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FORUM

Fibrinolysis and COVID-19: A plasmin paradox

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Abstract

The COVID-19 pandemic has provided many challenges in the field of thrombosis and hemostasis. Among these is a novel form of coagulopathy that includes exceptionally high levels of D-dimer. D-dimer is a marker of poor prognosis, but does this also imply a causal relationship? These spectacularly raised D-dimer levels may actually signify the failing attempt of the fibrinolytic system to remove fibrin and necrotic tissue from the lung parenchyma, being consumed or overwhelmed in the process. Indeed, recent studies suggest that increasing fibrinolytic activity might offer hope for patients with critical disease and severe respiratory failure. However, the fibrinolytic system can also be harnessed by coronavirus to promote infectivity and where antifibrinolytic measures would also seem appropriate. Hence, there is a clinical paradox where plasmin formation can be either deleterious or beneficial in COVID-19, but not at the same time. Hence, it all comes down to timing.

KEYWORDS

coronavirus, COVID-19, D-dimer, fibrinolysis, tranexamic acid

1 | INTRODUCTION

The severity of SARS-coronavirus-2 (SARS-CoV-2) disease (COVID-19) has focused much attention on understanding its pathogenesis and what distinguishes this disease from other causes of pneumonia. The most prominent complication of COVID-19 is respiratory failure, but one clear hallmark of severe disease is a unique form of coagulopathy[1,2] with exceedingly high levels of D-dimer.[3] Older patients and those with co-morbidities appear to have higher levels of D-dimer, which in turn has been found to be a predictor of critical illness and mortality.[3] Indeed, it has been recommended that patients with elevated D-dimers be admitted to hospital even in the absence of other clinical criteria, given the high risk of morbidity and mortality in this group. Although the prothrombin time (PT) can be prolonged in non-survivors of COVID-19, this abnormality is only moderate and subtle changes are at risk of being missed if reported as an international normalized ratio (INR). Thrombocytopenia on the other hand does not appear to be a consistent prognosticator of severe disease. The International Society on Thrombosis and Haemostasis recommends measuring D-dimer, PT, and platelet count (in decreasing order of importance) in all patients presenting with COVID-19 infection.[4] Presently, low dose molecular weight heparin (LMWH) is the mainstay of thromboembolic prophylaxis in hospitalized patients, including COVID-19; however, this landscape is rapidly changing.[3,5]

2 | FIBRINOLYSIS AND ACUTE LUNG INJURY IN COVID-19

In normal lung physiology the pulmonary alveolar space has been considered as a profibrinolytic environment.[6] However, the fibrinolytic system is often suppressed during acute lung injury (ALI) and in pleural pathology,[7,8] including acute respiratory distress syndrome (ARDS) where fibrin accumulation can promote hyaline membrane

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formation and alveolar fibrosis. Depressed pulmonary fibrinolysis is largely due to increased levels of plasminogen activator inhibitor (PAI)-1 in both plasma and the bronchoalveolar lavage fluid.[6]

It has long been considered that any means to enhance lung fibrinolysis is likely to be of clinical benefit in patients with ALI, including ARDS. Restoration of pulmonary fibrinolysis in animal models of lung injury has been achieved using nebulized forms of tissue-type plasminogen activator (t-PA); monoclonal antibodies/inhibitors against PAI-1; or by intravenous administration of t-PA, urokinase, or plasmin.[9,10] A recent meta-analysis of preclinical studies revealed that fibrinolytic therapy for ALI improved gas exchange, and reduced alveolar neutrophils, pulmonary edema, and histological severity,[11] although none of these studies included viral pneumonia-induced ARDS. Human studies are limited, although a phase I study of patients with terminal ARDS administered either urokinase or streptokinase was shown to reduce mortality with no adverse bleeding events.[12]

While plasmin effectively removes fibrin, it also cleaves numerous matrix proteins[13] but, importantly also misfolded/necrotic proteins,[14] the latter being a feature prevalent in ARDS and COVID-19 affected lungs, ie, hyaline membrane formation, where necrotic proteins accumulate. Plasmin removes misfolded/necrotic proteins with the same kinetics as for fibrin and also in a lysine-dependent manner as this process is inhibited by the lysine analogue, tranexamic acid (TXA).[14] While the massive increase in D-dimer levels reflects fibrin breakdown, there is no marker available to evaluate the cleavage of these non-fibrin substrates that is likely to occur in COVID-19 patients. Hence, D-dimer levels, despite already being exceedingly high, may actually underrepresent the extent of plasminogen activation occurring in COVID-19, and indeed in related conditions where both fibrin and necrotic/misfolded proteins accumulate.

Direct fibrinolytic approaches for patients with severe/critical COVID-19 have now been reported.[15,16] One case series evaluating the effect of intravenous t-PA in three patients with critical COVID-19 pneumonia reported beneficial effects.[15] Although a perilously small sample size, the potential of this therapeutic approach has received recent commentary.[17] In the same vein, Wu et al restored lung fibrinolytic activity in 13 patients with severe/critical COVID-19 pneumonia by administration of *nebulized* plasminogen.[16] Plasminogen-treated patients had improved lung function, reduced heart rate, and improved oxygen saturation, at least temporarily. The use of the substrate, plasminogen, rather than using a direct fibrinolytic agent, is noteworthy and is likely to have an appealing safety profile as it relies on the availability of endogenous plasminogen activators to generate plasmin in situ from the exogenous plasminogen. By avoiding the need of using a direct fibrinolytic agent (ie, t-PA or u-PA), one would expect that the bleeding risks commonly associated with thrombolysis would be reduced.

Over the past few years, the fibrinolytic system has been corralled into various phenotypes including hyperfibrinolysis, hypofibrinolysis, occult fibrinolysis, physiological fibrinolysis, and fibrinolytic shutdown.[18] The particular fibrinolytic phenotype almost certainly will have a bearing on patient outcome.[19] In the example of COVID-19 in which massive D-dimer levels are a common feature of late stage disease, it would appear that the endogenous fibrinolytic system is in fact functional (hence not "hypo" or "shutdown"). Perhaps a state of transient hyperfibrinolysis existed to explain the D-dimer levels but in the end the fibrinolytic system failed to cope with the sheer extent of fibrin and necrotic material needing to be removed. Is this failure due to consumption of key factors, or is this a case of the system being simply overwhelmed? However, the fact that plasminogen supplementation was beneficial in COVID-19 patients[16] suggests that sufficient levels of the endogenous plasminogen activators (u-PA or t-PA) were in fact available locally to generate plasmin and, apparently, not impeded by PAI-1 that has been reported to block pulmonary fibrinolysis in related conditions. The apparent beneficial effects of plasminogen supplementation further suggests that endogenous levels of plasminogen in the pulmonary compartment had been depleted, given that its restoration appears to be beneficial.[16] Therefore, we propose that local fibrinolytic failure in COVID-19 is due, at least in part, to local consumption, most likely of plasminogen itself, but this remains to be tested.

We suggest that the massively elevated levels of D-dimer do not necessarily sit on the causal pathway of progression to critical disease and ARDS as widely implied, but rather are a marker of the (failed) attempt of the host to clear fibrin. We propose that in patients with severe/critical COVID-19 disease there develops a "consumptive fibrinolysis" due to overwhelming levels of fibrin and misfolded proteins/necrotic tissue in the lung and this can be relieved by enhancing plasmin formation either via administration of t-PA or its substrate, plasminogen. Clearly further studies are needed to support or refute this hypothesis. Nonetheless, if plasminogen consumption does indeed occur in late stage COVID-19 pneumonia, reduction in plasminogen antigen levels in the blood and in the bronchoalveolar lavage (BAL) fluid could be used as a relevant biomarker for disease severity.

3 | PLASMIN: FRIEND OR FOE?

Despite the positive sentiment above of a therapeutic role for enhanced fibrinolysis in patients with late stage COVID-19 lung disease, there is also a glaring paradox. This paradox is due to the various roles of plasmin in vivo that have little or in fact nothing to do with fibrin removal. Indeed, viruses[20,21] (and other pathogens[22]) generate plasmin from host plasminogen for their own purposes to cleave surface proteins important for cell infection or to evade host immunity (below). That plasmin has been referred to as "friend or foe"[22] is an apt description. This ability of plasmin to specifically promote viral infection has implicated plasmin(ogen) as a major risk factor for COVID-19 susceptibility.[23] It was even proposed in this study that elevated plasmin(ogen) in patients with pre-existing conditions may further contribute to SARS-CoV-2 infection and fatality. Although plasmin formation is yet to be directly linked with SARS-CoV-2 infectivity, it has been associated with other coronavirus strains.[23,24] Furthermore, earlier studies reported that plasmin can directly cleave the SARS-CoV spike (S) protein in vitro.[25]

4 | PLASMIN AS A MODULATOR OF THE IMMUNE RESPONSE

There is cause for concern for a deleterious role of plasmin in early COVID-19 progression, but to make sense of this it is important to realize the extent to which plasmin can impact many key processes outside of conventional fibrinolysis. Plasmin can not only assist in the early stages of viral infection, it can also be harnessed to suppress the immune response.[26] Plasmin can trigger cytokine production[27] and activate inflammation through many pathways including factor XII/bradykinin that in turn can promote edema.[28] Plasmin can indeed be both deleterious and beneficial. In a mouse model of *S aureus* infection, plasmin was shown to be protective in mice when infected with a non-lethal load of bacteria. In contrast, when bacterial infection was increased 10-fold, mimicking sepsis, plasmin increased mortality.[29]

The reason for these contrasting effects remains speculative but may reside in the differential expression of up to 12 distinct plasminogen receptors which exist on essentially all immune cells that can modulate cell signaling and cytokine release.[30] For example, the $PlgR_{KT}$ plasminogen receptor is differentially expressed on monocytes depending on their state of inflammation[31] and can regulate phenotypic and functional changes in macrophages.[32] Furthermore, deletion of $PlgR_{KT}$ impaired recruitment of mononuclear cells to the pleural cavity in a mouse model of pleurisy.[32] The plasminogen receptor enolase-1 (ENO-1) has been shown to recruit monocytes to inflamed lung tissue while patients with pneumonia displayed increased ENO-1 expression on blood monocytes and in the alveolar space.[33] Similarly, cytokine production by airway smooth muscle cells is regulated by the plasminogen receptor, annexin A2.[34] It is likely that plasminogen receptors will influence key inflammatory signaling pathways that ultimately alter cell behavior. The prevailing outcome will vary depending on the temporal expression pattern of these receptors during disease progression. It could be speculated that low level or a gradual increase in infection would provide time for the host to react, permitting a coordinated counterattack in which plasmin can help to initiate an appropriate release of regulatory cytokines. In contrast, an overwhelming, sudden onset of infection denies this orderly process and the initial plasmin response is deleterious. Hence, while the primary action of plasmin is proteolytic in nature, the end game of plasmin's actions can be at the level of receptor-initiated cell signaling, impacting the inflammatory and immune responses.

Evidence that plasmin impacts the immune response in humans was shown in healthy volunteers administered TXA.[35] Plasmin blockade caused rapid suppression of baseline levels of pro-inflammatory cytokines and increased immune cell activation markers on myeloid and lymphoid cells.[35] Hence, in non-challenging circumstances,

TABLE 1 The temporal opposing roles of plasmin in the pathogenesis of COVID-19

Evolving COVID-19 clinical course	Pathology	Plasmin(ogen) activity	Potential role of antifibrinolytics
Stage 1			
Presymptomatic or mild disease, without distressing symptoms and able to maintain oxygen saturation > 92% with up to 4 L/minute oxygen via nasal prongs	SARS-Cov-2 harnesses extracellular proteases including plasmin to infect cells. Plasmin levels further increase in response to infection. Results in an immunosuppressive state	++	Blocks plasmin activity—likely anti-inflammatory and immune enhancing; potentially therapeutic
Stage 2			
Moderate or severe disease, with prostration, fever, persistent cough, and/or shortness of breath. Oxygen saturation typically ≤ 92% at rest, so requires supplemental oxygen, noninvasive ventilation, or tracheal intubation	Plasmin levels continue to rise. Increase in cell permeability in lungs Plasmin pro-inflammatory and immunosuppressive	+++	As above Commence thromboprophylaxis if not already started
Stage 3			
Critical disease (ICU), respiratory failure with PaO_2/FiO_2 ratio < 200 (acute lung injury/ARDS), shock, DIC, and other organ failure Mechanical ventilation, with or without prone positioning or extra-corporeal membrane oxygenation Large scale plasminogen activation to remove fibrin deposits and DIC	Hyperfibrinolytic state D-dimer levels greatly elevated Fibrinolytic system overwhelmed and fails to remove fibrin	Relative deficiency	Fibrinolytic capacity needs to be enhanced Exogenous plasmin(ogen) or plasminogen activators may be beneficial Antifibrinolytics should not be trialled in critical disease Heparin thromboprophylaxis/anticoagulation recommended

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; ICU, intensive care unit; PaO_2/FiO_2, partial pressure arterial oxygen/fraction inspired oxygen.

plasmin formation places a check on the inflammatory and immune systems, and this can be transiently relieved by TXA, effectively providing an immune-priming effect. This suggests a potential beneficial mechanism given the cytokine storm reported in patients with COVID-19 disease.[1,36] Moreover, in patients undergoing cardiac surgery, TXA reduced the risk of postoperative infection in a manner unrelated to its hemostatic effects.[35]

5 | COULD FIBRINOLYTIC INHIBITIION BE OF BENEFIT IN COVID-19?

The actions of the fibrinolytic system during COVID-19 pathogenesis can therefore be both deleterious and protective to the host, *but not at the same time*. So, while boosting fibrinolysis seems appealing during late stage disease to remove fibrin deposits, blocking fibrinolysis in mild-moderate cases to reduce viral load and possibly improve the immune response may well avoid progression to more severe disease. Both approaches seem logical, but it does pose a clinical dilemma because at present it is unclear how early fibrinolysis should be suppressed, and when (how late) should it be actively promoted? (See Table 1.) Consideration of early use of TXA in COVID-19 might have merit but there is a perceived pro-thrombotic risk, especially considering that patients with severe or critical COVID-19 can develop disseminated intravascular coagulation (DIC) and have a higher risk of pulmonary embolism, myocardial injury, and stroke.[37] Although a recent meta-analysis of previous trials indicated that TXA does not pose thrombotic risk,[38] this still remains to be shown in patients with COVID-19. It is noteworthy that a clinical trial has commenced in the United States to evaluate TXA in patients with COVID-19 (NCT04338074).

The use of antifibrinolytic agents as a therapy for COVID-19, if of any benefit at all, would appear to be of therapeutic value early, even in presymptomatic stages of COVID-19 infection during which blockade of plasmin production may have antiviral actions and would not conflict with the need to remove fibrin. Although this remains speculative at present, it is all about timing, because preservation, even enhancement of plasmin formation is essential to combat pulmonary fibrin and DIC formation that occurs as the disease progresses (Table 1). So, if an antifibrinolytic agent such as TXA were to be given early to COVID-19 patients, at what point would this need to be stopped? For this to be of clinical benefit it can only be considered prior to the build-up of fibrin yet many COVID-19 patients with ALI, particularly ARDS, may have already passed the point of no return. In addition, could antifibrinolytic treatment be reasonably considered as a prophylactic measure for front-line health-care workers and other high-risk populations?

6 | CONCLUSIONS

COVID-19 has a pathogenesis and clinical profile like nothing seen before and for which there is currently no vaccine and uncertain immunity. Those with an interest in thrombosis and hemostasis have found themselves in new territory navigating a novel coagulopathic condition and now with a likely dual role of the fibrinolytic system. The fibrinolytic system clearly intersects at many levels in biology and in clinical medicine. Randomized clinical trials are needed to determine whether early suppression or late activation of the fibrinolytic system will not only improve outcome in the current COVID-19 crisis but may also help to better prepare us for the next challenge.

CONFLICTS OF INTEREST

The authors declare there are no conflict of interest with this manuscript.

AUTHOR CONTRIBUTIONS

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