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THROMBELASTOGRAPHY AND THROMBELASTOMETRY

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Abstract

The term thrombelastography / thrombelastometry was used to describe the trace produced from measurement of the viscoelastic changes associated with fibrin polymerization. The result of measurement is a compact mapping of the various stages of haemostasis. One of the first real clinical applications of this method was the haemostatic monitoring of liver transplantation and cardiac surgery using extracorporeal circulation. In trauma patients the thrombelastography /thrombelastometry was proved to predict early transfusion requirements. Another authors suggest thrombelastography /thrombelastometry as a possible tool for early identification of pregnant women at increased risk of fetal loss. This article provides overview on the development of thrombelastography / trombelastometry and its possible use in laboratory of haemostasis.

Key words : thrombelastography (TEG), rotation thrombelastometry (ROTEM), global haemostasis tests

INTRODUCTION

The thrombelastography (TEG) was first described by Hartert in 1948 as a measurement of the viscoelastic changes associated with fibrin polymerization as well as the overall clot strenght is assessed. TEG and also rotation thrombelastometry (ROTEM) as real-time clotting tests enable a complete evaluation of the process of clot initiation, formation and stability, using whole blood or plasma. The advantage the TEG/ROTEM offers is its bedside capability to deliver within 30 min a representation of the sum of platelet function, coagulation proteases and inhibitors, and the fibrinolytic system. The time to clot formation is used as a guide for fresh frozen plasma (FFP), the clot strength to judge platelet infusion, addition of heparinase to assess protamine dosage. It is only recently that the TEG/ROTEM has been used within haemostasis laboratories. The poor acceptance of the technology stems largely from the lack of agreement with standard laboratory variables (1).

The use of this method in the laboratory setting represents a significant change of use for the instrument. It was originally designed as a bedside monitor using native whole blood. To perform tests within the laboratory it is not practical to use native blood and citrated samples are used for analysis (2). In the laboratory the technology has been applied to areas where conventional testing is inadequate. The present report gives an overview of the development related to TEG/ROTEM, and its application in haemostasis and thrombosis laboratory.

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TERMINOLOGY AND PRINCIPLE OF MEASUREMENT

The term thrombelastography (TEG) has been used generically in the literature since the first description of the technique. However, in 1996 the term TEG became a registered trademark of the Haemoscope Corporation and from that time has been used to describe the assay performed using Haemoscope instrumentation. Alternative instrumentation marketed by Pentapharm GmbH uses the terminology thromboelastometry (ROTEM) for the process of measurement. The descriptive data associated with the either the Haemoscope or Pentapharm instruments is summarized in Table 1 (1).

Table 1. Nomenclature used for TEG and ROTEM (1)

Instrumentation	TEG®	ROTEM®
Measurement period	–	RT
Clot time (period to 2 mm amplitude)	*r*	CT
Period from 2 to 20 mm amplitude	*k*	CFT
Alpha angle	α (slope between *r* and *k*)	α (angle of tangent at 2 mm amplitude)
Maximum angle	–	CFR
Maximum strength	MA	MCF
Time to maximum strength	TMA	MCF-t
Amplitude (at set time)	A (A30, A60)	(A5, A10...)
Clot elasticity	G	MCE
Maximum lysis	–	ML
Lysis at a fixed time	CL30, CL60	LY30, LY45, LY60
Time to lysis	TTL (2 mm drop from MA)	CLT (10% from MCF)
Maximum lysis	–	CLR (maximum tangent post-MCF)

TEG/ROTEM is intended for *in vitro* diagnostic use as a „point of care" instrument in laboratory or as bedside test. The system graphically records kinetic changes of citrated whole blood samples during the clot formation and during its lysis. The result is a compact mapping the various phases of haemostasis in the form of tromboelastogram (TEM-gram). The technology is based on a solid cup containing a blood sample with reagents and constantly oscillating vertical pin. 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. Rotation of measuring pin is converted graphically to amplitude, where free rotation corresponds to the amplitude of 0 mm (non-coagulated blood) and no rotation amplitude corresponds to 100 mm (maximum possible strength of the clot). The result is interpreted by special software. The software uses a special algorithm and filter eliminates potential errors of mechanical or electronic noise. The parameters are determined in real time during the test, calculated and graphically interpreted in TEM-gram (see Figure 1) (3).

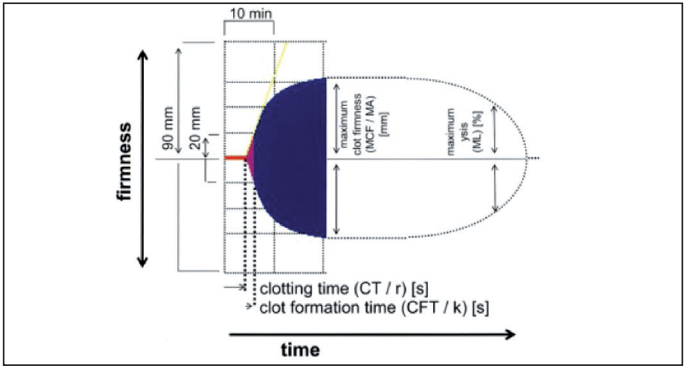

Fig. 1. Main thrombelastometry parameters (3)

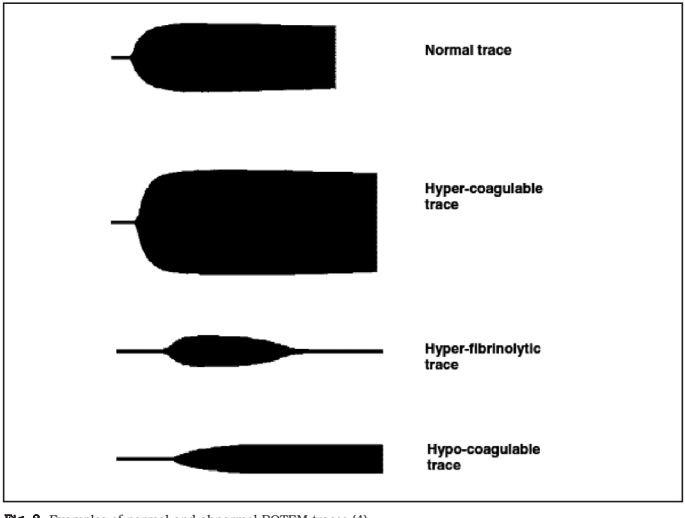

Fig. 2. Examples of normal and abnormal ROTEM traces (4)

Coagulation activators, such as tissue factor (EXTEM test) or ellagic acid (INTEM test) speed up the analysis and falicitate more specific exploration of the related extrinsic pathway with EXTEM and intrinsic pathway with INTEM. The FIBTEM test evaluates the fibrinogen component to clot formation and uses a platelet inhibitor. The APTEM test evaluates fibrinolysis by using fibrinolysis inhibitor (aprotinin) (4).

TEG/ROTEM is currently irreplaceable in the laboratory diagnosis of haemostasis disorders. As a dynamic global coagulation test provides valuable information involving clot formation and degradation. It is a very sensitive indicator of fibrinolysis. TEG/ROTEM enables to use the heparinase method to assess the level of heparinization, including the detection of residual heparinization after exercise. Examples of curves generated by various pathological conditions are depicted in Figure 2 (4).

APPLICATION OF THROMBELASTOGRAPHY / THROMBELASTOMETRY IN SURGERY

One of the first clinical applications of TEG was the haemostatic monitoring of orthotopic liver transplatation (OLT). During OLT the haemostasis is often disturbed and coagulation monitoring is mandatory. Coagulation abnormalities are characterised by decreased coagulation factors, antifibrinolytic factors and endogeneous anticoagulant factors. The results of the study suggest that point of care methods can reliably detect these large changes in

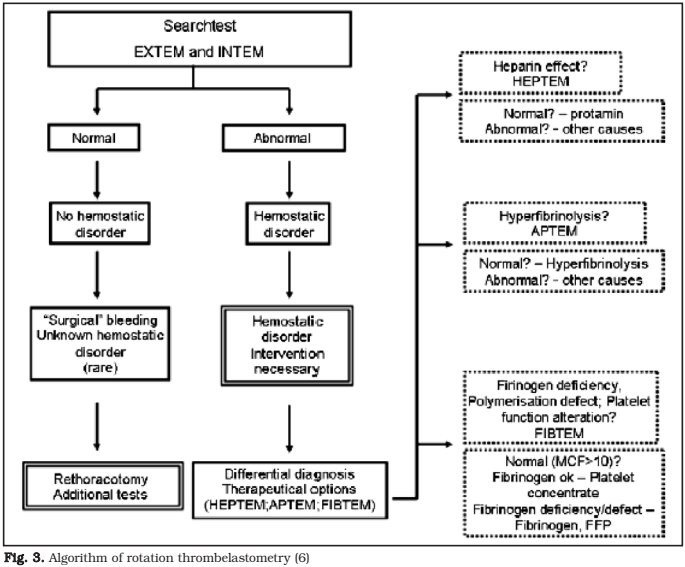

Fig. 3. Algorithm of rotation thrombelastometry (6)

coagulation. A further advantage of point of care assays is that diagnosis of coagulopathy can be achieved within 10–15 min, while other laboratory assays commonly require 30–45 min (5).

TEG/ROTEM has been used to predict blood loss in patients undergoing cardiac surgery using extracorporeal circulation. ROTEM diagnostic algorithm is shown demonstrating the consecutive analytical steps beginning with the search-tests EXTEM and INTEM followed by differential diagnosis in case of a pathological finding utilizing HEPTEM, APTEM, and FIBTEM (Figure 3). Cumulative costs for treatment of perioperative coagulation disorders can be reduced by 'bedside' ROTEM analysis to achieve a selective substitution management. Saved costs for blood products (- 32%) and coagulation products (- 50%) clearly outweighted the expenses of ROTEM (6).

SCREENING FOR HYPERCOAGULABLE STATES

In the laboratory the 'global' aspects of the TEG/ROTEM are used to identify or monitor specific defects. It has been demonstrated that the TEG/ROTEM can clearly distinguish a group of patients as hypercoagulable from a cohort of patients who is not necessarily identified by routine thrombophilia screening. It was demonstrated that 34% of patients had a positive thrombophilia screen whereas 45% had a positive TEG/ROTEM trace. This study did arise questions whether these individuals are at higher risk of further thrombotic events (7).

The considerable success of this method has been observed in the assessment of coagulation changes in pregnant women. Study using TEG / ROTEM confirmed that the healthy pregnant women develop increased coagulation status, which minimizes the risk of bleeding during pregnancy and after birth. This phenomenon was observed by ROTEM also in our group of healthy pregnant women (unpublished data) as well as in the study of Huissoud et al. (Figure 4) (4). Other study of the same authors suggests postpartum as a period at high risk for thrombosis. Conventional coagulation screening and thrombelastometry objectively indicate that the risk period may remain very high until 25 days after delivery. The study showed that reactive thrombocytosis is a common phenomenon during the postpartum period which is associated with an increased incidence of thrombosis (8).

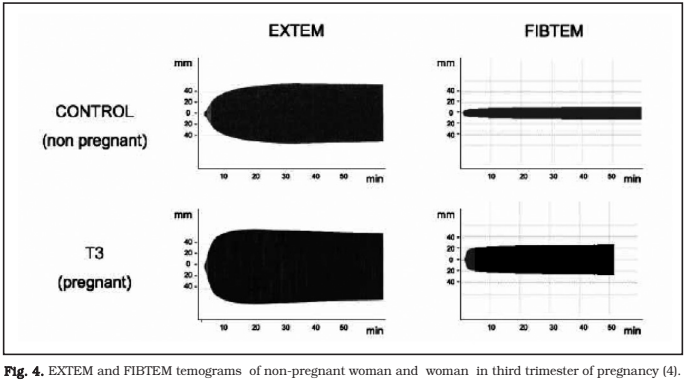

Fig. 4. EXTEM and FIBTEM temograms of non-pregnant woman and woman in third trimester of pregnancy (4).

TEG/ROTEM also identified a subset of women with recurrent fetal loss (RFL) as a group with hypercoagulation. Those who had an increase in the maximum amplitude before pregnancy were found to have an increased risk of miscarriage (9). Another group of authors suggests TEG/ROTEM as a possible tool for early identification of women at risk of fetal loss. Consideration should be taken about the possibility of initiating antithrombotic prophylaxis before pregnancy after positive analysis (10).

SCREENING OF HYPOCOAGULABLE STATES AND MONITORING OF PHARMACOLOGICAL AGENTS

There are few reports about the use of TEG/ROTEM for the screening of inherited bleeding disorders in association with the monitoring of therapeutic intervention using coagulation factor concentrates, fresh frozen plasma (FFP), cryoprecipitate, activated prothrombin complex concentrate or recombinant activated factor VII (11,12).

Recent data suggest that whole-blood viscoelastic tests, such as TEG/ROTEM reproduce trauma induced coagulopathy (TIC) more accurately and substantially faster than standard coagulation tests. There is an increasing evidence that these coagulation monitoring devices are helpful in guiding coagulation therapy for heavily bleeding trauma patients according to their actual needs. Figure 5 displays an ROTEM example of the patient with severe bleeding and therapy according to the guideline (13).

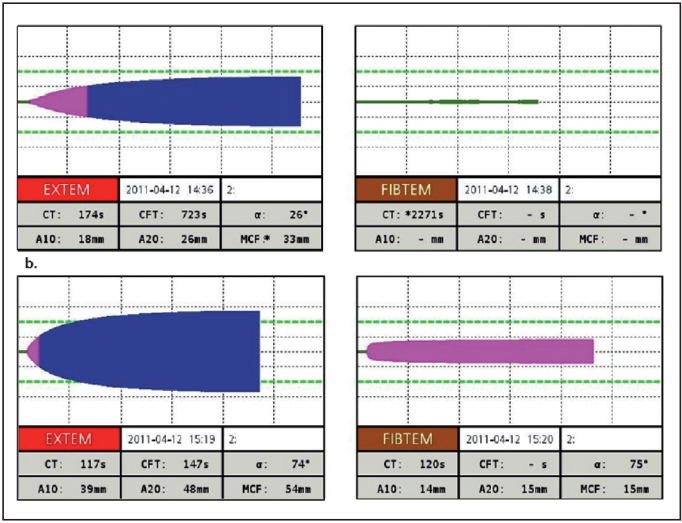

Fig. 5. Rotation thrombelastometry traces from trauma patients before and 40 min. after treatment with prothrombin complex concentrate and fibrinogen concentrate (13).

The use of heparinase-modified TEG to monitor haemostasis in the presence of heparin is commonly found in cardiac surgery using extracorporeal circulation. TEG/ROTEM can be of benefit to monitor the effect of unfractionated heparin, low molecular weight heparin and heparinoid. A dose-dependent change in TEG/ROTEM was generally observed but the degree of abnormality did not always agree with the plasma anti-Xa levels (14).

CONCLUSIONS

The TEG/ROTEM has been used for many years as a guide to blood product and drug administration during cardiac and hepatic surgery. Both global coagulation methods are able to provide an effective and inexpensive monitoring of haemostasis. The search for an ideal 'global' assay of haemostasis continues and the TEG/ROTEM or a derivative of this technology may provide the answer, or part of the answer, to that question. There is more work to be carried out particularly with regard to standardization and reagent optimization before this potential can be fully evaluated.

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