Role of Thromboelastography and Rotational Thromboelastometry in the Management of Cardiovascular Diseases

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Abstract

The monitoring of coagulation by viscoelastometric methods—thromboelastography and rotational thromboelastometry—may detect the contributions of cellular and plasma components of hemostasis. These methods might overcome some of the serious limitations of conventional laboratory tests. Viscoelastic testing can be repeatedly performed during and after surgery and thus provides a dynamic picture of the coagulation process during these periods. Several experiences with the use of these methods in cardiovascular surgery have been reported, but there is perspective for more frequent use of these assays in the assessment of platelet response to antiplatelet therapy and in the assessment of coagulation in patients on long-term dabigatran therapy. This article reviews the current role and future perspectives of thromboelastography and thromboelastometry in the management of cardiovascular diseases.

Introduction

The monitoring of coagulation by viscoelastometric methods—thromboelastography (TEG; Haemoscope; Haemonetics, Niles, Illinois) and rotational thromboelastometry (ROTEM; Instrumentation Laboratory, Bedford, Massachusetts)—has evolved as a point-of-care (POC) tool capable of detecting the contributions of cellular and plasma components of hemostasis. These methods might overcome some of the serious limitations of conventional laboratory tests, such as long turnaround time, lack of sensitivity to smaller decreases in coagulation abnormalities and limited ability to test platelet functions (PFs), the inability to diagnose complex coagulation disorders, the inability to assess coagulation under hypothermic conditions, and the low predictability of bleeding resulting from invasive procedures. Viscoelastic testing can be repeatedly performed during and after surgery and thus provides a dynamic picture of the coagulation process during these periods. This article reviews the role of TEG and ROTEM in the management of cardiovascular diseases.

Thromboelastography and ROTEM—Assay Principles, Similarities, and Differences

The term thrombelastograph was used to describe the trace produced from the measurement of the viscoelastic changes associated with fibrin polymerization. The terms thrombelastography, thrombelastograph, and TEG have been used generically in the literature since the first description of the technique,[1] while a modified TEG system was later developed in Munich, Germany. Calatzis et al reported the development of an improved method of viscoelastic testing called "rotational thromboelastography" or RoTEG.[2] This new method minimized many of the interferences that plagued classic TEG. Later referred to as "rotational thromboelastometry" or "ROTEM," the test was made simpler by the automation of the analytical processes. The sensitivity to agitation was also minimized, which allowed the device to be used in a broader range of clinical settings.[3]

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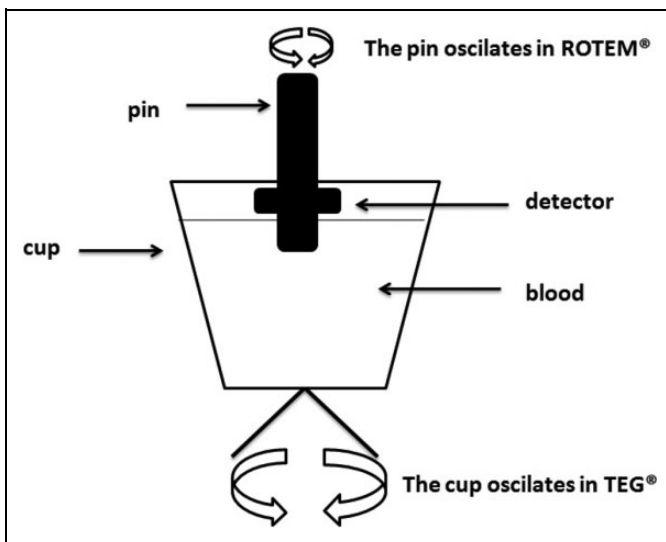Email: matej.samos@gmail.com

Figure 1. Rotational thromboelastometry (ROTEM)/thromboelastography (TEG) assay principle.

Both ROTEM and TEG are POC viscoelastic tests of hemostasis that use whole blood in real time, with slightly different operating characteristics. Rotational thromboelastometry and TEG assess clot formation/dissolution and strength by measuring and displaying the amount of a continuously applied rotational force that is transmitted to an electromechanical transduction system by the developing clot (Figure 1). In the TEG system, a rotating cylindrical cup containing a 340 μL whole blood sample oscillates through 4°45′ every 5 seconds while a pin on a torsion wire is suspended in the blood. As the viscoelastic strength of the clot increases, more rotation is transmitted to the torsion wire and is detected by an electromagnetic transducer. In the ROTEM system, a cylindrical cup containing 340 μL of whole blood (300 μL of whole blood, 20 μL of $CaCl_2$, and 20 μL of an activator) remains fixed, while a pin suspended on a ball-bearing mechanism initially oscillates through 4°75′ every 6 seconds through the application of a constant force. As the viscoelastic strength of the clot increases, the rotation of the pin is impeded and is detected optically using a charge-coupled device image sensor system.[4,5]

Assays[6] graphically record kinetic changes in citrated whole blood samples during clot formation and its lysis. The result is a compact mapping of the various phases of hemostasis in the form of thromboelastogram. As mentioned previously, the technology is based on a solid, constantly oscillating cup containing a blood sample with reagents. If there is no clot formation, rotation is not blocked. If a clot forms, there is a link between the cup wall and pin and rotation is blocked. The rotation of the measuring pin/cup is converted graphically to amplitude, where free rotation corresponds to an amplitude of 0 mm (noncoagulated blood) and no rotation corresponds to an amplitude of 100 mm (maximum possible strength of the clot). The interpreting software uses a special algorithm and filter that eliminates potential mechanical or electronic errors. The parameters are determined in real time during the test and calculated and graphically interpreted in thromboelastogram (Figure 2).

A standard ROTEM device is capable of analyzing 4 samples simultaneously, as opposed to a TEG device, which is only capable of analyzing 2 samples simultaneously. The above-mentioned operational characteristics give ROTEM more flexibility compared to TEG. Although both ROTEM and TEG provide essentially the same information on clot strength and kinetics, this information is not interchangeable. This is due to the use of different assays and coagulation activators (Tables 1 and 2), as well as the use of different nomenclature.[5]

However, ROTEM/TEG may have several limitations. In fact, hemostasis is associated with a wide range of normal values due to the extensive variability in the components of the hemostatic system, including platelet count and function, glycoprotein IIb/IIIa receptor number, and fibrinogen concentration. Ideally, therefore, each patient should have baseline ROTEM/TEG measurements before undergoing treatment or procedure to ensure that there is an internal, individualized reference for change. In addition, there are difficulties with assay validation and standardization. The standardization of assays between centers seems a distant possibility, as the technique continues to diversify in terms of equipment, activators, and modifications. Rotational thromboelastometry/TEG can be performed with a variety of activators and inhibitors that will alter the assay specificity. To some extent, these issues have been overcome by the use of computer software to analyze the ROTEM/TEG trace which allows for the standardization of results. Further standardization has been achieved by the use of disposable cups and pins, individual temperature control, and the use of activators such as kaolin to standardize the initiation of the clotting process.

Thromboelastography and ROTEM in Cardiovascular Surgery

Massive bleeding, mediastinal re-exploration, and the transfusion of allogeneic blood products have been associated with increased morbidity and mortality after cardiac surgery.[7-12] Dual-antiplatelet therapy, oral anticoagulants, hypofibrinogenemia, residual heparin, prolonged cardiopulmonary bypass, and intraoperative hypothermia were previously identified as the main causes of increased bleeding after cardiac surgery.[13,14] Bleeding is associated with an increased risk of renal failure, cerebrovascular events, prolonged mechanical ventilation, sepsis, and prolonged stays in critical care units.[15,16] Screening for coagulation abnormalities and the selected application of hemostatic interventions in the transfusion algorithms have been dependent on coagulation tests including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and the Clauss fibrinogen assay.[17] However, PT and aPTT are poor predictors of bleeding during invasive procedures[18-20] and are usually not available quickly enough to be clinically useful for a patient who has an active bleeding.
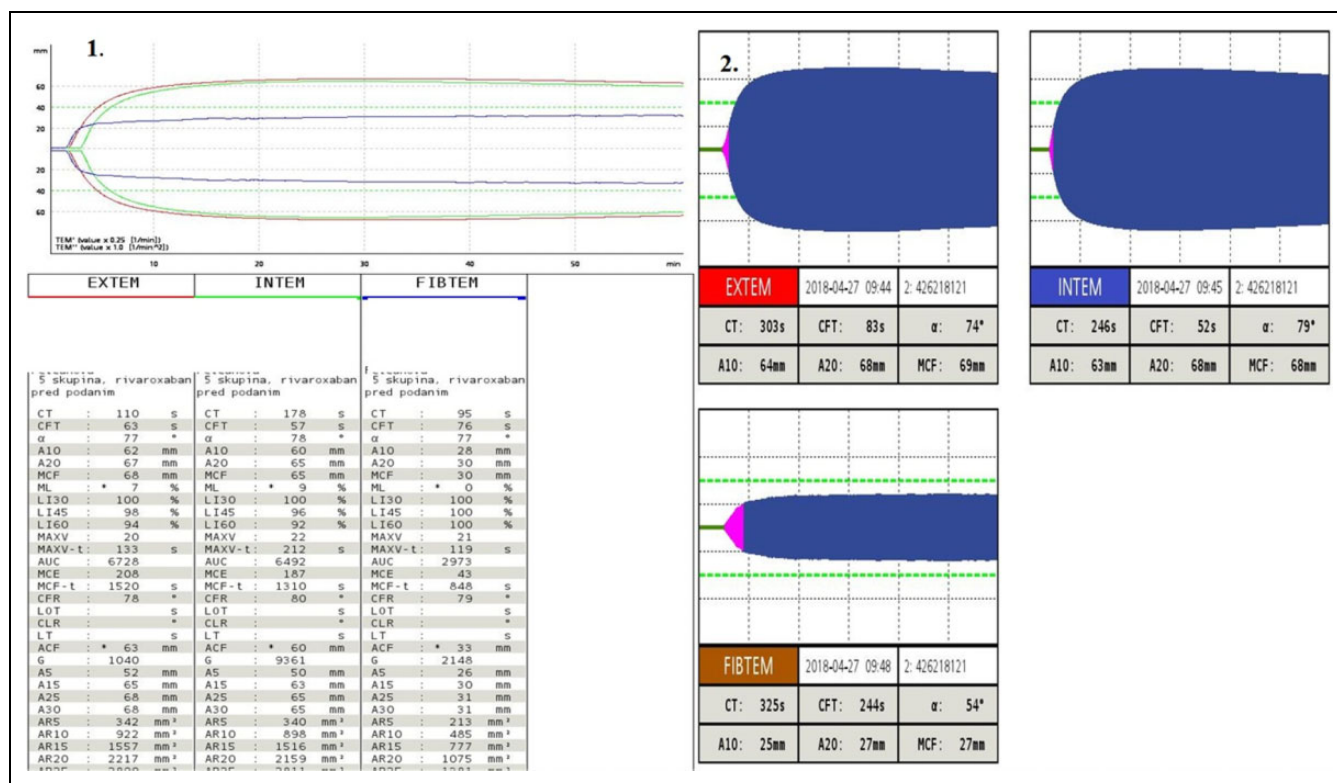
Figure 2. Graphical example of rotational thromboelastometry (ROTEM) test result.

On the other hand, bedside ROTEM or TEG can rapidly detect changes in blood coagulation and therefore provide goal-directed, individualized coagulation therapy. Point-of-care transfusion and coagulation management algorithms using viscoelastometric methods have been published by several authors.[21-26] In addition, Weber et al[26] reported that these algorithms seemed to be the most effective with regard to reductions in transfusion requirements, hospital costs, and the improvement in patient outcomes. Studies using these algorithms have been performed in a patient population undergoing complex cardiac and aortic surgery. Considering the fact that the transfusion of red blood cells, fresh frozen plasma (FFP), and platelets may lead to serious adverse events, such as transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-related immunomodulation, and nosocomial infections,[10,27-31] the reduction or even avoidance of the transfusion of these blood products is the goal for patient blood management. The strategy of reduced blood product transfusion has been advocated by the recent guidelines of the European and American Society of Cardiothoracic Surgeons and Anesthesiologists as a 1A recommendation,[32,33] and this strategy might be effectively achieved using POC-guided hemostatic transfusion algorithms.[23,26,34]

Finally, it is important to discuss the use of antifibrinolytics in cardiac surgery. Both TEG and ROTEM can detect systemic fibrinolysis when profibrinolytic enzymes override the endogenous antifibrinolytic system.[35] In cardiac surgery, ε-amino-caproic acid or tranexamic acid is routinely used during cardiopulmonary bypass, and therefore, detectable fibrinolysis on TEG or ROTEM is rare in patients undergoing cardiac surgery. The lack of systemic fibrinolysis does not exclude the usefulness of antifibrinolytic therapy because lysine analogues have been repeatedly shown to reduce postoperative bleeding in cardiac and other surgical procedures.[36] In contrast, in high-risk cases of thrombosis, it may be important to selectively use an antifibrinolytic agent only when fulminate fibrinolysis is detected on TEG or ROTEM.[17]

Thromboelastography and ROTEM in Cardiology

Management of Anticoagulation

Vitamin K antagonist (VKA) therapy is still the most frequent therapy used for long anticoagulation in patients with atrial fibrillation and also for the treatment and secondary prevention of venous thromboembolism.[37-40] However, the management of this therapy needs regular PT and international normalized ratio (INR) monitoring to achieve the longest time in therapeutic range (TTR), for which therapeutic INR is 2.0 to 3.0.[41-43] Patients on VKA with poor anticoagulation quality (eg, low TTR) have been shown to have a higher risk of thromboembolic and bleeding complications and thus a worse risk–benefit ratio.[37,41,44,45] Although clinical trials have shown that direct-acting oral anticoagulants (DOACs) offer therapeutic benefits over VKA,[46-48] clinical equipoise still exists when patients are likely to have good anticoagulation control based on

Table 1. Assays Used in Rotational Thromboelastometry (ROTEM).[5]

Assay	Activator/Inhibitor	Information Provided	Liquid Reagents
INTEM	Contact activation	Fast assessment of clot formation, fibrin polymerization, and fibrinolysis via the intrinsic pathway	In-tem
HEPTEM	Contact activation + heparinase	ROTEM analysis without heparin influence: specific detection of heparin (compared to INTEM), assessment of clot formation in heparinized patients	Hep-tem
EXTEM	Tissue factor activation	Fast assessment of clot formation, fibrin polymerization, and fibrinolysis via the extrinsic pathway	Ex-tem
FIBTEM	Tissue factor activation + platelet inhibition	ROTEM analysis without platelets: qualitative assessment of fibrinogen status	Fib-tem
APTEM	Tissue factor activation + aprotinin	In vitro fibrinolysis inhibition: fast detection of lysis when compared with EXTEM	Ap-tem
NATEM	Recalcification only = classical TEM (thromboelastometry)	Very sensitive assessment of the equilibrium of coagulation activation or inhibition	Star-tem

(continued)

Table 2. Thromboelastogram (TEG) Assays.[5,6]

Assay	Description
Kaolin	Kaolin acts as contact activators.
Rapid TEG	Reagent contains tissue factor and kaolin as activators.
HTEG	Reagent contains lipophilized heparinase to neutralize unfractionated heparin. Used in conjunction with kaolin to assess heparin effect.
Functional fibrinogen	Reagent contains tissue factor and abciximab, a GPIIb/IIIa platelet receptor inhibitor that blocks the platelet contribution to clot formation. Allows qualitative analysis of the fibrinogen contribution to clot strength independent of platelets.
Native	Native whole blood sample analyzed following only recalcification. Impractical for clinical use given long R time.
Platelet mapping	Assay utilizes heparinized blood mixed with activator F (reptilase and factor XIIIa). Sufficient heparin is present to entirely suppress thrombin generation while fibrinogen is converted into fibrin and cross-linked due to the presence of reptilase and factor XIIIa. Subsequent addition of either ADP or arachidonic acid (AA) allows determination of the platelet activation response to these agonists in the absence of thrombin. These results are compared to kaolin analysis to determine platelet response to ADP and AA. This assay requires the use of 4 simultaneous TEG channels (2 devices).

Abbreviation: ADP, adenosine diphosphate; GP, glycoprotein.

pretreatment characteristics.[44,49] This choice is particularly difficult to make in older adults because DOACs have been associated with a higher risk of major gastrointestinal bleeding than VKAs in the older population.[50-52] Moreover, chronic kidney disease is highly prevalent in older adults,[53] which makes the lack of routine monitoring tests for DOACs a challenge rather than an advantage.[37] The predictability of DOAC-induced anticoagulation allows fixed dosing without the need for routine monitoring. However, there are instances during which the measurement of DOAC activity might be useful to guide the therapy.[54-56] These situations include urgent or emergent invasive procedure, major injuries, the need for thrombolysis, or active hemorrhage. If these situations occur, clinicians need to be familiar with the role, limitations, and local availability of various coagulation assays as they relate to DOACs.[57]

The INR does not vary significantly from hour to hour due to the long half-life of warfarin, and the timing of INR in relation to the last warfarin dose is not important. In contrast, the timing of the last DOAC dose relative to the coagulation assay is important for interpretation, given the relatively short half-life of DOACs.[55] Most scenarios that would trigger laboratory testing for DOACs are urgent (eg bleeding or thrombosis); thus, laboratory results will often be random out of necessity. In settings of active bleeding, it is likely sufficient to have a rapidly available quantitative test that will reliably determine whether DOAC is present in measurable quantities (yes or no). In the setting of thrombosis or suspected treatment failure, the ideal test would indicate not only whether the drug was present but also whether the concentration was consistent with observed on-treatment levels. In the event of concern for DOAC accumulation due to renal insufficiency or drug interactions, trough levels are preferred.[55,57] Knowledge of the assay principles as well as the mechanism of action of the anticoagulant and its reversal agent are inevitably related to an adequate use of global assays in anticoagulation management. The wide variety of available global assays and reagents underscores the need for standardization and assay validation.[58] Thromboelastography/ROTEM-based assays can be affected by direct oral anticoagulants.[59,60] Several clinical experiences with the use of TEG for the monitoring of dabigatran on-treatment levels and the management of dabigatran reversal strategies have been reported,[61-66] but there is only limited information regarding the role of ROTEM assays in patients on dabigatran therapy.[67,68] In a small-sample study on dabigatran-treated patients,[67] ROTEM clotting time correlated strongly with dabigatran concentrations when activated with the reagents EXTEM and FIBTEM, while with INTEM

the correlation was weaker. On the other hand, TEG seems to be insensitive to VKA,[69] and the results from TEG/ROTEM assays do not show dose-dependent responses at clinically relevant concentrations for rivaroxaban and apixaban.[60,70-72] This fact implies that viscoelastic assays would probably be more specific for direct thrombin inhibitors than for oral factor Xa inhibitors. However, this issue needs further research for final clarification.

Management of Antiplatelet Therapy

Antiplatelet therapy is increasingly prescribed for primary and secondary prevention of cardiovascular diseases to decrease the incidence of acute cerebrovascular and cardiovascular events. Antiplatelet drugs are typically targeted to inhibit cyclooxygenase 1/thromboxane A2 receptors (eg, aspirin), adenosine diphosphate (ADP) receptors (eg, clopidogrel), or glycoprotein IIb/IIIa receptors (eg, abciximab, tirofiban). Although antiplatelet drugs are thought to work primarily by decreasing platelet aggregation, they might also affect coagulation: activated platelets facilitate thrombin generation by providing a catalytic cell surface on which coagulation reactions may occur and they release activated factor V.[73-75] Because platelets play a key role in overall coagulation, the assessment of the PF (more than their number) is critical in the perioperative setting.[76,77] Traditional assays, such as turbidimetric platelet aggregometry, are still considered a clinical standard for PF testing. However, conventional platelet aggregometry is labor-intensive, costly, time-consuming, and requires a high degree of experience and expertise to perform and interpret. Furthermore, platelets are tested under relatively low shear conditions in platelet-rich plasma, conditions that do not accurately simulate primary hemostasis.[77] Viscoelastic POC coagulation analyzers may provide information on PF, but these tests also assess coagulation under low shear conditions. The maximum amplitude (MA)/maximum cloth firmness (MCF) from TEG/ROTEM reflects overall PF and fibrinogen levels. It is recommended that 2 different tests be run simultaneously, for example, EXTEM (tissue factor-activated test) and FIBTEM (EXTEM plus cytochalasin D to inhibit PF), as the difference between clot firmness of EXTEM and FIBTEM then represents the platelet contribution. However, since conventional TEG/ROTEM is not sensitive to targeted pharmacological inhibition, a more sophisticated test has recently been developed for the TEG to specifically determine PF in the presence of antiplatelet therapy (PlateletMapping).[78,79] Briefly, the maximum 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 thromboxane A2 receptors to the clot formation is provided by the addition of the appropriate agonists, ADP, or arachidonic acid. The results from these different tests are then compared with each other and the calculated PF.[73,80] However, currently, there are

only limited data about the utility of this assay for the monitoring of dual antiplatelet therapy (DAPT), especially in patients with acute coronary syndrome (ACS). This assay was previously tested in healthy volunteers,[80] in patients not having ACS with or without antiplatelet therapy,[81] in small samples of aspirin- and clopidogrel-treated patients requiring acute surgical therapy,[82] or in patients with coronary artery bypass surgery[83] to predict bleeding in a larger sample of patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention[84] and also for the detection of DAPT nonresponsiveness in a small sample of patients.[85,86] However, no larger study examining the ability of a platelet mapping assay to detect DAPT nonresponsiveness in patients with acute STEMI was performed; thus, despite the fact that results of heretofore published studies with a platelet mapping assay for ROTEM are generally promising, more research is definitely needed for the determination of its role in monitoring the efficacy of antiplatelet agents in cardiovascular medicine.

Invasive Procedures and Patients With Cardiac Devices

As mentioned previously, ROTEM and TEG might be useful for the management of antiplatelet therapy in patients undergoing a coronary stenting. Furthermore, ROTEM and TEG were shown to be useful for monitoring coagulation during cardiac assist device support, for the management of anticoagulation in patients with total artificial hearts, during extracorporeal membrane oxygenation, during invasive procedures in patients with liver cirrhosis and coagulopathy, to predict bleeding after central venous cannulation in patients with liver cirrhosis, and for the identification of intensive care unit patients on whom minor surgery can be performed without the risk of bleeding despite increased PT.[87-92]

Future Perspectives and Possible Limitations

At this time, there is sufficient understanding of viscoelastic assays to advance them from the setting of experimental research to the setting of clinical trials, with the ultimate goal of applying them in clinical practice. In fact, with the explosion of novel clotting factors with enhanced properties, some with a longer duration of action and others with a more potent hemostatic effect, it is now the ideal time to begin incorporating global assays into clinical trials. Importantly, global assays may be ideal for monitoring the effect of these new therapies. The incorporation of these assays into such studies will allow the correlation of a clinical response (still to be measured by validated, presumably subjective, measures) with an objective laboratory end point. These clinical studies should ultimately determine the potential clinical utility of these assays.[93]

Point-of-care testing has a shorter turnaround time and represents a more global and therefore more relevant reflection of coagulation status; it is also increasingly popular for general and cardiac surgery as perioperative bedside testing, in trauma units, in intensive care, and obstetrics.[94]

Thromboelastography/ROTEM offers the bedside capability to quickly deliver the sum of PF, coagulation processes, and the fibrinolytic system. The elements of the TEG/ROTEM trace have been dissected to assess the need for blood component therapy. The time to clot formation is used as a guide for FFP administration, the clot strength is used to judge platelet infusion, the addition of heparinase is used to assess protamine dosage, and the degree of lysis is used to indicate the need for antifibrinolytic therapy.[1]

However, there are also limitations to using POC, as there are no universal algorithms across the specialties, and local protocols are usually based on institutional experiences. There is limited interchangeability between TEG and ROTEM, and the development and validation of separate treatment algorithms for the 2 devices is required.[95,96] If INTEM and EXTEM show regular CT and MCF, the following limitations of ROTEM analysis should be considered. First, impaired in vivo hemostasis due to disturbed preconditions of hemostasis (Hb, Ca++, pH, core temperature) cannot be detected if ROTEM analysis is performed at 37°C.[4] Second, although ROTEM analysis can be performed at the patient's temperature (between 30°C and 40°C), usually it is performed at 37°C since the detection or exclusion of a coagulation factor deficiency is aimed by assessing clotting time (CT) in EXTEM and INTEM. A coagulopathy based on hypothermia, acidosis, or hypocalcemia can be assumed based on measuring patients' core temperature and blood gas analysis. Furthermore, impaired primary hemostasis due to von Willebrand disease or antiplatelet drugs (eg, induced by acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, cangrelor, or low-dose abciximab, eptifibatide, or tirofiban) cannot be detected by standard ROTEM analysis. Platelet aggregation induced by thrombin generated in ROTEM analysis will overlay a potential drug-induced platelet dysfunction.[97]

Conclusion

Viscoelastic methods, TEG and ROTEM, can offer several benefits in the laboratory monitoring of hemostasis, including the bedside capability to rapidly assess the sum of PF, coagulation, and the fibrinolytic system. These methods are well established in cardiovascular surgery, but there is perspective for more frequent use of these assays in the assessment of PF on antiplatelet therapy and for the assessment of coagulation in patients on long-term dabigatran therapy.

Authors' Note

This research was done according to ethical standards. Formal approval is not required for this type of study.

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Declaration of Conflicting Interests

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