Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.1,2 SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells. Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids in vitro.3 Here we demonstrate endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19 (further case details are provided in the appendix).

Patient 1 was a male renal transplant recipient, aged 71 years, with coronary artery disease and arterial hypertension. The patient’s condition deteriorated following COVID-19 diagnosis, and he required mechanical ventilation. Multisystem organ failure occurred, and the patient died on day 8.

Post-mortem analysis of the transplanted kidney by electron microscopy revealed viral inclusion structures in endothelial cells (figure A, B). In histological analyses, we found an accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies, in the heart, the small bowel (figure C) and lung (figure D). An accumulation of mononuclear cells was found in the lung, and most small lung vessels appeared congested.

Patient 2 was a woman, aged 58 years, with diabetes, arterial hypertension, and obesity. She developed progressive respiratory failure due to COVID-19 and subsequently developed multi-organ failure and needed renal replacement therapy. On day 16, mesenteric ischaemia prompted removal of necrotic small intestine. Circulatory failure occurred in the setting of right heart failure consequent to an ST-segment elevation myocardial infarction, and cardiac arrest resulted in death. Post-mortem histology revealed lymphocytic endotheliitis in lung, heart, kidney, and liver as well as liver cell necrosis. We found histological evidence of myocardial infarction but no sign of lymphocytic myocarditis. Histology of the small intestine showed endotheliitis (endothelioliths) of the submucosal vessels.

Patient 3 was a man, aged 69 years, with hypertension who developed respiratory failure as a result of COVID-19 and required mechanical ventilation. Echocardiography showed reduced left ventricular ejection fraction. Circulatory collapse ensued with mesenteric ischaemia, and small intestine resection was performed, but the patient survived. Histology of the small intestine resection revealed prominent endotheliitis of the submucosal vessels and apoptotic bodies (figure C).

We found evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation. Although the virus uses ACE2 receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, thereby causing lung injury, the ACE2 receptor is also widely expressed on endothelial cells, which traverse multiple organs.3 Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis (figure D).

The vascular endothelium is an active paracrine, endocrine, and...
autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis.6 Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a pro-coagulant state.7

Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilise the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins.8–11 This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19.

ZV and AJF contributed equally as first authors, and RAS, FR, and HM contributed equally as last authors. AJF reports fees from Ailylam, Amgen, AstraZeneca, Fresenius, Imedos Systems, Novartis, Pfizer, Roche, Vifor, and Zoll, unrelated to this Correspondence. MRM reports consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticos, Baim Institute for Clinical Research, Riovant, and Triple Gene, unrelated to this Correspondence. FR has been paid for the time spent as a committee member for clinical trials, advisory boards, other forms of consulting and lectures or presentations. These payments were made directly to the University of Zurich and no personal payments were received in relation to these trials or other activities. All other authors declare no competing interests.

Zsuzsanna Varga, Andreas J Flammer, Peter Steiger, Martina Haberecker, Rea Andermatt, Annelies S Zinkernagel, Mandeep R Mehra, Reto A Schuepbach, *Frank Ruschitzka, Holger Moch
frank.ruschitzka@usz.ch

Department of Pathology and Molecular Pathology (ZV, MH, HM), Department of Cardiology, University Heart Center (AJF, FR), Institute for Intensive Care Medicine (PS, RA, RAS), and Division of Infectious Diseases (ASZ), University Hospital Zurich, CH-8091 Zurich, Switzerland; and Department of Internal Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA (MMR)