Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

37. Greene R, Lind S, Jantsch H, et al. Pulmonary vascular obstruction in severe ARDS: angiographic alterations after i.v. fibrinolytic therapy. AJR Am J Roentgenol 1987;148:501–508.
38. Hardaway RMHH, Tyroch AH, et al. Treatment of severe acute respiratory distress syndrome: a final report on a phase I study. Am Surg 2001;67:377–382.
39. Moore HB, Barrett CD, Moore EE, et al. Is there a role for tissue plasminogen activator (tPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)? J Trauma Acute Care Surg 2020 March 20. https://doi.org/10.1097/TA.0000000000002694 [Epub ahead of print].
40. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. J Thromb Haemost 2020 Apr 9. https://doi.org/10.1111/jth.14828 [Epub ahead of print].
41. Choudhury R, Barrett CD, Moore HB, et al. Salvage use of tissue plasminogen activator (tPA) in the setting of acute respiratory distress syndrome (ARDS) due to COVID-19 in the USA: a Markov decision analysis. World J Emerg Surg 2020;15:29.

Invited Commentary

Fibrinolysis Shutdown and Thrombosis in Severe COVID-19

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The coagulopathy associated with COVID-19 has emerged as a key driver of morbidity and mortality, especially in patients with severe disease. There is mounting evidence that a prothrombotic picture dominates, with both macrothrombi in the venous and arterial circulations and microthrombi, as evidenced by multisystem organ failure. The reported incidence of venous thromboembolism (VTE) in critically ill patients with COVID-19 has been alarmingly high. An observed VTE incidence of 20% by day 7 of hospital admission has been reported in a retrospective study, despite thromboprophylaxis, with an estimated cumulative VTE incidence as high as 42% by day 21.[1] In observational data, heparin anticoagulation in these patients has also been associated with a reduced mortality rate and may be due to both the anticoagulant and immunomodulatory effects of heparin molecules.[2,3] Identification of COVID-19 patients at greatest risk for thrombosis and end organ damage has been an area of keen interest, as are prognostic indicators for morbidity (including VTE) and mortality.

In this study from the University of Colorado Anschutz Medical Campus and Shock Trauma Center at Denver Health, Wright and colleagues[4] assessed the clinical utility of thromboelastography (TEG) for the prediction of macro- and microvascular thrombosis in a severe COVID-19 patient cohort. The authors analyzed kaolin/ kaolin-heparinase TEG measurements performed on 44 COVID-19 patients to characterize the TEG profile and integrate these results with those of conventional coagulation assays, including D-dimer levels, fibrinogen, platelet count, prothrombin time, and activated partial thromboplastin time.[4] They described an elevated maximum amplitude (MA) in TEG analyses, consistent with a hypercoagulable state, and a low lysis at 30 minutes in 57% of patients, suggestive of fibrinolysis shutdown. The combination of fibrinolysis shutdown and a D-dimer concentration greater than 2,600 ng/mL FEU (fibrinogen equivalent units) was associated with VTE in 50% of patients and the need for hemodialysis in 80% of patients, compared with 0% and 14%, respectively, in patients who did not manifest either finding. Contrary to the findings of Tang and associates,[5] demonstrating a high prevalence of disseminated intravascular coagulation (DIC) (71.4%) in nonsurvivors of COVID-19, however, the authors of this study mentioned that none of their patients met clinical criteria for DIC based on the criteria of the International Society on Thrombosis and Hemostasis (ISTH).

This study sheds some light on the changes in procoagulant and fibrinolytic pathways caused by COVID-19, but it also raises some important questions for future research. The markedly elevated D-dimer concentrations described in cases of severe COVID-19 is strongly suggestive of plasmin-mediated hyperfibrinolysis, which appears to be inconsistent with the finding of fibrinolysis shutdown on TEG. Fibrinolysis is an essential dynamic process of fibrin clot maturation and degradation initiated by the conversion of plasminogen to plasmin by activators, such as tissue-type plasminogen activator (tPA), and subsequent plasmin-mediated cleavage of fibrin polymers.[6] Inhibitors of fibrinolysis, mainly plasminogen activator inhibitor-1 (PAI-1) and α_2-antiplasmin, maintain a delicate homeostasis in the normal physiologic state. Derangements in the relative concentrations of the activators and inhibitors of fibrinolysis can result in a spectrum of abnormalities, from overly active plasmin-mediated fibrin cleavage (hyperfibrinolysis) to fibrinolysis shutdown. While suppressed fibrinolysis is typical of sepsis-associated DIC, markedly elevated D-dimer levels are relatively infrequent.[7] In fact, patients with severe sepsis and normal D-dimer levels have been shown to have the highest mortality, reflecting the vital role of plasmin in clearing microvascular thrombi.[8] Because hyperfibrinolysis is a dynamic process, it

is possible that the timing of specimen collection is a critical factor in the detection of a hyperfibrinolytic state, especially given the short half-life of active tPA in the circulation, and the fact that both PAI-1 and α_2-antiplasmin are acute phase reactants that become elevated in inflammatory conditions.[9] However, a recently published study on the viscoelastic profile of COVID-19 using rotational thromboelastometry analysis did collect samples on days 0, 5, and 10, after admission to the intensive care unit, and also found no evidence of fibrinolytic activity, despite a hypercoagulable pattern.[10]

In the setting of fibrinolysis shutdown observed in viscoelastic tests in patients with severe COVID-19, the source of the (often markedly) elevated D-dimer levels remains unclear. It is possible that localized hyperfibrinolysis is occurring that is not detectable at the systemic level in whole blood assays. Microparticles have been shown to efficiently generate both thrombin and plasmin locally on their membrane surfaces and may also be critical mediators of thrombosis in COVID-19 that require further study.[11] Likewise, the interplay between inflammation and thrombosis is well established, but the contributions of neutrophils to the pathogenesis of VTE, by virtue of the formation of neutrophil extracellular traps, has only recently been appreciated.[12] Other investigators have also postulated a key role of monocyte expression of tissue factor in response to proinflammatory cytokines as a driver of hypercoagulability in patients with severe infection.[13] Future research should profile the changes in activators and inhibitors of fibrinolysis, including tPA, PAI-1, and plasmin-antiplasmin complex levels over time, to further characterize the dynamic process of fibrinolysis in COVID-19, and should also study the role of neutrophil and monocyte activation in promoting thrombosis and altering fibrinolysis in patients with severe COVID-19.

REFERENCES

1. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020 May 5. Online ahead of print.
2. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094−1099.
3. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020 May 5. Online ahead of print.
4. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlates to thromboembolic events in severe COVID-19 Infection. J Am Coll Surg 2020 May 15. Online ahead of print.
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844−847.
6. Schaller J, Gerber SS. The plasmin-antiplasmin system: structural and functional aspects. Cell Mol Life Sci 2011;68:785−801.
7. Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. J Intensive Care 2014;2:20.
8. Semeraro F, Ammollo CT, Caironi P, et al. Low D-dimer levels in sepsis: Good or bad? Thrombosis Res 2019;174:13−15.
9. Festa A, D'Agostino R Jr, Tracy RP, et al. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes 2002;51:1131−1137.
10. Pavoni V, Gianesello L, Pazzi M, et al. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J Thromb Thrombolysis 2020 May 11. Online ahead of print.
11. Vallier L, Cointe S, Lacroix R, et al. Microparticles and fibrinolysis. Semin Thromb Hemost 2017;43:129−134.
12. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med 2020 Jun 1;217:e20200652.
13. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;PMID:32376901.

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