

## COVID-19: Vascular Endothelium and Organ Dysfunction



The effect of COVID-19 on endothelial cells (ECs) is emerging to be an important area of research for the effective management of severely ill patients. In the early phase of the pandemic, there was little attention paid to this effect and how it mediates organ dysfunction and even failure in extreme cases.

The endothelium has several critical physiologic functions in regulating the entry of fluids and substances in and out of tissue, vasomotor tone, preserving the osmotic balance, and initiation of immune response.

Coronavirus enters a cell through endocytosis and is mediated by an interplay of ACE2 and the protease transmembrane protease serine 2 (TMPRSS-2). The viral spike (S) protein binds to receptors on the cell as well as ACE2 on the membrane of endothelial cells to facilitate its entry inside the endothelial cell. It, therefore, needs both to be able to enter cells. Studies are underway to deal with it by using recombinant angiotensin-converting enzyme 2 (ACE2) and blocking transmembrane protease serine 2 (TMPRSS-2).

When attacked by viruses, endothelial cells lose their ability to maintain normal function, which means they can no longer regulate the entry of fluids and substances and fluids going in and out of tissues. This increased endothelial permeability makes it lose its tone, causes microvascular leaks, inflammation, a procoagulant state, immune-thrombosis, and organ ischaemia. These are all precursors of the severe acute respiratory distress syndrome characterised by vasculopathy, microcirculatory dysfunction, and ventilation-perfusion mismatch.

In light of understanding gleaned about the role of endothelium and endothelial cells in the management of COVID-19 infections, the following are some treatment considerations:

- Corticosteroids have robust anti-inflammatory properties and have shown benefits in some studies. More evidence is needed to determine its efficacy. Tocilizumab, an interleukin-6 receptor antibody, is a treatment that has shown promise without any apparent side effects.
- To deal with the prothrombotic state causing disruptions in microcirculation, hospitals should make coagulation tests and anticoagulation therapies part of the management protocol. Several studies have shown a decrease in mortality with the use of anticoagulant therapy. Eculizumab, a monoclonal antibody, is also being used and studied for its inhibition of complement activation.

Another mechanism by which COVID-19 wreaks havoc in the body is through intense inflammation. The body releases increased amounts of pro-inflammatory cytokines such as interleukin-6, interleukin-2, and tumor necrosis factor-α. This is also referred to as cytokine release syndrome or CRS and cytokine storm.

These cytokines, in turn, adversely affect endothelial function and recruit leukocytes. For example, interleukin-6 (IL-6) increases endothelial permeability, causes further secretion of cytokines by endothelial cells, and activates C5a complement, leading to coagulation. The concentration of IL-6 seems to be directly proportional to the severity of the infection and associated with mortality.

COVID-19, therefore, uses inflammation and coagulation as its two primary effects by which it harms the human body. To successfully manage these effects, treatment has to be directed and focused on endothelial cells by finding ways to control coagulation activation, complement activation, and therapies that modulate the body's immune response.

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