

COVID-19: Respiratory Vascular Endothelial Repercussions

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INTRODUCTION

The endothelium of the blood vessels is a structurally intricate and physiologically functional interface between the blood compartment and tissues. Endothelium exhibits exceptional regulatory mechanisms at the molecular level that include homeostasis, fibrinolysis, vasomotion, inflammatory response, countering oxidative stress, membrane permeability, in addition to being a physical barrier. Vascular endothelium also regulates the circulation as well as coordinates the defense mechanism of the host upon a pathogenic attack. However, when the homeostasis and defense function of the vascular endothelium is challenged exceeding the limits, it becomes dysfunctional due to the endothelial injury thus rendering the host become susceptible to the pathogenic agent. This systematic review covers the latest findings and significant interpretations associated with endothelial consequences to the SARS-CoV-2 infection and pathogenesis.

Under normal physiological conditions, the angiotensin converting enzyme generates angiotensin fragments for regulating cardiovascular homeostasis. As a response to SARS-CoV-2 infection, the respiratory vascular endothelium expresses the genes of angiotensin converting enzyme 2. The surface spike protein of the virus interacts with ACE2 and invades the host cell. As a consequence, the immune response is activated and the cytokines are produced. Owing to the endothelial injury, vascular damage takes place resulting in complications.

Therefore, vascular endothelial cells are integral to COVID-19 pathogenesis including expression of angiotensin converting enzyme, vasculitis, and are susceptible to direct infection by SARS-CoV-2 virus. Zhang et al. (2020) have elucidated upon the role of endothelial cells during the pathogenesis of COVID-19 and explained the sequence of pathogenic molecular mechanisms that result in the severe acute respiratory syndrome. Evidence shows that upon the viral infection, the angiotensin converting enzyme, ACE is expressed in the endothelial cells of the arteries, veins and capillaries of not only lungs but also of heart, kidneys and intestines. The cellular infection by the virus causes endothelial dysfunction and leads to production of higher levels of interleukin -1, interleukin-6, tumor necrosis factor- α , chemokines, von Willebrand factor antigen, and factor VIII acute phase reactants such as IL-6, C-reactive protein, and D-dimer. Endothelial

damage also causes coagulopathy like pulmonary fibrinous and microthrombi in alveolar capillaries.

So it is now well established that SARS-CoV-2 infection leads to pathogenesis of heart, lungs, brain, kidneys and respective vasculature. It is now confirmed that during the development of COVID-19 induced endothelial complications, the endothelial functioning gets affected severely. The pro-inflammatory protein mediators and cytokines shift the endothelial function from regular homeostasis to host defense mode. During pathogenesis, the cytokines production overwhelms the counter regulatory mechanisms of the endothelial cells.

Ackermann et al. (2020) compared the histological patterns of peripheral lungs including the morphological and molecular changes during the autopsy of patients who succumbed to COVID-19, acute respiratory distress syndrome (ARDS) and influenza A (H1N1) based on immunohistochemical analysis, micro-computed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression. The study revealed that in case of COVID-19, alveolar damage with perivascular T cell infiltration, severe endothelial injury, presence of intracellular virus, cell membrane disruption along with widespread thrombosis and microangiopathy in pulmonary vessels were observed. Intussusceptive angiogenesis was higher in case of COVID-19 when compared to that in case of H1N1 influenza.

In the context of these evidences pertaining the endothelial role in COVID-19 pathogenesis, Evans et al. (2020) have identified the potential of vascular endothelial cell biomarker and other flow mediated dilation tests as a useful screening tools for classification of the risk level during COVID-19 pathogenesis and further emphasized greater and in-depth exploration of micro and macrovascular endothelial biology and endothelial function as a follow-up to convalescent COVID-19 patients for pre-emptive detection of cardiovascular complication risk. Libby and Luscher (2020) therefore suggested that the rational treatment strategy for COVID-19 must include the study of endothelial pathophysiology. To identify new and effective therapeutic strategies, Amraei and Rahimi (2020) reviewed the molecular mechanisms of SARS-CoV-2 infection and the signaling pathways associated with endothelial dysfunction. Yamaoka-Tojo (2020) suggested that endothelial dysfunction may be recommended as prediction factor

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for ascertaining the level of risk. Since the fragmented vascular endothelial glycocalyx (VEGLX) was found to be elevated among COVID-19 patients, it was suggested as a predictive indicator for the risk of severe complications. Siddiqi et al. (2021) have reported that there is the emerging evidence for SARS-CoV-2 mediated respiratory endothelial dysfunction and injury and therefore suggested that therapeutic approaches need to focus on addressing the vascular system dysfunction, which may prove to be important for treating the infection and reduce the risk of associated complications [1-7].

The cardiovascular system cannot be excluded from the pathogenesis. COVID-19 has cardiac effects including myocarditis, arrhythmias and myocardial damage and the vasculature gets affected directly by the pathogen and also due to systematic inflammatory cytokine circulation as secondary response. Inflammatory leukocytes lead to tissue damage thus leading to SARS, intravascular coagulation and cardiovascular complications.

CONCLUSION

COVID-19 did not give much time to the health care professionals to think and decide as to how to control its spread and how to treat the people who got infected effectively. Even before the therapeutic drug or the preventive vaccine was developed the disease has already caused havoc all over the world. Vascular endothelial damage and dysfunction were identified as a common clinical feature among high-risk patients who were susceptible to COVID-19. Patients with advanced age, hypertension, diabetes, obesity, and cardiovascular disease are more likely to experience severe conditions upon infection. The vascular molecular pathogenic mechanisms that

take place under these chronic degenerative conditions and old age are similar to the molecular pathogenesis caused by SARS-CoV-2 viral infection and therefore there is a high probability of the aggravation and complications in these age and physiological groups of susceptible people. Effective treatment strategies must include ensuring proper functioning of the vascular endothelium for reducing the risk of complications.

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