University of Groningen

Fibrinolytic Shutdown in COVID-19 Is Likely a Misnomer

Lisman, Ton

Published in:
Shock

DOI:
[10.1097/SHK.0000000000001665](https://doi.org/10.1097/SHK.0000000000001665)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Lisman, T. (2021). Fibrinolytic Shutdown in COVID-19 Is Likely a Misnomer. *Shock*, 55(6), 844-845.
<https://doi.org/10.1097/SHK.0000000000001665>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Binghu Li

Tao Li

Liangming Liu

State Key Laboratory of Trauma, Burns and Combined Injury,
Department of Traumatic Shock and Transfusion, Arm Medical
Center, Army Medical University, Chongqing
People's Republic of China
liangmingliu@yahoo.com

The authors report no conflicts of interest.

REFERENCES

1. Li B, Zhao H, Zhang J, Yan Q, Li T, Liu L: Resuscitation fluids in septic shock: a network meta-analysis of randomized controlled trials. *Shock* 53(6):679–685, 2020.
2. Corradi F, Via G, Tavazzi G: What's new in ultrasound-based assessment of organ perfusion in the critically ill: expanding the bedside clinical monitoring window for hypoperfusion in shock. *Intensive Care Med* 46(4):775–779, 2020.
3. Lahmer T, Rasch S, Schnappauf C, Schmid RM, Huber W: Influence of volume administration on Doppler-based renal resistive index, renal hemodynamics and renal function in medical intensive care unit patients with septic-induced acute kidney injury: a pilot study. *Int Urol Nephrol* 48(8):1327–1334, 2016.
4. Corradi F, Brusasco C, Vezzani A, Palermo S, Altomonte F, Moscatelli P, Pelosi P: Hemorrhagic shock in polytrauma patients: early detection with renal Doppler resistive index measurements. *Radiology* 260(1):112–118, 2011.
5. Rozemeijer S, Haitsma Mulier JLG, Rottgering JG, Elbers PWG, Spoelstra-de Man AME, Tuinman PR, de Waard MC, Oudemans-van Straaten HM: Renal resistive index: response to shock and its determinants in critically ill patients. *Shock* 52(1):43–51, 2019.

Fibrinolytic Shutdown in COVID-19 Is Likely a Misnomer

To the Editor: Patients with COVID-19 have a substantially increased risk for thrombotic events (1), which appears to be related to a profound hypercoagulable status in combination with a decreased propensity to break down clots (2, 3). In addition, the hypercoagulable status appears to drive disease progression by facilitating pulmonary thrombosis (4). Better insight in the mechanisms underlying the acquired hemostatic abnormalities in COVID-19 is vital to develop better strategies to treat or prevent thrombotic events, and possibly to improve disease outcome.

Similar to patients with trauma, patients with COVID-19 appear characterized by “fibrinolytic shutdown.” In a recent paper published in *Shock*, Creel-Bulos et al. (5) demonstrate that half of a small cohort of COVID-19 patients admitted to an intensive care unit had fibrinolytic shutdown on rotational thromboelastometry (ROTEM), with fibrinolytic shutdown in eight of nine patients that developed venous thrombosis during their admission. These data align with a previous study that used thromboelastography (TEG) to diagnose fibrinolytic shutdown (6).

While I agree that decreased fibrinolytic capacity is part of the hemostatic profile of COVID-19, and is a likely contributor to thrombotic events, I think the term “fibrinolytic shutdown” does not accurately describe the fibrinolytic status

in COVID-19 patients. In addition, I think ROTEM and TEG are not the ideal tests to detect a decreased fibrinolytic state.

The term “fibrinolytic shutdown” suggests that there is no fibrinolytic activity whatsoever. Biochemically, a complete fibrinolytic shutdown would indicate a lack of plasmin-mediated breakdown of fibrin. However, patients with COVID-19 are characterized by very high plasma levels of D-dimers (1), which are generated by plasmin-mediated cleavage of fibrin that has been crosslinked by coagulation factor XIIIa. In other words, the high D-dimer levels demonstrate that fibrinolysis is taking place in COVID-19 patients, and the elevated plasmin–antiplasmin levels present in COVID-19 patients directly confirm plasmin is being generated (3). There is however a decrease in the fibrinolytic capacity in the circulation of COVID-19 patients, and it is also likely that the large amounts of fibrin deposited in lungs and other organs in patients with COVID-19 simply overwhelm the physiological fibrinolytic response.

Although TEG and ROTEM have been used to identify “fibrinolytic shutdown” in various other patient groups, including trauma, sepsis, and liver disease, these tests are poorly suitable to detect decreased fibrinolytic activity. Both TEG and ROTEM define fibrinolytic shutdown by looking at the decrease in signal over time. Whereas in normal individuals, TEG or ROTEM signals decrease slightly (by a few percent), fibrinolytic shutdown is defined by an absent or very marginal decrease in signal. In studies comparing fibrinolytic status in patients and controls, fibrinolytic parameters (LY30 or LI30 values) thus are marginally (but significantly) different, for example medians of 2% lysis in healthy individuals in patients, and 0.8% in patients. The biggest problem, however, is that both in TEG and ROTEM 0% lysis are part of the normal range (7, 8). In other words, a “no lysis” situation or a full fibrinolytic shutdown in TEG or ROTEM occurs in healthy individuals. Thus, per definition, a hypofibrinolytic state or a fibrinolytic shutdown cannot be reliably assessed using TEG or ROTEM.

Tests that are better suited to assess a hypofibrinolytic status include tPA-modified TEG or ROTEM, or plasma-based clot lysis assays that use exogenously added tPA to lyse plasma clots. In such tests there is appreciable or full fibrinolysis within the time frame of the experiment, in contrast to the marginal (few %) clot breakdown in TEG or ROTEM. Recent studies using tPA-modified ROTEM, and plasma-based clot lysis assays confirm an impaired fibrinolytic status in COVID-19 patients, but also demonstrate that clot lysis does still occur (2, 3). Thus, COVID-19 patients are hypofibrinolytic in the systemic circulation, but the capacity to break down fibrin clots is not fully impaired. I propose to abandon the use of the phrase “fibrinolytic shutdown,” not only in COVID-19, but also in other situations in which decreased fibrinolytic potential is accompanied by increased D-dimer and plasmin–antiplasmin levels. I also urge caution in the interpretation of data from TEG or ROTEM that indicate a hypofibrinolytic state.

Ton Lisman

Surgical Research Laboratory and Section of Hepatobiliary
Surgery and Liver Transplantation

Department of Surgery
University of Groningen
University Medical Center Groningen
Groningen, The Netherlands
j.a.lisman@umcg.nl

The author reports no conflicts of interest.

REFERENCES

1. Levi M, Hunt BJ: Thrombosis and coagulopathy in COVID-19: an illustrated review. *Res Pract Thromb Haemost* 4(5):744–751, 2020.
2. 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* 18(9):2215–2219, 2020.
3. Blasi A, von Meijenfeldt FA, Adelmeijer J, Calvo A, Ibañez C, Perdomo J, Carlos Reverter J, Lisman T: In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation. *J Thromb Haemost*; 2020. doi: 10.1111/jth.15043.
4. Thachil J, Srivastava A: SARS-2 coronavirus–associated hemostatic lung abnormality in COVID-19: is it pulmonary thrombosis or pulmonary embolism? *Semin Thromb Hemost* 46(7):777–780, 2020.
5. 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* 55(3):316–320, 2021.
6. Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, Urban S, Nydam TL, Moore PK, McIntyre RC: Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. *J Am Coll Surg* 231(2):193–203.e1, 2020.
7. Scarpellini S, Rhind SG, Nascimento B, Tien H, Shek PN, Peng HT, Huang H, Pinto R, Speers V, Reis M, et al.: Normal range values for thromboelastography in healthy adult volunteers. *Braz J Med Biol Res* 42(12):1210–1217, 2009.
8. Schenk B, Görlinger K, Trembl B, Tauber H, Fries D, Niederwanger C, Oswald E, Bachler M: A comparison of the new ROTEM sigma with its predecessor, the ROTEMdelta. *Anaesthesia* 74(3):348–356, 2019.

Fibrinolysis Shutdown and Thrombosis in a COVID-19 ICU

To the Editor: Thank you for your interest in our work and correspondence. We appreciate some of the confusion that the term “fibrinolytic shutdown” may evoke and would like to address some of the misunderstanding regarding its use. We also recognize that viscoelastic testing has limitations, but would caution against dismissing a potentially useful diagnostic signal in a widely available test in favor of less established methods.

The concept of diminished activity of the fibrinolytic system evolved from work more than six decades ago. Lakner and Merskey reported decreased fibrinolytic activity as measured by the euglobulin and blood clot lysis times in patients who suffered a myocardial infarction in 1960 (1). This was expanded upon by other investigators in other patient populations including trauma patients. The work pointed to a common theme of some patients having a biphasic fibrinolytic response to injury—initially being increased, but then followed by greatly diminished activity for some period of time. Chakrabarti et al. (2) are largely credited with the specific phrase “fibrinolytic shutdown,” which was mentioned in their 1969 paper looking at the phenomenon in patients undergoing surgery, electroconvulsive therapy, and post myocardial

infarction. Specifically, they demonstrated the euglobulin lysis time, a marker of fibrinolysis where longer times indicate less activity, peaked on day 4 after the myocardial infarction and then diminished to control levels over the next 10 days. It is therefore an incorrect assertion that “the term fibrinolytic shutdown suggests there is no fibrinolytic activity whatsoever.” What the term does refer to is a phenotype of patients that have evidence of prior fibrinolytic activation with subsequent low current activity. This is excellently illustrated in the recent review on the subject by Moore et al. (3)

It is well known that COVID-19 patients have extremely elevated levels of d-dimers, and the cohort of patients in our study was no exception. It is certainly correct to point out that endogenous fibrinolytic activity was likely very high at some point. However, the typical half-life of d-dimers is 8 h, and can be longer in patients with compromised renal function and in the elderly (4). Therefore, it would be expected that patients experiencing fibrinolytic shutdown would still have high levels of this biomarker present despite decreased plasmin activity. Our findings were consistent with Ibanez et al. (5), who also found diminished fibrinolytic activity on ROTEM (Instrumentation Laboratories, Bedford, Mass) despite high d-dimer levels. To be clear, high d-dimer levels do not indicate that fibrinolysis is currently occurring, but rather that fibrinolysis had taken place at some earlier time point. As suggested, the main source of fibrinolysis may be the lungs, but definitive evidence of this is currently lacking.

We disagree that viscoelastic tests cannot be used to identify impaired fibrinolytic activity. Moore et al. have produced a large body of literature on this subject using thromboelastography (Haemonetics, Boston, Mass). We admit identifying hypofibrinolysis is less well-defined using rotational thromboelastometry (e.g. ROTEM) and does represent one of the mentioned limitations in our report (6). However, our defined cut-off for fibrinolytic shutdown of a maximum lysis < 3.5% came from Gomez-Builes et al. who derived this value from 550 injured patients. While there are likely undefined differences between trauma patients and COVID-19 patients, the fact that within our cohort, 8 of the 11 patients experiencing fibrinolytic shutdown suffered a venous thrombotic event would suggest there is some value in this definition (6).

With respect to diagnostics more ideal to assess hypofibrinolysis, we utilized the tools readily available to our clinical ICU teams. Plasma-based clot lysis assays such as the euglobulin lysis time, which takes anywhere from 4 to 6 h to perform, were not among them. We do not perform non-standard viscoelastic testing outside of a research setting at our institution, so cannot comment on the clinical usefulness of adding Thrombolytics to viscoelastic testing for COVID-19 patients. We look forward to further research in this area.

Christina Creel-Bulos
Roman Sniecinski
Emory University Healthcare, Department of Anesthesiology,
Atlanta, Georgia
mcreelb@emory.edu

The author reports no conflicts of interest.