9 COVID-19 Is an Endothelial Disease: Implications of Nitric Oxide

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Abstract

Endothelial cells are a clinically important infection site for COVID-19, both as a mechanism for disease pathogenesis and as a therapeutic target. People with dysfunctional endothelium, defined by nitric oxide deficiency, appear to have a more severe disease course. As such, nitric oxide has therapeutic potential to mitigate COVID-19 severity. Inhaled nitric oxide appears to improve outcomes, although this strategy neglects systemic endothelium. Meanwhile, early studies have documented that endothelial protective medications, such as the administration of statins and ACE-inhibitors, are associated with less severe disease and reduced mortality. Importantly, these medications augment endothelial sources of nitric oxide, which may explain this effect.

Keywords

COVID-19 · Sars-CoV-2 · Endothelium · Endothelial dysfunction · Nitric oxide · Statins · ACE inhibitors

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9.1 Introduction

Our vascular endothelium is under attack by Sars-CoV-2. Researchers from China believe that while initial infection occurs within the respiratory epithelium, subsequent viremia results in multiorgan infection as well as infection of the distal vasculature [1]. This was recently corroborated by Swiss researchers who demonstrated

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infection of the endothelium by autopsy [2]. In response to these results, they went as far as to call COVID-19 an "endothelial disease." Both groups independently attribute the coagulopathies associated with COVID-19 to endothelial damage and acknowledged that those who are most at risk for severe disease appear to have underlying dysfunctional endothelium at baseline [1, 2]. This arguably makes endothelial dysfunction a significant risk factor for mortality from COVID-19, making it a likely therapeutic target.

The endothelium is a single layer of cells that lines all 60,000 miles of our blood vessels which perfuse every organ in the body and has such diverse functions that it can be considered as an organ in its own right. It regulates blood flow by controlling vascular smooth muscle tone and checks vessel narrowing by preventing cell and platelet aggregation along its surface. Additionally, it is also an important immune system activator. Instrumental to a healthy endothelium is its ability to produce nitric oxide, which is the linchpin for these functions [3]. Therefore, decreased nitric oxide production is central to the pathology of dysfunctional endothelium, and deficiency is ubiquitous among people with hypertension, cardiovascular disease, diabetes, and chronic kidney disease [3]. These are all notably on the top tier of risk factors for severe COVID-19, which is likely not a coincidence. Therefore, nitric oxide may have therapeutic potential to mitigate the disease course, particularly in the most at-risk populations.

The idea that nitric oxide has immunogenic and antiviral activity is not entirely novel. It has known antimicrobial activity against a wide range of organisms including bacteria, fungus, protozoa, helminths, and an assortment of viruses [4]. Jan Martel and colleagues recently published a medical theory paper on the importance of nasal nitric oxide regarding natural immunity, which suggested that variations in nasal nitric oxide levels may explain variable susceptibility to COVID-19 [4]. The paper also suggested that people with higher basal expired nitric oxide are less symptomatic to the common cold. Alternatively, animal studies have shown that mice deficient in nitric oxide are more prone to respiratory viral infections [4]. Additionally, prior research has demonstrated that administering nitric oxide donors to mice suffering from coxsackievirus-induced myocarditis improves outcomes [5] and that inhibition of nitric oxide synthase increases viral load [6].

9.2 Nitric Oxide, Demographics, and COVID-19

While several aforementioned chronic disease states associated with nitric oxide deficiency are considered to be high risk for severe COVID-19 illness, disease risk can also be stratified by demographics defined by race and sex in the absence of chronic disease. These factors also seem to correlate well with population-specific nitric oxide levels. For instance, estrogen and progesterone have a stimulating effect on nitric oxide synthase, which results in comparatively greater nitric oxide production in women compared with men [7, 8], and pregnant women have a surge in nitric oxide levels associated with elevated sex hormones [8]. This presents a dose-like protective effect of nitric oxide with women conferring an ~50% reduction in risk of death. Statistics suggests additional protection in pregnancy with ~96% of symptomatic pregnant women having mild symptoms [9] and 87% of pregnant women screening positive for COVID-19 being asymptomatic altogether [10].

Black adults are at increased risk of both incidence and severity of COVID-19 illness, and while these observations are largely attributed to social factors, it has been recently suggested there is likely to be a concomitant biological component. A possible explanation is that this population is comparatively deficient in nitric oxide compared to white adults [11]. This relative deficiency, and subsequent endothelial dysfunction, is recognized as a primary cause of increased risk of hypertension, cardiovascular disease, and kidney disease in this population [11]. Furthermore, reduced endothelial function is observed across the lifespan and apparent even in healthy, young Black adults [12].

9.3 Evidence for Inhaled Nitric Oxide and Systemic Therapy

Trials are underway investigating the utility of supplemental nitric oxide. These are largely based on a study that came from the SARS outbreak in 2003, in which nitric oxide given via mechanical ventilation had improved oxygenation and earlier hospital discharge [13]. Another study during this same period demonstrated specific viricidal effects of nitric oxide on Sars-CoV [14]. Additionally, nitric oxide appears to remove palmitic acid from the spike protein (depalmytoilation), which decreases the virus's ability to bind to the ACE-2 receptor [14]. Recently, Gilly Regev of SaNOtize (Vancouver, Canada) showed that nitric oxide is viricidal against Sars-CoV-2 in vitro. SaNOtize is now exploring the application of a nitric oxide solution to the nasopharynx in a multicenter prevention and efficacy trial against COVID-19 [15]. While inhaled or topical nitric oxide applications are promising therapies, they fail to address deficient vascular sources of NO and therefore the associated systemic consequences that define illness severity.

The benefits of nitric oxide are also indicated in the action of some drugs. Statins are mostly known for their cholesterol-lowering effects, but many lipid-independent actions have also been discovered for these drugs [16–21]. Among these so-called pleiotropic effects, statins increase endothelial nitric oxide via multiple pathways, and some studies have theorized that many of the cholesterol-independent effects of statins are mediated by this gas [22, 23]. Such effects may be at play in a study carried out by Zhang and colleagues, which demonstrated reduced mortality in hospitalized patients with COVID-19 receiving in-hospital statins [24]. The risk reduction was apparent before matching for age and comorbid conditions, with the statin group being older and more burdened by chronic disease. Specifically, the higher-risk statin-treated group had a mortality rate of 5.5% compared with 6.8% in the younger, healthier cohort. After matching the groups for age and comorbidities, the improvement was predictably more profound with a 5.2% death rate in the statin-treated group and a 9.4% mortality rate in the non-statin group [24]. The study authors hypothesized that the anti-inflammatory properties and immune modulating effects of statins likely explain the survival benefit; however, it should not be overlooked that these pleiotropic effects of statins are possibly mediated by nitric oxide [22, 23].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers also lead to increased nitric oxide [25–27], and Zhang et al. similarly demonstrated mortality benefit of both types of compounds in hospitalized COVID-19 patients [28]. The mortality rate was less than 5% in the treated group, while those not taking the medications had a mortality rate of greater than 10%. Unfortunately, this study did not evaluate the medication classes separately to examine superiority, as ACE inhibitors have a more robust nitric oxide response than angiotensin receptor blockers [26]. Independent studies have shown an increase in nitiric oxide production of 64% to 110% in response to ACE inhibitors compared with a peak increase of 30% observed with angiotensin receptor blockers [26, 27]. Therefore, it may be informative that a study currently in press associates ACE inhibitors with a 40% reduction in hospitalization of older adults, but no benefit was observed with angiotensin receptor blockers [29].

9.4 Conclusions

Given the antiviral, immunologic, vasodilatory, and antithrombotic properties of nitric oxide (Fig. 9.1), a deficiency may create an environment in which the endothelium is both more susceptible to infection and more prone to severe consequences. After infection ensues, subsequent inflammation results in further decreases in bioavailability of nitric oxide. Several inflammatory cytokines inhibit nitric oxide synthase, thereby limiting production, and reactive oxygen species scavenge existing nitric oxide further decreasing bioavailability [3]. Pro-inflammatory cytokines have a direct effect on vasoconstriction and hypercoagulation, usually countered by processes including nitric oxide [3]. Theoretically, a

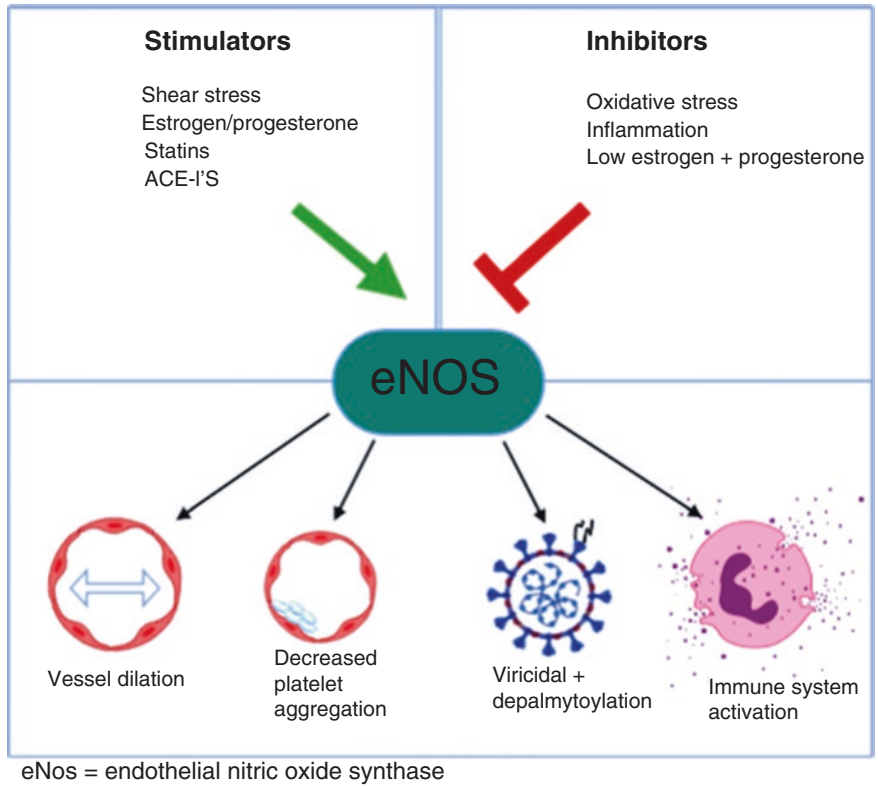

Fig. 9.1 Relevant inhibitors and stimulators of eNOS regarding COVID-19 and subsequent physiological responses

person who is already deficient in nitric oxide with preexisting endothelial inflammation will have less reserve to address the cytokine storm associated with COVID-19, and the scales begin to be unfairly tipped in the direction of dysfunction.

The variability of nitric oxide production across populations in both health and disease appears to accurately predict protection from and susceptibility to COVID-19 disease in a dose-like fashion. Furthermore, there are rational mechanisms to explain the conferred protection from elevated levels of endothelial nitric oxide. There are some studies underway exploring this relationship, although most are limited to inhaled nitric oxide. Meanwhile, some have investigated endothelial stabilizing medications with evidence of benefit. While it remains unclear as to what mechanism explains the protective effect of these medications, increased nitric oxide is a plausible answer. Although these studies are encouraging, a clearer understanding of the role of systemic nitric oxide on disease course is needed to define the path to potentially important therapeutic discoveries.

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