


Thrombin Generation Assays: Possibilities and Limitations

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Abstract

Thrombin generation assays (TGA) provide a dynamic and integrative assessment of thrombin generation in clotting plasma *ex vivo*. The method is characterized by triggering coagulation, typically via the extrinsic pathway, and continuously measuring thrombin activity using a fluorogenic peptide substrate to derive key parameters such as peak thrombin and the endogenous thrombin potential. Several assay platforms are currently available, with the original Calibrated Automated Thrombogram (CAT) still being widely used in clinical and research settings, not least due to its flexibility and ability to analyze both platelet-poor as well as platelet-rich plasma. Thrombin generation assays have the potential to support the evaluation and monitoring of treatment of bleeding disorders, including hemophilia A and B and other inherited or acquired coagulation factor deficiencies. They may contribute to risk stratification in thrombotic disorders, and support the assessment of anticoagulant therapies. However, besides ongoing developments and optimization of trigger reagents, inter-assay variability and susceptibility to pre- and analytical variables challenge assay standardization and inter-laboratory comparability. Continued refinement, harmonization, and prospective clinical validation will be essential to unlock the full diagnostic potential of TGA.

Keywords

- ▶ thrombin generation
- ▶ diagnostic tool
- ▶ hemophilia
- ▶ thrombosis risk
- ▶ anticoagulation

Introduction

In daily clinical practice, plasmatic coagulation is predominantly evaluated using global or single-parameter endpoint assays such as the prothrombin time (PT), the activated partial thromboplastin time (aPTT), or specific factor assays.¹ Although these tests are invaluable for detecting coagulation factor deficiencies or anticoagulant effects etc., they do not provide information on the dynamic process of thrombin generation (TG), the amount of thrombin formed or fibrin clot formation.²

While whole blood thromboelastography mechanically monitors clot formation (and dissolving) in real time, the thrombin generation assay (TGA) has emerged as an assay format that provides an integrated assessment of thrombin formation and inactivation in plasma and has therefore become a cornerstone in experimental and clinical hemostasis.^{3,4}

Nonetheless, widespread implementation of TGA in routine diagnostics remains limited due to issues of assay standardization, variability, and interpretation.^{5,6} This brief overview outlines the principles of TGA, current technical developments, its clinical and research applications, as well as potential limitations that challenge integration of TGA into clinical laboratory practice.

The General Principle of the TGA and Derived Parameters

Thrombin is the central enzyme of the plasmatic coagulation cascade. It converts fibrinogen into fibrin, activates platelets, and amplifies further thrombin generation through positive feedback activation by the tenase and prothrombinase complexes.⁷ Furthermore, it also participates in natural

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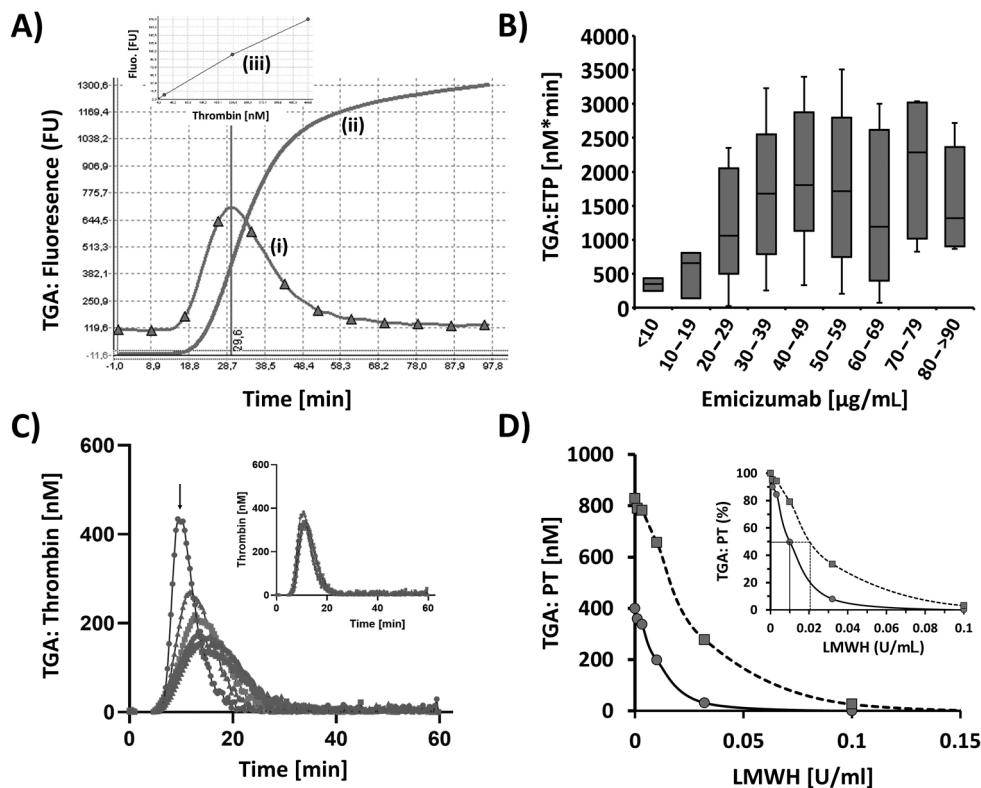


Fig. 1 Principle and applications of thrombin generation assays (TGA). (A) Signals and parameters using an automated system (Ceveron s100). The first derivative (i) is calculated from the originally recorded sigmoidal curve (ii) with thrombin values calculated from a thrombin standard curve (iii), resulting in the final “thrombogram” (C). (B) Boxplots of TGA:ETP found at different plasma activities of emicizumab (pooled data of analyzed patient samples, Ceveron s100). (C) Inhibitory effect of increasing concentrations of an inhibitory anti-PEG-antibody on pegylated FVIII (turoctocog alfa pegol) spiked into FVIII-deficient plasma as monitored by thrombin generation (TG) over time using the microtiter plate (MTP)-based calibrated automated thrombogram (CAT). Arrow shows control (absence of anti-PEG-antibody). Inlet shows no effect on non-pegylated FVIII (turoctocog alfa) analyzed in parallel. (D) Inhibitory effect of increasing concentrations of low-molecular-weight heparin (LMWH) on peak thrombin (PT) values as measured by MTP-based CAT. Circles (solid line) show normal plasma; boxes (dashed line) show plasma obtained from patient harboring the heterozygous antithrombin (AT) Budapest III mutation (p.Leu131Phe) in the heparin-binding site of AT. Note the higher basic PT value in the patient sample compared to the normal plasma due to corresponding impairment of AT activity. Inlet shows relative values (w/o LMWH = 100%) that demonstrate an approximately 2-fold higher LMWH dose needed for comparable anticoagulant effect in the patient sample. FU, fluorescence units.

anticoagulant pathways via activation of protein C (PC) when bound to thrombomodulin (TM) present on the surface of endothelial cells.⁸ These properties make thrombin the central enzyme of the plasmatic coagulation cascade, which is physiologically initiated via the tissue factor (TF)/activated FVII (FVIIa) complex and proceeds on the surface of activated platelets at the site of injury.⁷ Thrombin activity is regulated by naturally occurring inhibitors, including antithrombin (AT), heparin cofactor II (HCII), and alpha-2-macroglobulin.⁹

The TGA reproduces these processes *in vitro* by initiating coagulation in platelet-poor plasma (PPP) or platelet-rich plasma (PRP), using (small) amounts of TF (and phospholipids [PL] as a platelet substitute in PPP). Thrombin activity is continuously monitored over time via a fluorogenic peptide substrate cleaved by the active enzyme. The first derivative is calculated from the resulting sigmoidal curve in order to reflect the slope of the curve at the respective time points recorded. Calibration against a thrombin standard finally yields the actual “thrombogram,” which provides a global

representation of the kinetics of combined thrombin formation and inhibition over time (→Fig. 1A).³

Several parameters are derived from the “thrombogram.” The lag time (LT) reflects the initiation phase until measurable thrombin initially appears. The peak thrombin (PT) indicates the maximal enzyme concentration reached. The time to peak (TTP) describes how rapidly this peak is achieved, while the endogenous thrombin potential (ETP), the area under the curve, represents the total amount of thrombin formed. An additional parameter is the velocity index (VI), which describes the rate of thrombin formation. Together, these parameters offer a dynamic and integrated profile of the pro- and anticoagulant mechanisms in clotting plasma examined by TGA *in vitro* (→Fig. 1A).^{3,10}

Currently Available TGA Platforms

The first practical implementation of continuous, fluorogenic thrombin measurement was the Calibrated Automated Thrombogram (CAT), developed in the early 2000s by

Hemker et al, with reagents still commercially available to date.¹¹ A unique feature of CAT is the application of an internal thrombin calibrator to correct for optical interferences (inner filter effect) and substrate consumption.^{12,13} Originally established as a semi-automated assay in the microtiter plate (MTP) format, this assay has also been made available as a fully automated version.¹⁴ However, MTP-based CAT remains the reference method in many research settings and has also provided the basis for TG analysis in various clinical studies.^{15–17} This is due to the fact that the method offers a high degree of flexibility with regard to the application of modified assay protocols. In addition, the use of PRP as sample material is possible in MTP-based CAT, whereas this option is not available with fully automated systems. At least one other fully automated method for determining TG is available at present. This system (Cerveron) differs fundamentally from the CAT method in terms of the relative plasma content in the reaction mixtures, the applied calibration method, as well as the composition of available reagents. Accordingly, due to lack of overall standardization, assay discrepancies between platforms exist.¹⁸

Clinical Applications of Thrombin Generation Assays

Independent of the TGA platform used, TF/PL-based reagents, albeit differing in composition between manufacturers, are currently available for assessing (i) bleeding or (ii) thrombotic tendencies, as well as (iii) anticoagulant therapies.³ The fundamental idea behind TGA was (and is) to replicate the physiological conditions of the plasma coagulation cascade as closely as possible. This explains the choice of TF, the principal molecule of the extrinsic pathway, as predominantly applied trigger reagent.¹¹ While tests for bleeding tendency are performed at relatively low TF concentrations to also cover the activity of the tenase complex (FVIII/FIX deficiency), reagents for testing a thrombotic tendency (e.g., AT deficiency) usually contain an intermediate TF concentration. In order to monitor anticoagulant therapies, higher TF concentrations are applied. Regardless of the clinical issue investigated, the validity of the results of TGA depends on both adequate pre-analytical and analytical conditions.^{5,6}

Pre-analytical and Analytical Variables

The reliability of TGA results strongly depends on pre-analytical sample handling. Blood should be collected into citrate tubes, avoiding prolonged stasis and excessive suction. PPP is obtained by double centrifugation, while PRP must be prepared to prevent spontaneous platelet activation. Corn trypsin inhibitor (CTI), added to the blood collection tubes, minimizes *ex vivo* activation of factor XII.¹⁹ Although some studies suggest that performing TGA at low TF concentrations (“bleeding”) may benefit from corresponding blockage of the intrinsic pathway, others did not show an advantage of using CTI.^{20–23} Current guidelines emphasize that the use of CTI remains debatable and is not recommended for routine practice.^{5,6}

Analytical conditions also require standardization. As mentioned above, the concentration of TF as well as the concentration, source, and composition of phospholipids influence assay results. Low TF concentrations are more sensitive to subtle coagulopathies but less reproducible, whereas higher concentrations yield more stable signals at the expense of sensitivity.³ Although the advent of automated instruments has the potential to reduce assay variability, correct handling of reagents, verification of their on-board stability, and assay verification/validation remain key.

Assessment of Bleeding Tendencies and Treatment Monitoring in Hemophilia

Often, the severity of hemophilia A or B does not correlate with residual factor activities, whereas patients with comparable FVIII/FIX plasma levels show markedly differing bleeding tendencies, reflecting individual differences in the overall capacity to generate thrombin.²⁴ Similarly, acquired hemophilia or the development of anti-drug (FVIII/-FIX) antibodies adds further complexity, as standard inhibitor or total antibody titers not always correlate with bleeding risk.²⁵ In such cases, TGA has the potential to offer more comprehensive assessment of overall hemostasis, helping to characterize individual bleeding or thrombotic phenotypes.²⁶

A wide range of hemophilia therapies, including plasma-derived and recombinant factor concentrates, extended half-life (EHL) products, bi-specific FVIII-mimicking antibodies, rebalancing strategies, including agents targeting AT or tissue factor pathway inhibitor (TFPI), as well as gene therapies, can be, and have been, evaluated using TGA. This assay has been, and continues to be, used extensively in clinical approval studies, whereas the hemostatic potential of the individual drugs is particularly reflected by the TGA:PT and TGA:ETP parameters.²⁷

It should be noted that even in currently published study data, the semi-automated MTP-CAT remains the primary method used.^{15–17} It must be assumed that included patient samples were analyzed under best possible (pre)analytical conditions. However, it remains to be determined whether such study results can also be reproduced in clinical practice when using distinct TGA systems and/or differently composed reagents.

The data presented in **Fig. 1B** exemplify the relationship between categorized emicizumab plasma levels and thrombin generation (TGA:ETP) as determined by an automated platform. Although a general correlation can be acknowledged, the overall dispersion of individual measurements underscores the need for longitudinal evaluation of each individual patient, including clinical data. Corresponding evaluation is essential for assessing the potential utility of (adapted) TGA as a parameter in therapeutic monitoring.^{28,29}

The use of TGA in routine diagnostics is currently particularly discussed for monitoring rebalancing therapies. This is due to the fact that, at least at present, there is no established routine test available for the targeted monitoring of the active substances or, in case of anti-TFPI-antibodies, (residual) target (TFPI) activity.^{10,30–32}

Assessment of Thrombotic Disorders

Thrombin generation assays have been increasingly explored as tools to predict thrombotic risk across various clinical settings. Several studies suggest that elevated thrombin generation parameters, such as TGA:PT and TGA:ETP, might be associated with a higher likelihood of first or recurrent thrombosis and/or venous thromboembolism (VTE), particularly in individuals with inherited thrombophilia, or patients with antiphospholipid syndrome (APS).^{33–35} In cardiovascular disease, TG patterns might be useful for identifying patients with increased hypercoagulability, such as those with acute coronary syndromes or stent thrombosis, and may help detect individuals who could benefit from intensified antithrombotic treatment.³⁶ In cancer-associated thrombosis, elevated TG parameters appear to correlate with a higher risk of VTE and may help stratify patients into corresponding risk categories.³⁷ Overall, although further clinical validation is required, TGA shows promise as a complementary laboratory tool for more refined, individualized assessment of thrombotic risk across multiple clinical situations.

Monitoring of Anticoagulant Therapies

Treatment with direct oral anticoagulants (DOACs) requires estimation of the anticoagulant effect in vulnerable and/or high-risk patients. Although drug-specific assays for quantification of DOAC plasma levels are available, corresponding thresholds are partly empirical and may not accurately reflect the *in vivo* anticoagulant effect. The TGA as a global assay has the potential to provide a more comprehensive assessment of anticoagulant activity by capturing the dynamics of (residual) thrombin formation over time.^{2,38} Emerging evidence indicates that TGA might help assess the impact of DOACs, characterize patient-specific responses, and support the monitoring of reversal strategies.³⁹ In addition, TGA may aid in distinguishing anticoagulant effects from underlying coagulopathies. However, further clinical studies are needed to establish validated cut-offs and to determine the potential role of TGA in guiding personalized anticoagulant management.

TGA as an Evolving Tool for Various Research Purposes

Beyond routine clinical applications, the TGA is an adaptable experimental platform that can be tailored to investigate specific aspects of coagulation biology or drug response. The following examples only provide a limited insight into the possibilities associated with the TG methodology.

Monitoring the Activation of Factor VIII Molecules and the Effect of Inhibitory Antibodies

Since TGA reflects the overall capacity to generate thrombin, it has proven to be useful to reveal impairments caused by, e.g., anti-PEG antibodies that interfere with PEGylated EHL-FVIII molecules. Thus, it offers a physiologically relevant estimate of how antibody-FVIII interactions affect hemostatic efficacy⁴⁰ (→ Fig. 1C).

Assessment of Heparin Sensitivity

Adding defined concentrations of low-molecular-weight heparin (LMWH) to patient plasma allows investigation of heparin responsiveness. This approach is valuable in conditions with altered AT function, such as mutations in its heparin-binding site (HBS).⁴¹ By quantifying the inhibition of thrombin generation after heparin spiking, the assay can identify patients with, e.g., relative heparin resistance, supporting individualized anticoagulant dosing (→ Fig. 1D).

Monitoring the Protein C System

Incorporating TM into the TGA reaction enables evaluation of the protein C anticoagulant pathway in a functional context. The degree to which TM suppresses thrombin generation reflects the activity of generated activated protein C (APC) and protein S.^{42,43} This assay variant is particularly useful for assessing deficiencies of these inhibitors or the impact of agents that modulate this pathway.^{44,45}

Assessment and Application of Alternative Trigger Reagents

A key consideration in TGA is the choice of triggering reagent. Traditional TGA typically use TF to stimulate the extrinsic pathway, whereas the intrinsic pathway can be initiated with reagents such as kaolin, silica, or activated factor XI (FXIa).^{46–48} Although TF composition and concentration in commercial reagents vary, low TF levels provide increased sensitivity for detecting bleeding tendencies.³ However, TF-triggered TGA, though commonly used, might not be optimal in all clinical contexts. For instance, some studies suggest it may have limited ability to reflect the activity of emicizumab.²⁸ Indeed, it has been demonstrated that FXIa-triggered TGA has the potential to offer more sensitive and meaningful assessment of various hemophilia treatment strategies. Furthermore, it has also been proposed that combining TF with FXIa as a dual trigger may provide more physiological assessment and might better correlate with clinical treatment efficiency.⁴⁹

Limitations and Open Questions

Despite considerable technical refinement, several limitations and unresolved questions continue to restrict routine implementation of TGA. Reproducibility and inter-laboratory comparability remain major challenges. Even with automated platforms, variability persists due to differences in reagent composition, calibration, and analytical algorithms. Trigger selection introduces additional complexity. Low versus high tissue factor concentrations, FXIa-based initiation, or dual-trigger approaches yield different sensitivity profiles. Although each strategy may address specific clinical or research needs, current absence of a consensus on the optimal trigger hampers assay standardization. Pre-analytical factors pose another important limitation. Deviations in blood collection, centrifugation, freezing, or storage of samples may substantially influence assay results. PRP assays, limited to semi-automated CAT, are particularly vulnerable, as inadvertent platelet activation during preparation may

obscure physiologic responses.^{5,6} In general, well-defined pre-analytical protocols and internal quality controls remain essential. Biological variability also contributes to uncertainties. Lipid content, inflammatory status, hematocrit, and other patient-specific factors may modulate thrombin kinetics.⁵⁰ Another open question concerns the clinical interpretability of TGA results. Although associations between TGA parameters and bleeding or thrombotic tendencies have been described, validated decision thresholds are lacking, and it remains uncertain to what extent *in vitro* TG really reflects *in vivo* hemostatic performance.²⁴ Accordingly, prospective studies linking (standardized) TGA results to clinical outcomes are required to define the potential role of TGA in routine diagnostics.

Conclusion

Thrombin generation assays offer a dynamic and integrative assessment of plasmatic coagulation that extends well beyond traditional endpoint tests. Their ability to capture the combined kinetics of thrombin formation and inhibition provides valuable insight into bleeding tendencies, thrombotic risk, and anticoagulant effects, while (system-dependent) methodological adaptability makes TGA a highly flexible research platform for exploring coagulation biology and drug mechanisms. Despite this broad potential, substantial barriers still limit widespread diagnostic implementation. Variability introduced by trigger selection, reagent composition, pre-analytical factors, and platform differences continues to challenge inter-laboratory comparability while clinically validated decision thresholds remain lacking. Moreover, the relationship between *in vitro* thrombin-generation profiles and *in vivo* hemostatic efficacy is not yet fully established. Continued efforts in assay harmonization and prospective clinical validation will be essential. Addressing these methodological and clinical gaps may allow TGA to assume a complementary role alongside routine coagulation assays and to contribute to more individualized and mechanistically informed hemostatic assessment.

Authors' Contributions

J.M.: wrote the manuscript; B.P. and J.O.: provided additional scientific/clinical data. All authors reviewed, revised, and finally agreed on the final version of the manuscript.

Conflict of Interest

B.P. has received institutional grants for research from Biotest, Octapharma, and NovoNordisk as well as honoraria for lectures or consultancy from Novo-Nordisk and Octapharma. J.O. has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum, and Takeda and has received consultancy, speakers bureau, honoraria, and scientific advisory board honorarium from Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda. J.M. has

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