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.

MAYO CLINIC

Arterial Thrombosis and Coronavirus Disease 2019

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Thrombotic complications from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections (coronavirus disease 2019 [COVID-19]) have generated considerable interest and concern due to the adverse effect on outcomes, including survival. Although macrovascular thrombosis involving named vessels have been reported with varying incidence, microvascular thrombosis, particularly involving the pulmonary circulation, seems to be widespread, particularly in patients with severe and critical disease.[1-3] There is growing understanding of the mechanisms of thrombosis that seem to be unique and engage various contributions from the immune system such that a recently coined term, *immunothrombosis*, is aptly applied.[4] After inhalation, viral entry into the host alveolar epithelium occurs through endocytosis facilitated by engagement of the viral capsid spike protein and the host angiotensin-converting enzyme 2 receptor.[5-7] Once infected, the intimate relationship between alveolar epithelium and capillary endothelium promotes rapid inflammation and injury of both such that loss of the epithelial-endothelial cell barrier with diffuse alveolar damage (acute respiratory distress syndrome), increased lung stiffness, and impaired gas transfer ensues. On the capillary side, endothelial activation leads to expression of cellular adhesion molecules (intercellular cell adhesion molecule, vascular cell adhesion molecule, P-selectin, E-selectin), release of ultra-large von Willebrand factor multimers, and recruitment of neutrophils and platelets. Neutrophil-macrophage feedback mechanisms result in a "storm" of cytokine release, including tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, and C-reactive protein, each of which has been associated with disease progression and mortality outcomes. Complement activation may be unique to this thrombotic pathophysiology. Although viral opsonization, lysis of infected cells, and inflammation amplification may be beneficial, bystander host cellular damage with associated thrombosis can occur as a consequence. Beyond direct endothelial injury, biochemical changes occur that promote local vasoconstriction through loss of nitric oxide synthesis and endothelin-1 release. Tissue factor expression, loss of endogenous anticoagulant pathways, and fibrinolysis inhibition promote microvascular thrombosis, further worsening pulmonary perfusion. These combined host responses explain autopsy findings of a high incidence of diffuse alveolar damage and pulmonary microvascular thrombosis. This latter finding seems to be particularly prevalent in patients dying of COVID-19 pneumonia. Compared with patients dying of influenza A, those with SARS-CoV-2 have a 9-fold increased prevalence of pulmonary microthrombosis, implying a unique pathophysiology beyond simple diffuse lung injury.[8] Although SARS-CoV-2 has also been shown to infect endothelial cells from other vascular beds, including heart, liver, and kidney, widespread microthrombosis has not been consistently found when complete autopsies have been performed. This finding suggests that the thrombotic response requires not only endothelial cell infectivity but also damage from adjacent tissues, more prevalent in the lungs compared with other organ systems.

Macrovascular thrombosis of named arteries and veins have also been well described. Most reports have focused on venous thromboembolism, with much higher event rates recorded for the pulmonary circulation compared with arm or leg veins. Some have speculated that this finding argues for pulmonary artery thrombus in situ as

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opposed to a more traditional embolic event from leg veins. One could envision a thrombus originating in the pulmonary arterioles, capillaries, or venules, with propagation into the main pulmonary arteries as a consequence. Alternatively, a thrombus could originate in a large pulmonary artery after sufficient endothelial infection and injury. Unraveling this distinction is complicated. Some have suggested that finding occlusive thrombi in the macrocirculation of pulmonary arteries suggests thrombus in situ. Neither this finding nor the absence of deep venous thrombosis on arm or leg imaging is sufficient proof for this hypothesis.

Arterial thrombotic events have received less attention. Many recent epidemiology studies have not reported an incidence of myocardial infarction, stroke, or peripheral embolism. The few studies that have provided numbers reported incidences varying from 2% to 5%. The report in this issue of the *Proceedings* is, therefore, a welcomed addition to this effort. Fournier et al[9] assessed the incidence of arterial thrombotic events in patients hospitalized with COVID-19. Consecutive patients with COVID-19 infection hospitalized during April 2020 were retrospectively assessed to determine the incidence of arterial thrombosis and associated risk factors. To be included in the analysis, patients had to have polymerase chain reaction—confirmed SARS-CoV-2 infection or strong suspicion of the disease based on clinical presentation and chest radiographic imaging. Disease severity was assigned based on the percentage of lung involvement by computed tomography. Results were compared with those from a control cohort of patients admitted with arterial thrombosis in the absence of COVID-19 infection. Of the 531 patients with COVID-19 admitted, 5.6% experienced an arterial thrombotic event including myocardial infarction (n=9), stroke (n=8), or acute/subacute limb ischemia (n=6). A minority developed thrombi at atypical locations, including the aorta, splenic and renal arteries, and small vessels of the brain. Cardiovascular risk profiles were similar to patients without COVID hospitalized for ischemic events. Mortality rates were nearly 3-fold higher compared with patients with COVID without arterial thrombosis and more than 10-fold higher compared with patients with other thrombosis without COVID. Elevated fibrin D-dimer levels were an independent predictor of arterial thrombosis in patients with COVID, and the authors provide a D-dimer threshold of 1250 ng/mL above which the receiver operating characteristic curves show reasonable sensitivity and specificity for arterial thrombotic events.

Although microvascular thrombotic mechanisms seem to be well explained by direct infection and injury of pulmonary endothelial cells, the macrovascular arterial thrombotic mechanisms are less clear. Although arterial endothelial injury in this context is plausible, it is also possible that these events represent a response to critical illness in the context of native arterial disease and associated risk factors. For example, a troponin leak in the setting of hypotension and coronary artery stenosis could generate demand ischemia, so-called type 2 non—ST-segment elevation myocardial infarction. Stress-induced cardiomyopathy (Takotsubo cardiomyopathy), paroxysmal atrial fibrillation, or paradoxical embolization through a patent foramen ovale in the setting of pulmonary hypertension related to acute lung injury could each provide a source of embolism to the brain, splanchnic circulation, or peripheral arteries. Vasospasm related to pressor therapy, iatrogenic arterial injury, or spontaneous dissection are also plausible mechanisms in these critically ill patients. Although it may be tempting to simply attribute the arterial occlusion to COVID-19, it is imperative to explore these potentially treatable entities in the diagnostic evaluation.

Management of these patients is clearly complicated. Adding an arterial occlusion to a patient already tenuous from a respiratory insult clearly adds to both morbidity and mortality. When identified, the underlying status of the patient often precludes a surgical intervention whereby the patient is in the intensive care unit, on a ventilator, and requiring pressor support. The experience

with thrombolytic therapy is limited to small case series and cannot be advocated under general circumstances. Lost in this discussion is the limited reporting of major hemorrhage outcomes, an area that requires further study and emphasis. Without a thorough understanding of bleeding outcomes, designing prevention and treatment strategies for this potentially devastating illness is challenging.

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