Rapid and accurate diagnosis of haemostasis is necessary to discriminate coagulopathic bleeding from surgical bleeding.

Anticoagulation for cardiopulmonary bypass

Unfractionated heparin

Unfractionated heparin is a negatively charged acid glycosaminoglycan with a molecular weight of 3000–40 000 Da. Heparin binds ATIII and potentiates its inhibitory effect on factor Xa and thrombin. Although all fractions of heparin inhibit Xa, only longer chain molecules will inhibit thrombin. Long-chain molecules also catalyse thrombin inhibition by heparin cofactor II. In addition, heparin influences activation of coagulation through heparin-mediated TF pathway inhibitor (TFPI) and stimulates fibrinolysis.[4]

The advantages of unfractionated heparin are its rapid onset of action, clinical efficacy, rapid neutralization by protamine, safety, and low cost. The dose of heparin used to prevent blood clotting during CPB is 300–400 U kg^{-1} plus additional doses to achieve and maintain an activated clotting time (ACT) of greater than 480 s (Table 1). However, the individual response to a fixed dose of heparin varies. Higher doses of heparin may result in better thrombin inhibition, thereby preserving coagulation factors on CPB.[3,4]

Table 1 Standard sequence for anticoagulation management for adults undergoing CPB

Arterial blood sample for baseline ACT
300–400 IU kg^{-1} of unfractionated heparin via central venous catheter
Arterial blood sample for ACT after 3–5 min
Ensure ACT above 3–4 times of baseline ACT (>480 s) before initiating CPB
5000 IU unfractionated heparin in CPB prime solution
Monitor ACT at least every 30 min during CPB
Maintain ACT 400–480 s during hypothermia while on CPB (24–30°C).
Reverse heparin with protamine after separation from CPB. Dose ratio 1 mg protamine per 10 IU of heparin, based on pre-CPB heparin dose.
Arterial blood sample for ACT after 3–5 min

Heparin resistance

Heparin resistance can be defined as a need for higher than usual doses of heparin to achieve adequate anticoagulation. This may be due to ATIII deficiency or increased protein binding of heparin. Protein binding is variable and increases in acute illness. ATIII deficiency may be either inherited or acquired (Table 2). Inherited ATIII deficiency follows an autosomal dominant pattern with a prevalence of 1:2000–20 000. Affected individuals usually have ATIII levels below 50% of normal and are prone to venous thrombosis. Acquired ATIII deficiency is more common and is usually due to recent heparin administration. Additional heparin is usually all that is required for heparin resistance, but ATIII deficiency should be suspected if an ACT > 480 s cannot be achieved after administration of more than 600 IU of heparin per kilogramme. Recombinant ATIII concentrates are the treatment of choice. Fresh frozen plasma (FFP) contains normal concentrations of ATIII and is a cheaper alternative, but carries the risks associated with transfusion.[2,3,6]

Alternatives to unfractionated heparin

Heparin-induced thrombocytopenia (HIT) and protamine or heparin allergy might necessitate avoidance of heparin. A number of alternatives to heparin for CPB have been investigated.

Low molecular weight heparin (LMWH) exhibits poor thrombin inhibition, has a long half-life, and its reversal by protamine is incomplete. Anticoagulation monitoring by measuring anti-Xa levels is more cumbersome. Although LMWH has been used for CPB, excessive postoperative bleeding often occurs. Danaparoid is a mixture of glycosaminoglycan heparinoid molecules that has been used successfully in patients with HIT undergoing CPB. Its effect is also monitored by anti-Xa activity.

Lepirudin is a recombinant polypeptide thrombin inhibitor, originally obtained from the medicinal leech and known as hirudin. The ecarin clotting time must be used to monitor hirudin anticoagulation for CPB. This test is based on the inhibition of the snake venom ecarin by hirudin and is not widely available. Other disadvantages are its long plasma half-life and lack of reversal agent. Bivalirudin is a synthetic thrombin inhibitor based on the combined structures of hirudin and antithrombin. This much shorter-acting drug is also monitored by the ecarin time and may prove more useful.

Table 2 Causes of ATIII deficiency

Drug induced
Heparin
Accelerated consumption
Disseminated intravascular coagulation
Sepsis
Dilution
CPB
Decreased synthesis
Liver cirrhosis
Increased excretion
Protein-losing states
Familial

Ancrod is derived from snake venom and acts as a defibrinogenating agent. It can be used for CPB, but cryoprecipitate and FFP are required to restore coagulation.

Argatroban is an arginine analogue thrombin inhibitor with a short half-life that can be monitored using the APTT or ACT. However, there is very limited experience of argabotran anticoagulation for CPB.[2,3]

Heparin reversal with protamine

Protamine sulphate is obtained from salmon sperm and used to reverse heparin-induced anticoagulation. The positively charged molecules form 1:1 complexes with heparin.

Protamine is associated with arterial hypotension, reduced cardiac output, pulmonary vasoconstriction, and anaphylaxis. In addition to aiding coagulation with its heparin neutralising properties, unbound protamine inhibits platelet reactivity, adhesion, and aggregation. Therefore, excess protamine administration can contribute to bleeding after cardiac surgery. Although most individuals use the fixed dose of 1.0–1.5 mg protamine per 100 IU heparin, dosing based on heparin levels is associated with reduced protamine requirement. Protamine dose titration in this way has been associated with less postoperative bleeding.[4] Heparin released from protein binding sites after protamine reversal can increase postoperative bleeding. This 'heparin rebound' effect may be clinically apparent after large intra-operative doses of heparin, requiring additional protamine.

Monitoring anticoagulation

Activated clotting time

The ACT has been used to monitor heparin anticoagulation during CPB since the 1970s. Blood 1 ml is placed in a glass tube containing a magnetic rod and an activator (celite or kaolin). The tube is warmed to 37°C and slowly rotated in a machine while a timer runs. Clotting is detected by resistance to movement of the magnetic rod in a magnetic field which automatically stops the timer. The normal ACT value is 100–140 s and increases in a linear fashion with increasing heparin concentration. Aprotinin prolongs the celite ACT, but the value is less affected if kaolin is used. Other factors that prolong ACT include thrombocytopenia or decreased platelet function due to antiplatelet agents such as GpIIbIIIa inhibitors. Haemodilution and hypothermia routinely occur while on CPB and also prolong the ACT. For these reasons, once CPB is established, the ACT ceases to correlate well with heparin concentration or measures of heparin anticoagulation effect such as anti-Xa activity.[3,4,6]

Other measures of anticoagulation

Heparin concentration can be measured and used as an adjunct to the ACT during CPB. The most common method is a point-of-care protamine titration assay. As initiation of CPB results in a decrease in heparin concentration without a corresponding decrease in the ACT, larger doses of heparin are needed to maintain the target heparin concentration. In theory, heparin concentration monitoring should result in better inhibition of thrombin generation, preservation of coagulation factors and platelet function.

The high-dose thrombin time and the heparin management test are point-of-care tests of heparin-based anticoagulation; they are less susceptible to artefact on CPB than the ACT. Heparin dose–response and individual calculation of protamine dose for each patient is also possible with the heparin management test.[4,6]

Individual patient dosing and more accurate control of anticoagulation would seem preferable; however, the ACT is simple, familiar, cheaper and remains the standard monitor for CPB anticoagulation.[6]

Monitoring coagulation to guide haemostatic blood transfusion

Monitoring coagulation to guide transfusion therapy has been shown to be associated with a reduction in transfusion of blood products. Reduced exposure to allogenic transfusion should improve outcome and reduce costs.[7]

Laboratory tests of coagulation

Laboratory tests of coagulation are of no value during CPB. They are useful in preoperative assessment of patients and for the diagnosis of postoperative coagulopathy.

The partial thromboplastin time (PTT) and APTT are similar and are both sensitive to prolongation by low concentrations of heparin. Since aprotinin inhibits several coagulation factors, patients receiving aprotinin also exhibit a prolonged APTT or PTT.

A prolonged PT, or international normalized ratio, after cardiac surgery indicates clotting factor deficiency. If the patient is bleeding, this can be treated with FFP.

Platelet count is the only readily available laboratory test to guide platelet transfusion. Platelet function can be sufficiently poor after cardiac surgery to result in bleeding, despite normal numbers. Conversely, good platelet function can maintain haemostasis with a low platelet count.

Cryoprecipitate is occasionally required in cases of severe coagulopathic bleeding with a low fibrinogen level.[8]

Thromboelastography

Thromboelastography (TEG) measures whole blood viscoelastic changes associated with fibrin polymerization. Its ability to generate information about coagulation factor activity and platelet function within 10–20 min has made it an increasingly popular test for monitoring coagulation during and after CPB. A pin, attached to a torsion wire, is suspended into a blood sample contained in an oscillating cuvette. Clot forms gradually in the blood sample creating increasing displacement of the pin. This is translated into a graphical representation (Fig. 1). Fibrinolysis can be detected later as the clot begins to dissolve. Cuvettes containing heparinase eliminate the heparin effect, allowing tests although the patient is still

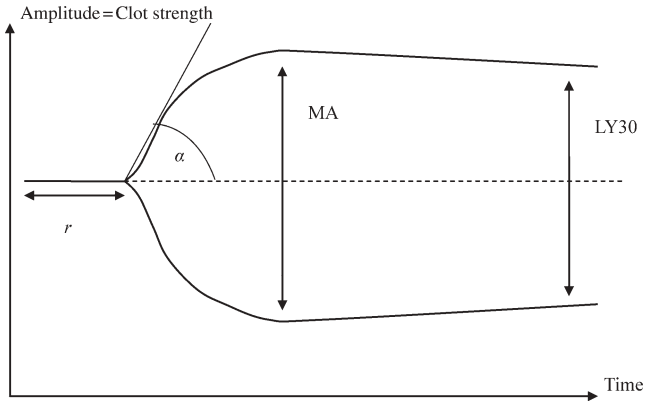

Fig. 1 Thromboelastography (TEG) trace. ***r*** is the reaction time, from start of test to initial clot formation. Prolonged with clotting factor deficiencies and heparin. α is the α angle; it assesses rate of clot formation and decreased in the presence of clotting factor deficiencies, platelet dysfunction, thrombocytopenia, and hypofibrinogenaemia. *MA* is the maximum amplitude, the widest point of the trace. Represents maximum clot strength and is reduced with platelet dysfunction. *LY 30* is the lysis 30, percentage decrease in amplitude 30 min after MA, measures the degree of fibrinolysis.

on CPB to predict coagulation function after heparin reversal. Newer reagents enable TEG to detect the effects of antiplatelet drugs.[9] Abnormal TEG patterns were illustrated in an earlier article in this journal.[10]

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Please see multiple choice questions 12–16