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Monitoring anticoagulation and hemostasis in cardiac surgery

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The hemostatic management of patients undergoing cardiac surgery is a complex issue because there exists the need to maintain a delicate balance between anticoagulation for cardiopulmonary bypass (CPB) and hemostasis after CPB. These two opposing goals must be managed carefully and modified with respect to the patient's initial hematologic status, specific timing during cardiac surgery, and desired hemostatic outcome. During CPB, optimal anticoagulation dictates that coagulation be antagonized and platelets be prevented from activating so that microvascular clots do not form on the extracorporeal circuit. After surgery, coagulation abnormalities, platelet dysfunction, and fibrinolysis can occur, creating a situation whereby hemostatic integrity must be restored. The complex process of anticoagulation with heparin, antagonism with protamine, and postoperative hemostasis therapy cannot be performed without careful and accurate monitoring.

Anticoagulation for CPB

CPB could not be conducted safely without anticoagulation of the blood that will contact the extracorporeal circuit. The most common anticoagulant in clinical use is heparin [1], because it is easy to acquire, dose, administer, measure, and reverse. Heparin acts as an ATIII agonist and accelerates ATIII binding to thrombin. In the absence of ATIII, heparin is clinically ineffective as an anticoagulant, thus adequate ATIII activity is necessary in patients about to undergo heparinization for cardiac surgical procedures [2].

Monitoring heparin effect

Cardiac surgery has been performed for decades using empiric heparin dosing in the form of a bolus and subsequent interval dosing. Empiric dosing has since

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Table 1
Measurement of anticoagulation for cardiac surgery

Test	Advantages	Disadvantages
ACT (Hemochron, Actalyke)	Functional Linear to heparin level	Two mL blood volume Affected by temperature, hematocrit
ACT (Hemotec)	Kaolin available (aprotinin) Much data support 0.4 mL blood volume	Celite affected by aprotinin Non-specific Affected by temperature, hematocrit
HMT (Bayer Diagnostics)	Linear to heparin level Kaolin activator Small 30 μ L of blood	Non-specific Need data for minimum threshold HMT
Heparin concentration (Hepcon)	Pediatrics: beneficial HMS machine Protamine titration Not affected by temperature, hct	Not a functional test
High dose thrombin time (HiTT)	Hemochron machine Not affected by temperature, hematocrit Not affected by aprotinin Measures shorter pathway	Needs reconstitution Highly variable Need more data
Ecarin clotting time	Measures hirudin	May need to add plasma
Plasma modified ACT	Better correlation with heparin	Need to add plasma
High dose thromboplastin time	Not affected by aprotinin	Need more data

Abbreviations: ACT, activated clotting time; HMT, heparin management test.

been supplanted by the monitored use of heparin. Currently, many assays are available to measure the response to the heparin dose given to institute extracorporeal circulation (Table 1). Functional tests of anticoagulation or quantitative measures of the level of circulating heparin may be used. The anticoagulant effect of heparin should at least be monitored functionally before instituting CPB. The mere administration of heparin does not guarantee that all patients will be adequately anticoagulated because there are differences in levels of circulating co-factors and inhibitors that can alter the pharmacokinetics and pharmacodynamics of the drug.

Activated clotting time

Functional tests of heparin activity are related to the whole blood clotting time. The original whole blood clotting time required that whole blood be placed in a glass tube, maintained at 37°C, and manually tilted until blood fluidity was no longer detected. This test has been updated and activated, and it is now referred to as activated clotting time (ACT).

Whole blood is added to a test tube containing diatomaceous earth (celite), kaolin, glass, or a combination of activators. The presence of an activator augments the contact activation phase of coagulation, which stimulates the

intrinsic coagulation pathway. Detection of ACT values can be performed manually but is more commonly automated, as it is in the Hemochron and Hemotec systems [3]. In these automated systems, the test tube is placed in a device that warms the sample to 37°C. The Hemochron device (International Technidyne Inc, Edison, NJ) houses a test tube that contains activator and a small iron cylinder into which whole blood (2 mL) is added. The device rotates the test tube, and the iron cylinder rolls along the bottom of the rotating test tube before the blood begins to clot. At the time the clot forms, the cylinder is pulled away from a magnetic detector, interrupting a magnetic field and signaling the end of the clotting time. Normal ACT values range from 80 to 120 seconds. The Hemotec ACT device (Medtronic Hemotec, Parker, CO) is a cartridge with two chambers containing kaolin activator that is heated. Blood (0.4 mL) is automatically placed into each chamber and a daisy shaped plunger rises and falls into the chamber. The formation of clot will slow the rate of descent of the plunger, and the decrease in velocity of the plunger is detected by a photo-optical system that signals the end of the ACT test. Comparisons between the Hemochron and Hemotec tests are difficult because there are differences in the heparin and activator concentrations and in the measurement technique; therefore, the tests are not interchangeable [4,5]. In adult patients given 300 U/kg of heparin for CPB, the Hemochron and Hemotec (Hepcon) ACT were therapeutic at all time points; however, at two points, the Hemochron ACT was statistically longer [6]. The apparent “overestimation” of the ACT by the Hemochron device during hypothermic CPB may be due to the different volumes of blood that each assay warms to 37°C.

The ACT test can be modified by the addition of heparinase. With this modification, the coagulation status of the patient can be followed during CPB, and 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 the assessment of a circulating heparin-like substance or for residual heparinization after CPB [7,8].

With the introduction of ACT monitoring into the cardiac surgical arena, clinicians have been able to more accurately titrate heparin and protamine dosages. As a result, some investigators report reductions in blood loss and transfusion requirements. The improvements in postoperative hemostasis with ACT monitoring are potentially attributed to better intraoperative suppression of microvascular coagulation and improved monitoring of heparin reversal with protamine [9,10].

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. It has been suggested that many factors can alter the ACT, and these factors are prevalent during cardiac surgical procedures. For example, when the extracorporeal circuit prime is added to the patient's blood volume, hemodilution occurs, which may theoretically increase the ACT [4]. Hypothermia also increases the ACT in a “dose-related” fashion. However, Culliford et al [11] reported that although hemodilution and hypothermia significantly increase the ACT of a heparinized blood sample, similar increases do not occur in the absence of added heparin. Extreme thrombocytopenia (less than

30,000/ μ L) will prolong the baseline and heparinized ACT [12]. Patients treated with platelet inhibitors such as prostacyclin, aspirin, or platelet membrane receptor antagonists will have a prolonged heparinized ACT compared with patients not treated with platelet inhibitors [13]. Platelet lysis, however, will significantly shorten the ACT because of the release of platelet membrane components, which may have heparin neutralizing activities [14]. Finally, Gravlee et al [15] reported that anesthesia and surgery decrease the ACT and create a hypercoagulable state, possibly by creating a thromboplastic response or by activation of platelets.

The consumption of heparin is higher in the pediatric population than in adults. Thus the heparin administration protocol for pediatric patients undergoing CPB should account for a large volume of distribution, increased consumption, and a shorter elimination half-life. While monitoring the effects of heparin in pediatric patients, the minimum acceptable ACT value should be increased or an additional monitor should be employed. During pediatric congenital heart surgery, some investigators recommend the maintenance of heparin concentrations in addition to the ACT to ensure that optimal anticoagulation is being achieved [16].

During cardiac surgical procedures, the belief that a safe minimum ACT value (300–400 seconds) is required for CPB, is based on a relative paucity of scientific data in which increased production of fibrin monomer was seen in 6 out of 9 monkeys when the ACT fell less than 400 seconds [17]. Theoretically, the inability to attain this degree of anticoagulation could potentially incite a microvascular consumptive coagulopathy in the extracorporeal circuit. However, others have reported no adverse effects of consumption, thrombosis, or excessive bleeding in patients [18] or in animals [19] undergoing CPB in which the ACT was less than 400 seconds.

Heparin resistance

Heparin resistance is documented by an inability to raise the ACT 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 giving increased doses of heparin in a competitive fashion [20]. Many clinical conditions are associated with heparin resistance. Some investigators have documented decreased levels of ATIII secondary to heparin pretreatment and suggest the addition of ATIII [21]. Others question the need for an ACT of 400 seconds in these patients [22–24]. Esposito et al [25] measured coagulation factor levels in patients receiving preoperative heparin infusions and found that a lower baseline ACT was the only predictor for heparin resistance when compared with patients not receiving preoperative heparin.

Heparin sensitivity measurement

Even in the absence of heparin resistance, patient response to an intravenous bolus of heparin is extremely variable. The variability stems from different

concentrations of various endogenous heparin-binding proteins, such as vitronectin and PF4. Because of the large inter-patient 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 for cardiac surgical patients. Bull et al [26,27] documented a three-fold range of ACT response to a 200 U/kg heparin dose and thus recommended the use of individual patient dose-response curves to determine the optimal heparin dose. Point-of-care individual heparin dose-response tests are based on this concept.

A heparin dose-response curve can be generated manually 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. First described by Bull et al [26], this methodology forms the basis for the automated dose-response systems in clinical use, which are produced by several different manufacturers. Using a baseline ACT and the ACT with a known quantity of heparin, an algorithm that incorporates the patient's estimated blood volume will estimate the heparin dose-response curve [2,28,29]. The patient's heparin sensitivity can also be calculated.

The *in vitro* dose response to protamine can also be measured using these point-of-care instruments. The protamine dose that is needed to return the ACT to the desired value is calculated using the patient's ACT and the ACT in response to a known amount of *in vitro* protamine. The use of a protamine dose-response curve results in calculation of lower protamine doses than would be given if the dose were calculated based on the amount of heparin administered [28,30]. Lower protamine doses are desirable because protamine is associated with a host of hemodynamic and hematologic adverse effects.

Heparin concentration

During CPB, the sensitivity of the ACT to heparin is increased. The ACT is prolonged even in conjunction with unchanged or decreasing heparin levels. For this reason, the functional measure of heparin anticoagulation may be supplemented with the quantitative measure of the whole blood heparin concentration. The heparin concentration can be measured and maintained at a predetermined level using the Hepcon HMS system (Medtronic Hemotec, Parker, CO), which uses an automated protamine titration technique. Because protamine neutralizes heparin (1 mg:100 U ratio), the concentration of heparin in the blood sample can be calculated. The maintenance of a stable heparin concentration rather than a specific ACT level usually results in higher doses of heparin being administered because the hemodilution and hypothermia during CPB increase the sensitivity of the ACT to heparin [31]. During CPB, the measure of heparin concentration has been shown to more closely correlate with antifactor XA activity measurements than with the ACT, although the precision and bias of the test may not prove to be acceptable for exclusive use clinically [4].

In a prospective randomized trial, Despotis et al [32] demonstrated that by using a transfusion algorithm in association with Hepcon-based heparin man-

agement, chest tube drainage was minimally reduced and transfusion of non-red blood cell products was significantly reduced (platelets, $P = 0.003$; plasma, $P = 0.0001$; cryoprecipitate, $P = 0.04$) relative to a group of patients who had ACT-based heparin management. They attributed this to better preservation of the coagulation system by high heparin doses, because the doses of heparin administered in the Hepcon group were nearly twice the doses administered in the ACT management group. However, other investigators have been unable to confirm suppression of ongoing coagulation using Hepcon CPB management. Nevertheless, Hepcon remains one of the more sensitive tests for detecting residual heparinization after protamine reversal, because the heparin concentration can be measured by protamine titration to levels as low as 0.4 IU/mL.

High dose thrombin time

A functional test of heparin-induced anticoagulation that correlates well with heparin levels is the high dose thrombin time (HiTT) (International Technidyne Inc., Edison, NJ). The thrombin time (TT) is a whole blood clotting time that measures the conversion of fibrinogen to fibrin by thrombin. Because the TT is sensitive to low levels of heparin, a high dose of thrombin is necessary for the TT to accurately assay the high doses of heparin used for CPB. The HiTT is performed by adding whole blood (1.2 mL) to a prewarmed, prehydrated test tube that contains a lyophilized thrombin preparation (0.3 mL of rabbit brain thromboplastin). This test measures the time required for coagulation by way of the extrinsic pathway, which is activated by tissue damage. Unlike ACT, HiTT is not altered by hemodilution and hypothermia and has been shown to correlate better with heparin concentration than with the ACT during CPB [33].

HiTT monitoring is also advantageous for patients receiving aprotinin therapy. In the presence of heparin, aprotinin augments the celite ACT [34], possibly because its kallikrein inhibiting capacity prolongs activation of the intrinsic coagulation pathway by XIIa. However, this should not be interpreted to represent enhanced anticoagulation. Most likely, the kaolin ACT is less affected by aprotinin therapy than is the celite ACT because kaolin, unlike celite, activates the intrinsic pathway by stimulation of factor XI directly. Others have suggested that kaolin binds to aprotinin and reduces the anticoagulant effect of aprotinin *in vitro* [35]. The HiTT has the advantage of being a measure of anticoagulation that is unaffected by aprotinin therapy [36].

Heparin management test

A completely different technology for measuring the effect of heparin is used by the Rapid Point coagulation analyzer (Bayer, Tarrytown, NY). The test system comprises disposable cards that contain the reagents used for the particular coagulation test being conducted. The card contains iron oxide particles that move in response to an oscillating magnetic field within the device. When clot formation is detected, movement of the iron oxide particles is decreased, and the

end of the test is signaled. This system is capable of measuring prothrombin time (PT), activated partial thromboplastin time (aPTT), and a variation of the ACT called the heparin management test (HMT). HMT correlates well with anti-Xa heparin activity in cardiopulmonary bypass patients and is less variable than standard ACT measures [37]. In a comparison with ACT, the coefficients of variation were similar between the tests at baseline but were three times higher for the ACT during heparinization. HMT was prolonged by the presence of aprotinin because celite is the activator used in the card for that test [38].

Thrombin inhibitors

Selective thrombin inhibitors are a viable alternative to heparin anticoagulation for CPB. These agents include hirudin, argatroban, bivalirudin, and other agents. Compared with heparin, these agents are able to effectively inhibit clot-bound thrombin in an anti-thrombin III-independent fashion. Because surface-bound thrombin is more effectively suppressed, thrombin generation can be reduced at lower levels of systemic anticoagulation than are achieved during anticoagulation by the heparin/ATIII complex. This translates into less bleeding, despite the lack of a clinically useful antidote for the thrombin antagonists. Thrombin antagonists are also useful in certain patients with heparin-induced thrombocytopenia for whom the administration of heparin and subsequent antibody-induced platelet aggregation would be dangerous [39,40]. The lack of a potent antidote (such as protamine) and a prolonged duration of action are the major reasons that hirudin and others have not gained widespread clinical acceptance for use during CPB procedures. The shorter half-life of bivalirudin makes it an attractive alternative, specifically in patients with renal dysfunction.

Though not yet clinically available, the ecarin clotting time is a card available for use with the Rapid Point coagulation analyzer. The ecarin clotting time correlates well with plasma hirudin levels [41,42]. The anticoagulant effects of the thrombin antagonists can also be monitored using the ACT, aPTT, or TT.

Heparin neutralization

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. Gravlee et al [43] suggest that without careful monitoring for heparin rebound in the postoperative period, increased bleeding may occur, specifically when higher doses of heparin have been administered. Monitoring for heparin rebound can be accomplished using tests that are sensitive to low levels of circulating heparin. The tests are also useful monitors for confirmation of heparin neutralization at the conclusion of CPB.

At the levels of heparinization needed for cardiac surgery, tests that are sensitive to heparin become unclottable. The ACT is insensitive to heparin and is ideal for monitoring anticoagulation at high heparin levels, but it is too insensitive to accurately diagnose incomplete heparin neutralization. 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 concentration, aPTT, and TT. Thus, after CPB, confirmation of a return to the non-anticoagulated state should be performed with a sensitive test that detects heparin anticoagulation.

The Hepcon cartridge with a lower concentration of protamine in the titration is useful for the detection of residual circulating heparin and is sensitive to levels of heparin as low as 0.4 U/mL. The heparin neutralized thrombin time (HNNT) is a TT assay with a small dose of protamine sufficient to neutralize 1.5 U/mL of heparin. Because the TT is elevated in the presence of other systemic disorders besides excess heparin, HNNT and TT should be performed together to discriminate the cause. A normal HNNT in the presence of an elevated TT would confirm a residual heparin effect and would indicate the need for protamine administration. If the HNNT and the TT are prolonged, the cause of bleeding may be attributed either to a fibrinogen problem or to a concentration of heparin higher than that which could be neutralized by the HNNT.

Hemostasis and transfusion algorithms

Hemostasis is the body's response to vascular injury. The three major components of hemostasis include the vascular endothelium; the platelets, which determine primary hemostasis; and the coagulation cascade glycoproteins, which determine secondary hemostasis. Fibrinolysis is the normal physiologic response to clot formation and ensures that coagulation remains localized to the area of vascular injury. The greatest advantage of hemostasis testing for cardiac surgical patients has been the incorporation of this testing into transfusion algorithms. Transfusion algorithms are designed with the purpose of minimizing unnecessary and indiscriminate blood product transfusions. Conversely, to avoid delay in necessary reexploration for surgical bleeding, rapid and accurate diagnosis of normal hemostasis in a patient who is bleeding postoperatively is also important. Ideally, a goal-directed algorithm for transfusion therapy after CPB would enable more accurate diagnosis of bleeding abnormalities and would thus limit transfusions to those for whom they are absolutely indicated [44–46]. This algorithm should include a test that measures platelet function, platelet number, coagulation factor integrity, and fibrinolysis. The particular tests that are chosen for a transfusion algorithm should be dictated by the surgical population of interest, the common hemostasis abnormalities in that population, and cost factors.

Tests of coagulation

Testing the coagulation cascade after CPB is an important part of a transfusion algorithm that will determine the integrity of the hemostasis system. PT and aPTT tests performed on whole blood are available for use in the operating room or at the bedside. These tests can be performed using 2 mL of blood in a test tube, as in the Hemochron PT and aPTT test tubes; using 0.4 mL of blood in a cartridge, as

in the Hemotec system; or using a drop of blood on a card, as in the Rapid Point or “junior” Hemochron systems. The aPTT is sensitive to heparin concentrations as low as 0.2 U/mL and displays a linear relationship with heparin concentrations of up to 1.5 U/mL.

Although these point-of-care tests have an acceptable correlation with laboratory analyses of coagulation [47,48], this has not been demonstrated in all complex clinical situations [49]. The rapid turn-around times using these point-of-care coagulation monitors may be useful for predicting those patients who will bleed after cardiac surgery [50] and who may benefit from transfusion algorithms. In turn, this may reduce the number of allogeneic blood products given to cardiac surgical patients [44].

Platelet function

The most frequently implicated post-CPB hemostasis abnormality is platelet dysfunction, which is still poorly understood and difficult to measure. A critical part of any transfusion algorithm for post-CPB patients is the measure of platelet function. It is known that CPB induces defects of the GPIb, the GPIIb-IIIa, the thrombin, and other platelet receptors. The following tests of platelet function

Table 2
Tests of platelet function

Test/Monitor	Advantages	Disadvantages
Bleeding time	Inexpensive No new technology	Impractical Doesn't correlate with perioperative bleeding
Thromboelastography	Correlates with CPB bleeding Much data available	Operator-dependent New technology needed
Sonoclot	Correlates with CPB bleeding	More data required New technology needed
Hemostatus	Correlates with CPB bleeding Measures response to platelet therapy	Data not consistent Depends on ACT technology New technology needed
Ultegra	Measures GPIIb-IIIa Correlates with thrombosis reduction	Single activator New technology needed More data required in CPB
Platelet works	Many activators available Platelet count included	1 mL volume per test More data required in CPB
Platelet function Analyzer (PFA-100)	Two activators available In vitro bleeding time	Low predictive value for bleeding Too sensitive in CPB
Clot signature analyzer	Mimics in vivo shear force Predictive for platelet transfusion	More data required; not FDA approved New technology needed
Standard aggregometry	Gold standard	Technical laboratory methods
Whole blood Aggregometry	Aggregation measure Uses whole blood	More data required Highly variable

Abbreviations: ACT, activated clotting time; CPB, cardiopulmonary bypass.

have been evaluated for clinical use and may be incorporated into a transfusion algorithm for use with the bleeding patient (Table 2).

Bleeding time and point-of-care hemostasis monitors

The bleeding time is performed by creating a skin incision and measuring the time to clot formation by way of the platelet plug. Numerous prospective blinded investigations have confirmed that bleeding time has little or no value in predicting excessive hemorrhage after cardiac surgery [51,52]. Because the bleeding time does not follow the temporal course of postoperative coagulopathy, it may be a nonspecific and impractical test for detecting an existing platelet defect but may be suitable for following patient response to platelet-directed therapies.

Dynamic tests such as bleeding time or the viscoelastic measures of clot formation better reflect the contribution of platelet function to overall clot formation because they take into account the time-dependent nature of platelet-mediated hemostasis. Although such tests are nonspecific in nature because of the absence of a platelet-specific agonist, they can generally be modified to overcome this limitation. One such dynamic test is the thromboelastograph assay (TEG) (Haemoscope, Skokie, IL), which is a whole blood test of viscoelastic blood clot formation. The TEG test is performed “on site,” either in the operating room or in a laboratory, and provides a rapid whole blood analysis that yields information about clot formation and dissolution. Within minutes, information is obtained regarding platelet function, platelet-fibrin interactions, fibrinolysis, and the integrity of the coagulation cascade. The specific platelet-related parameters measured by the TEG test include α angle, which measures the speed of clot formation, and the maximum amplitude (MA), which measures platelet-fibrin interactions (Fig. 1). Use of the TEG assay has been reported to reduce bleeding and transfusion requirements during cardiac surgery [46] and the number of reoperations for bleeding after cardiac surgery [53].

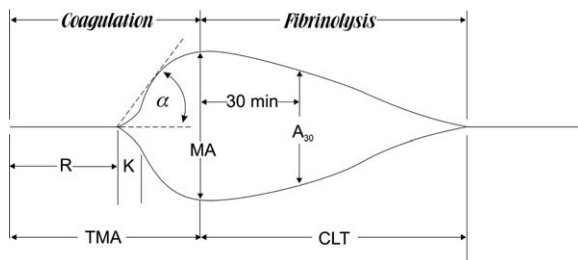


Fig. 1. The kinetics of clot formation can be measured using the Thromboelastograph analyzer (Haemoscope Inc., Skokie, IL). After blood is placed in an oscillating cuvette, the piston is lowered into the blood sample. As the blood begins to clot, the elastic force exerted on the piston is translated to a signature tracing that reveals information about fibrin formation, platelet-fibrin interactions, platelet clot strength, and fibrinolysis. The maximal amplitude (MA) is the parameter most frequently measured, because it correlates with platelet dysfunction in cardiac surgery. CLT, clot lysis time; K, kinetic clot formation time; R, reaction time; TMA, time to maximal amplitude. (Figure courtesy of Haemoscope Inc.)

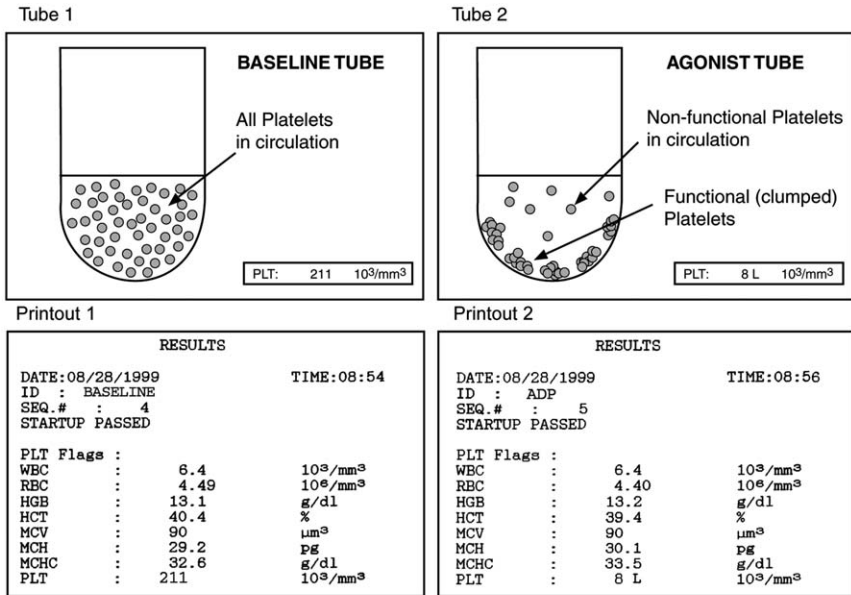
Another test of the viscoelastic properties of blood is the Sonoclot (Sienco Inc., Wheat Ridge, CO). The Sonoclot is a coagulation analyzer that measures the changing impedance on an ultrasonic probe that is immersed in a coagulating blood sample [54]. The electronic mechanism that drives vibration of the probe also acts as a transducer that measures the impedance to vibration and subsequently converts it to a signal on paper. The Sonoclot reflects coagulation in real time, from the start of the fibrin formation to fibrin cross-linkage and platelet mediated clot strengthening, then eventually to clot retraction and fibrinolysis. The Sonoclot has been successfully used for diagnosing and treating coagulation abnormalities in patients undergoing cardiac surgery [55–57].

The Hemostatus (Medtronic Inc., Parker, CO), a device that measures the platelet activated clotting time, has been approved by the US Food and Drug Administration (FDA) for the monitoring of platelet function during cardiac surgery. The Hemostatus has been evaluated for use in cardiac surgical patients and has been shown to accurately demonstrate improved platelet function after platelet-related therapy [58]. The test measures the ACT without a platelet activator and compares this value to the ACT obtained when increasing concentrations of a platelet-activating factor (PAF) are added. The percent reduction of the ACT caused by the addition of PAF is related to the ability of the platelets to be activated and to shorten clotting time. The Hemostatus has been incorporated into transfusion algorithms for cardiac surgical patients.

Platelet Works (Helena Laboratories, Beaumont, TX) is a test that uses the principle of the platelet count ratio to assess platelet reactivity. The instrument is a Coulter counter that measures the platelet count in a standard ethylenediaminetetraacetic (EDTA)-containing tube. The platelet count is also measured in tubes containing platelet agonists (eg, adenosine diphosphate [ADP]). When blood is added to these agonist tubes, it causes the platelets to activate, adhere to the tube, and be effectively eliminated from the platelet count. The ratio of the activated platelet count to the non-activated platelet count is a function of the reactivity of the platelets (Fig. 2). Early investigation indicates that this assay is useful for providing a platelet count and that it is capable of measuring the platelet dysfunction induced by the GPIIb-IIIa receptor inhibitors [59].

Ultegra (Accumetrics, San Diego, CA), also known as the “rapid platelet function assay,” is a point-of-care monitor specifically designed to measure the platelet response to a thrombin receptor agonist peptide (TRAP). In whole blood, it measures platelet-agglutination of fibrinogen-coated beads using an optical detection system. Because of the importance of the GPIIb-IIIa receptor in mediating fibrinogen-platelet interactions, the Ultegra has been especially useful in accurately measuring receptor inhibition in invasive cardiology patients receiving GPIIb-IIIa inhibiting drugs [60].

The Platelet Function Analyzer (PFA-100) (Dade Behring, Miami, FL) is a monitor of platelet adhesive capacity that is able to identify drug-induced platelet abnormalities, von Willebrand’s disease, and other acquired and congenital platelet defects [61]. The test is conducted as a modified *in vitro* bleeding time. Whole blood is drawn through a chamber by vacuum and is perfused across an aperture in



$$\frac{\text{Baseline Platelet Count} - \text{Agonist Platelet Count} \times 100}{\text{Baseline Platelet Count}} = \% \text{ Aggregation}$$

$$\frac{211 - 8 \times (100)}{211} = 96.2\%$$

Users may refer to the % Aggregation Chart in each box of Plateletworks tubes.

Fig. 2. Platelet Works (Helena Laboratories, Beaumont, TX) is a test that uses the principle of the platelet count ratio to assess platelet reactivity. The ratio of the activated platelet count to the non-activated platelet count is a function of the reactivity of the platelets. (Figure courtesy of Helena Laboratories.)

a collagen membrane coated with an agonist (epinephrine or ADP). Platelet adhesion and formation of aggregates will seal the aperture, thus indicating the “closure time” measured by the PFA-100. In cardiac surgical patients, the PFA-100 closure time has a high negative predictive value and may help in identifying patients who are unlikely to need platelet transfusions to reduce bleeding [62].

The Hemostatometer, or Clot Signature Analyzer (CSA) (Xylum, Scarsdale, NY), is a point-of-care device that evaluates the function of platelets under conditions of normal shear. With this device, which is being studied experimentally, whole blood is maintained under a constant driving pressure of 60 mm Hg as it is forced out into a synthetic vessel. The pressure distally in the vessel is monitored. The tubing of this synthetic vessel is perforated and the distal pressure drop is measured. The time to restoration of this distal pressure will be a function of the development of a platelet plug. Thus, the time for initial closure is a measure of platelet function. Another chamber of this device contains a collagen-coated fibrin upon which platelets adhere and form a plug. A similar pressure measurement technique indicates formation of a platelet thrombus. In cardiac surgical patients, the effects of heparin and protamine on platelet reactivity have

been studied using this device [63]. In one prospective study, the device had predictive accuracy for platelet transfusions [64].

Summary

The need to monitor anticoagulation and hemostasis during and after cardiac surgery has led to recognition of the importance of evaluation and use of hemostasis monitors in this setting. Consequently, rapid and accurate identification of abnormal hemostasis has been the major impetus for the development of point-of-care tests and their use in transfusion algorithms for cardiac surgical and other critically ill patients.

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