(REVIEW ARTICLE)

Endothelial dysfunction in COVID-19 with smoking

Anditri Weningtyas [1, *], Dessy Amelia [1], Laras Putri Gamagitta [2] and Titin Andri Wihastuti [3]

[1] Department of Sport Science, Faculty of Sports and Science, Malang State University, Malang, Indonesia.
[2] Department of Physical Education, Health and Recreation, Faculty of Sports and Science, Malang State University, Malang, Indonesia.
[3] Department of Basic Nursing Science, Faculty of Medicine, University of Brawijaya, Malang, Indonesia.

Abstract

Endothelial dysfunction is one of the mechanisms that most likely to play a role in the occurrence of poor clinical outcomes in patients with COVID-19. The hyperinflammatory and pro-coagulation state in COVID-19 suggests an important role for the endothelium, both as an effector contributing to inflammation and thrombosis, as well as a target organ. This state of endothelial dysfunction is also believed to be exacerbated by a history of previous smoking. Tobacco can increase the severity of infectious diseases such as influenza, by increasing viral replication through suppression of antiviral mechanisms, and changes in cytokine patterns in cells also increase ACE2 expression. Smoking is associated with endothelial dysfunction because it can increase the concentration of free radicals and proinflammatory cytokines. So, it is very possible that SARS-CoV-2 will damage the endothelium of smokers who have previously been injured as a result of smoking habits. The literature that we used in this study was obtained through searching engines from the Google Scholar and PubMed databases, with the inclusion criteria being literature that used English. We managed to take 1,613 literature articles, then we selected 81 articles that were most relevant to the discussion of our study. In this study we conclude that endothelial dysfunction may play a role in the mechanism of clinical deterioration in COVID-19 and may be exacerbated by a history of previous smoking.

Keywords: Endothelial dysfunction; COVID-19; SARS-CoV-2; Smoking; Cytokine

1. Introduction

Novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in December 2019, and was declared a pandemic in March 2020 [1]. SARS-CoV-2 is a virus that binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed in human tissues including lung epithelium, myocardium, and vascular endothelium, which are responsible for the coronavirus disease 2019 (COVID-19) [2]. COVID-19 is a syndrome with many clinical manifestations ranging from flu-like symptoms to severe complications that require treatment in the intensive care unit (ICU). Complications that can arise with COVID-19 are persistent pulmonary disorders that can last for months after the acute phase [3]. In addition, cardiovascular and thromboembolic complications have also been reported in COVID-19 survivors [4,5].

Therefore, given the high number of patients with persistent clinical manifestations, a new paradigm of "post-acute COVID-19 syndrome" has been introduced[3]. However, the pathophysiological mechanisms underlying these manifestations are not fully understood[6]. Studies developed recently have shown that endothelial dysfunction may play an important role in the pathogenesis of COVID-19 and its clinical manifestations [7]. SARS-CoV-2 can directly infect vascular endothelial cells [8], causing systemic endotheliitis and cellular apoptosis[9]. Furthermore, inflammatory

---

* Corresponding author: Anditri Weningtyas

cytokines are able to bind to specific receptors on the surface of vascular endothelial cells, thus increasing platelet activation and leukocyte adhesion as well as reducing the bioavailability of nitric oxide (NO) [9,10].

Currently the known risk factors for severe clinical syndrome in COVID-19 are the need to be admitted to the ICU and/or need for mechanical ventilation, age 65 years or older, long-term institutional care, chronic obstructive pulmonary disease (COPD), moderate asthma to severe oxygen dependence, severe or decompensated heart disease, decompensated hypertension, chromosomal disease, immunocompromise, end-stage renal disease, high-risk pregnancy, severe obesity at any age (BMI > 40), and other clinical conditions such as liver disease [11,12]. However, there is possibly an important risk factor for COVID-19 that has so far not been included in global guidelines for pandemic control, namely smoking. Smokers are part of the risk group for COVID-19. In a meta-analysis study showed that the prevalence of COPD patients and smokers in cases of COVID-19 was 2% and 9%, respectively. COPD patients are at higher risk of experiencing more severe disease, with a risk of severity of 63%, compared to patients without COPD, which is 33.4%, with a RR of 1.88. The study also showed that 22% of patients who smoked while experiencing COVID-19 and 46% of former smokers experienced severe complications, with an RR of 1.45, indicating that smokers are 1.45 times more likely to experience severe complications compared to patients who have never smoke. Current smokers also have a higher mortality rate of 38.5% [82].

In addition, studies in animal and human cells show that tobacco increases the severity of infectious diseases such as influenza, increases viral replication through suppression of antiviral mechanisms and changes in cytokine patterns in cells with a central role in mucosal innate immunity [13]. Smoking also increases ACE-2 expression [14]. Smoking is associated with endothelial dysfunction and increased free radical concentrations [15]. So, it is very possible that SARS-CoV-2 will damage the endothelium of smokers who have previously been injured as a result of smoking. The existence of this gap is the reason for the authors to discuss the relationship between smoking history and endothelial dysfunction in COVID-19.

2. Material and methods

We searched for some relevant literature through a search engine from Google Scholar regarding endothelial dysfunction in COVID-19 with smoking risk factors. We searched for keywords such as "endothelial dysfunction in COVID-19", "endothelial dysfunction in smoker", and "COVID-19 and smoking". We are looking for various sources that have been published until 2021. We do not exclude relevant in-vitro, in-vivo, meta-analyses, literature reviews, and systematic reviews, while our inclusion criteria are English language literature.

A systematic review was conducted on the PubMed database to identify articles examining the association between the occurrence of endothelial dysfunction in COVID-19 and smoking using the following keywords: ("smoking" and "COVID-19") and ("smoking" and "COVID-19" and "endothelial dysfunction). The results for the keywords "smoking" and "COVID-19" obtained 1,613 literatures, while the results for the keywords "smoking" and "COVID-19" and "endothelial dysfunction" obtained 7 literatures. In the end, we selected 81 literature relevant articles that met our inclusion criteria.

3. Results

From all the sources that appeared in electronic searches through the PubMed database, the results obtained were 1,613 literature that examined the keywords "smoking" and "COVID-19", while the keywords "smoking" and "COVID-19" and "endothelial dysfunction "The results obtained were 7 literatures. Then we selected the literature that was most relevant to our topic of discussion in 81 articles. It was found that among the 81 article sources found, 44 literature or the equivalent of 54.32% were articles that discussed COVID-19 and its mechanism in endothelial dysfunction, while 16 literature or the equivalent of 19.80% were articles that discussed endothelial dysfunction in exposure to secondhand smoke acutely or chronically. Then as many as 8 literature or the equivalent of 9.88% is literature that discusses the incidence of endothelial dysfunction in COVID-19 which can be exacerbated by previous smoking history and possible underlying mechanisms. The remaining 13 literature or the equivalent of 16.10% is literature that discusses therapies that may have the potential to improve endothelial dysfunction in COVID-19, of the 13 literature as many as 9 literature that discusses currently available cardiovascular drugs that have potential to improve endothelial dysfunction, while as many as 4 literatures discuss new therapeutic agents that may be able to prevent and improve the incidence of endothelial dysfunction in COVID-19 accompanied by smoking.

Table 1 Mechanisms of endothelial dysfunction in COVID-19 with smoking

Events	Mechanism	Reference
COVID-19	Apoptosis, induction of cytokines and adhesion molecules, altered metabolism, increased pro-thrombotic phenotype	Tang et al., 2020; Colmenero et al., 2020
	Hyperinflammation, exposure of the endothelium to pro-thrombotics, upregulation of the clotting cascade and activation of thrombin as well as fibrin production	Evans et al., 2020; Riphagen et al., 2020
	Immune response and leukocyte recruitment	Xu et al., 2020; Riphagen et al., 2020
	ACE2 expression and function in the endothelium	Nicin et al., 2020; Fang et al., 2020
	Decreased pericytes due to pericytic apoptosis	Chen et al., 2020; He et al., 2020
Smoking	Downregulates sirtuin-3, increases mitochondrial ROS formation, reduces NO* bioavailability	Dikalov et al., 2019; Münzel et al., 2020
	Cardiovascular and brain oxidative stress, NOX-2 activation, increased endothelin-1 expression.	Olfert et al., 2020; Divo et al., 2015; Yasuo et al., 2011
	Direct toxic effects on endothelial cells, auto-antibodies that attack endothelial cells, hyperinflammation, increased release of endothelial cell mediators, which act as vasoconstrictors, pro-inflammatory, and remodeling (endothelin-1), and decrease expression of endothelial cell mediators that act as vasodilators and endothelial cell homeostasis, such as nitric oxide and prostacyclin, increased endoplasmic reticular stress, decreased expression of Vascular Endothelial Growth Factor (VEGF)	Polverino et al., 2019; Divo et al., 2015; Yasuo et al., 2011
COVID-19 with smoking	Hyperinflammation, oxidative stress, ACE2 expression and function in the endothelium, increased pro-thrombotic phenotype	Polverino et al., 2021

4. Discussion

4.1. Pathophysiology of endothelial dysfunction in COVID-19

The vascular endothelium has an important role in cardiovascular homeostasis by regulating the transport of cells, nutrients, and metabolites between the circulation and tissues [17]. The hyperinflammatory and pro-coagulation state in COVID-19 suggests an important role for the endothelium, both as an effector contributing to inflammation and thrombosis, as well as a target organ, which if dysfunction occurs can contribute to poor clinical outcomes [18]. Endothelial dysfunction in COVID-19 occurs due to loss of integrity, for example through apoptosis, which is associated with increased permeability, induction of cytokines and adhesion molecules, metabolic changes, pro-thrombotic phenotype and de-differentiation [19,20].

Recent studies have shown that endothelial cell dysfunction is the main pathophysiology of COVID-19. This is evidenced by the important role of the vascular endothelium in inflammation, which is the main driver of cytokine dysregulation in acute respiratory distress syndrome (ARDS) and various cardiovascular pathologies. In addition, the pro-thrombotic phenotype and disseminated intravascular coagulation (DIC) observed in COVID-19 attests to endothelial cell dysfunction, which promotes thrombosis by reducing integrity leading to exposure to pro-thrombotic sub-endothelial

substances, platelet arrest and regulation of the clotting cascade, activation of thrombin as well as production of fibrin [21].

There is some other evidence supporting a role for endothelial dysfunction in COVID-19 (Figure 1):

4.1.1. Leukocyte recruitment, immune response, and tissue injury.

Leukocytes play an important role in the pathogenesis of SARS-CoV-2. The importance of the leukocyte-endothelial cell association is demonstrated by the observation that patients with poor clinical presentation exhibit marked increases in blood neutrophils with lymphopenia, with CD4+ T cells and CD8+ T cells being lower in severe cases than in moderate cases [22]. Meanwhile, on histological examination of cases with poor clinical results, those who died from SARS CoV-2 showed pulmonary interstitial mononuclear inflammatory infiltrates dominated by lymphocytes [23]. Through the systemic inflammatory response in COVID-19, which is referred to as a cytokine storm, or cytokine release syndrome, the endothelium will be directly exposed to pro-inflammatory cytokines that initiate the transcription program, thereby inducing adhesion molecules and chemokines to promote leukocyte recruitment and inflammation. This can lead to endothelial cell death which contributes to increased vascular permeability and causes damage to various organs [24].

Research on the immunology of SARS-CoV-1 infection shows that the survival of SARS-CoV-1 patients is associated with an immune skewed CD825 cytotoxic response. Indeed, there is evidence that an expansion of virus-specific CD4 T cells and a robust Th2 response (including increased plasma IL-4, IL-5 and IL-10) is associated with lethality in SARS-CoV-1 [22]. However, whether this is what happened to SARS Cov-2 still requires further research. However, it appears that adaptive immune response is an important outcome determinant in SARS-CoV-2, as there is a reported association between plasma IgA titers and disease severity. It is possible that in SARS-CoV-2, antibody-dependent enhancement (ADE) in inflammation plays a role in endothelial cell dysfunction [27].

4.1.2. Endothelial and thrombosis

When endothelial dysfunction occurs, the thrombotic and coagulant properties of the endothelium change. Decreased production of anti-aggregation prostacyclin from endothelial cells and increased synthesis of pro-aggregation thromboxane from activated platelets can alter homeostasis leading to a pro-thrombotic and pro-inflammatory phenotype [28]. Under inflammatory conditions, endothelial cells express adhesion receptors such as von Willebrand factor on their surface, this condition is intended to promote platelet recruitment and activation to the intact endothelial monolayer[29], which in turn can lead to platelet-dependent secondary recruitment of leukocytes, either through leukocyte-platelet interactions. adherence to endothelial cells, by recruitment of heterotypic aggregates of circulating platelets and leukocytes, or by transfer of platelet-innate receptors such as GFPIb to the leukocyte membrane by micro vesicles derived from platelets [30, 31].

It is assumed that tri-cellular aggregates, i.e., endothelial cells, platelets, leukocytes in the walls of smaller blood vessels will cause loss of microvascular perfusion in the lung and other organs. Thrombosis and further intravascular coagulation can also damage the endothelium and contribute to inflammation and endothelial dysfunction [24]. In some COVID-19 patients with severe microvascular endothelial injury, it is directly mediated by activation of alternative complement pathways and lectins, which are associated with a pro-coagulant state [32].

4.1.3. Expression and function of ACE2 in the endothelium

ACE2 is closely related to cardiovascular physiology as part of the renin-angiotensin-aldosterone system (RAAS), which controls blood pressure by altering vascular tone and function. ACE-related molecules convert angiotensin (Ang) I to Ang II, which triggers vasoconstriction, hypertension, and vascular inflammation. Because of these properties, antihypertensive drugs have been developed to reduce the production (ACE inhibitors, ACE-i) or downstream (Ang II receptor blocker, ARB) effects of Ang II. The effect of ACE is counteracted by ACE2, which converts Ang II to the molecule Ang 1-7 thereby increasing vasodilation and reducing blood pressure [33]. Because ACE2 is expressed on cells of the cardiovascular system [34], there is a high possibility that this class of antihypertensive drugs may increase the risk of infection with SARS-CoV-2 by increasing ACE2 expression in vascular cells [35]. However, population-based studies reveal that ACE inhibitors and ARBs do not increase the risk of COVID-19 or disease severity and the European Society of Cardiology recommended that hypertensive patients should continue anti-hypertensive medication during the pandemic [36,37].

The spike (S) protein of the corona virus mediates entry of the virus into target cells. Entry of SARS-CoV-2 depends on the physical interaction of the surface unit, S1, of the S protein to the host cell receptor, which facilitates attachment of

the virus to the surface of the target cell. SARS-CoV-2 involves ACE2 as the main receptor and it is therefore possible that COVID-19 may lead to reduced ACE2 bioavailability due to endosome/lysosome processing [38, 39, 40].

4.1.4. SARS-CoV-2-induced endothelial disease

Apart from the respiratory tract, SARS-CoV-2 viral load was detected in the kidney, liver, heart and brain [41], which are highly vascularized tissues. Early indications of the tropism of SARS-CoV-2 in vascular tissue by showing that this virus can infect human blood vessels and kidney organoids through ACE2 [40]. Tests by electron microscopy and histology show that SARS-CoV-2 can be detected in kidney endothelial cells (glomerular capillaries), small intestine, lungs and myocardium [42].

SARS-CoV-2 infection in the endothelium may directly trigger endothelial complications in COVID-19. SARS-CoV-2-infected endothelium is associated with endothelial cell apoptosis, which suggests a possible mechanism by which the endothelium is dysfunctional in COVID-19 [42]. A recent report on the Kawasaki disease-like syndrome associated with COVID-19 infection in children highlights the importance of infection virus in blood vessels [43, 44]. Kawasaki disease is the most common systemic vasculitis in children and specifically targets the myocardium and coronary arteries. Although the etiology of Kawasaki disease is unknown, infectious agents including RNA viruses have previously been postulated as causative and the association between Kawasaki disease and coronavirus infection was first described in 2005 [45].

4.1.5. Perisit

Pericytes are microvascular multifunctional mural cells and have an important role in maintaining endothelial integrity [46]. Studies show that pericytes are involved in COVID-19-associated vasculopathy. Single-cell or single-nucleus RNA sequencing analysis showed that ACE2 is highly expressed in pericytes in various organs, such as the heart [47, 48]. In the alveolar capillaries of the lungs infected with SARS-CoV-2, pericytes were markedly decreased, possibly due to apoptosis [49]. In a genetically modified mouse model of pericyte deficiency (pdgf-b$^{ret/ret}$ mouse) induced by PDGF-B retention motif deletion, loss of pericytes induces a thrombogenic reaction in endothelial cells [48]. Pericytes are therefore likely a direct target for SARS-CoV-2, which may play an important role in microvascular dysfunction and coagulopathy [47, 48].
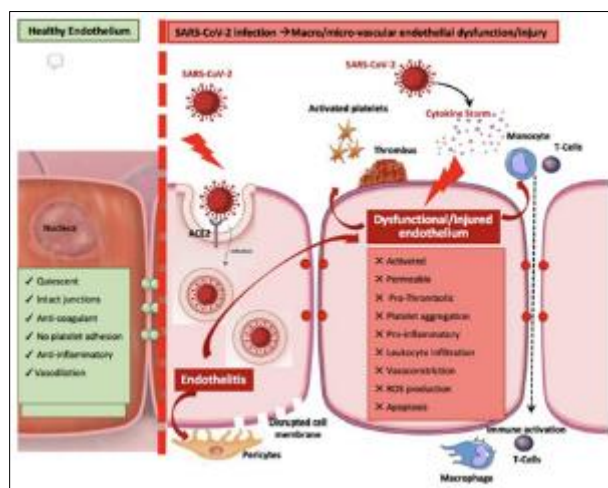

Figure 1 Endothelial dysregulation by SARS-CoV-2.

On figure 1 A healthy endothelium (left) is characterized by an intact junction, anti-inflammatory anti-coagulant phenotype and an intact vasodilatory phenotype. Endothelial cells are infected with SARS-CoV-2 (center), while the image on the right shows cells activated as a result of cytokine release and activation of the prothrombotic pathway. SARS-CoV-2 infection through ACE2 which is then endocytosed, has the potential to reduce ACE2-mediated regulation of vascular tone. SARS-CoV-2 infection causes endothelial dysfunction through various mechanisms including activation of the inflammatory process, cytokine storm, leukocyte infiltration, increased permeability, thrombosis, platelet aggregation, vasoconstriction, ROS production, and apoptosis [21]

4.2. Pathophysiology of smoking-induced endothelial dysfunction

Chronic exposure to tobacco cigarette smoke can impair acetylcholine-dependent vascular relaxation and coronary blood flow in rats which is associated with increased plasma cholesterol levels. Exposure to tobacco smoke for two weeks caused mild hypertension and endothelial dysfunction in rats by downregulating sirtuin-3 and increasing mitochondrial ROS formation which was influenced by overexpression of mitochondria-targeted catalase. Chronic smoking (>32 weeks) also reduces NO* bioavailability and causes cardiac remodeling in rats which is also associated with structural endothelial damage. This is also supported by research on exposure to cigarette smoke for several weeks in rabbit experimental animals which showed impaired endothelial function of the vascular tissue which could be corrected by ascorbic acid therapy and exacerbated by a hypercholesterolemic diet [50].

Whereas exposure to e-cigarette smoke for 5 days in rats can also cause aortic endothelial dysfunction, which is associated with cardiovascular and brain oxidative stress, eNOS release, NOX-2 activation, endothelin-1 expression, and the formation of acrolein-adduct [51]. This detrimental effect may be corrected by the endothelin receptor blocker macitentan and NOX-2 genetic deletion, as well as pharmacological inhibition of NOX-2. Studies of endothelial function in various animal models have shown comparable effects on smoking or vape-induced endothelial dysfunction. Also, chronic exposure of rats to e-cigarette smoke or tobacco smoke over 8 months resulted in a degree of arterial stiffness or endothelial dysfunction in the same vessels [52].
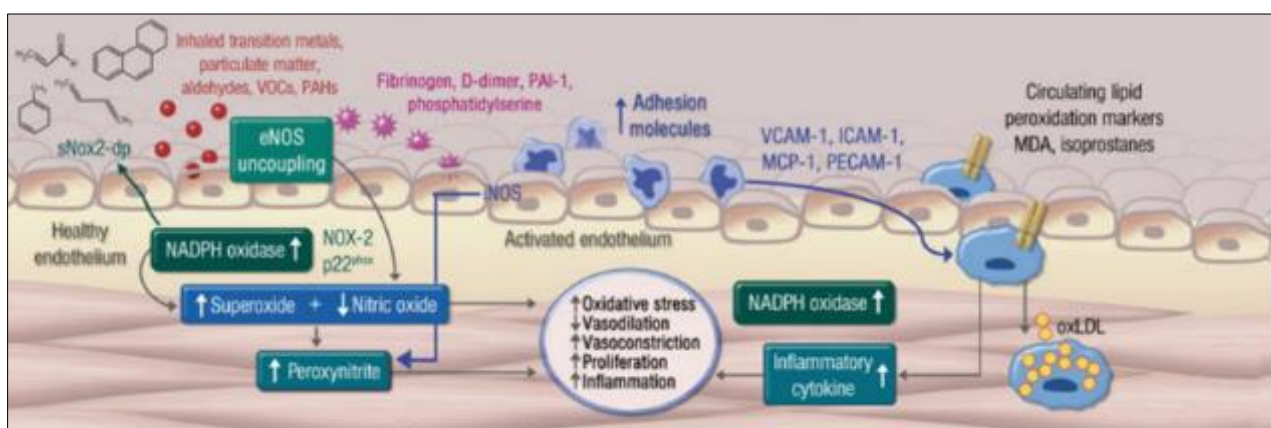

Figure 2 Mechanisms of DNA damage and adverse epigenetic regulation, play a role in endothelial dysfunction and cardiovascular disorders caused by smoking

4.3. Pathophysiology of endothelial dysfunction in COVID-19 with smoking

Tobacco increases the severity of infectious diseases such as influenza through suppression of antiviral mechanisms and changes in cytokine patterns in cells with a central role in innate mucosal immunity, thereby increasing viral replication [53]. Smoking is also associated with endothelial dysfunction and increased free radical concentrations [54]. So that endothelial dysfunction in COVID-19 with a history of smoking habits will cause endothelial dysfunction to get worse [55]

COVID-19 patients show high C reactive protein (CRP) and D-dimer levels, indicating an increased risk of thrombosis56. This diagnostic marker of thrombosis is also increased in smokers [57,58,59]. High D-dimer levels (>1µg/L) will increase mortality by 18 times in COVID-19 patients [61]. The mechanism of this complication is still not known with certainty, but may have relevance to the impact of smoking on endothelial dysfunction in COVID-19 [61]. COVID-19 with a history of smoking habits is 3.25 times more likely to lead to poor clinical manifestations when compared to non-smokers [62].

In addition, smoking can also increase susceptibility to infection, which is associated with upregulation of the angiotensin converting enzyme 2 (ACE2) receptor, the main receptor used by SARS-CoV-2 to enter the host mucosa and induce infection. Smoking contributes to worse clinical manifestations and increased susceptibility to SARS-CoV-2 infection through activation of peripheral nicotinic acetylcholine receptors (nAChRs) which are expressed in various organ systems. Nicotine affects the homeostasis of the renin-angiotensin system (RAS) and contributes to upregulation of the angiotensin converting enzyme (ACE)/angiotensin (ANG)-II/ANG II type 1 receptor axis, which contributes to the increased incidence of cardiovascular and pulmonary disease in COVID-19 [63].

Chronic cigarette smoke exposure has been associated with multiple organ dysfunction including systemic vascular endothelial dysfunction or injury [64, 65]. Endothelial dysfunction due to cigarette smoke can cause arterial hypertension, atherosclerosis, systemic inflammation, pulmonary arterial hypertension, cor-pulmonale, venous thromboembolism, and microalbuminuria[66]. A number of mechanisms underlie endothelial dysfunction in chronic cigarette smoke exposure, which include: (1) direct toxic effects of cigarette smoke on endothelial cells; (2) auto-antibodies that attack endothelial cells; (3) vascular inflammation and oxidative stress, with reduced activation of anti-oxidant pathways in endothelial cells; (4) increased release of endothelial cell mediators, which act as vasoconstrictors, pro-inflammatory, and remodeling (endothelin-1), and decreased expression of endothelial cell mediators, which act as vasodilators and endothelial cell homeostasis, such as nitric oxide and prostacyclin; 5) increased endoplasmic reticular stress; and (6) decreased expression of Vascular Endothelial Growth Factor (VEGF) caused by a decrease in hypoxia inducible factor-1, which is a transcription factor to encourage the expression of genes involved in endothelial function[65,67]. Some of these pathological mechanisms have the same mechanism in endothelial dysfunction caused by SARS-CoV-2 infection. Clinically, patients infected with the corona virus show a hypercoagulable state with thrombosis, and clot fibrin is one of the most common histopathological findings in the lungs and other organs of COVID-19 patients [68]. It is possible that cigarette smoke can further exacerbate the endothelial dysfunction induced by SARS-CoV- 2 (Fig. 3) [68]. The mechanisms underlying this potential synergy are still not clearly explained. Further research is needed to elucidate the direct effects of cigarette smoke and COPD on endothelial cells in SARS-CoV-2 infection.
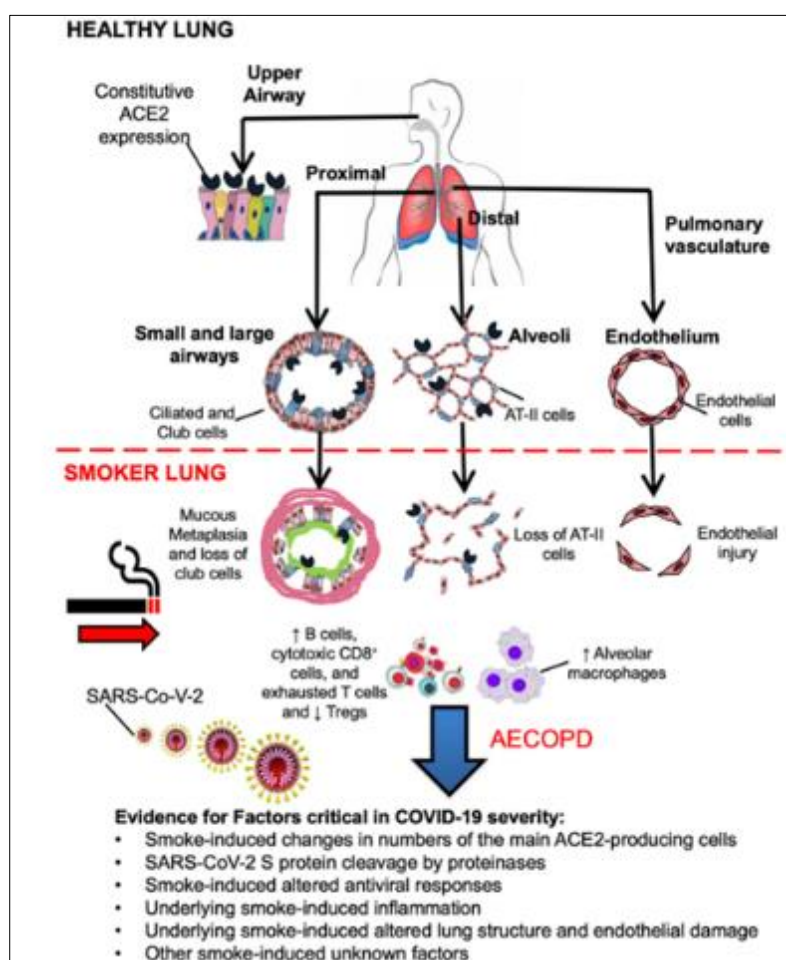

Figure 3 ACE2 expression across the respiratory tract.

As explained on figure 3, the highest ACE2 expression was found in the nasal epithelium followed by the larger airway epithelium, reduced in the more distal bronchiolar and alveolar areas. Cigarette smoke induces alveolar cell type II (AT-II) loss and extensive goblet cell hyperplasia. In addition, cigarette smoke induces an increase in the number of alveolar macrophages, which are the main cells expressing proteinases, and upregulates B cells, cytotoxic CD8+ T cells, and downregulates the regulatory T cell compartment. Chronic damage from innate and acquired immune responses leads to viral clearance. delayed, increased mucus production, impaired secretion of antimicrobial peptides during SARS-CoV-2 infection. In addition, the injury to the endothelium caused by SARS-CoV-2 infection may also be exacerbated by a

history of exposure to chronic cigarette smoke. The occurrence of endothelial dysfunction in the pulmonary blood vessels will lead to AECOPD (Acute Exacerbations of COPD) in COVID-19 patients with a history of chronic cigarette smoke exposure [68]

4.4. Therapeutic targets

Further research still needs to be done to determine whether the endothelial dysfunction and injury that occurs in COVID-19 is due to direct infection of endothelial cells by SARS CoV-2 or indirect injury due to several factors including cytokines, leukocytes, neutrophils, and complement activation [69]. Nonetheless, an important consideration is the effect of cardiovascular drugs on this mechanism (Figure 4). On the one hand, it may play a role in enhancing endothelial protection, while on the other hand it may also increase endothelial vulnerability. Drugs including HMG-CoA reductase inhibitors (statins), alpha- and beta-adrenergic blockers and antagonists of the renin-angiotensin-aldosterone system are widely administered to patients with diabetes mellitus, hypertension, and coronary artery disease, which are the highest risk group from COVID-19 [19, 21].

In pre-clinical studies showed that statins increase ACE2 expression. In addition, increased expression of ACE2 has cardiovascular benefits [70]. The beneficial effects observed previously in influenza and statin administration demonstrated the ability of statins to reduce CD147 expression, optimize lipid raft function, regulate autophagy, decrease pro-thrombotic pathways and enhance anti-thrombotic effects, in addition statins may exert an important endothelial protective effect against SARS-CoV-2 infection [71, 72, 73].

While the reported beneficial effect of beta-adrenergic blockers in ARDS and respiratory failure is the potential ability to reduce viral entry by downregulating ACE2 has led to this drug being suggested as adjunctive therapy for COVID-19 [74]. Retrospective analysis of alpha-1 adrenergic receptor antagonists in patients with ARDS or pneumonia has shown that alpha blockers are less likely to require ventilation. In contrast, the administration of beta-adrenergic blockers has no effect. Clinical studies show that alpha-blockers can prevent ARDS-associated cytokine storm and death in rats by disrupting the catecholamine loop [75, 77]. Further research will focus on Ang 1-7 peptides, ACE2 itself, and monoclonal antibodies that prevent SARS-CoV-2 from binding to ACE2 [70, 75, 76].
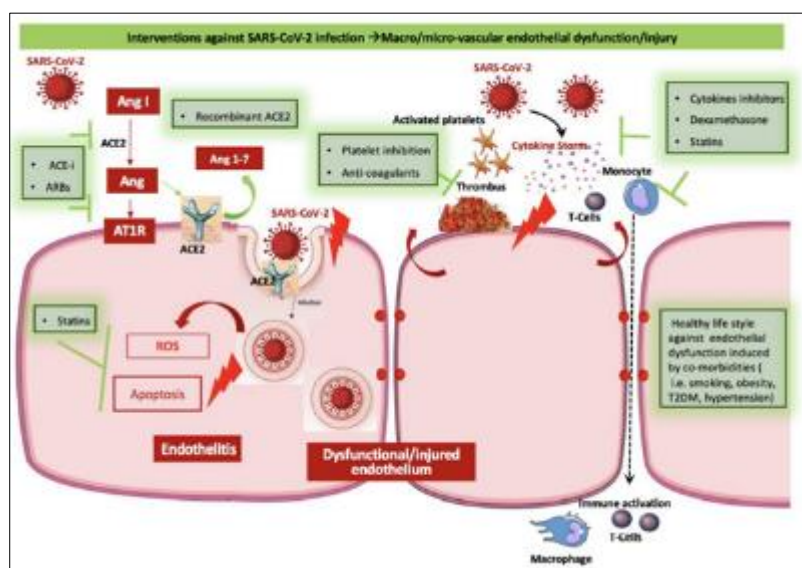

Figure 4 Potential interventions to reduce endothelial injury and activation.

On figure 4, Endothelial infection with SARS-CoV-2 infection causes RAAS dysregulation, apoptosis, thrombosis and inflammation (red). Several interventions (green) can reduce endothelial dysfunction in COVID-19 including RAAS modulators (ACE-i, ARB, ACE2); anti-inflammatory molecules (cytokine inhibitors, dexamethasone, statins); ROS/apoptosis inhibitors (statins); platelet inhibitors and anticoagulants. A healthy lifestyle can also reduce endothelial dysfunction in COVID-19 patients [21]

Apart from testing the effect of existing drugs in improving endothelial dysfunction in COVID-19, several studies have also led to the discovery of new drugs in improving endothelial dysfunction in COVID-19. One of the molecules that is often used to test its effect in repairing endothelial dysfunction is nitric oxide (NO). NO is a multifunctional signaling

molecule that influences activities that are fundamental to humans and therefore could possibly play an important role in the treatment of COVID-19 symptoms. The physiological effects of NO that may have relevance in the prevention and treatment of SARS-Cov-2 infection (Figure 5), which can act as an anti-microbial, stimulate the ciliary movement effect, repair damage to the upper and lower respiratory tract epithelium can also act as a vasodilator, antithrombotic, and anti-inflammatory, which are some of the main mechanisms in endothelial dysfunction in COVID-19. SARS-CoV-2 infection is associated with a higher risk for venous thromboembolism, so the vasodilatory and antithrombotic action of NO is expected to prevent or ameliorate this complication [78, 79]. In addition, previous studies demonstrated that NO has the potential for the anti-thrombotic effect of eplerenone in a murine model of diabetes and for prolonging bleeding time in rabbits and humans after inhalation [78, 80, 81]. However, further research is needed to know exactly how the effect of giving NO molecules is on COVID-19, especially in preventing or improving endothelial dysfunction in SARS-CoV-2 infection.
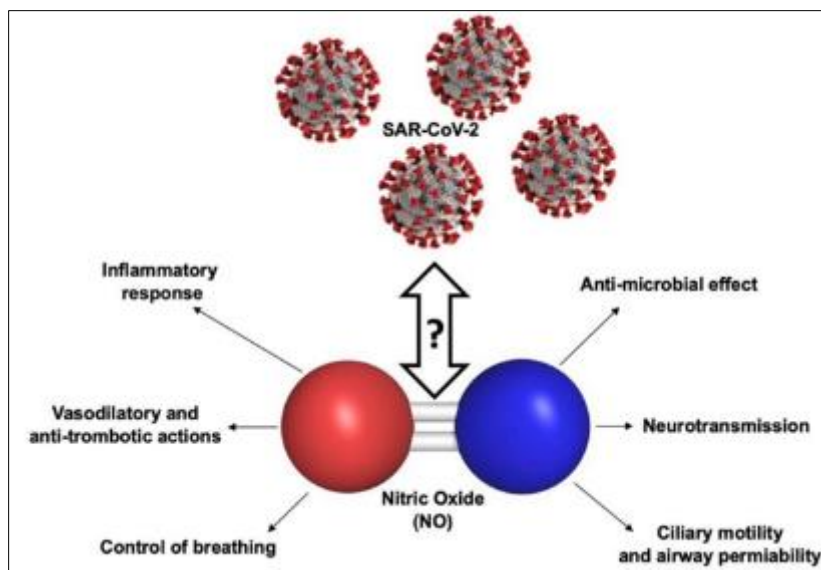

Figure 5 The potential important role of NO in the treatment of COVID-19 symptoms

5. Conclusion

The pathophysiology of endothelial dysfunction in COVID-19 with a history of smoking still requires further research. However, it is thought that several mechanisms play a role in endothelial dysfunction in this condition, such as the direct toxic effect of cigarette smoke, auto-antibodies that attack endothelial cells, inflammation and oxidative stress, increased release of endothelial cell mediators, which act as vasoconstrictors, pro-inflammatory, and remodeling, and decreased expression of endothelial cell mediators that act as vasodilators and endothelial cell homeostasis, increased endoplasmic reticular stress, and decreased VEGF expression due to decreased hypoxia inducible factor-1. A new treatment that has the potential to improve endothelial dysfunction in COVID-19 is giving NO, because it can act as a vasodilator and anti-thrombotic, but further research is needed to know exactly how the effect of giving NO molecules is on COVID-19.

Compliance with ethical standards

Disclosure of conflict of interest

The authors and all co-authors declare that they have no conflicts of interest in connection with this document.

Statement of ethical approval

Authors read and agreed with the final manuscript.

References

[1]   Wang FS, Zhang C. 2020. What to do next to control the 2019-nCoV epidemic? Lancet, 395: 391–393.

[2]   Mosleh W, Chen K, Pfau SE, Vashist A. 2020. Endothelitia and Endhothelial Dysfunction in Patients with COVID-19: Its Role in Thrombosis and Adverse Outcomes. Journal of Clinical Medicine, 9(1862): 1-4.

[3]   Amdal CD, Pe M, Falk RS, Piccinin C, Bottomley A, Arraras JI, Darlington AS, Hofso K, Holzner B, Jorgensen NMH. 2021. Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review. Qual. Life Res, 1–15.

[4]   Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. 2020. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc. Imaging, 13: 2330–2339.

[5]   Gerotziafas GT, Catalano M, Colgan, MP, Pecsvarady Z, Wautrecht JC, Fazeli B, Olinic DM, Farkas K, Elalamy I, Falanga A. 2020. Guidance for the Management of Patients with Vascular Disease or Cardiovascular Risk Factors and COVID-19: Position Paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost, 120: 1597–1628.

[6]   Garg P, Arora U, Kumar A, Wig N. 2021. The "post-COVID" syndrome: How deep is the damage?. J. Med. Virol, 93: 673–674.

[7]   Amraei R, Rahimi N. 2020. COVID-19, Renin-Angiotensin System and Endothelial Dysfunction. Cells, 9: 1652.

[8]   Pons S, Fodil S, Azoulay E, Zafrani L. 2020. The vascular endothelium: The cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit. Care, 24: 353.

[9]   Calabretta E, Moraleda JM, Iacobelli M, Jara R, Vlodavsky I, O'Gorman P. Pagliuca A, Mo C, Baron RM, Aghemo A. 2021. COVID-19-induced endotheliitis: Emerging evidence and possible therapeutic strategies. Br. J. Haematol, 193: 43–51.

[10]   Ambrosino P, Calcaterra I, Molino A, Moretta P, Lupoli R, Spedicato GA, Papa A, Motta A, Maniscalco M, Di Minno M. 2021. Persistent Endothelial Dysfunction in Post-Acute COVID-19 Syndrome: A Case-Control Study. Biomedicines, 9(957): 1-15.

[11]   Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S. 2020. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med.

[12]   Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. 2020. Is COVID-19 an endothelial disease? Clinical and basic evidence. 2020040204. https://www.pre prints.org/manuscript/202004.0204/v1WHO. Accesed on 19 September 2021.

[13]   Framework Convention on Tobacco Control. Increased risk of COVID-19 infection amongst smokers and amongst waterpipe users. https://untobaccocontrol.org/kh/water pipes/covid-19/ (accessed on 15 September 2021).

[14]   Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. 2020. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19). J Clin Med, 9:E841.

[15]   Evora PRB, Baldo CF, Celotto AC, Capellini VK. 2009. Endothelium dysfunction classification: why is it still an open discussion?. Int J Cardiol, 137: 175-6.

[16]   Da Silva ALO, Moreira JC, Martins SR. 2020. COVID-19 and smoking: a high-risk association. Cad Saude Publica, 36(5): 1-4.

[17]   Alexander Y, Osto E, Schmidt-Trucksass A, Shechter M, Trifunovic D, Duncker DJ, Aboyans V, Back M, Badimon L, Cosentino F, De Carlo M, Dorobantu M, Harrison DG, Guzik TJ, Hoefer I, Morris PD, Norata GD, Suades R, Taddei S, Vilahur G, Waltenberger J, Weber C, Wilkinson F, Bochaton-Piallat ML, Evans PC. 2020. ENDOTHELIAL FUNCTION IN CARDIOVASCULAR PRECISION MEDICINE: A POSITION PAPER ON BEHALF OF THE EUROPEAN SOCIETY OF CARDIOLOGY. Cardiovasc Res.

[18]   Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. 2020. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research.

[19]   Tang N, Li D, Wang X, Sun Z. 2020. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis, 18: 844-847.

[20] Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, Wiesner T, Rodríguez-Peralto JL, Requena L, Torrelo A. 2020. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultraestructural study of 7 paediatric cases. The British journal of dermatology.

[21] Evans PC, Rainger G, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Bäck M. 2020. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. European Society of Cardiology, 1-21.

[22] Zhang B, Zhou X, Zhu C, Feng F, Qiu Y, Feng J, Jia Q, Song Q, Zhu B, Wang J. 2020. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. medRxiv.

[23] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory medicine, 8: 420-422.

[24] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. 2020. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet.

[25] Ng OW, Chia A, Tan AT, Jadi RS, Leong HN, Bertoletti A, Tan YJ. 2016. Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. Vaccine, 34: 2008-2014.

[26] Li CKF, Wu H, Yan HP, Ma SW, Wang LL, Zhang MX, Tang XP, Temperton NJ, Weiss RA, Brenchley JM, Douek DC, Mongkolsapaya J, Tran BH, Lin CLS, Screaton GR, Hou JL, McMichael AJ, Xu XN. 2008. T cell responses to whole SARS coronavirus in humans. Journal of Immunology, 181: 5490-5500 .

[27] Ma H, Zeng W, He H, Zhao D, Yang Y, Jiang D, Zhou P, Qi Y, He W, Zhao C, Yi R, Wang X, Wang B, Xu Y, Yang Y, Kombe Kombe AJ, Ding C, Xie J, Gao Y, Cheng L, Li Y, Ma X, Jin T. 2020. COVID-19 diagnosis and study of serum SARS-CoV-2 specific IgA, IgM and IgG by chemiluminescence immunoanalysis. medRxiv.

[28] Petri MH, Tellier C, Michiels C, Ellertsen I, Dogne JM, Bäck M. 2013. Effects of the dual TP receptor antagonist and thromboxane synthase inhibitor EV-077 on human endothelial and vascular smooth muscle cells. Biochem Biophys Res Commun, 441: 393-398.

[29] Tull SP, Anderson SI, Hughan SC, Watson SP, Nash GB, Rainger GE. 2006. Cellular pathology of atherosclerosis: smooth muscle cells promote adhesion of platelets to cocultured endothelial cells. Circ Res, 98: 98-104.

[30] Kuckleburg CJ, Yates CM, Kalia N, Zhao Y, Nash GB, Watson SP, Rainger GE. 2011. Endothelial cell-borne platelet bridges selectively recruit monocytes in human and mouse models of vascular inflammation. Cardiovascular Research, 91: 134-141.

[31] Chimen M, Evryviadou A, Box CL, Harrison MJ, Hazeldine J, Dib LH, Kuravi SJ, Payne H, Price JMJ, Kavanagh D, Iqbal AJ, Lax S, Kalia N, Brill A, Thomas SG, Belli A, Crombie N, Adams RA, Evans SA, Deckmyn H, Lord JM, Harrison P, Watson SP, Nash GB, Rainger GE. 2020. Appropriation of GPlb alpha from platelet-derived extracellular vesicles supports monocyte recruitment in systemic inflammation. Haematologica, 105: 1248-1261.

[32] Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J. 2020. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. The journal of laboratory and clinical medicine.

[33] Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. 2020. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res, 126: 1456-1474.

[34] Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, Schmitto JD, Heineke J, Emrich F, Arsalan M, Holubec T, Walther T, Zeiher AM, Dimmeler S. 2020. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. European heart journal.

[35] Fang L, Karakiulakis G, Roth M. 2020. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? The Lancet Respiratory medicine, 8:e21.

[36] Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. 2020. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. The New England journal of medicine.

[37]   Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. 2020. The New England journal of medicine.

[38]   Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell, 181: 271-280.

[39]   Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. 2013. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature, 426: 450-454.

[40]   Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado Del Pozo C, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. 2020. Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. Cell.

[41]   Puelles VG, Lutgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfefferle S, Schroder AS, Edler C, Gross O, Glatzel M, Wichmann D, Wiech T, Kluge S, Pueschel K, Aepfelbacher M, Huber TB. 2020. Multiorgan and Renal Tropism of SARS-CoV-2. The New England journal of medicine.

[42]   Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. 2020. Endothelial cell infection and endotheliitis in COVID-19. Lancet, 395:1417-1418.

[43]   Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. 2020. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet.

[44]   Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. 2020. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet.

[45]   Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. 2020. Association between a novel human coronavirus and Kawasaki disease. The Journal of infectious diseases, 191: 499-502.

[46]   Attwell D, Mishra A, Hall CN, O'Farrell FM, Dalkara T. 2016. What is a pericyte? Journal of cerebral blood flow and metabolism. Official journal of the International Society of Cerebral Blood Flow and Metabolism, 6: 451- 455.

[47]   Chen L, Li X, Chen M, Feng Y, Xiong C. 2020. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res, 116: 1097-1100.

[48]   He L, Mäe MA, Sun Y, Muhl L, Nahar K, Liébanas EV, Fagerlund MJ, Oldner A, Liu J, Genové G, Pietilä R, Zhang L, Xie Y, Leptidis S, Mocci G, Stritt S, Osman A, Anisimov A, Hemanthakumar KA, Räsenen M, Björkegren J, Vanlandewijck M, Blomgren K, Hansson E, Mäkinen T, Peng X-R, Arnold TD, Alitalo K, Eriksson LI, Lendahl U, Betsholtz C. 2020. Pericyte-specific vascular expression of SARS-CoV-2 receptor ACE2 – implications for microvascular inflammation and hypercoagulopathy in COVID-19 patients. bioRxiv.

[49]   Cardot-Leccia N, Hubiche T, Dellamonica J, Burel-Vandenbos F, Passeron T. 2020. Pericyte alteration sheds light on micro-vasculopathy in COVID-19 infection. Intensive care medicine: 1-2.

[50]   Dikalov S, Itani H, Richmond B, Arslanbaeva L, Vergeade A, Rahman SMJ, Boutaud O, Blackwell T, Massion PP, Harrison DG, Dikalova A. 2019. Tobacco smoking induces cardiovascular mitochondrial oxidative stress, promotes endothelial dysfunction, and enhances hypertension. Am J Physiol Heart Circ Physiol, 316: 639–646.

[51]   Münzel T, Hahad O, Kuntic M, Keaney JF, Deanfield JE, Daiber A. 2020. Effects of tobacco cigarettes, e-cigarettes, and waterpipe smoking on endothelial function and clinical outcomes. European Heart Journal.

[52]   Olfert IM, DeVallance E, Hoskinson H, Branyan KW, Clayton S, Pitzer CR, Sullivan DP, Breit MJ, Wu Z, Klinkhachorn P, Mandler WK, Erdreich BH, Ducatman BS, Bryner RW, Dasgupta P, Chantler PD. 2018. Chronic exposure to electronic cigarettes results in impaired cardiovascular function in mice. J Appl Physiol, 124: 573–582

[53]   WHO Framework Convention on Tobacco Control. Increased risk of COVID-19 infection amongst smokers and amongst waterpipe users. https://untobaccocontrol.org/kh/water pipes/covid-19/ (accessed on 10 September 2021).

[54]   Evora PRB, Baldo CF, Celotto AC, Capellini VK. 2009. Endothelium dysfunction classification: why is it still an open discussion? Int J Cardiol, 137: 175-6.

[55] U.S. Department of Health and Human Services. 2020. Smoking cessation: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services.

[56] Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. 2020. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19). J Clin Med, 9:E841.

[57] U.S. Department of Health and Human Services. 2014. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services.

[58] Das I. 2015. Raised C-reactive protein levels in serum from smokers. Clin Chim Acta, 153: 9-13.

[59] Lee AJ, Fowkes GR, Lowe GD, Rumley A. 2015. Determinants of fibrin D-dimer in the Edinburgh Artery Study. Arterioscler Thromb Vasc Biol, 15:1094-7.

[60] Vardavas CI, Nikitara K. 2020. COVID-19 and smoking: a systematic review of the evidence. Tob Induc, 18: 20.

[61] Cai H. 2020. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med, 8:e20.

[62] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J. 2020. Clinical characteristics of coronavirus disease 2019 in China. N Engl J M, 382:1708-20

[63] Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. 2018. Nicotine and the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol, 315: 895-906.

[64] Polverino F, Laucho-Contreras ME, Petersen H, Bijol V, Sholl LM, Choi ME. 2017. A Pilot Study Linking Endothelial Injury in Lungs and Kidneys in COPD. Am J Respir Crit Care Med, 195:1464–76.

[65] Polverino F, Celli BR, Owen CA. 2018. COPD as an endothelial disorder: endothelial injury linking lesions in the lungs and other organs? (2017 Grover Conference Series). Pulmonary circulation, 8: 204-218.

[66] Divo MJ, Casanova C, Marin JM, Pinto-Plata VM, de-Torres JP, Zulueta JJ. 2015. COPD comorbidities network. Eur Respir J, 46: 640–50.

[67] Yasuo M, Mizuno S, Kraskauskas D, Bogaard HJ, Natarajan R, Cool CD. 2011. Hypoxia inducible factor-1alpha in human emphysema lung tissue. Eur Respir J, 37: 775–83.

[68] Polverino, F dan Kheradmand, F. 2021. COVID-19, COPD, and, AECOPD: Immunological, Epidemiological, and Clinical Aspects. Frontiers in Medicine, 7: 1-8.

[69] Gustafson D, Raju S, Wu R, Ching C, Veitch S, Rathnakumar K, Boudreau E, Howe KL, Fish JE. 2020. Overcoming Barriers: The Endothelium As a Linchpin of Coronavirus Disease 2019 Pathogenesis? Arteriosclerosis, thrombosis, and vascular biology. Atvbaha,12(03): 145-58.

[70] South AM, Diz DI, Chappell MC. 2020. COVID-19, ACE2, and the cardiovascular consequences. American journal of physiology Heart and circulatory physiology, 318: 1084-1090.

[71] Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, Rayego-Mateos S, Sanchez LS, Marchant V, Santamaria LT, Ramos AM, Ortiz A, Egido J, Ruiz-Ortega M. 2020. Statins: Could an old friend help the fight against COVID-19? Br J Pharmacol.

[72] Bifulco M, Gazzerro P. 2020. Statin therapy in COVID-19 infection: much more than a single pathway. European Heart Journal - Cardiovascular Pharmacotherapy.

[73] Castiglione V, Chiriacò M, Emdin M, Taddei S, Vergaro G. 2020. Statin therapy in COVID-19 infection. European Heart Journal - Cardiovascular Pharmacotherapy 2020. Vasanthakumar N. Can beta-adrenergic blockers be used in the treatment of COVID-19? Med Hypotheses, 142: 809-815.

[74] Staedtke V, Bai RY, Kim K, Darvas M, Davila ML, Riggins GJ, Rothman PB, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S. 2018. Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. Nature, 564: 273-277.

[75] Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. 2020. Angiotensin-Converting Enzyme 2 and Antihypertensives (Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors) in Coronavirus Disease 2019. Mayo Clin Proc, 95: 1222-1230.

[76] Wu Y, Wang F, Shen C, Peng W, Li D, Zhao C, Li Z, Li S, Bi Y, Yang Y, Gong Y, Xiao H, Fan Z, Tan S, Wu G, Tan W, Lu X, Fan C, Wang Q, Liu Y, Zhang C, Qi J, Gao GF, Gao F, Liu L. 2020. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2. Science, 368: 1274-1278

[77] Evans PC, Rainger GE, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Bäck M. 2020. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. European Society of Cardiology.

[78] Jin R C and Loscalzo J. 2010. Vascular nitric oxide: formation and function. J. Blood Med, 147–62

[79] Gromotowicz-Poplawska A, Kloza M, Aleksiejczuk M, Marcinczyk N, Szemraj J, Kozlowska H, Chabielska E. 2019. Nitric oxide as a modulator in platelet- and endothelium-dependent antithrombotic effect of eplerenone in diabetic rats J. Physiol. Pharmacol, 70: 187-98.

[80] Högman M, Frostell C, Arnberg H and Hedenstierna. 2013. Bleeding time prolongation and NO inhalation. Lancet, 341: 1664–5.

[81] Ricciardolo FLM, Bertolini F, Carriero V, Högman M. 2020. Nitric oxide's physiologic effects and potential as a therapeutic agent against COVID-19. J. Breath Res, 15: 1-7.

[82] Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani, AS, Hurst JR. 2020. Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. PLOS ONE, 15(5): e0233147. doi:10.1371/journal.pone.0233147