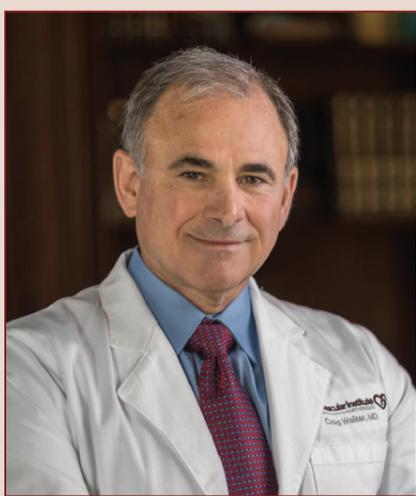# COVID-19 and Cardiovascular Complications: Still Many Unanswered Questions

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Hello and welcome to the March 2023 edition of *Vascular Disease Management*. I have chosen to comment on the case series by Drs. Evan Pramudito Mulyadi and Sahudi Abdul Mijib, "Acute Limb Ischemia as a Complication of COVID-19." In this report, a series of 4 patients presenting with acute limb ischemia (ALI) are reported, of which 3 had acute leg limb ischemia and 1 had acute arm ischemia. All the individuals had highly symptomatic, documented COVID-19 infection, were over age 40, and had comorbidities. Patient 1 was a 45-year-old man presenting with ALI, treated with an above-the-knee (AKA) amputation and femoral thrombectomy with subsequent discharge after 17 days. Patient 2 was a 45-year-old man presenting with ALI of the right leg that was successfully treated with thrombectomy of the femoral and tibial vessels and was discharged on day 17 without amputation. Patient 3 was a 59-year-old woman with right-leg ALI treated with thrombectomy and AKA who succumbed on day 6 in the ICU. Patient 4 was a 47-year-old woman who presented with ALI of the left upper extremity that was treated with brachial, ulnar, and radial thrombectomy and was discharged with limb preservation after 30 days.

As of February 28, 2023, the World Health Organization estimates that 758,390,564 individuals were reported to have had COVID-19, resulting in 6,859,093 deaths globally. Obviously, accurate determination is impossible as many cases are unreported and there may also be overreporting. There have been more than 250,000 articles published in the medical literature since the beginning of the COVID crisis, making it one of the most scrutinized illnesses of all time. Comorbid factors such as age, diabetes, obesity, and heart failure affect prognosis with COVID-19 infection. There are gender and racial disparities in survival, with men and Black people having higher mortality rates.

The majority of deaths with COVID-19 are related to pulmonary complications and exacerbation of underlying conditions. Major thrombotic complications represent a significant cause of death and morbidity. These thrombotic complications are most commonly venous in etiology, but there have been many documented cases of severe life- and limb-threatening arterial thromboses.

COVID-19 is caused by SARS-CoV-2, a single-stranded RNA virus that enters cells via ACE-2 receptors, most commonly via the epithelial cells of the respiratory tract. ACE-2 receptors are found in the kidneys, liver, heart, brain, endothelium, and other organs. Spread of the virus within the host appears to be via these receptors.

Endothelial dysfunction involves reduced endothelium-dependent vasodilation, resulting in a proinflammatory, procoagulant state. Endothelial damage and disruption of intracellular junctions exposes subendothelial matrix-containing tissue factor and collagen, resulting in thrombin generation, the conversion of fibrinogen to fibrin, and platelet activation. Tissue factor is a subendothelial

transmembrane protein that potentially activates the coagulation cascade. Markers of endothelial dysfunction include increased von Willebrand factor, Factor VII, and P-selectin (a cell adhesion molecule that enables the recruitment of platelets and leukocytes).

Hypoxia, which is frequently noted in hospitalized patients with pulmonary infiltrates, can also lead to endothelial dysfunction and hypercoagulability. The hypoxemia results in upregulation of endothelial P-selectin and adhesion molecules. Monocytes bind activated endothelial cells, resulting in further expression of prothrombotic factors such as tissue factor. Endothelial release of PAI-1 and inflammatory cytokines activate the immune system and subsequent risk of thrombosis.

Complement activation involves a cascade of events, resulting in the formation of the terminal C5b-9 membrane attack complex triggering cell lysis, platelet activation, and secretion of von Willebrand factor.

Pulmonary emboli and smaller pulmonary artery microthrombosis (possibly representing in situ thrombosis) are common with autopsy reports. These findings are noted in more than one-third of patients dying from COVID-19 infection. Deep venous thrombosis is markedly increased. Although arterial thrombosis is less common than venous, it is also profoundly increased in individuals presenting with COVID-19 infection. Among peripheral arterial thrombotic events, ALI is the most life- and limb-threatening consequence of coronavirus. The profound associated hypercoagulable state, the frequent complete occlusion of large and small terminal vessels with poor runoff, and the comorbid conditions affecting the individual including hypoxemia and hypotension, are associated with poor prognosis. Urgent surgical or mechanical thrombectomy, coupled with adequate anticoagulation, can successfully augment chances of limb and life preservation. It has been my personal experience that during interventional procedures it is more difficult to achieve therapeutic activated clotting times and that there are more bleeding complications with the procedures.

Prevention of thrombotic complications by prophylactic systemic anticoagulation in high-risk patients remains the most effective treatment. Unfortunately, with self-isolation policies, often the peripheral artery occlusions go unrecognized, initially resulting in greater likelihood of thrombotic occlusion of runoff vessels, making thrombectomy more difficult or in some cases impossible. There is insufficient data regarding the administration of thrombolytic therapy to determine safety and efficacy in patients with COVID-19 infection and thrombotic lesions.

Recently, there have been several reports of arterial thrombotic occlusions following COVID-19 vaccination without active signs of infection. This has brought into debate the previously expressed opinion by some health care experts that the vaccine is innocuous and results in a "dead end" for the virus. Clearly, immunized patients can remain infectious to others.

The COVID-19 epidemic has resulted in many deaths and significant disability. It has strained health care systems and delayed treatment of patients with other critical health problems because of lack of capacity. The lack of capacity is not only related to occupied beds, but to lack of nurses, in part related to health systems' mandated vaccination policies, even among those who are young and have already had documented COVID-19 illness. Many nurses have chosen to not return to work rather than have vaccination.

There remains great skepticism in the general public as to mandated vaccination policies, particularly in the young and in those who have already contracted COVID-19 and have recovered. Several reports have suggested that natural immunity gained from having experienced COVID-19 infection is superior to the immunity gained from vaccination. Others worry that the potential harm of vaccination has been understated.

We have learned much about this disease process, but there remain many unanswered questions. There have been more than 250,000 publications on COVID-19, and I suspect many more to come. How this crisis has been handled will remain under scrutiny for years to determine how future outbreaks of other illnesses should be handled. ■

To watch Dr. Walker's video commentary on this topic, click here.