Chapter 13

Coagulation Monitoring

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Key Points

1. Monitoring the effect of heparin is done using the activated coagulation time (ACT), a functional test of heparin anticoagulation. The ACT is susceptible to prolongation because of hypothermia and hemodilution and to reduction because of platelet activation or thrombocytopathy.
2. Heparin resistance can be congenital or acquired. Pretreatment heparin exposure predisposes a patient to altered heparin responsiveness because of antithrombin III depletion, platelet activation, or activation of extrinsic coagulation.
3. Before considering a transfusion of plasma, it is important to document that the effect of heparin has been neutralized. This can be done using a heparinase-neutralized test or a protamine-neutralized test.
4. Point-of-care tests are available for use in transfusion algorithms that can measure coagulation factor activity (normalized ratio, activated partial thromboplastin time) and platelet function.
5. Newer thrombin inhibitor drugs are available for anticoagulation in patients who cannot receive heparin. These can be monitored using the ecarin clotting time or a modified ACT. Bivalirudin and hirudin are the two direct thrombin inhibitors that have been used most often in cardiac surgical procedures.
6. Platelet dysfunction is the most common reason for bleeding after cardiopulmonary bypass. Point-of-care tests can be used to measure specific aspects of platelet function.
7. The degree of platelet inhibition as measured by standard or point-of-care instruments has been shown to correlate with decreased ischemic outcomes after coronary intervention. However, cardiac surgical patients who are receiving antiplatelet medication are at increased risk for postoperative bleeding.

The need to monitor anticoagulation during and after surgical procedures is the reason that the cardiac surgical setting has evolved into a major area for the evaluation and use of hemostasis monitors. The rapid and accurate identification of abnormal hemostasis has been the major impetus toward the development of point-of-care (POC) tests that can be performed at the bedside or in the operating room. The detection and treatment of specific coagulation disorders in a timely and cost-efficient manner are major goals in hemostasis monitoring for the cardiac surgical patient.

MONITORING HEPARIN EFFECT

Cardiac surgical procedures had been performed for decades with empiric heparin dosing in the form of a bolus and subsequent interval dosing. Empiric dosing continued

because of the lack of an easily applicable bedside test to monitor the anticoagulant effects of heparin.

The first clotting time used to measure heparin effect was the whole-blood clotting time (WBCT) or the Lee-White WBCT. This test simply requires whole blood to be placed in a glass tube, maintained at 37°C, and manually tilted until blood fluidity is no longer detected. This test fell out of favor for monitoring cardiac surgical patients because it was so labor intensive and required the undivided attention of the person performing the test for up to 30 minutes. Although the glass surface of the test tube acts as an activator of factor XII, the heparin doses used for cardiac surgical procedures prolong the WBCT to such a profound degree that the test is impractical as a monitor of the effect of heparin during cardiac operations. To speed the clotting time so that the test was appropriate for clinical use, activators were added to the test tubes, and the activated coagulation time (ACT) was introduced into practice.

Activated Coagulation Time

The ACT was first introduced by Hattersley in 1966 and is still the most widely used monitor of heparin effect during cardiac surgical procedures. Whole blood is added to a test tube containing an activator, either diatomaceous earth (Celite) or kaolin. The presence of activator augments the contact activation phase of coagulation, which stimulates the intrinsic coagulation pathway. The ACT can be performed manually, whereby the operator measures the time interval from when blood is injected into the test tube to when clot is seen along the sides of the tube. More commonly, the ACT is automated, as it is in the Hemochron (International Technidyne Corp., Edison, NJ) and ACT Plus (Medtronic Perfusion Services, Minneapolis, MN) systems. In the automated systems, the test tube is placed in a device that warms the sample to 37°C. The Hemochron device rotates the test tube, which contains Celite activator and a small iron cylinder, to which 2 mL of whole blood is added. Before clot forms, the cylinder rolls along the bottom of the rotating test tube. When clot forms, the cylinder is pulled away from a magnetic detector, interrupts a magnetic field, and signals the end of the clotting time. Normal ACT values range from 80 to 120 seconds. The Hemochron ACT also can be performed using kaolin as the activator in a similar manner.

The ACT Plus (formerly Hemotec [Hepcon] ACT) device is a cartridge with two chambers that contain kaolin activator and are housed in a heat block. Blood (0.4 mL) is placed into each chamber, and a daisy-shaped plunger is raised and passively falls into the chamber. The formation of clot slows the rate of descent of the plunger. This decrease in velocity of the plunger is detected by a photo-optical system that signals the end of the ACT test. The Hemochron and Hemotec ACT tests have been compared in several investigations and have been found to differ significantly at low heparin concentrations. However, differences in heparin concentration, activator concentration, and the measurement technique make comparison of these tests difficult and have led to the realization that the results of the Hemochron and Hemotec ACT tests are not interchangeable. In adult patients given 300 IU/kg of heparin for cardiopulmonary bypass (CPB), the Hemochron and Hemotec ACTs were both therapeutic at all time points, although the Hemochron ACT was statistically longer at two time points.

The ACT test can be modified by the addition of heparinase. With this modification, the coagulation status of the patient can be monitored during CPB while the anticoagulant effects of heparin are eliminated. Because this test is a side-by-side comparison of the untreated ACT with the heparinase ACT, it also has the advantage of being a rapid test for assessment of a circulating heparin-like substance or for residual heparinization after CPB.

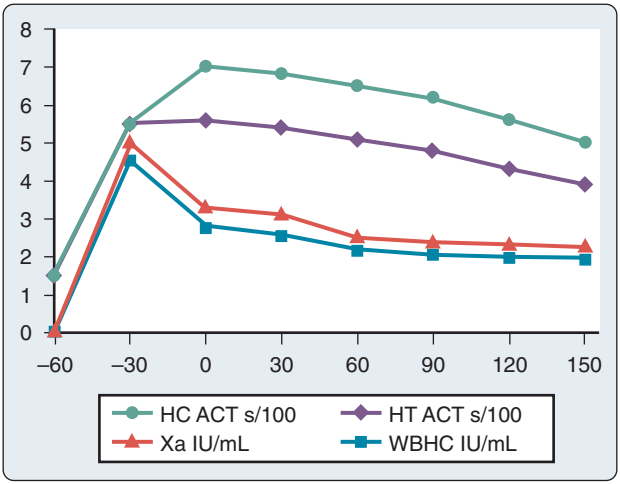


Fig. 13.1 Anticoagulation measured at baseline (–60 minutes), at heparinization (–30 minutes), and six time points after institution of cardiopulmonary bypass. Note the close correlation between the anti–factor Xa *(Xa; triangles)* activity and whole-blood heparin concentration *(WBHC; squares)*, which does not parallel the change in Hemochron (International Technidyne Corp., Edison, NJ) activated coagulation time (ACT) *(HC ACT; circles)* or Hemotec (Medtronic Perfusion Services, Minneapolis, MN) ACT *(HT ACT; diamonds)*. (Modified from Despotis GJ, Summerfield AL, Joist JH. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. *J Thorac Cardiovasc Surg*. 1994;108:1076–1082.)

With the introduction of ACT monitoring into cardiac surgical practice, clinicians have been able to titrate heparin and protamine dosages more accurately. As a result, many investigators report reductions in blood loss and transfusion requirements, although many of these studies used retrospective analyses. The improvements in postoperative hemostasis documented with ACT monitoring are potentially attributable to better intraoperative suppression of microvascular coagulation and improved monitoring of heparin reversal with protamine.

ACT monitoring of heparinization is not without pitfalls, and its use has been criticized because of the extreme variability of the ACT and the absence of a correlation with plasma heparin levels (Fig. 13.1). Many factors have been suggested to alter the ACT, and these factors are prevalent during cardiac surgical procedures. When the extracorporeal circuit prime is added to the patient's blood volume, hemodilution occurs and may theoretically increase the ACT. Evidence suggests that this degree of hemodilution alone is not enough to alter the ACT. Hypothermia increases the ACT in a "dose-related" fashion. Although hemodilution and hypothermia significantly increase the ACT of a heparinized blood sample, similar increases do not occur in the absence of added heparin. The effects of platelet alterations are more problematic. At mild-to-moderate degrees of thrombocytopenia, the baseline and heparinized ACTs are not affected. It is not until platelet counts are reduced to less than 30,000 to 50,000/μL that the ACT may be prolonged. Patients treated with platelet inhibitors such as prostacyclin, aspirin, or platelet membrane receptor antagonists have a prolonged heparinized ACT compared with patients not treated with platelet inhibitors. This ACT prolongation is not related exclusively to decreased levels of platelet factor 4 (PF4; PF4 is a heparin-neutralizing substance) because it also occurs when blood is anticoagulated with substances that are not neutralized by PF4. Platelet lysis, however, significantly shortens the ACT because of the release of PF4 and other platelet membrane

components, which may have heparin-neutralizing activities. Anesthesia and operation decrease the ACT and create a hypercoagulable state, possibly by creating a thromboplastic response or through activation of platelets.

During CPB, heparin decay varies substantially, and its measurement is problematic because hemodilution and hypothermia alter the metabolism of heparin. In a CPB study, the consumption of heparin varied from 0.01 to 3.86 IU/kg/min, and no correlation was noted between the initial sensitivity to heparin and the rate of heparin decay.

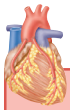
Heparin Resistance

Heparin resistance is documented by an inability to increase the ACT of blood to expected levels despite an adequate dose and plasma concentration of heparin. In many clinical situations, especially when heparin desensitization or a heparin inhibitor is suspected, heparin resistance can be treated by administering increased doses of heparin in a competitive fashion. If an adequately prolonged clotting time is ultimately achieved using greater-than-expected doses of heparin, a better term than heparin resistance would be "altered heparin responsiveness." During cardiac surgical procedures, the belief that a safe minimum ACT value of 300 to 400 seconds is required for CPB is based on a few clinical studies and a relative paucity of scientific data. However, an inability to attain this degree of anticoagulation in the heparin-resistant patient engenders the fear among cardiac surgical providers that the patient will experience microvascular consumptive coagulopathy or that clots will form in the extracorporeal circuit.

Many clinical conditions are associated with heparin resistance. Sepsis, liver disease, and pharmacologic agents represent just a few. Many investigators have documented decreased levels of antithrombin III (AT III) secondary to heparin pretreatment. Patients receiving preoperative heparin therapy traditionally require larger heparin doses to achieve a given level of anticoagulation when that anticoagulation is measured by the ACT. Presumably, this "heparin resistance" is the result of deficiencies in the level or activity of AT III. Other possible causes include enhanced factor VIII activity and platelet dysfunction leading to a decrease in ACT response to heparin. In vitro addition of AT III enhances the ACT response to heparin. AT III concentrate is available as a heat-treated human product or in recombinant form, and its use is a reasonable method of treating patients with documented AT III deficiency (Box 13.1).

Measurement of Heparin Sensitivity

Even in the absence of heparin resistance, patients' responses to an intravenous bolus of heparin are extremely variable. The variability stems from different concentrations of various endogenous heparin-binding proteins such as vitronectin and PF4. This variability exists whether measuring heparin concentration or the ACT; however,



BOX 13.1 ***Heparin Resistance***

It is primarily caused by antithrombin III deficiency in pediatric patients.
It is multifactorial in adult cardiac surgical patients.
The critical activated coagulation time value necessary in patients who demonstrate acquired heparin resistance is not yet determined.
Heparin resistance also can be a sign of heparin-induced thrombocytopenia.

variability seems to be greater when measuring the ACT. Because of the large interpatient variation in heparin responsiveness and the potential for heparin resistance, it is critical that a functional monitor of heparin anticoagulation (with or without a measure of heparin concentration) be used in the cardiac surgical patient. Bull documented a threefold range of ACT response to a 200 IU/kg heparin dose and similar discrepancy in heparin decay rates and thus recommended the use of individual patient dose-response curves to determine the optimal heparin dose. This is the concept on which POC individual heparin dose-response (HDR) tests are based.

An HDR curve can be generated manually by using the baseline ACT and the ACT response to an in vivo or in vitro dose of heparin. Extrapolation to the desired ACT provides the additional heparin dose required for that ACT. Once the actual ACT response to the heparin dose is plotted, further dose-response calculations are made based on the average of the target ACT and the actual ACT (Fig. 13.2). This method was first described by Bull and forms the scientific basis for the automated

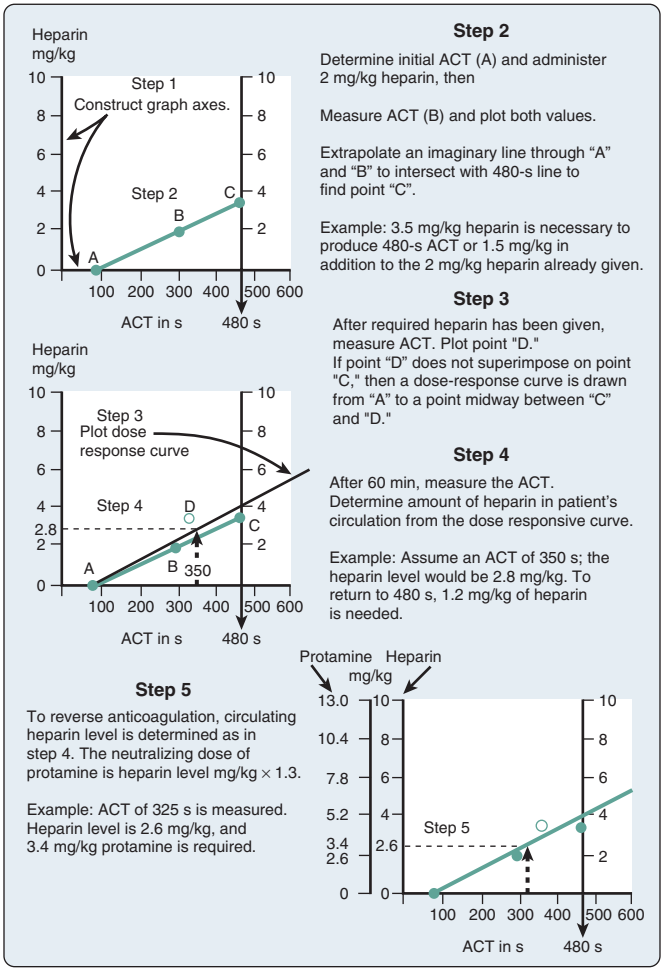


Fig. 13.2 Construction of a dose-response curve for heparin. *ACT*, Activated coagulation time. (From Bull BS, Huse WM, Brauer FS, et al. Heparin therapy during extracorporeal circulation. II. The use of a dose-response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg*. 1975;69:685–689.)

dose-response systems in the proprietary Hemochron and Hemotec devices. The Hemochron RxDx (International Technidyne Corp., Edison, NJ) system uses the heparin-response test, which is an ACT with a known quantity of in vitro heparin (3 IU/mL). A dose-response curve is generated that enables calculation of the heparin dose required to attain the target ACT by using an algorithm that incorporates the patient's baseline ACT, estimated blood volume, and heparin-response test. The patient's heparin sensitivity can be calculated in seconds per international units per milliliter (s/IU/mL) by dividing the heparin-response test by 3 IU/mL.

The Hemochron RxDx system also provides an individualized protamine dose based on the protamine-response test (PRT). This is an ACT with one of two specific quantities of protamine, depending on the amount of circulating heparin suspected (2 or 3 IU/mL). The protamine dose needed to return the ACT to baseline can be calculated on the basis of a protamine-response curve using the patient's heparinized ACT, the PRT, and an estimate of the patient's blood volume.

Heparin Concentration

Proponents of ACT measurement to guide anticoagulation for CPB argue that a functional assessment of the anticoagulant effect of heparin is mandatory and that the variability in ACT represents a true variability in the coagulation status of the patient. Opponents argue that during CPB, the sensitivity of the ACT to heparin is altered, and ACT does not correlate with heparin concentration or with anti–factor Xa activity measurement. Heparin concentration can be measured using the Hepcon HMS system, which uses an automated protamine titration technique. With a cartridge with four or six chambers containing tissue thromboplastin and a series of known protamine concentrations, 0.2 mL of whole blood is automatically dispensed into the chambers. The first channel to clot is the channel in which the protamine concentration most accurately neutralizes the heparin without a heparin or a protamine excess. Because protamine neutralizes heparin in the ratio of 1 mg protamine per 100 IU heparin, the concentration of heparin in the blood sample can be calculated. A cartridge that monitors heparin concentration over a wide range can be used first, followed by another cartridge that can measure heparin concentrations within a more narrow range. The maintenance of a stable heparin concentration rather than a specific ACT level usually results in administration of larger doses of heparin because the hemodilution and hypothermia during CPB increase the sensitivity of the ACT to heparin.

HEPARIN NEUTRALIZATION

Protamine Effects on Coagulation Monitoring

Reversal of heparin-induced anticoagulation is most frequently performed with protamine. Different successful dosing plans have been proposed. The recommended dose of protamine for heparin reversal is 1 to 1.3 mg protamine per 100 IU heparin; however, this dose often results in a protamine excess.

Monitoring for Heparin Rebound

The phenomenon referred to as heparin rebound describes the re-establishment of a heparinized state after heparin has been neutralized with protamine. The most commonly postulated explanation is that rapid distribution and clearance of protamine

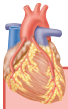
occur shortly after protamine administration, thus leaving unbound heparin remaining after protamine clearance. Furthermore, endogenous heparin antagonists have an even shorter life span than protamine and are eliminated rapidly, resulting in free heparin concentrations. Also possible is the release of heparin from tissues considered heparin storage sites (endothelium, connective tissues). Endothelial cells bind and depolymerize heparin through PF4. Uptake into the cells of the reticuloendothelial system, vascular smooth muscle, and extracellular fluid may account for the storage of heparin that contributes to the reactivation of heparin anticoagulation referred to as heparin rebound.

Residual low levels of heparin can be detected by sensitive heparin concentration monitoring in the first hour after protamine reversal and can be present for up to 6 hours postoperatively. Without careful monitoring for heparin rebound in the postoperative period, increased bleeding as a result of heparin rebound may occur, specifically when larger doses of heparin have been administered. Monitoring for heparin rebound can be accomplished using tests that are sensitive to low levels of circulating heparin. These tests are also useful monitors for confirmation of heparin neutralization at the conclusion of CPB.

Heparin Neutralization Monitors

To administer the appropriate dose of protamine at the conclusion of CPB, it would be ideal to measure the concentration of heparin present and give the dose of protamine necessary to neutralize only the circulating heparin. As a result of heparin metabolism and elimination, which vary considerably among individual patients, the dose of protamine required to reverse a given dose of heparin decreases over time. Furthermore, protamine antagonizes the anti–factor IIa effects of heparin more effectively than the anti–factor Xa effects and thus varies in its potency depending on the source of heparin and its anti–factor IIa properties. Administration of a large fixed dose of protamine or a dose based on the total heparin dose given is no longer the standard of care and may result in an increased incidence of protamine-related adverse effects. An optimal dose of protamine is desired because unneutralized heparin results in clinical bleeding, and an excess of protamine may produce undesired coagulopathy. The use of individualized protamine dose-response curves uniformly results in a reduced protamine dose and has been shown to reduce postoperative bleeding. One such dose-response test, the Hemochron PRT test, is an ACT performed on a heparinized blood sample that contains a known quantity of protamine. With knowledge of the ACT, PRT, and the estimated blood volume of the patient, the protamine dose needed to neutralize the existing heparin level can be extrapolated. The Hepcon instrument also has a PRT, which is the protamine titration assay. The chamber that clots first contains the dose of protamine that most closely approximates the circulating dose of heparin. The protamine dose required for heparin neutralization is calculated on the basis of a specified heparin/protamine dose ratio by measuring the circulating heparin level.

At the levels of heparinization needed for cardiac surgical procedures, tests that are sensitive to heparin become unclottable. The ACT is relatively insensitive to heparin and is ideal for monitoring anticoagulation at high heparin levels, but it is too insensitive to detect incomplete heparin neutralization accurately. The ACT has a high predictive value for adequate anticoagulation (confirmed by laboratory activated partial thromboplastin time [aPTT]) when the ACT is longer than 225 seconds but is poorly predictive for inadequate anticoagulation when the ACT is shorter than 225 seconds. The low levels of heparin present when heparin is incompletely neutralized are best measured by other, more sensitive tests of heparin-induced anticoagulation, such as heparin



BOX 13.2 *Heparin Neutralization*

The most benign form of bleeding after cardiac surgical procedures results from residual heparinization.
Treatment is with either protamine or another heparin-neutralizing product.
Transfusion of allogeneic blood products is rarely indicated.
Residual heparin can be measured by using the following:

- A protamine titration assay
- A heparin-neutralized thrombin time assay
- A heparinase-activated coagulation time (ACT) compared with ACT
- Any other heparinase test that compares itself with the test without heparinase added.

concentration, aPTT, and TT. Thus, after CPB, confirmation of return to the unanticoagulated state should be performed with a sensitive test for heparin anticoagulation (Box 13.2).

TESTS OF COAGULATION

Standard tests of coagulation, the prothrombin time (PT) and the aPTT, are performed on plasma to which the anticoagulant citrate has been added. Because these tests are performed on plasma, they require centrifugation of blood and generally are not feasible for use at the bedside. The aPTT tests the integrity of the intrinsic and the final coagulation pathways and is more sensitive to low levels of heparin than the ACT. Factors IX and X are most sensitive to heparin effects, and thus the aPTT is prolonged even at very low heparin levels. The test uses a phospholipid substance to simulate the interaction of the platelet membrane in activating factor XII. (Thromboplastin is a tissue extract containing tissue factor and phospholipid. The term *partial thromboplastin* refers to the use of the phospholipid portion only.) The aPTT is prolonged in the presence of the following deficiencies: factors XII, XI, IX, and VIII; HMWK (high-molecular-weight kininogen); and kallikrein. The aPTT reaction is considerably slower than the PT, and an activator such as Celite or kaolin is added to the assay to speed activation of factor XII. After incubation of citrated plasma with phospholipid and activator, calcium is added, and the time to clot formation is measured. Normal aPTT is 28 to 32 seconds, which often is expressed as a ratio with a control plasma sample from the same laboratory. This is important because partial thromboplastin reagents have different sensitivities to heparin, and many have nonlinear responses to heparin in various concentration ranges.

The PT measures the integrity of the extrinsic and common coagulation pathways. The PT is prolonged in the presence of factor VII deficiency, warfarin sodium (Coumadin) therapy, or vitamin K deficiency. Large doses of heparin also prolong the PT because of factor II inactivation. The addition of thromboplastin to citrated plasma results in activation of extrinsic coagulation. After a 3-minute incubation and recalcification, the time to clot formation is measured and is recorded as the PT. Normal PT is 12 to 14 seconds; however, because of differences in the quality and lot of the thromboplastin used, absolute PT values are not standardized and are difficult to compare across different testing centers. The international normalized ratio (INR) has been adopted as the standard for coagulation monitoring. The INR is an

internationally standardized laboratory value that is the ratio of the patient's PT to the result that would have been obtained if the International Reference Preparation had been used instead of the laboratory reagents. Each laboratory uses reagents with a specific sensitivity (International Sensitivity Index [ISI]) relative to the International Reference Preparation. The ISI of a particular set of reagents is provided by each manufacturer so that the INR can be reported.

Bedside Tests of Coagulation

The PT and aPTT tests performed on whole blood are available for use in the operating room or at the bedside. The Hemochron PT test tube contains acetone-dried rabbit brain thromboplastin to which 2 mL of whole blood is added, and the tube is inserted into a standard Hemochron machine. Normal values range from 50 to 72 seconds and are automatically converted by a computer to the plasma-equivalent PT and INR. The Hemochron aPTT contains kaolin activator and a platelet factor substitute and is performed similarly to the PT. The aPTT is sensitive to heparin concentrations as low as 0.2 IU/mL and displays a linear relationship with heparin concentration up to 1.5 IU/mL.

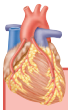
A comparison of bedside coagulation monitors after cardiac surgical procedures documented acceptable accuracy and precision levels for the Hemochron and Ciba Corning Biotrack PTs in comparison with the standard laboratory plasma PT, thus making them potentially valuable for use in the perioperative period. Neither the Hemochron aPTT nor the Ciba Corning aPTT reached this level of clinical competence compared with standard laboratory tests. Because of rapid turnaround times, these POC coagulation monitors may be useful in predicting which patients will bleed after cardiac surgical procedures, and they have also been used successfully in transfusion algorithms to decrease the number of allogeneic blood products given to cardiac surgical patients.

Fibrinogen Level

A whole-blood POC fibrinogen assay is available using the Hemochron system. The specific test tube contains a lyophilized preparation of human thrombin, snake venom extract, protamine, buffers, and calcium stabilizers. The test tube is incubated with 1.5 mL of distilled water and is heated in the Hemochron instrument for 3 minutes. Whole blood is placed into a diluent vial, where it is 50% diluted, and from this vial, 0.5 mL of diluted whole blood is placed into the specific fibrinogen test tube. The clotting time is measured using standard Hemochron technology, as described previously. The fibrinogen concentration is determined by comparison with a standard curve for this test. Normal fibrinogen concentration of 180 to 220 mg/dL correlates with a clotting time of 54 ± 2.5 seconds. Fibrinogen deficiency of 50 to 75 mg/dL correlates with a clotting time of 150 ± 9.0 seconds.

MONITORING THE THROMBIN INHIBITORS

A newer class of drugs, the selective thrombin inhibitors, provides a viable alternative to heparin anticoagulation for CPB. These agents include hirudin, argatroban, bivalirudin, and experimental agents. A major advantage of these agents over heparin is that they can effectively inhibit clot-bound thrombin in an AT III–independent fashion. They are also useful in patients with heparin-induced thrombocytopenia (HIT), in whom the administration of heparin and subsequent antibody-induced



BOX 13.3 *Thrombin Inhibitors*

These anticoagulant drugs are superior to heparin.
They inhibit both clot-bound and soluble thrombin.
They do not require a cofactor, activate platelets, or cause immunogenicity.
These drugs include hirudin, argatroban, and bivalirudin.
Heparin remains an attractive drug because of its long history of safe use and the presence of a specific drug antidote, protamine.

platelet aggregation would be dangerous. The lack of a potent antidote (eg, protamine) and a prolonged duration of action are the major reasons that hirudin and other thrombin inhibitors have not found widespread clinical acceptance for use in CPB procedures.

Bivalirudin

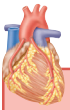
Bivalirudin is a small, 20–amino acid molecule with a plasma half-life of 24 minutes. It is a synthetic derivative of hirudin and thus acts as a direct thrombin inhibitor. Bivalirudin binds to both the catalytic binding site and the anion-binding exosite on fluid-phase and clot-bound thrombin. The part of the molecule that binds to thrombin is actually cleaved by thrombin itself, so the elimination of bivalirudin activity is independent of specific organ metabolism. Bivalirudin has been used successfully as an anticoagulant agent in interventional cardiology procedures as a replacement for heparin therapy (Box 13.3).

Multicenter clinical trials comparing bivalirudin with heparin anticoagulation in off-pump coronary artery bypass operations and in CPB demonstrated "noninferiority" of bivalirudin. Efficacy of anticoagulation and markers of blood loss were similar in the two groups, a finding suggesting that bivalirudin can be a safe and effective anticoagulant agent in CPB. These multicenter trials used the ACT as the monitor of anticoagulant activity intraoperatively, but ideal monitoring is performed using the ecarin clotting time. The ecarin clotting time has a closer correlation with anti–factor IIa activity and plasma drug levels than does the ACT. For this reason, standard ACT monitoring during antithrombin therapy is not preferred if ecarin clotting time can be measured. A plasma-modified ACT can be used to assay the anticoagulant effects of the thrombin inhibitor drugs more accurately than ACT. This test requires the addition of exogenous plasma and thus is not readily available as a POC assay.

MONITORING PLATELET FUNCTION

Platelet Count

Numerous events during cardiac surgical procedures predispose patients to platelet-related hemostasis defects. The two major categories are thrombocytopenia and qualitative platelet defects. Thrombocytopenia commonly occurs during cardiac surgical procedures as a result of hemodilution, sequestration, and destruction by nonendothelial surfaces. Platelet counts commonly decline to 100,000/μL or less; however, the final



BOX 13.4 *Platelet Function*

The platelet count does not correlate with bleeding after cardiac surgical procedures.
Patients frequently have extreme degrees of thrombocytopenia but do not bleed because they have adequate platelet function.
The measure of platelet function correlates temporally with the bleeding course seen after cardiac surgical procedures.
The thromboelastogram maximal amplitude, mean platelet volume, and other functional platelet tests are useful in transfusion algorithms.

platelet count greatly depends on the starting value and the duration of platelet-destructive interventions (ie, CPB). Between 10,000 and 100,000/μL, the bleeding time (BT) decreases directly; however, at platelet counts greater than 50,000/μL, neither the BT nor the platelet count has any correlation with postoperative bleeding in cardiac surgical patients

Qualitative platelet defects occur more commonly than thrombocytopenia during CPB. The range of possible causes of platelet dysfunction includes traumatic extracorporeal techniques, pharmacologic therapy, hypothermia, and fibrinolysis; the hemostatic insult increases with the duration of CPB. The use of bubble oxygenators (although infrequent), noncoated extracorporeal circulation, and cardiotomy suctioning causes various degrees of platelet activation, initiates the release reaction, and partly depletes platelets of the contents of their α granules.

Protamine-heparin complexes and protamine alone also contribute to platelet depression after CPB. Mild-to-moderate degrees of hypothermia are associated with reversible degrees of platelet activation and platelet dysfunction. Overall, the potential coagulation benefits of normothermic CPB compared with hypothermic CPB require further study in well-conducted randomized trials (Box 13.4).

BEDSIDE COAGULATION AND PLATELET FUNCTION TESTING

Viscoelastic Tests

Thromboelastography

The Thrombelastograph (TEG, Haemonetics, Braintree, MA) can be used on-site either in the operating room or in a laboratory and provides rapid whole-blood analysis that yields information about clot formation and clot dissolution (Table 13.1 and Fig. 13.3). Within minutes, information on the integrity of the coagulation cascade, platelet function, platelet-fibrin interactions, and fibrinolysis is obtained. The principle is as follows: whole blood (0.36 mL) is placed into a plastic cuvette into which a plastic pin is suspended; this plastic pin is attached to a torsion wire that is coupled to an amplifier and recorded; the cuvette then oscillates through an arc of 4 degrees, 45 minutes at 37°C. When the blood is liquid, movement of the cuvette does not affect the pin. However, as clot begins to form, the pin becomes coupled to the motion of the cuvette, and the torsion wire generates a signal that is recorded. The recorded tracing can be stored by computer, and the parameters of interest are calculated using a simple software package. Alternatively, the tracing can be generated online with a

Table 13.1 Mechanisms of Point-of-Care Platelet Function Monitors

Instrument	Mechanism	Platelet Agonist	Clinical Utility
Thrombelastograph (Haemonetics, Braintree, MA)	Viscoelastic	Thrombin (native), ADP, arachidonic acid	Post CPB, liver transplant, pediatrics, obstetrics, drug efficacy
Sonoclot (Sienco, Arvada, CO)	Viscoelastic	Thrombin (native)	Post CPB, liver transplant
ROTEM (TEM Systems, Durham, NC)	Viscoelastic	Thrombin (native)	Post CPB, transfusion algorithm
HemoSTATUS (Medtronic Perfusion Services, Minneapolis, MN)	ACT reduction	PAF	Post CPB, DDAVP, transfusion algorithm
Plateletworks (Helena Laboratories, Beaumont, TX)	Platelet count ratio	ADP, collagen	Post CPB, drug therapy
PFA-100 (Siemens Medical Solutions USA, Malvern, PA)	In vitro bleeding time	ADP, epinephrine	vWD, congenital disorder, aspirin therapy, post CPB
VerifyNow (Accriva Diagnostics, Accumetrics, San Diego, CA)	Agglutination	TRAP, ADP	GpIIb/IIIa receptor blockade therapy, drug therapy, post CPB
Clot Signature Analyzer (Xylum, Scarsdale, NY)	Shear-induced in vitro bleeding time	Collagen (one channel only)	Post CPB, drug effects
Whole-blood aggregometry	Electrical impedance	Multiple	Post CPB
Impact Cone and Plate(let) Analyzer (Matis Medical, Beersel, Belgium)	Shear-induced platelet function	None	Post CPB, congenital disorder, drug effects
Multiplate Analyzer (Roche Diagnostics, Indianapolis, IN)	Electrical impedance	ADP, arachidonic acid, collagen, ristocetin, TRAP-6	Drug therapy, congenital disorder, post CPB

ACT, Activated clotting time; *ADP,* adenosine diphosphate; *CPB,* cardiopulmonary bypass; *DDAVP,* desmopressin; *Gp,* glycoprotein; *PAF,* platelet-activating factor; *ROTEM,* rotational thrombelastometry; *TRAP,* thrombin receptor agonist peptide; *vWD,* von Willebrand disease.

recording speed of 2 mm/min. The tracing generated has a characteristic conformation that is the signature of the TEG. The most current commercially available TEG incorporates this viscoelastic measurement into a cartridge-based hemostasis test, thus eliminating the need for blood pipetting and reducing the instrument sensitivity to motion.

The specific parameters measured by TEG include the reaction time (R value), coagulation time (K value), "α" angle, maximal amplitude (MA), amplitude 60 minutes after the maximal amplitude (A60), and clot lysis indices at 30 and 60 minutes after MA (LY30 and LY60, respectively) (Fig. 13.4). The R value represents the time for initial fibrin formation and measures the intrinsic coagulation pathway, the extrinsic

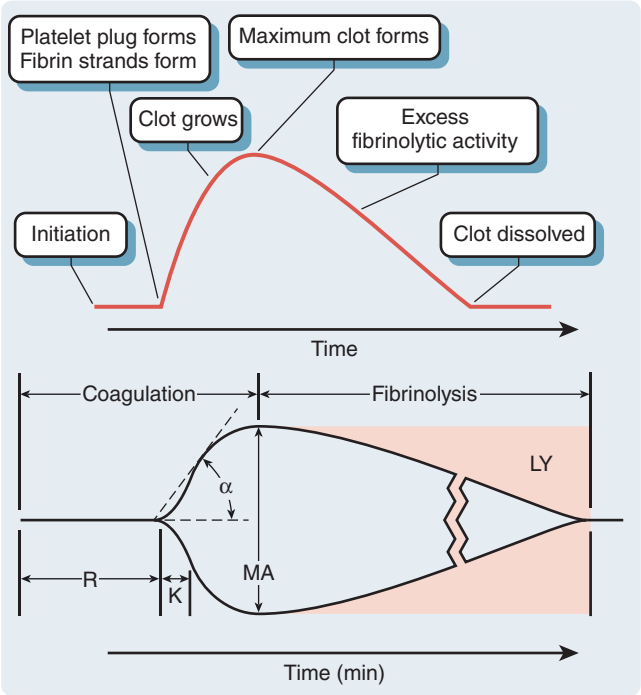


Fig. 13.3 Normal Thrombelastograph (TEG, Haemonetics, Braintree, MA) tracing with standard parameters. *R,* The reaction time or the latency time from placing blood in the cup until the clot begins to form and the tracing opens to 2 mm (typically relates to function or amount of coagulation factors); *K,* a parameter arbitrarily assigned as the time between the TEG trace reaching 2 mm and going up to 20 mm (thought to reflect fibrinogen levels); *α,* the angle between the line in the middle of the TEG tracing and the line tangential to the developing TEG tracing (predictive of maximal amplitude); *MA,* maximal amplitude (largest measured width on the TEG tracing) and is considered to represent maximal thrombin-induced platelet activity and clot formation (total clot strength representing platelet function and clot interactions); *LY,* lysis index, which is the percent of lysis, typically measured as LY30 or 30 minutes after achieving MA.

coagulation pathway, and the final common pathway. R is measured from the start of the bioassay until fibrin begins to form, and the amplitude of the tracing is 2 mm. Normal values vary by activator, but they range from 7 to 14 minutes using Celite activator, or in the rapid TEG from 1 to 3 minutes using tissue factor activator. The K value is a measure of the speed of clot formation and is measured from the end of the R time to the time the amplitude reaches 20 mm. Normal values (3–6 minutes) also vary with the type of activators used. The α angle, another index of speed of clot formation, is the angle formed between the horizontal axis of the tracing and the tangent to the tracing at 20-mm amplitude. The α values normally range from 45 to 55 degrees. Because both the K value and the α angle are measures of the speed of clot strengthening, each is improved by high levels of functional fibrinogen. MA (normal is 50–60 mm) is an index of clot strength as determined by platelet function, the cross-linkage of fibrin, and the interactions of platelets with polymerizing fibrin. The peak strength of the clot, or the shear elastic modulus "G," has a curvilinear relation with MA and is defined as follows: G = (5000 MA)/(96 – MA). The percentage reduction in MA after 30 minutes reflects the fibrinolytic activity present and normally is not more than 7.5%.

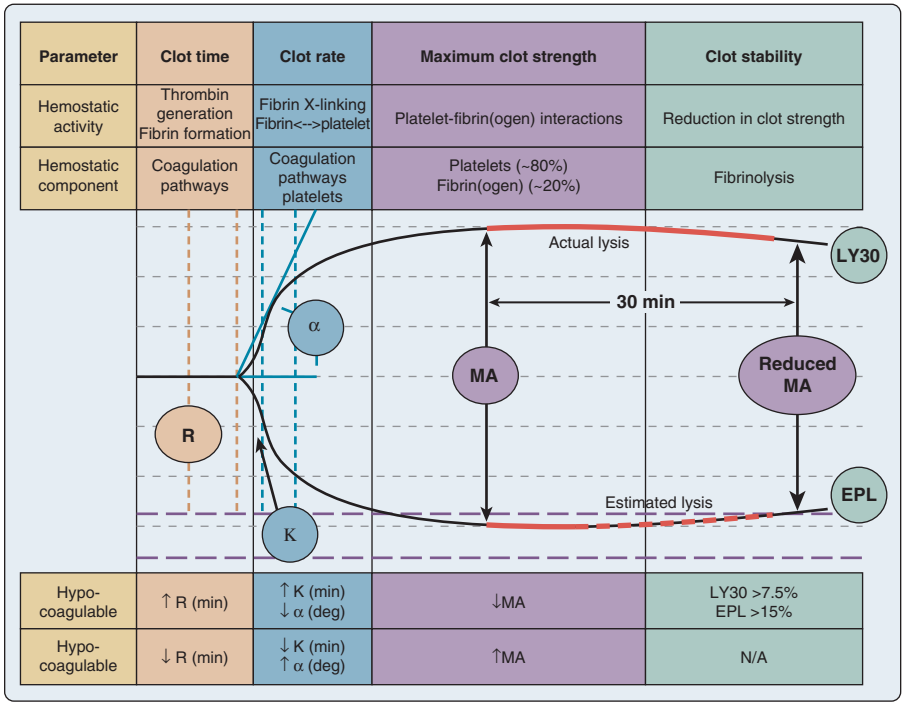


Fig. 13.4 Normal Thrombelastograph (TEG, Haemonetics, Braintree, MA) tracing with standard parameters. *α,* An angle between the line in the middle of the TEG tracing and the line tangential to the developing TEG tracing (predictive of maximal amplitude); *K,* a parameter arbitrarily assigned as the time between the TEG trace reaching 2 mm and going up to 20 mm (may represent fibrinogen levels); *LY,* lysis index; *MA,* maximal amplitude, considered to represent maximal thrombin-induced platelet activity and clot formation (total clot strength representing platelet function and clot interactions); *R,* reaction time or the latency time from placing blood in the cup until the clot begins to form, reaching a TEG tracing amplitude of 2 mm (typically relates to function or amount of coagulation factors).

Characteristic TEG tracings can be recognized to indicate particular coagulation defects. A prolonged R value indicates a deficiency in coagulation factor activity or level and is seen typically in patients with liver disease and in patients receiving anticoagulant agents such as warfarin or heparin. MA and the α angle are reduced in states associated with platelet dysfunction or thrombocytopenia and are reduced even further in the presence of a fibrinogen defect. LY30, or the lysis index at 30 minutes after MA, is increased in conjunction with fibrinolysis. These particular signature tracings are depicted in Fig. 13.5.

TEG is a useful tool for diagnosing and treating perioperative coagulopathy in patients undergoing cardiac surgical procedures because of a variety of potential coagulation defects that may exist. Within 15 to 30 minutes, on-site information is available regarding the integrity of the coagulation system, the platelet function, fibrinogen function, and fibrinolysis. With the addition of heparinase, TEG can be performed during CPB and can provide valuable and timely information regarding coagulation status. Because TEG is a viscoelastic test and evaluates whole-blood hemostasis interactions, proponents suggest that TEG is a more accurate predictor of postoperative hemorrhage than are routine coagulation tests. Detractors of POC testing point to variance in the results with the earlier instruments and to some evidence that standard parameters have better correlation with bleeding.

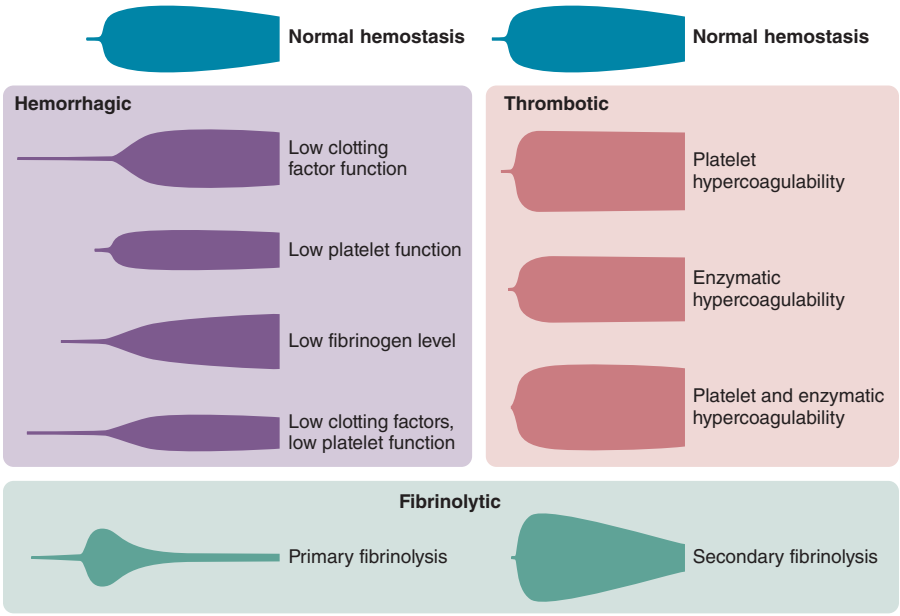


Fig. 13.5 Thrombelastograph (TEG, Haemonetics, Braintree, MA) tracings in various coagulation states.

Thromboelastography Modifications

PlateletMapping is a modification of TEG that assesses platelet function by comparing the MA tracing induced by activation with arachidonic acid (AA) or adenosine diphosphate (ADP) receptors (MA_{pi} [platelet inhibitor]) to the MA achieved with no platelet activity (MA_f), and with maximal platelet activation (MA_{kh}). For PlateletMapping, the reaction is carried out in the setting of heparinized blood, thus inhibiting thrombin platelet activation. The MA produced in this setting, when reptilase and factor XIII are used to form the clot, is the MA with "no platelet activity," or MA_f (fibrin). The MA_{pi} is the maximal activation of platelets and fibrin and is the largest amplitude that can be achieved with the specific platelet activators (ADP or AA). MA_{pi} tracings are compared with the MA_f. In addition, a standard kaolin-heparinase–activated TEG tracing is created to demonstrate maximal platelet activation that occurs when thrombin is present (MA_{kh}) (Fig. 13.6). The following formula calculates the percentage reduction in platelet activity using this assay:

$$\%\ \text{inhibition} = 100 - [(MA_{pi} - MA_f)/(MAkh - MA_f) \times 100]$$

PlateletMapping has demonstrated consistent correlation with optical platelet aggregation assays. PlateletMapping studies demonstrate sensitivity in detecting aspirin resistance, as well as updated timeframes on when platelet function returns following cessation of clopidogrel therapy. The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to coronary artery bypass grafting (CABG) (TARGET-CABG) study investigated the utility of PlateletMapping in stratifying the waiting period for patients needing CABG who were taking clopidogrel. Results indicated not only that PlateletMapping could be used to individualize this waiting period based on platelet activity, but also that a 50% reduction in these wait times occurred without any increased bleeding complications. PlateletMapping has been

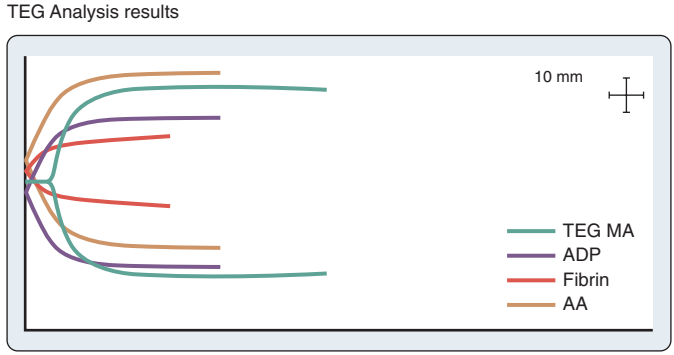


Fig. 13.6 Multitracing displaying standard four reactions involved in the PlateletMapping modification of the Thrombelastograph (TEG, Haemonetics, Braintree, MA). The percentage of inhibition (% inhibition) of platelets is calculated according to the following equation: % inhibition = 100 – [(MA_{pi} – MA_f) / (TEG MA – MA_f) × 100] where MA_f is maximum amplitude of *fibrin*-activated curve, MA_{pi} is maximum amplitude by specific platelet activators (either adenosine diphosphate [*ADP*] or arachidonic acid [*AA*], and *TEG MA* is maximum amplitude of kaolin-activated TEG.

shown to be useful in prediction of post-CPB bleeding in multiple small-scale studies, mostly in patients receiving antiplatelet medications. The percentage of inhibition, as well as the MA_{ADP}, was shown to predict postoperative chest tube output, which was the strategy used in the TARGET-CABG trial.

ROTEM (Rotational Thrombelastometry)

Rotational Thrombelastometry (ROTEM, TEM Systems, Durham, NC) gives a viscoelastic measurement of clot strength in whole blood. A small amount of blood and coagulation activators are added to a disposable cuvette that is then placed in a heated cuvette holder. A disposable pin (sensor) that is fixed on the tip of a rotating shaft is lowered into the whole-blood sample. The loss of elasticity on clotting of the sample leads to changes in the rotation of the shaft that is detected by the reflection of light on a small mirror attached to the shaft. A detector records the axis rotation over time, and this rotation is translated into a graph or thromboelastogram. ROTEM functions to measure changes in viscoelastic properties of clot formation in a fashion similar to that of TEG, but with some key differences.

The main descriptive parameters associated with the standard ROTEM tracing (Fig. 13.7) are the following:

- Clotting time: corresponding to the time in seconds from the beginning of the reaction to an increase in amplitude of the tracing of 2 mm. It represents the initiation of clotting, thrombin formation, and start of clot polymerization.
- CFT (clotting formation time): the time in seconds of an increase in amplitude from 2 to 20 mm. This identifies the fibrin polymerization and stabilization of the clot with platelets and factor XIII.
- Alpha (α) angle: the tangent to the clotting curve through the 2-mm point. It reflects the kinetics of clotting. Therefore, a larger α angle reflects the rapid clot formation mediated by thrombin-activated platelets, fibrin, and activated factor XIII [factor XIIIa]); CFT becomes shorter as the α angle becomes larger, and the two parameters are closely linked.
- A10 (amplitude obtained at 10 minutes): this directly relates to maximum clot firmness (MCF) and can be used to predict MCF and platelet function.

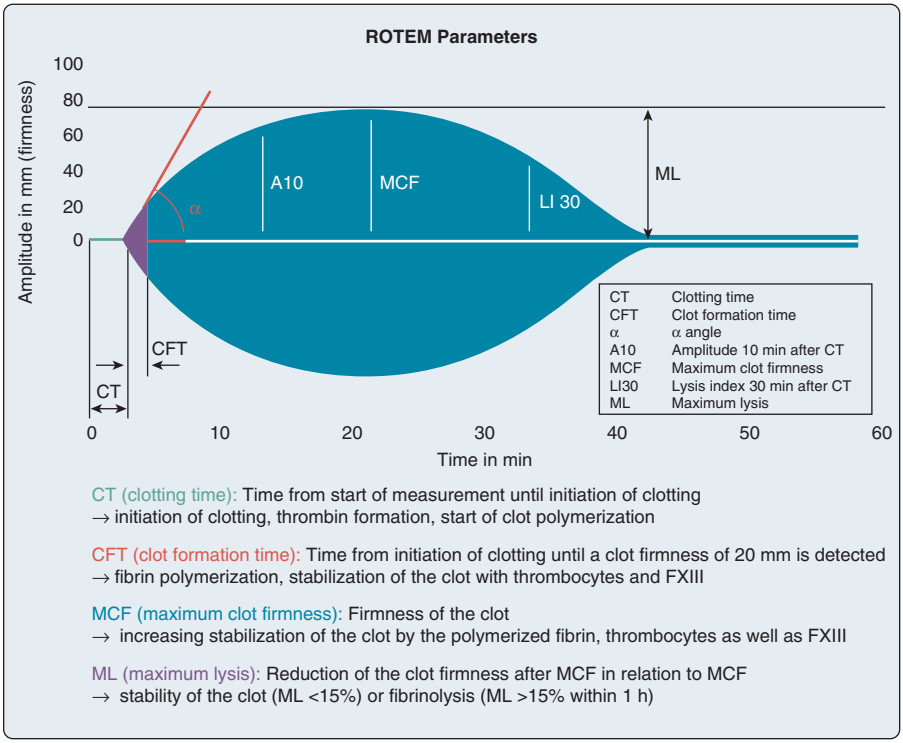


Fig. 13.7 Rotational thrombelastometry (ROTEM, TEM Systems, Durham, NC) parameters.

- MCF: the maximum amplitude in millimeters reached in the tracing that correlates with platelet count, platelet function, and with the concentration of fibrinogen.
- LI30 (lysis index % at 30 minutes): a parameter representing fibrinolysis at a determined time point (typically 30 minutes). It correlates to the MCF (clot % remaining).
- ML (maximum lysis): this is the ratio of the lowest amplitude after reaching the maximum clot firmness to the maximum clot firmness. Like the LI30, this parameter can evaluate for hyperfibrinolysis.

ROTEM has been used extensively in Europe and increasingly in the United States after receiving approval from the US Food and Drug Administration (FDA) in 2011. ROTEM tests coagulation by using various reagents (Table 13.2), and the most common tests include INTEM (intrinsic system), EXTEM (extrinsic system), HEPTEM (intrinsic system in presence of heparin), FIBTEM (measures fibrinogen activity), and APTEM (tissue factor activation + tranexamic acid or aprotinin). Fig. 13.8 provides an example of a series of ROTEM reactions for a hematologically normal patient, compared with a patient with platelet dysfunction.

In 2015 ROTEM released a module that attaches to the standard platform that adds the capability to monitor platelet aggregation function in response to three platelet agonists (ADP, AA, and thrombin receptor agonist peptide [TRAP]) called the ADPTEM, ARATEM, and TRAPTEM, respectively. This system functions using the same concept as standard whole-blood aggregometry and is similar to the Multiplate aggregometer.

Table 13.2 Standard Rotational Thrombelastometry Reagents and Assessment Pattern

EXTEM	Tissue factor activation; factors VII, X, V, II, I, platelets, and fibrinolysis
INTEM	Contact phase activation; factors XII, XI, IX, VIII, II, I, platelets, and fibrinolysis
FIBTEM	EXTEM + cytochalasin D (platelet blocking); assessment of fibrinogen
APTEM	EXTEM plus aprotinin; useful to rule out fibrinolysis when compared to EXTEM
HEPTEM	INTEM plus heparinase; useful to detect residual heparin

APTEM, Tissue factor activation + tranexamic acid/aprotinin; *EXTEM,* extrinsic system; *FIBTEM,* measure of fibrinogen activity; *HEPTEM,* intrinsic system in presence of heparin; *INTEM,* intrinsic system.

Point-of-Care Tests of Platelet Response to Agonists

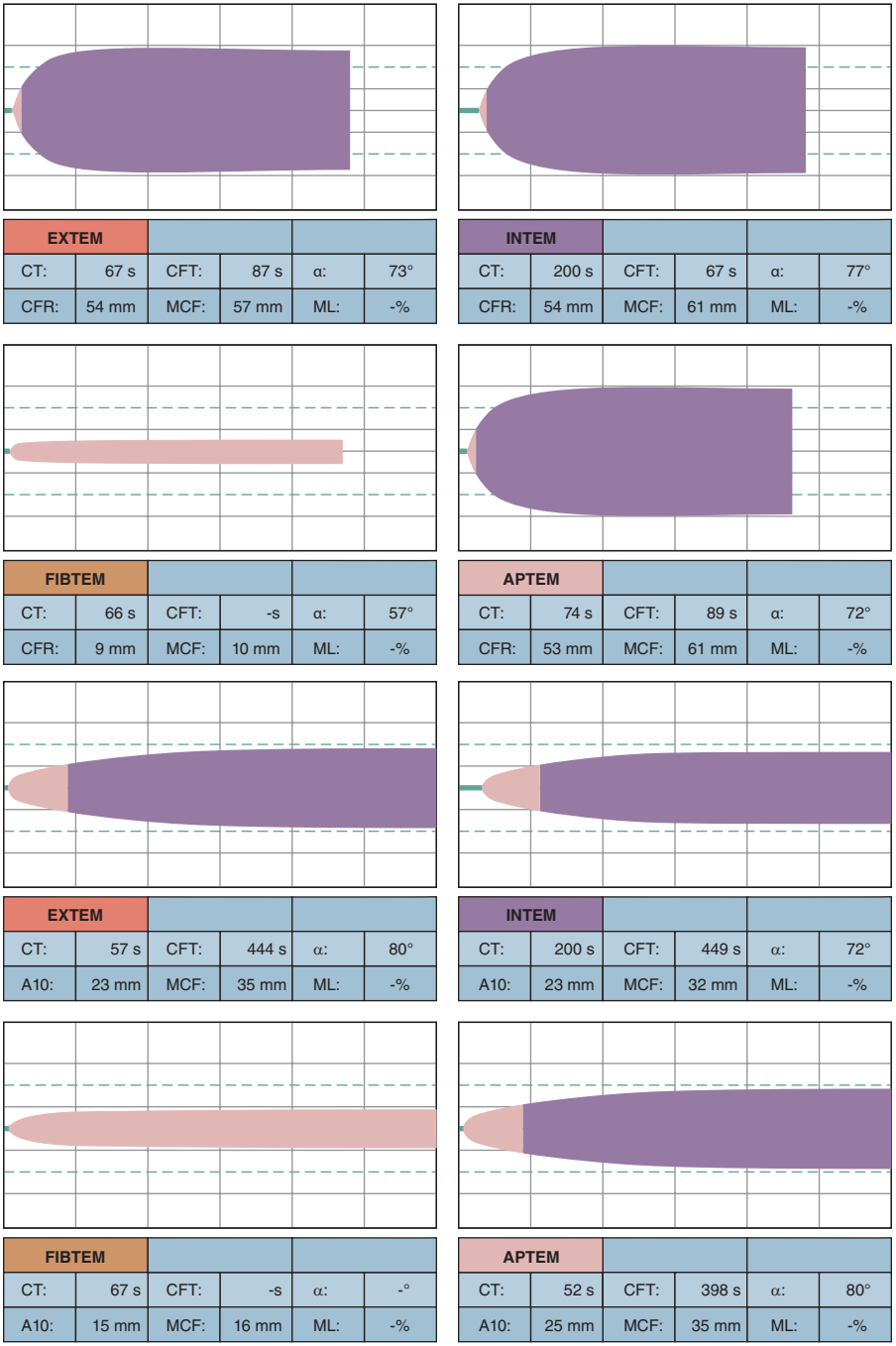
In contrast to viscoelastic testing, various platforms are now available as POC devices that allow for platelet function testing in response to agonists. Each system uses unique concepts, although most have been well validated with laboratory-based light transmission aggregometry (LTA), and some have been validated with the previously described viscoelastic tests.

VerifyNow

VerifyNow (Accumetrics, San Diego, CA) is a POC monitor approved by the FDA for use as a platelet function assay. In whole blood, it measures TRAP activation–induced platelet agglutination of fibrinogen-coated beads by using an optical detection system. After anticoagulated whole blood is added to the mixing chamber, the platelets become activated if they are responsive to the agonist. The activated glycoprotein (Gp)IIb/IIIa receptors on the platelets bind to adjacent platelets through the fibrinogen on the beads and cause agglutination of the blood and the beads. Light transmittance through the chamber is measured and increases as agglutination increases, much as in standard aggregometry. Antithrombotic drug effects cause diminished agglutination (measured by light transmittance); the degree of platelet inhibition can thus be quantified. VerifyNow has agonists to examine the antiplatelet activity of GpIIb/IIIa inhibitors, aspirin, and clopidogrel and can report and quantify the degree of platelet inhibition with good correlation with LTA.

Platelet Function Analyzer

The Platelet Function Analyzer (PFA-100; Siemens Medical Solutions USA, Malvern, PA) is a monitor of platelet adhesive capacity that is currently approved by the FDA and is valuable to identify drug-induced platelet abnormalities, platelet dysfunction of von Willebrand disease and other acquired and congenital platelet defects. The test is conducted as a modified in vitro BT. Whole blood is drawn through a chamber by vacuum and is perfused across an aperture in a collagen membrane coated with an agonist (epinephrine or ADP). Platelet adhesion and formation of aggregates seal the aperture, thus indicating the "closure time" measured by the PFA-100. In cardiac surgical patients, the preoperative PFA-100 closure time significantly correlated with postoperative blood loss (Box 13.5).



EXTEM					
CT:	67 s	CFT:	87 s	α:	73°
CFR:	54 mm	MCF:	57 mm	ML:	-%

INTEM					
CT:	200 s	CFT:	67 s	α:	77°
CFR:	54 mm	MCF:	61 mm	ML:	-%

FIBTEM					
CT:	66 s	CFT:	-s	α:	57°
CFR:	9 mm	MCF:	10 mm	ML:	-%

APTEM					
CT:	74 s	CFT:	89 s	α:	72°
CFR:	53 mm	MCF:	61 mm	ML:	-%

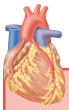
EXTEM					
CT:	57 s	CFT:	444 s	α:	80°
A10:	23 mm	MCF:	35 mm	ML:	-%

INTEM					
CT:	200 s	CFT:	449 s	α:	72°
A10:	23 mm	MCF:	32 mm	ML:	-%

FIBTEM					
CT:	67 s	CFT:	-s	α:	-°
A10:	15 mm	MCF:	16 mm	ML:	-%

APTEM					
CT:	52 s	CFT:	398 s	α:	80°
A10:	25 mm	MCF:	35 mm	ML:	-%

Fig. 13.8 *Left,* Normal tracings for the four standard parameters in the rotational thrombelastometry (ROTEM, TEM Systems, Durham, NC) system. *Right,* Platelet dysfunction, which is demonstrated by the prolonged clot formation time *(CFT),* as well as a decreased maximum clot firmness *(MCF)* in both the extrinsic system *(EXTEM)* and the intrinsic system *(INTEM)* tests. *A10,* Amplitude 10 min after CT; *APTEM,* tissue factor activation + tranexamic acid/aprotinin; *CFR,* clot formation rate; *CT,* clotting time; *FIBTEM,* measure of fibrinogen activity.



BOX 13.5 *Platelet Function Tests*

The appropriate test to measure platelet function depends on the suspected platelet defect.

The Thrombelastograph (TEG, Haemonetics, Braintree, MA), Rotational Thromboelastometry (ROTEM, TEM Systems, Durham, NC), and thromboelastometry, and possibly other viscoelastic tests, are useful to measure platelet defects after cardiopulmonary bypass. VerifyNow (Accumetrics, San Diego, CA) and Multiplate (Helena Laboratories, Beaumont, TX) are useful to measure the effects of glycoprotein IIb/IIIa and adenosine diphosphate receptor-blocker therapy and aspirin therapy.

The PFA-100 test (Siemens Medical Solutions USA, Malvern, PA) is useful to measure the effects of aspirin on platelet adhesion.

It is important to understand the platelet defect being sought to use the proper test accurately.

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