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REVIEW ARTICLE

Endothelial Dysfunction in Covid-19 Infection

Hassan M. Otifi, PhD and Balkur K. Adiga, MD, DNP

Department of Pathology, College of Medicine, King Khalid University, Abha, Saudi Arabia

ABSTRACT

COVID-19 is an evolving systemic inflammatory pandemic disease, predominantly affecting the respiratory system. Associated cardiovascular comorbid conditions result in severe to critical illness with mortality up to 14.8 % in octogenarians. The role of endothelial dysfunction in its pathogenesis has been proposed with laboratory and autopsy data, though initially it was thought of as only acute respiratory distress syndrome (ARDS). The current study on endothelial dysfunction in SARS CoV-2 infection highlights its pathophysiology through the effects of direct viral-induced endothelial injury, uncontrolled immune & inflammatory response, imbalanced coagulation homeostasis, and their interactions resulting in a vicious cycle aggravating the disease process. This review may provide further light on proper laboratory tests and therapeutic implications needed for better management of patients. The main objective of the study is to understand the pathophysiology of COVID-19 with respect to the role of endothelium so that more additional relevant treatment may be incorporated in the management protocol.

Key Indexing Terms: COVID-19; Endothelial dysfunction; ACE2; NO; Endotheliitis; Hypercoagulopathy. **[Am J Med Sci 2022;363(4):281–287.]**

INTRODUCTION

The unchecked exponential increase in the incidence of COVID-19 is of serious concern to public health, health care systems, and the global economy. The highly contagious SARS CoV-2 has infected more than 179,686,071 people, involving 198 nations with mortality of 3,899,172.[1] In Saudi Arabia, the total infected cases are about 487,500 with 7,819 deaths as of 4th July 2021.[2]

COVID-19 is a spectrum of asymptomatic cases (1.2%), mild to moderate cases (80.9%), severe cases (13.8%), critical cases (4.7%), and death (2.3% of all cases.[3] Among hospitalized patients, cardiovascular (CV) & cerebrovascular comorbidities are associated in up to 40% of cases and diabetes in 12% of cases.[4] The case fatality rate increases with advanced age (with 14.8% in elderly over 80 years) and severity of disease (49% in critical illness), which in turn are associated with comorbid conditions.[3,5] In a Chinese cohort study of 138 hospitalized patients, 31% associated with hypertension (58% requiring ICU), 15% with cardiovascular diseases (25% requiring ICU), and 10% with diabetes (22% requiring ICU).[6] Also, the patients suffering from CV diseases are more vulnerable to severe COVID-19 and increased risk of mortality.[7] The autopsy studies showed distinct features of fibrin thrombi in small pulmonary arteries in 33 of 38 deceased cases.[8] Fogarty et al, are of opinion that the significant coagulopathy is the major pathogenesis in 67 Caucasian patients.[9] This might reflect the crucial role of endothelial cells (ECs) in critical COVID-19 and its further understanding might be of therapeutic implications.

Severe COVID-19 is more common in patients with comorbid diseases, many of which are known to be associated with endothelial dysfunction. The thrombotic, myocardial, and renal complications of severe COVID-19 could imply the role of endothelial damage. SARS CoV-2 is known to infect endothelial cells. So there likely to be a relationship between COVID-19 and endothelial dysfunction directly and indirectly. The main objective is to study the role of endothelial dysfunction in COVID-19 which may reflect newer and more relevant treatments to improve the patients' management.

Several reviews have been published on this field,[10-12] however, this review on endothelial dysfunction in SARS CoV-2 infection highlights its pathophysiology through the effects of direct viral-induced endothelial injury, uncontrolled inflammatory response, imbalanced coagulation homeostasis, and their interactions resulting in a vicious cycle aggravating the disease process.

SARS COV-2 AND HOST CELLS

SARS CoV-2 is known to infect epithelial cells of pharyngeal mucosa, alveolar cells, distal bronchial club cells, intestinal epithelium, renal tubular epithelium, cardiomyocytes, myocardial interstitial cells, lymphoid tissue, pericytes, and endothelium. Viral particles are demonstrated in all these tissues including endothelial cells of many organs.[13,14]

Viral spike(S) protein gets attached to Angiotensin-converting enzyme-2 (ACE2) receptor on host cells, along with coreceptors which help in viral entry by cleaving the S protein with conformational change. Though the virus has the highest affinity towards type 2 pneumocytes with overexpression of ACE2R, other cells including endothelial cells are also prone to infection.[5] ACE2R is widely distributed in epithelial and endothelial cells of various tissues like nasal mucosa, bronchus, lungs, heart, GIT, kidney, bladder, brain, skin, oral mucosa, lymph nodes, spleen, thymus, bone marrow, adipose tissue & testis.[3,15-17] Thus, COVID-19 can evolve from primary respiratory infection to systemic disease. Immunofluorescent double staining confirmed that the majority of SARS CoV-2 are observed in ACE2-overexpressed cells and CD68 or CD169-overexpressed macrophages.[18] The cell invasion depends on both ACE2 expression and the availability of the coreceptor, protease transmembrane protease serine 2 (TMPRSS-2).[17] TMPRSS-2 expression may vary among microvascular and macrovascular beds and across organs. Other host proteins like HSPA5, Sialic acid receptors, CD147, cathepsin B & L, may play a synergistic or alternate role in viral entry into endothelial cells.[13,19] The severity of disease involving different organs and individuals may depend on the expression of these receptors & cofactors.

The wide distribution of ACE2R in arterial and venous endothelial cells and its role in viral entry into host cells might exhibit various pathophysiologic alterations involving endothelium resulting in the severity of COVID-19 with different cardiovascular complications.

ENDOTHELIAL DYSFUNCTION IN COVID-19

COVID-19 is initially considered as causing viral pneumonia leading to acute respiratory failure, however, the evolving clinical, laboratory, and postmortem findings suggest a crucial role of altered endothelial function in its pathophysiology contributing to multiorgan dysfunction. Many autopsy studies have revealed, along with varying stages of diffuse alveolar damage in the lungs, several platelet-fibrin microthrombi in the venous and arterial circulation of different organs, and angiocentric inflammation.[18,20] There has been evidence of unexplained organ damage like multifocal individual cardiomyocyte injury, patchy hepatocellular degeneration, acute renal tubular damage, foci of depletion of lymphoid tissue in lymph nodes and spleen, necrotic lymphoid cells in lymph nodes, fibrinoid necrosis of small vessels, areas of perivascular inflammation in lungs and intestine, hemorrhage in lungs and spleen,[18,21] which might explain endothelial dysfunction. Abnormal endothelial function is involved in organ failure during viral infection by inducing microvascular leak, inflammation, pro-coagulant state, and organ ischemia.[22]

Pathophysiology of endothelial dysfunction in COVID-19

The possible pathogenesis of endothelial dysfunction may be categorized under direct viral effect, through cytokine release, oxidative stress, coagulation disturbance, and immune cells response (Figure 1).

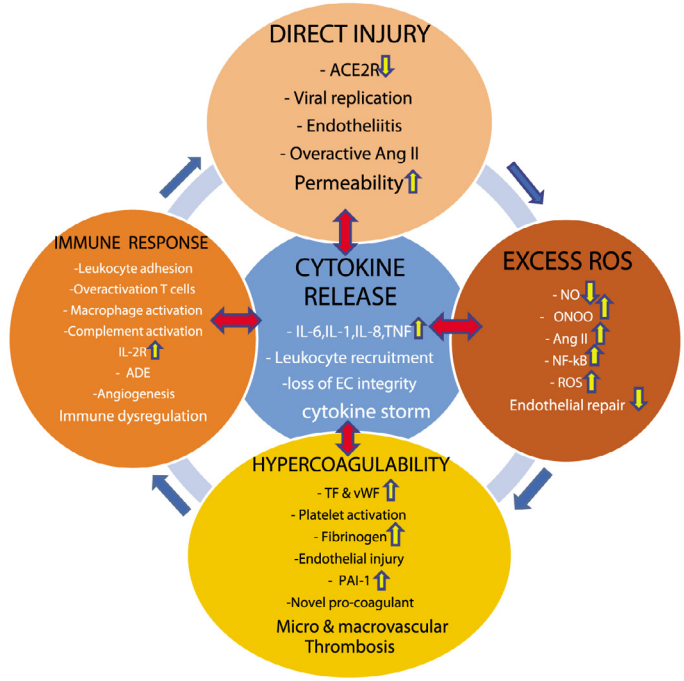

FIGURE 1. Pathogenesis of endothelial dysfunction in COVID-19 with the interaction of major mediators causing a vicious cycle of events.

Direct viral effect

ECs represent an important target for direct infection of SARS CoV-2 by binding to host cell receptors (ACE2) and through viral spike protein priming by coreceptors or proteases accessing entry into cytoplasm. Just as ACE2 is markedly expressed in type 2 pneumocytes of pulmonary alveoli compared to other epithelial tissue, ACE2 expression on endothelial cells among micro and macrocirculation in various organs may differ. The protease TMPRSS-2 is variably expressed in ECs of different organs.[22] In postmortem lung biopsies performed in 6 patients who died from SARS-CoV-2 infection, Copin et al. demonstrated endothelial injury (cytopathic change) with cytoplasmic vacuolization and cell detachment in small to medium-sized pulmonary arteries.[23] In another study, there was foamy degeneration of renal endothelial cells with fibrin thrombi in glomeruli.[24] In a study on 3 autopsy cases, Varga et al identified viral inclusion structures and lymphocytic endotheliitis in deceased with multiorgan failure affecting lungs, heart, kidneys, liver & mesenteric ischemia.[25] These findings might indicate endothelial cell dysregulation with loss of integrity of endothelial barrier, giving rise to pro-coagulant state.

As the virus enters the host cells along with membrane receptor ACE2, functionally ACE2 is down-regulated, thereby attenuating ACE—ACE2—Ang II—Ang 1-7—Mas receptor axis and amplifying ACE- Ang II- AT1R axis. Normally ACE2 reduces the effect of Angiotensin II (Ang II) by degrading it as well as counteracting its effects by generating Ang 1-7. In COVID-19, overactivity of angiotensin II, unopposed by Ang 1-7, leads to increased production of pro-inflammatory cytokines like IL-6, TNF alpha, and TGF beta; exert pro-thrombotic effects by reducing nitric oxide (NO) and prostacyclin release. Ang II is also a powerful vasoconstrictor and aldosterone release action, along with exerting oxidative stress, endothelial dysfunction, myocardial hypertrophy & interstitial fibrosis.[15] Ang II can induce matrix metalloproteinases-2 release and ROS generation in the endothelium.[21] As there is already baseline ACE2R deficiency in the elderly (to a greater extent in men) and in patients with diabetes, hypertension, cardiac hypertrophy and heart failure, SARS-CoV-2 infection is likely to manifest more severely.[15]

Via immune response

Severe COVID-19 with cytokine release results in immune cells recruitment which activates ECs. ECs interact with complement and humoral components of immunity to produce or respond to cytokines.[17] ECs also act as antigen-presenting cells as they express both class I and class II MHC molecules [26] and mediate Th1, Th2, and CD8 lymphocytes. Overactivation of T cells with an increase in tissue proinflammatory CD4 cells and cytotoxic CD8 cells noted in COVID-19 patients, though there was a reduction in peripheral CD4 & CD8 lymphocytes in severe patients.[27] Lymphopenia in severe patients is probably related to a reduction in lymphoid tissue of lymph nodes and white pulp of the spleen.

Gao et al in their autopsy study suggested that SARS CoV-2 nucleocapsid protein, which was demonstrated on alveolar cells and blood vessels, is highly pathogenic to lung damage through MASP-2 induced overactivation of complement.[18] Complements are also activated by IL-6 induced EC activation.[28] There was evidence of complement deposits in 5 COVID-19 patients in lungs with microvascular thrombosis.[17]

Ang II activates macrophages with consequent production of inflammatory cytokines.[15] Activated endothelial cells secrete monocyte chemoattractant protein 1; adherent activated monocytes, in turn, express large amounts of tissue factor (TF) at the site of infection. IL-1alpha released by necrotic tissue activates macrophages, which upregulate cytokine and adhesive molecules expression on adjacent endothelium. Recruitment of monocytes activates inducible NO synthase (iNOS), resulting in vasodilation, opening endothelial gaps, and loss of barrier function.[29] Macrophages express angiopoietin receptors which promote endothelial repair and angiogenesis. ECs promote macrophage viability and differentiation to M2 phenotype, which has anti-inflammatory effects.[30] Elevated serum levels of soluble IL-2R observed in COVID-19, likely to be induced by pulmonary endothelial cells and immune cell activation.[31,32] Activated T & B lymphocytes, NK cells, regulatory T cells express IL-2R on their surface, which combined with IL-2 mediates different stimulatory & regulatory immune functions.[33] Antibody-dependent enhancement (ADE) facilitates persistent inflammation and viral replication in target cells among some patients.[34]

Through inflammatory mediators

The cytokine release syndrome is characteristic of severe SARS CoV-2 infection with increased blood levels of cytokines, particularly IL-1beta, IL-6, IL-2R, TNF alpha.[31] These cytokines are secreted by different cell types including ECs. IL-6 also activates ECs inducing increased permeability, the release of cytokines, the expression of adhesive molecules, and activation of complement 5a.[28,35] ECs also secrete IL-8 and monocyte chemoattractant protein-1 to recruit neutrophils and monocytes, which activate iNOS resulting in vasodilatation & opening of endothelial gaps.[29] Houston autopsy cases revealed frequent entrapped neutrophils in precipitated fibrin inside pulmonary capillaries.[14] Elevated cytokines also cause platelet activation and leukocyte recruitment to microcirculation.[35] The blood level of cytokines, particularly IL-6, correlate with the severity of COVID-19. The initial rapid viral replication with epithelial and endothelial damage triggers exaggerated proinflammatory cytokine release and further enhancement of inflammation mediated by the failure of the renin-angiotensin system with loss of ACE2 function.[3] The genetic susceptibility related to genes of ACE2, TNF, VEGF, IL-

10, etc. also determines the extent of the inflammatory storm causing ARDS.[36] The excessive activation of pyroptosis through proinflammatory caspases 1 & 11 trigger cell death and release of proinflammatory cytokines like IL-1 & IL-8, damage-associated molecular patterns (DAMPs), and tissue factor.[19]

Coagulation pathway

The thrombo-embolic events are another remarkable feature of COVID-19 involving both microcirculation and macrovasculature. In a study of 184 critical COVID-19 patients, 31% of them showed thrombosis.[37] In another study of 150 patients, pulmonary embolism was reported in 16.7% of critical COVID-19 patients, with only 2% of deep vein thrombosis.[17] Fibrin microthrombi were reported in pulmonary arterioles and capillaries, glomeruli, skin, prostatic venous plexus, brain, peritesticular veins.[14] Intra-alveolar and interstitial fibrin deposits were also noted in autopsy cases. Most patients of Helms et al revealed elevated blood levels of D dimer and fibrinogen. Von Willebrand factor activity, factor VIII, and vWF antigen were significantly raised indicating the inflammation-mediated endothelial activated procoagulant state.[17] In SARS coronavirus infection, the production of novel pro-coagulant by infected cells induced by viral nucleocapsid protein is proposed as a mechanism for thrombosis.[38] Direct viral infection of ECs, viral-induced endotheliitis and other coinfection with SARS CoV-2 appear to be the mechanisms of thrombotic events in different patients.[25,39]

The direct viral invasion of ECs or indirect activation mediated by complement could be responsible for EC dysfunction and exocytosis of unusually large vWF multimers as well as platelet activation.[40,41] Plasminogen activator inhibitor is elevated in cases of severe ARDS caused by SARS-CoV infection, indicating a hypofibrinolytic state.[17] The prophylactic anticoagulants are associated with decreased mortality in COVID-19.[42]

Role of ROS

The accompanied comorbid conditions and risk factors for severe COVID-19 and severe SARS CoV-2 respiratory infection per se produce various reactive oxygen species, causing endothelial dysfunction with reduced NO bioavailability. ECs maintain vascular tone by producing various vasoactive molecules, of which NO is the major regulator. NO is mainly generated by endothelial nitric oxide synthase (eNOS & iNOS) in the presence of a cofactor like a tetra hydrobiopterin.

NOS is activated by signaling molecules like bradykinin, VEGF (as in hypoxia), serotonin (as with platelet aggregation). The eNOS normally maintain the quiescent state of endothelium with anti-inflammatory, anti-thrombotic, antioxidant and anti-proliferative functions; but can switch to an uncoupling state resulting in a reduction in NO and generating ROS. The oxidative stress could activate endothelium from its quiescent phenotype, causing dysregulation of NO and ROS. Endothelial ROS signaling may also be initiated by inflammatory cytokines, growth factors, and leukocyte interaction.[43]

The functions of NO are quite opposing to that of Ang II. It is not merely a potent vasodilator but also reduces permeability, platelet aggregation, leukocyte adhesion molecules, tissue oxidation, inflammation, activation of thrombogenic factors and favors fibrinolysis.[44] Sustained ROS signaling and reduced NO bioavailability reverse these actions and induce senescence of endothelial cells, apoptosis, impaired endothelial repair, and decreased mobilization of endothelial progenitor cells.[45] The oxidative stress directly or through HSP-60 stimulates NF-kB replication that leads to the production of proinflammatory cytokines like TNF alpha, IL-1, IL-6, which inhibit eNOS resulting in reduced NO production and favor Ang II synthesis. Endothelial cell apoptosis is induced by TNF-alpha. The excess of ROS, especially superoxide anion, oxidizes NO into peroxynitrite (ONOO), which can oxidize tetrahydrobiopterin.[44] The lung autopsy showed a striking feature of megakaryocytes with active platelets production in capillaries.[14] The circulatory endothelial progenitor cells may differentiate into another lineage like myeloid cells by the influence of inflammatory mediators.[45] The proinflammatory cytokines stimulate NF-KB replication leading to a vicious cycle amplifying the inflammatory response.[46]

CV diseases & endothelial dysfunction in COVID-19

Although COVID-19 usually manifests as acute febrile respiratory illness, an array of cardiovascular diseases like myocardial infarction, arrhythmias, myocarditis, epicarditis, pericarditis, stroke, acute renal tubular necrosis, vasculitis, and Kawasaki-like disease are reported.[13,14,18,47-49] Though initial autopsies concluded the ARDS-associated vascular changes, the later autopsies revealed widespread multiorgan involvement with arterial platelet-fibrin thrombi, hemorrhage, and endotheliitis in different organs.[8,18,49] Autopsy has also revealed multifocal myocardial ischemic injury without much inflammation.[5,14,48] Hu et al reported a case showing evidence of troponin-I level, clinical and ECG findings of myocardial injury with non-obstructive coronary artery disease.[50] Laboratory markers revealing markedly increased D dimer associated with high fibrinogen and normal platelet counts, establishing hypercoagulable state also indicate the role endothelial malfunction.[9,51]

The monolayered endothelium is the main regulator of blood clotting, vascular tone, as well as immune and inflammatory processes by generating and balancing various active molecules. Endothelial dysfunction is the condition in which the endothelial layer of small arteries fails to perform its normal function effectively. Infections are one of the several varied causes of endothelial dysfunction. Comorbid conditions like CV diseases, diabetes mellitus, hyperlipidemia; lifestyle measures like smoking, alcoholism, sedentary life are already compromised with

endothelial function. The dysregulated microcirculatory response to infectious agents leading to pro-coagulant state and multiorgan failure is well known in sepsis.[52]

Wang et al reported CV complications of acute myocardial injury (21%), arrhythmia (10.4%), and cardiac insufficiency (17.4%).[53] These complications are higher among older patients with CV risk factors like hypertension, diabetes, and severe COVID-19. Multiple pathogenetic pathways have been proposed like direct virus-induced cardiac toxicity, systemic hyper inflammation, thrombogenesis, atherosclerotic plaque rupture, and sepsis-induced DIC.[54] The possible persistence of endothelial dysfunction with thrombotic microangiopathy is also implicated in post-COVID-19 syndrome causing myocardial infarction, Kawasaki-like syndrome, cardiac insufficiency, pulmonary fibrosis, renal dysfunction.[53–57]

CONCLUSIONS

COVID-19 is a multi-systemic inflammatory pandemic disease, mainly affecting the lungs and heart, characterized by cytokine release syndrome, thromboembolic phenomenon, and microcirculatory dysfunction, causing severe to critical illness in some patients. Widespread EC dysfunction may contribute significantly to the pathogenesis of severe and critical illness of COVID-19. There are dual aspects of ECs dysregulation in COVID-19. The common cardiovascular comorbid conditions in SARS CoV-2 infected elderly persons are already associated with endothelial dysfunction and ACE 2 receptor deficiency. The SARS CoV-2 infection itself can induce change in endothelial function by various means like direct viral replication with loss of barrier integrity; downregulation of ACE2 & antibody-dependent enhancement culminating in inflammatory storm & hypercoagulability. This exuberant pain inflammatory & pro-thrombotic response of ECs dysfunction result in detrimental effects as refractory ARDS, diffuse microvascular and macrovascular thrombo-embolism, fatal cardiovascular complications, and multi-organ failure. Long-term effects of endothelial dysfunction in COVID-19 survivors, which might be related to persistent chronic inflammation and hypercoagulable state, need to be determined.

The understanding of role of endothelial function serves as potential targets for further study on relevant prognostic or predictive biomarkers and newer therapeutic options to manage patients. In severe COVID 19, endothelial dysfunction involves not only pro inflammatory and pro coagulant pathways, but also pro-oxidant, anti-fibrinolytic, direct barrier function, vasoconstrictor and complement pathways. Along with standard regimens of steroids and anticoagulants, other newer therapies to augment the function of endothelium like ACE inhibitors, angiotensin receptor blockers, statins, complement (C3 and C5) inhibitors, vasodilators (Nicorandil) and antioxidants have been proposed.

TABLE 1. Effects of potential drugs and their targets.

ACTION (DRUGS)	TARGET
C3 Inhibitor (AMY-101) C3 convertase inhibitor	C3 inhibition
Anti-C5 (Eculizumab) C5a antagonists (Vilobelimab)C5aR inhibitor (Avdoralimab)	C5 inhibition
C1 esterase inhibitors MASP2 antibodies (Narsoplimab)	C pathway blockers
Anti-IL6 Anti- TNF	Cytokine inhibitors
Methylprednisolone dexamethasone	Broad-spectrum anti-inflammatory drugs
Anticoagulants (LMW heparin) Endothelial cell protector (Defibrotide)	Endothelial cell-related targets

One of the main pathogeneses of endothelial damage resulting in thrombotic microangiopathies is through 'cytokine storm', which in turn is due to complement dysregulation. The initial effector mechanism is by over activation of C3, which may favor procoagulation over fibrinolysis and inflammation. Magro et al demonstrated deposition of C5b-9, C4d, and MASP2 in the microvasculature of lungs and skin in severe COVID-19 patients with thrombogenic vasculopathy.[58] The hyper-inflammatory response may be controlled by modulating complement cascade through complement pathway inhibitors, C3 inhibitors, and anti-C5 and anti-cytokine therapeutics.[59,60] Though both C3 and C5 blockade brings a rapid reduction in inflammatory markers with good clinical response in severe COVID-19, C3 inhibitors show broader therapeutic effects, especially on a microvascular injury. This effect of C3 inhibitors is likely mediated by C3a mediated P selection upregulation, C3b mediated opsonophagocytosis, C3aR dependent endothelial platelet adhesion, and C3 dependent endothelial adhesion of lymphocytes and by intercepting alternate pathway amplification.[61] Mastaglio et al reported the first case of successfully treated COVID-19 with severe ARDS in a patient with advanced coronary artery disease & peripheral arterial diseases.[62] The endothelial cell-based therapeutics like defibrotide are emerging as a potential target to reduce endothelial activation with anti-thrombotic, fibrinolytic, anti-inflammatory, antioxidant, and anti-adhesive properties.[63]

It is challenging to reduce mortality and long-term complications in the survivors of critically ill COVID-19. The therapeutic regimens aiming at endothelial activation and complement inhibition showing significant outcomes in the management of severe COVID-19. Table 1 summarises the role of certain drugs with potential benefits.

AUTHORS CONTRIBUTIONS STATEMENT

The authors have contributed equally to this work. Hassan Otifi conceived and designed the study, edited

the paper, and corresponded to the reviewers' comments. Balkur Adiga wrote the first draft of the review.

DECLARATION OF COMPETING INTEREST

There is no conflict of interest.

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Corresponding author: Hassan M. Otifi, PhD, Assistant Professor of Pathology, Department of Pathology, College of Medicine, King Khalid University, Abha, Saudi Arabia, P.O. Box 641 (E-mail: hotifi@kku.edu.sa).