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# The mystery of COVID-19-associated arterial thrombosis

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I read with interest the article by Indes et al<sup>1</sup> regarding the arterial complications in patients with severe acute respiratory syndrome coronavirus (SARS-CoV)-2. Their study has added to the growing body of data on this unique viral complication. Coronavirus disease 2019 (COVID-19)-associated coagulopathy is associated with elevated fibrinogen, D-dimer, and C-reactive protein. Some centers have described higher-than-expected rates of venous thromboembolism.<sup>2</sup> Markedly elevated D-dimer levels have also been reported in association with severe COVID-19 infections and mortality.<sup>2,3</sup> The proposed hypotheses to explain the presence of venous thrombosis in COVID-19 have centered on a dysregulated inflammatory response manifesting as a cytokine storm, complement activation, and endothelial injury.<sup>4,5</sup> The observation of an increased risk of venous thrombosis in association with severe illness due to viral infections in itself is not novel. However, whether (and to what degree) severe COVID-19 infection is associated with a uniquely prothrombotic phenotype remains uncertain.

Although venous thromboembolism has been reported in previous outbreaks of coronaviruses, including SARS-CoV-1 and Middle Eastern respiratory syndrome, and influenza A H1N1 acute respiratory distress syndrome,<sup>6,7</sup> the association between SARS-CoV-2 infection and arterial thrombosis has not been reported with other viral infections. The coagulopathy observed in patients with COVID-19 differs from the disseminated intravascular coagulopathy typically seen in sepsis. Specifically, the associated thrombocytopenia and prolonged activated partial thromboplastin time and/or prothrombin time have been mild.<sup>4</sup> This observation led to speculation that the arterial thrombosis is a direct result of SARS-CoV-2 infection of endothelial cells through the angiotensin-converting enzyme 2 receptor and subsequent endotheliitis.<sup>5,8</sup> Also intriguing is the unpredictable nature of this arterial thrombosis among patients infected with COVID-19. Indes et al,<sup>1</sup> and others, observed no correlation between COVID-19 disease severity and the degree of arterial thrombosis, although others have observed arterial

thrombosis in severely ill patients.<sup>1,8,9</sup> This is not unusual, because reports of rare disease entities can appear seemingly contradictory, especially in the early phases of understanding a disease process. However, these observations also suggest that perhaps the underlying mechanism of COVID-19-associated arterial thrombosis is independent of the cytokine storm that occurs in patients with COVID-19-associated venous thrombosis.

The growing experience with COVID-19-associated arterial thrombosis raises the question of the optimal dose of heparin anticoagulation for patients with COVID-19 infection and whether prophylactic antiplatelet therapy could have a role. Variable protocols have been proposed at local institutional levels to address this concern. Ultimately, the optimal management will continue to evolve as we continue to gain insight into the pathophysiology of COVID-19.<sup>10</sup> I look forward to learning from the growing body of data via multicenter collaborations such as the Vascular Surgery COVID-19 Collaborative and the numerous observational trials on thrombosis in patients with COVID-19.<sup>7</sup> Should the pandemic continue, we might also need to consider well-designed randomized trials to determine which patients will be at risk of arterial events and how best to prevent them. In addition, we must remain vigilant to the risk of COVID-19-associated arterial thrombosis and act expeditiously to recognize and treat this complication when it does occur.

*The opinions or views expressed in this commentary are those of the author and do not necessarily reflect the opinions or recommendations of the Journal of Vascular Surgery or the Society for Vascular Surgery.*

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