

Personalizing Antithrombotic Therapy in COVID-19: Role of Thromboelastography and Thromboelastometry

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Coronavirus-2019 (COVID-19) infection is responsible for the pandemic outbreak across the world. The pathophysiology of COVID-19 has been characterized by endothelial dysfunction, and a thromboinflammatory state. Severe infection and poor clinical outcomes have been associated with diffuse endothelial dysfunction and a hyperinflammatory state leading to a cytokine storm which further enhances thrombotic complications.^{1,2} The pathophysiology uniquely affects the lungs in its early stages as evidenced by autopsy reports of diffuse alveolar damage along with pulmonary intravascular microthrombi in the absence of known venous thromboembolism (VTE).³ Multiple retrospective and prospective clinical trials have evaluated thromboinflammatory biomarkers linking them to poor prognosis among patients with COVID-19 infection.^{4–6} The thrombotic biomarkers evaluated include D-dimer levels, fibrinogen levels, prothrombin time (PT), and activated partial thromboplastin time (aPTT). There have been several reports and meta-analyses linking elevated D-dimer levels with poor prognosis including severity and mortality with COVID-19 infection.^{5,7} However, several concerns have been raised with the use of D-dimer as a biomarker among COVID-19 infected patients. D-dimer has low specificity and elevated levels are often seen with advanced age, African American race, female sex, active malignancy, surgery, pregnancy, immobility, cocaine use, connective tissue disorders, end-stage renal disease, and prior thromboembolic disease.⁸ Also, D-dimer reflects a later stage in the hemostatic process and is released when a clot is degraded by the fibrinolytic processes. Other standard laboratory tests including PT and aPTT measure the clotting activity from the plasma and ignore other components of the coagulation such as the platelets and the fibrinolysis. The platelet count and fibrinogen concentration also have the

caveat of providing static measures with no information regarding their functionality.

On the other hand, whole blood viscoelastic analysis can be rapidly performed by thromboelastography (TEG) or rotational thromboelastometry (ROTEM), which measure the whole blood capability to make and sustain clot formation.⁹ Several reports have now been published describing early experience with TEG or ROTEM for patients admitted with severe COVID-19 to critical care settings in Italy and the United States.^{10–12} The TEG parameters include reaction time (*R*, represents the initiation phase and measures the time of latency from start of the test to initial fibrin formation), clot formation time (*K*, represents amplification phase and measures the time taken to achieve 20 mm of clot strength), angle or α (*K* angle, represents the propagation phase and measures the rate of clot formation), maximum amplitude (*MA*, represents the overall stability of the clot), and amplitude at 30 minutes (*LY30*, represents the fibrinolysis phase and measures the percentage decrease in amplitude at 30 minutes post-*MA*). Panigada et al demonstrated a hypercoagulable profile measured by TEG in 24 patients admitted to the intensive care unit (ICU) with COVID-19.¹⁰ They noted that the reaction time (*R*) and clot formation time (*K*) were shorter than those of the reference population in 50 and 83% of the COVID-19 patients, respectively. *K* angle and *MA* values were higher than those of the reference population in 72 and 83% of the COVID-19 patients, whereas clot lysis at 30 minutes (*LY-30*) was lower in 100% of the COVID-19 population.¹⁰ Similar results were observed by Maatman et al and Wright et al, showing a COVID-19-associated hypercoagulable state measured by TEG and associated fibrinolysis shutdown (defined by *LY-30* <0.8%)¹¹ in 12 and

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Table 1 Summary of TEG and ROTEM parameters in COVID-19 infection (data presented as mean values in COVID-19/reference range)

TEG						
	R (min)	K (min)	Angle K (degree)	MA (mm)	LY30 (%)	D-dimer (ng/mL)
Panigada et al ¹⁰ (n = 24)	6.3/4–8	1.5/0–4	69.4/47–74	79.1/54–72	7.8/0–8	4,877/< 500
Wright et al ¹¹ (n = 44)	5.8/2–8	N/A	71/55–78	73/50–70	0/0.8–3	1,840/< 500
Maatman et al ¹² (n = 12)	4.8/5–11	1.4/1–3	69.6/53–73	70.8/50–72	0.8/0–7	506/321–973
Mortus et al ¹³ (n = 21)	6/4–7	N/A	73/61–73	74/55–65	2.1/0–5	8,300
ROTEM						
	CT (s)	CFT (s)	Angle K (degree)	MCF (mm)	ML (%)	D-dimer (ng/mL)
Pavoni et al ¹⁴ (n = 40)	78.3/38–79	41.6/34–159	N/A	76.6/50–72	9.4	1,556

Abbreviations: CFT, clot formation time; CT, clotting time; K, clot formation time; LY30, amplitude at 30 minutes; MA, maximum amplitude; MCF, maximum clot firmness; ML, maximum lysis; R, reaction time; ROTEM, rotational thromboelastometry; TEG, thromboelastography.

44 patients admitted to the ICU, respectively (► **Table 1**).^{11,12} The patients with hypercoagulable profile and/or fibrinolysis shutdown were found to have a higher rate and shorter time to VTE (40 vs. 5% in patients without shutdown, $p = 0.013$).¹² Similarly, Mortus et al found high K/α or high MA in 19 out of 21 patients admitted with severe COVID-19 when measured by TEG.¹³ Finally, Pavoni et al showed consistent evidence of a hypercoagulable state in severe COVID-19 with the ROTEM platform with improvement of fibrinogen clot firmness measurements after 10 days of illness, suggesting a dynamic component of changes in coagulation that accompany the rise and fall of inflammatory parameters.¹⁴

In summary, all the current studies support COVID-19 as a hypercoagulable and hypofibrinolytic state in the ICU setting. It should be noted that all the above-mentioned studies used the TEG5000 hemostasis analyzer (Haemonetics, Braintree, Massachusetts, United States) instead of the TEG-6S, which is a point-of-care device and did not measure fibrin clot strength.⁹ Prior studies have shown fibrin clot strength as a strong and independent predictor of ischemic outcomes.¹⁵

All intubated ICU patients with low risk of bleeding are recommended low-intensity pharmacologic prophylaxis including low-molecular-weight heparin (nadroparin 65 IU/kg/day, or dalteparin 5,000 IU/day, or enoxaparin 40 mg/day) and low-dose unfractionated heparin (5,000 units twice a day) for VTE prevention.¹⁶ However, due to the very high incidence of thromboembolic complications despite standard low-dose VTE prophylaxis among severe COVID-19 infections with elevated D-dimer levels, intermediate-intensity or full-dose anticoagulation as opposed to standard low-intensity prophylaxis is now routinely used.¹⁷ The data regarding the best biomarkers to guide decisions about intensification of anticoagulant prophylaxis in patients with severe COVID-19 are rapidly evolving.¹⁷ Due to the ease of testing and their properties as a single test that is able to evaluate different components and stages of coagulation and platelet function at the bedside, TEG or ROTEM may be ideally suited to predict thrombotic risk in patients with moderate or severe COVID-19. Other advantage, especially in the setting of COVID-19, includes the flexibility of point-of-care testing with the newer TEG6s and ROTEM-Sigma devices, which can be safely performed without

the risk of aerosolization. To this end, we are conducting an ongoing study—*The evaluation of hemostasis by thromboelastography, platelet function testing, and biomarker analysis in hospitalized COVID-19 patients (TARGET-COVID Study)*—to determine an individual patient's degree of thrombotic and bleeding risk using TEG. We propose that the development of individual thrombotic phenotypes will help personalize antithrombotic therapy in patients affected by COVID-19 and improve outcomes.

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Conflict of Interest

R.P.K. has received consulting fees from Haemonetics. P.A. G. receives honoraria for lectures and consultations, including service on speakers' bureaus from Bayer, Merck, Janssen, Medicare, and World Medical, and is receiving grants from the National Institutes of Health, Janssen, Merck, Bayer, Haemonetics, Instrumentation Labs, and Amgen. P.A.G. holds stock or stock options in Merck, Medtronic, and Pfizer, and is holding patents in the area of personalized antiplatelet therapy and interventional cardiology. Other authors report no disclosure.

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