# Uncovering Hypercoagulability in Sepsis Using ROTEM® Thromboelastometry: A Case Series

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**Abstract:** This case series presents three patients with sepsis/septic shock in whom standard coagulation tests (international normalized ratio, activated partial thromboplastin time, fibrinogen, antithrombin, thrombocytes) and ROTEM® thromboelastometry (InTEM, ExTEM, FibTEM) were simultaneously performed. Although all patients showed significantly prolonged plasmatic coagulation times with a putatively increased risk of bleeding, ROTEM® thromboelastometry revealed normal clotting times and even signs of hypercoagulability. Therefore, no coagulation active therapy was performed in any patient, not even before invasive procedures or major surgical interventions. No bleeding occurred in any study patient during surgery or the subsequent stay on the intensive care unit. These observations suggest that some critically ill patients with sepsis and abnormal standard coagulation tests may in fact have hypercoagulability. ROTEM® thromboelastometry can add important information in these patients and enable that blood products are used targeted and only for substitution of relevant deficencies. Future studies are necessary to validate these preliminary findings.

**Keywords:** Sepsis, thromboelastometry, ROTEM®, coagulopathy, hypercoagulability.

## INTRODUCTION

The coagulation system is a cascade of central physiologic and pathophysiologic importance in sepsis. Closely interconnected with the immunologic and endothelial system, recent data have indicated a contributing role of the coagulation system in the development of microcirculatory dysfunction and multiple organ failure in patients with sepsis [1-3]. Accordingly, anticoagulatory and anti-inflammatory therapies could reduce the severity of organ failure [4-6] and improve mortality in patients with sepsis and a high risk of death [7].

In clinical practice and most organ failure scores, assessment of the coagulation system includes the measurement of prothrombin time or the international normalized ratio, activated partial thromboplastin time, fibrinogen concentrations, and/or platelet count [8, 9]. For special clinical questions, activities of antithrombin or single coagulation factors, fibrinogen degradation products, and thrombin-antithrombin complexes may expand the diagnostic evaluation of the coagulation system.

Although first described in 1948 [10], recent technological improvements as well as employment of various activators and inhibitors have re-introduced thromboelastography (TEG®) into clinical practice. Using citrated whole blood, thromboelastography analyzes the viscoelastic changes occurring during coagulation and gives a graphic representation of the clotting process. Thromboelastography enables a rapid and global evaluation of coagulation initiation and propagation kinetics, fibrin-platelet interaction, clot firmness, and fibrinolysis [11].

In this case series, we report on the beneficial use of ROTEM® thromboelastometry in three patients with severe sepsis or septic shock.

## METHODOLOGY

In all patients, exclusively arterial blood was sampled into citrate containing tubes (0.129 molar) in order to determine standard coagulation tests (international standardized ratio, activated partial thromboplastin time, fibrinogen concentration, antithrombin activity) (Table **1**) and for ROTEM® thromboelastometry analysis using point of care devices (Table **2**). In all patients, ROTEM® thromboelastometry (ROTEM®, Pentapharm GmbH, Munich, Germany), which is based on the thrombelastography® system (TEG®) after Hartert [10], was performed bedside in citrated whole blood at 37°C within five minutes after blood sampling. The ROTEM® thromboelastometry assays are easy to perform and guided by an automatic pipetting system. In addition, a specific power transduction system permits that measurements are not disturbed by external movement or vibration [12]. Samples were analyzed using intrinsically (InTEM test: 20 µL $CaCl_2$ 0.2 M, 20 µL thromboplastin-phospholipid, 300 µL blood) and extrinsically activated tests (ExTEM test: 20 µL $CaCl_2$ 0.2 M, 20 µL tissue factor, 300 µL blood). In addition, polymerized fibrinogen/fibrin was measured using a platelet-inactivating test (FibTEM test: 20 µL $CaCl_2$ 0.2 M plus cytochalasin D, 20 µL tissue factor, 300 µL blood). All reagents were purchased from Pentapharm GmbH (Munich, Germany). A recent multicenter study has evaluated the reference ranges for and the variability of ROTEM® thromboelastometry. Investigating three laboratory centers, the coeffi-

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cients of variation were 1-5% (clot firmness, alpha angle), 3-12% (clotting time, clot formation time), and 6-13% (FibTEM clot firmness) [11].

The parameters of ROTEM® thromboelastometry are "coagulation time" corresponding to the reaction time (r time) of conventional TEG®, "clot formation time" corresponding to the coagulation time (k time), and "maximum clot firmness", which is equivalent to the maximum amplitude of the conventional TEG®. Initiation of coagulation is measured as coagulation time (CT; sec) and depends on concentrations of coagulation factors/inhibitors. Propagation of clot formation follows when a sufficient thrombin burst has been built up, is measured as clot formation time (CFT; sec) and defined as the time needed to reach a clot firmness of 20 mm. The alpha angle describes the kinetic of this clot formation. The final clot strength measured as maximum clot firmness (MCF; mm) depends on sufficient thrombin generation as well as on counts and function of platelets, fibrinogen concentrations, and concentrations of coagulation factor XIII. Presence of clinically relevant fibrinolysis can be detected as an early or pronounced decrease in maximum clot firmness. The fibrinogen/fibrin part of the clot can be assessed by clot strength as measured with the FibTEM assay. Typical ROTEM® thromboelastometry tracings for a healthy volunteer, a patient with severely impaired haemostasis and a patient with hypercoagulability (Patient 3) are presented in Fig. (**1**).

## CASE PRESENTATIONS

### Patient 1

A 60 year old female presented with clinical signs of severe sepsis because of a perforated sigma diverticle. She was tachycardic (sinus rhythm, 125/min), hypotensive (mean arterial blood pressure, 55 mmHg) and had signs of peripheral hypoperfusion (cold, mottled skin). Since twelve hours ago she had not passed urine. After infusion of 1.5 litres of lactated Ringer's solution, hemodynamic parameters could be stabilized, and the patient started to pass small amounts of urine. Preoperative coagulation tests revealed significantly prolonged prothrombin and activated partial thromboplastin times suggesting relevant coagulopathy with an increased risk of intraoperative bleeding. Therefore, five fresh frozen plasmas were ordered to be transfused before surgery. However, ROTEM® thromboelastometry showed hypercoagulability with coagulation times in the lower normal range and strongly increased clot firmness. In view of these results, no blood products were transfused. No anticoagulants or colloid solutions were administered before coagulation tests had been performed. Anaesthesia was introduced with thiopentone, fentanyl, and rocurconium, and maintained with isoflurane. During one hour and forty minutes, laparotomy and sigma resection was performed. Blood loss amounted to approximately 100 mL. No blood was transfused. Fluid therapy included one litre of crystalloids and 500 mL of gelatine. Four hours after admission to the intensive care unit, the patient could be extubated. She was discharged to the surgical ward on the first postoperative day. Routine thromboembolic prophylaxis with a low molecular weight heparin was uneventfully performed from that time on. Standard coagulation tests normalized within the next three days.

### Patient 2

A 62 year old male developed anastomotic dehiscence and septic shock one week after colonic resection. Large amounts of gelatine colloids, high dosages of norepinephrine (0.76 mcg/kg/min) and milrinone (0.55 mcg/kg/min) were required to stabilize cardiac output and arterial blood pressure. By that time, multiple organ dysfunction including anuric renal failure, somnolence (Glasgow Coma Scale, 10), and pulmonary failure ($PaO_2/FiO_2$ quotient, 191) had established. Standard coagulation tests showed a prothrombin time of 36% and an activated partial thromboplastin time of 80 seconds. Together with the fact that no anticoagulants had been administered and antithrombin activity were low this was interpreted as disseminated intravascular coagulation with a relevant intraoperative bleeding risk. Five fresh frozen plasmas and 1000 IU of prothrombin complex were prepared to be transfused before surgery. In contrast, ROTEM® thromboelastometry suggested normal coagulation times with increased clot stability indicative of hypercoagulability. Laparotomy, peritoneal lavage, and colonostomy were then performed without coagulation active treatment. During one hour of surgery, blood loss was approximately 200 mL, and no blood had to be transfused. Postoperatively, the patient was treated on the intensive care unit because of sepsis-associated six organ failure. Within 48 hours after surgery, unfractionated heparin was initiated as thromboembolic prophylaxis and to allow continuous veno-venous hemofiltration. Four weeks later, the patient could be discharged to the surgical ward.

### Patient 3

A 44 year old female with recurrent inflammatory bowel disease was admitted from the surgical ward to the intensive care unit because of bilateral pneumonia (*Staphylococcus aureus* cultivated from the bronchoalveolar lavage), acute respiratory distress syndrome ($PaO_2/FiO_2$ quotient, 73) and sepsis-associated five organ failure (pulmonary failure; septic shock; acute renal failure requiring continuous veno-venous hemofiltration; sopor with a Glasgow Coma Scale of 9; coagulopathy). After admission to the intensive care unit the patient was intubated and mechanically ventilated. Antibiosis was empirically started with piperacilline/tazobactam and vancomycine. Cardiovascular stabilization could only be achieved after vigorous volume resuscitation using crystalloid and gelatine colloid (2.5 L) solutions as well as installation of norepinephrine at dosages up to 0.37 μg/kg/min. Standard coagulation tests indicated disseminated intravascular coagulation with a relevantly prolonged international ratio and activated partial thromboplastin time as well as thrombopenia. Only fibrinogen concentrations were high (Table **1**). In contrast, ROTEM® thromboelastometry revealed only a moderate prolongation of clotting times but a substantial hypercoagulability in all assays (Table **2**, Fig. (**1C**)). In view of these results and the clinical picture (mottled skin with further signs of tissue hypoperfusion), no coagulation active therapy was initiated. All central venous catheters were placed without transfusion of fresh frozen plasma or administration of coagulation factors. In accordance with ROTEM® thromboelastometry findings, the blood immediately clotted in the syringe during insertion of a central venous and pulmonary artery catheter. On the next

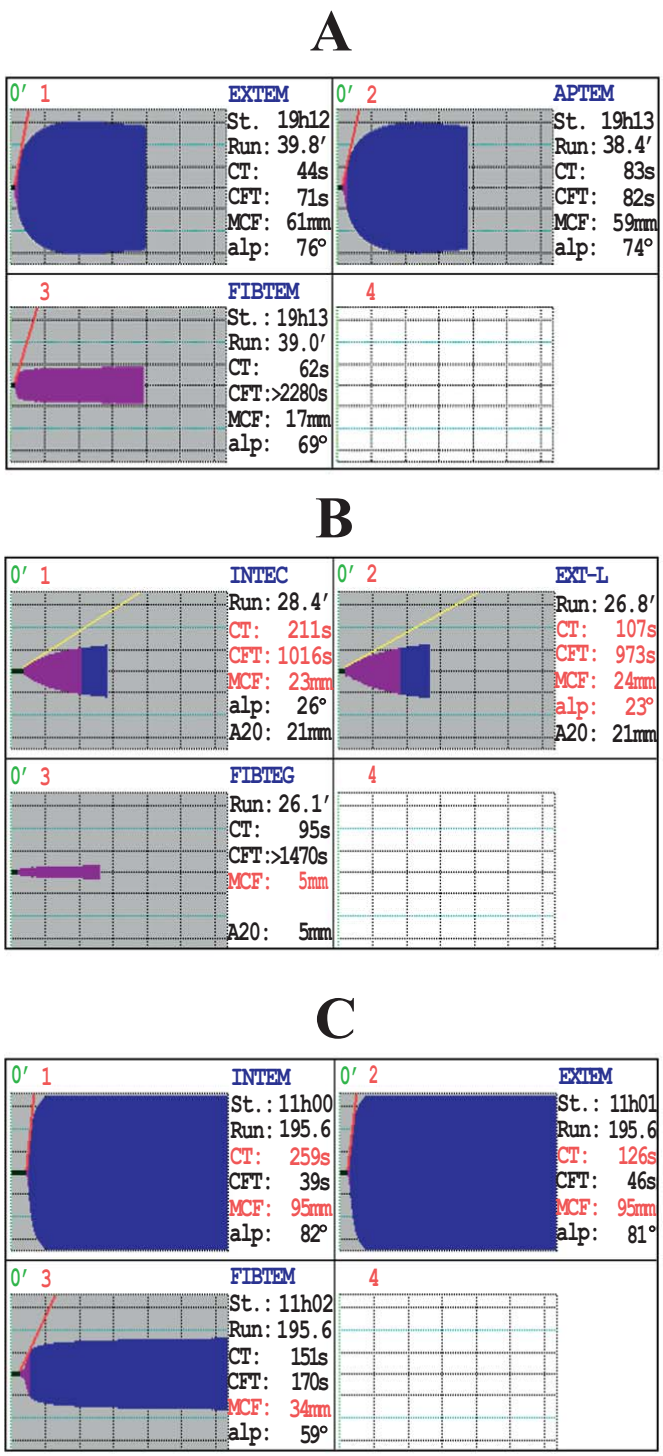


**Fig. (1).** ROTEM® thromboelastometry in a healthy volunteer (**A**), a patient with hypocoagulation (**B**) (*not presented*), and a patient with sepsis and hypercoagulation (**C**) (*patient 3*). Fig. (**1A**) shows ROTEM® thromboelastometry tracings of intrinsically, extrinsically activated and the platelet inactivating assays obatined from a healthy volunteer. (Fig. **1B**): In this sample, initiation of coagulation is prolonged in the extrinsically activated assay suggesting some deficency of coagulation factors of the extrinsic pathway. Most pronounced, clot formation time, alpha angle and maximun clot firmness are severely impaired, indicating deficency of platelets and fibrinogen. (Fig. **1C**): Despite prolongation of initiation of coagulation in the intrinically and extrinsically activated test the clot is formed immediately and shows a strength above normal values, most likely due to increased fibrin polymerization (FibTEM maximum clot firmness above upper normal values). APTEM, aprotinin thromboelastometry using aprotinin to inactivate fibrinolysis and uncover premature lysis when compared to ExTEM readings; St., standard running time; Run, run time of sample; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; alp: alpha angle; A20, clot firmness at 20 minutes.

**Table 1. Standard Coagulation Tests**

| Patient | Age | Sex | Diagnosis | Outcome | INR | aPTT (sec) | Fib (mg/dL) | AT (%) | TC (G/L) |
|---|---|---|---|---|---|---|---|---|---|
| *Normal Ranges* | | | | | 0.9-1.15 | 20-36 | 230-350 | 80-130 | 150-400 |
| 1 | 60 | F | Peritonitis | Survived | 3.1 | 72 | 611 | 32 | 612 |
| 2 | 62 | M | Peritonitis | Survived | 2.5 | 80 | 223 | 29 | 280 |
| 3 | 44 | F | Pneumonia | Survived | 4.4 | 61 | 800 | 31 | 80 |

INR, international normalized ratio; aPTT, activated partial thromboplastin time; Fib, fibrinogen plasma concentration; AT, antithrombin activity; TC, thrombocyte count.

day, unfractionated heparin was cautiously started at a continuous dosage of 5.000 IE/d. No adverse bleeding event occurred. During the following days, standard coagulation tests improved despite of the infusion of increasing dosages of heparin. Forty-three days after intensive care unit admission, the patient was discharged to another hospital.

## DISCUSSION

Activation of the coagulation system during sepsis is common and results from a generalized inflammatory reaction to bacterial antigens, primarily involving the tissue factor pathway [1]. In this case series, three critically ill patients with sepsis were presented in which ROTEM® thromboelastometry identified significant hypercoagulability although standard coagulation tests suggested coagulopathy and an increased risk of bleeding.

It is well known that during the initial phase of disseminated intravascular coagulation hypercoagulability with hastened clot formation occurs thus initiating the consumption of clotting factors [1, 13]. During this process standard coagulation tests such as prothrombin time or activated partial thromboplastin time are typically normal, whereas fibrinogen may be slightly elevated and antithrombin activity decreased. In contrast, in all of the patients presented, hypercoagulability persisted even though laboratory results showed prolonged *in vitro* coagulation times. These observations are striking, since according to current clinical protocols, transfusion of fresh frozen plasma or administration of coagulation factors would have been initiated before surgery or insertion of central lines.

While standard coagulation tests separately analyze the plasmatic coagulation system only and may be influenced by several co-factors (e.g. VLDL-C-reactive protein complexes [14], antiphospholipid antibodies [15]), ROTEM® thromboelastometry provides a global overview of the plasmatic and cellular coagulation process by analyzing whole blood. Moreover, it has been shown that platelets are of great importance for the primary thrombin burst [16]. Thus, measurements obtained in whole blood might reflect thrombin generation more accurately than standard coagulation tests which are limited to the phase of initiation of coagulation [17]. The use of extrinsically and intrinsically activated tests together with interpretation of specific ROTEM® thromboelastometry parameters allow a detailed analysis of the specific components of the coagulation system and the fibrin polymerization process (Fig. **1**). Considering the above mentioned differences in performance and interpretation of standard coagulation and ROTEM® thromboelastometry assays discrepancies in coagulation test results can be explained.

So far, only one similar case has been reported in a liver transplant patient whose standard coagulation studies were compatible with coagulopathy and fibrinolysis. Even though thromboelastography demonstrated normal clot formation, aprotinin, fresh frozen plasma, cryoprecipitate, and thrombocyte concentrates were administered. Intraoperatively, the patient became asystolic and could not be resuscitated. The autopsy revealed multiple arterial and venous hyperacute thromboses. Retrospectively, thromboelastography was sensitive enough to detect hypercoagulability in this patient, while standard coagulation tests failed and suggested a clinically relevant coagulation defect [18].

Since this is only a collection of three patients, the prevalence and cause of hypercoagulability despite of pathologic standard coagulation tests in sepsis remains unknown. Nonetheless, it is conceivable that a certain constellation of components of the coagulation system predisposes to the observed differences between *in vitro* laboratory tests and the actual coagulation process *in vivo*. Because the maximum clot firmness is mainly determined by platelet count and fibrinogen, it may be hypothesized that high platelet count and/or high fibrinogen concentrations significantly contrib-

**Table 2. Results of ROTEM Thromboelastometry Analyses**

| Patient | InTEM | | | | ExTEM | | | | FibTEM |
|---|---|---|---|---|---|---|---|---|---|
| | CT (sec) | CFT (sec) | MCF (mm) | Alpha (°) | CT (sec) | CFT (sec) | MCF (mm) | Alpha (°) | MCF (mm) |
| *Normal Ranges* | *137-246* | *40-100* | *52-72* | *71-82* | *42-74* | *46-148* | *49-71* | *63-81* | *9-25* |
| 1 | 148 | 33 | 81 | 83 | 68 | 42 | 79 | 83 | 47 |
| 2 | 171 | 41 | 73 | 80 | 61 | 39 | 72 | 79 | 38 |
| 3 | 259 | 39 | 95 | 82 | 126 | 46 | 95 | 81 | 34 |

CT, coagulation time; CFT, clot formation time; MCF, maximum clot firmness; Alpha, alpha angle.
Normal ranges are adopted from Lang T *et al*. [11].

ute to hypercoagulability in sepsis. Accordingly, two of the three presented patients had hyperfibrinogenemia and normal or elevated platelet counts.

Concerns may arise that fibrinogen concentrations could also be measured by standard laboratory assays. However, it is known that especially at very low and high ranges standardization of these tests is difficult [19]. Moreover, other authors have observed that in the presence of colloids, which are frequently used in critically ill patients with sepsis, measurement of fibrinogen concentration might be falsely high [20] or do not correlate with functional measured fibrinogen/fibrin polymerization [21]. Despite of the principal advantage of thrombelastographic techniques to immediately render results at the bedside and allow for a differentiated diagnosis of underlying problems, it might be more helpful to measure the functional response instead of concentrations alone. Results of a multicenter trial show that the variability of ROTEM® thromboelastometry assays is within those of standard laboratory tests and for assessment of maximum clot firmness and alpha angle even below accepted ranges [11]. Thus, provided intensivists and anesthesiologist are well trained and quality controls are conducted at regular intervals, the ROTEM® thromboelastometry or TEG® technique can be used as an accurate point of care testing system both in the intensive care unit and operating room. Studies have already shown that the point of care use of TEG® during cardiac surgery can reduce transfuion requirements [22].

Liberate transfusion of fresh frozen plasma or administration of prothrombin complex in patients with hypercoagulability may aggravate intravascular clot formation and perpetuate microcirculatory failure [23]. Fibrin deposition is known to cause diffuse obstruction of the microvascular bed resulting in progressive organ dysfunction, such as the development of renal insufficiency, pulmonary and cardiovascular failure [1-3, 23]. Moreover, avoidance of fresh frozen plasma transfusions or administration of prothrombin complex may further reduce the incidence of transfusion-related [24] and thromboembolic complications [25], respectively. Therefore, our data strongly support the current recommendations of the Surviving Sepsis Guidelines that abnormal coagulation tests must only be corrected when clinical signs of bleeding exist [26-28]. However, as shown in our patients, routine treatment of abnormal laboratory parameters may not even be indicated before invasive procedures or surgical interventions, but requires further laboratory testing in order to avoid potentially harmful therapeutic steps.

Some critically ill patients with sepsis and abnormal standard coagulation tests may have hypercoagulability. ROTEM® thromboelastometry can add important information in these patients and enable that blood products are used targeted and only for substitution of relevant deficencies. Future studies are necessary to validate these preliminary findings.

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