Transfusion and Apheresis Science 40 (2009) 119–123

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Thrombelastography

Håkon Reikvam [a], Egil Steien [b], Bjørn Hauge [b], Knut Liseth [c], Kristin Gjerde Hagen [c], Rolf Størkson [c], Tor Hervig [c,*]

[a] Institute of Internal Medicine, Haukeland University Hospital, 5021 Bergen, Norway
[b] Department of Anaesthesiology and Intensive Care, Haukeland University Hospital, 5021 Bergen, Norway
[c] Blood Bank, Haukeland University Hospital, Jonas Liesvei 65, 5021 Bergen, Norway

A B S T R A C T

Background: Thromboelastography (TEG) records the continuous profiles of whole blood coagulation by measurement of the viscoelastic changes associated with fibrin polymerization, and thereby provides a global assessment of haemostatic function. In the past decades there has been an increasing interest for TEG in clinical practice. In this paper we present the rationale for the method and a discussion of the possible application of TEG.

Material and methods: This review is based on personal experience and literature retrieved from searches in PubMed.

Results and interpretation: Currently TEG is used with standard coagulation tests to decrease the risk for bleeding and reduce the homologous blood transfusion in cardiac surgery with cardiopulmonary bypass and in liver surgery. Other applications are severe trauma, obstetric medicine, haemophilia and hypercoagulable conditions. Development of a modified TEG, using heparin in combination with reptilase and factor XIIIa, has the potential to monitor the effects of platelet inhibiting drugs. It should be kept in mind that the TEG is a global test of coagulation and therefore the need for additional haemostatic tests should be evaluated when applicable. The main advantage for TEG is an inexpensive patient near method for quick evaluation of the patient's global haemostatic system. Used by experienced hands, TEG is a valuable haemostatic test, the future of which is already present.

1. Background

The use of thrombelastography (TEG) as a tool for evaluation of bleeding and the effects of blood components and blood products is increasing. TEG is visualizing the viscoelastic changes that occur during coagulation *in vitro*, and provides a graphical representation of the fibrin polymerization process. In this paper we present an overview of the method and the use of TEG in clinical practice. The paper is based on review of published literature and our own experience with TEG.

TEG was first used in the 1940s. The technology is based on measurements of the viscoelastic changes that are happening during coagulation of a whole blood sample *in vitro*. Thus, TEG is providing a unique possibility to evaluate initialisation, formation and stability of the clot strength. Due to technological limitations, the clinical application of the method was limited for nearly 60 years. However, technical developments have now led to standardization of the method and the reproducibility has improved accordingly. Digitalisation of the procedure, combined with possibilities for bedside evaluation of the bleeding episode – have caused increased interest in and usage of the method.

* Corresponding author. Tel.: +47 55 97 24 92; fax: +47 55 97 24 84.
E-mail addresses: Hakon.Reikvam@med.uib.no (H. Reikvam), Egil.Steien@helse-bergen.no (E. Steien), Bjorn.Hauge@helse-bergen.no (B. Hauge), Knut.Liseth@helse-bergen.no (K. Liseth), Kristin.Gjerde.Hagen@helse-bergen.no (K.G. Hagen), Rolf.Storkson@helse-bergen.no (R. Størkson), Tor.Hervig@helse-bergen.no (T. Hervig).

1473-0502/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.transci.2009.01.019

2. The TEG methodology

The principles behind thrombelastography are based on the known changes occurring during the coagulation process. A whole blood sample, with or without citrate, is incubated in a cup at 37 °C. A stationary pin attached to a wire which can monitor movements, is immersed into the sample. The cup oscillates back and forth six times per minute. Caolin is added to activate the coagulation cascade, leading to thrombin formation [1] – and subsequently fibrinogen is converted to fibrin. Finally a stable clot is formed as fibrin polymers are stabilized by factor VIII and activated platelets [2], which also is an effect of thrombin formation. The clot strength will influence the oscillation of the pin, and these dynamic changes are converted to a curve (Fig. 1). The curve reflects the different phases of the clotting process and enables qualitative evaluation of the individual steps involved. These steps are defined as follows (Fig. 1):

R (reaction/clotting) time is the period from the initiation of test till the beginning of the clot formation. *K*-time (*K*) is the period from the start of the clot formation to the curve reaches amplitude of 20 mm; thus indicating clot kinetics. The α-angle is the angle between the baseline and the tangent to the TEG curve through the starting point of coagulation (the split after the end point of the *R*-time). The α-angle is visualizing the acceleration and the kinetics of fibrin formation and cross-linking.

Maximal amplitude (MA) is a direct measure of the highest point on the TEG curve and represents clot strength. MA is dependent of platelet concentration, platelet function and platelet–fibrin interaction. The amplitude after 30 min (*A*30) is also measured and the difference between MA and *A*30 reflects the degree of fibrinolysis. This is more often reported as Ly30, which is providing information of the fibrinolytic activity during the first 30 min after MA. Ly30 is calculated on basis of the reduction in the area under the curve. The clot lysis index (CLI) is the ratio between the amplitude at a given time point and MA given as percent of MA. CLI is thus a measurement of fibrinolysis at a given time. The clot index (CI) represents the haemostasis profile, and is calculated based on *R*, *K*, α and MA parameters. The normal range is from –3 to +3.

The same procedure – and the same parameters may be tested in a parallel run in a cup where heparinase is added (Fig. 2). This enzyme reverses the effects of heparin, if present in the whole blood sample.

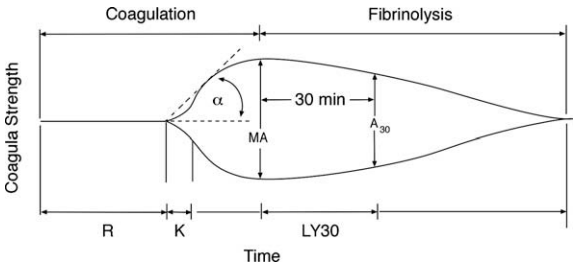

Fig. 1. Presents major TEG parameters. *R* reflects coagulation factor activities, *K* and α show fibrinogen and coagula formation. MA indicates platelet function. Ly 30 reflects fibrinolysis. *A*30 is the amplitude 30 min after MA.

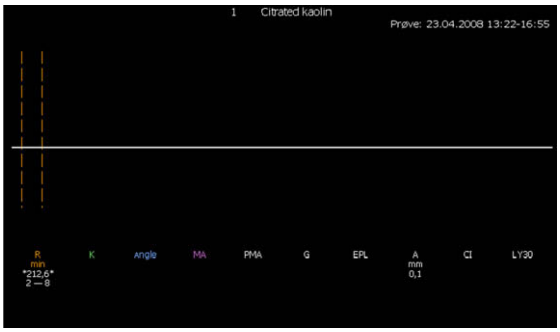

Fig. 2a. TEG in patient with abdominal aorta aneurism: postoperative TEG (after 4.5 L bleeding) without heparinise.

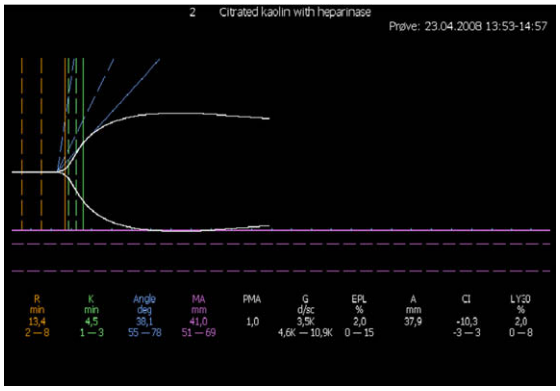

Fig. 2b. TEG in the same patient as shown in Fig. 2a – but now with heparinise in the cup. These curves show how heparin effects may be evaluated by TEG.

This may be very illustrative, as e.g., prolonged *R-time* may be caused by heparin effects as well as by dilution of the blood volume or other causes of impaired synthesis of coagulation factors.

A practical advantage of monitoring the coagulation process is that is possible to tailor make transfusion therapy; including administration of drugs. As the different parameters reflect different phases of coagulation, the intervention may be individualized – and additionally, repeated testing after treatment will enable evaluation of the effects of the intervention. Prolonged *R*-time will indicate lack of coagulation factors and if this is not due to heparin therapy, transfusion of plasma containing normal coagulation factors may reverse the pathology. If a heparin effect is present – protamin sulphate alone or in combination with plasma infusion will be able to normalize the prolonged *R*-time. Reduced α-angle indicates shortage of fibrinogen, which may be corrected by fibrinogen concentrate or plasma, judgments that can be made dependent on the clinical situation. Low MA indicates reduced platelet function; and again – based on knowledge of the individual patient, desmopressin and/or platelet concentrates may be indicated. Evaluation of the Ly30 and CI values, together with evaluation of the morphology of the TEG curve, will

provide information on the fibrinolytic situation in the patient. Importantly, the patterns of primary and secondary fibrinolysis differ, as certainly does the correct treatment. If primary fibrinolysis is present, the patient needs antifibrinolytic medication, whereas a patient with secondary fibrinolysis could favourably receive anticoagulation. In addition to the different TEG curve pictures, elevated Ly30 combined with low CI indicated primary fibrinolysis, whereas elevated Ly30 and elevated CI points to secondary fibrinolysis.

3. TEG and conventional test of the coagulation system

The standard coagulation tests are mostly analysing factors in plasma and isolated components or fractions of the whole system are analysed. TEG differs by providing an "overall" view on the coagulation and may detect interactions between platelets and coagulation factors, which may be of importance for the patient. However, TEG does also have limitations. A normal TEG curve does not exclude defects in the haemostatic process. A surgical bleeding will not be detected, and adhesion defects will not be identified. The method is not sensitive to F VII deficiency and is not suitable for monitoring vitamin *K* antagonist treatment. Neither does the standard TEG testing disclose increased bleeding risks due to treatment with acetyl salicylic acid or ADP receptor inhibitors as clopidogrel or ticlopidin [3]. Heparin effects are easily shown using plain cup and heparinase cup in parallel runs. When the TEG curve points to abnormalities related to fibrinogen or platelets, the causes may be both qualitative and quantitative. Additional measurement of fibrinogen concentration or platelet count is therefore important. In patients with more complex disturbances of haemostasis, TEG may disclose hypercoagulability [4]. It is then important to bear in mind that TEG is not able to detect changes in the natural anticoagulants, as this is important in the evaluation of thromboembolic complications. Similar considerations apply to pathology in the primary haemostasis, as the bleeding tendency related to von Willebrand disease.

4. Modified TEG – "platelet mapping"

As the potency of new drugs modifying the platelet function has increased, enhanced risks for clinically significant bleeding has developed along. Therefore, there is great need for tests that may assume the drug effects in each individual. A modified TEG test is a candidate. By adding heparin to the TEG cup, the thrombin production is inhibited. Thus, without other platelet agonist present, even reptilase and F XIIIa do not affect the coagula formation and the MA value is low. But, if alternate platelet agonist as ADP or arachidonic acid is added, the platelets will be stimulated causing coagula production and increased MA value [5]. Thus, comparison of the standard and modified ("platelet mapping") TEG curves (use of heparin, ADP or arachidonic acid) will visualize effects of glycoprotein IIb/IIIa inhibitors, acetylic acid or ADP agonists [6]. Although the usefulness of platelet mapping, especially concerning monitoring of ADP inhibitor effects is debatable, further developments of the test may overcome these problems [3]. In patients undergoing cardiac interventions, antiplatelet therapy is needed to avoid in-stent thrombosis, and tools to individual monitoring of these very potent drugs would increase patient safety as the exact level of platelet inhibition would be known [6]. Both the high responders – where the drug dose should be reduced – and the low responders – where the drug dose should be increased or alternate treatment given – would then by recognised.

5. Clinical applications

As TEG is a rather simple procedure which may be performed close to the patient bed, the use of the method is increasing. We shortly describe the clinical areas where the test is in common usage.

6. Liver surgery

During liver surgery, different coagulation problems often appear. This may be due the procedure itself, or to liver dysfunction, which causes both qualitative and quantitative alterations in pro- ant anticoagulants – and platelets. Reduced degradation of activated components, hyperfibrinolysis and deficient metabolism of citrate in the blood components also contribute. Liver transplantation was one of the first procedures where TEG testing was implemented [7].

7. Cardiac surgery

Cardiac surgery affects both the platelets and the coagulation system. Reoperation due to bleeding is a predominant complication and is associated with significantly impaired prognosis [8]. Haemostatic abnormalities are due to extracorporeal circulation and use of anticoagulants, causing activation and consumption of platelets and coagulation factors. TEG has proved to be useful to diagnose coagulopathies [9] and to reduce the need for transfusions [10]. A special complication due to heparin usage during cardiac surgery is heparin induced thrombocytopenia (HIT). HIT is caused by antibodies to the heparin–platelet factor IV complex. The most feared complication is called HIT 2, leading to high risk of bleeding as well as thromboembolism and is associated with high mortality [11]. TEG may be used to identify patients with enhanced risk for HIT 2, which may induce early treatment and thus reduce the mortality [12].

8. Bleeding conditions

TEG has no established role in diagnosis of hereditary bleeding disorders. On the other hand, TEG may be useful in evaluation of disease severity and monitoring of treatment. In a study including 47 children with moderate to severe haemophilia, TEG results showed more rapid and stronger coagel production in patients with moderate disease than in more severely affected patents, indicating better thrombin/fibrin production [13]. Accordingly, TEG has also been shown to be effective in detecting responses to

treatment with recombinant F Via [14] and antifibrinolytic drugs [15].

9. Hypercoagulability

In a study comprising 87 persons with earlier thrombosis or a family history with thrombotic events, TEG was compared with biochemical screening for thrombophilia. In 45% of the patients, TEG showed thrombophilia, whereas 34% of the patients had biochemical markers increased risk of thrombosis. However, all the persons with biochemically thrombophilic disposition did not have corresponding TEG-patterns [16]. In a study with 240 patients who had been through surgery, a MA > 68 mm significantly related to incidence of thrombotic events, including myocardial infarction [17]. Cancer patients are known to have increased risk of venous thromboembolism (VTE), due to the disease itself and treatment, as surgery, chemotherapy and hormone therapy [18]. Earlier, it has not been possible to identify patients at risk for VTE in this group. TEG has shown to provide individual information on the coagulation status that has proved to be useful in assessing individual risk for VTE [19]. Further research is necessary to verify this important observation, as well as comparison with results from the biochemical test armament.

10. Obstetrics

The pregnancy is a prothrombotic state and the changes exist for a short period postpartum. TEG investigations of pregnant women have indicated that both preeclampsia and thrombocytopenia may be diagnosed [20], as well as prediction of risk for repeated spontaneous abortions [21]. A lot more evidence is needed to clarify if TEG has any place in prediction of risk pregnancies.

11. Trauma

Bleeding is a major cause for death in trauma patients. These patients are vulnerable for early development of coagulopathies, which in the most serious cases may be present before hospital admission. The aetiology is complex, involving tissue factor, consumption of platelets and coagulation factors, hypothermia, acidosis, hemodilution, transfusions and hyperfibrinolysis [22]. Early identification of coagulopathies may be lifesaving, and the standard biochemical tests may be inadequate. TEG may be useful to identify patients with hyperfibrinolysis that may respond to antifibrinolytic treatment [23] as well as hypercoagulable patients with increased risk of thromboembolic complications [24].

12. Conclusions

TEG is a rather simple test that may be performed close to the patients and that provides information on the full coagulation status within 30 min. Due to technical limitations, and possibly also lack of standardization, the method was not widely used the first decades after its introduction. Improved equipment and digitalisation of TEG curves have changed this, and TEG is now widely used in different clinical areas; foremost liver surgery and cardiac surgery. TEG may supplement standard biochemical testing for assessing bleeding risks and coagulation deficiencies, but TEG can not replace these tests. Coagulopathy is a clinically important feature in many severe conditions related to increased risk of morbidity and mortality [25]. Improved surveillance of the haemostatic status in these patients may therefore have significant impact, since the treatment may be more individualized accordingly. Targeted use of TEG, interpretation of the curves based on the clinical situation and combined with information coagulation tests, may be beneficial for the future patients.

References

[1] DiCera E. Thrombin as procoagulant and anticoagulant. J Thromb Haemost 2007(Suppl. 1):196–202.
[2] Bombeli T, Spahn DR. Updates in perioperative coagulation physiology and management of thromboembolism and haemorrhage. Crit Care 2004;93(2):275–87.
[3] Weber AA, Adamzik M, Bachmann HS, Gorlinger K, Grandoch M, Leineweber K, Muller-Beissenhirtz H, Wenzel F, Naber C. Methods to evaluate the pharmacology of oral antiplatelet drugs. Herz 2008;33(4):287–96.
[4] Gonano C, Sitzwohl C, Meitner E, Weinstabl C, Kettner SC. Four-day antithrombin therapy does not seem to attenuate hypercoagulability in patients suffering from sepsis. Crit Care 2006;10(6):R160.
[5] Craft RM, Chavez JJ, Bresee SJ, Wortham DC, Cohen E, Carroll RC. A novel modification of the Thrombelastograph assay, isolating platelet function, correlates with optical platelet aggregation. J Lab Clin Med 2004;143(5):301–9.
[6] Hobson AR, Agarwala RA, Swallow RA, Dawkins KD, Curzen NP. Thrombelastography: current clinical applications and its potential role in interventional cardiology. Platelets 2006;17(8):509–18.
[7] Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw Jr BW, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64(9):888–96.
[8] Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004;44(10):1453–62.
[9] Hertfelder HJ, Bos M, Weber D, Winkler K, Hanfland P, Preusse CJ. Perioperative monitoring of primary and secondary hemostasis in coronary artery bypass grafting. Semin Thromb Hemost 2005;31(4):426–40.
[10] Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999;88(2):312–9.
[11] Menajovsky LB. Heparin-induced thrombocytopenia: clinical manifestations and management strategies. Am J Med 2005;118(Suppl 8A):21S–30S.
[12] Kouerinis IA, El-Ali M, Theakos N, Dedeilias P. Can thromboelastography predict which patients with heparin-induced thrombocytopenia may suffer thrombotic complications of type II? Eur J Cardiothorac Surg 2007;32(3):544–6.
[13] Chitlur M, Warrier I, Rajpurkar M, Hollon W, Llanto L, Wiseman C, Lusher JM. Thromboelastography in children with coagulation factor deficiencies. Br J Haematol 2008 [Epub ahead of print].
[14] Dehmel H, Werwitzke S, Trummer A, Ganser A, Tiede A. Thrombelastographic monitoring of recombinant factor VIIa in acquired haemophilia. Haemophilia 2008;14(4):736–42.
[15] Ghosh K, Shetty S, Kulkarni B. Correlation of thromboelastographic patterns with clinical presentation and rationale for use of antifibrinolytics in severe haemophilia patients. Haemophilia 2007;13(6):734–9.
[16] O'Donnell J, Riddell A, Owens D, Handa A, Pasi J, Hamilton G, et al. Role of the Thrombelastograph as an adjunctive test in thrombophilia screening. Blood Coagul Fibrin 2004;15(3):207–11.
[17] McCrath DJ, Cerboni E, Frumento RJ, Hirsh AL, Bennett-Guerrero E. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. Anesth Analg 2005;100(6):1576–83.

[18] Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation 2003;107(23 Suppl. 1):I17–21.
[19] Papa ML, Capasso F, Pudore L, Torre S, Mango S, Russo V, et al. Thromboelastographic profiles as a tool for thrombotic risk in digestive tract cancer. Exp Oncol 2007;29(2):111–5.
[20] Orlikowski CE, Rocke DA, Murray WB, Gouws E, Moodley J, Kenoyer DG, et al. Thrombelastography changes in pre-eclampsia and eclampsia. Br J Anaesth 1996;77(2):157–61.
[21] Rai R, Tuddenham E, Backos M, Jivraj S, El'Gaddal S, Choy S, et al. Thromboelastography, whole-blood haemostasis and recurrent miscarriage. Hum Reprod 2003;18(12):2540–3.
[22] Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. World J Surg 2007;31(5):1055–64.
[23] Levrat A, Gros A, Rugeri L, Inaba K, Floccard B, Negrier C, et al. Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. Br J Anaesth 2008;100(6):792–7.
[24] Kaufmann CR, Dwyer KM, Crews JD, Dols SJ, Trask AL. Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma 1997;42(4):716–20. discussion 720–712.
[25] DeLoughery TG. Critical care clotting catastrophies. Crit Care Clin 2005;21(3):531–62.