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Review Article

A Link Between Endothelial Dysfunction and SARS-CoV-2 Infection in Patients With COVID-19

Kazumi Fujioka

Department of Radiology, Nihon University School of Medicine, Tokyo, Japan

***Correspondence to:** Dr. Kazumi Fujioka, Department of Radiology, Nihon University School of Medicine, Tokyo, Japan.

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Abstract

The emerging coronavirus disease 2019 (COVID-19) by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide outbreak, leading to a major threat to public health. The respiratory failure from acute respiratory distress syndrome (ARDS) as the major cause of mortality and multi-organ failure as other causes of mortality have been revealed in patients with COVID-19. The expression of angiotensin-converting enzyme 2 (ACE2) in the respiratory epithelium, vascular endothelium, and other cell types are recognized and can play a role as a primary mechanism of SARS-CoV-2 entry and infection process. It has been described that host cells infected by SARS-CoV-2 cause ARDS, sequentially stimulating the immune response or cytokine storm, vascular damage, and thrombosis in all arterial beds. It has been thought that clinical manifestations of COVID-19 in the severe stage present an endothelial disease and a systemic disease. In this article, the current knowledges of the link between endothelial dysfunction and SARS-CoV-2 infection have been reviewed. A close association between endothelial dysfunction and SARS-CoV-2 infection has been indicated in patients with COVID-19. The author also emphasizes that COVID-19 may be an endothelial disease and a systemic disease especially in the severe stage. In addition to antiviral and anti-inflammatory treatments, a new therapeutic strategy

of use of nitric oxide (NO) focusing on the vascular tone of the endothelial dysfunction may be a potential treatment in patient with COVID-19 especially in the moderate and severe stages.

Introduction

The respiratory failure from ARDS is the major cause of mortality [1] and multi-organ failure is regarded as other causes of mortality in patients with COVID-19 [2]. The worst outcomes have been reported in individuals with comorbidities such as hypertension, diabetes mellitus, obesity, and men [3]. Some studies have suggested hypercoagulability and increased inflammatory markers in patients with COVID-19 [4]. Amraei *et al*. [5] indicated the endothelial cell injury in lung organ and periphery caused by direct SARS-CoV-2 infection. Some studies provided that COVID-19 is an endothelial disease and a systemic disease in the severe stages. The author will review the current knowledges of a link between endothelial dysfunction and SARS-CoV-2 infection in detail.

Emerging COVID-19 Global Pandemic

The respiratory failure from ARDS is the major cause of mortality [1] and multi-organ failure involving heart and kidneys are regarded as other causes of mortality in patients with COVID-19 [2]. It has been described that in general, subjects with comorbidities such as hypertension, diabetes mellitus, obesity, and men have caused worst outcomes [3]. Some studies have suggested hypercoagulability such as raised D dimer and von Willebrand factor (VWF) value, and increased inflammatory markers including CRP, ferritin, interleukin (IL)-6, IP-10, MCP1, MIP1A, and TNF-α in patients with COVID-19 [4]. The theory has been provided that SARS-CoV-2 infection causes the endothelial cell injury in the lung and periphery. Endothelial cell injury can also activate the coagulation system and immune response enhances endothelial dysfunction [5]. It has been known that the raised VWF level is associated with endothelial dysfunction [5]. The notion that SARS-CoV-2 infection has induced endothelial dysfunction and/or damage was supported by the study of the elevated VWF level in patients with COVID-19 [6]. Marini *et al*. [7] have reported that the chest-X ray or computed tomography (CT) scan showed alveolar infiltrate appearances and the respiratory distress with important vascular insult in patients with COVID-19. They also noted that COVID-19 is a systemic disease that primarily affects the vascular endothelial cells [7].

Endothelial Function Assessed by FMD and RH-PAT Examinations

Flow-mediated vasodilation (FMD) and nitroglycerin-mediated vasodilation (NMD) in the brachial artery is a potential tool for assessing vascular endothelial and vascular smooth muscle cell (VSMC) function in atherosclerosis status [8]. The author has described several reports on the diseases of migraine, cardiovascular disease (CVD), chronic kidney disease (CKD), dyslipidemia, and aging liver [9-19] using FMD and NMD test. Another methodology estimating endothelial function implies the reactive hyperemia peripheral artery tonometry (RH-PAT) assessed by digital vascular function [20].

Endothelial Dysfunction Through RAS in Patients With COVID-19

The emerging COVID-19 global pandemic caused by SARS-CoV-2 infection has affected a major threat to public health. The expression of angiotensin-converting enzyme 2 (ACE2) which serves as an essential role in renin-angiotensin system (RAS) was recognized in the respiratory epithelium, vascular endothelium, and other cell types. It has been also considered as a primary mechanism of SARS-CoV-2 entry and infection processes. It has been known that SARS-CoV-2 through the surface spike glycoprotein interacts with ACE2 and invades and infects the host cells. Host cells infected by SARS-CoV-2 have caused ARDS, sequentially stimulating the immune response or cytokine storm and vascular damage. SRAS-CoV-2 infection has induced endothelial cell damage and exacerbated endothelial dysfunction which has been regarded as atherosclerotic condition. Amraei *et al.* [5] have supported the notion that a relationship between the presence of the endothelial dysfunction and endothelial damage caused by SARS-CoV-2 in COVID-19 associated mortality. They also concluded that ARDS induced by cytokine storm and/or vascular damage is the most critical manifestation in patient with COVID-19. The presence of endothelial dysfunction combines with the vascular damage caused by SARS-CoV-2 in patient with atherosclerotic condition, thereby leading to severe morbidity and mortality [5]. While, Hoffmann *et al.* [21] suggested that SARS-CoV-2 infection depends on ACE2 and TMPRSS2 as host cell factors. They also indicated that antibodies against SARS-CoV spike may offer the protection against SARS-CoV-2 [21].

Genomics Sequence in SARS-CoV-2

There is an envelope, a helical capsid, and a single-stranded, positive-sense RNA genome with a length of 27-32 kb in coronaviruses [5,22]. It has been revealed that the whole genome of SARS-CoV-2 was sequenced [23]. The 5' end of the viral genome encodes two polyproteins such as pp1a and pp1ab, leading to generation of 16 non-structual protein. While, the 3' end of the genome of SARC-CoV-2 encodes four structural proteins including spike (S), envelope (E), matrix/membrane (M), and nucleocapsid (N) [5,23]. It has been noted that the amino acid sequence between SARS-CoV and SARS-CoV S-proteins which are important for entry and infection processes of coronaviruses was revealed [5,23]. Similar to human coronavirus NL63 (hCoV-NL63) [24] and SARS-CoV [25], ACE2 was recognized as a receptor for SARS-CoV-2 [26]. While the spike protein encoded by the Middle East respiratory syndrome (MERS-CoV) recognizes CD26 as a receptor for cellular entry and infection [5,27].

A Link Between Endothelial Dysfunction and SARS-CoV-2 Infection

Gladka *et al.* [28] noted that the primary cell type involved in the initiation and propagation of ARDS caused by SARS-CoV-2 infection is endothelial cell. As a result, the severe endothelial injury and widespread thrombosis occur. The cytokine storm observed in severe COVID-19 patients contributes to destruction of endothelium, leading to cause ARDS, multi-organ failure, and death [29,30]. It is well known that the endothelium regulates the control of haemostasis, fibrinolysis, vascular tone or vasomotion, inflammation, oxidative stress, vascular permeability, and structure. Libby *et al.* [29] described that SARS-CoV-2 induces the protean clinical manifestations from head to toe, affecting the multiple organ systems including the lungs, heart, brain, kidney, and vasculature. With respect to the clinical course in COVID-19, in the initial

phase, the type I and II pneumocytes and alveolar macrophages participates in the initiation of infection. The disordered endothelial function has gradually promoted the destructive forces of SARS-CoV-2 in the lung as elsewhere. It has been described that impaired endothelial barrier function and IL-stimulation sequentially lead to a cytokine storm and aggravation of the ARDS in patients with COVID-19. It has been thought that COVID-19 in the advanced stage, represents an endothelial disease involving a cytokine storm and/or an inflammatory phenomenon. With respect to the pathophysiological mechanism of a cytokine storm, IL-1 induces its own gene expression and that of other pro-inflammatory cytokines including TNF-α and IL-6. In result, the induction of IL-6 which is produced by IL-1 provides another amplification loop, leading to the cytokine storm. In the advanced stage, SARS-CoV-2 serve as a destructive action beyond the lung organ, representing that predispose to thrombosis in the pulmonary circulation and the cerebral circulation. Furthermore, it has been noted that thrombosis can occur in all arterial beds within the microvasculature [29].

The Presence of SARS-CoV-2 in Endothelium

Varga *et al.* [31] described that pathological appearances of the endothelial cell dysfunction in COVID-19 represent the viral elements of the endothelial cells and diffuse endothelial inflammation. Based on the proof of the viral involvement and host inflammatory response, it has been suggested that SARS-CoV-2 infection predisposes the occurrences of endotheliitis in several organs [31]. They additionally mentioned that endothelial cell injury has developed by induction of apoptosis and pyroptosis in patients with COVID-19 [31]. They concluded that COVID-19-endotheliitis is regarded as the systemic impaired microcirculatory function in different vascular beds and their sequelae of injury [31]. In dermatological field, Colmenero *et al.* [32] have reported that immunohistochemical and electron microscopic features of SARS-CoV-2 infection in endothelial cells indicate that these lesions are part of the spectrum of COVID-19. They suggest that the pathophysiology of COVID-19 chilblains is due to the vascular damage caused by virus infection and secondary ischaemia. They also supported the notion that widespread endothelial infection induced by SARS-CoV-2 serve as a pathogenic role particularly in the severe types in patients with COVID-19.

Therapeutic Strategy for COVID-19

In the global pandemic, vaccine and antiviral drugs have been prioritized until now. The multiple other mechanisms which represent Achilles heels of SARS-CoV-2 infection have been reported. The recent study suggested that Camostat mesylate as TMPRSS2 inhibitor decreases SARS-CoV-2-spike-driven entry into lung epithelial cells [5,21]. Blocking the ectodomain shedding of ACE2 provides a unique treatment in patients with COVID-19. While inhibition of SARS-CoV-2's own peptidases such as 3CLpro and PLpro is another essential aspect of treatment targets against SRARS-CoV-2 and α-ketoamide inhibitor which inhibits SARS-CoV-2 RNA synthesis has been also identified [33]. While, the study provided that NO level and bioavailability decreased in patients with COVID-19, indicating exogenous supplementation of NO might assist prevention and therapeutic of infection [34]. In addition to antiviral and anti-inflammatory drugs, a new strategy of use of NO focusing on the vasomotion or vascular tone in endothelial dysfunction may be an essential therapeutic in patient with COVID-19.

In Summary

Clinical course in COVID-19 represented the initial infection of pneumocytes, leading to disordered endothelial function, impaired endothelial barrier function and IL-stimulation, cytokine storm and vascular damage, and thrombosis in all arterial beds, thereby suggesting that COVID-19 may be an endothelial disease and a systemic disease in severe stage. A close relationship between endothelial dysfunction including haemostasis, fibrinolysis, vascular tone or vasomotion, inflammation, oxidative stress, and vascular permeability, and SARS-CoV-2 infection has been suggested in patients with COVID-19. Pathologically, the proof of the presence of viral elements revealed that SARS-CoV-2 infection predisposes the induction of endotheliitis in several organs. With respect to the therapeutic, a new strategy of use of NO focusing on the vascular tone or vasomotion in endothelial dysfunction may be an essential treatment in patient with COVID-19.

Conclusion

1. A close relationship between endothelial dysfunction and SARS-CoV-2 infection has been suggested in patients with COVID-19.

2. The author also emphasizes that COVID-19 may be an endothelial disease and a systemic disease especially in the severe stage.

3. In addition to antiviral and anti-inflammatory treatments, a new treatment strategy of use of NO focusing on the vascular tone of the endothelial dysfunction may be an essential therapeutic in patient with COVID-19 especially in the moderate and severe stages.

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