Clinical and Applied Thrombosis/Hemostasis
Volume 28: 1-2

DOI: 10.1177/10760296221087692
journals.sagepub.com/home/cat
SAGE

Factor VIII, Fibrinogen and Heparin Resistance in COVID-19 Patients with Thromboembolism: How Should We Manage the Anticoagulation Therapy?

Felicio Savioli, MD, MSc[1], Maurício Claro, MD[1], Fernando Jose da Silva Ramos, MD, PhD[1], and Laerte Pastore, MD, PhD[1]

Date received: 21 January 2022; accepted: 28 February 2022.

Dear Editor,

Previous studies showed that patients with COVID-19 are at high risk for thrombotic events, even those that receive normal doses of thromboprophylaxis with unfractionated heparin (UFH).[1–3] Furthermore, in an autopsy series, pulmonary embolism and microvascular thrombosis was described in patients that had died from COVID-19. The authors found a high rate of thromboembolic events in such patients treated with therapeutic anticoagulation, with 56% of venous thromboembolism and 6% pulmonary embolisms.[4] Moreover, in an observational study examining the thrombotic complications of patients admitted in the intensive care unit (ICU) with COVID-19, White *et al* described a cumulative incidence of 30% for arterial and venous thrombosis in the ICU for such population.[5]

Due to increased incidence of thromboembolism, physicians have been using UFH guided by the aPTT ratio, to maintain a target between 1.5-2.0. However, some patients need higher doses of UFH to achieve their coagulation status based on the aPTT ratio.

In a narrative review, Iba *et al* described the mechanism of coagulopathy in COVID-19 patients. ACE2, the host cellular receptor of SARS-CoV-2, has been identified on the vascular endothelial surface. SARS-CoV-2 uses ACE2 to invade into the cell through the fusion of its membrane to the host cell membrane leading to endothelial injury. One of the unique features of the coagulopathy associated to COVID-19 is the increase in Von Willebrand Factor (VWF) and factor VIII (FVIII) and it is suggested to be the result of vascular response to SARS-CoV-2 infection. VWF and FVIII are stored in the Weibel-Palade body of endothelial cells and released in response to infectious stimulus.[6]

The aPTT test is a clotting assay that reflects the function of the intrinsic and common pathways of the coagulation cascade. The test is potentially affected by changes in the concentrations of coagulation factors, including FVIII, fibrinogen, and coagulation inhibitors such as lupus anticoagulant.[7] Mitsuguro *et al* evaluated the in vitro effect of increased concentrations of fibrinogen and FVIII on the assay results of aPTT and anti-Xa activity in plasma samples with various therapeutic concentrations of UFH. They observed that the aPTT was shortened by increased concentrations of fibrinogen and FVIII. However, the Anti Xa activity was not influenced by these concentrations of clotting factors.

The anti-Xa assay has been proposed by some experts as a better assay for heparin monitoring. The main reason is that anti-Xa testing offers the advantages of not being affected by coagulation factor deficiencies other than antithrombin and not being affected by higher FVIII activity and higher fibrinogen levels. Consequently, a number of medical centers have switched to the anti-Xa assay for UFH monitoring.[8]

For these reasons, anti–Xa activity seems the more appropriate way to monitor heparin anticoagulation regimens and to prevent a possible increased bleeding risk, especially when high dosages of heparin are administered, mainly among heparin resistance conditions.[9]

This rare phenomenon is defined as the need for high doses of UFH for more than 35 000 IU/24h to achieve the target aPTT ratio. Heparin resistance can result from increased heparin-binding protein levels, low ATIII levels, increased heparin clearance levels (due to splenomegaly in liver disease), high factor VIII and fibrinogen levels and factitious resistance such as when heparin is not connected to the intravenous line.[10] Beun *et al* evaluated 75 patients with COVID-19 in the ICU.

[1] Critical Care Medicine Department, Hospital Sírio Libanês, Sao Paulo, Brazil

Corresponding Author:
Felicio Savioli, Hospital Sírio Libanês, Department of Critical Care Medicine, Sao Paulo, Brazil, Zip Code: 013018050.
Email: felicio.savioli@hsl.org.br

Of those, 46% experienced thromboembolic events and four patients needed high doses of UFH. They observed extremely increased levels of FVIII and fibrinogen that explained heparin resistance and decreased the in vitro anticoagulant activity of UFH as measured by aPTT. Based on that, they guided anticoagulation therapy with Anti Xa activity.[11] Moreover, in a retrospective study, White and collaborators, evaluated 69 patients with COVID-19 in the ICU. Of 10 patients with UFH, 8 patients presented heparin resistance due to increased production of FVIII and fibrinogen.[5]

Furthermore, in a recent review, Levy and Connors described the mechanisms and causes of heparin resistance in COVID-19 patients. They mentioned that in patients with COVID-19, the anti–factor Xa level may more accurately reflect UFH activity, especially in those with substantial inflammation and elevated levels of fibrinogen and factor VIII.[12]

In conclusion, the concept of heparin resistance should be considered in critically ill COVID-19 patients with thromboembolism diagnosis due to higher levels of FVIII and fibrinogen that may reduce the in vitro activity of aPTT. Therefore, Anti Xa activity could be considered to guide anticoagulation therapy with UFH in such population and more reliable studies would be helpful to address this concern.

Authors' contributions

FS wrote this manuscript.

ORCID iD

Felicio Savioli https://orcid.org/0000-0003-3594-5226

References

1. Lisman T, Thachil J. Differentiating biochemical from clinical heparin resistance in COVID-19. *J Thromb Thrombolysis*. 2020;50(4):1015-1016.
2. 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(4):844-847.
3. Ren B, Yan F, Deng Z, et al. Extremely high incidence of lower extremity deep venous thrombosis in 48 patients With severe COVID-19 in wuhan. *Circulation*. 2020;142(2):181-183.
4. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18(7):1743-1746.
5. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. *J Thromb Thrombolysis*. 2020;50(2):287-291.
6. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. *Inflamm Res*. 2020;69(12):1181-1189.
7. Mitsuguro M, Okamoto A, Shironouchi Y, et al. Effects of factor VIII levels on the APTT and anti-Xa activity under a therapeutic dose of heparin. *Int J Hematol*. 2015;101(2):119-125.
8. Takemoto CM, Streiff MB, Shermock KM, et al. Activated partial thromboplastin time and anti-xa measurements in heparin monitoring: biochemical basis for discordance. *Am J Clin Pathol*. 2013;139(4):450-456.
9. Novelli C, Borotto E, Beverina I, Punzi V, Radrizzani D, Brando B. Heparin dosage, level, and resistance in SARS-CoV2 infected patients in intensive care unit. *Int J Lab Hematol*. 2021;43(6):1284-1290.
10. Durrani J, Malik F, Ali N, Jafri SIM. To be or not to be a case of heparin resistance. *J Community Hosp Intern Med Perspect*. 2018;8(3):145-148.
11. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. *Int J Lab Hematol*. 2020;42(Suppl 1):19-20.
12. Levy JH, Connors JM. Heparin resistance - clinical perspectives and management strategies. *N Engl J Med*. 2021;385(9):826-832.