Point-of-Care Coagulation Monitoring

40

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Introduction

Blood coagulation is a complex, sensitive, and tightly regulated physiological network of interacting cells, proteins, and cofactors [1, 2]. If deranged, it may dramatically influence a patient's outcome. A comprehensive understanding of perioperative hemostasis and its monitoring is a prerequisite for physicians working with patients at risk for major bleeding and thrombosis. The coagulation system represents a delicate balance of forces supporting coagulation (coagulation, antifibrinolysis) and forces inhibiting coagulation (anticoagulation, fibrinolysis). The distinctive challenge for the perioperative physician is to readily assess and judge both sides of this balance, provide an individualized and goal-directed therapy, and maintain homeostasis [3, 4].

Besides patients' medical history, clinical presentation, and routine laboratory-based coagulation tests, bedside coagulation analyses (point-of-care, POC) are increasingly being used to monitor blood coagulation and guide hemostatic therapy. POC coagulation analyzers may overcome several limitations of routine laboratory-based coagulation tests (i.e., PT/INR, PTT) and platelet count. Blood analyzed at the bedside allows for faster turnaround times. The coagulation status is assessed in whole blood (not plasma) and the plasmatic coagulation system interacts with platelets and red and white blood cells. If platelets are assessed, not only their number (quantity) but also their function (quality) will be tested. Furthermore, in certain devices, clot development can be visually displayed in real time and the coagulation analysis can be performed at the patient's temperature. POC coagulation analyzers, however, still assess blood coagulation in vitro in a cuvette: most analyzers measure coagulation under static conditions (no flow) and the cuvettes are not endothelialized. Therefore, results obtained from in vitro POC tests never reflect all aspects of hemostasis and must be carefully interpreted after considering the clinical conditions (e.g., overt microvascular bleeding in the surgical site) [5, 6].

There are several methods available to analyze blood coagulation at the bedside. According to their main objective and function, POC coagulation analyzers can be categorized into devices focusing on the analysis of:

- *Primary* (*cellular*) *hemostasis*, *mainly platelet function*. Tests analyzing primary hemostasis measure platelet count and function as well as von Willebrand factor (vWF) activity.
- *Secondary* (*plasmatic*) *hemostasis*. These bedside tests are being used to monitor

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anticoagulant therapy. Examples include the activated clotting time (ACT), whole blood PT/INR, and heparin management devices.

- *Entire hemostasis, from initial thrombin generation to maximum clot formation up to fibrinolysis*. Viscoelastic coagulation monitoring devices like TEG (Haemonetics Corp., formerly Haemoscope Corp., Braintree, MA), ROTEM (Tem International GmbH, formerly Pentapharm GmbH, Munich, Germany), and Sonoclot (Sonoclot Coagulation & Platelet Function Analyzer, Sienco Inc., Arvada, CO) assess the hemostatic system globally, analyzing primary and secondary hemostasis, clot strengths, and fibrinolysis.

POC Monitoring of Primary (Cellular) Hemostasis

Primary hemostasis plays a central role in the pathogenesis of arterial thromboembolic disease [7]. An increasing number of patients are on antiplatelet medication, such as cyclooxygenase-1 (COX-1) inhibitors, P2Y receptor (for binding adenosine diphosphate, ADP) antagonists, and glycoprotein (GP) IIb/IIIa receptor blockade (Fig. 40.1). In these patients, knowledge of residual platelet function (PF) is highly warranted in order to maintain an optimal balance between platelet function and inhibition (i.e., bleeding and thrombosis). Traditional assays, such as light transmission aggregometry (LTA; also called turbidimetric platelet aggregometry), are still considered clinical gold standards of PF testing. LTA is one of the most widely used tests to identify and diagnose specific PF defects. However, conventional LTA is labor-intensive, is costly, and requires a high degree of experience and expertise to perform and interpret. Additionally, platelets are tested under low shear conditions in platelet rich plasma, an in vitro setting that is different from in vivo primary hemostasis. Clinical medicine warrants more and more rapid, accurate, and reliable tests, simple to operate at the bedside, and availability 24/7. Over the last 20 years, several POC devices have been developed to measure PF that fulfill the above criteria

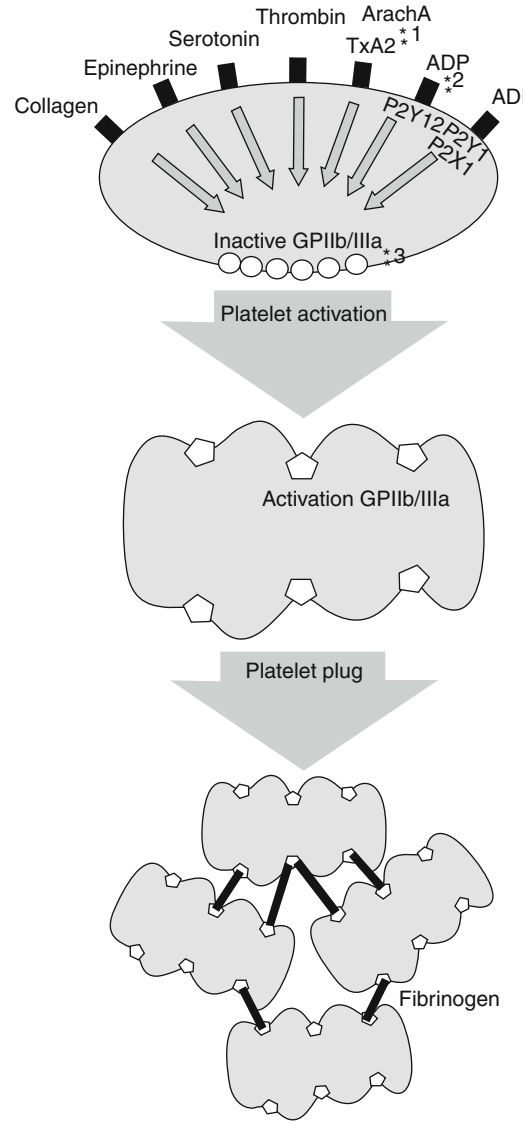

Fig. 40.1 Platelet activation and aggregation. Multiple pathways are implicated in platelet activation and aggregation. Some pathways can be therapeutically blocked in certain patients at risk for thromboembolic disease, e.g., thromboxane pathway (*1* aspirin), ADP pathway (*2* clopidogrel, prasugrel), and GPIIb/IIIa activation and interaction with fibrinogen (*3* abciximab, eptifibatide). Besides specific activating pathways (agonist-receptor binding; see Figure) and downstream signaling, platelets may become unspecifically activated by abnormal flow conditions, e.g., severe arterial stenosis (high shear stress) or artificial surfaces. Finally, as a result of initial activation, platelets change their shape and release dense and alpha granules (multiple activators, cytokines, chemokines), further activating themselves (amplification) and others

at least in part, allowing their use in routine clinical practice [6]. Limitations of all techniques have to be considered [8].

Whole Blood Impedance Platelet Aggregometry

Multiplate (Verum Diagnostica GmbH, Munich, Germany) is a widely used platelet aggregometer and represents significant progress in platelet aggregometry. The technique avoids several methodological problems of the original LTA, especially by using whole blood, disposable test cuvettes, commercially available test reagents, and an automated pipetting system. Furthermore, Multiplate assays have a high sensitivity in detecting effects of acetylsalicylic acid (aspirin), ADP antagonists, and GPIIb/IIIa inhibitors on platelets.

The working principle of Multiplate is based on two silver-coated conductive copper electrodes immersed into whole blood and the ability of activated platelets to adhere to the electrode surface. Each test cuvette consists of two pairs of electrodes allowing duplicate measurements simultaneously. The instrument continuously measures the change of electrical impedance, being proportional to the amount of platelets attached to the electrodes. The measured values are transformed to arbitrary aggregation units (AU), plotted against the time (Fig. 40.2). Three parameters are provided: aggregation units (AU), velocity (AU/min), and area under the aggregation curve (AUC), whereas AUC has the highest diagnostic power. Multiplate has five channels and parallel testing can be done at the same time. As for other techniques, different activators are commercially available: arachidonic acid (sensitive to aspirin, NSAID, GPIIb/IIIa antagonists), ADP with/without prostaglandin E1 (sensitive to P2Y and GPIIb/IIIa antagonists), TRAP-6 (thrombin receptor activating peptide, sensitive to GPIIb/IIIa antagonists), collagen (sensitive to aspirin, GPIIb/IIIa antagonists), and ristocetin (sensitive to Bernard-Soulier syndrome, severe von Willebrand's disease, aspirin) [9].

Multiplate has some limitations: test results are not independent of the actual platelet number and running the tests is time-consuming and complex and requires serial pipetting. Additionally, as with other platelet function tests, a resting time of 30 min after blood sampling is recommended before running the tests, which may impede immediate detection of platelet dysfunction in emergency cases.

VerifyNow/Ultegra

The VerifyNow Analyzer (Accumetrics, San Diego, CA) is an optical platelet aggregometer, and the technique was initially distributed as Ultegra Rapid Platelet Function Analyzer (RPFA). Activated platelets stick to fibrinogen-coated beads and aggregate with a consecutive increase in light transmission (Fig. 40.3). Variation of light absorbance over time is displayed as platelet aggregation units. Early clinical investigations yielded conflicting results and the assay has been modified to the VerifyNow assay, now detecting effects of acetylsalicylic acid and ADP and GPIIb/IIIa antagonists. This assay has been used to determine clopidogrel response in clinical trials and its results correlated well with those of platelet aggregometry [10].

VerifyNow tests are easy to perform, use small sample volumes, and do not require pipetting. The absence of flow conditions and the scarce consistency over time in the identification of aspirin-resistant individuals are limitations of this assay.

Platelet Function Analyzer

The INNOVANCE PFA-200 System, formerly PFA-100 (Siemens, Marburg, Germany), has been clinically introduced in 1985 by Katzer and Born as a screening test for inherent and acquired platelet disorders as well as von Willebrand's disease. Citrated whole blood is aspirated at high shear rates through a capillary with a membrane-coated microaperture: collagen and either epinephrine (COL-EPI) or ADP (COL-ADP). Recently, another test cartridge has been introduced, the PFA-P2Y (ADP and

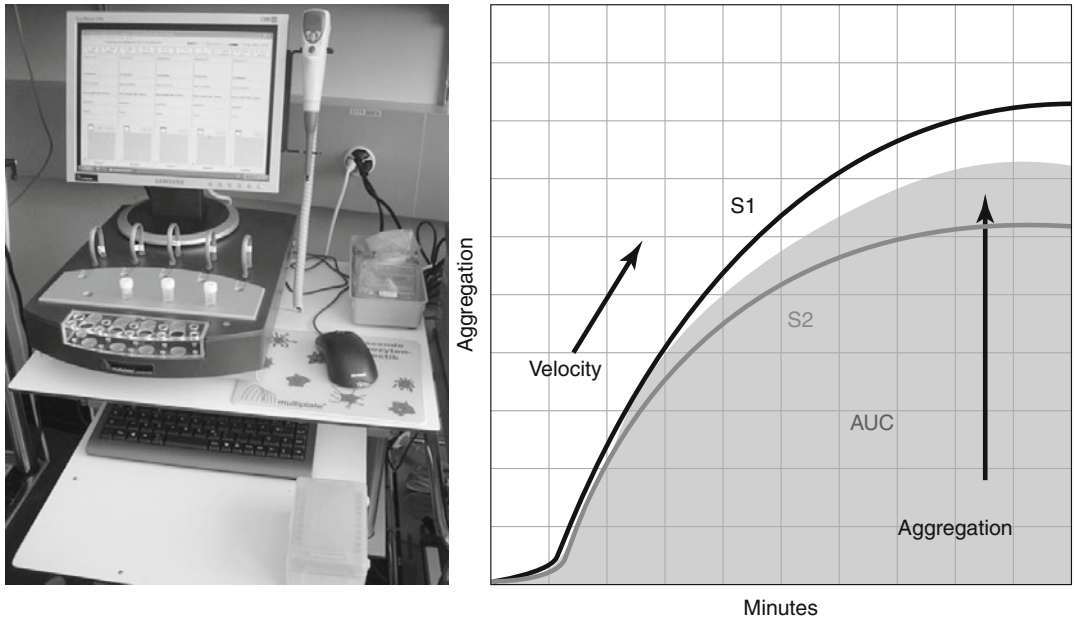

Fig. 40.2 Whole blood impedance platelet aggregometry (Multiplate). Impedance values are transformed to arbitrary aggregation units (AU), plotted against the time. In one cartridge, measurements are done in duplicates (*S1*, *S2*). The following parameters representing platelet function are provided (after averaging the duplicate results): maximum aggregation (AU), velocity of aggregation (AU/min), and area under the aggregation curve (*AUC*)

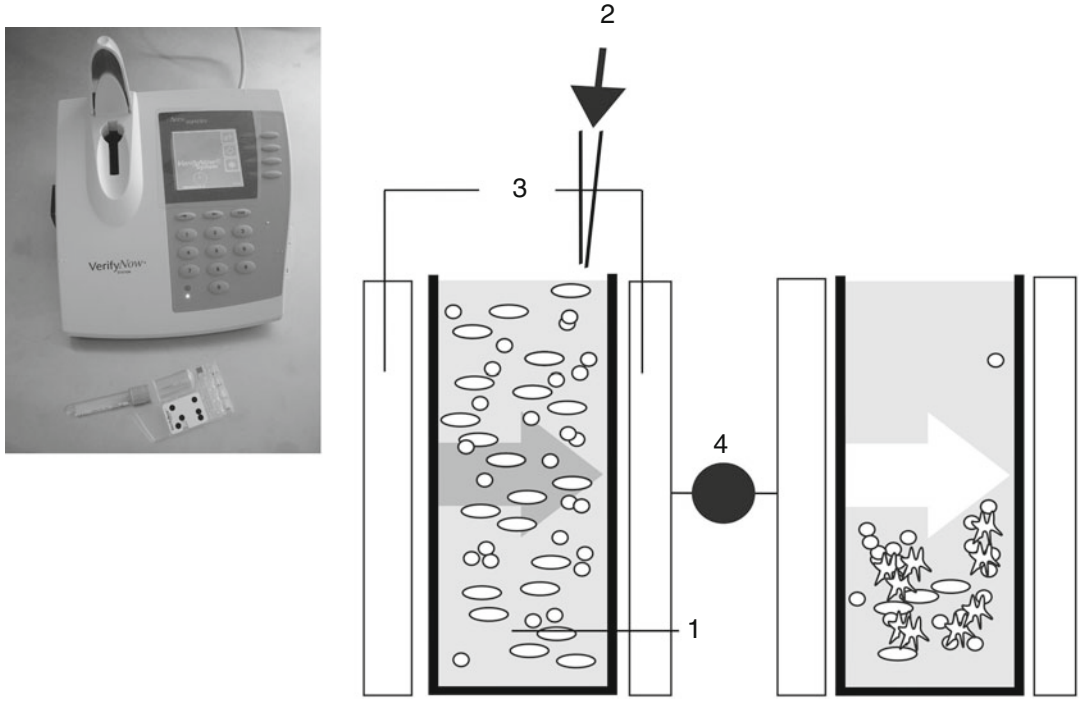

Fig. 40.3 Optical platelet aggregometry (VerifyNow). Platelets are activated and start to aggregate with fibrinogen-coated beads. Thereby, light transmission increases, which will be measured by the light detector. Activated platelets attach to fibrinogen-coated beads (*1*), platelet agonist (*2*), light source and detector measuring light transmission (*3*), and operating unit, transforming optical to electrical signal (*4*)

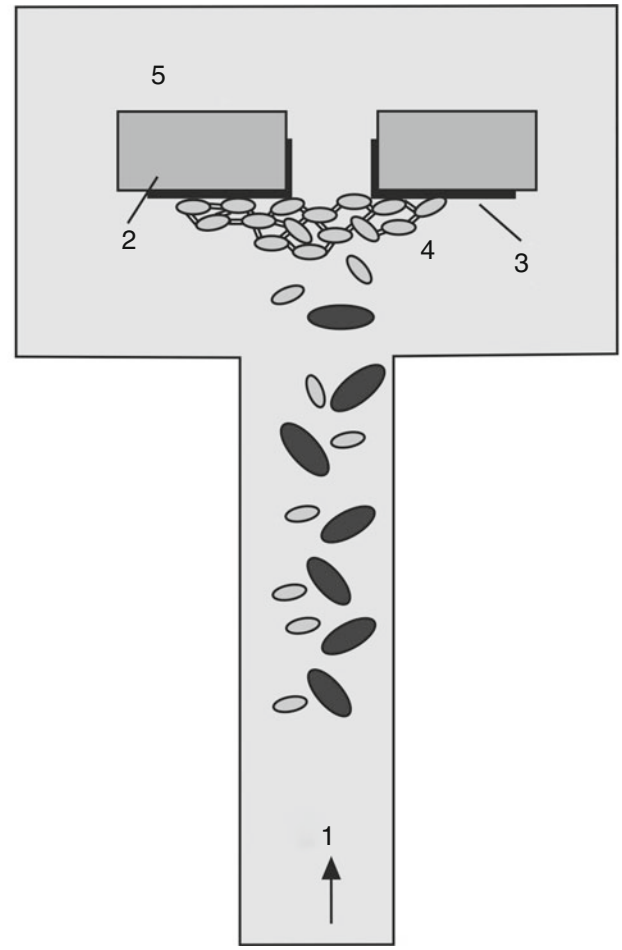

Fig. 40.4 Platelet function analyzer (PFA-100, PFA-200). Citrated whole blood is aspirated at high shear rates through a capillary (*1*) with a membrane-coated microaperture (*2*). The membrane may be coated with collagen and epinephrine (COL-EPI) or adenosine diphosphate (COL-ADP, PFA-P2Y) to activate platelets (*3*). The closure time is the time taken for activated platelets to occlude the membrane (*4*) in the cartridge (*5*)

prostaglandin E1), to assess the clinical effectiveness of ADP antagonists. Both shear stress and platelet agonists lead to attachment, activation, and aggregation of platelets forming a plug occluding this microaperture (Fig. 40.4). The time taken to occlude the aperture is known as closure time (CT) and is a function of platelet number and reactivity, von Willebrand factor activity, and hematocrit (inverse correlation of CT with Hct). The main advantages of this assay are that it does not require fibrin formation, provides rapid results, and is particularly useful in the diagnosis of von Willebrand's disease and overall platelet dysfunction. However, to get valid results, a hematocrit ≥30 % and platelet count ≥100,000/μL are required. Additionally, citrate concentration, blood type, and leukocyte count may interfere with its accuracy. Whereas early reports suggested a high sensitivity for detection of acetylsalicylic acid by prolonged PFA-100 COL-EPI closure time in association with normal values for COL-ADP, more recent investigations could not consistently confirm these results [11]. Taken together, PFA-100/200 has a high negative predictive value, i.e., primary hemostasis is functioning normally (with some exceptions: primary secretion defects, storage pool disease, mild von Willebrand's disease) if

CT is in normal range. However, formal and more specific platelet aggregation testing is required to establish the underlying cause if CT is abnormal.

Modified Thrombelastography: Platelet Mapping

Since conventional TEG/ROTEM are not sensitive to targeted pharmacological platelet inhibition, a more sophisticated test has been recently developed for TEG to specifically determine platelet function in presence of antiplatelet therapy (modified TEG, platelet mapping). Briefly, the maximal hemostatic activity of the blood specimen is first measured by a kaolin-activated whole blood sample. Then, further measurements are performed in the presence of heparin to eliminate thrombin activity: reptilase and factor XIII (activator F) generate a cross-linked fibrin clot to isolate the fibrin contribution to the clot strength. The contribution of the ADP or TxA2 receptors to the clot formation is provided by the addition of the appropriate agonists, ADP, or arachidonic acid. The results of these different tests are then compared to each other and the platelet function calculated.

Platelet mapping seems to be a suitable procedure for the assessment of all three classes of antiplatelet agents, but at present, the sensitivity and specificity compared to laboratory platelet aggregometry have not been determined in detail. Additionally, the reagents are expensive, multiple channels are required to run the tests, and well-trained personnel are required for optimal performance, limiting its use as POC procedure [12].

Platelet-Activated Clotting Time

Platelet-activated clotting time (PACT; HemoSTATUS, Medtronic HemoTec, Inc., Parker, CA) is a modified whole blood-activated clotting time test (ACT) adjoining platelet activation factor (PAF) to the reagent mixture for detection of platelet responsiveness by shortening of the kaolin-activated clotting time in whole blood samples. Until now, few studies investigating the correlation to clinical bleeding in patients undergoing cardiac surgery have been performed and their results were controversial.

ICHOR/Plateletworks System

This platelet count ratio assay from Helena Laboratories (Beaumont, TX) simply compares whole blood platelet count in a control EDTA blood sample with the platelet count in a similar sample that has been exposed to a platelet activator. In patients without platelet dysfunction or antiplatelet drug treatment, the presence of the agonist reduces platelet counts close to zero, due to aggregation of most of the platelets. The findings of recent studies indicate that adding the agonist ADP to the test sample appears useful for the assessment of both P2Y(12) inhibitors (clopidogrel, prasugrel) and GPIIb/IIIa antagonists. Minimal sample preparation and whole blood processing are advantages of this assay. The main disadvantage, however, is the lack of sufficient investigations.

Impact Cone and Plate(Let) Analyzer

The Impact Cone and Plate(let) Analyzer (CPA, DiaMed, Israel) tests whole blood platelet adhesion and aggregation under artificial flow conditions. A small amount of whole blood is exposed to a uniform shear in a spinning cone and platelet adhesion to the polystyrene wells is automatically analyzed by an inbuilt microscope. The quantity of moistening of the surface of the plates (surface covering) depends on platelet function, fibrinogen, von Willebrand factor levels, and the bioavailability of GPIb and GPIIb/IIIa receptors. The test duration is less than 6 min. The addition of arachidonic acid and ADP to the test specimens may assess the effect of acetylsalicylic acid and ADP antagonists on platelets. The Impact Analyzer is a simple and rapid whole blood platelet analyzer requiring small sample volumes. However, test results are dependent on platelet count and hematocrit and only limited published data are available on its clinical performance [6].

POC Monitoring of Secondary (Plasmatic) Hemostasis

Activated Clotting Time

Originally described by Hattersley in 1966, ACT reflects the amount of time to form a clot after contact activation of coagulation. The ACT is a functional coagulation test of the intrinsic clotting pathway and has been developed for guiding unfractioned heparin-induced anticoagulation at the bedside, particularly during cardiac surgery, extracorporeal membrane oxygenation (ECMO), and coronary interventions [13].

Several ACT instruments are commercially available and ACT measurements can be performed using different coagulation activators, each with unique characteristics and various interactions. Results from different ACT tests cannot be used interchangeably. This variability highlights the importance of establishing appropriate instrument-specific and locally adjusted reference values for monitoring anticoagulation [14].

ACT monitoring of heparinization is not without limitations, and its use has been criticized because of significant variability and the poor correlation with plasma heparin concentrations during cardiopulmonary bypass (CPB) [15]. It has been suggested that many factors—patient, operator, and equipment—can alter ACT. Therefore, ACT prolongation during CPB is not necessarily caused by heparin administration alone and may be associated with patient hypothermia, inadequacy of specimen warming, hemodilution, quantitative and qualitative platelet abnormalities, or administration of antifibrinolytic therapy. Furthermore, low factor XII levels, which are found in patients with sepsis and patients undergoing renal replacement therapy, may lead to "falsely" high ACT values without clinical relevance [13].

Heparin Concentration Measurement

Because of the limitations of ACT estimating plasma levels of heparin, POC devices have been developed to more accurately measure heparin concentration. The most studied device is the Hepcon HMS Plus Hemostasis Management System (Medtronic, Minneapolis, MN). It calculates heparin doses before initiation of CPB by performing a heparin dose response, measuring heparin concentrations, and calculating protamine doses based on residual heparin levels. A number of clinical studies report that Hepcon-guided anticoagulation results in higher total heparin but lower protamine doses than conventional management and may thereby decrease the activation of the coagulation and inflammatory cascade. Results are provided readily; however, higher costs, more complex handling, greater dimensions, and lack of large studies showing benefit on patients' outcome have limited its widespread use [16].

Monitoring Oral Anticoagulants

Several POC-INR coagulation devices have been developed to measure the effects of oral anticoagulants and to provide modified prothrombin time (PT)/INR values. No vein puncture is required (capillary blood samples) and test results are readily available for clinical use, particularly during phases of rapid changes in the coagulatory state. Most devices use electrochemical or optical clot detection [17].

POC Monitoring of the Entire Coagulation Process

TEG, ROTEM, and Sonoclot measure the clot's physical property under low shear conditions and graphically display the changes in viscoelasticity of the blood sample after initiating the coagulation cascade. In contrast to routine laboratory coagulation analyses, all phases of the developing and resolving a clot are displayed, including lysis, hyperfibrinolysis, and hypercoagulability.

Thrombelastography and Rotational Thrombelastometry

Thrombelastography is a method to study the entire coagulation potential of a single whole blood specimen and was first described by

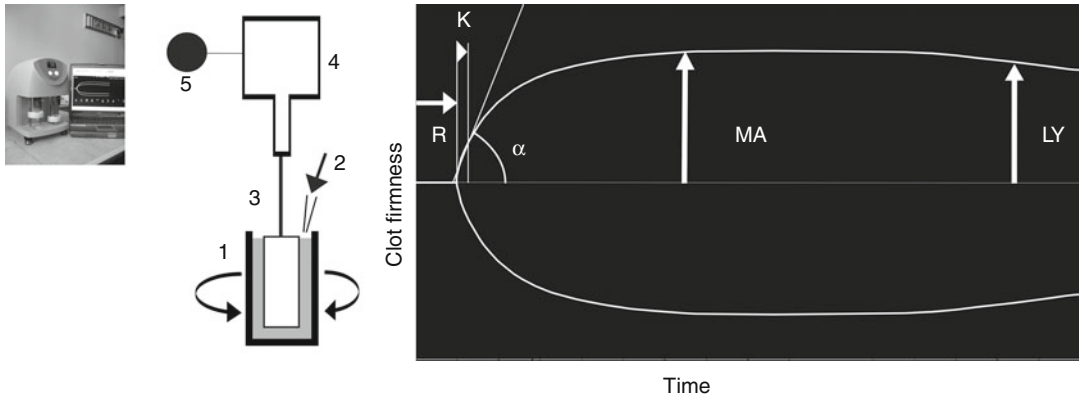

Fig. 40.5 Thrombelastography (TEG). Working principle: Rotating cup with blood sample (*1*), coagulation activator (*2*), pin and torsion wire (*3*), electromechanical transducer (*4*), and data processing unit (*5*). TEG tracing: *R* reaction time, *K* kinetics, *α* slope between r and k, *MA* maximum amplitude, *LY* lysis

Hartert in 1948 [18]. Because thrombelastography assesses the viscoelastic properties of blood, it is sensitive to all interacting cellular and plasmatic components. After starting the analysis, the thrombelastograph measures and graphically displays all stages of the coagulation process: the time until initial fibrin formation, the kinetics of fibrin formation and clot development, the ultimate strength and stability of the clot, as well as the clot lysis. In the earlier literature, the terms thrombelastography, thrombelastograph, and TEG have been used generically. However, in 1996, these terms became a registered trademark of Haemonetics Corp. (formerly Haemoscope Corp.), and from that time on, TEG has been employed to describe the proprietary 2-channel coagulation analyzer by Haemonetics Corp. only. Alternatively, Tem International GmbH (formerly Pentapharm GmbH) introduced a modified 4-channel coagulation analyzer in the year 2000 using the terminology rotational thrombelastometry, ROTEM.

In TEG, whole blood is added to a heated cuvette at a set temperature, typically 37 °C. A disposable pin connected to a torsion wire is suspended in the blood sample and the cup is oscillated through an angle of 4°45′ (rotation cycle 10 s; Fig. 40.5). As the blood sample starts to clot, fibrin strands connect and couple the cup with the pin and the rotation of the cup is getting transmitted to the pin. The rotation movement of the pin is converted by a mechanical–electrical transducer to an electrical signal, finally being displayed as the typical TEG tracing (see Fig. 40.5).

ROTEM technology avoids some limitations of traditional TEG and offers some advantages: measurements are less susceptible to mechanical shocks, four samples (TEG only two) can be run at the same time, and pipetting is made easier by providing an electronic pipette. In ROTEM, the disposable pin (not the cup) rotates back and forth 4°75′ (Fig. 40.6). The rotating pin is stabilized by a high precision ball bearing system. Signal transmission is carried out via an optical detector system (not the torsion wire). The exact position of the pin is detected by reflection of light on a small, embedded mirror on the shaft of the pin. Data obtained from the reflected light is then being processed and graphically displayed (see Fig. 40.6).

Although TEG and ROTEM tracings look similar, the nomenclature and reference ranges are not comparable (Table 40.1). Both systems use different materials (ROTEM cups and pins are composed of a plastic with greater surface charge resulting in greater contact activation compared to cups and pins used in TEG) and different proprietary formulas of coagulation activators (composition, concentration). For example, if the same blood specimen is analyzed by TEG and ROTEM with their proprietary intrinsic

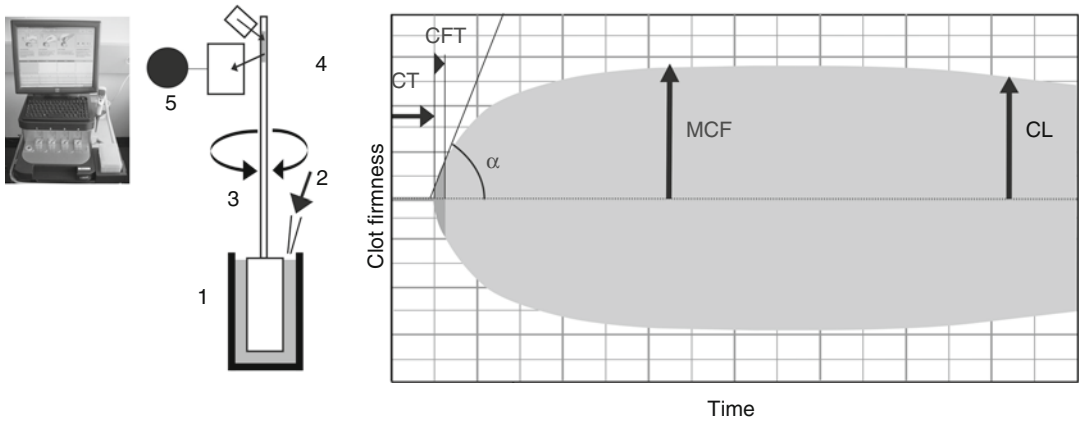

Fig. 40.6 Rotational thrombelastometry (ROTEM). Working principle: Stationary cuvette with blood (*1*), coagulation activator added by automated pipette (*2*), rotating pin stabilized by a high precision ball bearing system (*3*), electromechanical signal detection via light source and mirror mounted on the shaft of the pin (*4*), and data processing unit (*5*). *ROTEM tracing*: *CT* clotting time, *CFT* clot formation time, *α* slope of tangent at 2 mm amplitude, *MCF* maximal clot firmness, *CL* clot lysis

Table 40.1 Measured parameters and reference values for thrombelastography (TEG) and rotational thrombelastometry (ROTEM)

Parameter	TEG	ROTEM
Clotting time (period to 2 mm amplitude)	*R* (reaction time)	CT (clotting time)
	N (nWB, kaolin) 4–8 min	N (cWB, inTEM) 137–246 s
	N (cWB, kaolin) 3–8 min	N (cWB, exTEM) 42–74 s
Clot kinetics (period from 2 to 20 mm amplitude)	*K* (kinetics)	CFT (clot formation time)
	N (nWB, kaolin) 1–4 min	N (cWB, inTEM) 40–100 s
	N (cWB, kaolin) 1–3 min	N (cWB, exTEM) 46–148 s
Clot strengthening (alpha angle)	*α* (slope between *R* and *K*)	*α* (slope of tangent at 2 mm amplitude)
	N (nWB, kaolin) 47–74°	N (cWB, inTEM) 71–82°
	N (cWB, kaolin) 55–78°	N (cWB, exTEM) 63–81°
Clot strength at set time (amplitude)	A30, A60	A5, A10, A20
Maximum clot strength	MA (maximum amplitude)	MCF (maximum clot firmness)
	N (nWB, kaolin) 55–73 mm	N (cWB, inTEM) 52–72 mm
	N (cWB, kaolin) 51–69 mm	N (cWB, exTEM) 49–71 mm
		N (cWB, fibTEM) 9–25 mm
Clot elasticity	G	MCE (maximum clot elasticity)
Clot lysis at set time	LY30, LY60	CL30, CL60

Coagulation tests: intrinsic contact activation (kaolin; inTEM = partial thromboplastin phospholipids), extrinsic activation (exTEM = recombinant tissue factor), functional fibrinogen (fibTEM = tissue factor plus platelet inhibitor cytochalasin D). Reference values depend on coagulation activator, blood sampling technique, other pre-analytical factors, and studied population (see text) [5]

Abbreviations: *N* normal values, *nWB* native whole blood, *cWB* citrated and recalcified whole blood samples

coagulation activator, i.e., kaolin or inTEM reagent (partial thromboplastin phospholipids), respectively, the results obtained with both systems are significantly different [19]. TEG and ROTEM cannot be used interchangeably, and treatment algorithms have to be specifically adapted for each device [20].

In the perioperative setting, most coagulation analyses are done in citrated whole blood that is recalcified and specifically activated to reduce

variability and running time. Several commercial reagents are available and contain different coagulation activators, heparin neutralizers, platelet blockers, or antifibrinolytics to answer specific questions on the current coagulation status [5]. Thereby, blood samples can be extrinsically (tissue factor; e.g., exTEM reagent) and intrinsically (contact activator; e.g., inTEM reagent) activated. To determine functionality and levels of fibrinogen, reagents incorporate platelet inhibitors (e.g., cytochalasin D in fibTEM reagent). This concept has been proven to work and a good correlation of this modified MA/MCF with levels of fibrinogen measured in the laboratory has been shown, even in children [21, 22]. Finally, by adding an antifibrinolytic drug to the activating reagent (e.g., aprotinin in apTEM), the test provides information on the current fibrinolytic state (especially when compared to a test run without antifibrinolytics) and may help guide antifibrinolytic therapy [23].

The repeatability of measurements by both devices has shown to be acceptable, provided they are performed exactly as outlined in the user's manuals [5].

Sonoclot Coagulation & Platelet Function Analyzer

The Sonoclot Analyzer was introduced in 1975 by von Kaulla et al. and measures viscoelastic properties of a blood sample [24]. A hollow, oscillating probe is immersed into the blood and change in impedance to movement imposed by the developing clot is measured (Fig. 40.7). Different cuvettes with different coagulation activators and inhibitors are commercially available. Normal values for tests run by the Sonoclot Analyzer depend largely on the type of sample (whole blood vs. plasma; native vs. citrated sample), cuvette, and activator used [5].

The Sonoclot Analyzer provides information on the entire hemostasis process both in a qualitative graph, known as the Sonoclot Signature (see Fig. 40.7), and as quantitative results: the activated clotting time (ACT), the clot rate (CR), and the platelet function (PF). The ACT is the time in seconds from activation of the sample until fibrin formation. This onset of clot formation is defined as a certain upward deflection of the Sonoclot Signature and is detected automatically by the machine. Sonoclot's ACT corresponds to conventional ACT, provided that cuvettes containing a high concentration of typical activators (celite, kaolin) are used. The CR, expressed in units/min, is the maximum slope of the Sonoclot Signature during initial fibrin polymerization and clot development. PF is reflected by the timing and quality of the clot retraction. PF is a calculated value, derived by an automated numeric integration of changes in the Sonoclot Signature after fibrin formation has completed. To obtain reliable results for PF, cuvettes containing glass beads for specific platelet activation (gbACT+) should be used. The nominal range of values for the PF goes from 0, representing no PF (no clot retraction and flat Sonoclot Signature after fibrin formation), to approximately 5, representing strong PF (clot retraction occurs sooner and is very strong, with clearly defined, sharp peaks in the Sonoclot Signature after fibrin formation) [25].

Indications of POC Coagulation Monitoring

Patients with significant blood loss and those at risk for major hemorrhage or thrombosis require real-time POC coagulation monitoring to adequately assess hemostasis and individually guide targeted therapy. The modern practice of coagulation management is based on the concept of goal-directed and goal-specific therapy. Maintaining an adequate coagulation status is essential besides preserving sufficient blood volume and oxygen-carrying capacity [3, 4].

Guiding Procoagulants and Antifibrinolytics

Patients with massive hemorrhage develop an acquired coagulopathy due to intravascular volume resuscitation combined with absolute and

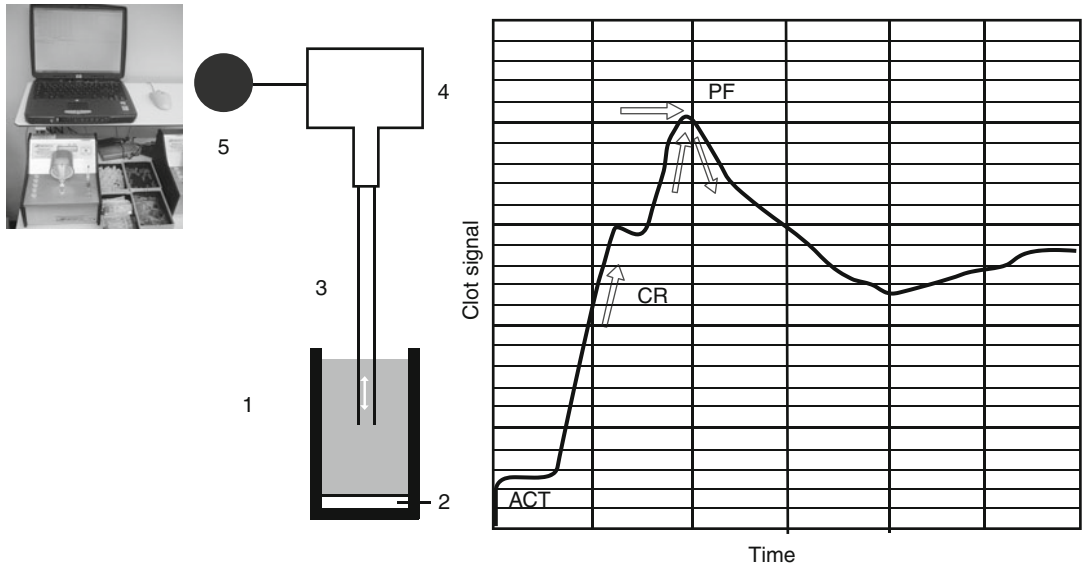

Fig. 40.7 Sonoclot Coagulation and Platelet Function Analyzer. Working principle: Blood sample in cuvette (*1*) containing specific coagulation activator (*2*), disposable plastic probe (*3*) oscillating in blood sample mounted on electromechanical transducer head (*4*), and data processing unit (*5*). Sonoclot Signature: *ACT* activated clotting time, *CR* clot rate, *PF* platelet function

functional loss of their coagulation potential. Fibrinogen is the first coagulation factor to decrease to critically low levels in acquired bleeding. It is the substrate to form a clot and required for platelet aggregation and establishment of a fibrin network [26]. If depleted, specific supplementation of fibrinogen is mandatory for rescue and maintenance of hemostatic function [27, 28]. Several guidelines like the updated European trauma treatment guidelines recommend replacing fibrinogen early, and in the last few years, this has become standard of care in many European centers [29]. However, there is still a debate on how fibrinogen levels should be assessed and monitored, what the critical threshold for fibrinogen substitution should be, and what target levels should be achieved [28]. At the bedside, functional fibrinogen levels can be analyzed with TEG, ROTEM, and Sonoclot measuring clot strength in presence of a platelet GPIIb/IIIa inhibitor (Table 40.2) or by assessing Sonoclot's CR [21]. It is recommended to keep fibrinogen levels >1.5–2.0 g/L, which corresponds to MCF levels greater than 8–10 mm in a fibTEM test [29, 30]. Factor XIII is required for full functionality of fibrinogen because factor XIII cross-links fibrin and stabilizes the clot. Major bleeding and/or extensive surgery may lead to acquired factor XIII deficiency that has been associated with increased bleeding. Therefore, it is recommended to keep factor XIII in normal range [31]. Since viscoelastic POC coagulation monitoring devices assess the entire coagulation process, they are additionally used (in combination with bedside tests measuring primary and secondary hemostasis only) to guide therapy with other coagulation factors (e.g., prothrombin complex concentrate, fresh frozen plasma), platelets, and antifibrinolytics. Specific algorithms on how to interpret measured parameters and on when to start a specific and targeted procoagulant or antifibrinolytic therapy have been published recently [30, 32, 33]. In patients with unknown life-threatening bleeding, POC devices may further detect presence of anticoagulants like heparin (e.g., heparinase-ACT, hepTEM) or Coumadin (e.g., POC-INR). Thereby, anticoagulant therapy can be diagnosed readily at the bedside and corrected individually according to clinical needs.

Table 40.2 Commonly used commercially available tests for viscoelastic point-of-care coagulation devices

Assay	Activator *Inhibitor*	Proposed indication
Thrombelastograph hemostasis system (TEG)		
Kaolin test	Kaolin	Overall coagulation assessment and platelet function
Heparinase test	Kaolin + *Heparinase*	Specific detection of heparin (modified kaolin test adding heparinase to inactivate present heparin)
FF (functional fibrinogen) test	TF + *Abciximab*	Assessment of functional fibrinogen levels
Platelet mapping	ADP + *Arachidonic acid*	Platelet function, monitoring antiplatelet therapy (aspirin, ADP and GPIIb/IIIa inhibitors)
Native test	None	Nonactivated assay Also used to run custom hemostasis tests
Rotational thrombelastometry (ROTEM)		
exTEM	Recombinant TF + *Heparin inhibitor* (*hexadimethrine*)	Extrinsic pathway; fast assessment of clot formation and fibrinolysis
inTEM	Contact activator	Intrinsic pathway; assessment of clot formation and fibrin polymerization
fibTEM	exTEM + *Cytochalasin D*	Assessment of functional fibrinogen levels
apTEM	TF + *Aprotinin*	Fibrinolytic pathway; fast detection of fibrinolysis when used together with exTEM
hepTEM	Contact activator + *Heparinase*	Specific detection of heparin (modified inTEM test adding heparinase to inactivate present heparin)
naTEM	None	Nonactivated assay Also used to run custom hemostasis tests
Sonoclot Coagulation & Platelet Function Analyzer		
SonACT	Celite	High-dose heparin management
kACT	Kaolin	High-dose heparin management
gbACT+	Glass beads	Overall coagulation and platelet function assessment
H-gbACT+	Glass beads + *Heparinase*	Overall coagulation and platelet function assessment in presence of heparin; detection of heparin
Native	None	Nonactivated assay Also used to run custom hemostasis tests

Abbreviations: *ACT* activated clotting time, *TF* tissue factor, *ADP* adenosine diphosphate, *GPIIb/IIIa* glycoprotein IIb/IIIa receptor

Guiding Anticoagulants

The complex process of full anticoagulation with heparin, e.g., for cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO), reversal with protamine, and post-interventional hemostasis therapy, requires careful and accurate bedside coagulation monitoring. Besides guiding heparin anticoagulation with ACT measurements, it has been shown that advanced POC coagulation monitoring may reduce allogeneic blood transfusion, save costs, and improve outcome [33–35].

Recognized risk factors for thrombosis are generally related to one or more elements of Virchow's triad (stasis, vessel injury, and hypercoagulability). Major surgery has been shown to induce a postoperative hypercoagulable state and this hypercoagulability has been implicated in the pathogenesis of postoperative thrombotic complications, including deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, and vascular graft thrombosis. Identifying hypercoagulability with conventional non-viscoelastic laboratory

tests is difficult unless fibrinogen concentration or platelet count is markedly increased. However, hypercoagulability is easily being diagnosed by viscoelastic POC coagulation analyzers (short R/CT time and the increased MA/MCF exceeding 65–70 mm) and specific anticoagulant treatment can be initiated.

Conclusion

Hemostasis is a complicated, vital system to our body. Normal blood coagulation exists when procoagulant and anticoagulant forces are in balance. Clinically relevant phenotypes of hemostasis, bleeding and thrombosis, occur immediately if the system is no longer in equilibrium. Patients with major bleeding and those at risk for thrombosis require real-time POC coagulation monitoring in combination with clearly defined algorithms to adequately assess hemostasis and individually guide targeted therapy. Thereby, unnecessary and blind administration of anti- and procoagulant substances can be avoided, resulting in reduced allogeneic blood transfusions. Ultimately, costs are saved and overall patients' outcomes are likely to be improved [3, 4, 32, 33, 36].

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