



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

## Correspondence

### Reply For: "Re: Endotheliitis in COVID-19-Positive Patients After Extremity Amputation for Acute Thrombotic Events"



We are thankful for the opportunity to address the comments by Dr. Bozzani et al. regarding our case series of histology findings of 4 COVID-positive patients with Rutherford III acute limb ischemia. Bozzani et al. describe the numerous factors that are associated with coagulopathy including "high-grade inflammation, hypoxia, immobilization, and diffuse intravascular coagulation," and state that "direct damage to the endothelium by the virus is not yet demonstrated."<sup>1</sup> They surmise that thrombosis may not be secondary to direct endothelial damage by virus particle but rather that it may be a result of an immune response to viral infection of the endothelial cells which persists long beyond the acute phase of infection.<sup>2</sup>

While hypoxia and immobilization can certainly enhance thrombosis in patients with COVID-19, we have seen arterial thrombosis in patients with COVID-19 who present without history of respiratory symptoms, without hypoxia, and who were completely ambulatory. In fact, the patient's first presentation to the hospital was a thrombotic event.<sup>3</sup> Furthermore, the case series published by Bozzani et al. included 2 patients with early re-thrombosis of the lower extremities within 24 hr of thrombectomy suggesting lower extremity tissue-specific preponderance in the acute phase rather than just the pleiotropic response of COVID-19 infection with global, unregulated inflammatory cascade.<sup>2</sup> In conclusion, we agree with Bozzani et al. that the mechanism of acute arterial thrombosis in COVID-19 patients is unclear and likely multifactorial.

We wish to encourage more tissue studies to clarify the question of an infectious angiitis as a component of this pathology. There have been reports of viral invasion in

the endothelium of cells outside of the respiratory tract. An early study by Varga et al. published in *The Lancet* demonstrated "viral invasion" in electron microscopy images of kidney tissue of autopsy specimens.<sup>4</sup> It would be interesting to see if electron microscopy could be utilized to answer the question of whether viral invasion is a component of thrombosis in the arteries of the lower extremities.

Nicole Ilonzo\*

Justin M. George

Krystina Choinski

Windsor Ting

Division of Vascular Surgery,

Department of Surgery, The

Icahn School of Medicine at

Mount Sinai, New York, NY

Correspondence to: Nicole Ilonzo, The Mount Sinai Medical Center, 1425 Madison Ave, 4th floor, New York, NY 10029.

E-mail: [nicole.ilonzo@mountsinai.org](mailto:nicole.ilonzo@mountsinai.org)

### REFERENCES

1. Bozzani A, Arici V, Tavazzi G, et al. Re: "Endothelitis in COVID-19-positive patients after extremity amputation for acute thrombotic events". *Ann Vasc Surg.* 2021 S0890-5096(21)00089-3.
2. Bozzani A, Arici V, Tavazzi G, et al. Acute thrombosis of lower limbs arteries in the acute phase and after recovery from COVID19. *Ann Surg.* 2021 Publish Ahead of Print.
3. Ilonzo N, Rao A, Berger K, et al. Acute thrombotic events as initial presentation of patients with COVID-19 infection. *J Vasc Surg Cases Innov Tech.* 2020;6:381-3.
4. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417-18.