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# Editorial commentary: Vascular injury in acute infections and COVID-19: everything old is new again ☆,☆☆

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In the current edition of the journal, Siddiqi and colleagues discuss the role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) -mediated endothelial injury, and discuss potential therapies that address vascular system dysfunction and its sequelae [1]. A growing number of commentaries report the role of vascular injury and resulting dysfunction associated with COVID-19 infection, a critical mechanism for understanding this viral disease state's clinical manifestations [2–5]. Although we agree with the thoughtful commentary and their focus on vascular aspects of COVID-19, clinicians should realize that infection associated vascular injury has long been described in many types of infections, especially in patients following sepsis and septic shock. Activation of multiple inflammatory responses as host defense mechanisms to immobilize or remove the inciting pathogen results in an inflammatory response that also causes significant vascular endothelial injury, a critical perspective to consider, especially when attempting to develop therapeutic approaches to a systemic disease [6–9]. In our commentary, we will further examine previous reports of vascular endothelial injury associated with acute infectious processes, the role of inflammation induced thrombosis, and the spectrum of inflammatory pathways producing injury that provide a conundrum for developing therapeutic approaches.

Previous reports have described thromboinflammatory responses that cause vascular endothelial damage through cellular and humoral amplification pathways [10]. Neutrophils and monocytes contribute to vascular injury and thrombus formation during acute infections by expressing tissue factor and generation of microparticles [6]. Further, neutrophil activation releases multiple additional mediators such as DNA, proteolytic enzymes, and pathogen-associated molecular patterns that contribute to microvascular thrombosis development with cytokines and other inflammatory mediators [6,11,12].

Beyond the local response, the systemic activation of proinflammatory cytokines significantly contributes to injury and thrombosis. Before COVID-19, this acute inflammatory response to infection was considered the hallmark of acute infections causing disseminated intravascular coagulopathy (DIC) associated with gram-negative or gram-positive bacteremia, fungemia, or viremia [7,8,13]. Host defense systems activate both humoral and cellular amplification pathways as part of thromboinflammatory responses, a term also called immunothrombosis, that propagate through multiple pathways including neutrophil extracellular traps (NETs), cell-free DNA, and histones that activate additional inflammatory responses and enhance other prothrombotic pathways [6,10,14–17].

What is unique about the endothelial vascular injury with SARS-CoV-2 infection that causes vascular injury? The ACE2 receptor tropism and entry via nasopharyngeal passages provide an initial infection in the lung, pulmonary alveoli, and vascular endothelial interfaces [18]. This initial viral load in the lung potentially produces the early major clinical manifestations of acute lung

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injury/adult respiratory distress syndrome (ARDS) and the characteristic findings of microvascular thrombotic sequela, as shown on postmortem findings [19,20]. However, pulmonary microvascular thrombosis is not new and was reported initially in 1983 in postmortem evaluations of 22 patients with ARDS due to infectious causes [21]. In COVID-19, the initial localized pulmonary inflammation and microvascular thrombosis occur, but without systemic endothelial injury initially [8,22,23]. The finding that D-dimer would track with the severity of disease and inflammation is not surprising given the evolving understanding of the interaction between inflammation and activation of coagulation. Some patients appear to have a more pronounced inflammatory response to infection with SARS-CoV-2, with manifestations of a systemic inflammatory response syndrome (SIRS) or cytokine storm. This perspective may explain variability in hypercoagulable responses and variability of coagulation testing, including significantly elevated D-dimer, especially as the disease progresses [24].

The first report describing COVID-19 as a thromboinflammatory response was in ventilated patients with ARDS, demonstrating increased IL-6 levels correlated with increased fibrinogen levels, supporting the thromboinflammatory response perspective [25]. Clinically, COVID-19 associated ARDS is due to vascular injury, where endothelial injury/apoptosis has been demonstrated with caspase staining, microcirculatory thrombin is formed, and increased capillary permeability occurs, all creating the clinical aspects of acute lung injury and reported in postmortem findings [19].

The authors also review potential therapeutic approaches to endothelial injury with COVID-19, including nonspecific immunomodulatory agents that might dampen the excessive host inflammatory response, such as colchicine and antagonists of the NLRP3 inflammasome, antithrombotic therapies including antiplatelet agents and anticoagulants, and treatments addressing the renin – angiotensin – aldosterone pathway such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockade. Despite their thoughtful commentary, one of the problems with treating the inflammatory injury is that treatment usually is administered after the onset of the acute inflammatory insult. As a result, treating after the event often limits the potential benefits of these therapeutic interventions. From our perspective, the other issue is that due to the incredible diversity of inflammatory responses arising from cellular and humoral amplification pathways, inhibiting a single limb of this complex universe often has limited benefits. Of equal importance is that few therapies have been shown to be useful in ARDS in the past. As a result, efforts to find the right mix of antithrombotic and antiinflammatory effects continue to be investigated. The other problem is that without specific antiviral therapies, the disease process of COVID-19 rages on and continues to drive these thromboinflammatory responses. The only therapy shown to alter mortality so far is the use of a broad-spectrum, nonspecific agent, corticosteroids – dexamethasone – for patients with acute lung injury with the characteristic acute hypoxemic respiratory failure.

As we have noted in an earlier review, clinicians are faced with a pathogen whose behavior continues to be defined and are desperately looking for treatments that might improve patient outcomes [5]. COVID-19 is associated with dramatic vascular endothelial injury as thoughtfully reviewed by the authors, however, this response producing vascular injury is extensively described in other acute infectious processes. It is the lack of immunity to SARS-CoV-2 that continues to drive both infection and the staggering number of patients as well as the severity of illness, with continued surges around the world. At this time when vaccines are in the early stages of clinical trials with as yet undetermined efficacy, and without prior acquired immunity for some time to come, clinicians should continue to focus on the vascular endothelial injury that occurs and evaluate potential therapeutic interventions as discussed by Siddiqui and colleagues.

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