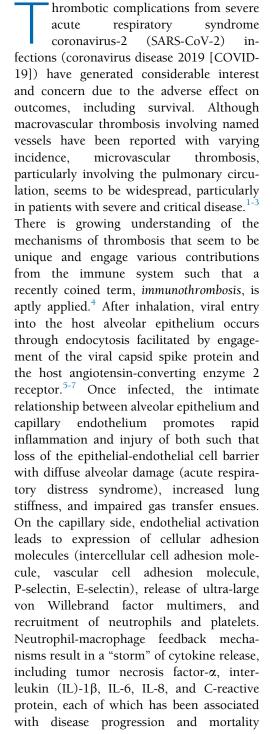


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MAYO CLINIC

Arterial Thrombosis and Coronavirus Disease 2019

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 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 al⁹ 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.

microvascular thrombotic Although 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 ischemia, demand 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.

Robert D. McBane II, MD

Vascular Division Department of Cardiology Gonda Vascular Center Mayo Clinic Rochester, MN

Correspondence: Address to Robert D. McBane II, MD, Vascular Division, Department of Cardiology, Gonda Vascular Center, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (mcbane.robert@mayo.edu).

ORCID

Robert D. McBane: b https://orcid.org/0000-0001-8727-8029

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