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1. Title: Hyper- and hypocoagulability in COVID-19 as assessed by thromboelastometry. Two case reports.

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Hyper- and hypocoagulability in COVID-19 as assessed by thromboelastometry: two case reports

Running title: Thromboelastometry in COVID-19
Abstract

**Background:** COVID-19-associated coagulopathy is most often characterized by elevated D-dimer, interleukin-6 and plasma fibrinogen concentration as well as hypercoagulability in thromboelastometry with increase clot firmness in EXTEM, INTEM and FIBTEM. Clinically, it strikes with a very high incidence of thrombosis, in particular in the pulmonary system, while bleeding complications are infrequent.

**Case:** Here, we describe two critically ill COVID-19 patients admitted to our intensive care unit with different thromboelastometry and biomarker patterns. One patient presents with hypercoagulability and the other patient with hypocoagulability and fibrinolysis shutdown in thromboelastometry. Pathophysiology and potential impact on treatment options are discussed.

**Conclusions:** Combinations of biomarkers and thromboelastometry results can be helpful in the future to decide which therapeutic strategy might be most appropriate in individual critically ill COVID-19 patients. This would be an important step to establish precision medicine in this high-risk patient population.

**Keywords:** Anticoagulation; Coagulopathy; COVID-19; Hypercoagulability; Thromboelastometry; Thrombosis.
COVID-19-associated coagulopathy is most often characterized by elevated D-dimer, interleukin-6 (IL-6) and plasma fibrinogen concentration as well as hypercoagulability in thromboelastometry with increase clot firmness in EXTEM, INTEM and FIBTEM [1-6]. Clinically, it strikes with a very high incidence of thrombosis, in particular in the pulmonary system, while bleeding complications are infrequent [7-10]. In contrast, sepsis-associated coagulopathy due to bacterial infection is characterized by hypocoagulability in thromboelastometry which has been shown to be a good predictor of increased mortality [11-13]. Here, we describe two critically ill COVID-19 patients admitted to our intensive care unit (ICU) at Brighton and Sussex University Hospitals NHS Trust presenting different thromboelastometry phenotypes, clinical course and outcomes.
Case Reports

The NHS Institutional Review Board waved getting the informed consents from each patient.

Patient A

A 48 years old South Asian female from Bangladesh (168 cm, 80 kg), was admitted to the medical ward three days before ICU admission with cough and increasing dyspnea for three days before hospital admission. Comorbidities included hypertension, hypercholesterinemia, coronary artery disease, previous stroke (fully recovered) and type-2 diabetes. Her laboratory results were as follows: hemoglobin (Hb) 143 g/L, white blood cell count (WBC) $9.0 \times 10^9$/L, lymphocytes $1.4 \times 10^9$/L, platelet count $261 \times 10^9$/L, international normalized ratio (INR) 1.1, D-dimer 0.51 µg/mL, fibrinogen plasma concentration 8.4 g/L, and C-reactive protein (CRP) 52 mg/L. Chest X-ray showed cardiomegaly and extensive bilateral peripherally predominant ground glass opacities. Polymerase-chain-reaction (PCR) was positive for SARS-CoV2 and negative for influence/respiratory-syncytial-virus (RSV). Blood cultures were negative. The patient was treated with nasal oxygen therapy and antibiotics (ceftriaxone and doxycycline according the hospital COVID-19 protocol). Antiviral therapy and dexamethasone were not administered. CRP increased to 137 mg/L on the second day at hospital. The patient was transferred to ICU on the third day at hospital because of increased respiratory rate and oxygen requirement. ROTEM was performed 2 hours after ICU admission (figure 1A). Patient A was hypercoagulable with the EXTEM showing an increased clot firmness with an amplitude of clot firmness 5 minutes after CT (A5) of 65 mm and a maximum clot firmness (MCF) of 78 mm, indicating hypercoagulability with a high risk of thrombosis [14-16]. The FIBTEM showed increased clot firmness (A5 41 mm and MCF 50 mm), too, indicating increased fibrinogen concentration and fibrin polymerization. EXTEM lysis index 60 (LI60) was with 97% in the physiologic range (82-97.9%) and FIBTEM LI60 was 100% [17].
Treatment consisted of continuing antibiotics, enoxaparin 40 mg twice a day in view of ROTEM, high flow nasal oxygen and intermittent face mask continuous positive airway pressure (CPAP). The patient never needed intermittent positive pressure ventilation (IPPV) or any vasoactive support. Laboratory results on the second day at ICU were: Hb 131 g/L, WBC 10.8 x 10⁹/L, platelet count 307 x 10⁹/L, INR 1.1, APTT-ratio 1.3, D-dimer 0.51, and CRP 196 mg/L. The patient recovered well and was discharged from the ICU back to the medical ward after two days at ICU with a CRP of 73 mg/L and was discharged home three days later on her usual medication plus enoxaparin 40 mg once daily for 2 weeks. The patient did not show any clinical signs of thrombosis during her hospital stay.

**Patient B**

A 68 years old Caucasian male from UK (177 cm, 85 kg), was admitted from home with cough and increasing dyspnea for one week. He was previously fit and well. His wife and his daughter probably had COVID-19, both reported symptoms resolving, and were all living in the same house. The patient became markedly short of breath on day of admission to the emergency department (ED) and therefore called an ambulance. His laboratory results were as follows: Hb 140 g/L, creatinine 117 µmol/L, WBC 8.6 x 10⁹/L, lymphocytes 0.2 x 10⁹/L, platelet count 126 x 10⁹/L, INR 1.4, APTT-ratio 1.3, D-dimer >20 µg/mL (i.e. higher than the upper limit of measurement range), fibrinogen plasma concentration 6.8 g/L, and CRP 336 mg/L. Chest X-ray showed dense bilateral mid-zone and right lower zone consolidation. PCR was positive for SARS-CoV2 and negative for influence/RSV. Blood cultures showed coagulase negative staphylococci. The patient was treated with antibiotics (ceftriaxone and doxycycline according the hospital COVID-19 protocol). Antiviral therapy and dexamethasone were not administered. Since the patient was severely hypoxemic in the ED, he was transferred directly to ICU. Orotracheal intubation and IPPV (PEEP
15 mmHg) were performed about 3 hours after ICU admission as respiratory effort was not improved by face mask CPAP. Chest X-ray was repeated after intubation showing bilateral interstitial lung changes similar to previous imaging from earlier the same day. Prone position did not improve oxygenation. Laboratory results from the next day were as follows: Hb 133 g/L, creatinine 265 µmol/L, WBC 16.3 x 10⁹/L, platelet count 56 x 10⁹/L, INR 1.6, APTT-ratio 1.5, D-dimer 4.34 µg/mL, fibrinogen plasma concentration 2.9 g/L, and CRP 478 mg/L. In ROTEM, Patient B presented hypocoagulability in EXTEM with prolonged coagulation time (CT 99 s) and clot formation time (CFT 253 s) and decreased clot firmness amplitudes (A5 22 mm and MCF 48 mm) (figure 1B). Furthermore, EXTEM and FIBTEM demonstrated a complete fibrinolysis shutdown [17]. Both hypocoagulability and fibrinolysis shutdown have been shown to be associated with increased mortality in bacterial sepsis [11-13,18,19]. The FIBTEM trace was within normal limits which may be due to impaired fibrin polymerization given that fibrinogen concentration was elevated. He deteriorated within a few hours of ICU admission and died the following day despite invasive ventilation, norepinephrine for hypotension and renal replacement therapy for acute kidney failure. Patient B did not show any clinical signs of thrombosis during his hospital stay.
Discussion

We have presented two patients who illustrate the additional value of using thromboelastometry to monitor patients with COVID-19. Increased clot firmness in EXTEM and INTEM (A10 > 61.5 mm or MCF > 68 mm) has been shown to be associated with increased incidence of thrombosis in adults and neonates undergoing cardiac and non-cardiac surgery [14-16]. Furthermore, increased clot firmness in FIBTEM (MCF > 25 mm) has been shown to be associated with increased incidence of thrombosis in patients with cirrhosis and hepatocellular carcinoma as well as in patients with thrombophilic predisposition after liver transplantation [20,21]. Thromboelastometry in patient A showed hypercoagulability despite D-dimers in the upper normal range and normal INR. It has been reported that patients with D-dimer > 3 µg/mL and/or sepsis-induced coagulopathy score (SIC score) ≥ 4 seem to benefit from increased anticoagulation [22]. However, in critically ill COVID-19 patients, the incidence of thrombosis and pulmonary embolism is high despite pharmacological thromboprophylaxis [7,8].

Patient B showed that not all critically ill COVID-19 patients present the same thromboelastometric pattern. This might be attributed to ethnic and genetic difference, such as gene polymorphisms, bacterial superinfection or the phase of the disease [23-25]. Both hypocoagulability and fibrinolysis shutdown, as presented by patient B, have been shown to be associated with increased mortality in bacterial sepsis [11-13,18,19]. Furthermore, lymphocytopenia has been shown to be associated with poor outcome in COVID-19 [26]. Even if thrombocytopenia, which is an important determinant of clot firmness, is rare in COVID-19, it is also associated with poor outcome in this patient population [9,27]. The mismatch between FIBTEM MCF (14 mm) and Clauss plasma fibrinogen concentration (6.8 g/L) in patient B might reflect an acquired factor XIII deficiency which often occurs in sepsis, cirrhosis, acute renal failure and malignancies [28-31]. Unfortunately, factor XIII activity is not available for patient B which leaves this interpretation speculative. The
The rapid deterioration of patient B with acute renal failure and fatal outcome is in-line with the data published by Wright et al. showing that patients with the combination of high D-dimer (> 2.6 µg/mL, here > 20 µg/mL) and fibrinolysis shutdown (TEG LY30 of 0% or ROTEM LI60 of 100%) are associated with the highest incidence of thrombosis (50%) and acute renal failure (80%) [32]. Here, increased D-dimers and fibrinolysis shutdown may reflect an imbalance of hemostasis with increased clot formation but impaired fibrinolysis – similar to disseminated intravascular coagulation (DIC). It remains to be seen whether fibrinolytic therapy with recombinant tissue plasminogen activator (rtPA) has a therapeutic role in critically ill COVID-19 patients who cannot be oxygenated adequately despite mechanical ventilation and prone positioning [33-36]. Notably, extracorporeal membrane oxygenation (ECMO) is associated with very high mortality in COVID-19 patients – in particular in patients with hyperinflammation characterized by high IL-6 levels [37]. Although this might support the use of fibrinolytic therapy with rtPA in these patients [33-36], Campello et al. demonstrated that a FIBTEM MCF < 14.5 mm is highly predictive for bleeding complications (such as hemorrhagic stroke) after rtPA [38]. Therefore, hypocoagulability in thromboelastometry, in particular a FIBTEM MCF < 14.5 mm, should be considered as a contraindication for fibrinolytic therapy in critically ill COVID-19 patients.

Of course, this case report has several limitations. First, no follow-up ROTEM analyses are available for these patients. Accordingly, the presented ROTEM analyses only represent a snapshot of the COVID-19-associated coagulopathy which can be considered as a dynamic process. Here, different thromboelastometry phenotypes may represent different patient’s conditions or different phases of the coagulopathy. Second, the cut-off values for fibrinolysis shutdown established in trauma and bacterial sepsis has been used since clear cut-off values for fibrinolysis shutdown in COVID-19-associated coagulopathy have not been established, yet. Further studies are needed to

These two cases demonstrate that thromboelastometric phenotype can be different and thromboelastometry can easily distinguish between hyper- and hypocoagulability in critically ill COVID-19 patients. Furthermore, thromboelastometry can identify patients with fibrinolysis shutdown [17-19]. The combination of thromboelastometry parameters (EXTEM and FIBTEM CT, CFT, A5, A10, MCF and LI60) and conventional biomarkers (D-dimer, Clauss fibrinogen, IL-6) might be superior in predicting clinical outcomes such as thrombosis, renal failure and death in COVID-19 patients compared to each diagnostic test alone [39]. Therefore, these test combinations can be helpful in the future to decide which therapeutic strategy might be most appropriate in individual critically ill COVID-19 patients. This would be an important step to establish precision medicine not only in thromboelastometry-guided bleeding management but also in this high-risk patient population [40,41].
References


Figure 1A. Critically ill COVID-19 patient A with a hypercoagulable phenotype.
Figure 1B. Critically ill COVID-19 patient B with a hypocoagulable phenotype.

EXTEM: extrinsically activated (tissue factor) thromboelastometric assay; FIBTEM: extrinsically activated thromboelastometric assay with the addition of cytochalasin to eliminate platelet contribution to clot firmness; CT: coagulation time, CFT: clot formation time, alpha: alpha angle; A5: amplitude of clot firmness 5 minutes after CT; A10: amplitude of clot firmness 10 minutes after CT; MCF: maximum clot firmness; LI60: lysis index in percentage of maximum clot firmness 60 minutes after CT; ML: maximum lysis during run time; *: Reference range for physiologic fibrinolysis in EXTEM as published by Stettler et al. [17].