Coagulation Monitoring

10

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Case Vignette

A 35-year-old patient with Marfan's disease presents for an aortic arch replacement which involved hypothermic circulatory arrest and a long bypass time. Prior to separation from cardiopulmonary bypass a TEG is performed as shown in Fig. 10.1. This demonstrates a long R time and low MA on the heparinase TEG (green trace) and a low MA on the fibrinogen TEG (blue trace) [note the test was done while the patient was still on CPB and anticoagulated, hence the straight line on the kaolin (red) trace]. How should this patient be treated?

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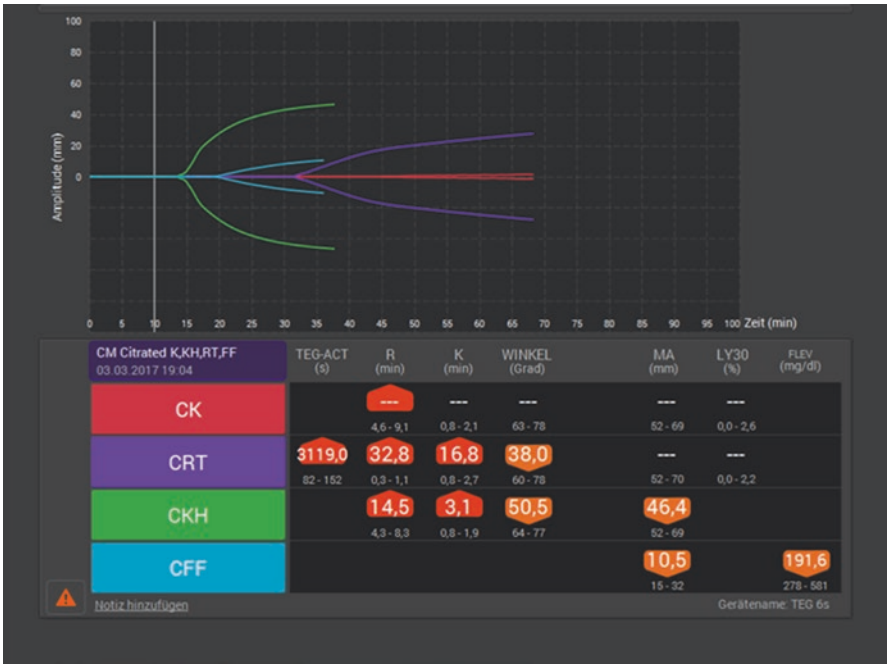

Fig. 10.1 Thromboelastography (TEG) tracing. Author's data (S. Agarwal, Manchester, United Kingdom). Red line = kaolin, purple line = kaolin + tissue factor, blue line = fibrinogen, green line = kaolin with heparinase; R time = time to clot formation, MA = clot strength

Why Is it Important?

Bleeding complications during and after cardiac surgery are common and associated with increased morbidity and mortality. The etiology of bleeding is multifactorial including surgical trauma, heparin rebound, platelet deficits in number and function, factor and fibrinogen deficiency, and fibrinolysis. Left untreated bleeding may lead to further coagulopathy as well as an unfavorable patient outcome. Transfusion of red cells and blood components is crucial; however, this same transfusion may also be associated with an increase in morbidity and mortality, particularly if used inappropriately [1]. While the safety of blood and blood products in terms of viral and pathogen transmission has improved vastly over the past decades, other risks such as transfusion associated acute lung injury (TRALI) and transfusion associated circulatory overload (TACO) remain.

It is therefore important to be able to elucidate the exact coagulation deficit from the array of possibilities and tailor therapy accordingly. Perioperative coagulation testing plays a vital role allowing the detection of any preoperative abnormalities, which may be addressed prior to surgery, intraoperative abnormalities, and can help to elucidate the cause of bleeding postoperatively. Testing may be divided into two

types depending on the location of testing: laboratory based testing and point-of-care testing (POCT). The purpose of this chapter is to give an overview of different coagulation monitoring modalities that can be used in cardiac surgery.

Laboratory Coagulation Monitoring

Principles and Use

Figure 10.2 gives an overview of the standard laboratory tests that are available for coagulation monitoring in cardiac surgery.

Laboratory coagulation tests can be used throughout the patient journey to assess for coagulation abnormalities. The prothrombin time (PT) will be long if warfarin is present, in vitamin K deficiency from malnutrition, biliary obstruction, or malabsorption syndromes, in liver disease, and due to deficiency or presence of an inhibitor to factors VII, X, II/prothrombin, V, or fibrinogen. The activated partial thromboplastin time (aPTT) will be prolonged if heparin is present as well as in the presence of the anti-phospholipid syndrome (with lupus anticoagulant), hemophilia A and B (factor VIII and IX deficiency, respectively), factor XII deficiency, and factor XI deficiency. The PT or aPTT may also be used to assess non-vitamin K oral anticoagulant (NOAC) therapy; however, they are affected to a varying degree depending on the reagents and NOAC used [2]. In general, normal PT or aPTT test results exclude excess levels of dabigatran, rivaroxaban, and edoxaban, but not apixaban. The aPTT correlates better for dabigatran, the PT may be used for factor Xa inhibitors, although one should be aware of the considerable variation in the

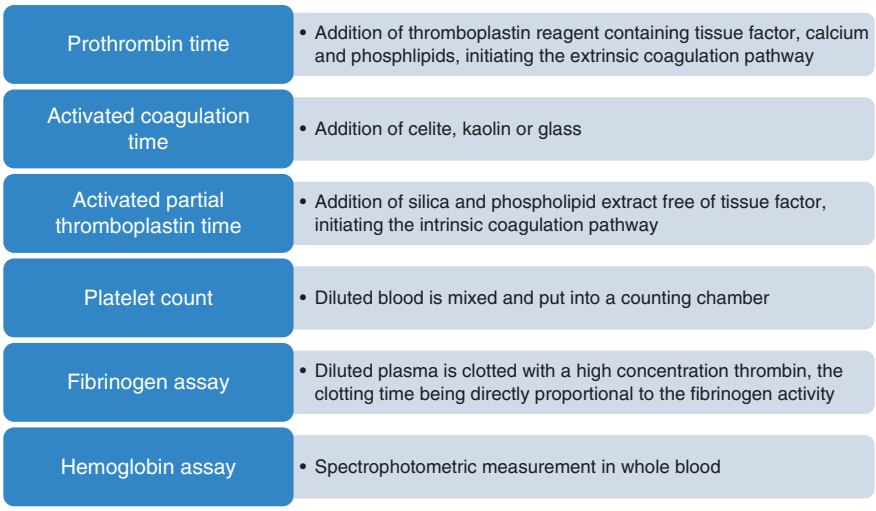

Fig. 10.2 Laboratory tests for coagulation monitoring during cardiac surgery

sensitivity of different PT reagents [3]. Sensitive PT assays, but not the aPTT, can indicate plasma levels of rivaroxaban and edoxaban, but not apixaban. However, the quantification of the concentration of these drugs is not reliable, so this parameter should be used as a screening test only, bearing in mind that low but clinically relevant plasma levels of FXa inhibitors may not be detected. For precise measurement of drug concentrations of all FXa inhibitors, chromogenic anti-FXa-tests are recommended [4]. The activated clotting time (ACT) will be discussed in the next chapter.

The platelet count will tell us the absolute platelet number; however, it will not tell us about platelet function, in particular if residual antiplatelet drug activity is present. Specialist platelet function tests (some of which can provide this information) are generally only available in hematology laboratories, and have turnaround times of hours.

Advantages and Disadvantages of Laboratory Testing

Laboratory testing has the major advantage of having rigorous quality control and is generally performed by highly skilled staff. The tests may be helpful in elucidating the cause of bleeding. However, there are numerous disadvantages. The tests measure one specific part of the coagulation system at one point in time and were not intended for the prediction of bleeding in cardiac surgery. With turnaround time in some laboratories that exceed 30 min, the results are often of little use in the dynamic situation of acute bleeding. Standard laboratory tests are regularly abnormal after cardiac surgery because of dilution and consumption associated low concentrations of procoagulant factors, without any deficit in thrombin generation and without bleeding and the critical values of these tests have not been well defined in cardiac surgery. The tests are performed mainly in plasma rather than whole blood, and at a standard temperature of 37 °C rather than the temperature of the patient. In light of these limitations, clinicians have sought to use point-of-care (POC) testing.

Point-Of-Care Coagulation Monitoring

Viscoelastic Testing

By their nature, point-of-care devices are situated close to the patient and so allow the clinician to see the results quickly, as they develop. They consistently detect changes in coagulation. In cardiac surgery, there are two main viscoelastic principles used: thromboelastography (TEG) and rotational thromboelastometry (ROTEM), while newer techniques (e.g., ultrasound based resonance sonorheometry, SEER) have come to the market recently (see below). Both techniques offer a global view of hemostasis with a visual representation of clot development as shown below. They are performed on citrated whole blood (TEG, ROTEM, and SEER), and the TEG may also be performed on fresh whole blood.

Principles and Use

The mentioned point-of-care devices work in a similar fashion to assess the viscoelastic properties of blood under low shear conditions. The thromboelastography principle is based on a cylindrical cup holding the blood which oscillates for 10 s at a time. A pin is suspended in the blood sample via a torsion wire and is monitored for motion. After fibrin–platelet bonding has occurred, linking the pin and the cup together, the torque of the rotation is transmitted to the pin which is then converted by an electromagnetic signal into an electrical signal, the so-called thromboelastography trace [5]. The strength of the bonds affects the magnitude of the pin motion, so output is directly related to the strength of the formed clot. With clot retraction and lysis, the fibrin–platelet bonds are broken. The same principles apply in rotational thromboelastometry, with the main technical difference being that it is the pin which rotates while the cup remains stationary. The rotational thromboelastometry system also uses a different activator—ellagic acid rather than kaolin, which may make it less sensitive to residual heparin. Both devices suffer from a lack of robust quality control and are operator dependent [6]. The results of two systems are closely related, but they are not completely interchangeable [7].

The SEER method uses ultrasound pulses to measure the stiffness of the clot during the coagulation process that is started by certain activators. Clotting times, clot stiffness, and break down of the clot are measured over time [8].

All POC devices are now available as new generation system to make them easier to use with automated measurement. All have introduced a cartridge-based device with more robust quality control and offer the advantages of a reduction in operator dependent error and technical faults. For thromboelastography, whole blood is inserted into the cartridge and delivered to a microcell that is excited with a multifrequency signal from a piezoelectric actuator. The resulting harmonic motion of the sample is measured optically; as the sample clots and moves from liquid to gel and solid phase the harmonic motion changes, this is represented as the familiar thromboelastography trace. It does not measure the viscoelasticity of the clot directly [9]. The mentioned POC devices are capable of performing four tests simultaneously from one citrated blood sample. Using these devices gives the user the opportunity to perform specific coagulation tests (Table 10.1). The addition of

Table 10.1 Different tests for thromboelastometry (TEG) or rotational thromboelastometry (ROTEM)

TEG™ test	ROTEM™ test	Function
Kaolin	INTEM	Activated test of global hemostasis via the intrinsic pathway—usually performed as a baseline
Functional fibrinogen	FIBTEM	Assessment of fibrinogen
RapidTEG®	EXTEM	Tissue factor activated test of the extrinsic pathway—assessment of clot strength quickly
Heparinase	HEPTEM	Test of global hemostasis via the intrinsic pathway with the effect of heparin removed

Table 10.2 Available point-of-care monitoring devices in 2019

Commercial name	Method
TEG-6S™	Indirect viscoelastometry through an optical method
ROTEM SIGMA™	Viscoelastometry
SonoClot™	Viscoelastometry
Quantra™	Ultrasound detection of resonance
ClotPro™	Viscoelastometry

Table 10.3 The commonly measured variables during thromboelastometry and rotational thromboelastometry

TEG	ROTEM	What does it measure?	Abnormality
R time	CT	Time to first significant clot formation—clot initiation	Increased in factor deficiency or excess heparin
MA	MCF	Maximum strength of clot	Decreased in fibrinogen or platelet deficiency (not in platelet inhibition)
LY30	CL 30	Percent lysis 30 min after maximal clot strength	Increased in fibrinolysis

CT clotting time, *MA* maximal amplitude, *MCF* maximal clot firmness, *LY* lysis, *CL* clot lysis

heparinase to the test reveals the underlying coagulation status when heparin is present.

In addition to thromboelastography and rotational thromboelastometry, a number of other systems exist or are in development. These systems are usually based on indirect or direct measurements of the viscoelastometric properties of the clot, for instance, with ultrasound detection of resonance. Another system uses viscoelastic methods to assess clot kinetics and stability, its novelty lies in the fact that all the reagents will be contained in the pipette tip. However, the newly developed devices do not have a wealth of clinical experience to back up its use nor data from controlled trials or algorithms for its use in clinical practice. Table 10.2 gives an overview of the available commercial devices in 2019 for thromboelastographic or thromboelastometric testing.

The commonly measured variables during thromboelastometry and rotational thromboelastometry are shown in Table 10.3 and Fig. 10.3.

Advantages and Disadvantages of Point-of-Care Testing

Point-of-care coagulation testing enables the assessment of patient hemostasis throughout the surgical procedure. The test results are available in minutes. The tests have limitations and this must be borne in mind. The tests are run at 37° centigrade so cannot reflect the effects of hypothermia. They are not sensitive to the effects of platelet adhesion so cannot detect von Willebrand factor deficiency. Hemodilution and low platelet count as well as the usage of hydroxyethyl starch solutions influence the results of most point-of-care devices. They are dependent on quality control and regular calibration to generate valid results, and the older devices give user-dependent test results.

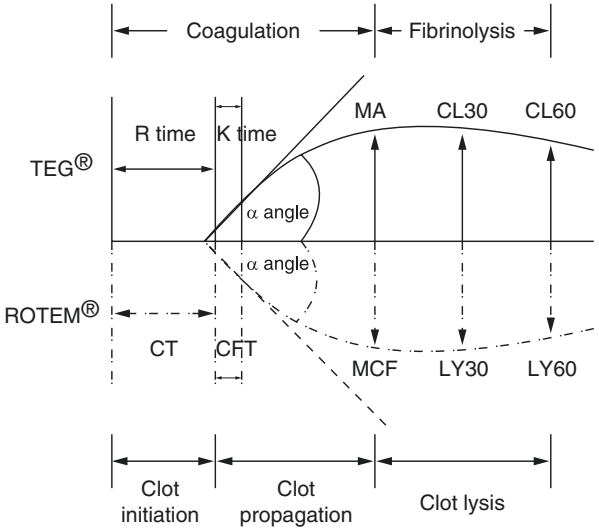

Fig. 10.3 The commonly measured variables obtained with TEG or ROTEM devices. R time/CT time: time from initiation of the test and the point where clotting provides enough resistance to produce a 2 mm amplitude reading on the tracing; K time/CFT (clot formation time): time from 2 min to 20 mm amplitude; alpha angle: slope between R and K for TEG, angle of tangent at 2-mm amplitude for ROTEM; MA: maximal amplitude; MCF: maximal clot firmness; CL and LY, clot lysis: percentage reduction in amplitude 30 min after reaching MA/MCF

Clinical Use of Point-of-Care Coagulation Monitoring

The exact timing of point-of-care testing remains open to debate as the evidence is not clear, with some recommending baseline testing while others prefer to test if a problem is apparent. It is worth noting that there is a poor correlation between baseline tests results and the prediction of subsequent bleeding.

Towards the end of cardiopulmonary bypass, tests may be performed to assess the extent of coagulopathy present. A test for the intrinsic coagulation pathway is usually performed together with an assessment of fibrinogen, both with the addition of heparinase to negate the effect of the systemic heparinization of the patient. These then allow blood products to be requested.

On separation from cardiopulmonary bypass, protamine is administered to reverse residual heparinization and any pre-ordered blood products may be administered specifically aiming at the detected coagulation defects. Further transfusions are then guided by further use of the point-of-care devices. At this point, the four common tests may be performed to assess whether there is any residual heparin, assess fibrinogen levels, obtain a quick assessment of clot strength, and assess whether factor levels are sufficient (Fig. 10.2).

All POC measurements are exquisitely sensitive to heparin. A comparison of a trace with and without heparinase (which neutralises heparin) may show differences. Heparin effect is evident with a prolonged time to clot formation and / or a reduced clot firmness in the trace without heparinase which corrects on the trace with

heparinase. Unfortunately, both thromboelastography and thromboelastometry tests are also sensitive to protamine, i.e., a protamine prolongs the CT of the heparinase assay. So far, it is unclear, whether this occurs with the SEER method as well.

Several algorithms have been published over the past 30 years, starting with relatively simple ones using kaolin and heparinase thromboelastography, to ones incorporating the newer tests such as point-of-care fibrinogen measurements. The use of these algorithms has been shown to reduce transfusion and resternotomy, and a few studies suggest that there is an association with reduced morbidity and mortality [10]. In one of the most recent studies, Karkouti and colleagues again demonstrated a reduction in transfusion and bleeding after cardiac surgery using a point-of-care based algorithm based on ROTEM™ and PlateletWorks™ [11].

In contrast, four recently published systematic reviews looked at the value of viscoelastic testing in cardiac surgery (namely, thromboelastography and thromboelastometry) with respect to treatment and prediction of bleeding, and their conclusions were more ambivalent [12–15]. They concluded that the implementation of thromboelastography or rotational thromboelastometry in a patient blood management program may reduce the need for blood products in patients with bleeding, but the results are mainly based on trials of elective cardiac surgery involving cardiopulmonary bypass, with low-quality evidence [12, 13]. Moreover, thromboelastometry does not predict which patients are at risk for major postoperative bleeding [14]. Finally, the third systematic review could not show an association between viscoelastic testing and a reduction in the proportion of patients receiving any blood product or all-cause mortality. They also concluded that these results are in part caused by the lack of robust randomized controlled trials [15].

All algorithms indicate that POC tests should be performed after protamine administration in the operating room, with continued testing on the intensive care unit if needed. Some also advocate a preoperative test. In a study of 52 patients, Ortmann and colleagues compared thromboelastography and rotational thromboelastometry heparinized tests performed towards the end of bypass to those performed after the administration of protamine, and found that the results were similar, particularly the amplitude of clot strength, confirming the utility of viscoelastic testing at this intraoperative timepoint [16]. Some validated algorithms include platelet function testing. The recommendations here are generally to perform platelet function testing to assess residual antiplatelet drug effects prior to bypass as described in Chap. 9. Viscoelastic testing has been assessed by the British National Institute of Health and Care Excellence (NICE), a government body that aims to improve outcomes for patients producing evidence-based guidance. The review of POC testing concluded that viscoelastic testing (methods assessed were thromboelastography and thromboelastometry) may be effective in reducing transfusion in cardiac surgery, as well as being cost saving [17].

Point-of-care coagulation monitoring should be continued postoperatively in the intensive care unit. Common causes of bleeding at this point include surgical bleeding, postoperative anemia due to hemodilution, acid/base disturbances, hypocalcemia, temperature drop as well as post-bypass platelet dysfunction that may be exacerbated by uremia.

Implications for Daily Practice

Perioperative coagulation testing with point-of-care devices provides a valuable addition to the armamentarium of the anesthesiologist when dealing with bleeding in the perioperative period. Tests should be performed in those patients that are bleeding, followed by repeated tests each time after a clinical intervention has taken place such as administration of blood products or fibrinogen for coagulopathy. This can then guide the indications and timing for surgical re-exploration. Best practice would be to order products based on the results of point-of-care testing and to administer them after protamine has been administered to the patient. The tests should then be repeated to ensure treatment has been successful.

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