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.

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Letter to the Editors-in-Chief

Is it hyperfibrinolysis or fibrinolytic shutdown in severe COVID-19?

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory virus that can cause severe illness (COVID-19) in infected individuals. Infected individuals with severe disease are at risk for developing thromboses, both macrovascular and microvascular. Due to these thromboembolic risks, anticoagulation regimens of varying intensities have been employed either prophylactically or therapeutically [1]. However, the evidence to support specific anticoagulation or fibrinolysis protocols based on a thorough understanding of the coagulopathic and fibrinolytic dysregulation associated with severe COVID-19 pathophysiology remains lacking.

2. Elevated D-dimers = systemic fibrinolysis or not?

Coagulation testing in COVID-19 has resulted in some interesting observations, specifically in regard to D-dimer levels and several parameters of viscoelastic testing (VET). While D-dimers are known to be a major fibrin breakdown product and as such serve as the primary indicator of fibrin(ogen) metabolism and have been used clinically as a biomarker to rule out venous thromboembolism (VTE), numerous studies in severe COVID-19 have demonstrated consistently elevated levels of D-dimers even in the absence of VTE. VET is a method of rapidly assessing global hemostasis in a variety of clinical settings by analyzing both plasma protein and cellular contributions to clot formation including coagulation factors, fibrinogen, and platelet quantity and function. In contrast to conventional plasma-based coagulation assays, VET can also identify the presence or absence of accelerated systemic fibrinolysis. In severe COVID-19, a strange fibrinolysis paradox has been observed – a striking elevation in D-dimer levels in the absence of demonstrable systemic hyperfibrinolysis by VET.

3. D-dimer and VET discrepancy

At its simplest level, an elevated D-dimer means that there must be a supra-normal degree of fibrin degradation occurring *somewhere* in the body. If the multiple reports of elevated D-dimer levels in severe COVID-19 are given any credence at all, it is a logical inference that COVID-19 infection leads to a hyperfibrinolytic state. However, multiple studies of both VET and fibrinolytic enzymatic activity have painted a starkly different picture. In striking fashion, multiple studies of COVID-19 patients utilizing a variety of VET platforms have reported near-identical findings – systemic fibrinolysis as assessed by these platforms is markedly depressed. For example, using a thromboelastography assay (TEG), Wright, et al. reported that 57% of their cases of severe COVID-19 tested manifested an extreme lack of fibrinolytic activity, even beyond that of what had previously been termed "fibrinolytic shutdown" [2]. Similarly, a study from Ibanez, et al. reported that clot lysis was essentially absent on standard rotational thromboelastometry (ROTEM) testing in 19 COVID-19 intensive care unit (ICU) patients [3].

4. The concept of fibrinolytic resistance

Other studies attempted to quantify not only the degree of depressed fibrinolysis, but the presence of *resistance* to plasma fibrinolytic activity by using VET assays paired with recombinant tPA (r-tPA). Here, Weiss, et al. reported that post-r-TPA maximal clot lysis ranged from 85 to 100% in controls, but only 4–20% in COVID-19 patients [4]. Bachler, et al. reported that the response to r-tPA was decreased in 70% of their COVID-19 cohort, and that the mean post-r-tPA clot lysis time (LT) was impressively elevated in the COVID-19 group compared to controls (508 s vs. 210 s, $p < 0.01$) [5]. Heinz and colleagues reported eerily similar findings – LT of 530 +/− 327 s vs. 211 +/− 80s ($p < 0.001$) [6]. In sum, viscoelastic testing in COVID-19 consistently indicated not only no signs of hyperfibrinolysis, but to the contrary, depressed fibrinolysis (even to

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LT, clot lysis time; PAI-1, plasminogen activator inhibitor-1; PAI-2, plasminogen activator inhibitor-2; PAP, plasmin-alpha 2-antiplasmin complexes; ROTEM, rotational thromboelastometry; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TAFI, thrombin activatable fibrinolysis inhibitor; TAT, thrombin-antithrombin complex; TEG, thromboelastography assay; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator; VET, viscoelastic testing; VTE, venous thromboembolism.

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the point of "shutdown") and significant resistance to exogenous fibrinolytics.

5. Co-existing hypofibrinolysis?

Other investigators studied fibrinolytic and anti-fibrinolytic pathways in severe COVID-19 and found strong indications of a hypofibrinolytic state. Nougier, et al. reported generally increased levels of the fibrinolysis inhibitors plasminogen activator inhibitor-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI) [7]. Tang, et al. found that in COVID-19 non-survivors, despite the presence of elevated levels of thrombin-antithrombin (TAT) complexes indicating excessive thrombin generation (i.e.: clot formation), plasmin-alpha 2-antiplasmin complexes (PAP) and tPA-PAI-1 complexes were markedly elevated, indicating a co-incident state of profound fibrinolytic suppression [8]. Similarly, Ranucci and colleagues found increased thrombin generation, modest-to-null release of endogenous tPA, and increased plasminogen activator inhibitor-2 (PAI-2), fibrinopeptide A, PAP and D-dimer in a cohort of 20 COVID-19 acute respiratory distress syndrome (ARDS) patients. The median value of tPA at the lower limits of the normal range (4,438 pg/mL) in survivors *and* non-survivors was an unexpected finding, as previous studies have reported levels in excess of 10,000 pg/mL in sepsis, with levels up to 50,000–70,000 pg/mL in fatal cases [9]. Additionally, consistent with the findings of Tang, et al., they discovered that while COVID-19 non-survivors had markers of increased thrombin generation, they also had dramatically higher plasminogen activator inhibitor-2 (PAI-2) levels and ten-fold higher PAI-2/PAP ratios, again signaling that fibrinolytic inhibition was not merely present, but that the degree of inhibition was associated with mortality. It is worthwhile to note that PAI-2 inactivates urokinase plasminogen activator (uPA), the primary activator of plasminogen in the lung [9].

6. A "Unifying Theory"

How then to reconcile the seemingly paradoxical observations that patients with COVID-19 possess indicators of both hyperfibrinolysis (elevated D-dimer levels) *and* hypofibrinolysis (depressed indices of clot lysis on VET and increased activity/concentration of fibrinolysis inhibitors)? The solution can be found by revisiting observations previously made of thrombolytic activity in non-COVID-19 ARDS – that the lungs are the primary location of fibrin breakdown and consequently the source of the D-dimers seeping into the systemic circulation. Hyperfibrinolysis can occur in the pulmonary extra- and intravascular compartments while a systemic hypofibrinolytic state co-exists. Thus, in COVID-19, elevated D-dimer levels, particularly in earlier phases of the pulmonary disease, may signify the attempt of the *local* fibrinolytic systems to remove fibrin and necrotic tissue from the injured lung parenchyma, and that plasma D-dimer levels, while increased, may actually under-represent the extent of plasminogen activation and thrombolysis occurring in the tissues [10].

Ongoing end-organ damage due to SARS-CoV-2, and particularly damage leading to demise, may thus represent a model of adequate tissue-level hyperfibrinolysis but *insufficient* systemic hyperfibrinolysis to overcome the burden of overwhelming fibrin deposition. This theory would explain many observations of severe COVID-19: the correlation between fibrinolysis inhibitors, especially PAI-2, and mortality (suppression of organ-level fibrinolysis leads to more fibrin-mediated tissue damage); that increasing plasma D-dimer levels predict mortality (plasma D-dimer levels are a marker of overwhelming un-checked fibrin deposition in tissues and potentially the systemic vasculature as well); and that only cut-off levels far above those typically used for the diagnosis of VTE have any prognostic utility in the setting of COVID-19 (additional, dynamic increases in D-dimer levels may occur in the setting of VTE that would otherwise be masked by the D-dimer being released from end-organ fibrinolysis).

While this theory does reconcile many of the seemingly contradictory findings in the studies of fibrinolytic activity in COVID-19 to date, in order to definitively establish the co-existence of two parallel, imbalanced fibrinolytic processes, one in the lung and the other within the lung or other tissues, additional data are still required. Specifically, data such has already been obtained in older studies of ARDS – indicators of pulmonary tissue-level fibrinolytic activity such as uPA, D-dimer, PAP, PAI-1/PAI-2 levels, etc. *in bronchoalveolar lavage fluid.*

7. Summary

In conclusion, the paradoxical findings of elevated D-dimers and lack of systemic hyperfibrinolysis represent a diagnostic dilemma that has persisted through the COVID-19 pandemic. At the time of this writing, studies to further explore hypotheses to explain these findings have not yet been undertaken, and until they are, our understanding of fibrinolysis in severe COVID-19 will remain woefully incomplete.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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