COVID-19 Pathogenesis and Severity: Oxidative Stress Hypotheses

Oxidative stress reflects an imbalance between the systemic manifestations of reactive oxygen species (ROS), e.g., free radicals and peroxides, and a biological system's ability to readily detoxify the resulting reactive intermediates and repair the consequent oxidative damage. By targeting proteins, lipids, and DNA, untethered ROS is thought to be a key factor in the development of a wide variety of diseases and conditions in the body, including cardiovascular diseases (CVD), insulin resistance/diabetes, the unwanted consequences of aging, and, most recently, the pathogenesis and severity of COVID-19 infection.

COVID-19 is caused by the SARS-CoV-2 RNA virus and gains access to humans by binding to the angiotensin-converting enzyme 2 (ACE2), which is abundantly expressed in many human tissues, including lung epithelium, vascular endothelium, heart, kidney, and intestine. What happens next in the pathogenesis of the COVID-19 infection and the emergence of its clinical sequela has been attributed by a variety of investigators to a number of interrelated 'oxidative stress' hypotheses.

Cecchini (July 2020) proposes that *"oxidative stress plays a role in the pathogenesis of COVID-19, perpetuates the cytokine storm cycle, blood clotting mechanism, and exacerbates hypoxia"* [1]. While recognizing that several other viruses induce oxidative stress in order to facilitate their replication inside the cell, these authors propose a pathogenesis model of primary lung injury and late hematological, tissue hypoxemia, and mitochondrial dysfunction due to oxidative stress, based on the body's analogous responses to other related viral infections.

Derouiche (May 2020) offers a similar explanation for COVID-19 morbidity, linking excessive activation of monocytes/macrophages with the development of a cytokine storm that leads to acute respiratory distress syndrome (ARDS)[2]. This prompted the authors to suggest that increasing the levels of antioxidants, e.g., glutathione (GSH), by dietary polyphenols, e.g., curcumin, is a logical approach to achieving protection against chronic inflammation and oxidant-mediated injury in lung infections like COVID-19.

Prompted by pathological evidence of diffuse endothelial inflammation induced by direct SARS-CoV-2 infection of endothelial cells in the lung, kidney, and small bowel, many investigators are now concluding that SARS-CoV-2 is best characterized as a **vasculotropic virus** that infects not only the lungs but progressively infects and damages endothelial cells throughout the body [3,4]. This scenario best explains why some people experience a variety of severe extrapulmonary complications -- including blood clots, myocarditis, and neurological symptoms -- from a virus that is supposed to just infect the lungs.

This vascular tropism appears to be unique to SARS-CoV-2, since influenza viruses like H1N1 are not known to do this and the original SARS-CoV-1 viral infection was largely confined to the lung. As depicted in **Figure 1**, after entering the body via ACE2 receptors present on the surface of epithelial cells lining the nose and throat, SARS-CoV-2 moves to the lung alveoli. Subsequent **vascular leakage and pulmonary edema** are caused by multiple mechanisms:

- Destruction of lung tissue breaks open blood vessels, exposing endothelial cells to subsequent infection and inflammation, i.e., **'endotheliitis' (or 'endothelialitis'),** characterized by **endothelial dysfunction (EDF)**, lysis, and cell death.
- Binding of the virus to the ACE2 receptor **impairs the activity of ACE2**, an enzyme that counteracts angiotensin vasopressors, and, by so doing, indirectly activates the kallikrein-bradykinin pathway that increases vascular permeability.
- **Activated neutrophils** recruited in this process produce **ROS,** among other histotoxic mediators.
- Immune cells, inflammatory cytokines, and vasoactive molecules lead to enhanced endothelial cell contractility and loosening of inter-endothelial junctions that soon result in **inter-endothelial gaps.**
- Multiple **cytokines** activate glucuronidases that lead to deposition of hyaluronic acid in the extracellular matrix, which promotes fluid retention.

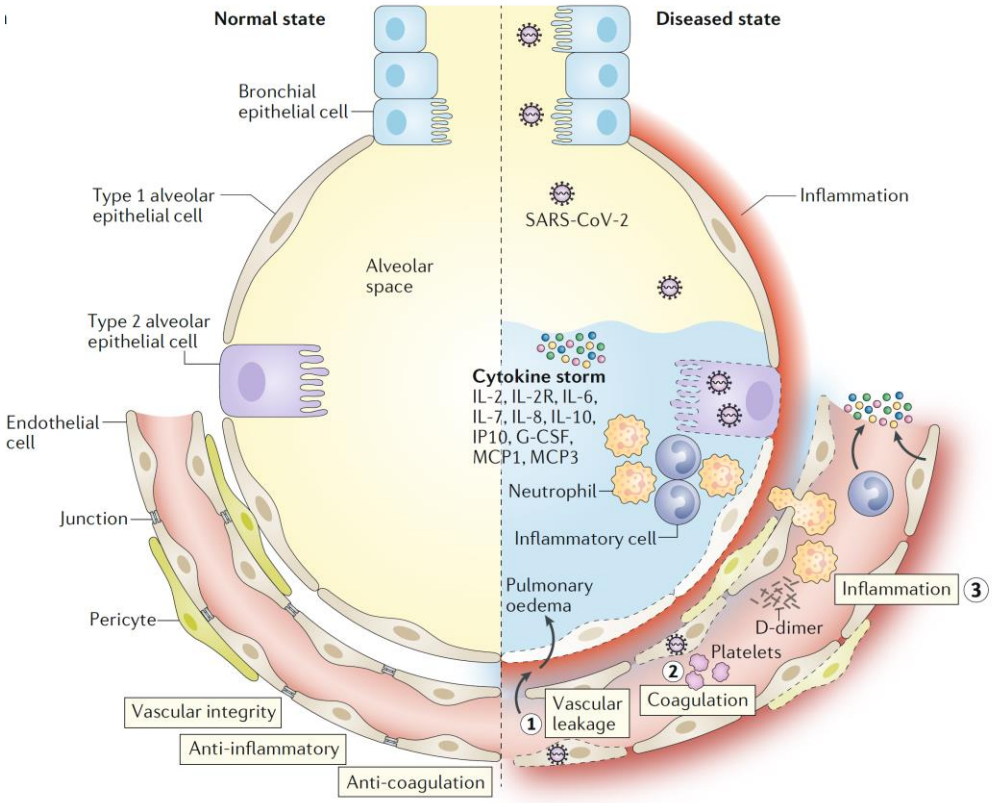

Figure 1. Proposed vessel-lung tissue interface in normal state and in COVID-19 disease [5]
On the left, the normal interface between the alveolar space and endothelial cells is depicted; the right-side highlights pathophysiological features of COVID-19 in the lung, including: 1) loss of vascular integrity; 2) activation of the coagulation pathway; and 3) inflammation.

On a background of **EDF**, endotheliitis likely plays a central role in the development of COVID-19 related venous and arterial thromboembolic phenomena and multi-organ inflammation, including the new pulmonary complication called *'microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS)'* – an atypical form of ARDS [6,7,8]. This progressive syndrome may also involve the microvascular bed of the brain and other vital organs, leading to multiorgan failure and death.

Mounting evidence suggests that **pre-existing EDF** – associated with obesity, hypertension, diabetes, and other components of metabolic syndrome -- could be a sine qua non for developing moderate-to-severe COVID-19 [9]. It follows that pre-existing EDF is likely one of the key underlying conditions that increases the risk for a significant adverse outcome to a COVID-19 infection and that the degree of EDF is positively correlated with the degree of this severity. Measurement of pre-existing EDF, therefore, is likely: 1) vital data for assessing the prognosis of COVID-19 infected patients; 2) a valuable source of information for all people to become more aware of their personal risk for a bad COVID-19 outcome, should they become infected; and 3) a potentially important motivating tool for adoption of a more healthy lifestyle, since most predisposing factors for EDF are modifiable.

EDF can be readily and accurately quantified using Everist Health's patented **AngioDefender** technology, with the AngioDefender Score put into appropriate perspective regarding how it influences one's risk for an adverse COVID-19 outcome by employing Everist Health's **COVIDAge Risk Calculator** (both accessible at: https://everisthealth.com).

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