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.[3] 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.[4] 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.
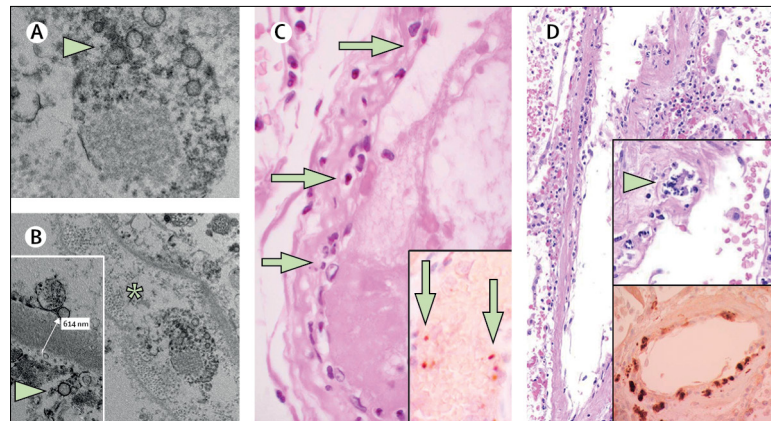

Figure: Pathology of endothelial cell dysfunction in COVID-19
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with dense circular surface and lucid centre. The asterisk in panel B marks peritubular space consistent with capillary containing viral particles. The inset in panel B shows the glomerular basement membrane with endothelial cell and a viral particle (arrow; about 150 nm in diameter). (C) Small bowel resection specimen of patient 3, stained with haematoxylin and eosin. Arrows point to dominant mononuclear cell infiltrates within the intima along the lumen of many vessels. The inset of panel C shows an immunohistochemical staining of caspase 3 in small bowel specimens from serial section of tissue described in panel D. Staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections, indicating that apoptosis is induced in a substantial proportion of these cells. (D) Post-mortem lung specimen stained with haematoxylin and eosin showed thickened lung septa, including a large arterial vessel with mononuclear and neutrophilic infiltration (arrow in upper inset). The lower inset shows an immunohistochemical staining of caspase 3 on the same lung specimen; these staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections. COVID-19=coronavirus disease 2019.

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 (endothelialitis) 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

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autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homoeostasis.[5] 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 procoagulant state.[6]

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.[7–11] 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.

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COVID-19: the case for health-care worker screening to prevent hospital transmission

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed unprecedented strain on health-care services worldwide, leading to more than 100 000 deaths worldwide, as of April 15, 2020.[1]

Most testing for SARS-CoV-2 aims to identify current infection by molecular detection of the SARS-CoV-2 antigen; this involves a RT-PCR of viral RNA in fluid, typically obtained from the nasopharynx or oropharynx.[2]

The global approach to SARS-CoV-2 testing has been non-uniform. In South Korea, testing has been extensive, with emphasis on identifying individuals with respiratory illness, and tracing and testing any contacts. Other countries (eg, Spain) initially limited testing to individuals with severe symptoms or those at high risk of developing them.

Here we outline the case for mass testing of both symptomatic and asymptomatic health-care workers (HCWs) to: (1) mitigate workforce depletion by unnecessary quarantine; (2) reduce spread in atypical, mild, or asymptomatic cases; and (3) protect the health-care workforce.

Staff shortages in health care are significant amidst the global effort against coronavirus disease 2019 (COVID-19). In the UK, guidance for staffing of intensive care units has changed drastically, permitting specialist critical care nurse-to-patient ratios of 1:6 when supported by non-specialists (normally 1:1) and one critical care consultant per 30 patients (formerly 1:8–1:15).[3] Fears of the impact of this shortage have led to other measures that would, in normal circumstances, be considered extreme: junior doctors' rotations have been temporarily halted during the outbreak; annual leave for staff has been delayed; and doctors undertaking research activities have been redeployed.