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Monitoring of COVID-19-Associated Coagulopathy and Anticoagulation with Thromboelastometry

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Abstract
Introduction: Thrombosis occurs frequently in COVID-19. While the exact mechanism is unclear, 3 processes seem to play important roles in sepsis-related thrombosis and mortality: tissue factor expression on circulating monocytes and microparticles, hypercoagulability (increased clot firmness), and hypofibrinolysis. Rotational thromboelastometry is a point-of-care viscoelastic technique that uses the viscoelastic properties of blood to monitor coagulation. Using various assays, viscoelastometry could monitor this triad of changes in severely ill, COVID-19-positive patients. Similarly, with the increased incidence of coagulopathy, many patients are placed on anticoagulants, making management more difficult depending on the agents utilized. Viscoelastometry might also be used in these settings to monitor anticoagulation status and guide therapy, as it has in other areas. ***Case Presentation:*** We present a case series of 6 patients with different stages of disease and different management plans. These cases occurred at the height of the pandemic in New York City, which limited testing abilities. We first discuss the idea of using the NaHEPTEM test as a marker of tissue factor expression in COVID-19. We then present cases where patients are on different anticoagulants and review how viscoelastometry might be used in a patient on anticoagulation with COVID-19. ***Conclusion:*** In a disease such as COVID-19, which has profound effects on hemostasis and coagulation, viscoelastometry may aid in patient triage, disease course monitoring, and anticoagulation management.

Introduction

Thrombosis occurs frequently in COVID-19 [1, 2]. While the exact mechanism is unclear, 3 processes seem to play important roles in sepsis-related thrombosis and mortality: Tissue factor (TF) expression on circulating monocytes and microparticles leading to increased thrombin generation, increased clot firmness, and hypofibrinolysis [3–6]. Viscoelastometry is a point-of-care technique that uses the viscoelastic properties of blood to monitor coagulation [7]. It measures the time it takes to form a clot (coagulation time [CT]), the firmness of the clot (maximum clot firmness [MCF]), and how much it has broken down over time (clot lysis parameter). In this way, with 1 test, one can gather information on clot formation, stability, and lysis (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000514486 for all online suppl. material) [8]. Therefore, using various assays, viscoelas-

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Table 1. Information on patients in case series

Age, years/sex	Hospital day of draw	BMI	SOFA score	INR	APTT, s	Platelets, $10^3/\mu L$	Fibrinogen, mg/dL	D-dimer, μg/mL FEU	CRP, mg/L	GFR, mL/min/1.73 m^2
51/female	5	26.2	9	1.4	43.2	511	–	4.06	180.1	4.98
62/female	2	51.2	3	2.0	36.2	214	–	1.14	148.7	>60
57/male	13	30.8	4	–	–	268	–	2.40	276.1	>60
58/male	21	25.2	3	1.3	–	140	743	1.85	82.3	>60
65/female	9	27.4	4	1.3	45.8	354	519	1.33	45.8	46.42
64/male	25	30.1	3	–	–	217	–	0.37	2.2	55.78

BMI, body mass index; SOFA, Sequential Organ Failure Assessment; INR, International Normalization Ratio; APTT, activated partial thromboplastin time; CRP, C-reactive protein; GFR, glomerular filtration rate.

tometry could, in theory, monitor this triad of coagulation changes (decreased clotting time, increased clot firmness, and hypofibrinolysis) in severely ill COVID-19-positive patients. It therefore might be utilized for early detection, diagnosis, and the identification of targets to prevent further coagulopathy and thrombosis (online suppl. Fig. 2).

As our knowledge of the disease process unfolds, an increasing number of patients may require anticoagulant or thrombolytic therapy [9, 10]. However, the proper medication, dosage, and frequency remain elusive. Furthermore, the variability of individual responses to anticoagulant medications and even the ability of the virus to impact concentrations of anticoagulant medications may need to be taken into account [11]. We present a series of cases providing examples of how viscoelastometry can be utilized in the treatment of COVID-19 patients. It must be noted that the data were collected during the increased influx of COVID-19 patients at the Mount Sinai Hospital, New York City, NY, USA. During this time, there was a tremendous strain on resources, with many of the tests and therapeutics we would have normally deployed being unavailable. The application and utilization of viscoelastometry was one such resource. We would have preferred to utilize this test in a prescriptive manner, but this was not possible. The timings of the lab draws may seem haphazard; however, they were performed at the behest of the clinical teams to aid in management when possible. Furthermore, viscoelastometry can only be performed by trained personnel, and as its interpretation could only be performed by a very limited number of physicians during this time, it was difficult to obtain consistent testing. In each case, however, we have attempted to highlight critical or pivotal points in the cases where its utilization could have made/did make an impact on treatment decisions. Finally, given the small number of patients in this series, we cannot make statements about efficacy, nor was this the goal of this paper. We aim to proffer potential applications of this test in this patient population. As a final note, our data were garnered at the height of the pandemic surge in New York City. As such, many of the traditional testing pathways were inundated and the staff that was deployed to aid in taking care of these patients may not have been comfortable with viscoelastic testing at that time.

Case Presentation

Native Thromboelastometric Test with Heparinase and TF Expression on Circulating Monocytes and Microparticles

The native thromboelastometric (NaTEM) test, a nonactivated assay, provides data on TF expression on circulating cells and the subsequent generation of thrombin [4]. The first step of delocalized thrombin generation plays a vital role in patients with disseminated intravascular coagulation (DIC) and has been associated with mortality in sepsis [4]. By adding heparinase to this assay, one can analyze patients who are on heparin, creating the native thromboelastometric (NaHEPTEM) assay. In patients with COVID-19, it may be that the NaHEPTEM CT is inversely correlated with disease severity and shortens as TF expression increases with worsening hypercoagulability of disease progression. In this manner, NaHEPTEM CT may be used to monitor disease progression as well identify patients at a risk of thrombosis. If the increased thrombin generation is the upstream cause of D-dimer elevation, then NaHEPTEM CT shortening provides earlier evidence of coagulopathy. If so, this could be trended at admission. Current clinical practice tracks elevations in D-dimer, a late-stage marker of clot generation and breakdown. By waiting for D-dimer elevation, it may be that thrombosis and organ damage have already occurred. As such, the NaHEPTEM test may be used early to trend thrombosis risk and inflammatory changes in COVID-19 and help to guide early treatment. It should be noted that TF expression is not unique to SARS-CoV-2 but can also be caused by other viruses such as H1N1; this may extend the utility of viscoelastic testing [12].

We present a 51-year-old female with cardiovascular disease, who presented to the ED with fatigue and generalized weakness and was found to be febrile with COVID-19 (Table 1). Although initially saturating well on a nonrebreather, the patient quickly became tachypneic, hypoxemic, and was intubated. She was subsequently placed on a heparin drip (18 U/kg/h). On hospital day 5, thromboelastometry (Fig. 1a) demonstrated a NaTEM CT of 608 s and a NaHEPTEM CT of 477 s, indicating elevated TF expression [2]. The heparin therapy, which was ongoing at the time of the blood draw, exhibited minimal effect (NaTEM-to-NaHEPTEM

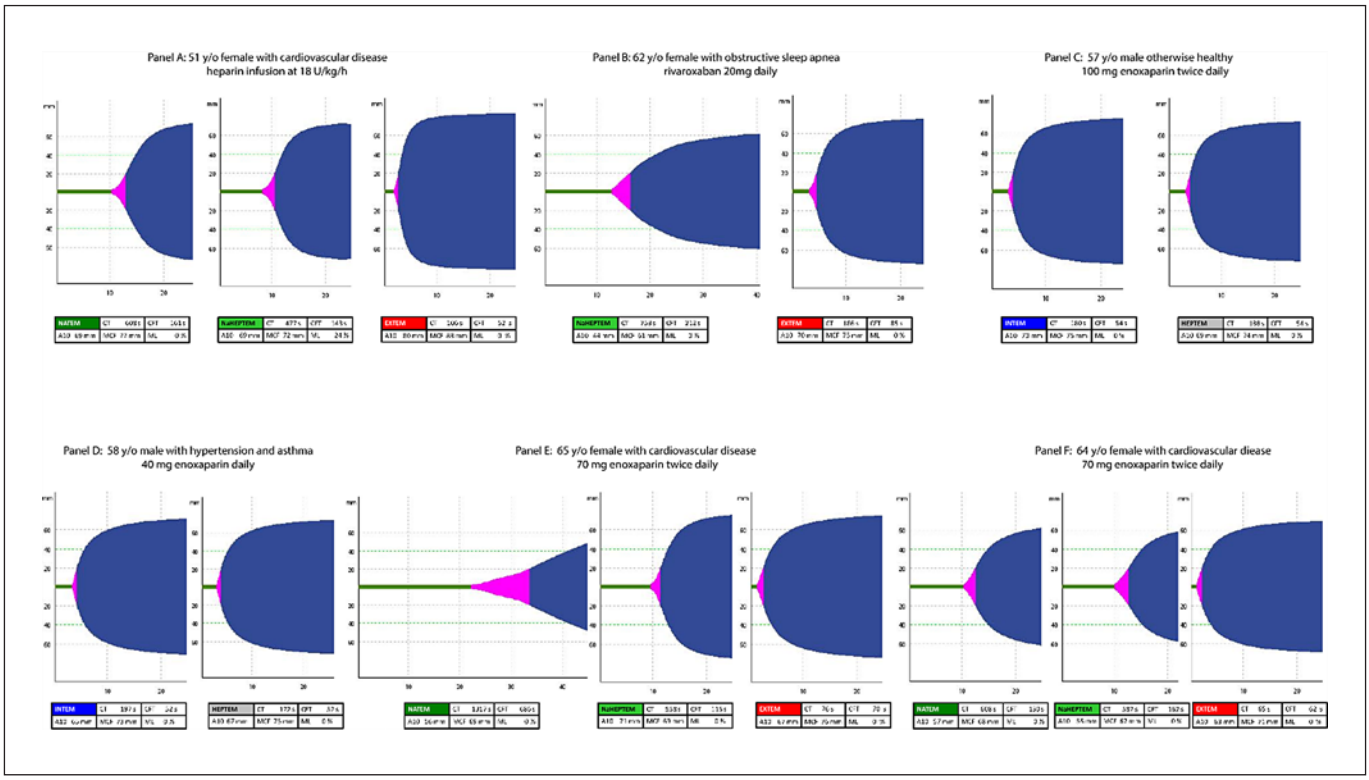

Fig. 1. Thromboelastomeric profiles of different patients on varying anticoagulants. A10, amplitude of clot firmness 10 min after CT in mm; CT, coagulation time in seconds; CFT, clot formation time in seconds; EXTEM, extrinsically activated thromboelastometric test; INTEM, intrinsically activated thromboelastometric test; MCF, maximum clot firmness in mm; ML, maximum lysis characterized by the decrease in clot firmness in % of MCF during test run; NaHEPTEM, native thromboelastometric test with heparinase; y/o, years old.

CT ratio = 1.27), with continued signs of clinically significant hypercoagulability (an extrinsically activated TEM [EXTEM] MCF of 83 mm) [3]. Unfortunately, the patient expired soon afterwards.

Anticoagulation Management

Thromboprophylaxis is recommended for all patients hospitalized with COVID-19 [9, 13, 14]. Tang et al. [15] found that anticoagulation therapy was associated with decreased mortality of patients with a sepsis-induced coagulopathy score ≥4 or D-dimer >3 μg/mL among 449 patients with severe COVID-19. However, in the total population of patients, anticoagulation was not associated with a reduction in mortality. In this study, prophylactic low-molecular-weight heparin (LMWH) was mostly utilized. While the optimal anticoagulation regimen is currently unknown, viscoelastometry can provide guidance for choosing an appropriate regimen [16]. In cases of direct oral anticoagulant (DOAC) administration, EXTEM and NaHEPTEM are presented [17, 18]. In cases where enoxaparin was utilized, either intrinsically activated TEM [INTEM] and HEPTEM or NaTEM and NaHEPTEM values and the corresponding CT ratios are presented [19]. It should be noted that, for patients on DOACs, the sensitivity of the NaHEPTEM assay has not yet been demonstrated, and the numbers are reported for informational purposes only.

We present 5 additional patients and briefly discuss their profiles (Fig. 1b–f). The goal of these reports is to demonstrate how viscoelastometry may be deployed for the evaluation and management of patients with COVID-19 and their response to varied anticoagulants.

A 62-year-old female with cardiovascular disease, obstructive sleep apnea, atrial fibrillation, and on rivaroxaban 20 mg once daily, was admitted with diarrhea, nonproductive cough, and hypoxemia (Table 1). She was started on hydroxychloroquine, azithromycin, and methylprednisolone. Thromboelastometry was performed on hospital day 2, 20.5 h after the last dose, and demonstrated a prolonged EXTEM CT of 186 s and a NaHEPTEM CT of 753 s, indicating a rivaroxaban plasma concentration >250 ng/mL (Fig. 1b) [17, 18]. Testa et al. [11] demonstrated recently that antiviral therapy in COVID-19 patients can result in a striking increase of DOAC plasma levels. Although safety in patients on hydroxychloroquine has been documented in patients with antiphospholipid syndrome, the manufacturers recommend careful monitoring of patients on both medications [20, 21]. The patient remained in the hospital for 84 days after the last dose of rivaroxaban and was then transferred to inpatient rehabilitation for another 50 days. She did not require intubation or renal replacement therapy during her stay, but did receive biphasic positive airway pressure (BiPAP) for a significant portion of her hospital course.

A hypoxic, otherwise healthy 57-year-old male was admitted to the hospital with COVID-19 pneumonia (Table 1). On hospital day 4, he was intubated for hypoxic respiratory failure. Following 5 days of treatment with prophylactic enoxaparin (40 mg daily), he was transitioned to therapeutic dosing (100 mg BID) and thromboelastometry was performed. Thromboelastometry performed on hospital day 13 and drawn 2 h after a 100-mg enoxaparin dose revealed an INTEM CT of 180 s and a HEPTEM CT of 188 s, suggesting inadequate anticoagulation, confirmed by

a value of 0.24 IU/mL on anti-Xa testing (Fig. 1c). After being extubated the following day, the patient was reintubated 5 days later after being found unresponsive on a high-flow nasal cannula. The patient required a tracheostomy on hospital day 20. After a 26-day hospital stay, he was discharged home with a trach collar.

A 58-year-old male with hypertension and asthma was admitted for hypoxemia and COVID-19 pneumonia (Table 1). He was placed on 40 mg of enoxaparin on hospital day 9. Thromboelastometry drawn on hospital day 21, 4.5 h after enoxaparin 40 mg, revealed an INTEM CT of 197 s and a HEPTEM CT of 172 s (INTEM-to-HEPTEM CT ratio = 1.15), indicating a minimal heparin effect (Fig. 1d). The patient was transitioned to therapeutic (70 mg BID) dosing after clinical decompensation. During his hospitalization, the patient was intubated for 6 days but was then discharged home on hospital day 32.

A 65-year-old female with coronary artery disease, congestive heart failure, and prior stroke presented to the ED with COVID-19 pneumonia and urosepsis (Table 1). Therapeutic enoxaparin (70 mg BID) was initiated. Thromboelastometry drawn on hospital day 9, 2 h after a 70-mg enoxaparin dose, demonstrated a NaTEM CT of 1,317 s and a NaHEPTEM CT of 558 s (NaTEM-to-NaHEPTEM CT ratio = 2.36), indicating an enoxaparin effect (enoxaparin anti-Xa-activity of approx. 0.4 IU/mL) [19] below the typical therapeutic target, and a lysis index 60-min (LI60) value of 99% on both NaTEM and NaHEPTEM which indicated hypofibrinolysis. EXTEM MCF showed hypercoagulability with 76 mm (Fig. 1e). The patient remained in the hospital for 26 days complicated by further respiratory failure necessitating ICU admission. Thirty-eight days after discharge, she was readmitted for multifocal pneumonia. Currently the patient is stable at a long-term care facility.

A 64-year-old female with cardiovascular disease was admitted with COVID-19 pneumonia. Prophylactic enoxaparin (40 mg daily) was initiated and she was transitioned to therapeutic (70 mg BID) dosing secondary to hospital protocol, at which time thromboelastometry was performed (Table 1). Thromboelastometry drawn on hospital day 25, 2 h after a 70-mg enoxaparin dose, demonstrated a NaTEM CT of 608 s and NaHEPTEM CT of 587 s (NaTEM-to-NaHEPTEM CT ratio = 1.04, corresponding to enoxaparin anti-Xa activity <0.1 IU/mL) [19]. The EXTEM MCF was 71 mm, indicating an inadequate impact of anticoagulation as well as a continued hypercoagulable state, although at this time the enoxaparin dosage was not changed (Fig. 1f). During her hospitalization, the patient was intubated for 7 days but then extubated to a high-flow-oxygen nasal cannula at the time of thromboelastometric evaluation. Her hospitalization was further complicated by deep vein thrombosis (DVT) that occurred after the increase in the enoxaparin dose as well as a subsequent gastrointestinal bleed. She was discharged on hospital day 77.

It should be noted that these last 2 patients had a similar body size, with weights of 68.5 and 72.3 kg, and BMIs of 27.4 and 30.1, respectively. They were also of a similar age and had similar renal function (GFR 46.42 and 55.78 mL/min/1.73 m^2, respectively). Both were also at similar disease stages and required high-flow-oxygen nasal cannula to maintain oxygenation. However, as one can see, their responses to the same doses of enoxaparin were exceedingly different. Patients with COVID-19 may demonstrate signs of heparin resistance [22], even to LMWH, one of several explanations which are beyond the scope of this paper. However, regardless of the etiology, the variability of effectiveness of anticoagulants in this patient population adds to the importance of monitoring the coagulation system of COVID-19 patients on anticoagulation.

Discussion

Based on our cases and others reported, we believe that thromboelastometry could provide insights into the triad of coagulopathy in COVID-19 patients (online suppl. Fig. 2) as well as information about the effectiveness of current anticoagulation regimens involving a variety of agents. It is apparent that many patients are overtly resistant to standard anticoagulation dosing regimens and careful monitoring is warranted. It is also clear that the hypercoagulable state of COVID-19 persists despite standard anticoagulation, and the consideration of alternative anticoagulant agents as well as thrombolysis may be indicated in cases of clinical decompensation [10, 23].

Given the positive impact of anticoagulation on survival, managing coagulopathy is likely a cornerstone of COVID-19 management [15, 24, 25]. Viscoelastometry is a versatile point-of-care test that can serve many functions and may enable us to predict outcomes or risk stratify patients [20]. Turnaround times tend to be shorter than traditional assays, and certain assays may serve as substitutes for traditional laboratory tests when laboratories are overburdened with samples. Moreover, the coagulation changes that occur in COVID-19 patients with severe disease, from hypercoagulability (due to TF expression, increased fibrinogen concentration, and platelet activation) to hypofibrinolysis, can all be detected and managed using viscoelastometry parameters. Viscoelastometry may also be useful in both assessing the effect of anticoagulant or thrombolytic medication in COVID-19 patients and directing therapy [10, 16]. However, it should be noted that rotational viscoelastometry is not the gold standard for monitoring the effect on DOACs and LMWH and should be combined with tests such as anti-Xa activity. Its clinical application is best seen as one piece of the mosaic of decision-making for these complex patients. Further investigation into the diagnostic value of viscoelastometry in COVID-19 is warranted.

Statement of Ethics

The Mount Sinai Program for the Protection of Human Subjects granted a waiver of approval for this case series. Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

Dr. Klaus Görlinger holds a position with Tem Innovations. No other author has any competing interests to declare.

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Author Contributions

D.K., P.M., C.G., J.H., S.Z., and J.M. played an important role in data collection, analysis and interpretation of lab results, and the writing of the paper. K.G. played an important role in the interpretation of lab results and the writing of the paper.

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