Received: 25 November 2020 | Accepted: 27 November 2020

DOI: 10.1002/rth2.12473

COMMENTARY

COVID-19–related prothrombotic changes increase with lung injury and remain unaffected by anticoagulation therapy

Alice Assinger PhD

Institute of Vascular Biology and Thrombosis Research, Center for Physiology and Pharmacology, Medical University of Vienna, Vienna, Austria

Correspondence: Alice Assinger, Medical Unviersity of Vienna, Center for Physiology and Pharmacology, Institute of Vascular Biology and Thrombosis Research, Schwarzspanierstraße 17, 1090 Vienna, Austria.
Email: alice.assinger@meduniwien.ac.at

Handling Editor: Dr Cihan Ay.

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) evokes an intricate global public health crisis. Scientists all over the world are trying to decipher the mechanisms by which SARS-CoV-2 induces a systemic response in severely affected individuals, which contributes to a high mortality rate. Hence, a clear understanding of the underlying pathology is warranted to allow for optimal treatment of patients, which—in the case of COVID-19—seems diverse and complex.

Recently, the pathogenesis of COVID-19 was elegantly compared to four horsemen of a viral apocalypse, consisting of four intertwined loops, which include the viral loop, the hyperinflammatory loop, the noncanonical renin-angiotensin system axis loop, and the hypercoagulation loop.[1] Of particular interest, the hypercoagulatory state induced by SARS-CoV-2 shows characteristics distinct from those seen in bacterial sepsis-induced coagulopathy and disseminated intravascular coagulation.[2] The importance of COVID-19–associated coagulopathy (CAC) is further underlined by an increased risk for thrombotic events in SARS-CoV-2–infected individuals, making prophylactic anticoagulation and vigilant monitoring for thrombotic complications a central task in management of patients with COVID-19.

However, there is a gap in understanding the underlying cause of CAC and its precise mechanism. Neither do we know why some patients are more prone to CAC compared to others and how adverse events should be treated and prevented.

The new study in *Research and Practice in Thrombosis and Haemostasis* by von Meijenfeldt et al[3] adds an important piece of knowledge to our understanding of the underlying pathology of CAC and the impact of anticoagulation. In a cohort of 102 hospitalized patients with COVID-19, the authors extensively analyzed coagulation and fibrinolysis parameters. They found that patients with COVID-19 on higher respiratory support had increased in vivo activation of coagulation (D-dimers and thrombin-antithrombin complexes), increased fibrinogen, factor VIII, and von Willebrand factor plasma levels, while ADAMTS-13 levels were lower, compared to patients with less affected lung injury and healthy controls. In addition, in vivo activation of fibrinolysis, C-reactive protein (CRP), and leukocyte counts increased with higher respiratory support (Figure 1). Further, and in line with previous reports, the authors found minimal abnormalities in prothrombin time and platelet count within the first days of admission.[2,3] Also, ex vivo thrombin generation was higher in these patients, while ex vivo fibrinolysis capacity was diminished. This is of special interest as the majority of patients were anticoagulated and patients on higher respiratory support even received higher doses of anticoagulants. So despite higher doses of anticoagulants, patients with COVID-19 with higher respiratory support have increased procoagulatory activity, clearly indicating that current anticoagulation therapies in patients with COVID-19 must be reevaluated. These data are supported by previous findings from the same group in another cohort of patients with COVID-19 treated with low-molecular-weight heparin (LMWH), which showed no effect of this drug on in vivo coagulation activation and fibrinolysis.[4]

Intriguingly, in a large case series of over 4000 patients with COVID-19, it was recently shown that anticoagulation is associated with improved survival.[5] These observational data suggest that there is a benefit in anticoagulation therapy in these patients. Moreover, the authors found no difference in outcome between the types of anticoagulation therapy, LMWH or direct oral anticoagulants (DOACs). This could indicate that patients with COVID-19 on anticoagulation do better, but

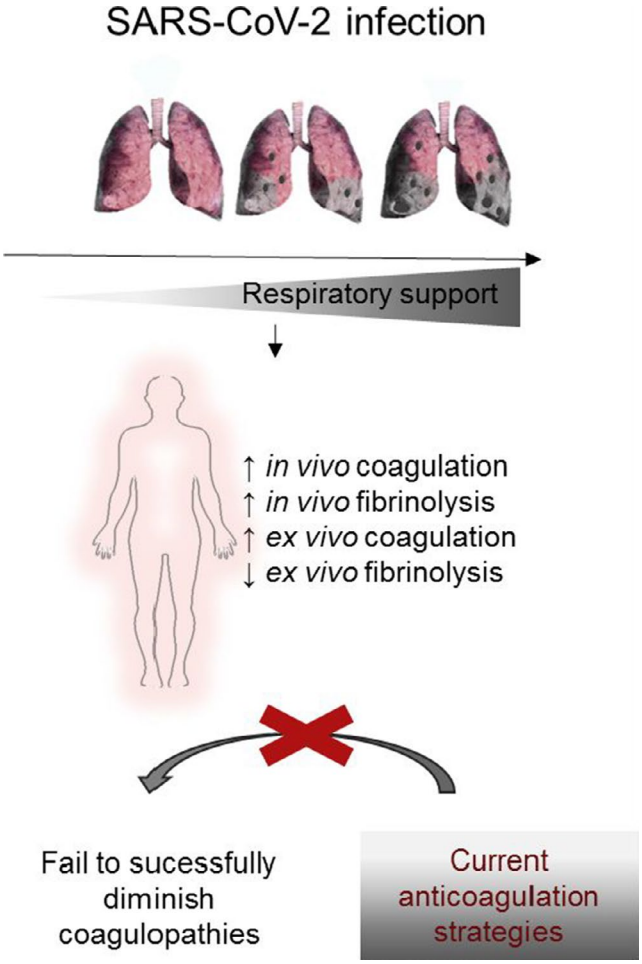

FIGURE 1 Patients with COVID-19 with SARS-CoV-2 infection requiring higher respiratory support show more lung injury and increased in vivo coagulation and fibrinolytic activity. Plasma of these patients showed increased ex vivo coagulation and decreased ex vivo fibrinolysis despite higher doses of anticoagulatory agents in these patients. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

there is still potential for improvement in patient treatment. Moreover, anticoagulants could bear beneficial effects beyond hemostasis in patients with COVID-19. Endothelial dysfunction and loss of endothelial barrier function are common features of COVID-19. Recently, the endothelial glycocalyx-degrading enzyme heparanase, which contributes to vascular leakage and inflammation, has been shown to be elevated in patients with COVID-19.[6] LMWH is an inhibitor of heparanase and could therefore bear beneficial effects by preventing glycocalyx degradation.[6] Moreover, heparin was recently found to bind SARS-CoV-2 with high affinity, thereby inhibiting virus binding on angiotensin-converting enzyme 2–expressing cells in vitro.[7] There are multiple inflammatory and pathogenic mechanisms targeted by heparin[8]; therefore, it is warranted to conduct clinical studies that evaluate therapeutic doses of these compounds in patients with COVID-19.

In clear contrast, little is known on the pathomechanistic effects of DOACs on COVID-19 disease progression to this date, while an improvement in survival was seen for patients treated with DOACs.

Importantly, alternatives to current therapeutic strategies need to be evaluated in the near future. Neutrophils, immunogenic platelets, and a dysregulated coagulation cascade cooperate to propagate immunothrombotic tissue injury in COVID-19, revealing that immunothrombosis is not just a bystander in COVID-19 but rather a link between systemic hypercoagulability and respiratory failure.[9] Also in the study by von Meijenfeldt et al, D-dimer levels were associated with increased CRP, indicating an interplay between inflammation and coagulation.[3]

Targeting immunothrombotic mechanisms could therefore provide a novel therapeutic strategy to prevent SARS-CoV-2 and other viral- or bacterial-induced thromboinflammatory events but bears a number of yet unsolved challenges. Therapeutic intervention in NETosis for treating inflammatory and thrombotic diseases has a narrow therapeutic window as timing of neutrophil extracellular trap–degrading deoxyribonuclease (DNase) treatment seems crucial. Administration too early may result in harmful effects due to ineffective prevention of pathogen dissemination. Moreover, DNase cleavage may result in the liberation of unwanted cell-free DNA and DNA-binding proteins, which in turn may propagate inflammation.[10] Therapeutic intervention of systemic inflammation and thrombosis via histone modification by peptidyl arginine deiminase 4 has been successful in mouse models but not yet translated to clinical settings.[10]

In summary, the optimal dose and type of anticoagulant intervention in hospitalized patients with COVID-19 is unknown, and immediate answers from high-quality randomized trials are urgently needed. Patients from all over the world would benefit from a collaborative effort to complete trials more quickly, conduct pooled analyses, and bring effective interventions to patients more quickly as recently suggested.[11] On the other hand, novel interventions targeting pathomechanistic differences observed in severe and critical COVID-19 cases need to be explored in detail. Studies like the one by von Meijenfeldt et al are important to decipher the precise pathological features of CAC to be able to define patients at risk for thrombotic complications and evaluate therapeutic strategies.

TWITTER

Alice Assinger @PlateletVienna

REFERENCES

1. Domingo P, Mur I, Pomar V, Corominas H, Casademont J, de Benito N. The four horsemen of a viral apocalypse: the pathogenesis of SARS-CoV-2 infection (COVID-19). *EBioMedicine*. 2020;58:102887.
2. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. *Crit Care*. 2020;24:360.
3. von Meijenfeldt FA, Havervall S, Adelmeijer J, Rudberg A, Magnusson M, Mackman N, et al. Prothrombotic changes in COVID-19 patients are associated with disease severity and mortality. *Res Pract Thromb Haemost*. 2020.1–10. https://doi.org/10.1002/rth2.12462
4. Blasi A, von Meijenfeldt FA, Adelmeijer J, Calvo A, Ibañez C, Perdomo J, et al. In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation. *J Thromb Haemost*. 2020.
5. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno P, Pujadas E, et al. Anticoagulation, mortality, bleeding and pathology among

patients hospitalized with COVID-19: a single health system study. *J Am Coll Cardiol*. 2020.

6. Buijsers B, Yanginlar C, de Nooijer A, Grondman I, Maciej-Hulme ML, Jonkman I, et al. Increased plasma heparanase activity in COVID-19 patients. *Front Immunol*. 2020;11:575047.
7. Kwon PS, Oh H, Kwon SJ, Jin W, Zhang F, Fraser K, et al. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. *Cell Discov*. 2020;6:50.
8. Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q, van der Vlag J. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. *EBioMedicine*. 2020;59:102969.
9. Nicolai L, Leunig A, Brambs S, Kaiser R, Weinberger T, Weigand M, et al. Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. *Circulation*. 2020.
10. d'Alessandro E, Becker C, Bergmeier W, Bode C, Bourne JH, Brown H, et al. Thrombo-inflammation in cardiovascular disease: an expert consensus document from the Third Maastricht Consensus Conference on Thrombosis. *Thromb Haemost*. 2020;120:538–64.
11. Tritschler T, Mathieu ME, Skeith L, Rodger M, Middeldorp S, Brighton T, et al. International Network of VTCRNI-VTE. Anticoagulant interventions in hospitalized patients with COVID-19: a scoping review of randomized controlled trials and call for international collaboration. *J Thromb Haemost*. 2020.

How to cite this article: Assinger A. COVID-19–related prothrombotic changes increase with lung injury and remain unaffected by anticoagulation therapy. *Res Pract Thromb Haemost*. 2021;5:11–13. https://doi.org/10.1002/rth2.12473