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Nägele, Matthias P; Haubner, Bernhard; Tanner, Felix C; Ruschitzka, Frank; Flammer, Andreas J

Abstract: Coronavirus disease 2019 (COVID-19) increases the risk of several non-pulmonary complications such as acute myocardial injury, renal failure or thromboembolic events. A possible unifying explanation for these phenomena may be the presence of profound endothelial dysfunction and injury. This review provides an overview on the association of endothelial dysfunction with COVID-19 and its therapeutic implications. Endothelial dysfunction is a common feature of the key comorbidities that increase risk for severe COVID-19 such as hypertension, obesity, diabetes mellitus, coronary artery disease or heart failure. Preliminary studies indicate that vascular endothelial cells can be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and evidence of widespread endothelial injury and inflammation is found in advanced cases of COVID-19. Prior evidence has established the crucial role of endothelial cells in maintaining and regulating vascular homeostasis and blood coagulation. Aggravation of endothelial dysfunction in COVID-19 may therefore impair organ perfusion and cause a procoagulatory state resulting in both macro- and microvascular thrombotic events. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and statins are known to improve endothelial dysfunction. Data from smaller observational studies and other viral infections suggests a possible beneficial effect in COVID-19. Other treatments that are currently under investigation for COVID-19 may also act by improving endothelial dysfunction in patients. Focusing therapies on preventing and improving endothelial dysfunction could improve outcomes in COVID-19. Several clinical trials are currently underway to explore this concept.

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Review article

Endothelial dysfunction in COVID-19: Current findings and therapeutic implications

Matthias P. Nägele, Bernhard Haubner, Felix C. Tanner, Frank Ruschitzka, Andreas J. Flammer *

Department of Cardiology, University Heart Center Zurich, University Hospital Zurich, Zurich, Switzerland

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ABSTRACT

Coronavirus disease 2019 (COVID-19) increases the risk of several non-pulmonary complications such as acute myocardial injury, renal failure or thromboembolic events. A possible unifying explanation for these phenomena may be the presence of profound endothelial dysfunction and injury. This review provides an overview on the association of endothelial dysfunction with COVID-19 and its therapeutic implications. Endothelial dysfunction is a common feature of the key comorbidities that increase risk for severe COVID-19 such as hypertension, obesity, diabetes mellitus, coronary artery disease or heart failure. Preliminary studies indicate that vascular endothelial cells can be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and evidence of widespread endothelial injury and inflammation is found in advanced cases of COVID-19. Prior evidence has established the crucial role of endothelial cells in maintaining and regulating vascular homeostasis and blood coagulation. Aggravation of endothelial dysfunction in COVID-19 may therefore impair organ perfusion and cause a procoagulatory state resulting in both macro- and microvascular thrombotic events. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and statins are known to improve endothelial dysfunction. Data from smaller observational studies and other viral infections suggests a possible beneficial effect in COVID-19. Other treatments that are currently under investigation for COVID-19 may also act by improving endothelial dysfunction in patients. Focusing therapies on preventing and improving endothelial dysfunction could improve outcomes in COVID-19. Several clinical trials are currently underway to explore this concept.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is significantly affecting socioeconomic and healthcare systems worldwide. The pathophysiology of its associated disease, coronavirus disease 2019 (COVID-19), is still largely unclear and under active investigation. This article provides an overview on recent evidence linking endothelial dysfunction with COVID-19 and its potential implications for preventing adverse outcomes and treating the disease.

1.1. Endothelial dysfunction: a common denominator in patients at risk for COVID-19

Preliminary studies indicate that patients with cardiovascular risk factors and/or established cardiovascular disease have the highest risk of being hospitalized with COVID-19 and developing a more severe disease course. These risk factors include older age (>65 years), hypertension, obesity, diabetes mellitus, chronic lung disease, coronary artery disease and heart failure [1–4].

Interestingly, a common denominator of all these cardiometabolic diseases is endothelial dysfunction. The endothelium is crucial for maintaining vascular tone and homeostasis – dysfunction is associated with vasoconstriction, inflammation, permeability, and coagulation. It is associated with major risk factors such as age, hypertension, diabetes mellitus, and obesity, as well as development and progression of cardiovascular diseases [5]. Classically, endothelial function is assessed by measuring the dilatation of brachial or coronary arteries in response to shear stress or external stimuli [6]. Newer methods also allow the assessment of smaller vascular beds such as the retinal microcirculation [7].

1.2. SARS-CoV-2 target endothelial cells

The primary site of infection in COVID-19 is the upper and lower...
respiratory tract. There, SARS-CoV-2 infects goblet secretory cells of the nasal mucosa and alveolar type II pneumocytes by binding to membrane-bound angiotensin-converting enzyme 2 (ACE2) [8]. After priming of the virus spike protein and cleavage of ACE2 by the human protease TMPRSS2, the virus is internalized into the cell and viral replication begins. In severe COVID-19, there is a progressive infection of alveolar pneumocytes with significant viral shedding resulting in apoptosis and necrosis [9]. Interferon-mediated upregulation of ACE2 may facilitate infection of adjacent pneumocytes [8]. The subsequent immune reaction leads to progressive interstitial and alveolar edema, which impairs gas exchange and may eventually result in acute respiratory distress syndrome (ARDS).

Already shortly after the outbreak, reports suggested that COVID-19 affects other organs beyond the lung, most importantly the heart and kidney [10,11]. In severe COVID-19, evidence of acute myocardial injury (elevation of cardiac troponins) is common, and is associated with impaired prognosis. In light of the tissue tropism of SARS-CoV-2 for ACE2-expressing cells, another major organ of the body is an important target of infection: the vascular endothelium [57]. Indeed, ACE2 is expressed abundantly on vascular endothelial cells of both small and large arteries and veins [56]. We recently demonstrated viral inclusion structures within endothelial cells of glomerular capillary loops and signs of widespread endothelitis in the heart, lung, kidney, liver and gastrointestinal tract in pathological specimens from 3 patients with severe COVID-19 [12]. Endothelial injury and dysfunction may be the result of direct infection by SARS-CoV-2 (e.g. by inducing intracellular oxidative stress [13]) as well as due to the profound systemic inflammatory response. In light of the potential association of COVID-19 with endothelial injury, it seems plausible that patients with preexisting endothelial dysfunction are vulnerable to a more severe disease course given the crucial role of endothelial cells for vascular homeostasis and organ perfusion.

1.3. COVID-19-associated endotheliitis triggers organ damage and thrombotic events

Systemic endotheliitis can explain end-organ damage in severe COVID-19. In a case series from New York [14], one third of COVID-19 patients with electrocardiographic signs of active ischemia showed non-obstructive coronary artery disease, and thus microvascular dysfunction as a likely cause of ischemia. Myocardial inflammation as evidenced by increased cardiac troponins or magnet resonance imaging abnormalities is not uncommon in severe COVID-19 [15,16]. SARS-CoV-2 has been isolated from cardiac autopsies samples, however, this was not regularly associated with an infiltration of immune cells as seen in myocarditis [17]. The virus may rather affect the endothelium leading to secondary myocardial inflammation and dysfunction. The phenotype of myocardial dysfunction and ischemic electrocardiographic features in the absence of coronary obstruction or myocarditis is reminiscent of Takotsubo syndrome, which is also associated with endothelial dysfunction [18].

Vascular endothelial cells play a critical role in vascular homeostasis and the coagulation system. While healthy endothelial cells naturally express factors that induce vascular relaxation and increase blood flow, inhibit platelet aggregation and coagulation, and promote fibrinolysis, dysfunctional endothelial cells shift the balance towards vascular contraction and thrombus formation [19]. Most cardiovascular risk factors indeed cause a decreased endothelial production of vasorelaxing and antithrombotic mediators and a concomitantly increased formation of contracting and prothrombotic factors [20]. In severe COVID-19, markers of both endothelial and platelet activation are increased compared to controls [21]. Extensive microthrombosis promoted and aggravated by endothelial dysfunction could explain the profound elevation of markers of endothelial dysfunction in severe COVID-19 [3]. In line with these haematologic findings, recent reports show increased risk of both venous and arterial thrombotic events in COVID-19 [22,23]. A recent case series also suggested that pulmonary microthrombi and pulmonary endothelial dysfunction explain the unusual dead-space and shunt physiology found in severe COVID-19 patients [24]. Indeed, significant pulmonary endotheliitis, microvascular thrombosis and evidence of pulmonary endothelial infection by SARS-CoV2 was observed in another pathological case series [25]. Pulmonary microvascular dysfunction may therefore be an underlying mechanism behind the phenomenon of severe hypoxia despite relatively preserved lung mechanics in COVID-19 [26]. In children with COVID-19-associated chillblains of the extremities, profound endothelial inflammation along with endothelial infection with SARS-CoV2 was observed in a small case series [27].

1.4. Targeting endothelial dysfunction in COVID-19

Most therapies under active investigation for COVID-19 focus on inhibition of viral replication and suppression of the excessive immune response. However, in light of the above, treatment of endothelial dysfunction is a promising approach to protect vulnerable patients and to improve outcomes in COVID-19. Many studies have demonstrated the possibility to enhance vascular function via lifestyle interventions and drug therapies [28]. Two widely used drug classes, renin angiotensin system (RAS) inhibitors and statins, have been shown in an abundant number of studies to consistently improve endothelial function in patients. Both drug classes exert pleiotropic effects on the endothelium and promote endothelium-induced stimulation of vascular relaxation as well as endothelium-mediated inhibition of thrombus formation.

1.4.1. RAS inhibitors

Angiotensin II is a well-known mediator of endothelial dysfunction, which is in part mediated by increased oxidative stress following angiotensin II receptor type 1 activation [29]. Indeed, both ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to improve endothelial dysfunction [30,31]. They may also attenuate procoagulatory states by reducing the expression of tissue factor in endothelial cells and other cell types [32]. The use of RAS inhibitors is not without controversy in COVID-19: They are associated with an upregulation of ACE2, which may (theoretically) increase susceptibility to infection. However, ACE2 is a part of the natural host response against pulmonary infections [33] and antagonizes RAS activation by hydrolysis of angiotensin II into angiotensin (1–7), a vasodilator with anti-oxidant and anti-inflammatory effects [34]. ACE2 is downregulated after infection of SARS-CoV-2 into cells. This may lead to unopposed RAS activation resulting in endothelial injury and a pro-inflammatory and pro-thrombotic state in COVID-19 – which may be amendable by pharmacological RAS blockade [35]. Indeed, the use of RAS inhibitors was not associated with a higher risk of SARS-CoV-2 infection or an adverse outcome in recent observational studies [36–39]. In a Spanish population-based study, a borderline-significant reduced risk for COVID-19 hospital admissions was found with ACE inhibitors and a lower risk for patients with diabetes who were treated with RAS inhibitors vs. non-users [40]. A trend of lower COVID-19-related mortality with RAS inhibitors was also found in a meta-analysis of four studies [41]. In a UK cohort study, RAS inhibitors were associated with a lower risk of COVID-19 [42]. Recently, results from the first randomized trial on this topic were presented (BRACE-CORONA) [43]. In this trial, discontinuation of RAS inhibitors in hospitalized patients with COVID-19 had no beneficial effect compared to continuation of therapy. Therefore, it is recommended to continue RAS inhibitors in COVID-19 patients who are already on such therapies as long as there are no acute contraindications such as severe kidney injury, significant hyperkalemia or symptomatic hypotension. Whether general RAS blockade in COVID-19 is beneficial needs to be confirmed in clinical trials. Several intervention studies with ACE inhibitors and ARBs currently explore this hypothesis (Table 1 and Supplementary Table 1).
Table 1

| Trial identifier (Trial acronym) | Description of intervention                                                                 | Country     | Estimated enrollment |
|---------------------------------|----------------------------------------------------------------------------------------------|-------------|----------------------|
| NCT04328012 (COVIDMED)          | Losartan vs placebo (other arms: lopinavir/ritonavir, hydroxychloroquine) in patients with COVID-19 and not on previous RAS inhibition | USA         | 4000                 |
| NCT04330300 (CORONACION)        | Continuation of RAS inhibitors vs. switch to different antihypertensive drug in patients with COVID-19, hypertension and previously on a RAS inhibitor | Ireland     | 2414                 |
| NCT04366050 (RAMIC)             | Ramipril vs placebo for 14 days in patients with COVID-19 in non-intensive care setting       | USA         | 560                  |
| NCT04343001 (CRASH-19)          | Aspirin, losartan, simvastatin or combinations thereof vs. standard of care (2 × 2 × 2) in hospitalized COVID-19 patients | International | 10,000               |
| EudraCT-2020-001319-26 (FJD-COVID-ESTATINAS) | Rosuvastatin vs. no treatment in patients with COVID-19 who required hospitalization | Spain       | 1080                 |
| NCT04335084 (HELPCOVID-19)      | Vitamin C, hydroxychloroquine, vitamin D and zinc vs placebo for the prevention of COVID-19 infection in non-infected patients | USA         | 600                  |
| NCT04404218 (ACAI)              | Acai palm berry extract for 30 days vs. placebo in patients with mild to moderate COVID-19 | Canada      | 480                  |
| NCT04400890 Plant polyphenol supplement vs. placebo on top of vitamin D in outpatients with mild COVID-19 | USA         | 200                  |
| NCT04350280 (C-19-ACS)          | Atorvastatin combined with aspirin, clopidogrel, omeprazole and very-low dose rivaroxaban vs. control in patients with COVID-19 and elevated cardiovascular risk | International | 3170                 |
| NCT04343001 (CRASH-19)          | Aspirin, losartan, simvastatin or combinations thereof vs. standard of care (2 × 2 × 2) in hospitalized COVID-19 patients | International | 10,000               |

COVID-19, coronavirus disease 2019; NCT, national clinical trial identifier; RAS, renin angiotensin system.

* For the complete list see Supplementary Table 1.

Fig.1. Mechanisms of endothelial dysfunction in COVID-19.

SARS-CoV-2 could aggravate endothelial dysfunction and lead to systemic complications by several mechanisms. (1) The inflammatory reaction in COVID-19 can activate the renin angiotensin system (RAS) either directly via increasing angiotensin I (Ang I), or indirectly by reducing the surface expression of angiotensin-converting enzyme 2 (ACE2). ACE2 is responsible for the hydrolysis of Ang II into the vasodilator Ang (1-7), which opposes the actions of Ang II thereby countering RAS activation. (2) Activation of the angiotensin II type 1 receptor (AT1R), along with direct infection of endothelial cells by the virus, (3) increases reactive oxygen species (ROS) and activates nuclear factor kappa B (NF-kB), which inactivates nitric oxide (NO) to peroxynitrite and reduces its production by uncoupling endothelial NO synthase (eNOS). (4) Activation of several cytokine receptors (e.g. tumor necrosis factor alpha receptor, interleukin 6 receptor) can directly or indirectly impair endothelial function. Endothelial dysfunction in turn impairs organ perfusion by disrupting the balance between vasoconstriction and dilatation, increases inflammation and leads to a pro-thrombotic state in both larger and smaller vessels, such as by increasing tissue factor and favoring platelet activation. This vicious cycle may be amendable by treatments targeting different steps of the cascade, such as ACE inhibitors, angiotensin receptor blockers (ARBs), cytokine inhibitors (e.g. interleukin 6 receptor antibodies) or statins. Statins may be helpful by reducing oxidized LDL levels and NADPH oxidase activity, which decrease reactive oxygen species (ROS), directly or indirectly affecting the transcription of NF-kB or by improving coupling of eNOS. Measures to prevent and treat important comorbidities could also be helpful along with selected supplements such as antioxidants.
1.4.2. Statins

Statins are another promising drug class for treating endothelial dysfunction and preventing vascular damage in COVID-19. Similar to RAS inhibitors, statins improve endothelial function in patients with or at risk for cardiovascular disease [44]. They improve endothelial function via different mechanisms, including reduction of oxidized low-density lipoprotein cholesterol, increased expression and improved coupling of endothelial nitric oxide synthase (eNOS), suppression of pro-oxidant enzymes such as NADPH oxidase and inhibition of nuclear factor kappa B (NF-κB) and other pro-inflammatory transcriptional and signal transduction pathways [45–47]. Independent of nitric oxide, statins prevent tissue factor expression in endothelial cells [48] which may favorably affect blood coagulation and platelet activation [46]. We previously showed that statins improve endothelial dysfunction in rheumatoid arthritis [49], suggesting that they may be particularly helpful in inflammatory conditions characterized by endothelial dysfunction. Some evidence points toward a beneficial effect in viral pneumonias such as influenza [50]. Larger studies on the effects of statins in COVID-19 are still pending. A small observational study in elderly nursing home subjects suggested a higher chance of a symptom-free COVID-19 infection in statin-users vs. non-users [39]. In a retrospective cohort study in China, statin use was associated with lower mortality compared to non-use in COVID-19 [51]. Several intervention studies studying the role of statins in COVID-19 have recently been announced (Supplementary Table 1). Until then, it seems prudent to continue statins in COVID-19 patients who already received the drugs before infection and initiate statins in all patients who meet cardiovascular guideline-criteria supporting their use.

1.4.3. Anti-inflammatory therapies

Several anti-inflammatory therapies under investigation for COVID-19 may partly act by improving endothelial function. For example, improvement of endothelial dysfunction has been described for tumor necrosis factor alpha inhibitors [52] or anti-IL-6 receptor antibodies [53].

1.4.4. Other approaches

Beyond drug therapies, the importance of effective preventive measures cannot be overstated during the current pandemic. In that regard, improving or maintaining a normal endothelial function by well-established lifestyle measures (i.e. keeping a normal weight, regular physical activity, abstaining from smoking and consuming a healthy and nutritious diet) may be helpful to reduce the risk of COVID-19. Specific supplemental interventions that reduce endothelial dysfunction (e.g. antioxidants [54], flavonoids [55]) could also be considered for further testing. Of note, several trials studying the effects of vitamin C, antioxidants and polyphenols in COVID-19 have been started (Supplementary Table 1).

2. Conclusions

Accumulating evidence points toward an important role of endothelial dysfunction in the pathogenesis of COVID-19 (Fig. 1). Therapies aiming to improve endothelial dysfunction such as RAS inhibitors or statins may be particularly helpful to prevent and manage systemic complications of SARS-CoV-2 infection. Based on the current evidence, we recommend to continue RAS inhibitors and statins in patients with COVID-19 as long as there are no acute contraindications. For prevention, we recommend that patients with a cardiovascular indication as per current guidelines should be prescribed RAS inhibitors and statins along with optimal lifestyle measures. Whether these therapies are beneficial in COVID-19 patients without such indications needs to be evaluated and tested in upcoming clinical trials.

Author contributions

M.P.N. A.J.F. and F.R. conceptualized the manuscript. M.P.N. created and finalized the manuscript, table and figure. B.H., F.C.T., F.R. and A.J.F. critically revised and expanded sections of the manuscript. No compensation was paid for any work on the manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.10.014.

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