Endothelial Dysfunction in Coronavirus disease: A Literature Review

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Abstract
Coronavirus disease (COVID-19), caused by Sars-Cov-2, affects several cell types, including the vascular endothelium, which can lead to immunological phenomena and coagulopathies with vascular and systemic lesions. Thus, the objective was to describe, through a bibliographic review, the endothelial dysfunction induced by coronavirus. The data collected in this study suggest that the lesion of the endothelium caused by the coronavirus leads to cell death and exposure of the vascular glycocalyx, resulting in activation of neutrophils and platelets, with consequent production of cytokines, and activation of blood clotting, inducing the formation of thrombi/clots. The consequences are hypoxia and widespread lesions in several organs, resulting in life-threatening patients with COVID-19. Endothelial dysfunction is well established in cardiovascular diseases and diabetes, in such a way that these comorbidities could aggravate the endothelium-induced lesions by Sars-Cov-2, with more serious clinical outcomes. Thereby, a close relationship was observed between the endothelial dysfunctions induced by COVID-19 and inflammatory and thrombotic events, with worsening of clinical cases and fatal consequences. Therefore, early diagnosis can assist in the therapy that stabilizes the endothelium and reduces thrombotic events, with consequent aggravation and risk of death, especially in patients with chronic cardiovascular diseases and diabetes.

Keywords: Coronavirus, Dysfunction, Endothelium

1. Introduction
Coronaviruses are enveloped RNA viruses associated with the coronavirus disease (COVID-19) pandemic, whose etiological agent is now called Sars-Cov-21,2. And affects different epithelial cells, using the receptor, an angiotensin-converting enzyme 2 (ACE2) as the connection sector, resulting in pulmonary, vascular, and systemic changes, such as cardiac, renal, hepatic, and neurological changes. Partly, tissue impairments are associated with lesions in the vascular endothelium, induced by the coronavirus3,4.

The vascular system has basic functions, the distribution of oxygen and nutrients to tissues, as well as the removal of carbon dioxide and metabolites. Being structurally constituted generically by three layers (Tunic Adventitious, Medium, and Intimate). The latter is formed by a vascular endothelium (lining epithelial cells) anchored to a basement membrane (Glycocalyx)5,6.

The vascular endothelium is a monolayer of flat epithelial cells that line the lumen of the vessels, being at the interface between blood and tissue. The endothelium plays a role in cardiovascular homeostasis, including selective barrier, blood flow/vascular resistance modulation, immune response modulation, and thrombogenic barrier5,7.

The thrombogenic barrier is exerted by the endothelial layer since it can produce/express anticoagulant substances, such as thrombomodulin, which acts as an

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anticoagulant and antiplatelet agent. In addition, they cover the glycocalyx (basement membrane), which has components on its surface that lead to the activation of coagulation. Thus, inflammatory/infectious phenomena can promote dysfunction at the endothelial level, which can induce thrombotic processes and tissue injuries. These dysfunctions can be intensified in pre-existing pathological conditions, such as hypertension, diabetes, and obesity.

COVID-19 can lead to endothelial lesions and activation of inflammatory cells, such as neutrophils, contributing to hypercoagulability and inflammatory processes, cell death, and systemic tissue damage. Thus, a better understanding of this pathophysiology is essential for adequate clinical management of patients. In this context, the objective was to describe, through a bibliographic review, the endothelial dysfunction induced by coronavirus.

2. **Vascular Structure and Functions**

The peripheral vascular system consists of a network of tubes (vessels) that can be divided into veins, arteries, and capillaries. The vessels transport nutrients and oxygen to organs/tissues, and remove metabolites from these structures. Structurally, the main vessels (veins and arteries) are made up of three layers:

- The adventitia or outer layer that provides structural support and shape to the vessel
- The middle tunic or intermediate layer composed of elastic and muscular tissue that regulates the internal diameter of the vessel
- The tunica intima or inner layer consisting of an endothelial lining that provides a non-frictional path for the movement of blood and anchored in the basement membrane (glycocalyx).

The schematic structure of the vessels is shown in Figure 1. Since the capillaries are differentiated from the larger caliber, since they only have the endothelial layer, since it is inserted in the tissues with the function of facilitating the distribution of nutrients and oxygen at the tissue level.

The endothelial layer is formed by a monolayer of flattened and enlarged cells, which are anchored to the basement membrane (glycocalyx). Endothelial cells perform several functions in blood homeostasis, among which: Selective barrier, blood flow/vascular resistance modulation, immune response modulation, and thrombogenic barrier.

The endothelial cells are also related to many pathogens, including coagulopathies, induced by infectious and inflammatory processes. The endothelial membrane expresses several compounds that inhibit coagulation, including thrombomodulin (anticoagulant and antiplatelet action). Its role as a thrombogenic barrier is still reinforced because it covers the glycocalyx (basement membrane) since this structure expresses molecules that activate the coagulation activation.

They also express the receptor, ACE2, which acts in the regulation of the renin-angiotensin system, important in the regulation of blood pressure, heart rate, and osmotic pressure. The receptor is used by Sars-Cov-2 as a local of viral adhesion to endothelial cells.

Thus, inflammatory/infectious phenomena, such as COVID-19, can promote dysfunction at the endothelial level, which may induce thrombotic processes and tissue injuries. These dysfunctions can be intensified in pre-existing pathological conditions, such as hypertension, diabetes, and obesity, which previously intensify the endothelium injury, which can aggravate the patient’s clinical condition and increase the risk of death.

3. **Coronavirus - COVID-19**

Coronaviruses are positive-sense RNA viruses with envelopes ranging from 60 nm to 140 nm in diameter, presenting the light of electron microscopy to a crown, thus being called coronavirus. This virus presents itself
morphologically (Figure 2) viral envelope consisting of glycoprotein and hemagglutinin, which are responsible for adhesion to the host cell. Internally, there is the nucleocapsid where the viral RNA is inserted\(^1,2,13,14\).

This virus is responsible for the COVID-19 pandemic, initially observed in Wuhan - China, resulting in millions of deaths and infections around the world. The coronavirus associated with COVID-19 came to be called Sars-Cov-2. Transmission occurs through contact with contaminated objects or droplets that are released into the environment by infected people\(^2,13\).

On contact with the cells of the tissue mucosa, the viral replication cycle begins (Figure 2), the coronavirus connects to the membrane receptors (ACE2) (Adhesion), followed by viral internalization and viral genome release. This genetic material it is used in viral transcription and translation. Finally, the virus is assembled, and the viral particle is externalized by germination. These new particles can invade new cells and spread through the body through a hematogenic pathway, being able to interact with endothelial cells through the ACE2 receptor\(^1,13,14\).

### 4. Vascular Injury

Coronavirus is replicated at the pulmonary level or tissue entering the body, spreads to the local capillaries, being able to interact with the endothelial cells directly, through the ACE2 receptor or indirectly due to the inflammatory responses induced by the virus. Since these cells express numerous anticoagulant and antiplatelet molecules, such as thrombomodulin, and cover the basement membrane (glycocalyx), the impairment of this barrier contributes to endothelial dysfunction, resulting in inflammatory, and thrombotic processes – Figure 3\(^4,11,15\).

The infection of the respiratory epithelium by Sars-Cov-2 together with vascular injury contributes to the release of pro-inflammatory substances (multiple cytokines, chemokines, and interferons). These cause leukocyte activation, such as macrophages and neutrophils. In large numbers, these leukocytes can lead to harmful effects on the lungs and tissues since they contribute, together with endothelial death, to platelet activation and disseminated micro coagulation (Figure 3), and with risks of hypoxia and tissue death\(^10,12,13\).

A hypercoagulable state is observed due to tissue damage, among which the endothelium, leukocyte/neutrophil activation, and the cytokine cascade, resulting in abnormalities of the coagulation factors, such as high von Willebrand factor, factor VIII, D-dimer, fibrinogen, prothrombotic microparticles, anionic phospholipids, and platelet activation\(^5,6,12\).

The relationship between endothelial dysfunction and subsequent thrombotic events is already well known in cardiovascular, renal and diabetes diseases, being considered comorbidities of risk of aggravation for patients becoming infected with Sars-Cov-2, among

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**Figure 2.** Viral structure, transmission, and replication. Created with biorender.com.
which are quoted: Systemic arterial hypertension, dyslipidemia, renal failure, and diabetes mellitus. Lesions can be seen in superficial and/or deep tissues and can be life-threatening to the patient.\textsuperscript{10,11}

Garrido et al.\textsuperscript{16} collected skin samples from 25 patients in Salamanca. There are vascular alterations that lead to extravasation and tissue inflammation, with more frequent lesions: Palpable purple, rashes, and urticarial eruptions.

Vetter et al.\textsuperscript{12} points out that there are cardiovascular injuries and among the most recurring are: Myocarditis, cardiac arrhythmias, and heart failure.

Ackermann et al.\textsuperscript{3} indicates that at the pulmonary level, destruction of vessels and cells occurs, resulting in loss of respiratory capacity, and risk of death. These authors performed an autopsy of the lungs of patients who died from COVID-19, with the following being observed: Severe endothelial injury associated with the presence of intracellular virus, and rupture of cell membranes. Histological analysis of pulmonary vessels in patients with COVID-19 showed generalized thrombosis with microangiopathy.

Iba et al.\textsuperscript{10} implies that the most common finding of coagulopathy in SARS-CoV-2 infections is an increase in D-dimer, occurring on average in more than 50% of patients with severe conditions, being a predictor of worsening and mortality in these patients. Thus, the authors estimate that in more than 50% of the cases of thrombotic phenomena are observed, which can cause tissue damage in the kidneys, liver, lung, and heart in more than 50% of critically ill patients.

5. Conclusion

It is concluded from the data collected in the present study that Sars-covi-2 infection is related to lesions at the

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3}
\caption{Pathophysiology of coagulopathy induced by COVID-19. Created with biorender.com.}
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endothelial level, resulting in changes in coagulability and consequent thrombotic events. In patients with comorbidities, there may be a contribution to the worsening of the clinical picture and risk of death. Therefore, early diagnosis can contribute to adequate therapy and monitoring of laboratory parameters, reducing the risks of thrombogenic events, systemic inflammatory response syndrome, and multiple organ failure.

6. References


