

Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients

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Background. Blood loss and uncontrollable bleeding are major factors affecting survival in trauma patients. Because treatment with antifibrinolytic drugs may be effective, early detection of hyperfibrinolysis with rotation thrombelastography (ROTEM[®]) may be beneficial.

Methods. Eighty-seven trauma patients were included in this prospective observational study. Blood samples were collected at admission. After *in vitro* activation with tissue factor (EXTEM) and inhibition with aprotinin (APTEM), ROTEM[®] parameters including maximal clot firmness (MCF) and clot lysis index at 30 min (CLI₃₀) were determined. Hyperfibrinolysis was defined as a euglobulin lysis time (ELT) <90 min. Threshold for ROTEM[®] parameters were determined with receiver-operating characteristic curves (ROC) analysis according to the ELT results.

Results. ELT was determined in a subgroup of 23 patients. In this group of patients, ROC analysis showed that for a threshold of 18 mm (MCF-EXTEM), 71% (CLI₃₀) and 7% (increase of MCF-APTEM), sensitivity was, respectively, 100%, 75%, and 80% with a specificity of 100%. With the application of these thresholds to the whole trauma cohort, ROTEM[®] analysis detected hyperfibrinolysis in five patients [6%, 95% confidence interval (CI): 2–13%]. As expected, patients with hyperfibrinolysis were more severely injured (median Injury Severity Score: 75 vs 20, $P<0.05$), had greater coagulation abnormalities [international normalized ratio (INR): 8.2 vs 1.3, $P<0.05$; fibrinogen: 0.0 vs 2.2 g litre⁻¹, $P<0.05$], and a higher mortality rate (100%, CI: 48–100% vs 11% CI: 5–20%, $P<0.05$).

Conclusions. ROTEM[®] provided rapid and accurate detection of hyperfibrinolysis in severely injured trauma patients.

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Blood loss and uncontrollable bleeding are major factors affecting survival in trauma patients^{1–4} and haemorrhage continues to be one of the leading causes of death after trauma.^{5,6} Coagulopathy that is frequently encountered in haemorrhagic shock has been shown to be an independent risk factor for death after trauma.³ Critically ill trauma patients suffer from a complex coagulopathy with multiple aetiologies, including overwhelming activation of tissue factor, consumption of coagulation factors and platelets, haemodilution, hypothermia, metabolic acidosis, massive

transfusions, and hyperfibrinolysis.^{5,7} The ability to detect and treat coagulopathy early appears to be a key component of the multi-factorial approach to haemorrhage control in the trauma patient.^{5,8}

We have recently shown that rotation thrombelastography (ROTEM[®]) is a point-of-care device that rapidly detects systemic changes in *in vivo* coagulation and that a coagulopathy can be observed in almost 30% of trauma patients.⁴ Moreover, these patients may also develop disseminated intravascular coagulation which includes both

activation of coagulation factors and fibrinolysis. Because early treatment with antifibrinolytic drugs such as aprotinin or tranexamic acid may be effective, early detection of hyperfibrinolysis during the initial management of bleeding trauma patients may be beneficial.⁹

The goal of this study was to evaluate the accuracy of ROTEM® in detecting hyperfibrinolysis in trauma patients and to describe the incidence of hyperfibrinolysis in a prospective trauma cohort.

Methods

Design, setting, and inclusion criteria

This prospective observational study was carried out between July 4 and October 30, 2004 in the trauma resuscitation unit (TRU) of a 1000-bed university hospital. The study protocol was approved by the institutional review board (IRB) of the Hospices Civils de Lyon. Waived informed consent was authorized by the IRB as this study did not impact patient care. All trauma patients admitted during the study period were included in the study.

Protocol

The characteristics of each patient and their injury, and Injury Severity Score (ISS) were recorded.¹⁰ Blood samples were collected immediately after the patient's arrival at the TRU.

Blood samples were collected by venipuncture into vacutainer tubes (Becton Dickinson, Plymouth, UK) containing ethylenediaminetetraacetic acid (EDTA) for platelet and haemoglobin counts (SE-9500®, Sysmex, Japan) or citrate (0.129 M trisodium citrate) for standard tests: prothrombin time (PT) and international normalized ratio (INR) (Neoplastin® CI plus, Diagnostica 7Stago, Asnières, France), activated partial thromboplastin time (aPTT, MDA Platelin® LS, Biomérieux, France), fibrinogen (Clauss technique, Fibriquick® reagent, Biomérieux), and ROTEM® measurements. Standard coagulation tests and ROTEM® measurements were performed within 2 h of blood sample collection and at least 15 min after venipuncture.¹¹

ROTEM® measurements

The ROTEM® coagulation analyzer (Pentapharm, Munich, Germany) and the parameters of thrombelastography have been described previously in detail.^{11–13} Briefly, thrombelastography measures shear elastic modulus during clot formation and subsequent fibrinolysis. The ROTEM® uses a ball-bearing system for power transduction, which makes it less susceptible to mechanical stress, movement, and vibration. In the ROTEM® analyzer, coagulation is mildly activated either with ellagic acid (INTEM test) or tissue factor from rabbit brain (EXTEM test). This is performed in order to standardize the *in vitro* coagulation process and

also to speed up the analysis that typically lasts 15–20 min.¹¹ In addition to the INTEM and EXTEM screening tests, additional reagents such as aprotinin (APTEM) or cytochalasin D (FIBTEM) can be used in order to study the EXTEM with *in vitro* inhibition of fibrinolytic activity and the EXTEM with inhibition of platelets, respectively. All pipetting steps and mixing are standardized by utilizing an automated electronic program. The ROTEM® analysis was performed at 37°C, in parallel, on the four channels (INTEM, EXTEM, FIBTEM, and APTEM). The following ROTEM® parameters were analysed: clotting time (CT); clot formation time (CFT); maximum clot firmness (MCF); and the amplitude of clot at 10 and 15 min (CA₁₀, CA₁₅). The clot lysis index (CLI₃₀–CLI₆₀) describes the ratio between MCF and CA 30–60 min after CT and thus describes the progress of fibrinolysis at that particular time. In Figure 1, four patterns of coagulation that may be encountered with ROTEM® are illustrated: normal tracing (Fig. 1A), hyperfibrinolysis (Fig. 1B), severe coagulopathy (Fig. 1C) and severe coagulopathy with the complete absence of any clotting ('ultimate coagulopathy', Fig. 1D).

Reference ranges for ROTEM® parameters were obtained from a control group (healthy volunteers) previously described,⁴ and were determined according to National Committee for Clinical Laboratory Standards (NCCLS) Guidelines calculating the 2.5 and 97.5% percentiles (Table 3).¹⁴ These values were very similar to those previously published by Lang and colleagues.¹¹

Assessment of fibrinolysis

Plasma fibrinolytic activity was evaluated by measuring D-Dimer concentrations (Asserachrom® D-DI, Diagnostica Stago, Asnières, France), fibrin degradation products (FDP) (FDP Plasma, Diagnostica Stago, Asnières, France) and euglobulin lysis time (ELT). ELT represents a test of global fibrinolysis and has been described in 1948 by McFarlane and Biggs.^{15 16} Briefly, the citrated plasma was precipitated with cold acetic acid. The precipitate contained fibrinogen, plasminogen, and plasminogen activators, with fibrinolytic inhibitors theoretically removed. The precipitate was redissolved and the euglobulin solution was clotted with 0.025 M CaCl₂. The clotted sample was then incubated at 37°C and was observed at 10-min intervals for clot lysis. ELT was scored from 0 to 5 as follows: 0 (ELT >90 min), 1 (60–90 min), 2 (30–59 min), 3 (15–29 min), 4 (5–14 min), and 5 (<5 min). ELT was utilized in our study as the reference diagnostic method for the assessment of fibrinolysis with a threshold value of <90 min for the diagnosis of hyperfibrinolysis (i.e. ELT score from 1 to 5).^{17 18}

Because of logistic limitations (manpower and time), ELT could not be tested in all trauma patients and was only performed in the subgroup of patients that was considered to have severe injuries by the physician in charge. All patients who did not have an ELT determination had an assessment of their fibrinogen concentrations as a

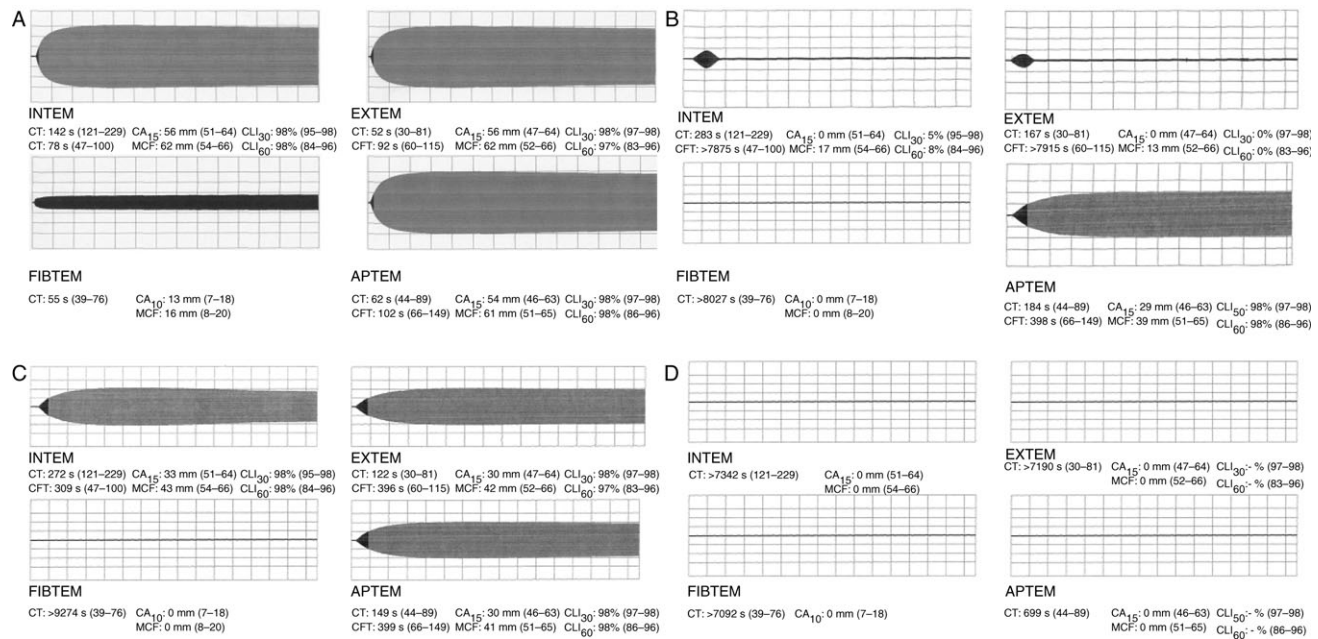


Fig 1 (A) Normal ROTEM® tracing with reference ranges in brackets. CT, clotting time; CFT, clotting formation time; CA, clot amplitude at 10 or 15 min; MCF, maximum clot firmness; CLI, clot lysis index at 30 or 60 min. (B) ROTEM® tracing depicting severe coagulation abnormalities (decrease of MCF and CA₁₅ in EXTEM, absence of clot in FIBTEM) with hyperfibrinolysis (MCF-EXTEM <18 mm and ΔMCF >9%). Severe coagulation abnormalities were confirmed by standard coagulations parameters (INR: 4.7, fibrinogen: 0.4 g litre⁻¹) and hyperfibrinolysis by an ELT score of 2. (C) ROTEM® tracing depicting severe coagulation abnormalities (decrease of MCF and CA₁₅ in EXTEM, the absence of clot in FIBTEM) but without evidence of hyperfibrinolysis (MCF-EXTEM >18 mm and ΔMCF <7%). Severe coagulation abnormalities were confirmed by standard coagulation parameters (INR: 3.9, fibrinogen: 0.5 g litre⁻¹) and the absence of hyperfibrinolysis by an ELT score of 0. (D) ROTEM® tracing depicting severe coagulation abnormalities with virtually no coagulation process on ROTEM® (no clot on any ROTEM® channel testing). Severe coagulation abnormalities were confirmed by standard coagulation parameters (INR: 10, fibrinogen: 0 g litre⁻¹) and hyperfibrinolysis by an ELT score of 4.

surrogate marker of hyperfibrinolysis. None of these patients had a fibrinogen concentration <0.9 g litre⁻¹.

In the group of patients with ELT determination, the accuracy of ROTEM® parameters from the EXTEM channel (CA₁₀, CA₁₅, MCF, CLI₃₀ and CLI₆₀) was assessed for the diagnosis of hyperfibrinolysis with receiver-operating characteristic curve (ROC) analysis and subsequent thresholds were defined.^{19,20} Moreover, we studied the ability of aprotinin to reverse the decrease of the following EXTEM parameters: MCF, CA₁₀, CA₁₅, CLI₃₀, and CLI₆₀ by calculating Δ parameter = [(parameters-APTEM – parameter-EXTEM)/parameter-EXTEM] × 100. Utilizing the diagnostic criteria previously defined with ROTEM®, the incidence of hyperfibrinolysis in the whole trauma cohort was calculated.

Statistical analysis

Results are expressed as median [inter-quartile range (IQR)], mean (SD), or % [95% confidence interval (CI)]. Normality of the distribution was tested using the Kolmogorov-Smirnov test and the Mann-Whitney *U*-test; the Student's *t*-test was used for continuous variables as appropriate. Statistical differences between groups were evaluated by χ^2 test or by Fisher's exact test when appropriate. A two-tailed *P*-value <0.05 was considered significant. ROC and the area under the curves (AUCs) were

constructed for ROTEM® parameters (EXTEM) for the diagnosis of hyperfibrinolysis. Sensitivity, specificity, and positive and negative predictive values were calculated for the best cut-off value (corresponding to the highest accuracy, i.e. minimal false-negative and false-positive results).²¹ Statistical comparison of the areas under two ROC curves was done with Wilcoxon rank-sum test as previously described by Hanley and McNeil.²² All statistical tests were performed using commercially available statistical software (NCSS 2004, Kaysville, UT, USA; Medcalc 9.3.6.0, Mariakerke, Belgium).

Results

During the study period, 89 consecutive trauma patients were admitted to the TRU. Two of these were excluded from analysis owing to missing data. Baseline characteristics of this trauma cohort have been previously reported.⁴

Definition of threshold for the detection of hyperfibrinolysis by ROTEM®

The reliability of ROTEM® for the diagnosis of hyperfibrinolysis was tested in a subgroup of 23 patients who had an ELT [age: 25 (21–47); sex male: 78% (95% CI: 56–93%);

Table 1 Receiver-operating characteristic curve analysis for the diagnosis of hyperfibrinolysis with ROTEM® (EXTEM). CA, clot amplitude at 10 or 15 min; MCF, maximum clot firmness; CLI, clot lysis index at 30 or 60 min; Δ MCF, variation of MCF after *in vitro* addition of aprotinin. Values are presented with 95% confidence interval in brackets. AUC, area under the curve

| Variables | Threshold | Sensibility | Sensitivity | AUC |
|--------------------------------|-----------|------------------|------------------|------------------|
| CA ₁₀ (mm) | ≤10 | 1.00 (0.48–1.00) | 1.00 (0.81–1.00) | 1.00 (0.85–1.00) |
| CA ₁₅ (mm) | ≤12 | 1.00 (0.48–1.00) | 1.00 (0.81–1.00) | 1.00 (0.85–1.00) |
| MCF (mm) | ≤18 | 1.00 (0.48–1.00) | 1.00 (0.81–1.00) | 1.00 (0.85–1.00) |
| CLI ₃₀ (%) | ≤71 | 0.75 (0.20–0.96) | 1.00 (0.75–1.00) | 0.87 (0.61–0.98) |
| CLI ₆₀ (%) | ≤1 | 1.00 (0.40–1.00) | 1.00 (0.63–1.00) | 1.00 (0.73–1.00) |
| Δ MCF (%) | >7 | 0.80 (0.29–0.97) | 1.00 (0.81–1.00) | 0.92 (0.72–0.99) |
| Δ CA ₁₅ (%) | >4 | 0.60 (0.15–0.94) | 1.00 (0.81–1.00) | 0.87 (0.66–0.97) |
| Δ CLI ₃₀ (%) | >2 | 0.75 (0.20–0.96) | 1.00 (0.71–1.00) | 0.75 (0.47–0.93) |
| Δ CLI ₆₀ (%) | >43 | 1.00 (0.40–1.00) | 1.00 (0.63–1.00) | 1.00 (0.73–1.00) |

blunt trauma: 87% (95% CI: 66–97%); ISS: 38 (24–75), haemoglobin: 106 g litre⁻¹ (82–128), platelet count: 160×10⁹ litre⁻¹ (110–209); INR: 1.6 (1.4–4.0); aPTT: 35 s (28–126); fibrinogen: 0.9 g litre⁻¹ (0.5–1.7)]. According to the ELT score, this group consisted of five patients with hyperfibrinolysis (Fig. 1B and D; respectively, with ELT score of 1, 2, 3, 4, and 5) and 18 patients without hyperfibrinolysis (Fig. 1A and C, ELT score of 0).

Linear regression analysis showed that among EXTEM parameters, MCF showed the best correlation with the ELT score (r^2 : 0.68; slope: -0.06; $P<0.001$) when compared with CA₁₀ (r^2 : 0.53; slope: -0.06; $P<0.001$), CA₁₅ (r^2 : 0.57; slope: -0.06; $P<0.001$), CLI₃₀ (r^2 : 0.15; slope: -0.02; $P=0.126$), and CLI₆₀ (r^2 : 0.63; slope: -0.03; $P=0.002$).

Results of ROC analysis are presented in Table 1. Pairwise comparisons of the areas under ROC curves did not show any significant difference between ROTEM® parameters.

Incidence of hyperfibrinolysis in the trauma cohort according to the ROTEM®

By using previously defined threshold (EXTEM), hyperfibrinolysis was observed in five out of the whole trauma patient cohort (6%, 95% CI: 2–13%).

As expected, patients with hyperfibrinolysis were more severely injured, had lower haemoglobin and platelet counts, more severe coagulation abnormalities, higher D-Dimers and FDP concentrations, and a greater mortality rate than patients of the control group (Table 2). Hyperfibrinolysis patients also had greater ROTEM® abnormalities than control patients (Table 3).

After addition of aprotinin in the test reaction cup, EXTEM parameters remained unchanged in one patient in the hyperfibrinolysis group (Fig. 1D), whereas one patient in the control group had a significant increase of MCF-EXTEM (9%).

Discussion

In the current study, ROTEM® was able to quickly (≤15 min) and accurately detect hyperfibrinolysis. This was

Table 2 Baseline characteristics and standard coagulation parameters of patients with hyperfibrinolysis group) and without hyperfibrinolysis (control group). Values are expressed as median [inter-quartile range (IQR)] or mean (sd). * $P<0.05$: control group vs hyperfibrinolysis group. ISS, Injury Severity Score; FDP, fibrin degradation products; aPTT, activated partial thromboplastin time; PT, prothrombin time

| Variables | Control group (n=82) | Hyperfibrinolysis group (n=5) |
|--|----------------------|-------------------------------|
| Age (yr) | 29 (21–43) | 30 (24–45) |
| Sex, n (male %) | 64 (78) | 4 (80) |
| Blunt, n (%) | 68 (83) | 5 (100) |
| ISS | 20 (11–29) | 75 (75–75)* |
| Mortality, n (%) | 9 (11) | 5 (100)* |
| Haemoglobin (g litre ⁻¹) | 129 (109–140) | 86 (83–98)* |
| Platelets (10 ⁹ litre ⁻¹) | 219 (77) | 106 (79)* |
| Fibrinolysis markers | | |
| D-Dimers (μg l ⁻¹) | 7 (3–21) | 164 (158–276)* |
| FDP (μg l ⁻¹) | 342 (269) | 640 (0)* |
| Standard coagulation | | |
| aPTT (s) | 27 (25–32) | 300 (300–300)* |
| PT (s) | 15 (15–17) | 62 (43–80)* |
| INR | 1.3 (1.2–1.5) | 8.2 (6.0–10.0)* |
| Fibrinogen (g litre ⁻¹) | 2.2 (1.6–2.6) | 0.0 (0.0–0.0)* |
| Coagulation factors | | |
| II (UI dl ⁻¹) | 67 (23) | 36 (28)* |
| V (UI dl ⁻¹) | 77 (61–93) | 5 (5–9)* |
| VII (UI dl ⁻¹) | 83 (30) | 65 (42) |

observed in 6% of our cohort of trauma patients. As previously described,^{2 3} we also observed a close relation between injury severity, coagulation abnormalities, and outcome (Table 2).

In our study, ELT was utilized as the gold standard test for the diagnosis of hyperfibrinolysis. ELT is the most commonly used test and it has been demonstrated to be a useful indicator of *in vivo* fibrinolysis in many physiologic as well as pathologic conditions.^{16 23–26} Nevertheless, because ELT remains a complex and time-consuming procedure that can take more than 180 min,²⁷ practically, it is not a feasible test for the diagnosis of hyperfibrinolysis in bleeding patients. For the same reasons, the other techniques used to diagnose hyperfibrinolysis (plasmin–antiplasmin complex, plasminogen activator inhibitor 1, thrombin activatable fibrinolytic inhibitor, D-Dimers/plasmin–antiplasmin)^{18 28} are also not relevant in the context of haemorrhagic shock. Furthermore, these tests

Table 3 Description of ROTEM® parameters in the control and hyperfibrinolysis groups. Values are expressed as median (inter-quartile range). CT, clotting time (s); CA, clot amplitude (mm) at 10 or 15 min; MCF, maximum clot firmness (mm); CLI, clot lysis index (%) at 30 or 60 min. For each ROTEM® parameter reference range are expressed in brackets. * $P < 0.05$: control vs hyperfibrinolysis group

| ROTEM® parameters | Control group (n=82) | Hyperfibrinolysis group (n=5) |
|---------------------------|----------------------|-------------------------------|
| INTEM | | |
| CT (121–229) | 143 (129–164) | 527 (429–607)* |
| CA ₁₀ (47–60) | 50 (44–54) | 10 (7–12)* |
| CA ₁₅ (51–64) | 55 (49–58) | 11 (0–13)* |
| MCF (54–66) | 58 (52–62) | 14 (12–17)* |
| CLI ₃₀ (95–98) | 98 (98–98) | 41 (10–76)* |
| CLI ₆₀ (84–96) | 92 (91–95) | 9 (6–11)* |
| EXTEM | | |
| CT (30–81) | 60 (55–72) | 313 (234–366)* |
| CA ₁₀ (41–60) | 49 (41–52) | 8 (3–9)* |
| CA ₁₅ (47–64) | 53 (46–57) | 10 (0–11)* |
| MCF (52–66) | 58 (51–62) | 11 (10–13)* |
| CLI ₃₀ (97–98) | 98 (98–98) | 36 (0–78)* |
| CLI ₆₀ (83–96) | 94 (92–96) | 0 (0–0)* |
| FIBTEM | | |
| CT (39–76) | 59 (55–67) | 10 000 (10 000–10 000)* |
| CA ₁₀ (7–18) | 9 (6–12) | 0 (0–0)* |
| MCF (8–20) | 11 (8–15) | 0 (0–0)* |
| APTEM | | |
| CT (44–89) | 67 (59–77) | 352 (311–373)* |
| MCF (51–65) | 58 (51–61) | 23 (17–23)* |
| CLI ₃₀ (97–98) | 98 (98–98) | 95 (89–98) |
| CLI ₆₀ (86–96) | 94 (92–96) | 98 (92–98) |

have to be performed in series and therefore cannot be done routinely for logistic and economic reasons.

Clinically, the treatment of coagulopathic bleeding is critically compromised by current coagulation monitoring technologies that can take up to 45–60 min. The entire blood volume of the bleeding trauma patient may have been exchanged several times during that time interval, making the results of the laboratory tests obsolete. In a previous study, we have recently demonstrated that ROTEM® can rapidly detect systemic changes in *in vivo* coagulation in trauma patients and may help to guide transfusion.⁴

In this study, we demonstrated the ability of ROTEM® to diagnose hyperfibrinolysis with a decrease in EXTEM parameters such as MCF or CA₁₅ and a significant increase of these parameters after the addition of aprotinin in the test reaction cup (Table 3). This was observed in all patients except for one, likely because the patient having reached the ‘ultimate’ state of fibrinolysis (Fig. 1b). At the opposite end of the spectrum, one patient from the control group had an increase of MCF-EXTEM exceeding the threshold value (9%) after *in vitro* addition of aprotinin. However, because the initial value of MCF-EXTEM of this patient was above the threshold (42 mm) and because there was no significant increase of the other EXTEM parameters (CA₁₀ and CA₁₅) after *in vitro* addition of aprotinin, the diagnosis of hyperfibrinolysis was not confirmed. In addition, standard coagulation assays confirmed that this patient did not present severe evidence of

coagulopathy (INR: 1.5; fibrinogen: 1.3 g litre⁻¹; platelets: 141×10^9 litre⁻¹; haemoglobin: 123 g litre⁻¹).

The use of antifibrinolytic agents is a management option for bleeding in trauma patients with hyperfibrinolysis.^{9–29} This treatment has been used successfully to reduce blood loss in various non-traumatic surgical settings, such as cardiac and orthopaedic surgery or hepatic transplantation.^{30–32} However, owing to the cost and because adverse events have been reported with their use,^{33–35} treatment with antifibrinolytics should be guided by laboratory testing or a point-of-care device. ROTEM® provides a rapid and accurate diagnosis of hyperfibrinolysis, which may guide therapy with antifibrinolytic agents. It is still unknown whether all patients with hyperfibrinolysis require antifibrinolytic therapy or if only those with a significant increase in EXTEM parameters as depicted in Figure 1b will benefit. Randomized prospective evaluation of the safety and efficacy of these treatments in bleeding injured patients with hyperfibrinolysis is warranted, such as the Crash 2 trial (<http://www.crash2.lshtm.ac.uk>).

This study has several limitations. First, the power of the study is limited by the small number of patients with hyperfibrinolysis (five patients). Secondly, the diagnosis of hyperfibrinolysis which was made by the ELT was not confirmed by another diagnostic tool, such as plasminogen activator inhibitor 1. However, there is to date no data showing that any of the other test parameters are superior to ELT.²⁸ Thirdly, vascular disorders and adhesion of platelets to collagenous fibres still cannot be estimated by thrombelastography. Fourth, because this study was done on admission, it did not take into account the effect of coagulation therapy on ROTEM® parameters and standard coagulation tests. Fifth, ROTEM® requires a fair degree of technical expertise that necessitates training of the physicians who will be utilizing it. However, we recently demonstrated that there was a very good correlation between results of ROTEM® done by trained physicians and haemostasis technicians.³⁶ Savry and colleagues also showed that ROTEM® sample processing by trained physicians took only a mean of 171 s.³⁷

In summary, ROTEM® accurately and quickly diagnosed hyperfibrinolysis in trauma patients. This may allow for the early identification of this subset of severely injured patients and are continuously bleeding who may benefit from treatment with antifibrinolytic agents.

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