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*

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Abstract.
The COVID-19 pandemic is an unprecedented healthcare emergency causing mortality and illness across the world. Although primarily affecting the lungs, the SARS-CoV2 virus also affects the cardiovascular system. In addition to cardiac effects e.g. myocarditis, arrhythmias, and myocardial damage, the vasculature is affected in COVID-19, both directly by the SARS-CoV-2 virus, and indirectly as a result of a systemic inflammatory cytokine storm. This includes the role of vascular endothelium in the recruitment of inflammatory leukocytes where they contribute to tissue damage and cytokine release, which are key drivers of acute respiratory distress syndrome (ARDS), in disseminated intravascular coagulation and cardiovascular complications in COVID-19. There is also evidence linking endothelial cells (EC) to SARS-CoV-2 infection including: (1) the expression and function of its receptor angiotensin converting enzyme (ACE) 2 in the vasculature, (2) the prevalence of a Kawasaki Disease-like syndrome (vasculitis) in COVID-19, and (3) evidence of EC infection with SARS-CoV-2 in patients with fatal COVID-19. Here, the working Group on Atherosclerosis and Vascular Biology together with the Council of Basic Cardiovascular Science of the European Society of Cardiology provide a Position Statement on the importance of the endothelium in the underlying pathophysiology behind the clinical presentation in COVID-19 and identify key questions for future research to address. We propose that endothelial biomarkers and tests of function (e.g. flow mediated dilatation) should be evaluated for their value in the risk stratification of COVID-19 patients. A better understanding of the effects of SARS-CoV-2 on endothelial biology in both the micro- and macro-vasculature is required, and endothelial function testing should be considered in the follow-up of convalescent COVID-19 patients for early detection of long-term cardiovascular complications.

Introduction

Coronavirus Disease 2019 (COVID-19) is caused by a single strand RNA virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that likely crossed from bats to humans following a gain-of-function mutation in the spike protein that allows infection of human cells[1]. Though primarily known as a disease affecting the respiratory system, cardiovascular complications are common in COVID-19[2 3]. These include myocarditis and myocardial injury that may lead to heart failure. Myocardial infarction (MI) and Takotsubo syndrome has been reported in patients with COVID-19[4 5]. An increase in troponin levels in COVID-19 is associated with more severe disease and mortality, underlining that myocardial injury as a prognostic factor[6]. Increased levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) is also an independent predictor of in-hospital death in COVID-19 patients, but at lower levels than in heart failure[7], suggesting that relatively mild alteration in cardiac function may critically determine outcome in COVID-19. In addition, arrhythmias are remarkably prevalent among patients with COVID-19 with an incidence of 16.7% reported in a Chinese cohort[8]. Cardiomyocytes are known to express angiotensin converting enzyme 2 (ACE2)[9], which is the receptor for SARS-CoV-2, however direct evidence of cardiomyocyte infection is lacking.

In addition, underlying cardiovascular disease may aggravate the clinical course of disease in COVID-19. Meta-analysis of data from Chinese cohorts revealed that fatality rates in hospitalised patients with COVID-19 were elevated in those with cardiovascular disease (10.5%), diabetes (7.3%) or hypertension (6%) compared to patients without comorbidities (0.9%)[10]. Cohorts of patients from Italy and U.S.[11] also show that hypertension, diabetes and obesity are common co-morbidities.

Increased D-dimer (fibrin degradation product) levels is a marker of adverse COVID-19 outcomes [12] and disseminated intravascular coagulation with significant risk of venous thromboembolism (VTE) and ischaemic stroke has been reported [13 14 15]. A study of systematic duplex ultrasound in 26 severe COVID-19 patients reported a cumulative VTE incidence of 69% despite anti-coagulation treatment[16]. Ischemic stroke has been linked to COVID-19 progression because it had a higher incidence in patients with severe disease compared to those with milder symptoms[17]. A report of six ischaemic stroke cases from the UK revealed an association with elevated D-dimers, systemic inflammatory changes, and anti-phospholipid antibodies, which are indicative of hypercoagulability [18]. However, caution should be exercised in attributing stroke to viral infection since there were several potential confounding factors including hypertension and atrial fibrillation, which enhance stroke risk.

We refer the reader to Guzik et al[19] for a more complete description of cardiac effects in COVID-19. The aim of this Position Statement from the Working Group on Atherosclerosis and Vascular Biology together with the Council of Basic Cardiovascular Science of the European Society of Cardiology is to draw attention to the importance of the endothelium in COVID-19 and to encourage research on endothelial dysfunction and

biomarkers to tackle the COVID-19 pandemic and its potential long-term cardiovascular complications.

Endothelium and COVID-19

The characteristic hyperinflammatory and pro-coagulatory state of COVID-19 implies a critical role of the endothelium, both as an effector contributing to inflammation and thrombosis, and as a target organ, whose dysfunction may contribute to poor outcome[20]. Of particular note, there is also evidence of SARS-CoV-2 infection of vascular ECs[21-24].

The vascular endothelium forms a critical interface between the circulatory system and underlying tissues and has vital and ubiquitous roles in cardiovascular homeostasis by regulating the transport of cells, nutrients and metabolites between the circulation and underlying tissues[25]. Several risk factors for cardiovascular disease including diabetes, obesity, dyslipidemia, smoking and disturbed blood flow can induce EC dysfunction which is characterised by a spectrum of phenotypes[262728]. These include loss of integrity (e.g. via apoptosis) which is associated with increased permeability; induction of cytokines and adhesion molecules to capture inflammatory cells from the circulation; metabolic changes; a pro-thrombotic phenotype and de-differentiation[2926]. This is exemplified in multiple studies showing that quantitation of EC function provides a useful marker for early disease detection and stratification of patients with cardiovascular disease[3031]. The European Society of Cardiology recently reviewed this subject and called for further investigation of EC pathophysiological states, optimisation and standardisation of methodologies for clinical measurement of EC function as well as larger clinical trials to establish reference values and assess clinical utility[25].

Emerging evidence indicates that EC dysfunction is a central feature of COVID-19. This is evidenced by the critical role of vascular endothelium in inflammation, which is the key driver of cytokine dysregulation in ARDS as well as multiple cardiovascular pathologies. Additionally, the pro-thrombotic phenotype and disseminated intravascular coagulation observed in COVID-19 reflect dysfunction of EC, which enhances thrombosis by reduced integrity leading to exposure of pro-thrombotic sub-endothelial material, capture of platelets and regulation of clotting cascades, thrombin activation and fibrin production[32].

There are several other lines of evidence that substantiate the role of endothelium in COVID-19 (Figure 1):

(1) Recruitment of leukocytes, immune response and tissue injury.

Leukocytes play an important role in the pathogenesis of SARS-CoV-2. The importance of the leukocyte-EC axis is exemplified by the observations that patients with severe disease demonstrate a marked increase in blood neutrophils which is associated with lymphopenia, with both $CD4^+$ T cells and $CD8^+$ T cells being lower in severe compared to moderate cases[33]. Moreover, histological examination of a severe case, who died of SARS-CoV-2 demonstrated lung interstitial mononuclear inflammatory infiltrates,

dominated by lymphocytes[34]. Through the systemic inflammatory response in COVID-19, referred to as cytokine storm, or cytokine release syndrome, the endothelium will be directly exposed to pro-inflammatory cytokines that initiate transcriptional programmes, that induce adhesion molecules and chemokines driving leukocyte recruitment and inflammation[35]. This process can also lead to EC death that contributes to increased vascular permeability and end-organ damage. Through an amplification loop of the inflammatory response, the endothelium may constitute a significant source of pro-inflammatory cytokines e.g. interleukin (IL)-1 and IL-6, that characterize the cytokine storm in COVID-19 [36 37]. Since the process of lymphocyte trafficking in chronic inflammatory and auto-immune diseases is a major therapeutic target, it is possible that anti-inflammatory therapies developed for these conditions could be repurposed to treat SARS-CoV-2 infection.

It is uncertain whether modulating EC function during the inflammatory response to SARS-CoV-2 would be beneficial, with the dilemma that anti-inflammatory agents might be counterproductive and compromise the immune response against the virus. However, in mouse models of pathogenic influenza and respiratory syncytial virus (RSV) infection, where there is evidence that the EC orchestrate a $CD8^+$ T cell-mediated cytokine storm, agonists of the $S1P_1$ receptor are effective in improving survival[38-40]. It is also noteworthy that adiponectin is protective in models of sepsis and ARDS through suppression of EC activation[41]. Such observations raise the question of whether the immune response itself may contribute to chronic inflammatory process in severe SARS-CoV-2 infection. The immunology of SARS-CoV-2 infection has recently been comprehensively reviewed by Vabret et al[42] who noted that in SARS-CoV-1 patients survival was associated with immunity skewed towards a CD8 cytotoxic response[43]. Indeed, there is evidence that expansion of virus specific CD4 T cells and a robust Th2 response (including increases in plasma IL-4, IL-5 and IL-10) are associated with death in SARS-CoV-1[44]. Whether this is the case in SARS-Cov-2 remains to be established. It does however appear that the adaptive immune response is an important arbiter of outcomes in SARS-CoV-2, as there is a reported association between plasma IgA titers and severity of disease[45]. It is possible that in SARS-CoV-2, antibody-dependent enhancement (ADE) of inflammation plays a role in EC activation and pathology. In this phenomenon non-neutralising antibodies facilitate Fc-mediated uptake of virus into macrophages, resulting in their activation and liberation of inflammatory cytokines, leading to the secondary recruitment of inflammatory leukocytes by local EC. The phenomenon of ADE is readily demonstrable in a number of experimental models of SARS infection but there is currently no evidence that ADE contributes to pathology in SARS-Cov-2[42]. Since the process of EC dependent leukocyte trafficking in chronic inflammatory and auto-immune diseases is a major therapeutic target, it is possible that anti-inflammatory therapies developed for these conditions could be repurposed to treat SARS-CoV-2 infection. Indeed, the recent success of low dose dexamethasone in the RECOVERY-trial, and its adoption as a front line therapy for SARS-CoV-2 in the UK, is an exemplar of the utility of such an approach (see below).

(2) Endothelium and thrombosis

When dysfunctional, the thrombotic and coagulant properties of the endothelium change[35]. In particular, a decreased anti-aggregatory prostacyclin production from EC and an increased pro-aggregatory thromboxane synthesis from activated platelets[46] may skew the homeostatic situation towards a pro-thrombotic and pro-inflammatory phenotype. Interestingly, under some inflammatory conditions EC express adhesion receptors such as von Willebrand Factor on their surface. Both in vitro and in vivo these conditions have been demonstrated to support the recruitment and activation of platelets to intact endothelial monolayers[47]. This in turn can lead to the platelet dependent secondary recruitment of circulating leukocytes, either by leukocyte interactions with platelets adherent to EC[48], by the recruitment of circulating heterotypic aggregates of platelets and leukocytes[49], or by the transfer of platelet borne receptors such as GPIb to the leukocyte membrane by platelet derived microvesicles[50]. It is reasonable to assume that such tri-cellular aggregates (EC-platelet-leukocyte) on the walls of smaller vessel would be sufficient to cause loss of microvascular perfusion in the lungs and other organs. Indeed, compromise of myocardial perfusion could play a role in the elevated levels of troponin evident in many SARS-CoV-2 patients. Intravascular thrombosis and coagulation in addition may further damage the endothelium and contribute to endothelial inflammation and dysfunction[35]. In some patients with COVID-19 severe micro-vascular endothelial injury directly mediated by activation of the alternative and lectin complement pathways has been demonstrated and associated with a pro-coagulant state[51]. It remains however to be established if anti-coagulation or platelet inhibition in COVID-19 improves endothelial function, and if dampened endothelial inflammation would attenuate the pro-coagulant state in COVID-19.

(3) ACE2 expression and function in endothelium.

ACE2 is intimately linked to cardiovascular physiology as part of the renin-angiotensin-aldosterone system (RAAS), which controls blood pressure by altering vascular tone and function. The related molecule ACE converts angiotensin (Ang) I to Ang II, which promotes vasoconstriction, hypertension and vascular inflammation. Because of these properties, anti-hypertensive drugs have been developed to reduce the production (ACE inhibitors, ACE-i) or downstream effects (Ang II receptor blockers, ARBs) of Ang II. The effects of ACE are opposed by ACE2, which converts Ang II into Ang 1-7 molecules thereby promoting vasodilatation and reducing hypertension[52]. Since ACE2 is expressed in cells of the cardiovascular system[53], there has been considerable interest in the hypothesis that this class of anti-hypertensive drugs may increase the risk of SARS-CoV-2 infection by increasing the expression of ACE2 in vascular cells[54]. However, population-based studies revealed that ACE inhibitors and ARBs do not enhance the risk of COVID-19 or disease severity[55 56] and the European Society of Cardiology and other learned societies recommend that patients should continue with their usual anti-hypertensive medications during the pandemic

(https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang).

The spike (S) protein of the coronaviruses mediates viral entry into target cells. Entry depends on physical interactions of the surface unit, S1, of the S protein to a host cell receptor, which facilitates viral attachment to the surface of the target cells. SARS-CoV-2 engages ACE2 as the primary receptor [57, 58, 59] and hence it is plausible that COVID-19 may cause reduced bioavailability of ACE2 due to endosomal/lysosomal processing[52]. Treatment of COVID-19 patients with recombinant ACE2 is currently under clinical trial because this may act as a decoy receptor[60], hence limiting viral entry. It is notable recombinant ACE2 treatment may have additional beneficial effects, by increasing its bioavailability at the endothelial surface. The S2 domain of the S protein facilitates membrane fusion, which requires conformational flexibility, achieved by proteolytic cleavages. The cleavage event employs the cellular transmembrane protease, serine 2 (TMPRSS2), and has profound implications on virulence. A TMPRSS2 inhibitor, approved for clinical use, was shown to block entry and might constitute a treatment option[57]. It has been reported that TMPRSS2 expression is below detection in microvascular endothelial cells[61] and only upregulated in endothelial cells actively undergoing angiogenic or tubulogenic responses. Further studies are needed to better understand the physiological expression and function of TMPRSS2 in adult endothelial cells. However, the expression of TMPRSS2 alone may not be predictive of its function since serine proteases, such as TMPRSS2, are regulated by nitrosylation[62]. Therefore it is plausible that eNOS activity and subsequent production of NO may influence viral infection of EC by altering TMPRSS2 activity. Taken together the S protein mediates entry by connecting the virus to the plasma membrane, and by catalysing subsequent virus-cell membrane fusions.

(4) SARS-CoV-2-induced endothelitis.
In addition to the respiratory tract, ARS-CoV-2 viral load is detected in kidneys, liver, heart, and brain[63], which are all highly vascularized tissues. Indeed, Monteil et al provided an early indication of SARS-CoV-2 tropism for vascularized tissues by demonstrating that this virus can infect human blood vessel and kidney organoids via ACE2[59]. It was suggested by Varga et al by electron microscopy and histology that SARS-CoV-2 can be detected in EC of the kidney (glomerular capillaries), small bowel, lung and myocardium[21], but these data were recently disputed[64]. Ackerman et al[22] have shown abnormalities within the pulmonary microvasculature with congestion and micro-thrombi similar to Menter et al[23], and by electron microscopy there is endothelial injury and congestion with cell fragments and degenerate organelles in the lumen. Scanning electron microscopy of corrosion casts shows microvasculature of larger diameter with an irregular surface, which may be due to endothelial injury and/or platelet aggregates/fibrin. Intriguingly there was also evidence of intussusceptive angiogenesis and the authors speculate that this feature may distinguish the pulmonary pathobiology of COVID-19 from other viral infections. SARS-CoV-2 has also been detected in skin EC[24] and circulating endothelial cells are elevated in patients admitted to hospital with COVID-19[65].

Taken together, these studies point to endothelial SARS-CoV-2-infection as a possible direct trigger of endothelial adverse effects in COVID-19. Indeed, SARS-CoV-2 infected endothelium has been associated with EC apoptosis, suggesting a possible mechanism though which the endothelium may become dysfunctional in COVID-19[21]. The recent reports of a Kawasaki Disease-like syndrome associated with COVID-19 infection in children highlights the importance of the virus on the vasculature[66 67]. Kawasaki disease is a systemic vasculitis most commonly seen in children which particularly targets the myocardium and coronary arteries. Although the etiology of Kawasaki disease is unknown, infectious agents including RNA viruses have been previously postulated as the cause and the first link to a coronavirus infection was published in 2005[68]. The current outbreaks following infection by SARS-CoV-2 are the subject of intense investigation. A recently reported group of 58 hospitalized children were diagnosed with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS). Of note, important differences were noted when compared with Kawasaki disease[69]. Moreover, anecdotal cases with evidence of medium and large vessel vasculitis suggest similar complications may be seen in some adults with COVID-19.

(5) Pericytes.

Pericytes are multifunctional mural cells of the microvasculature and are essential for the maintenance of the endothelium integrity[70]. Studies suggest that they are involved in COVID-19-related vasculopathy. Recent single-cell or single-nucleus RNA sequencing analyses have shown that ACE2 is highly expressed in pericytes of various organs, such as the heart, both in mouse and man[71 72]. In alveolar capillary of SARS-CoV-2 infected lung, pericytes are markedly decreased, likely through apoptosis[73]**.** In a genetically modified mouse model with pericyte deficiency (*pdgf-b*$^{ret/ret}$ mouse[74]) induced by deletion of the PDGF-B retention motif, loss of pericytes induced thrombogenic reactions in ECs[72]**.** Therefore, pericytes by acting as direct target for SARS-CoV-2 infection, could play a crucial role in microvascular dysfunction and coagulopathy. It is suggested that a permeable endothelial barrier as observed in hypertension, diabetes and obesity, which are co-morbidity factors in severe cases of COVID-19, allows the virus to reach the pericytes[72].

Therapeutic targets.

It remains to be determined whether the endothelial dysfunction and injury seen in COVID-19 predominantly reflects direct infection of EC by SARS-CoV-2 or indirect bystander injury by factors including cytokines, leukocytes, neutrophil nets and complement activation[75]. Notwithstanding, an important consideration is the effect of current cardiovascular drugs in this setting (Figure 2). On the one hand, they may offer enhanced endothelial protection, while on the other they may increase endothelial susceptibility. To date there are only retrospective data to rely upon and prospective clinical studies in

COVID-19 with clearly defined cardiovascular endpoints are required. Drugs including HMG-CoA reductase inhibitors (statins), alpha and beta adrenergic blockers and renin–angiotensin–aldosterone system antagonists are widely prescribed in those with diabetes mellitus, hypertension and coronary artery disease, groups known to be at the highest risk from COVID-19. Understanding how these drugs influence outcomes is therefore essential.

In pre-clinical studies, statins increase expression of ACE2. However, these in disease models this may reflect a return to normal levels. Moreover, enhanced expression of ACE2 has cardiovascular benefit[76]. Previously observed beneficial effects in influenza and actions of statins including their ability to reduce CD147 expression, optimise lipid raft function, regulate autophagy, minimise endothelial activation, down-regulate pro-thrombotic pathways and enhance anti-thrombotic effects, alongside immunomodulatory actions, suggest that statins may exert important endothelial protective effects both against and during SARS-CoV-2 infection[77-79]. COVID-19 clinical trials incorporating statins (NCT04333407; NCT04348695:NCT04380402) have commenced and the results are awaited with interest.

Reported beneficial effects of beta-adrenergic blockers in ARDS and respiratory failure, alongside a potential ability to reduce viral entry by down-regulating ACE2 has resulted in these drugs being suggested as an adjunct therapy for COVID-19, even in those without a primary indication[80]. Retrospective studies underway will help inform this hypothesis. An intriguing large, retrospective analysis of alpha-1 adrenergic receptor antagonists in patients suffering from ARDS or pneumonia has revealed that those incidentally prescribed alpha-blockers were less likely to require ventilation or to die following onset of ventilator support. In contrast, beta-adrenergic blockers had no effect. The clinical study was inspired by pre-clinical data, which demonstrated that alpha-blockade can prevent the ARDS-associated cytokine storm and death in mice by interfering with a catecholamine loop[81]. These findings suggest that alpha-1 adrenergic receptor antagonists merit retrospective and prospective analysis in COVID-19. The identification of the SARS-CoV-2-associated cytokine storm as a potential therapeutic target is also supported by the early data from the dexamethasone arm of the COVID-19 RECOVERY trial[82].

The ability of SARS-CoV-2 to utilise ACE2 as a co-receptor for cellular entry has led to significant interest in the impact of angiotensin-converting enzyme inhibitors ACE-i and ARBs. Similarly to statins, these commonly used drugs enhance ACE2[76]. Although clinical data are sparse, ACEi and ARBs are reported to improve outcomes in ARDS[83]. There has also been speculation that a dysfunctional RAAS is important for COVID-19 disease pathogenesis[84]. Initial concern regarding potential susceptibility to SARS-CoV-2 infection and/or exacerbation of its effects in those taking ACEi or ARBs have been allayed by retrospective clinical studies[85-87]. Current advice is to continue taking these drugs prescribed for hypertension, cardiac failure and chronic renal disease, and for physicians to prescribe them for new clinical indications as normal[84]. Prospective studies and clinical trials are now urgently needed. Two clinical trials will study the impact of losartan on

COVID-19 (NCT04311177 and NCT04312009). Interest will also focus upon Ang 1-7 peptides, ACE2 itself[76, 84] and monoclonal antibodies that prevent SARS-CoV-2 binding ACE2[88].

Position statements

Further research is urgently needed to combat the COVID-19 pandemic and we emphasize that the role of vascular endothelium requires close scrutiny. There are today several outstanding questions that need to be addressed to elucidate more precisely the role of EC in COVID-19 and to investigate potential routes to clinical translation.

1. Endothelial biomarkers and tests of function (e.g. flow-mediated dilation, arterial stiffness) should be monitored in studies of COVID-19 outcome and treatment effects. High-quality data collection is needed, with follow-up studies amongst the survivors of acute infection since there are little or no data available on EC function testing in COVID-19. Indeed, collaborative networks have already been established to analyse RNA biomarkers[89] and arterial stiffness (CARTESIAN STUDY) to assess vascular consequences of COVID-19. This may help to enable stratification of COVID-19 patients with highest pro-thrombotic and cardiovascular risk and allow tailored treatments.

2. The significance of SARS-CoV-2-mediated endocytosis and downregulation of ACE2 on cardiovascular health is uncertain, but data from ongoing clinical trials to test recombinant ACE2 may be instrumental in addressing this question.

3. The principle effects of SARS-CoV-2 on endothelial function should be determined, including studies of EC activation, leukocyte recruitment, platelet activation, turnover, signalling etc. EC from both micro and macrovasculature should be investigated. Aging is an important determinant of COVID-19 outcome thus the influence of cellular senescence, oxidative stress and other features of aging on SARS-CoV-2 infection of endothelium should also be assessed. The influence of gender on endothelial responses to SARS-CoV-2 and how this relates to the susceptibility and outcome of COVID-19 patients should be investigated.

4. The effects of common cardiovascular drugs such as statins and beta blockers on endothelial responses to SARS-CoV-19 should be explored, including their influence on ACE2 expression and viral infectivity.

5. The long-term cardiovascular effects following recovery from COVID-19 must be determined during planned patient follow up so that appropriate preventive measures can be taken in time if needed. Measuring endothelial function in addition to myocardial injury and respiratory function markers in convalescent patients may represent a possible means for early detection of vascular sequelae post COVID-19.

Conflicts of interest.

None declared.

Author contributions.

PCE and MB conceived and designed the manuscript, drafted the manuscript and revised it for important intellectual content. GER, JCM, TJG, EO, ZS, DN, IEH, MF, JW, CW, M-L B-P made substantial contributions to the conception and design of the manuscript, and drafted the manuscript or revised it for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for the work.

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Figure legends

Figure 1 Endothelial dysregulation by SARS-CoV-2.

Healthy endothelium (left) is characterised by quiescence, intact junctions, anti-coagulant anti-inflammatory phenotype and an intact vasodilation phenotype. The cell in the centre (endothelitis) is infected with SARS-CoV-2, whereas the cells to the right have been activated as a result of cytokine release and activation of pro-thrombotic pathways. Infection with SARS-CoV-2 is via ACE2 which is subsequently endocytosed, potentially reducing ACE2-mediated regulation of vascular tone. SARS-CoV-2 infection causes endothelial dysfunction at multiple levels including inflammatory activation, cytokine storm, leukocyte infiltration, increased permeability, thrombosis, platelet aggregation, vasoconstriction, ROS production and apoptosis.

Figure 2 Potential interventions to reduce endothelial injury and activation.

Endothelial infection with SARS-CoV-2 infection causes dysregulation of the RAAS, apoptosis, thrombosis and inflammation (red tones). Several interventions (green tones) can reduce endothelial dysfunction in COVID-19 including modulators of the RAAS (ACE-i, ARBs, ACE2); anti-inflammatory molecules (cytokine inhibitors, dexamethasone, statins); inhibitors of ROS/apoptosis (statins); platelet inhibitors and anti-coagulants. A healthy lifestyle may also reduce endothelial dysfunction in patients with COVID-19.

Figure 1

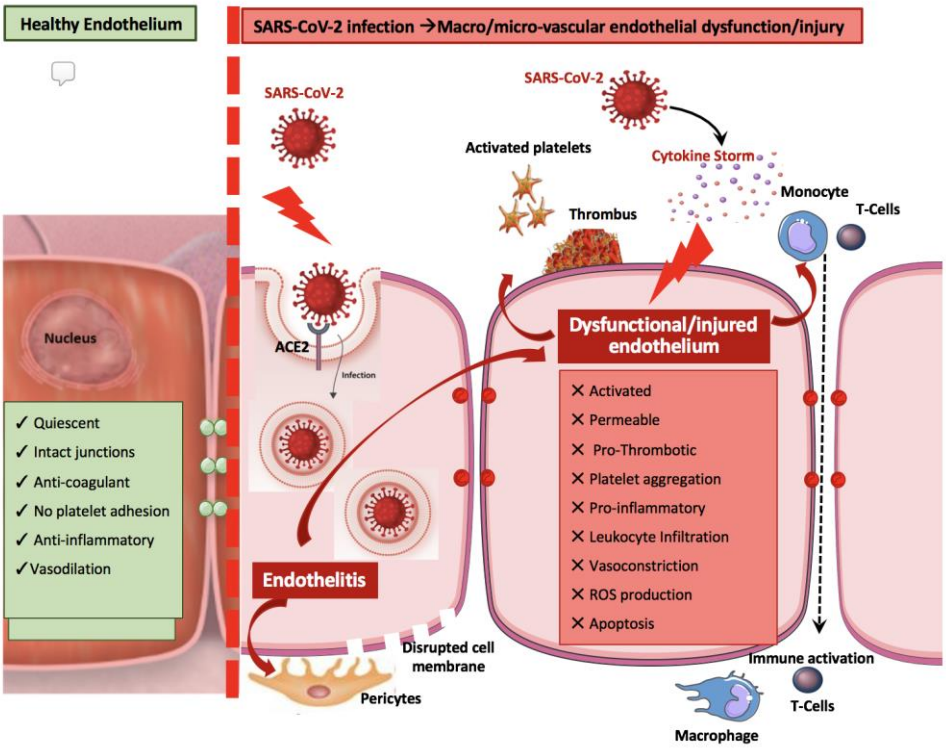

Figure 2