COVID-19–associated Coagulopathy

Less Fibrinolysis Can Be More Harmful!

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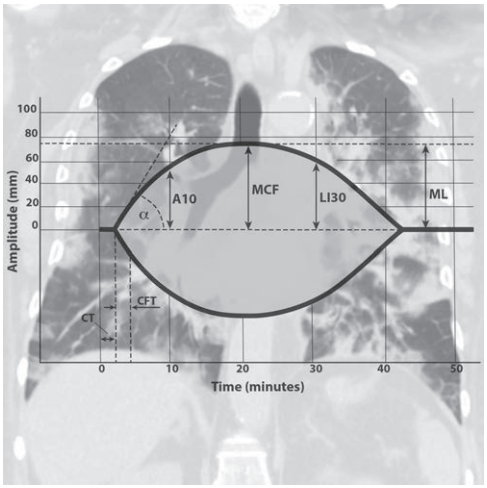
With more than 300,000 deaths, the United States is the country with the highest coronavirus disease 2019 (COVID-19) death toll globally, and the hospitalization attributable to COVID-19 continues to increase. Beyond respiratory and renal failure, COVID-19–associated coagulopathy is a major challenge with a very high incidence of thromboembolic complications.[1] In contrast to bacterial sepsis and disseminated intravascular coagulation, standard coagulation tests such as activated partial thromboplastin time, prothrombin time, and antithrombin level do not significantly change in most COVID-19 patients, despite a high incidence of thrombotic events.[2] This important finding further emphasizes that the classical cascade model of hemostasis and standard coagulation tests that focus on plasmatic clotting times do not reflect the pathophysiology of thromboinflammatory response/immunothrombosis as it occurs in COVID-19. With acute infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, virus–cell and cell–cell-interactions, particularly among platelets, macrophages, neutrophils, and endothelial cells, play an essential role. Accordingly, the cell-based model of hemostasis and whole blood viscoelastic and platelet function tests are more appropriate to mirror the pathophysiology of COVID-19–associated coagulopathy.[3,4]

In the current issue of Anesthesiology, Heinz *et al.*[5] report fibrinolysis resistance and platelet aggregation in critically ill COVID-19 patients measured with thromboelastometry and whole blood impedance aggregometry. In their study, critically ill COVID-19 patients showed hypercoagulability that was characterized by greater values of overall maximum clot firmness and the corresponding contribution of fibrin, as well as a greater fibrinolysis resistance to a tissue plasminogen activator (tPA) challenge—characterized by a longer lysis time. This is consistent with the recently published data by Nougier *et al.*,[6] noting that fibrinolysis resistance in tPA-thromboelastometry was associated with increased plasmin-activator inhibitor-1 concentrations. This thromboelastometry test modification has already been developed and validated previously to assess the resistance of clots against a tPA-challenge (*e.g.*, in patients with increased or decreased thrombin generation[7]). Other authors report hypofibrinolysis or fibrinolysis shutdown in patients with severe COVID-19, characterized by maximum lysis within a 60-min runtime of less than 3.5%. Creel-Bulos *et al.*[8] reported that eight of nine (89%) COVID-19 patients with thrombosis met the criteria for *fibrinolysis shutdown*, and eight of 11 (73%) patients with fibrinolysis shutdown developed thrombosis despite anticoagulation. In contrast, only one of 14 (7%) patients with physiologic fibrinolysis developed a thrombosis. Both thromboelastography (area under the receiver operating characteristics curve [AUC], 0.74 [95% CI, 0.58 to 0.9]; $P = 0.021$)[9] and thromboelastometry (AUC, 0.8 [95% CI, 0.7 to 0.9]; $P = 0.001$)[10] confirmed that hypofibrinolysis was associated with an enhanced incidence of thrombosis. In both studies, the combination of maximum lysis and



"…the systemic inflammatory response syndrome of acute infections, sepsis, disseminated intravascular coagulation, and COVID-19 are characterized by different viscoelastic and platelet function patterns."

Image: J. P. Rathmell.

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D-dimer concentrations provided the highest sensitivity and specificity of thromboembolic risk prediction (AUC, 0.92 [95% CI, 0.8 to 1]; $P < 0.001$)[10] as well as renal failure with the need for dialysis. For clinical interpretation, the combination of both hypofibrinolysis and elevated D-dimer concentrations has resulted in some confusion because elevated D-dimer concentrations have been misinterpreted as a sign of hyperfibrinolysis.[11] In fact, D-dimer concentrations rise with plasma fibrinogen concentration and thrombin generation, which are both increased in COVID-19, but only 0.02% of the fibrinogen mass is cleaved to D-dimers in COVID-19.[3–6,12] Accordingly, elevated D-dimer concentrations reflect an increased fibrin deposition (microthrombosis) rather than an increased fibrin breakdown (fibrinolysis) in severe COVID-19. To that effect, the combination of increased fibrin deposition and hypofibrinolysis/fibrinolysis shutdown results in thrombosis of the microcirculation with subsequent failure of the lungs and kidneys as well as neurologic disorders. This is not a new finding, because hypofibrinolysis has already been shown to discriminate between systemic inflammatory response syndrome and bacterial sepsis and to predict mortality in sepsis as reported previously.[13–15]

The current publication by Heinz *et al*. also reports only a slightly lower platelet aggregation attributable to adenosine diphosphate stimulation in critically ill patients with COVID-19 compared with a healthy controls.[5] This is contrary to findings in studies assessing viscoelastic and platelet function testing, where decreased maximum clot firmness and decreased platelet aggregation have been reported as early signs of bacterial sepsis and mortality.[16–18]

Limitations of the present study should be considered, because the number of patients evaluated was low and viscoelastic and platelet function testing were performed in ventilated patients after a mean of 7 days in the intensive care unit on one single occasion. Further, this study does not provide data on early COVID-19 hemostasis changes or during the clinical course of COVID-19 from hospital admission to discharge or death. Currently, other multicenter studies are underway to answer these questions (*e.g.*, the ROTEM Sigma in Hospitalized COVID-19 Patients [ROHOCO] Study, recruiting 500 patients in 16 hospitals and 11 countries; DRKS00023934).[3] Of note is that viscoelastic testing is reported to be superior to standard plasmatic coagulation tests such as activated partial thromboplastin time and prothrombin time in predicting thrombosis in COVID-19.[2,8–10]

During the last 150 yr, the knowledge about thrombosis has evolved from the macropathological model of the Virchow triad of venous thrombosis—based on blood flow, blood constituent and vessel wall issues (fig. 1)—to a micropathological model of thrombosis—characterized by tissue factor

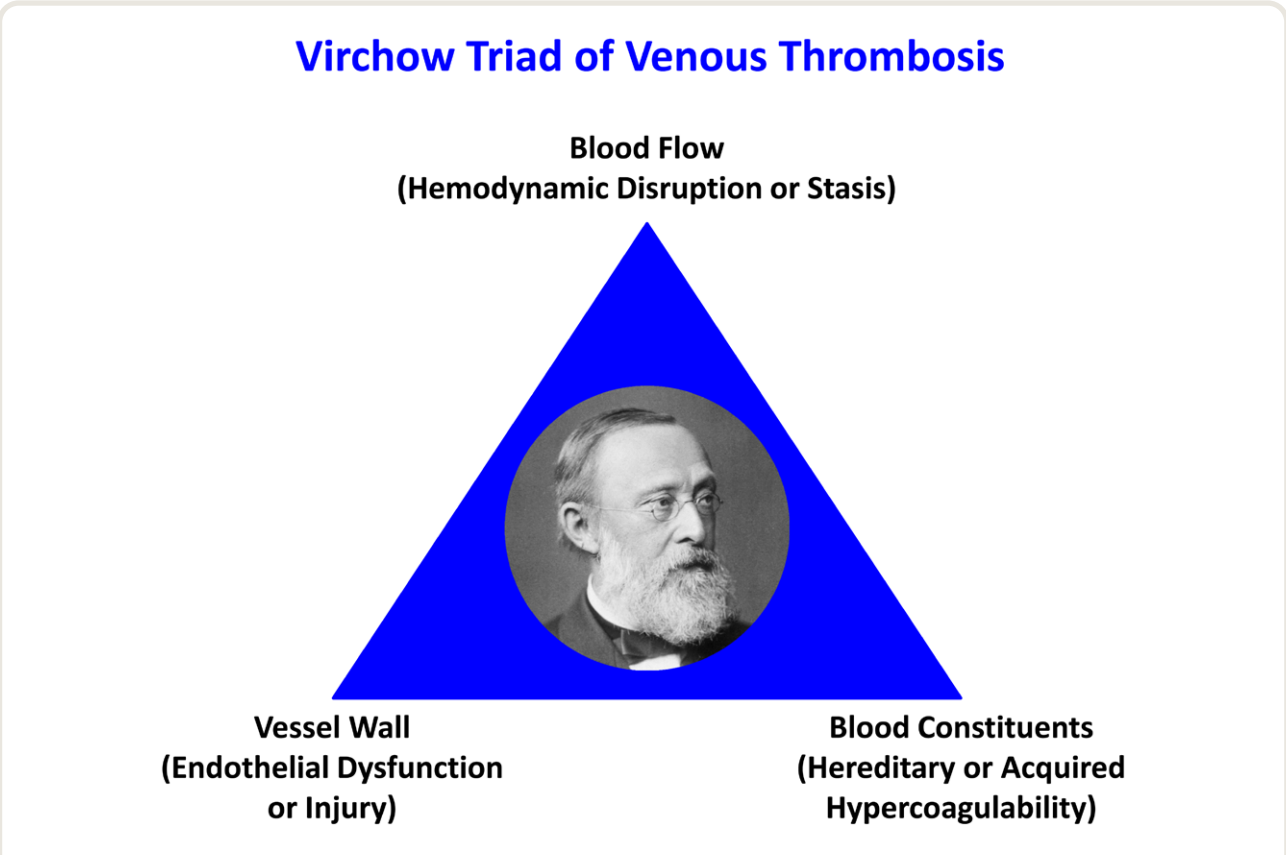

Fig. 1. Virchow triad of venous thrombosis.

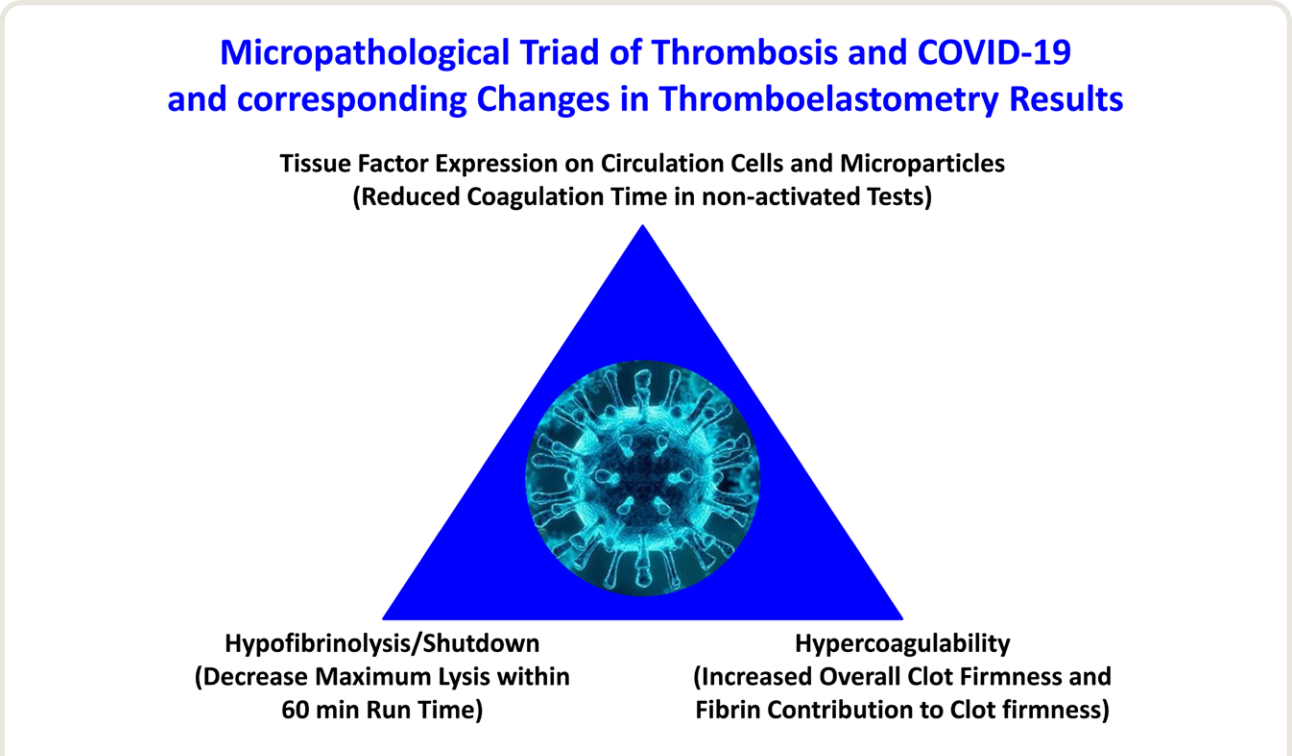

Fig. 2. Micropathological triad of thrombosis and COVID-19 and corresponding changes in thromboelastometry results.

expression of circulating cells and microparticles, hypercoagulability, and hypofibrinolysis (fig. 2). These changes on the cellular level are not reflected by plasmatic coagulation tests but by whole blood viscoelastic testing and are characterized by decreased coagulation times in nonactivated viscoelastic tests, increased clot firmness in viscoelastic tests with and without platelet contribution, as well as hypofibrinolysis/fibrinolysis shutdown (thromboelastometry triad of thrombosis and COVID-19).[1,2,8–10,19] Notably, the systemic inflammatory response syndrome of acute infections, sepsis, disseminated intravascular coagulation, and COVID-19 are characterized by different viscoelastic and platelet function patterns.[3,18] We believe that differentiation and outcome management strategies can be improved by multimodal testing that includes the combination of viscoelastic, platelet function, and conventional biomarkers such as D-dimers.[9,10,20] In combination with big data, machine learning, and pattern recognition, this may offer in the near future opportunities to detect these important issues early and may allow for personalized therapy in these critically ill patients in terms of precision medicine.[21,22]

Competing Interests

Dr. Görlinger is the medical director of Tem Innovations GmbH (Munich, Germany) since July 2012. Dr. Levy acts as a member of steering committees for Octapharma (Lachen, Switzerland), Instrumentation Laboratory (Bedford, Massachusetts), and Merck (Kenilworth, New Jersey).

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References

1. Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, Le Mao R, Rodríguez C, Hunt BJ, Monreal M: Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: A systematic review and meta-analysis. Chest 2020 [Epub ahead of print]
2. Spiezia L, Campello E, Cola M, Poletto F, Cerruti L, Poretto A, Simion C, Cattelan A, Vettor R, Simioni P: More severe hypercoagulable state in acute COVID-19 pneumonia as compared with other pneumonia. Mayo Clin Proc Innov Qual Outcomes 2020; 4:696–702
3. Görlinger K, Dirkmann D, Gandhi A, Simioni P: COVID-19-associated coagulopathy and inflammatory response: What do we know already and what are the knowledge gaps? Anesth Analg 2020; 131:1324–33
4. Iba T, Connors JM, Levy JH: The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res 2020; 69:1181–9
5. Heinz C, Miesbach W, Herrmann E, Sonntagbauer M, Raimann FJ, Zacharowski K, Weber CF, Adam EH: Greater fibrinolysis resistance but no greater

platelet aggregation in critically ill COVID-19 patients. Anesthesiology 2021; 134:457–67
6. Nougier C, Benoit R, Simon M, Desmurs-Clavel H, Marcotte G, Argaud L, David JS, Bonnet A, Negrier C, Dargaud Y: Hypofibrinolytic state and high thrombin generation may play a major role in SARS-COV2 associated thrombosis. J Thromb Haemost 2020; 18:2215–9
7. Kuiper GJ, Kleinegris MC, van Oerle R, Spronk HM, Lancé MD, Ten Cate H, Henskens YM: Validation of a modified thromboelastometry approach to detect changes in fibrinolytic activity. Thromb J 2016; 14:1
8. Creel-Bulos C, Auld SC, Caridi-Scheible M, Barker N, Friend S, Gaddh M, Kempton CL, Maier C, Nahab F, Sniecinski R: Fibrinolysis shutdown and thrombosis in a COVID-19 ICU. Shock 2020 [Epub ahead of print]
9. Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, Urban S, Nydam TL, Moore PK, McIntyre RC Jr: Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg 2020; 231:193–203.e1
10. Kruse JM, Magomedov A, Kurreck A, Münch FH, Koerner R, Kamhieh-Milz J, Kahl A, Gotthardt I, Piper SK, Eckardt KU, Dörner T, Zickler D: Thromboembolic complications in critically ill COVID-19 patients are associated with impaired fibrinolysis. Crit Care 2020; 24:676
11. Ibañez C, Perdomo J, Calvo A, Ferrando C, Reverter JC, Tassies D, Blasi A: High D dimers and low global fibrinolysis coexist in COVID19 patients: what is going on in there? J Thromb Thrombolysis 2020 [Epub ahead of print]
12. Almskog LM, Wikman A, Svensson J, Wanecek M, Bottai M, van der Linden J, Ågren A: Rotational thromboelastometry results are associated with care level in COVID-19. J Thromb Thrombolysis 2020 [Epub ahead of print]
13. Adamzik M, Eggmann M, Frey UH, Görlinger K, Bröcker-Preuss M, Marggraf G, Saner F, Eggebrecht H, Peters J, Hartmann M: Comparison of thromboelastometry with procalcitonin, interleukin 6, and C-reactive protein as diagnostic tests for severe sepsis in critically ill adults. Crit Care 2010; 14:R178
14. Schmitt FCF, Manolov V, Morgenstern J, Fleming T, Heitmeier S, Uhle F, Al-Saeedi M, Hackert T, Bruckner T, Schöchl H, Weigand MA, Hofer S, Brenner T: Acute fibrinolysis shutdown occurs early in septic shock and is associated with increased morbidity and mortality: Results of an observational pilot study. Ann Intensive Care 2019; 9:19
15. Levy JH, Iba T, Connors JM: Vascular injury in acute infections and COVID-19: Everything old is new again. Trends Cardiovasc Med 2021; 31:6–7
16. Adamzik M, Langemeier T, Frey UH, Görlinger K, Saner F, Eggebrecht H, Peters J, Hartmann M: Comparison of thrombelastometry with simplified acute physiology score II and sequential organ failure assessment scores for the prediction of 30-day survival: A cohort study. Shock 2011; 35:339–42
17. Brenner T, Schmidt K, Delang M, Mehrabi A, Bruckner T, Lichtenstern C, Martin E, Weigand MA, Hofer S: Viscoelastic and aggregometric point-of-care testing in patients with septic shock: Cross-links between inflammation and haemostasis. Acta Anaesthesiol Scand 2012; 56:1277–90
18. Adamzik M, Görlinger K, Peters J, Hartmann M: Whole blood impedance aggregometry as a biomarker for the diagnosis and prognosis of severe sepsis. Crit Care 2012; 16:R204
19. Adamzik M, Schäfer S, Frey UH, Becker A, Kreuzer M, Winning S, Frede S, Steinmann J, Fandrey J, Zacharowski K, Siffert W, Peters J, Hartmann M: The NFKB1 promoter polymorphism (-94ins/delATTG) alters nuclear translocation of NF-κB1 in monocytes after lipopolysaccharide stimulation and is associated with increased mortality in sepsis. Anesthesiology 2013; 118:123–33
20. Görlinger K: Biomarkers *versus* viscoelastic testing for the detection of fibrinolysis. ANZ J Surg 2020; 90:411–2
21. Burns ML, Kheterpal S: Machine learning comes of age: Local impact *versus* national generalizability. Anesthesiology 2020; 132:939–41
22. Chaudhary R, Kreutz RP, Bliden KP, Tantry US, Gurbel PA: Personalizing antithrombotic therapy in COVID-19: Role of thromboelastography and thromboelastometry. Thromb Haemost 2020; 120:1594–6