# Assessment of Early Thromboelastometric Variables from Extrinsically Activated Assays With and Without Aprotinin for Rapid Detection of Fibrinolysis

Daniel Dirkmann, Dr. med., Klaus Görlinger, Dr. med., and Jürgen Peters, Prof. Dr. med.

**BACKGROUND:** Although thromboelastometry (ROTEM®) and thrombelastography can be used for bedside diagnosis of fibrinolysis, the time needed for detection is often prolonged. Since untreated fibrinolysis can result in consumption of coagulation factors and bleeding, early diagnosis and decision making are desirable. Accordingly, we assessed ROTEM variables from extrinsically activated assays with (APTEM®) and without (EXTEM®) addition of aprotinin for their ability to rapidly identify fibrinolysis. Specifically, we tested the hypotheses that prolonged clotting time, clot formation time, low clot firmness (at 5, 10, 15, and 20 minutes, designated A5, A10, A15, and A20, respectively), low maximum clot firmness (MCF) in EXTEM assays, and differences in these variables from parallel APTEM and EXTEM assays (designated as Δvariables) predict fibrinolysis.

**METHODS:** Data from 411 thromboelastometric measurements (obtained from 352 patients) with fibrinolysis and from 2537 measurements without fibrinolysis (obtained from 1605 patients) were assessed and analyzed using receiver operating characteristics. Data were analyzed as a pooled fibrinolysis cohort, and subanalyses were performed from sets assigned to categories of fibrinolysis related to the timing of thrombus lysis (i.e., a decrease of clot firmness to <15% of MCF within 30, 45, and 60 minutes, respectively). A lower 95% confidence limit of the area under the receiver operating characteristic curve (AUC [SE] <0.6) was considered a failure to substantially improve detection of increased fibrinolysis. AUCs were compared to identify the variable providing the best predictive association with fibrinolysis. As a secondary end point, optimum cutoff values at the point estimate corresponding to the greatest Youden index were calculated along with the respective sensitivities and specificities.

**RESULTS:** In the pooled cohort, clot formation time (AUC: 0.652 [0.016]), α-angle (AUC: 0.675 [0.015]), A5 (AUC: 0.718 [0.013]), A10 (AUC: 0.734 [0.0.13]), A15 (AUC: 0.752 [0.013]), A20 (AUC: 0.771 [0.013]), and MCF (AUC: 0.799 [0.012]) predicted fibrinolysis. Fibrinolysis was also predicted by ΔA15 (AUC: 0.675 [0.016]), ΔA20 (AUC: 0.719 [0.015]), and ΔMCF (AUC: 0.812 [0.013]). AUCs increased in a time-related fashion. The ability to predict subsequent fibrinolysis based on thromboelastometry was higher when it occurred early rather than later during testing. However, for prediction of late fibrinolysis, only MCF (AUC: 0.655 [0.025]) appears to be potentially clinically useful.

**CONCLUSIONS:** Low early values of clot firmness in extrinsically activated thromboelastometric assays are associated with fibrinolysis and improve its early detection. Additional assays with aprotinin fail to improve the early diagnosis of fibrinolysis compared with assays without aprotinin. (Anesth Analg 2014;119:533–42)

While localized fibrinolysis is an essential, physiological process, extensive systemic fibrinolysis occurs when the precisely coordinated balance between fibrinolytic activators and their inhibitors is disturbed.[1] The incidence of fibrinolysis ranges from 9% to 75% in patients undergoing liver transplantation,[2,3] 14% in patients undergoing cardiopulmonary bypass,[4] and between 6% and 25% in those with severe multiple trauma.[5–8] Furthermore, fibrinolysis can occur with brain injury and major brain surgery,[9,10] postpartum hemorrhage,[11] under conditions of extracorporeal circulation,[4,12] and in settings with a disturbed microcirculation and shock.[13,14] Exaggerated fibrinolysis frequently leads to hemorrhage and allogeneic blood transfusion and is associated with morbidity and mortality in patients with[6,15–17] and without trauma[17] and after cardiopulmonary bypass surgery.[4] Nevertheless, empiric prophylactic treatment with antifibrinolytic drugs may result in severe adverse events including increased mortality when given >3 hours after injury.[18–25] Furthermore, although fibrinolysis is frequent during liver transplantation, current guidelines on the management of severe perioperative bleeding recommend omitting the prophylactic use of antifibrinolytics.[26]

The euglobulin lysis time is considered the "gold standard" for the diagnosis of fibrinolysis.[27] However, this test is complex, time consuming, and unsuitable for supporting rapid clinical decision making. For this reason, viscoelastic tests such as thrombelastography (TEG®, Haemonetics, Braintree, MA) and thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany) are commonly used clinically for point-of-care diagnosis of fibrinolysis.[28,29]

From the Klinik für Anästhesiologie und Intensivmedizin, Universität Duisburg-Essen, Universitätsklinikum Essen, Essen, Germany.

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Address correspondence to Daniel Dirkmann, Dr. med., Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Hufelandstraße 55, D-45122 Essen, Germany. Address e-mail to Daniel.Dirkmann@uk-essen.de.


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According to the manufacturer of the ROTEM device, a loss in the maximum clot firmness (MCF) >15% during measurements is defined as fibrinolysis. The device automatically detects this variable, and the associated time point is designated as lysis onset time. Furthermore, to quantify the extent of fibrinolysis, the percentage of the MCF due to fibrinolysis is automatically detected at 30, 45, and 60 minutes after initial clotting time (CT). These latter variables are referred to as lysis index (LI) 30, 45, and 60, respectively. Lysis onset time may vary widely, ranging from a few minutes up to >1 hour, and earlier clot lysis is associated with increased mortality.[8,17]

While there are definitions for the diagnosis of fibrinolysis, in clinical practice, the time to the onset of lysis is frequently unduly long in the setting of massive hemorrhage. To fill this diagnostic gap, it has been suggested that variables in extrinsically activated thromboelastometric assays with aprotinin (APTEM®, TEM International GmbH, Munich, Germany) compared with corresponding variables from extrinsically activated assays without aprotinin (EXTEM®, TEM International GmbH, Munich, Germany) allow for early diagnosis of fibrinolysis.[6,30–32] An association between a low MCF and the incidence of fibrinolysis has been suggested in small cohorts of trauma ($n = 5$)[6] and liver transplant ($n = 11$) patients having fibrinolysis.[33]

Accordingly, we assessed thromboelastometric variables from extrinsically activated assays with (APTEM) and without (EXTEM) for their ability to rapidly identify fibrinolysis. Specifically, we tested the hypotheses that prolonged CT, clot formation time (CFT), low clot firmness (at 5, 10, 15, and 20 minutes, designated A5, A10, A15, and A20, respectively), low MCF, and differences in these variables with and without aprotinin (designated as Δvariable) predict fibrinolysis.

## METHODS

After approval by the local ethics committee, thromboelastometric data sets from our institutional database of patients undergoing different types of noncardiac surgery (mainly liver transplantation) originating over a 10-year period were reviewed for inclusion. Due to the retrospective and anonymous character of our analyses, the necessity to obtain written informed consent was waived by the ethics committee. Thromboelastometry is a viscoelastic test based on thrombelastography originally described by Hartert[34] in 1948, and its details are described elsewhere.[28] In our institution, thromboelastometric assays are routinely performed during liver transplantation at defined time points and when indicated by clinical circumstances, as well as during other surgeries in the setting of excessive bleeding and/or suspected coagulopathy.

Measurements from the identified data were included in this analysis, if both EXTEM and APTEM assays were available and the assays had been started within 10 minutes of one another. If >1 measurement set was available for a single patient, both were included if they had been taken at different time points (e.g., preanhepatic, anhepatic, and neohepatic phase during liver transplantation). Respective measurement sets from individuals were statistically handled as independent measurements since data sets derived from each individual, from a clinical point of view, were separated from the next one by a clinically relevant time interval and interventions such as liver vascular clamping and declamping (reperfusion) and possibly, also by marked blood loss, intravascular volume and coagulation factor replacement, and/or other differences in coagulation status. The following variables were determined: CT, CFT, α-angle (AA), A5, A10, A15, A20, MCF, and LI (residual clot firmness compared with MCF expressed as percentage of MCF) determined 30, 45, and 60 minutes (designated LI30, LI45, and LI60, respectively) after CT (Fig. 1). Measurements were excluded if their CT was <20 or >1200 seconds, or if the MCF exceeded 90 mm.

To qualify data as fibrinolysis, we used the manufacturer's definition (i.e., a decrease in MCF by >15% during measurements).[35] Accordingly, a LI30, LI45, or LI60 of <85% or maximum lysis >15% in EXTEM assays was considered fibrinolysis. Fibrinolysis data were analyzed as a pooled cohort. Furthermore, to assess the ability of early thromboelastometric variables to detect fibrinolysis with various onset times, data sets were also assigned to 4 subcategories. These latter subcategories were designated according to the time from initial clotting to clot lysis of >90% (i.e., lysis time as defined by the manufacturer). Specifically, fibrinolysis was classified as "very early" if LI30 in EXTEM assays was <10% (LI30 <10%) or if there was no clot formation. Fibrinolysis was characterized as "early" if clot breakdown to <10% occurred within 45 minutes (LI45 <10%) and as "intermediate" if clot breakdown occurred between 45 and 60 minutes (LI60 <10%). If clot breakdown occurred after >60 minutes, fibrinolysis was characterized as "late."

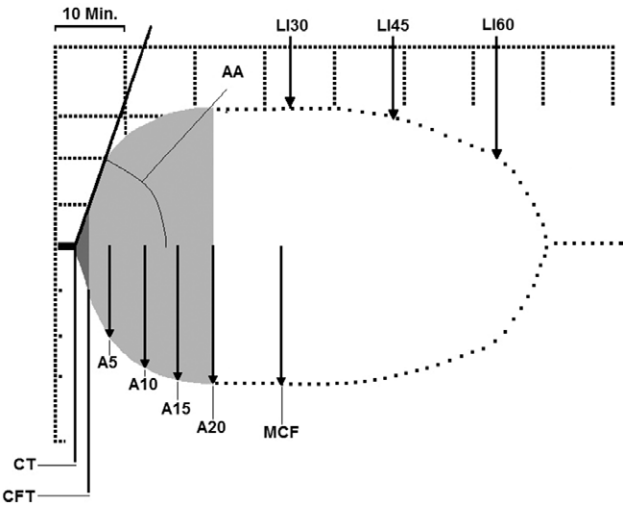


**Figure 1.** Schematic thromboelastometric tracing explaining the time course and the variables assessed during thromboelastometric measurements. Clotting time (CT) indicates the time from initiation of the test until initial clotting is detected (i.e., clot amplitude 2 mm). Clot formation time (CFT) indicates the time from CT until the clot amplitude has reached 20 mm. α-Angle (AA) is the angle measured between the horizontal baseline before initiation of clot formation and a tangential to the tracing. A5, A10, A15, and A20 indicate the amplitude (millimeters) of clot firmness 5, 10, 15, and 20 minutes after CT, respectively, and MCF (millimeters) is the maximum clot firmness eventually reached during measurements. Lysis index (LI) 30, 45, and 60 indicate the percentage of MCF still present at 30, 45, and 60 minutes after CT, respectively.

We also included measurements obtained from a control cohort of patients not demonstrating fibrinolysis. Assays were excluded from the control group if they were terminated earlier than 60 minutes (since this does not allow measurement of LI60). Furthermore, if clot lysis exceeded 15% at any time during measurements, data from the assays were assigned to the increased fibrinolysis group, not the control group.

Finally, all thromboelastometric data and traces were evaluated for their technical adequacy by a single investigator. Thromboelastometric traces with technical irregularities, which might have impaired correct measurements, were excluded from the analyses.

### Data Analyses

Since data were not normally distributed, according to the D'Agostino and Pearson omnibus normality test, descriptive data are presented as median (range). Differences in values of thromboelastometric variables from corresponding EXTEM and APTEM assays from patients classified as showing fibrinolysis or no fibrinolysis were calculated using Excel (Microsoft® Excel 2008 for MAC, Microsoft, Redmond, WA), considering each data set statistically independent.

Based on the recommendations of others,[6,30–32] we expected a shortening in CT and CFT, respectively, and an increase in the AA, early clot firmness values (i.e., A5, A10, A15, and A20, respectively), and MCF in those assays containing aprotinin (APTEM) compared with the corresponding EXTEM assays. Accordingly, differences in values of corresponding variables from these 2 assays were calculated as EXTEM minus APTEM values for CTs (i.e., CTs and CFTs) and as APTEM minus EXTEM for other variables. Differences are denominated as Δ values (differences) of the respective intraindividual corresponding variables. Receiver operating characteristics were used to assess the ability of the calculated Δ values and the variables obtained from the EXTEM assay alone, respectively, for early detection of fibrinolysis. Results are presented as area under the receiver operating characteristic (ROC) curve (AUC [SE]). The overall test performance, assessed as the AUC, was graded based on the traditional academic point system (0.5–0.6: fail; 0.6–0.7: poor; 0.70–0.80: fair; 0.80–0.90: good; and 0.90–1.00: excellent). Variables failing to substantially improve the detection of fibrinolysis, as indicated by a lower 95% confidence limit of the AUC <0.6, were not analyzed further. Areas under the ROC curve having 95% confidence limits >0.6 were statistically compared using the method of Hanley and McNeil[36] within the pooled cohort and in the subcategories in the time-related sequence, that is, with respect to the occurrence of these variables during each thromboelastometric measurement. This served to assess whether waiting for assessment of a later variable would significantly improve test performance. Furthermore, AUCs were compared between EXTEM variables and the difference in the respective variable between EXTEM and APTEM assays to assess whether performing additional aprotinin-modified assays would improve test performance. MedCalc (version 13, MedCalc Software, Ostend, Belgium) was used for all statistical analyses. An a priori α error $P$ of <0.05 was considered statistically significant.

As a secondary end point, cutoff values at the point estimate corresponding to the greatest Youden index[37] (i.e., the largest difference between sensitivity and 1 − specificity over all points of the ROC curve) were calculated along with the respective sensitivities and specificities with their corresponding sensitivities (95% confidence interval [CI]) and specificities (95% CI). These cutoff values frequently are considered a potential "optimum" cutoff, although the optimum biological cutoff may differ. CIs were computed based on the observed proportion using Clopper and Pearson's method.[38] Furthermore, positive and negative predictive values for these respective optimum cutoff values were calculated not considering uncertainty in the selection of the cutoff.

## RESULTS

Data demonstrating fibrinolysis were available from 411 measurements obtained from 352 patients. Control data included 2537 measurements obtained from 1605 patients not classified as having fibrinolysis. The patient characteristics for patients with and without fibrinolysis are shown in Table 1. The majority of patients in each group underwent liver transplant surgery.

Descriptive data for the thromboelastometric results based on subcategories of fibrinolysis (i.e., very early, early, intermediate, and late, respectively) as well as pooled fibrinolysis data and those for controls without are listed in Table 2. Representative thromboelastometric tracings of corresponding EXTEM and APTEM assays are shown in Figure 2.

### Reliability of EXTEM Assays Alone

Analyzing EXTEM variables from the pooled data set (Table 3) demonstrated that only CT (AUC: 0.559 [0.015]) failed to identify fibrinolysis. In contrast, CFT (AUC: 0.66 [0.016]), AA (AUC: 0.675 [0.015]), and A5 (AUC: 0.718 [0.013]) were able to identify increased fibrinolysis, albeit

**Table 1. Type of Surgery for Patients With ($n$ = 411) and Without ($n$ = 2537) Thromboelastometric Variables Fulfilling the Criteria for Fibrinolysis**

| Procedures | No. of measurement sets |
|---|---|
| Fibrinolysis cohort | |
| Liver transplantation | 352 |
| Combined pancreas/kidney transplantation | 7 |
| Multiple trauma | 3 |
| Ruptured aortic aneurysm | 2 |
| Liver resection | 3 |
| Radical cystoprostatectomy | 1 |
| Other abdominal surgery | 3 |
| Various surgical procedures/settings | 40 |
| Total | 411 |
| Nonfibrinolysis cohort | |
| Liver transplantation | 1664 |
| Combined pancreas/kidney transplantation | 21 |
| Kidney transplantation | 17 |
| Multiple trauma | 56 |
| (Ruptured) aortic aneurysm | 10 |
| Radical cystoprostatectomy | 2 |
| Liver resection | 72 |
| Other abdominal surgery | 245 |
| Thoracic surgery | 2 |
| Neurosurgical procedures | 80 |
| Orthopedic/trauma surgery | 97 |
| Postpartum hemorrhage | 3 |
| Intensive care patients | 89 |
| Various surgical procedures/settings | 179 |
| Total | 2537 |

**Table 2. Values of the Thromboelastometric Variables from the EXTEM® and APTEM® Assays for Patients With and Without Fibrinolysis**

| | CT (s) | CFT (s) | AA (°) | A5 (mm) | A10 (mm) | A15 (mm) | A 20 (mm) | MCF (mm) | LI30 (%) | LI45 (%) | LI60 (%) | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No fibrinolysis ($n$ = 2537) | | | | | | | | | | | | |
| EXTEM | 59 (20–294) | 167 (26–5160) | 62 (13–86) | 28 (3–78) | 38 (4–82) | 42 (6–83) | 45 (6–84) | 48 (10–85) | n.a. | n.a. | 95 (86–98) | n.a. |
| APTEM | 67 (20–1120) | 169 (23–3943) | 62 (13–85) | 28 (3–76) | 38 (5–82) | 42 (5–83) | 45 (7–84) | 48 (9–87) | n.a. | n.a. | 96 (86–98) | n.a. |
| Fibrinolysis (subcategories pooled) ($n$ = 411) | | | | | | | | | | | | |
| EXTEM | 64 (20–3144) | 323 (56–4879) | 52 (15–80) | 19 (0–55) | 26 (0–65) | 30 (0–68) | 30.5 (0–69) | 33 (4–69) | 88 (0–98) | 4 (0–98) | 0 (0–85) | 1315 (66–7277) |
| APTEM | 68 (11–935) | 299.5 (28–3979) | 48 (14–81) | 19 (3–64) | 27 (5–73) | 32 (6–76) | 34 (6–77) | 39 (8–78) | 98 (87–100) | 98 (88–100) | 96 (84–100) | n.a. |
| Very early fibrinolysis ($n$ = 135) | | | | | | | | | | | | |
| EXTEM | 79 (21–3144) | 546 (80–4879) | 45 (20–75) | 15 (0–43) | 19 (0–53) | 15 (0–57) | 1 (0–57) | 21 (4–58) | 0 (0–10) | 0 (0–0) | 0 (0–0) | 476 (66–1394) |
| APTEM | 79 (17–935) | 404.5 (77–2979) | 40.5 (16–74) | 15 (3–43) | 23 (5–54) | 27 (6–58) | 29 (6–60) | 34 (8–61) | 98 (87–100) | 98 (89–100) | 97 (87–100) | n.a. |
| Early fibrinolysis ($n$ = 84) | | | | | | | | | | | | |
| EXTEM | 63.5 (24–436) | 299 (76–3004) | 51.5 (15–75) | 20 (5–47) | 27 (9–57) | 32 (12–60) | 33 (11–60) | 34 (13–61) | 74.5 (11–98) | 0 (0–10) | 0 (0–0) | 1115 (581–2483) |
| APTEM | 61 (11–33) | 284 (86–2104) | 50 (14–73) | 20 (6–44) | 28 (10–54) | 32 (13–58) | 35 (15–60) | 39 (20–61) | 98 (97–100) | 98 (92–100) | 97 (88–98) | n.a. |
| Intermediate fibrinolysis ($n$ = 86) | | | | | | | | | | | | |
| EXTEM | 61 (25–380) | 254 (56–4283) | 55.5 (19–79) | 22 (5–55) | 29.5 (7–65) | 34 (9–68) | 35.5 (9–69) | 37.4 (10–69) | 98 (24–98) | 48 (9–91) | 0 (0–10) | 1653 (894–3283) |
| APTEM | 73.5 (26–905) | 260 (28–3383) | 50 (17–81) | 21 (4–64) | 29.5 (6–73) | 34.5 (6–76) | 37 (8–77) | 40.5 (10–78) | 98 (95–100) | 98 (88–100) | 96 (86–100) | n.a. |
| Late fibrinolysis ($n$ = 106) | | | | | | | | | | | | |
| EXTEM | 56.5 (20–414) | 219.5 (59–1321) | 57 (26–80) | 24 (6–51) | 32 (9–61) | 37 (12–63) | 40 (14–64) | 42 (18–66) | 98 (88–98) | 90.5 (60–98) | 52 (11–85) | 2600 (1394–7277) |
| APTEM | 67 (13–531) | 223 (59–792) | 55 (26–80) | 23 (4–52) | 31 (6–60) | 36 (7–63) | 38.5 (8–65) | 42 (14–74) | 98 (95–98) | 98 (90–98) | 95 (84–98) | n.a. |

Data are given as median (minimum–maximum).

CT = clotting time; CFT = clot formation time; AA = $\alpha$-angle; A5, A10, A15, and A20 = clot firmness after 5, 10, 15, and 20 minutes, respectively; MCF = maximum clot firmness; n.a. = not applicable.

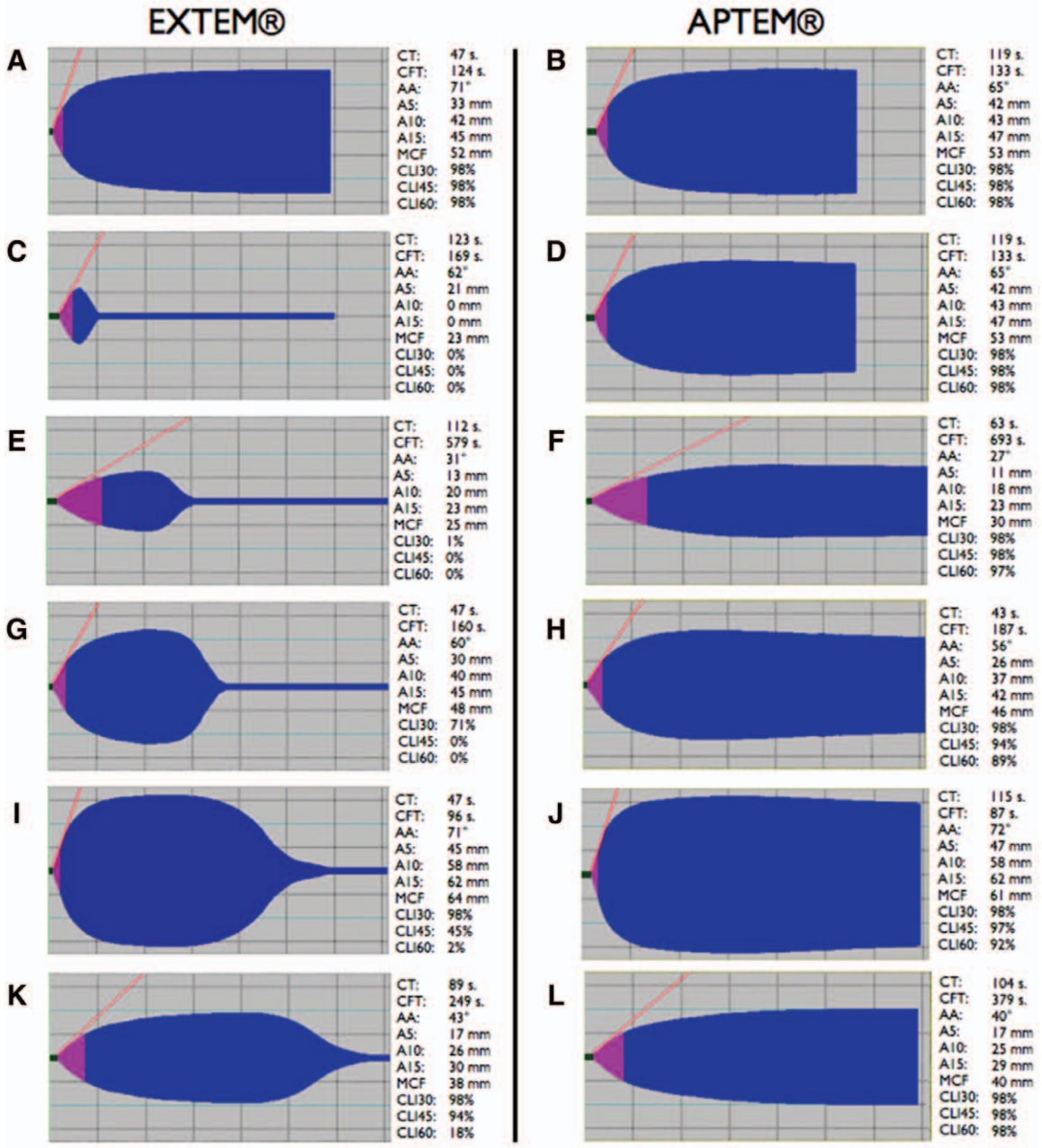


**Figure 2.** Representative thromboelastometry (ROTEM®, TEM International GmbH, Munich, Germany) tracings with corresponding tissue factor activated (EXTEM®; left panel) and tissue factor with aprotinin assay (APTEM®; right panel) from a patient without fibrinolysis (A and B), 2 patients with very early fibrinolysis (C–F), and patients with early (G and H), intermediate (I and J), and late (K and L) fibrinolysis. These tracings demonstrate the broad spectrum of fibrinolysis patterns occurring in clinical settings and were all encountered in our study cohort. CT = clotting time; CFT = clot formation time; AA = α-angle; A5, A10, A15 = clot firmness after 5, 10, and 15 minutes, respectively; MCF = maximum clot firmness; CLI30, CLI45, CLI60 = residual clot firmness compared with MCF expressed as percentage of MCF determined 30, 45, and 60 minutes after CT, respectively.

demonstrating poor overall test performance. Later values of clot firmness, that is, A10 (AUC: 0.734 [0.013]), A15 (AUC: 0.752 [0.013]), A20 (AUC: 0.771 [0.013]), and MCF (AUC: 0.799 [0.012]) demonstrated fair performance in identifying fibrinolysis (Table 3). Statistical comparison of the areas under the ROC curves revealed that overall test performance significantly increased in a time-related fashion (Table 3).

Except for MCF and ΔMCF, respectively, variables derived from EXTEM assays alone demonstrated significantly greater areas under the ROC curves than differences in variables between EXTEM and APTEM assays (Table 3).

Subcohort analyses demonstrated that all variables predicted very early fibrinolysis. However, CT failed to predict early and intermediate fibrinolysis and only MCF predicted late fibrinolysis.

### Reliability of Differences Between APTEM and EXTEM Assays

The ROC curves analyzing the pooled data revealed that differences in the thromboelastometric variables usually obtainable in <15 minutes during thromboelastometric measurements (i.e., ΔCT, ΔCFT, ΔAA, ΔA5, and ΔA10,

**Table 3. Receiver Operating Characteristics Results for Variables from EXTEM® Assays to Detect Fibrinolysis**

| Variable | AUC (SE) | "Optimum" cutoff | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|
| Pooled | | | | | | |
| CT (s) | 0.559 (0.016) | | | | | |
| CFT (S) | 0.652 (0.016); $P < 0.0001$* | >173.5 | 74.32 (69.26–78.94) | 51.78 (49.81–53.75) | 0.612 | 0.396 |
| AA (°) | 0.675 (0.015); $P < 0.0001$* | <60.5 | 72.34 (67.17–77.11) | 54.8 (52.78–56.81) | 0.592 | 0.416 |
| A5 (mm) | 0.718 (0.013); $P < 0.0001$†; $P < 0.0001$* | <25.5 | 74.7 (70.2–78.83) | 58.47 (56.47–60.34) | 0.583 | 0.424 |
| A10 (mm) | 0.734 (0.013); $P < 0.0001$†; $P < 0.0001$* | <33.5 | 72.02 (67.41–76.31) | 62.48 (60.56–64.36) | 0.55 | 0.449 |
| A15 (mm) | 0.752 (0.013); $P < 0.0001$†; $P < 0.0001$* | <33.5 | 62.29 (57.4–66.99) | 74.18 (72.42–75.88) | 0.478 | 0.529 |
| A20 (mm) | 0.771 (0.013); $P < 0.0001$†; $P = 0.0043$* | <35.5 | 63.64 (58.75–68.32) | 76.15 (74.45–77.8) | 0.477 | 0.53 |
| MCF (mm) | 0.799 (0.012); $P < 0.0001$† | <40.5 | 69.34 (64.64–73.77) | 75.13 (73.40–76.8) | 0.502 | 0.437 |
| Very early fibrinolysis | | | | | | |
| CT (s) | 0.65 (0.025) | >90.5 | 42.96 (34.48–51.76) | 81.16 (79.58–82.66) | 0.366 | 0.642 |
| CFT (s) | 0.752 (0.021); $P < 0.0001$†; $P < 0.0006$* | <189.5 | 86.3 (76.25–93.23) | 57.3 (55.34–59.24) | 0.623 | 0.384 |
| AA (°) | 0.788 (0.019); $P < 0.0001$* | <57.5 | 86.05 (76.89–92.58) | 61.53 (59.55–63.48) | 0.605 | 0.402 |
| A5 (mm) | 0.85 (0.015); $P < 0.0001$* | <21.5 | 85.19 (78.05–90.71) | 70.63 (68.82–72.4) | 0.569 | 0.438 |
| A10 (mm) | 0.879 (0.014); $P < 0.0001$* | <27.5 | 82.22 (74.71–88.26) | 77.85 (76.18–79.45) | 0.535 | 0.471 |
| A15 (mm) | 0.922 (0.012); $P < 0.0001$† | <27.5 | 78.52 (70.63–85.12) | 87.58 (86.24–88.84) | 0.494 | 0.512 |
| A20 (mm) | 0.961 (0.009); $P < 0.0001$† | <26.5 | 88.55 (81.82–93.45) | 92.55 (91.46–93.52) | 0.51 | 0.495 |
| MCF (mm) | 0.952 (0.009) | <34.5 | 88.15 (81.47–93.07) | 88.96 (87.68–90.16) | 0.519 | 0.486 |
| Early fibrinolysis | | | | | | |
| CT (s) | 0.536 (0.031) | | | | | |
| CFT (s) | 0.661 (0.028); $P = 0.0045$* | >173.5 | 74.67 (63.3–84.01) | 51.78 (49.81–53.75) | 0.613 | 0.395 |
| AA (°) | 0.674 (0.03); $P = 0.0001$* | <58.5 | 71.43 (59.38–81.6) | 58.98 (56.98–60.96) | 0.57 | 0.437 |
| A5 (mm) | 0.692 (0.027); $P < 0.0001$* | <22.5 | 61.9 (50.66–72.29) | 67.48 (65.62–69.3) | 0.501 | 0.507 |
| A10 (mm) | 0.705 (0.027); $P = 0.0011$* | <29.5 | 60.71 (49.45–71.2) | 72.61 (70.83–74.33) | 0.477 | 0.53 |
| A15 (mm) | 0.717 (0.027); $P = 0.0123$* | <33.5 | 60.71 (49.45–71.2) | 74.18 (72.43–75.88) | 0.472 | 0.536 |
| A20 (mm) | 0.743 (0.0261) | <34.5 | 61.9 (50.66–72.29) | 78.28 (76.62–79.87) | 0.463 | 0.544 |
| MCF (mm) | 0.797 (0.025); $P < 0.0001$† | <40.5 | 72.62 (61.8–81.79) | 75.13 (73.4–76.8) | 0.514 | 0.493 |
| Intermediate fibrinolysis | | | | | | |
| CT (s) | 0.52 (0.031) | | | | | |
| CFT (s) | 0.662 (0.028); $P = 0.006$* | >154.5 | 81.25 (70.97–89.11) | 45.24 (43.29–47.21) | 0.664 | 0.343 |
| AA (°) | 0.664 (0.028); $P > 0.0006$* | <65.5 | 85.9 (76.17–92.74) | 41.77 (39.79–43.78) | 0.694 | 0.313 |
| A5 (mm) | 0.681 (0.27); $P = 0.0009$* | <25.5 | 70.93 (60.14–80.22) | 58.42 (56.47–60.34) | 0.571 | 0.437 |
| A10 (mm) | 0.685 (0.27); $P = 0.0024$* | <33.5 | 66.28 (55.28–76.12) | 62.48 (60.56–64.36) | 0.537 | 0.47 |
| A15 (mm) | 0.642 (0.028) | <39.5 | 69.77 (58.92–79.21) | 59.09 (57.14–61.01) | 0.564 | 0.444 |
| A20 (mm) | 0.689 (0.027); $P = 0.0166$* | <43.5 | 74.42 (63.87–83.22) | 53.88 (51.92–55.84) | 0.603 | 0.405 |
| MCF (mm) | 0.737 (0.027) | <46.5 | 77.91 (67.67–86.14) | 56.72 (54.77–58.66) | 0.601 | 0.406 |
| Late fibrinolysis | | | | | | |
| CT (s) | 0.508 (0.028) | | | | | |
| CFT (s) | 0.592 (0.025) | | | | | |
| AA (°) | 0.582 (0.027) | | | | | |
| A5 (mm) | 0.602 (0.0245); $P = 0.0217$* | | | | | |
| A10 (mm) | 0.612 (0.025); $P = 0.0034$†; $P = 0.0217$* | | | | | |
| A15 (mm) | 0.615 (0.025); $P = 0.0039$* | | | | | |
| A20 (mm) | 0.616 (0.025); $P = 0.0188$* | | | | | |
| MCF (mm) | 0.655 (0.025); $P < 0.0001$† | <48.5 | 74.53 (65.14–82.49) | 49.55 (47.58–51.51) | 0.623 | 0.385 |

AUC (SE) and "optimum" cutoff (Youden index) with corresponding sensitivity (confidence interval), specificity (confidence interval), and positive and negative predictive values derived from the data. Results are presented for the pooled data including all increased fibrinolysis data sets and for subcohorts with very early, early, intermediate, and late fibrinolysis, respectively.

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CT = clotting time; CFT = clot formation time; AA = α-angle; A5, A10, A15, and A20 = clot firmness after 5, 10, 15, and 20 minutes, respectively; MCF = maximum clot firmness.

*$P$ values indicate differences in the AUC compared with the respective variable from Table 4.

†$P$ values indicate differences in the AUC compared with the variable preceding in time within the same measurement set providing at least a lower 95% confidence limit of the AUC of 0.6.

respectively) failed to predict fibrinolysis, as reflected by a lower 95% confidence limit of the areas under the ROC curve <0.6 (Table 4). In contrast, variables obtained later during the measurements demonstrated greater AUC values. Specifically, ΔA15 (AUC: 0.675 [0.016]) and ΔA20 (AUC: 0.719 [0.015]) demonstrated poor overall test performance, while only ΔMCF (0.812 [0.013]) demonstrated fair overall test performance for predicting fibrinolysis (Table 4).

Subcohort analyses demonstrated that differences among all variables predicted very early fibrinolysis, but

**Table 4. Receiver Operating Characteristics Results for Differences (Δ) Between Parallel APTEM® and EXTEM® Assays to Detect Fibrinolysis**

| Variable | AUC (SE) | Optimum cutoff | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|
| Fibrinolysis (pooled data) | | | | | | |
| ΔCT (s) | 0.562 (0.016) | | | | | |
| ΔCFT (s) | 0.578 (0.018) | | | | | |
| ΔAA (°) | 0.578 (0.017) | | | | | |
| ΔA5 (mm) | 0.564 (0.015) | | | | | |
| ΔA10 (mm) | 0.629 (0.016) | | | | | |
| ΔA15 (mm) | 0.675 (0.016) | >1.5 | 49.15 (44.22–54.09) | 77 (75.74–79.03) | 0.41 | 0.597 |
| ΔA20 (mm) | 0.719 (0.015); $P < 0.0001$* | >2.5 | 49.15 (44.22–54.09) | 86.52 (85.13–87.83) | 0.382 | 0.625 |
| ΔMCF (mm) | 0.812 (0.013); $P < 0.0001$* | >3.5 | 59.12 (54.20–63.92) | 89.4 (88.13–90.57) | 0.419 | 0.588 |
| Very early fibrinolysis | | | | | | |
| ΔCT (s) | 0.612 (0.028) | | | | | |
| ΔCFT (s) | 0.606 (0.033) | | | | | |
| ΔAA (°) | 0.528 (0.029) | | | | | |
| ΔA5 (mm) | 0.627 (0.024) | | | | | |
| ΔA10 (mm) | 0.782 (0.024); $P < 0.0001$* | >3.5 | 51.11 (42.37–59.81) | 92.87 (91.79–93.84) | 0.375 | 0.632 |
| ΔA15 (mm) | 0.905 (0.017); $P < 0.0001$* | >2.5 | 79.26 (71.44–85.75) | 86.76 (85.38–88.05) | 0.499 | 0.507 |
| ΔA20 (mm) | 0.966 (0.012); $P = 0.0024$* | >4.5 | 87.41 (80.61–92.49) | 95.03 (94.11–95.85) | 0.5 | 0.505 |
| ΔMCF (mm) | 0.971 (0.011) | >4.5 | 92.59 (86.8–96.39) | 92.94 (91.88–93.91) | 0.52 | 0.485 |
| Early fibrinolysis | | | | | | |
| ΔCT (s) | 0.586 (0.032) | | | | | |
| ΔCFT (s) | 0.537 (0.038) | | | | | |
| ΔAA (°) | 0.58 (0.036) | | | | | |
| ΔA5 (mm) | 0.536 (0.031) | | | | | |
| ΔA10 (mm) | 0.581 (0.032) | | | | | |
| ΔA15 (mm) | 0.621 (0.032) | | | | | |
| ΔA20 (mm) | 0.705 (0.031); $P < 0.0001$* | >0.5 | 70.24 (59.27–79.73) | 62 (60.08–63.9) | 0.554 | 0.454 |
| ΔMCF (mm) | 0.846 (0.027); $P < 0.0001$* | >2.5 | 76.19 (65.65–84.81) | 82.62 (81.09–84.07) | 0.501 | 0.505 |
| Intermediate fibrinolysis | | | | | | |
| ΔCT (s) | 0.501 (0.035) | | | | | |
| ΔCFT (s) | 0.518 (0.037) | | | | | |
| ΔAA (°) | 0.554 (0.034) | | | | | |
| ΔA5 (mm) | 0.554 (0.031) | | | | | |
| ΔA10 (mm) | 0.567 (0.031) | | | | | |
| ΔA15 (mm) | 0.582 (0.031) | | | | | |
| ΔA20 (mm) | 0.597 (0.03) | | | | | |
| ΔMCF (mm) | 0.769 (0.026) | >1.5 | 72.09 (61.38–81.23) | 72.84 (71.07–74.57) | 0.52 | 0.487 |
| Late fibrinolysis | | | | | | |
| ΔCT (s) | 0.529 (0.028) | | | | | |
| ΔCFT (s) | 0.501 (0.031) | | | | | |
| ΔAA (°) | 0.539 (0.033) | | | | | |
| ΔA5 (mm) | 0.519 (0.028) | | | | | |
| ΔA10 (mm) | 0.527 (0.029) | | | | | |
| ΔA15 (mm) | 0.505 (0.029) | | | | | |
| ΔA20 (mm) | 0.527 (0.03) | | | | | |
| ΔMCF (mm) | 0.623 (0.028) | | | | | |

AUC (SE) and "optimum" cutoff (Youden index) with corresponding sensitivities (confidence interval), specificities (confidence interval), and positive and negative predictive values. Results are presented for the pooled data including all fibrinolysis data sets and for subcohorts with very early, early, intermediate, and late fibrinolysis, respectively.

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CT = clotting time; CFT = clot formation time; AA = α-angle; A5, A10, A15, and A20 = clot firmness after 5, 10, 15, and 20 minutes, respectively; MCF = maximum clot firmness.

*$P$ values indicate differences in the AUC compared with the variable preceding in time within the same measurement set providing at least a lower 95% confidence limit of the AUC of 0.6.

only ΔA20 (AUC: 0.705 [0.031]) and ΔMCF (AUC: 0.846 [0.027]) predicted early increased fibrinolysis. Of note, all variables but ΔMCF (AUC: 0.769 [0.026]) failed to predict intermediate fibrinolysis and no difference in variables from EXTEM and APTEM assays predicted late fibrinolysis.

## DISCUSSION

Our data derived from a large cohort of patients demonstrate that low early values of clot firmness in extrinsically activated assays (e.g., EXTEM A5) are associated with subsequent fibrinolysis and improve its early detection, albeit with moderate reliability. Additional thromboelastometric assays with the addition aprotinin fail to substantially improve early diagnosis of fibrinolysis compared with assays without aprotinin. The predictive power of thromboelastometric early clot firmness is best with early, but not late fibrinolysis.

Early thromboelastometric variables are increasingly being used for fast, point-of-care assessment of coagulation in surgical patients.[39–41] Although viscoelastic assays like

thromboelastometry are capable of detecting fibrinolysis, its diagnosis can be delayed since fibrinolysis may become evident only after 45 minutes or longer following initial clot formation (CT). Accordingly, early assessment for fibrinolysis would allow for prompt initiation of antifibrinolytic therapy to potentially prevent progressive consumption of coagulation factors and platelets and subsequent life-threatening coagulopathic bleeding. This early diagnosis could further reduce the clinical need for inappropriate prophylactic treatment with antifibrinolytic drugs, which is associated with adverse effects.[18,19,25]

Different approaches using viscoelastic tests have been proposed to achieve faster assessment of fibrinolysis.[6,30–32] Levrat et al.,[6] for example, found in a cohort of 78 trauma patients (5 with fibrinolysis) that a 7-mm greater MCF in APTEM when compared with an EXTEM assay run in parallel predicted fibrinolysis (area under the ROC curve: 0.92). Furthermore, they suggested that an MCF using the EXTEM assay of <18 mm identified patients with fibrinolysis (area under the ROC curve: 1.0). Similarly, Steib et al.[33] reported that a thrombelastographic maximum amplitude <35 mm was associated with a 100% probability for developing fibrinolysis in 11 patients with fibrinolysis during liver transplantation. Our results derived from a larger cohort of mainly nontrauma patients support these finding that measurements of clot firmness can identify patients with fibrinolysis more promptly than making the diagnosis based on clot lysis metrics. However, we found that the difference in MCF between APTEM and EXTEM assays (AUC: 0.812) and a low MCF with the EXTEM assays (0.799) is less predictive of fibrinolysis than in these prior reports. This likely can be explained by the fact that the 5 trauma patients with fibrinolysis reported by Levrat et al.[6] had "very early" fibrinolysis (median, interquartile range for EXTEM LI30: 36%, 0%–78%). In contrast, our pooled fibrinolysis cohort of 411 data sets included 192 data sets with very early as well as intermediate or late fibrinolysis.

Although MCF in the EXTEM assay and differences in MCF results between the EXTEM and APTEM assays provided the best prediction of fibrinolysis, there are likely clinical limitations with this method of diagnosis. First, MCF is obtained relatively late during thromboelastometric measurements and is dependent on the intrinsic ability to form thrombus not at a predefined time point. Moreover, the added benefit from MCF measurements may be tempered by the fact that fibrinolysis can be inferred by visual inspection of the ongoing thromboelastometry tracing. To overcome this limitation, others have proposed that fibrinolysis can be detected earlier by comparison of variables from 2 extrinsically activated assays with and without addition of the antifibrinolytic drug aprotinin run in parallel.[30–32] Our findings, however, do not support the proposed benefit of additional APTEM assays for the early detection of fibrinolysis. In fact, using the "optimum" cut point derived from our data using ΔCT criteria, only 155 of our 411 patients (37.7%) would have been identified correctly as having fibrinolysis, while 626 of 2537 (24.8%) controls would have been falsely identified as having fibrinolysis, possibly resulting in exposure to antifibrinolytic drugs. The failure to improve early identification of fibrinolysis with additional APTEM assays may be related to the fact that aprotinin, in addition to its antifibrinolytic actions, exerts inhibitory effects on several coagulation factors that may decrease thrombin generation and prolong CTs.[42,43]

Our data suggest that the feasibility of thromboelastometric variables for the early detection of fibrinolysis varies widely with the onset time of fibrinolysis. Specifically, while several variables allow for the detection of very early fibrinolysis (Tables 3 and 4), only early variables of clot firmness from EXTEM assays and MCF allow for improved early detection of late fibrinolysis. This is readily explained by the fact that substantial plasmin generation, resulting in fibrinolysis, occurs only after fibrin formation. Thereafter, coagulation and fibrinolysis will proceed in parallel. However, fibrinolysis can become overt in viscoelastic tests only if the profibrinolytic potential exceeds the procoagulatory and antifibrinolytic potential or after all the procoagulatory and antifibrinolytic potential has been consumed.

Although additional APTEM assays did not improve early identification of fibrinolysis, these parallel assays have clinical value by potentially showing that only fibrinolysis hinders formation of a stable clot.[44] For example, a marked increase in MCF is seen with the APTEM assay compared with the corresponding EXTEM assay in Figure 1, C and D. Furthermore, the additional use of the APTEM test allows for discrimination between fibrinolysis and platelet-mediated clot retraction or factor XIII deficiency since only fibrinolysis is eliminated in the APTEM test.[45,46]

A limitation of our study is the nature of the optimum cutoff values of the thromboelastometric variables, which were chosen at the Youden index. This cutoff is considered optimum based on the arbitrary assumption that consequences and costs of false-positive and false-negative tests are of the same importance. This assumption might not be true in every clinical setting. Nevertheless, their use provides an estimate of the relative risk for false-positive and false-negative test results. A higher sensitivity for detecting fibrinolysis would possibly result in higher, unnecessary exposure to antifibrinolytic drugs for patients who do not subsequently develop fibrinolysis. For instance, Davenport et al.[47] demonstrated that an EXTEM A5 threshold of ≤35 mm detected 77% of the patients having acute traumatic coagulopathy (defined as a prothrombin ratio >1.2) and predicted the risk for massive transfusion (>10 U of packed red blood cells in 12 hours). Using this EXTEM A5 cutoff value instead of the optimum cutoff value of ≤25 mm derived from our data would have increased sensitivity for the detection of fibrinolysis from 74.7% to 92% (95% CI, 88.9%–95.0%) but simultaneously decreased specificity from 58.5% to 27.3% (95% CI, 27.3%–30.9%). Thus, while >90% of patients with fibrinolysis would have been detected, about 72% of the patients would have been considered to have been erroneously suspected of having fibrinolysis. Accordingly, the decision for an clinically relative cutoff value should be based on the severity of bleeding and the particular clinical setting since the impact of fibrinolysis on patient outcome is different for patients having severe trauma versus those undergoing liver transplantation.[8,15–17,48]

Another potential limitation may be that we cannot provide data using alternative methods to define fibrinolysis,

such as results from euglobulin lysis time, tissue plasminogen activator values, or plasmin–antiplasmin complex concentration.[29,49] These assays were not performed but are not considered to help clinical decision making since they are extremely time consuming and complex and hence unsuitable for point-of-care measurements.

In summary, low early values of clot firmness in extrinsically activated assays (e.g., EXTEM A5) are associated with fibrinolysis and improve its early detection, but with only moderate predictive capacity. The addition of aprotinin with APTEM test did not substantially improve the early diagnosis of fibrinolysis.

## DISCLOSURES

**Name:** Daniel Dirkmann, Dr. med.
**Contribution:** This author designed the study, collected and analyzed the data, and cowrote the manuscript.
**Attestation:** Daniel Dirkmann has seen the study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
**Conflicts of Interest:** Daniel Dirkmann has received honoraria for scientific lectures from CSL Behring, Marburg, Germany, and TEM international GmbH, Munich, Germany.
**Name:** Klaus Görlinger, Dr. med.
**Contribution:** This author helped design the study, helped analyze the data, and cowrote the manuscript.
**Attestation:** Klaus Görlinger has seen the study data, reviewed the analysis of the data, and approved the final manuscript.
**Conflicts of Interest:** Klaus Görlinger has received honoraria for scientific lectures from CSL Behring, Marburg, Germany, and TEM international GmbH, Munich, Germany. Since July 2012, Dr. Görlinger is the Medical Director of TEM international GmbH, Munich, Germany.
**Name:** Jürgen Peters, Prof. Dr. med.
**Contribution:** This author helped design the study, helped analyze the data, and cowrote the manuscript.
**Attestation:** Jürgen Peters has seen the compiled study data, reviewed the analysis of the data, cowrote the manuscript, and approved the final manuscript.
**Conflicts of Interest:** This author has no conflicts of interest to declare.
**This manuscript was handled by:** Charles W. Hogue, Jr, MD.

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