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Nitric Oxide 128 (2022) 72–102

Contents lists available at ScienceDirect

Nitric Oxide

journal homepage: www.elsevier.com/locate/yniox

Utility of NO and H_2S donating platforms in managing COVID-19: Rationale and promise

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ARTICLE INFO

Keywords:
Nitric oxide
Hydrogen sulfide
COVID-19
Inflammation
Endothelium
iNOS
Cytokine storm
Antiviral

ABSTRACT

Viral infections are a continuing global burden on the human population, underscored by the ramifications of the COVID-19 pandemic. Current treatment options and supportive therapies for many viral infections are relatively limited, indicating a need for alternative therapeutic approaches. Virus-induced damage occurs through direct infection of host cells and inflammation-related changes. Severe cases of certain viral infections, including COVID-19, can lead to a hyperinflammatory response termed cytokine storm, resulting in extensive endothelial damage, thrombosis, respiratory failure, and death. Therapies targeting these complications are crucial in addition to antiviral therapies. Nitric oxide and hydrogen sulfide are two endogenous gasotransmitters that have emerged as key signaling molecules with a broad range of antiviral actions in addition to having anti-inflammatory properties and protective functions in the vasculature and respiratory system. The enhancement of endogenous nitric oxide and hydrogen sulfide levels thus holds promise for managing both early-stage and later-stage viral infections, including SARS-CoV-2. Using SARS-CoV-2 as a model for similar viral infections, here we explore the current evidence regarding nitric oxide and hydrogen sulfide's use to limit viral infection, resolve inflammation, and reduce vascular and pulmonary damage.

1. Introduction

The widespread global impact of the current coronavirus disease 2019 (COVID-19) pandemic highlights the human population's vulnerability to the consequences of viral infections. Newly emerging and re-emerging viruses pose a significant and continuing threat to human health. In the last few decades, the world has seen multiple Ebola virus outbreaks throughout West Africa, the HIV/AIDS epidemic of the 1980s, the H1N1 or swine flu pandemic of 2009, and three separate major β coronavirus outbreaks – Severe Acute Respiratory Syndrome (SARS, heretofore referred to as SARS-CoV-1) in 2002, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, and most recently, Coronavirus Disease 2019 (COVID-19) from SARS-CoV-2 [1–3].

The emergence and transmission of such viruses are facilitated by factors including population growth, international travel, climate and ecological changes, and increased animal-human contact [4]. Revolutionized by the acceptance of modern germ theory and the advent of vaccines, the approach to controlling the spread of viral infections includes measures such as social distancing, personal protective equipment, quarantine, lockdown, and vaccination efforts [5]; however, as seen in the current pandemic, there are many obstacles to successful control of transmission even with stringent precautionary measures [6]. Additionally, the delay between viral emergence and successful vaccine development, relatively rapid viral mutations potentially leading to new vaccine-resistant strains, and cases of morbidity and mortality that occur despite vaccination, highlight the importance of management therapies and control of the transmission.

Current therapies for viral infections are limited to antivirals and symptom management with supportive therapies that are often insufficient. The majority of antiviral agents are virus-specific and act by inhibiting viruses from infecting and proliferating in the host [7]. Thus, virus-specific antiviral agents are limited because many viruses lack antiviral medications [8]. Overuse of these agents may contribute to drug resistance as mutated viral strains continue to develop [9]. Furthermore, the effectiveness of antiviral therapy is based on early intervention, which may pose a challenge [10]. Virus-specific drug development is a significantly longer process, a major obstacle in the

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https://doi.org/10.1016/j.niox.2022.08.003
Received 24 June 2022; Received in revised form 1 August 2022; Accepted 10 August 2022
Available online 24 August 2022

Abbreviations

3-MST	3-mercaptopyruvate sulfurtransferase
ACE2	angiotensin converting enzyme 2
ALI	acute lung injury
Ang	angiotensin
ARDS	acute respiratory distress syndrome
Atf3	activating transcription factor 3
Ca^{2+}	calcium ion
CAT	cysteine aminotransferase
CBS	cystathionine β-synthase
CCHFV	Crimean-Congo hemorrhagic fever virus
CF	cystic fibrosis
cGMP	cyclic guanosine monophosphate
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CSE	cystathionine γ-lyase
EBOV	recombinant Zaire Ebola virus
ECMO	extracorporeal membrane oxygenation
ED	emergency department
eNOS	endothelial nitric oxide synthase
GADD45α	growth arrest and DNA-damage-inducible 45 alpha
GSH	glutathione
H_2S	hydrogen sulfide;
hMPV	human metapneumovirus
H_2S_n	polysulfide;
HSV	herpes simplex virus
HSNO	thionitrous acid
HNO	nitroxyl
HUVEC	human umbilical vein endothelial cells
IFN	interferon
iH_2S	inhaled hydrogen sulfide;
IL,	interleukin
IMV	invasive mechanical ventilation
iNO	inhaled nitric oxide;
iNOS	inducible nitric oxide synthase
L-NAME	N^G-Nitro arginine methyl ester
L-NMA	L-Nω-methylarginine;
L-NMMA	Nω-monomethyl-L-arginine;
LPS	lipopolysaccharide;
MCP-1	monocyte chemoattractant protein 1
MERS-CoV	Middle East respiratory syndrome coronavirus
MPO	myeloperoxidase
MV	mechanical ventilation
NAC	N-acetylcysteine;
NAP	N-acetylpenicillamine;
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NiV	Nipah virus
nNOS	neuronal nitric oxide synthase
NO	nitric oxide;
NONS	nitric oxide nasal spray
$ONSS^-$	nitropersulfide
PAG	dl-propargylglycin
PDE5	phosphodiesterase 5
PRCV	porcine respiratory coronavirus
PRRSV	porcine reproductive and respiratory syndrome virus
ROS	reactive oxygen species
RSSEV	far-eastern tick-borne flavivirus
RSNO	nitrosothiol
RSV	respiratory syncytial virus
RVFV	Rift Valley fever virus
S protein	spike protein
SARS	severe acute respiratory syndrome
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
sGC	soluble guanylyl cyclase
SNAP	S-nitroso-L-acetyl penicillamine;
SNP	sodium nitroprusside;
Socs3	suppressor of cytokine signaling 3
SOD	superoxide dismutase
TMPRSS2	transmembrane serine protease 2
TNF	tumor necrosis factor
VILI	ventilator-induced lung injury
VSV	vesicular stomatitis virus

face of emerging and re-emerging viruses [11]. These limitations emphasize the importance of having a broad range of antiviral agents for the early-stage management, few of which are currently available. Additionally, viral infections, including but not limited to SARS-CoV-2, may cause hyperinflammatory responses and corresponding tissue damage [12,13], pneumonia [14,15] that may progress to acute respiratory distress syndrome (ARDS) [16,17], endothelial dysfunction [18–20] and coagulation disorders [21,22] with possible repercussions even after microbiological recovery. The severity of the potential complications indicates the necessity of management for these additional components.

Nitric oxide (NO) and hydrogen sulfide (H_2S), once thought solely to be toxic environmental pollutants [23], are endogenously produced in humans as part of the innate immune response. NO and H_2S have a broad range of antiviral activity and act as the first line of defense against invading viruses. In addition to their antiviral effects, they are critical in maintaining vascular integrity and endothelial function, regulating the immune response, and have pulmonary protective properties [24]. This indicates that enhancement of endogenous NO and H_2S bioavailability through exogenous administration or modulation of the endogenous machinery presents a promising avenue for combatting viral infections, including the current COVID-19 pandemic. This review highlights the properties of NO and H_2S that promise to manage early- and later-stage viral infections, including but not limited to influenza, rhinovirus, respiratory syncytial virus (RSV), parvovirus B19, and cytomegalovirus (CMV), with a particular focus on SARS-CoV-2.

2. The COVID-19 pandemic

In December 2019, there was an outbreak of pneumonia cases of unknown origin at a seafood market in Wuhan City, China, which was subsequently linked to the novel SARS-CoV-2 [3]. Since then, the virus has infected more than 590 million people across the globe and has claimed the lives of more than 6.4 million [25]. While less fatal than SARS-CoV-1 and MERS-CoV, SARS-CoV-2 has significantly higher transmissibility and presents with long-lasting symptoms [3,26] that have had global ramifications for upwards of two years. COVID-19 encompasses a wide range of symptoms, presenting as asymptomatic in 25–40% of patients [26–28], mild respiratory illness in others, or viral pneumonia progressing to respiratory failure and, in the most severe cases, death [26]. COVID-19 severity and mortality are associated with several factors, including age, race (which may be due to healthcare and systemic disparities), and comorbidities such as hypertension, obesity, chronic lung disease, cardiovascular disease, and diabetes [29–32]. Despite promising results of vaccination efforts in containing the pandemic, as with other viruses, the resurgence of multiple SARS-CoV-2

variants, so far most prominently the delta and omicron variants, proves to be a substantial obstacle [33].

2.1. SARS-CoV-2: mechanism of entry

SARS-CoV-2 is an enveloped positive-strand RNA β coronavirus [34] that spreads through droplets, aerosols, contact with body fluids, and contact with contaminated surfaces or objects [35]. Based on a review of 12 studies, SARS-CoV-2 has higher transmissibility than SARS-CoV-1, with a median and mean R0 of 2.79 and 3.28, respectively [36]. In addition, the Omicron variant has higher transmissibility [37], and the latest variant, BA.2 has even a higher transmissibility rate [38]. The most commonly reported incubation period is between 5 and 7 days [27,39,40]; peak viral load in the upper respiratory tract is detected usually within the first week of symptom onset, and the mean shedding duration is approximately 17 days [41].

SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) receptors for entry into the host [42,43] (Fig. 1), and cells lacking ACE2 have significantly reduced or absent SARS-CoV-2 entry [42]. Similarly, antiserum raised against the human ACE2 drastically reduces SARS-CoV-2 entry into human cells in vitro [43], whereas transfection of ordinarily non-ACE2 containing BHK (kidney origin) cells with human ACE2 enables SARS-CoV-2 viral entry [44]. Viral entry is mediated by the spike (S) protein expressed on the outer envelope of SARS-CoV-2, which is responsible for binding onto the host ACE2 receptor and mediating membrane fusion (Fig. 1). The S protein has two subunits, S1 for binding to the ACE2 receptor and S2 for anchoring to the host membrane and mediating membrane fusion [44]. Viral entry requires S protein cleavage at the S2' site, for which SARS-CoV-2 preferentially utilizes the host transmembrane serine protease 2 (TMPRSS2) present at the cell membrane [45]. Inhibition of TMPRSS2 using camostat mesylate blocks SARS-CoV-2 infection of lung cells, confirming this entry mechanism [43]. Alternatively, SARS-CoV-2 may enter the host cell through ACE2-mediated endocytosis, utilizing a different host protease in the late endolysosome, cathepsin L, for S2' protein cleavage [45] (Fig. 1).

2.1.1. ACE2 and its role in COVID-19

Immunostaining reveals that ACE2 is widely expressed throughout the body, including the endothelial cells of the arteries and veins, the smooth muscle of arteries, alveolar epithelial cells in the lung, and the nasal mucosa, all of which are targets of SARS-CoV-2 infection and damage [46]. The ACE2 protein is a component of the Renin-Angiotensin-Aldosterone System responsible for cleaving circulating Angiotensin (Ang) II to Ang 1–7 [47]. Ang II is a vasoconstrictive, pro-inflammatory agent that increases the formation of superoxide anions, reduces NO bioavailability, and enhances the breakdown of the H_2S-producing enzyme, cystathionine γ-lyase (CSE), discussed below. Thus, ACE2 has protective effects mediated through Ang 1–7, leading to reductions in inflammation and upregulation of the endothelial NO-producing enzyme, endothelial nitric oxide synthase (eNOS) [48].

Following SARS-CoV-2 infection, the ACE2 protein is downregulated, leading to lung function deterioration [49]. Furthermore, in a mouse model of SARS-CoV-1, ACE2 protein downregulation exacerbated acute lung failure [50]. Consistent with the infection-associated downregulation of ACE2, Ang II levels are reportedly higher in COVID-19 patients and are correlated with greater viral load and lung injury [51], suggesting that restoration of ACE2 after infection is a possible avenue toward ameliorating COVID-19 lung pathology. In fact, ACE2 knockout mice with experimentally induced lung injury can be rescued when injected with recombinant human ACE2, demonstrating direct protective actions of ACE2 in lung injury [52].

3. Major features of COVID-19 infection: points of intervention

SARS-CoV-2 can be transmitted before the onset of symptoms [53–55]; in fact, Seyed et al. reported that 48% of all COVID-19 transmissions come from infected individuals still in the pre-symptomatic stage [55]. The initial stages of infection are characterized by a viral

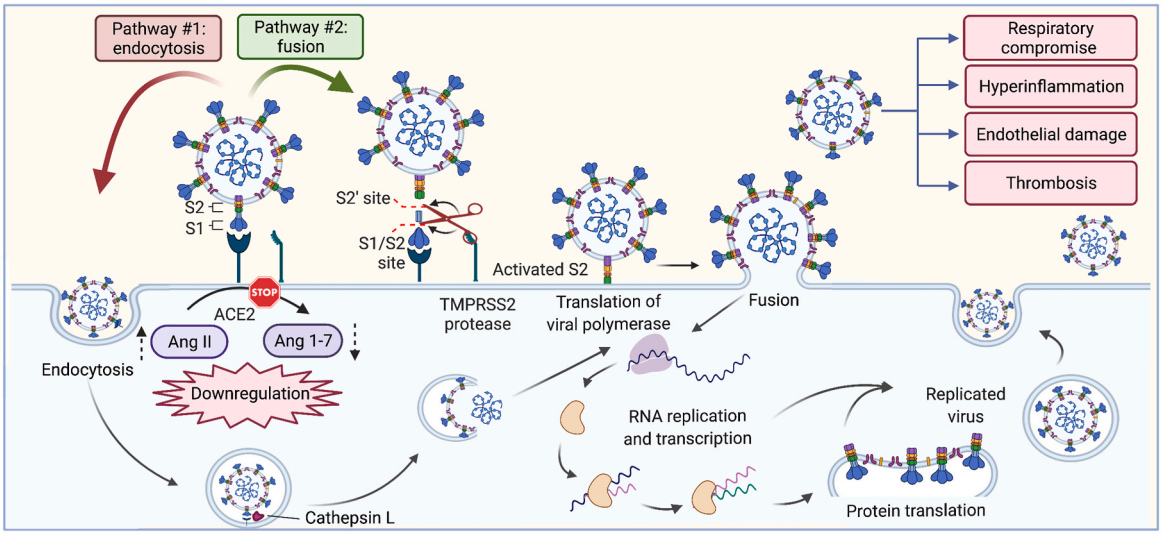

Fig. 1. SARS-CoV-2 entry into the host cell. As an enveloped virus, SARS-CoV-2 can enter the host cell through one of two pathways - pathway #1, endosomal entry and pathway #2, direct cell surface entry. In both entry forms, the S protein binds to the ACE2 receptor and must be primed and activated by proteases at the S1/S2 and S2' site. SARS-CoV-2 infection results in the downregulation of the ACE2 receptor, leading to an increase in Ang II and decrease in its conversion to Ang 1–7. In pathway #1, SARS-CoV-2 undergoes clathrin-mediated endocytosis, and is primed by host protease Cathepsin L present in the endolysosome, followed by membrane fusion and release of viral genomic material. In pathway #2, the S protein is cleaved by TMPRSS2 at the cell membrane, where it directly fuses and releases viral RNA without entering an endolysosome. Both pathways join in the host cytoplasm, where a viral polymerase is translated, followed by RNA replication, structural protein translation, viral assembly, and release of progeny virus that continue to spread the infection to other cells. SARS-CoV-2 infection leads to respiratory compromise by causing lung injury, results in excessive inflammation with overactivation of leukocytes and production of inflammatory mediators, results in direct and inflammation-mediated damage to the endothelium, and induces a pro-thrombotic state.
Abbreviations: ACE2, angiotensin converting enzyme 2; Ang, angiotensin; S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2.

host response, which starts before and continues past the onset of symptoms. This stage is followed by an inflammatory and possibly hyperinflammatory phase, with arising pulmonary and thrombotic complications in more severe cases [48,56–58]. In most cases, COVID-19 is a mild illness, commonly reported as fever, headache, cough, fatigue, and myalgia [59]. A large case series of 72,314 COVID-19 cases in China reported approximately four out of five cases to be mild to moderate, with severe and critical cases accounting for 5% of the patients [60]. In severe cases, individuals present with extensive pulmonary and cardiovascular complications that can be fatal. COVID-19 complications align with components of several other viruses; thus, symptom-specific therapeutic applications discussed in the context of SARS-CoV-2 infection extend to all viruses which share those features with SARS-CoV-2 infection.

3.1. Respiratory complications

As a respiratory virus, SARS-CoV-2 presents flu-like symptoms with lung involvement that are apparent on CT scans even in asymptomatic patients [61]. According to a meta-analysis, the most common CT scan findings include ground-glass opacities, bilateral lung involvement, and vascular enlargement [62]. In addition, a large number of patients develop pneumonitis and pneumonia that can progress to ARDS [63], seen in approximately one out of three hospitalized COVID-19 patients [64]. Similar respiratory complications have been described in rhinovirus, influenza, enterovirus, RSV, herpes simplex virus (HSV), and CMV [14,16,17].

ARDS is characterized by diffuse alveolar damage and compromised gas exchange, lung stiffness, and edema [34,65], with patients experiencing shortness of breath and hypoxemia, many requiring mechanical ventilation (MV) [66]. Mortality rates among COVID-19 patients requiring invasive mechanical ventilation (IMV) are reportedly high, with an estimated overall fatality rate of 45% among 57,420 COVID-19 IMV cases from 69 studies [67]. In addition, IMV comes with a high risk of increased lung damage, thrombosis, secondary infection, and corresponding mortality; in fact, higher rates of ventilator-associated infections and mortality have been reported for COVID-19 compared to other conditions including influenza [68–70]. Therefore, managing lung damage, respiratory failure, and preventing secondary infections are particularly interesting.

3.2. Cardiovascular complications

Abnormal coagulopathy has been described in various viral infections, including influenza, parvovirus B19, HSV, CMV, hepatitis A and C, and most recently, SARS-CoV-2 [21]. The incidence of pulmonary embolism (PE) in patients with COVID-19 pneumonia was twice that of influenza pneumonia patients in one case series [71]. Another study of ICU COVID-19 pneumonia patients reported a 31% incidence rate of thrombotic complications despite thromboprophylaxis, with PE accounting for most thrombotic events [72].

Abnormal coagulopathy in COVID-19 is associated with increased mortality; according to one study that compared survivors and non-survivors of COVID-19 pneumonia, 71.4% of non-survivors were found to have disseminated intravascular coagulation, compared to only 0.6% of survivors [73]. Correspondingly, elevations in markers of coagulopathy have been associated with increased mortality from COVID-19, including increased d-dimer [73,74], fibrin degradation product, prothrombin, and partial thromboplastin time [73,75], which are independently predictive of thrombotic complications [72]. Furthermore, lung tissue from deceased COVID-19 pneumonia patients shows evidence of thrombosis, microangiopathy, and hemorrhage in the small vessels and capillaries of the [76], in addition to signs of diffuse alveolar damage [76–78]. Similarly, in an analysis of skin and lung tissue from 5 severe COVID-19 patients, 3 showed microvascular thrombotic disorder and a systemic procoagulant state, including elevated d-dimer levels [79].

COVID-19 pulmonary tissue shows increased signs of vascular damage compared to other viral infections that cause lung injury. When comparing COVID-19 with non-COVID-19 pneumonia, the former could be distinguished through chest CT scans by multiple features, including vascular thickening, which is associated with thrombosis [80]. Furthermore, in a comparison of lung features of 7 individuals deceased from COVID-19 vs. age-matched non-survivors of ARDS secondary to influenza A, both showed evidence of diffuse alveolar damage and perivascular T-cell infiltration; however, only the lungs of the COVID-19 non-survivors presented with vascular damage and endothelial injury resulting from the intracellular presence of the virus; microthrombi were 9 times as prevalent for COVID-19 and angiogenesis was also almost triple compared with influenza of equal severity [78]. Mitigation of vascular damage is thus at the forefront of resolving severe COVID-19 complications.

3.3. Hyperinflammation

Much of the organ damage in SARS-CoV-2 is attributable to an excessive inflammatory response, termed ‘cytokine storm,’ reported in more severe COVID-19 cases [81,82] (Fig. 2). Hyperinflammation is characterized by overproduction and an uncontrolled cascade of pro-inflammatory cytokine release, leading to a continuing cycle of inflammation and organ damage [81]. There is evidence that SARS-CoV-2 suppresses or delays the type I interferon (IFN) (IFN-α, IFN-β) and type III IFN (IFN-λ) innate antiviral response [81,83–85], reducing clearance of the virus and contributing to an excessive inflammatory response. Dysregulation of the immune response is further evidenced by reports of lymphopenia and exhaustion markers, neutrophilia, an uncontrolled cascade of pro-inflammatory cytokine release, including interleukin (IL)-1β, IL-2, IL-6, and tumor necrosis factor (TNF)-α, and elevations in inflammatory markers such as C-reactive protein (CRP) and lactate dehydrogenase (LDH) to an extent associated with case severity and mortality [74,83,86–95]. Resolving inflammation is of great utmost for ameliorating outcomes and future complications of COVID-19, as well as other viral infections in which hyperinflammation has been described, including but not limited to CMV, variola virus, influenza virus, and SARS-CoV-1 [12].

3.4. Endothelial dysfunction

Endothelial dysfunction that occurs during viral infections and inflammation contributes to disrupted vascular homeostasis and lung injury seen in severe viral infections, including CMV, influenza, and dengue virus [19,20,96]. Leukocyte and platelet adhesion to the endothelium is inhibited in the basal state, preventing inflammation and thrombus formation [97,98]. In an inflammatory state, endothelial cells undergo activation, promoting platelet activation and adhesion [99] and localized inflammation by recruiting pro-inflammatory agents and increased leukocyte transmigration [97,98] (Fig. 2). Direct infection of endothelial cells and excess inflammation can cause endothelial dysfunction, resulting in increased vascular permeability and a shift towards a vasoconstrictive, prothrombotic state, contributing to pulmonary and vascular complications [97,98].

Endothelial cells possess ACE2 receptors [46] and are directly infected by SARS-CoV-2; in one study, COVID-19 patients were found to have increased circulating endothelial cells damaged with multiple fenestrae in their cell membranes, which were similar in size to SARS-CoV-2 supercapsid [100]. Similarly, histological analysis and transmission electron microscopy confirm direct SARS-CoV-2 viral infection of the endothelial cells and signs of endotheliitis in the vasculature of multiple organs, including the lungs [78,101]. Furthermore, elevated levels of endothelial activation markers Angiopoietin-2 and sE-selectin were found to be predictive of higher severity of COVID-19, and Angiopoietin-2 was further found to be strongly

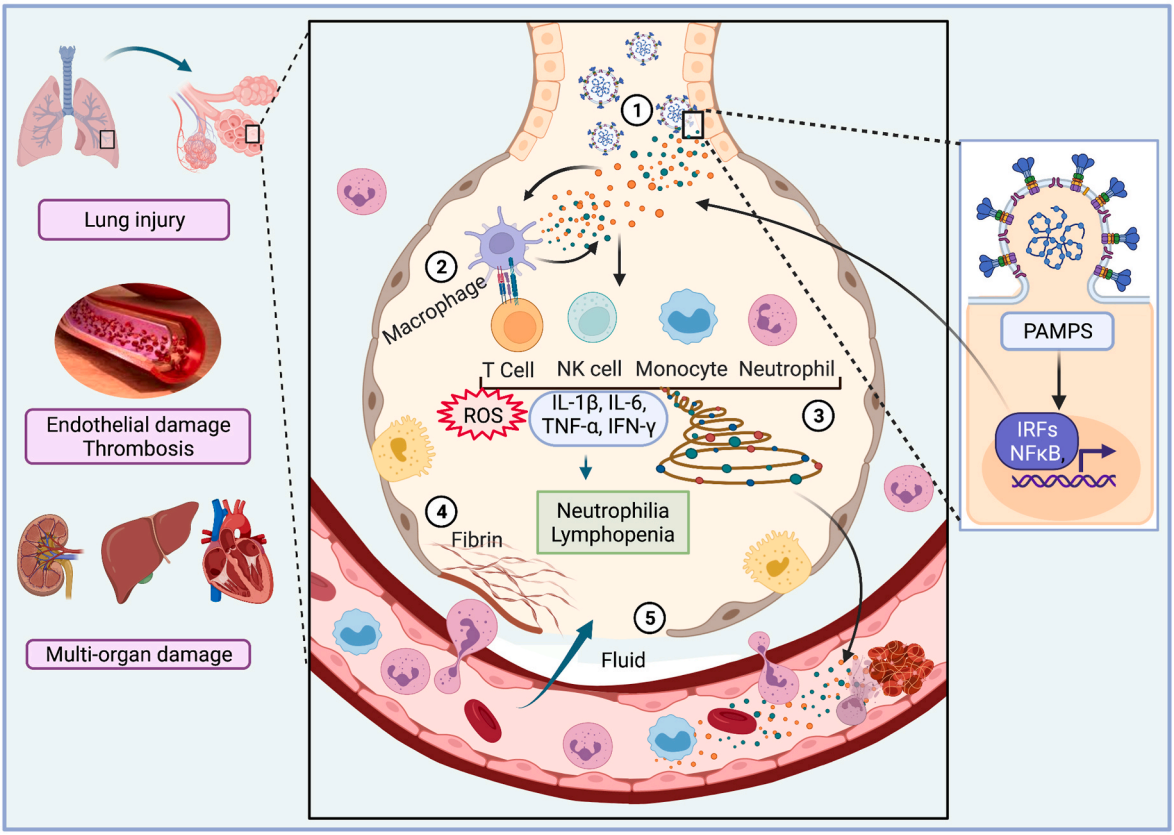

Fig. 2. Cytokine storm in COVID-19. Cytokine storm is characteristic of severe COVID-19 cases and results in lung injury, endothelial damage and thrombosis, and multi-organ damage that can lead to death. The following steps are responsible for the hyperinflammatory response that occurs in COVID-19: 1) SARS-CoV-2 enters the lung and infects the lung cells. These cells recognize PAMPS from the virus and begin pro-inflammatory gene transcription using transcription factors such as IRFs and NFκB, resulting in the release of pro-inflammatory cytokines and other mediators, which are recognized by leukocytes. 2) PAMPs and DAMPs are recognized by tissue macrophages, which become activated and secrete more pro-inflammatory cytokines to recruit and activate other leukocytes to the site of infection, including T lymphocytes, NK cells, neutrophils, and more monocytes to enter through the blood and differentiate into macrophages. 3) Together, these activated cells produce excess cytokines and chemokines, including IL-1β, IL-6, TNF-α, among others, that continue the cycle, diffusing into the blood and recruiting even more leukocytes. Microbial killing by these activated leukocytes involves neutrophil production of ROS as well as T cell mediated cytotoxicity, leading to inflammatory damage to the tissue, lymphocyte exhaustion, excessive neutrophil infiltration. In the vasculature, the endothelium undergoes activation, causing a shift to a pro-inflammatory, prothrombotic state which can facilitate thrombus formation and leukocyte migration into the infected tissue. 4) Fibrin deposition in the air spaces exacerbates the damage. 5) Inflammation leads to increased gaps between endothelial cells, resulting in vascular leakage and edema in the air spaces, leading to respiratory failure.
Abbreviations: COVID-19, coronavirus disease 2019; DAMPs, damage associated molecular patterns; IL, interleukin; IRF, interferon regulatory factors; NFκB, nuclear factor kappa light chain enhancer of activated B cells; NK, natural killer; PAMPs, pathogen associated molecular patterns; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome; TNF, tumor necrosis factor.

associated with CRP, creatinine, and d-dimer, all of which are also associated with greater severity of and mortality from COVID-19 [73,74,95].

In addition to direct infection of endothelial cells, an excessive inflammatory response is a major contributor to endothelial dysfunction through increased oxidative stress and reduced NO bioavailability [102]. The role of inflammation has already been explored in comorbidities, including obesity, diabetes, and hypertension, which are characterized by endothelial dysfunction [103–105]. These comorbidities are also risk factors for severe COVID-19, in addition to other factors such as age, which is also associated with endothelial dysfunction; thus, damage to the endothelium plays a major role in COVID-19 complications [106].

3.5. Long-term complications

Multiple reports of long-term complications of COVID-19, both in asymptomatic and symptomatic cases, suggest lasting damage from the virus. In a study of 143 recovered COVID-19 patients discharged from the hospital (Italy in 2020), with an average follow-up of approximately 60 days after symptom onset, revealed that the majority (87%) had persistence of at least one COVID-19 symptom, most commonly fatigue, and 21.7% reported persisting chest pain [107]. Signs of lasting myocardial damage were also seen among competitive college athletes with mild or asymptomatic cases [108], suggesting that 'long COVID' is not only restricted to severe cases linked with comorbidities. Accordingly, while persisting COVID-19 symptoms are typically more common in more severe cases, patients with mild COVID-19 also report long-lasting symptoms [109]. In addition, even asymptomatic patients have been found to have extensive lung involvement, and lasting pulmonary complications have been noted in recovered COVID-19 patients [109]. Organ damage and persistent inflammation are suggested to contribute to the lasting COVID-19 symptoms, and mitigation of these factors through therapeutic avenues during and after infection may be of the utmost importance to prevent future complications, the scope of which cannot still be fully known.

With the persistence of infection and mortality despite large-scale vaccination, the resurgences of new variants with slightly different transmissibility and severity, and evidence of persisting damage from infection long after microbiological recovery, even in mild cases, this

review highlights the promise of NO and H_2S as management therapies for SARS-CoV-2 infection and other viruses in which the previously discussed respiratory, inflammatory, and vascular complications arise.

4. Nitric oxide homeostasis

Nitric oxide (NO) is a small endogenously produced gaseous signaling molecule with critical functions in cardiovascular homeostasis, neurotransmission, defense against pathogens, and oxidative damage [110]. As a free radical that is highly reactive in the presence of oxygen, hemoglobin, thiols, and other radicals [111], NO is short-lived in biological fluids, with a reported intravascular half-life of 0.1–2 ms due to consumption by erythrocytes through hemoglobin binding, and a slightly longer half-life ranging from 6 ms to 2 s in tissues [112–115]. NO is produced endogenously from the amino acid L-arginine by the enzyme nitric oxide synthase (NOS), which is expressed in three isoforms: neuronal NOS (nNOS or NOS-1), endothelial NOS (eNOS or NOS-3), and inducible NOS (iNOS or NOS-2) [116]. nNOS and eNOS are constitutively expressed, and their activation is dependent on an elevation in intracellular Ca^{2+} levels and the Ca^{2+}/calmodulin complex, producing small quantities of NO upon stimulation [117]. On the other hand, iNOS is an inducible isoform absent in most cells in the healthy state; its transcription is induced by the presence of inflammatory cytokines or toxins that signal the need for host defense against pathogens [118]. Once synthesized, iNOS can bind calmodulin and be active independent of Ca^{2+} levels [119]. It is responsible for the sustained production of large quantities of NO that exceed normal physiological concentrations [119]. The respiratory system expresses all three NOS isoforms [120]. NO can also be synthesized by a NOS-independent pathway through the anaerobic conversion of nitrite to NO using nitrite reductases, mainly in the gastrointestinal tract [121,122] NO production from this pathway is upregulated in conditions of reduced oxygen availability or acidosis [123]. Additionally, nitrate, which was previously thought to be biologically inert, can also be reduced to nitrite in the body [124], yielding the nitrate-nitrite-NO pathway; as such, dietary nitrates from rich sources such as beets and leafy vegetables can contribute to endogenous NO levels and are suggested as an NO boosting method, especially for cardiovascular conditions [98].

4.1. NO signaling and functions

NO diffuses across cell membranes and binds to its intracellular receptor soluble guanylyl cyclase (sGC), resulting in cGMP production and activation of protein kinase G (PKG), through which the majority of its functions are carried out [125]. Within the vasculature, eNOS-derived NO is responsible for cGMP-dependent vasodilation through vascular smooth muscle relaxation and the inhibition of platelet and leukocyte adhesion to the endothelium [126,127]. nNOS-derived NO is important for cGMP-dependent non-adrenergic non-cholinergic (NANC) nervous system signaling, functioning as an inhibitory neurotransmitter with roles including neural regulation of smooth muscle as in peristalsis [116]. In addition, NO can exert cGMP-independent effects by affecting mitochondrial function, formation of peroxynitrite, and protein modifications such as S-nitrosylation and tyrosine nitration [128,129]. Owing to its short half-life, NO is mainly a paracrine and autocrine signaling molecule; however, there is evidence of endocrine functions as well [130]. NO signaling pathways are more extensively outlined in other review articles [128,129].

In the inflammatory state, pro-inflammatory cytokines, including IFN-γ, TNF-α, or IL-1, and some toxins induce iNOS through activation of transcription factors such as nuclear factor kappa light chain enhancer of activated B cells (NF-κB) [131]. The effects of NO are concentration-dependent: whereas basal NO levels act as an anti-inflammatory modulator within the vasculature, large amounts of iNOS-derived NO have pro-inflammatory properties and show antimicrobial effects against invading pathogens [132–134]. In uncontrolled inflammation, dysregulation of NO production and bioavailability occurs despite existing control mechanisms such as negative feedback regulation on NO production [116,135,136] and inhibition of iNOS by anti-inflammatory cytokines such as IL-10 [131]. This dysregulation is exacerbated by further induction of NO synthesis by increased oxidative stress [135]. Excessive NO production from iNOS during a hyperinflammatory response can produce reactive nitrogen species, causing a self-reinforcing cycle of inflammatory damage and NO depletion [98,137].

Inflammatory damage to the vascular endothelium, which can be partly mediated by excessive iNOS-derived NO, also results in decreased vascular bioavailability of eNOS-derived NO due to impaired eNOS function [138–140]. NO deficiency is a hallmark of endothelial dysfunction [141] and is associated with a shift to pro-thrombotic, pro-inflammatory, and vasoconstrictive states with systemic repercussions. Restoring NO to the endothelium may ameliorate endothelial damage and alleviate tissue injury.

4.2. NO dysregulation in infection

Consistent with the role of NO as the first line of defense against pathogens, NO production and iNOS expression increases during viral infections [111,119,142,143]. Reduced NO levels are associated with increased infection severity in multiple animal models of viral infections. iNOS inhibition in CMV-infected mice increases viral replication and susceptibility to lethal infection [144,145]. Similarly, iNOS deficient mice have a higher mortality rate from Coxsackievirus B4 [146]. Reduced NO levels have also been reported in conditions that predispose individuals to frequently recurring and often severe respiratory infection, including cystic fibrosis (CF) [147] and Kartagener syndrome, for which a 98% reduction in nasal NO has been measured [148]. During a viral infection, increased NO levels can be seen either in a normal immune response or in an abnormal, hyperinflammatory response, whereas decreased NO levels can also result from NO depletion in a normal or hyperinflammatory response. Both increased and decreased NO levels have been described among COVID-19 patients and may correlate to case severity and infection stage.

Among COVID-19 pneumonia patients, one study found significantly reduced total plasma NO metabolites, free nitrite, and S-nitrosothiol levels compared to healthy controls; however, there was an increase in plasma nitrotyrosine, a NO-derived marker of oxidative stress-mediated by peroxynitrite [149]. Together, these results suggest that NO depletion, despite induced iNOS expression, is due to NO's consumption to produce radicals such as peroxynitrite, reducing NO bioavailability while increasing oxidative stress. Monitoring NO metabolite levels in a healthy individual who later contracted COVID-19 showed the same trend of reduced NO bioavailability during infection [149]. Slight decreases in serum NO metabolites were also found in another cross-sectional study comparing COVID-19 patients with controls [150]. In contrast, increased NO metabolite and nitrotyrosine levels were found in severe COVID-19 patients and non-survivors [149], suggesting excessive NO production as part of a hyperinflammatory response reported in more severe cases. Similarly, significantly increased serum nitrate and nitrite levels were reported when comparing 25 healthy individuals and 25 critically ill COVID-19 pneumonia patients [151]. Another study in which the severity of COVID-19 cases was unclear also reported increased NO metabolite levels among infected patients [152].

Disruptions in NO levels have also been reported after recovery from COVID-19, suggesting longer-lasting damage from the virus. One study measuring serum nitrate and nitrite levels in patients four months after COVID-19 recovery found decreased nitrite and increased nitrate levels compared to uninfected controls [153]. The authors propose that the reduced nitrite levels in the recovered patients indicate long-lasting endothelial damage by COVID-19 [153] since nitrite levels are a biomarker of endothelial dysfunction, mirroring eNOS activity [154,155]. However, increases in peroxynitrite may explain the observed

increases in nitrate levels, pointing to increased iNOS and NO production during infection [153]. This study highlights that COVID-19 has a lasting damaging impact on the body even in milder cases, emphasizing the need for proper management during the infection to minimize the risk of future complications. Furthermore, a study measuring alveolar NO concentrations (CaNO) in patients three months after COVID-19 recovery found significantly higher CaNO levels in the recovered patients compared to healthy controls; increased CaNO was also observed to correspond to fibrosis and ground-glass opacity [156].

NO levels may indicate the stage and severity of the infection, and differentiating between an appropriate immune response and hyperinflammation based on NO levels may provide insight into the therapeutic approach required on a case-by-case basis. While antiviral therapy would be more appropriate in the early stage of infection; focusing on anti-thrombotic and anti-inflammatory treatments may be necessary for later stages where there is evidence of hyperinflammation.

5. Therapeutic potential of NO as an antiviral

NO has been documented to combat various pathogens, including viruses, bacteria, fungi, helminths, and protozoa [157]. In addition, constant NO production in the paranasal sinus epithelial cells [158] by constitutive expression of an iNOS-resembling isoform functions as the body's innate defense of the airways against airborne pathogens [157, 158]. Indeed, nose-breathing has also been suggested as one protective measure during the current COVID-19 pandemic [157].

Restoration of NO has shown promise in alleviating conditions in which individuals are predisposed to viral infections. For example, in an in vitro study, the introduction of iNOS transgene and using NO donors S-nitroso-L-acetyl penicillamine (SNAP) and (Z)-1-[N-(2-aminoethyl)-N-(2-aminoethyl)amino]diazen-1-ium-1,2-diolate (detaNONOate) led to decreases in viral load in CF airway epithelial cells [159]. Additionally, there are multiple clinical trials using exogenous NO administration to reduce viral infections in CF patients [160] (Table 1). NO therapy may thus be beneficial for combatting viral infections in the early stages.

5.1. NO vs range of viruses

Early evidence for the direct antiviral properties of NO came from an in vitro study in which administration of the NO donor SNAP substantially decreased the replication of HSV type 1 in a dose-dependent manner [161]. Since then, endogenous NO has been identified as a broad-range antiviral, protecting the body against respiratory and non-respiratory viruses, DNA and RNA viruses, and enveloped and nonenveloped viruses [111].

NO exhibits general defense mechanisms, including activation of

Table 1
Clinical trials using exogenous NO to reduce viral infections in cystic fibrosis patients.

NCT number	Ref	Study title	Status	Intervention	Outcome Measures
NCT02295566	[450, 451]	RATNO (Reducing Antibiotic Tolerance Using NO) Reducing Antibiotic Tolerance Using Low Dose Nitric Oxide in Cystic Fibrosis - a Phase 2 Pilot Study	Completed	10 ppm iNO delivered continuously for 8 h a night for 7 nights via nasal canulae	Efficacy of iNO in disrupting *Pseudomonas aeruginosa* biofilms in CF patients with acute infection, in reducing the bacterial density when given with standard antibiotic therapy, and in improving lung function as measured by the forced expiratory volume in 1 s (FEV1) ***Findings***: significant reduction in pseudomonas aeruginosa biofilm by day 7, some benefits in FEV1
NCT01958944	[452]	Phase II Prospective, Open Labeled, Multi-Center, Evaluation of the Safety and Tolerability of Nitric Oxide Given Intermittently Via Inhalation to Subjects With Cystic Fibrosis	Completed	160 ppm iNO for 30 min thrice daily for 10 working days	Safety, tolerability of treatment in CF patients colonized with *Pseudomonas aeruginosa*; improvement in FEV1
NCT02498535	[453]	Prospective, Randomized, Placebo Controlled Trial of the Efficacy and Safety of Inhaled Nitric Oxide (NO) in Cystic Fibrosis (CF) Patients	Terminated	160 ppm NO gas for 30 min 4 times a day for 7.5 days by nasal inhalation	Efficacy of treatment in terms of change in FEV1, 6-min test performance, organisms recovered in sputum (colony forming units), and clinical improvement among CF patients with chronic lung colonization with *Pseudomonas aeruginosa*, *Staphylococcus aureus* or Stenotrophomonas maltophilia
NCT05101915	[454]	Phase II Open Label Study of a Nebulized Nitric Oxide Generating Solution in Patients with Cystic Fibrosis	Not yet recruiting	nebulized NO-producing solution RESP301 for 28 das	Change in treatment-naïve/treatment-refractory Mycobacterium abscessus load in CF patients following therapy with RESP301; safety, tolerability of RESP301
NCT04685720	[455, 456]	A Pilot Study to Assess the Effect of Intermittent Inhaled Nitric Oxide on the Treatment of Nontuberculous Mycobacteria (NTM) Lung Infection in Cystic Fibrosis and Non-Cystic Fibrosis Patients	Recruiting	iNO in doses up to 250 ppm, delivered using LungFit device (2 weeks of iNO four times a day followed by 10 weeks of 250 ppm iNO twice daily)	Safety of treatment in CF and non-CF patients with nontuberculous mycobacterial infection; efficacy in terms of change in bacterial load, culture conversion, 6-min test performance, quality of life measures, FEV1 ***Findings***: treatment was well tolerated and safe, led to improvements in 6-min walk scores and FEV1, led to reductions in sputum bacterial load; further study needed with larger cohort to demonstrate statistical significance
NCT00255242	[457]	Effect of Simvastatin on CF Airway Inflammation	Completed	40 mg/day simvastatin (inhibitor of Rho proteins which inhibit NOS) for 28 days	Treatment effect on exhaled NO levels, airway inflammation, NOS2 expression in CF patients
NCT02694393	[458]	Phase I/II Study of Inhaled Sodium Nitrite as an Antimicrobial for Pseudomonas Infection in Cystic Fibrosis	Active, not recruiting	46 or 80 mg inhaled sodium nitrite twice daily for four weeks by electronic nebulization	Safety of sodium nitrite inhalation at 46 or 80 mg doses in CF patients with pseudomonas infections; efficacy of treatment in terms of Pseudomonas density in sputum after treatment, pulmonary function measured by FEV1, exhaled NO and sputum nitrite concentrations, self-reported respiratory symptoms

mucociliary clearance that can function in the removal of harmful particles and pathogens from the respiratory tract [157] (Fig. 3). Low NO levels have been linked to significantly impaired mucociliary action in chronic or recurrent respiratory diseases [162]. In the rabbit maxillary sinus mucosa, ciliary beat frequency has increased in the presence of L-arginine and other NO-donors [163]. The same has been reported in mouse nasal and tracheal epithelial cells [164]. These actions are mediated through the cGMP pathway [165,166]. Additionally, NO increases mucus secretion, stimulating the feline and human submucosal glands by L-arginine and isosorbide dinitrate enhanced secretion activity [167]. Removing airborne pathogens from the respiratory tract provides the first part of the NO-linked antiviral defense.

NO has direct antiviral actions; it directly inhibits the replication and latency of a number of viruses in vitro, including influenza A and B [168,169], CMV [144,170], ectromelia virus [119], HSV [171], rhinovirus [172], hantavirus [173], Coxsackievirus B3, B4 [146,174], Japanese encephalitis virus [175], vaccinia virus [176], SARS-CoV-1 [177,178] and more recently, SARS-CoV-2 [179,180]. Direct antiviral activity of NO involves inhibition of viral replication and viral entry into the host (Fig. 3) through modification of viral replication machinery and, in some cases, host proteins by nitration, S-nitrosylation, and oxidation [119]. In the case of Coxsackievirus B3, administration of SNAP or iNOS transfection inhibited viral RNA and protein production in vitro [174]. Further study indicated dose-dependent inhibition of an early step in viral replication through S-nitrosylation of cysteine residues at the active site of Coxsackievirus protease 3C, which is critical in viral replication [181]. Similar results were observed with macrophages experimentally induced to express iNOS [181]. This supports the notion that both exogenous and endogenous NO have antiviral effects. In vitro studies using NO-donors with other viruses show multiple mechanisms of viral replication inhibition through modifications of both viral and host machinery; inhibition of HIV-1 reverse transcriptase by oxidation of a cysteine residue [182], inhibition of RNA-dependent RNA polymerase in dengue virus type-2 [183], as well as a reduction in the activity of ribonucleotide reductase [184], transcription factors, integrase, and disruptions in post-translational modifications, summarized in Ref. [185]. Further details on the antiviral therapeutic effects of NO are given in Ref. [110].

It should be noted that some studies have found that the antiviral effects of NO may not extend to all viruses. In some cases, NO may actually contribute to viral pathogenesis [186]. Furthermore, the antiviral effects of NO may also depend on the release kinetics of the NO delivery platform [187]. Whether NO exerts antiviral effects or contributes to the virus's pathogenic effects depends on the virus's identity,

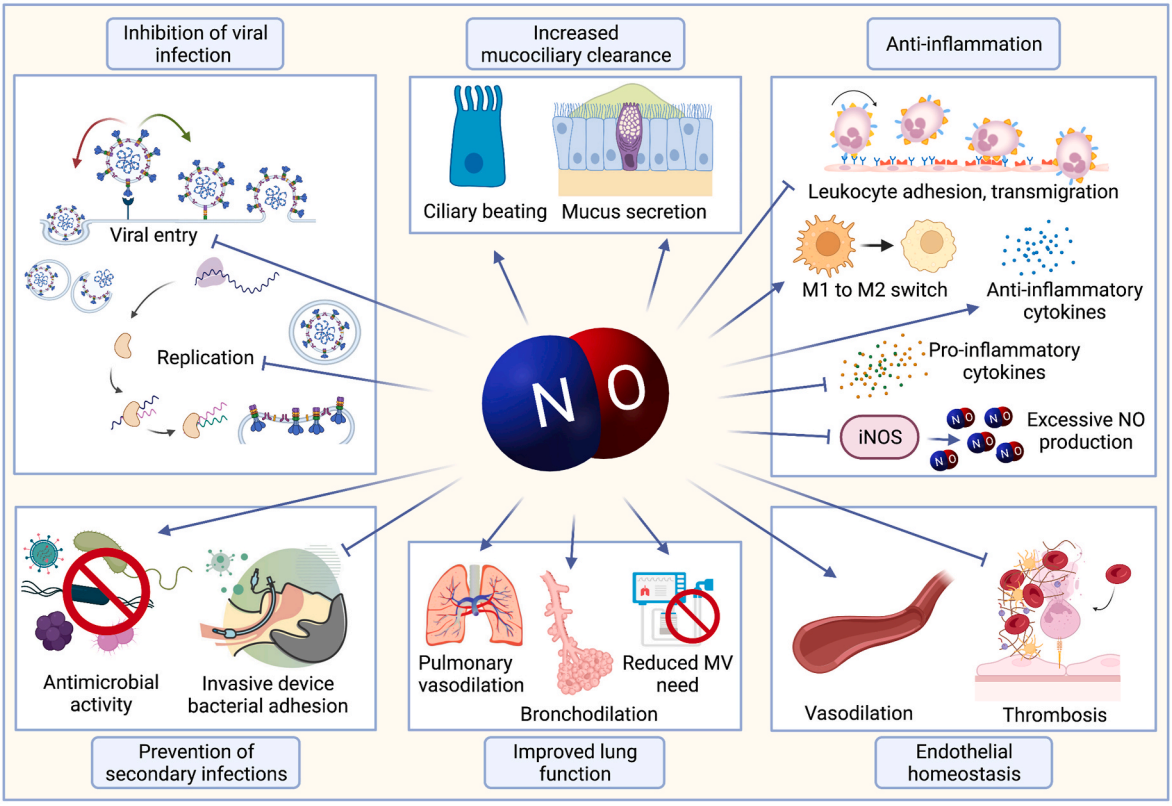

Fig. 3. Role of NO in COVID-19. Previous studies with SARS-CoV-1 suggest that NO may inhibit viral entry of SARS-CoV-2 by disrupting post-translational palmitoylation of the S protein, and studies conducted with SARS-CoV-2 demonstrate that NO inhibits viral replication by inhibiting SAS-CoV-2 3CL protease that is necessary for replication. NO increases mucociliary clearance by increasing ciliary beat frequency as well as mucus secretion, acting as a first line of host defense against airborne pathogens in the respiratory tract. During later stages of infection, NO plays a role in resolving inflammation - NO inhibits the expression of adhesion molecules in the endothelium thus inhibiting leukocyte adhesion and transmigration, promotes macrophage switching from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, upregulates the release of anti-inflammatory cytokines while suppressing pro-inflammatory cytokines, and exerts feedback inhibition on iNOS to curtail excess NO production that can occur in hyperinflammation. Within the vasculature, NO induces vasorelaxation through cGMP-mediated signaling and reduces platelet aggregation and thrombus formation. Within the lungs, NO improves ventilation and perfusion through broncho- and pulmonary vasodilation, respectively, and limits the need for MV, thereby reducing the occurrence of lung injury from MV. The antimicrobial actions of NO are also important in preventing secondary infections, and application of NO donors has been shown to reduce bacterial adhesion to biomedical devices, an important application where MV, ECMO, and other invasive support is needed.

Abbreviations: cGMP, cyclic guanosine monophosphate; ECMO, extracorporeal membrane oxygenation; iNOS, inducible nitric oxide synthase; M1, classically activated macrophage; M2, alternatively activated macrophage; MV, mechanical ventilation; NO, nitric oxide; S protein, spike protein; SARS-CoV-1, severe acute respiratory syndrome 1; SARS-CoV-2, severe acute respiratory syndrome 2.

stage, and severity of the infection.

Murine studies with influenza A and vaccinia virus have presented results wherein iNOS deficiency did not impact virus clearance from the host [188,189]. These results need to be interpreted cautiously since eNOS and nNOS effects were not evaluated in these studies. Furthermore, administering the non-specific NOS inhibitor Nω-monomethyl-L-arginine (L-NMMA, also known as L-Nω-methylarginine (L-NMA) [190]) on days 3–7 post-inoculation, or the day of infection, improved survival and alleviated viral pneumonitis without impacting virus yield [189,191]. Administering inhaled NO (iNO) to mice infected with a lethal dose of influenza A failed to decrease viral lung load or improve survival; in fact, continuous iNO administration at 80 ppm decreased survival [192]. In this study, iNO was administered prophylactically and post-infection [192], taking into account the possible differences in response throughout different stages of infection. Since the inocula were lethal, itraises questions about whether mortality was preventable considering the dosage and methods of NO administration. In these studies, NO did not seem to have any antiviral activity; further, inhibition of NO synthesis did not improve the host condition.

While the prior studies found results suggesting NO to be either ineffective or unnecessary for viral suppression and may even contribute to damaging the host, other studies have indicated that suppression of NO production alleviates host damage despite increases in viral levels. For example, in HSV-1-induced pneumonia, L-NMMA administered on the day of inoculation was found to improve survival and suppress pneumonia despite an increased viral load [193]. Moreover, in interstitial pneumonitis induced in the virus-free lungs of mice previously infected with murine CMV, administration of PBN, which reduces iNOS and NO production, significantly reduced lung lesions but not mortality, suggesting that NO-mediated the pneumonitis but did not decrease the mortality rate [194]. The antiviral effects of NO may additionally depend on the identity of the virus. For example, an in vitro study used SNAP against cells infected with either porcine respiratory coronavirus (PRCV) or porcine reproductive and respiratory syndrome virus (PRRSV) replication; SNAP caused significant inhibition of PRCV replication but did not affect PRRSV [195].

Overall, these studies emphasize that NO's antiviral vs. damaging actions depend on multiple factors and will not be consistent across all conditions. In some cases, iNOS was a greater contributing factor to exacerbation of the infection than it was in suppressing the virus. It appears that NO is typically most effective as the first line of defense capacity. When regulated, it typically has more antiviral actions against respiratory viruses and more negative consequences against non-respiratory viruses [111]. Likely, the stage of infection, the balance between NOS isoforms, the concentration or dosage of NO, and the identity of the virus are all factors that need to be considered when discussing NO as a therapeutic agent.

5.2. NO against SARS-CoV-1

In vitro studies have demonstrated direct antiviral actions of NO against SARS-CoV-1. In 2005, Akerstrom et al. showed dose-dependent inhibition of SARS-CoV-1 replication using the NO donor SNAP [177]. RNA replication and expression of nucleocapsid protein were reduced without cytotoxic effects; treatment with N-acetylpenicillamine (NAP), which lacks the NO-donating S-nitroso group, produced no such reduction in SARS-CoV-1 replication [177]. The antiviral effects of SNAP were consistent with endogenous NO production through iNOS, induced in this study by IFN-γ, which drastically reduced the replication of SARS-CoV-1. This effect was reversed by treating cells with the NOS inhibitor L-NMMA [177]. In a similar in vitro study, NO donors SNAP, and sodium nitroprusside (SNP) were found to inhibit viral replication of SARS-CoV-1; however, SNAP, as a direct NO donor, was more efficacious than SNP, which requires a reducing agent for NO release, indicating the importance of the mechanism of NO release from the donor compounds [180]. Further inquiry revealed two antiviral mechanisms specific to SARS-CoV-1: first, reduction in palmitoylation of spike (S) protein by nitration, inhibiting S-protein fusion of the nascent virus with the ACE2 receptor in the host cells, preventing viral entry; and second, reduction of RNA replication possibly through alteration of the viral cysteine proteases necessary for replication [178]. Predictably, neither of these antiviral functions were seen using NAP [178].

5.3. NO against SARS-CoV-2

Recently, an in vitro study that replicated the one done with SARS-CoV-1 found that SNAP exerted a dose-dependent inhibitory effect on SARS-CoV-2 replication and delayed or completely prevented the development of cytopathic effects [179]. Discontinuation of treatment led to a partial rebound in replication, although cells treated with 400 μM of SNAP still had a 92.64% (±1.59 SD) inhibition of viral replication 36 h after discontinuation of treatment compared to only about 25% inhibition remaining in cells that were treated with 200 μM of SNAP [179]. Expectedly, treatment with the non-NO donor NAP failed to produce any effect on the viral replication or cytopathic effects [179]. Moreover, fluorescence resonance energy transfer (FRET)-based enzymatic assay showed dose-dependent inhibition of SARS-CoV-2 3CL protease, a likely mechanism for inhibition of viral replication [179] (Fig. 3). iNO has thus been suggested as a protective measure against COVID-19; in fact, despite the consistently poorer outcomes observed for smokers with COVID-19, disproportionately lower rates of infected smokers [196] have led to suggestions that the short bursts of NO from cigarette smoking may provide a first-line defense against infection [197,198]. In a phase 2 clinical trial, early intervention using nitric oxide nasal spray (NONS) 5–6 times per day for 9 days in patients with mild cases of COVID-19 similarly showed a 95% reduction in viral load 24 h after the initiation of treatment, and 99% reduction in 72 h, with faster symptom resolution, compared to the placebo group [199]. Average SARS-CoV-2 RNA concentration was reduced by a factor of 16.2 on days 2 and 4 after initiation of NONS treatment compared with patients receiving placebo [199]. The results of another phase 2 pre-print publication were in keeping with the previously observed antiviral actions of NO against SARS-CoV-2; with doses of 10–80 ppm in short bursts, COVID-19 pneumonia patients demonstrated accelerated reductions in viral load, lower 28-day mortality, and reduced requirement for invasive ventilation compared to controls [200]. In silico analysis has identified the NO donor phenyl furoxan as a possible main protease inhibitor of SARS-CoV-2 [201].

6. NO for management of hyperinflammation

As alluded to, NO has a dual effect in the context of inflammation; low basal levels of NO, as produced by eNOS, are anti-inflammatory through inhibition of leukocyte adhesion (Fig. 3), whereas higher levels as produced by iNOS tend to be pro-inflammatory [133]. While controlled inflammation is beneficial against pathogens, an excessive inflammatory response can result in vascular and organ damage [202,203]. Considering the hyper-inflammatory response in severe cases of viral infection, including in COVID-19 [81], exogenous NO administration may seem in direct opposition to the patient's need to alleviate the inflammatory response. However, there is evidence that NO therapy may have anti-inflammatory effects rather than contributing to the already present pro-inflammatory response, as discussed below.

Experimentally induced inflammation models reveal NO's beneficial anti-inflammatory properties (Fig. 3). Treatment of LDL-deficient mice on a high-fat diet with NCX 6560, a NO-donating derivative of atorvastatin, significantly reduced aortic plaque macrophage infiltration compared to the parent compound, with dose-dependent reductions in circulating IL-6 levels [204]. Other drug combinations and derivatives, Ibuprofen-arginine and NCX-1005 (a NO-donating dexamethasone derivative), exhibited similar anti-inflammatory effects attributable to NO

supplementation both in vitro and in vivo; inhibiting apoptosis, decreasing myeloperoxidase (MPO) activity to reflect reduced neutrophil infiltration, reducing pro-inflammatory cytokine levels [205,206]. NO therapy also shows promise in mitigating sepsis; L-arginine treatment of human umbilical vein endothelial cells and neutrophils induced with plasma from septic patients significantly reduced neutrophil activation, adhesion, and aggregation reversed by the nonselective NOS inhibitor L-NMMA but not by the iNOS inhibitor 1400W [207]. This strongly suggests that restoration of eNOS may have some utility in managing sepsis [207]. The anti-inflammatory properties of NO are also promising for reducing ventilator-induced lung injury (VILI). In a model of shear-stress induced epithelial cells resembling VILI, pre-treatment with NO-releasing nanoparticles pre-and post-exposure reduced cell injury and cell death, with ROS and IL-6 levels significantly reduced [65]. These findings indicate a potential in severe COVID-19 cases to curtail excessive inflammation and ameliorate lung injury through MV. In a study with a SARS-CoV-2-infected rhesus macaque, arginine supplementation to isolated peripheral blood mononuclear cells inhibited the release of pro-inflammatory cytokines, including IL-6 and TNF-α [208].

The anti-inflammatory effects of NO may be mediated through NO-induced repolarization of the pro-inflammatory M1 macrophages that produce to IL-6 to the anti-inflammatory M2 phenotype producing IL-10 [209] (Fig. 3). Overexpression of eNOS in mice fed a high-fat diet to induce inflammation revealed that eNOS is protective against hepatic inflammation and reduces the expression of M1 markers compared to control mice while preserving M2 markers levels [210]. The same results were found in macrophages stimulated by either lipopolysaccharide (LPS) and IFN-γ or IL-4 – eNOS-derived NO limited M1 activation and stimulation repolarization to M2, and the NO donor DETA-NO did the same [210]. Likewise, in LPS-induced endotoxemia in mice, treatment with NO-releasing nanoparticles increased M2 expression while reducing M1, with corresponding reductions in pro-inflammatory and increased anti-inflammatory cytokines; overall, 3-day survival was significantly improved in NO-treated mice compared to controls [211].

In addition to inducing macrophage phenotype switching, NO treatment also inhibits the production of reactive oxygen and nitrogen species limiting endogenous NO production (Fig. 3). Connelly et al. report that after LPS activation of murine macrophages, inhibition of endogenous NO production by L-NG-Nitro arginine methyl ester (L-NAME) or placement in L-arginine free solution increases iNOS expression and dysregulates the immune response, with reduced IL-6 levels in early stages of the activation, and significantly higher IL-6 levels at later stages of infection [132]. Additionally, administration of exogenous NO using DEA-NO demonstrated a biphasic effect; whereas treatment with lower concentrations (30 nM–3 μM) increased NF-κB activity and iNOS expression, higher concentrations (30 μM–300 μM) did the opposite [132]. Taking advantage of the extensive feedback regulation of NO levels on NO production may provide a functional therapeutic approach to controlling hyperinflammation, in which there is a simultaneous decrease in endothelial NO bioavailability and increases in iNOS. Indeed, treatment of LPS-activated mouse macrophages with nitrite, which can endogenously be reduced to NO, limited superoxide anion production similar to therapy with DETA-NONOate, and attenuated peroxynitrite formation downregulating iNOS expression [212]. Furthermore, the reduction in superoxide generation was conserved in human monocytes [212]. In this way, exogenous administration of NO during excessive inflammation can restore endothelial NO and reduce the excessive iNOS-derived NO production and the corresponding inflammatory damages.

7. NO for respiratory distress

In addition to antiviral and anti-inflammatory properties, NO is a known vaso- and broncho-dilator and is continuously produced by the paranasal sinuses [158]. It is important in respiratory oxygenation; thus, nose-breathing is especially emphasized for marathon runners. In addition, the use of iNO is widely explored in ameliorating respiratory distress associated with many pulmonary diseases.

In 1991, Frostell et al. demonstrated that iNO administration to lambs with acute pulmonary hypertension reversed hypertension through pulmonary, but not systemic, vasodilation [213]. This apparent iNO selectivity was found to be due to the presence of hemoglobin which restricts the vasodilating effect of iNO on the pulmonary circulation [214]. In the same year, a study with 8 patients with severe pulmonary hypertension, 10 cardiac patients, and 10 healthy volunteers showed iNO to be a selective pulmonary vasodilator in humans, reducing pulmonary vascular resistance without impacting systemic vascular resistance [215]. Two years later, iNO was confirmed to induce pulmonary vasodilation and reverse hypoxic pulmonary vasoconstriction in nine healthy human volunteers without affecting systemic arterial pressure [216]. iNO has thus sparked much interest in its potential to alleviate pulmonary stress, as it provides a path toward targeting pulmonary vasculature without inducing systemic hypotension.

iNO is used for the clinical management of hypoxic respiratory failure in neonates. Several studies have shown that iNO improves oxygenation, reduces pulmonary arterial pressure, and reduces the need for extracorporeal membrane oxygenation (ECMO) in newborns with persistent pulmonary hypertension [217–222]. In 1999, the FDA approved the use of iNO for treating persistent pulmonary hypertension in newborns. iNO has also proved helpful in managing other pulmonary conditions such as hypoxemic respiratory failure, acute lung injury (ALI), and ARDS. While there is some promise, studies have shown mixed results in managing respiratory damage.

In a pediatric study of ARDS, iNO significantly increased the survival rate without ECMO and reduced the need for MV [223]. In severe ARDS in adults, both short-term and continuous iNO improved oxygenation, decreased pulmonary arterial pressure, and improved ventilation/perfusion ratio [224,225]. In fact, iNO treatment was used in one study to facilitate the transfer of ICU patients with severe hypoxia and cardiopulmonary failure to a tertiary care center; iNO significantly improved oxygenation and allowed transportation without complications, but for patients who were transported without iNO, there was a 50% mortality rate [226]. Furthermore, in premature lambs with experimentally induced hyaline membrane disease, iNO improved lung gas exchange and decreased neutrophil accumulation [227], showing promise in attenuating lung injury that often accompanies viral infection and is a complication of MV [228].

While many studies report dramatic improvements in oxygenation in the presence of NO, some have found that the positive effects may not always extend to other outcome measures. For example, in one study of ALI, while iNO improved oxygenation and reduced severe respiratory failure, it failed to alter mortality rates or the frequency of ALI reversal [229]. Low dose NO similarly was found to improve oxygenation in non-sepsis-related ALI, albeit this improvement was transient but did not affect the duration of ventilatory support needed or mortality [230]. Several systematic reviews and meta-analyses have correspondingly found iNO to produce only temporary improvements in oxygenation, with no effects on mortality or duration of ventilatory support [231–233].

These contrasting effects bring up several points:

1. We must consider methodological differences between studies, including dosage and duration of treatment, measurement methods for outcomes, and the stage of pulmonary dysfunction at which iNO treatment was begun.
2. Repeated results showing transient effects of iNO in improving oxygenation may implicate it as having potential as a rescue therapy that will be most effective in combination with other therapies for successful management rather than an end-all treatment approach, similar to the function of an epi-pen in an acute allergic response.

This may hold especially true in more severe cases of pulmonary dysfunction.

3. Although relatively fewer studies have been conducted with forms of NO delivery other than iNO, it is possible that an alternative delivery approach may have more consistent results.

7.1. NO in SARS-CoV-1 and SARS-CoV-2 pulmonary complications

Despite contrasting results with different models of lung injury, the use of iNO with SARS-CoV-1 has yielded promising results for patients suffering the pulmonary complications of the infection. Chen et al. administered iNO to 6 of 14 patients admitted to the ICU for SARS-CoV-1 as rescue therapy, finding that compared to the eight patients who did not receive iNO, it improved arterial oxygenation and reduced the need for respiratory support, and these physiological effects continued after discontinuation of treatment [234]. With the similarity between the clinical manifestation of SARS-CoV-1 and SARS-CoV-2, the results may hold promise for the current COVID-19 pandemic.

Exogenous NO administration, mainly through iNO, has received much attention in the context of COVID-19 pulmonary morbidity and has also shown mixed results.

In 2020, Zamanian et al. reported on the successful outpatient management of a 34-year-old patient with vasoreactive idiopathic pulmonary arterial hypertension exacerbated by COVID-19 using iNO [235]. iNO was administered at 20 ppm with oxygen through a nasal cannula for 12–14 h daily, with nightly gradual weaning [235]. In the eighteen days over which the patient was monitored through a telehealth treatment and monitoring program, the patient had a reduction in symptoms, an increase in 6-min-walk-test scores, and had no requirement for urgent care, emergency department (ED), or hospital visits [235].

Retrospective analyses of patients with moderate to severe COVID-19-induced ARDS show similar improvements in oxygenation and reduction in pulmonary vascular resistance upon administration of iNO at 20 ppm for 15–30 min [236], as well as at 20 or 40 ppm continuously, after cessation of which refractory hypoxemia was not observed [237]. Improvements in oxygenation were accompanied by self-reported improvements in ease of breathing following rescue therapy with multiple treatments of 160 ppm iNO for 30 min twice daily in spontaneously breathing COVID-19 patients with rapidly progressing hypoxemic respiratory failure [238]. In this study, two patients near respiratory failure were administered iNO only once and transferred to comfort care due to the severity of their condition, and both ultimately died [238]. It is unclear whether improvements for these patients could have been achieved if iNO treatment had been continued. The subjective self-reported improvements seen in this study are confirmed in another study in which the same dose and duration of iNO administration was found to improve oxygenation in hypoxemic patients and cause an immediate and prolonged reduction in the respiratory rate in tachypneic patients [239]. Twice a day high dose iNO, from 160 to 200 ppm, demonstrated similar results in a case series with six pregnant women [240]. Altogether these studies suggest a role of iNO in ameliorating respiratory distress in COVID-19.

Alleviation of respiratory distress also decreases the need for invasive respiratory support (Fig. 3); in spontaneously breathing hospitalized COVID-19 patients, 30 ppm iNO therapy for an average of 2.1 days led to more than half of the treated patients not requiring MV [241]. Studies with iNO far outnumber other NO-donating platforms in the management of pulmonary conditions in COVID-19; however, a recent study with 40 patients hospitalized in the sub-intensive care unit with COVID-19 pneumonia found that L-arginine supplementation reduced the duration of ventilation and period of stay in the sub-intensive care unit compared to patients receiving standard therapy [242]. Reducing the need for or duration of MV is a promising therapeutic avenue in reducing ventilator-associated injury in COVID-19 patients. In addition, the antimicrobial properties of NO are promising for reducing the risk of infection associated with MV, support that may be required in severe respiratory viral infection cases. Ventilator-associated bacterial infections are more associated with mortality among COVID-19 patients than non-coronavirus patients with ventilator-associated bacterial infections [70]. Application of NO-donating platforms on biomedical devices such as extracorporeal circuits and catheters decrease bacterial adhesion of gram-positive and gram-negative bacteria associated with common hospital-acquired infections [243,244] (Fig. 3).

Yet exogenous NO supplementation may not always be sufficient for outcome improvement, especially in more severe COVID-19 cases. In one case study, a severe COVID-19 patient presented with pulmonary hypertension and progressive refractory hypoxemia that ECMO could not mitigate due to backflow of oxygenated ECMO blood and increased recirculation resulting from right ventricular pressure overload [243]. Continuous iNO administration starting at 20 ppm and rising to 30 ppm resulted in a dramatic improvement, oxygen stabilization, a reduction in blood recirculation, and decreased right ventricular dimensions with corresponding increases in cardiac function 24 h after initiating treatment [243]. Still, despite initial improvements, iNO treatment was insufficient to overcome complications from multi-organ failure in the long term [243]. Similarly, in a case series with five critically ill COVID-19 patients with normal heart function and severe ARDS with respiratory failure who were treated with MV and ECMO, iNO administration at 10–20 ppm to three of the five patients reversed the illness-induced elevation of pulmonary arterial systolic pressure, which was restored to normal in two of the three patients [244]. Oxygenation was improved or stabilized by iNO treatment as well. However, whereas two of three treated patients survived, both untreated patients experienced right heart failure, decreased pulmonary arterial systolic pressure, and oxygenation and died [244]. The patient who died despite iNO treatment, experienced overwhelming complications following the elevation in pulmonary arterial systolic pressure, including multi-organ failure [244]. As the severity of COVID-19 increases, the oxygenation improvements and temporary stabilization exerted by iNO are likely insufficient to alter the outcome, emphasizing the importance of initiating treatment at earlier stages and combining it with other therapies if needed at later stages.

Some studies have also found iNO to produce limited effects regarding measures such as oxygenation. For example, in 34 ICU patients with severe COVID-19 pneumonia, administration of iNO at 10 ppm produced a 65% response rate, defined as a 20+% increase in PaO_2/FiO_2, with more responders having had lower baseline PaO2/FiO2. Yet, for both responders and non-responders, positive end-expiratory pressure, respiratory lung compliance, and driving pressure remained unchanged after iNO administration [245]. Furthermore, Longobardo et al. reported that one-time 10–20 ppm iNO administration to moderate to severe COVID-19 ARDS patients with pneumonia failed to improve oxygenation [246], as did two separate studies using a single 20–30 ppm dose of iNO in mechanically ventilated ICU patients with COVID-19 refractory hypoxemia [247,248]; oxygenation was only improved by iNO in a small subgroup of patients with right ventricular dysfunction [248]. Interestingly, a retrospective study found that iNO was more effective in improving oxygenation in non-COVID-related ARDS than COVID-related ARDS [249]. Additionally, treatment with Sildenafil, known to inhibit the cGMP-degrading activity of phosphodiesterase 5 (PDE5), thus prolonging NO-mediated vascular effects [250], has also been associated with reduced need for IMV and reduced duration of hospital stay in COVID-19 patients [251].

Several studies have also investigated iNO treatment with other agents like almitrine. Among 10 intubated COVID-19 patients with severe ARDS, the use of iNO (10 ppm) in combination with almitrine over 30 min demonstrated much greater increases in oxygenation than iNO alone [252]. In a similar study with 12 COVID-19 patients with moderate to severe ARDS requiring MV, 30 min of 10 ppm iNO with almitrine resulted in the greatest increase in oxygenation, followed closely

by almitrine alone; however, iNO independently produced no significant improvement in arterial oxygenation [253]; however, it is noteworthy that this study excluded patients with pulmonary artery hypertension.

Multiple clinical trials are currently underway for the use of NO as a treatment for COVID-19, most focusing on iNO, (Table 2). From available studies, it is evident that the effects of exogenous NO administration are not clear-cut. Some differences in observed effects may be attributable to different dosage regimens, patient characteristics, and infection stage and severity.

8. NO for management of cardiovascular complications

Decreased endothelial NO bioavailability is a feature of endothelial damage due to reduced eNOS function and eNOS uncoupling [140,254]. eNOS uncoupling leads to excess production of superoxide anions, with which NO reacts to form damaging radicals such as peroxynitrite [255–258]. The effects of this are two-fold – reducing NO bioavailability through consumption to form radicals and the endothelial damage that is caused by the radicals. In addition, the upregulation of iNOS in infection and the corresponding excessive increase in NO that is seen in severe infections seems to contribute further to damaging radical formation and reductions in endothelial NO bioavailability.

eNOS-derived NO is responsible for the maintenance of basal vasorelaxation (Fig. 3). In eNOS knockout mice, the lack of NO is associated with excessive aortic vasoconstrictor response [259], diminished acetylcholine-induced relaxation, and increased mean arterial blood pressure [260]. In a study of 10 hypertensive patients, the vasodilator responses to bradykinin and acetylcholine were significantly reduced compared to controls [261]. Furthermore, inhibition of NO synthesis by NG-monomethyl-L-arginine, while having no impact on the hypertensive patients, significantly reduced the vasodilatory response in the normal subjects; thus, NOS inhibition abolished the differences in vasodilatory response among the groups [261]. Similarly, NOS inhibition eliminated the difference in the vasodilatory response between normo- and hyper-tensive adults [262]. In fact, dysfunctional eNOS is implicated in hypertension, reviewed in Ref. [263]. Viral infections can cause endothelial damage directly and/or endothelium inflammation, resulting in diminished endothelial function and a shift to a vasoconstrictive, prothrombotic state. Restoration of NO in such a setting may ameliorate endothelial damage and reduce associated complications.

In addition to its vasorelaxant effects, NO is an important antithrombotic agent (Fig. 3). A study with dogs reported that NO decreased platelet aggregation and cyclic flow variations [264]. In normal arteries, infusion of L-NMMA and L-arginine caused arterial vasoconstriction and vasodilation, respectively; neither demonstrated any effects in experimentally induced arterial endothelium damage [264]. L-NMMA was found to increase platelet aggregation and induce cyclic flow variations, a marker of platelet aggregation, whereas L-arginine decreased platelet aggregation and reversed cyclic flow variations [264]. Considering the thrombotic complications reported in multiple viral infections, including influenza, CMV, and SARS-CoV-2 [21], the antithrombotic activity of NO is of interest in managing viral-induced vascular complications.

A recent study found significantly reduced eNOS levels in ARDS COVID-19 patients compared to those who did not have ARDS and in patients requiring MV [265]. This effect was independent of age, sex, and comorbidities, significant only with ARDS [265]; this correlates well with increased incidences of pulmonary embolism seen in COVID-19 patients [71,72]. NO donors SNP and nitroglycerin have a long history of use in cardiovascular medicine for their vasodilatory effects [266,267] and other agents such as NO-releasing aspirin (NCX 4215) have also been observed to exert antithrombotic effects [268]. Restoration of NO to the endothelium appears to be a promising approach to mitigating endothelial damage in COVID-19. An ex vivo study also found significant reductions in platelet activation and aggregation, as well as neutrophil activation through enhancement of eNOS activity [207], suggesting that in addition to its resolution of the thrombotic state, increasing NO in the endothelium will dampen excessive inflammatory response, and thus protect the endothelium from further damage. Additionally, fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), has demonstrated amelioration of COVID-19 symptoms [269,270], potentially through modulation of eNOS [271]. This agent is now in a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950) for the treatment of COVID-19.

The antithrombotic properties of NO also show promise in reducing the risks of thrombosis that accompany veno-venous ECMO [272] and other biomedical devices that patients with severe COVID-19 frequently require. In addition, the application of NO donating platforms has conferred thromboresistant properties to invasive biomedical devices [273,274], providing another pathway through which NO may be of value as a therapeutic option in severe viral infections.

9. NO delivery platforms

Exogenous administration of NO is challenging because of its high reactivity and short half-life in biological fluids. Therefore, multiple approaches have been investigated for increasing NO levels in the body. However, considering the dual nature of NO - its ability to exert both protective and cytotoxic effects based on the concentration, as well as the practical difficulties that arise with clinical administration of iNO to patients, the importance of delivery methods cannot be understated.

Current strategies of exogenous NO administration include inhalation of gaseous NO, which thus far has received the most attention in the clinical setting for lung pathologies; synthetic NO donors; delivery platforms using nanoparticles; NO-boosting agents; and dietary sources. Different synthetic donors have varied kinetics and, therefore, differences in therapeutic potential. For example, SNAP, a direct NO donor, was found to be more effective in reducing SARS-CoV-1 replication than SNP, which requires a reducing agent for NO release, underscoring the importance of the underlying mechanisms by which NO is released from the donor compounds [180]. Historically, organic nitrates like nitroglycerin and the organic salt SNP (commonly referred to as Nitropress) have been widely used as NO donors due to their therapeutic effects in angina and hypertensive crisis [129]. However, their use is limited due to unfavorable kinetics of NO release, systemic hypotensive effects, the development of tolerance with chronic use, and damaging effects on the endothelium [129]. Alternative options that circumvent these issues have been explored, including inorganic nitrates and nitrites, and different NO donors such as S-nitrosothiols, amine-based diazeniumdiolates having a diolate group, combination of donors with polymers, etc., [187,275]. The role of nanoparticles for greater stability and more controlled, sustained, and locally targeted release of NO accompanied by fewer side effects is a promising approach under investigation. Combination with different nanoparticles – chitosan, copper, etc., has demonstrated slower and more sustained NO release, lower required doses for the intended effect, greater antimicrobial actions, and greater NO flux with decreased cytotoxicity even at high concentrations that are cytotoxic when not combined with nanoparticles [273,276–278]. One study found that against two separate bacterial strains in aerobic and anaerobic conditions in human lung cells, NO-releasing chitosan oligosaccharides require considerably lower doses for antibacterial action than iNO [279]. Other reviews have extensively covered various NO delivery methods [280,281].

Still, iNO has received the most attention as a delivery method for NO due to its localized actions, starting with its approval for use in persistent pulmonary hypertension in newborns. In addition, it has been used in rescue therapy for ARDS and SARS-CoV-1; of note, the FDA has granted emergency access for its use in mild to moderate COVID-19 [187]. Although multiple clinical trials for iNO are currently underway for use in COVID-19 (Table 2), questions remain about dosage, frequency, and duration of administration - whether low dose continuous inhalation or short bursts of high dose NO like that in cigarettes

Table 2
Clinical trials for the use of NO as a treatment for COVID-19.

NCT Number	Ref	Study Title	Status	Intervention	Outcome Measures
NCT05109611	[459]	A Multicenter, Randomized, Double-blinded, Placebo-controlled, Phase 3 Clinical Efficacy Study Evaluating Nitric Oxide Nasal Spray (NONS) as Prevention for Treatment of Individuals at Risk of Exposure to COVID-19 Infection	Recruiting	Self-administered nasal spray with nitric oxide releasing solution thrice daily for four weeks	NONS efficacy in reducing the risk of COVID-19 infection and preventing severe COVID-19 in individuals at risk for COVID-19; treatment tolerability
NCT05012319	[460]	A Double-Blinded, Placebo-Controlled Parallel, Phase 3 Clinical Efficacy Study Evaluating Nitric Oxide Nasal Spray (NONS) To Treat and Prevent the Exacerbation of Infection in Individuals With Documented Asymptomatic or Mild COVID-19	Recruiting	Nitric oxide nasal spray "Enovid"	NONS efficacy in reducing: the need for urgent care, mortality, time for symptom improvement, and viral load in high-risk asymptomatic and symptomatic COVID-19 patients; treatment safety and tolerability
NCT04858451	[461]	Community Participants with COPD or Bronchiectasis and at Risk of Respiratory Viral Infections Including SARS-CoV-2: An Open-label, Multicentre Feasibility Study of an Inhaled Nitric Oxide Generating Solution (RESP301)	Recruiting	Single dose of liquid NO-producing solution RESP301 (1–6 mL dose corresponding to groups 1–6) Short-acting bronchodilator administered 10 min prior to administration of maximum tolerated dose RESP301 Self-administered RESP301 thrice daily for seven days in patients with flare-ups	RESP301 safety and tolerability among COPD/Bronchietasis patients at risk of viral infections to determine maximum tolerated dose; feasibility of self-administration and treatment compliance; efficacy in terms of recovery, timing to recovery, prevention of exacerbations, patient-reported symptoms
NCT04842331	[462]	A Randomised, Multicentre Post-exposure Prophylaxis (PEP) Clinical Trial Evaluating RESP301, an Inhaled Therapy for Treatment of Lung Infections, for Prevention of Onward Transmission of Viral Infections Including SARS-CoV-2 to Household Members	Recruiting	7-day treatment with NO-producing liquid solution RESP301	Prevention of onward transmission of SARS-CoV-2 infection among household members; tolerability; compliance with treatment schedule
NCT04606407	[463]	Prospective, Open-label, Randomized, Multi-Center Study for Safety and Efficacy Evaluation of Inhaled Nitric Oxide (NO) Given Intermittently to Adults With Viral Pneumonia	Recruiting	150 ppm iNO 4 times daily for 40 min delivered using device LungFit™ for up to seven days in addition to standard of care	iNO safety among patients with viral pneumonia (including from SARS-CoV-2); efficacy in terms of time to resolve fever, time to eliminate supportive oxygen requirement, ICU admissions, oxygen saturation
NCT04601077	[464]	Pilot Study: The Evaluation of Nitric Oxide Generating Lozenges on Outcome in Newly Diagnosed COVID-19 Patient of African American and Hispanic Origin	Recruiting	30 mg NO lozenges taken twice daily for 30 days	Safety and tolerability of NO lozenges in terms of side effects including low blood pressure, dizziness; effects of therapy on incidence of hospitalization, ICU admission, intubation, dialysis, death
NCT04476992	[465, 466]	A Safety Study on the Use of Intermittent Versus Continuous Inhalation of NO in Spontaneous Breathing COVID-19 Patients	Active, not recruiting	200 ppm NO twice daily for 30 min (high concentration group) Twice daily 200 ppm + 20 ppm NO taken continuously (high concentration + continuous low dose group)	Safety of NO treatment in terms of methemoglobin levels between groups, rate of acute kidney disease; efficacy in terms of improvement in oxygenation, negativization of SARS-CoV-2 RT-PCR, time to recovery, reduction in inflammatory markers, lung function in hypoxemic COVID-19 patients ***Findings:*** intermittent high dose therapy iNO therapy combined with continuous low-dose NO supplementation was safe and significantly improved physiological interactions in the heart-lung blood circulation system
NCT04460183	[467]	An Open-label, Adaptive Randomized, Controlled Multicenter Study to Evaluate the Efficacy and Safety of RESP301 Plus Standard of Care (SOC) Compared to SOC Alone in Hospitalized Participants With COVID-19 WHO Grade 3&4 (NOCoV2)	Completed	Inhaled RESP301 (NO-producing solution) thrice daily by nebulizer for up to ten days in addition to standard of care	Treatment safety in COVID-19 patients; efficacy in reducing progression to severe COVID-19 in terms of progression/improvement in WHO ordinal scale, time to progression/improvement, change in oxygen saturation, change in National Early Warning Score (NEWS) 2 symptom score
NCT04397692	[468]	Inhaled NO for the Treatment of COVID-19 Caused by SARS-CoV-2 (US Trial)	Recruiting	80 ppm iNO 4 times a day, 40 min using device LungFit™ in addition to the standard of care	Treatment safety; efficacy in terms of time to requirement of non-invasive ventilation/high flow nasal cannula/intubation, time to oxygen saturation stabilization, change in viral load, need for supplemental oxygen, hospital length of stay, mortality rate
NCT04383002	[469]	Use of High Dose Inhaled Nitric Oxide in Intubated Patients Admitted With COVID-19	Completed	160 ppm iNO for 6 h, once a day for 2 days	Treatment safety; efficacy in terms of reversing virus burden COVID-19 patients requiring MV (measured by COVID-19 PCR status)
NCT04337918	[470]	Multi-Center, Randomized, Controlled, Phase II Clinical Efficacy Study Evaluating Nitric Oxide Releasing Solution Treatment	Completed	Daily self-administration of nitric oxide releasing solution (NORS) (Nitric Oxide Gargle, Nitric Oxide Nasopharyngeal	Efficacy of NORS in prevention of COVID-19 infection and progression among healthcare workers in terms of swab positive COVID-19

(*continued on next page*)

Table 2 (*continued*)

NCT Number	Ref	Study Title	Status	Intervention	Outcome Measures
		for the Prevention and Treatment of COVID-19 in Healthcare Workers and Individuals at Risk of Infection		Irrigation, Nitric Oxide Nasal Spray) for 14 days	results, virucidal effects, reduction of clinical symptoms and speed of recovery; treatment tolerability
NCT04312243	[471]	Nitric Oxide Gas Inhalation for Prevention of COVID-19 in Healthcare Providers	Active, not recruiting	160 ppm iNO for 15 min before and after work shift	Efficacy of intermittent iNO in preventing COVID-19 among healthcare providers
NCT04306393	[472]	Nitric Oxide Gas Inhalation Therapy for Mechanically Ventilated Patients With Severe Acute Respiratory Syndrome Caused by SARS-CoV2: a Randomized Clinical Trial.	Active, not recruiting	80 ppm iNO for 48 h followed by 40 ppm and continued weaning until PaO_2/FiO_2 ≥300	Efficacy of treatment in improving oxygenation in patients with hypoxic SARS-CoV-2 in terms of change in oxygenation, time to reach normoxia, survival, viral load, need for MV/mechanical circulation, length of ICU stay/hospital stay/MV requirement
NCT04305457	[473]	Nitric Oxide Gas Inhalation Therapy in Spontaneous Breathing Patients With Mild/Moderate COVID-19: a Randomized Clinical Trial	Active, not recruiting	140–180 ppm iNO twice daily for 20–30 min through noninvasive CPAP system for 14 days	Efficacy of early-stage iNO administration in preventing progression of SARS-CoV-2 in terms of reduction in the requirement for MV and intubation, mortality, time to clinical recovery, negative conversion of COVID-19 RT-PCR
NCT04456088	[474]	Inhaled NO for the Treatment of COVID-19 Caused by SARS-CoV-2	Withdrawn	80 ppm iNO for 40 min four times a day for up to 14 days + standard supportive care (group 1) 150 ppm iNO as above, (group 2)	Treatment safety; efficacy in terms of time to deterioration measured by requirement of non-invasive ventilation/high flow nasal cannula/intubation or death, time to stable oxygen saturation
NCT04443868	[475]	Double-Blinded, Placebo-Controlled Parallel, Phase II Clinical Efficacy Study Evaluating NORS To Treat and Prevent the Exacerbation of Infection in Individuals With Documented Mild COVID-19	Withdrawn	NO nasal spray + nasal irrigation for 14 days	Treatment tolerability; efficacy of treatment in terms of reducing SARS-CoV-2 viral load, preventing progression of COVID-19, patient reported outcomes
NCT04421508	[476]	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Pulsed, Inhaled Nitric Oxide (iNO) Versus Placebo in Subjects With Mild or Moderate Coronavirus (COVID-19)	Terminated	Pulsed iNO through nasal cannula	Safety of treatment; efficacy in terms of mortality, respiratory failure occurrence, recovery and survival, clinical status, hospitalization duration
NCT04401527	[477]	Treatment of Lung Injury From COVID-19 Infection With Intravenous Sodium Nitrite: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Clinical Study	Withdrawn	Continuous sodium nitrite IV infusion (30 mg/mL)	Safety of treatment; efficacy in terms of survival with unassisted breathing, and survival without hospitalization, MV, intensive care, ECMO
NCT04398290	[478]	Randomized Controlled Trial Of A Delivered Continuously By Nasal Cannula For The Treatment Of Patients With COVID-19 And Mild To Moderate Hypoxemia Requiring Supplemental Oxygen	Withdrawn	Continuous iNO Pulse (250 mcg/kg ideal body weight (IBW)/hour) with supplemental oxygen for up to 28 days	Safety of treatment; efficacy in terms of progression of SARS-CoV-2 respiratory failure, duration of hospitalization, time until resolution of hypoxemia, mortality
NCT04388683	[479]	Prevention of COVID-19 Progression Through Early Administration of Inhaled Nitric Oxide	Terminated	iNO using the INO pulse device at a dose of 125 mcg/kg IBW/hr (approximately 20 ppm)	iNO ability to prevent progression of COVID-19 among hospitalized patients
NCT04338828	[480]	Nitric Oxide Inhalation Therapy for COVID-19 Infections in the Emergency Department	Terminated	iNO 140–300 ppm for 20–30 min	Efficacy of treatment in terms of preventing COVID-19-related ED return visits, inpatient hospitalization rate, intubation requirement, mortality
NCT03331445	[481]	An Open Label Safety Study of Inhaled Gaseous Nitric Oxide (gNO) for Adults & Adolescents With Non-Tuberculous Mycobacteria, Burkholderia Spp, Aspergillus Spp and Corona-like Viral (Sub-Study) Infections	Terminated	160 ppm iNO	Safety of treatment; antimicrobial and antiviral effects, efficacy of treatment in terms of reduction of mortality, clinical improvement, respiratory symptoms, reduction of requirement for respiratory interventions, quality of life

[197]. Additionally, the requirement for skilled technicians, attributed financial costs, and possible adverse effects, including methemoglobinemia [282], etc., have been cited as potential obstacles to the clinical use of iNO. However, developing alternatives such as NONS, still requiring Phase 3 investigation, may reduce some of these challenges. Other approaches include compounds such as R-107, a NO-releasing pyrrolidine (2,2,5,5-tetramethyl-3-((nitrooxy)methyl)pyrrolidin-1-yl acetate) [283], and IFMC, an integrated functional mineral crystal composed of haematite (Fe_2O_3), olivine (Mg_2SiO4 and Fe_2SiO4), rhodolite ($MnCO_3$), zincite ($ZnCO_3$) that increases intravascular NO [284], and PDE5 inhibitors to prolong the effects of NO in the vasculature [285], and dietary supplementation through foods rich in inorganic nitrates, such as beet juice [98,286].

10. H_2S homeostasis

H_2S is a foul-smelling gas that has been present in the earth's atmosphere since the beginning of time and historically has been regarded as a toxic environmental pollutant [287]. However, in 1996, Abe and Kimura reported that H_2S was an endogenous signaling molecule [288]. Since then, its role in most mammalian tissues has been established; for example, it has vasorelaxant effects [289], it has protective properties in an animal model of myocardial ischemia-reperfusion injury [290] and can act against pathogens and oxidative stress [291].

H_2S is produced endogenously from L-cysteine and homocysteine by the enzymes cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST) in cooperation with cysteine aminotransferase (CAT) [292]. There is evidence that CSE and CBS are dependent on the Ca^{2+}/calmodulin complex [293,294]. CSE is the predominant enzyme in the cardiovascular system,

heart, vascular smooth muscle, endothelium, liver, and kidneys. In contrast, CBS is mainly expressed in the central nervous system [295,296]. The respiratory system expresses both CSE and CBS, and the endothelium contains all three enzymes [297,298]. H_2S can also be produced through nonenzymatic pathways, including through the reduction of sulfates by gut bacteria [299] and by liberation from the acid-labile and sulfur sulfane storage pools [292], pathways that become important during hypoxia [297].

There is extensive crosstalk between NO and H_2S. In 2001, Zhao et al. reported concentration-dependent upregulation of H_2S production in the rat aortic tissue through administration of SNP and upregulation of CSE transcriptional expression by SNAP [300]. Patel et al. reported similar findings in rat fetal tissue [301]. H_2S also impacts NO bioavailability, essential in resolving inflammation and endothelial damage, as discussed below.

11. H_2S signaling and functions

H_2S can be released immediately upon production or stored in acid-labile or sulfane sulfur pools to be released upon stimulation [302]. As a small molecule that is permeable to the lipid bilayer [303], H_2S diffuses across cell membranes, primarily exerting its effects through S-sulfhydration, a protein modification on the cysteine residues of its targets [292,304]. In the vascular endothelium, muscarinic receptor activation stimulates CSE-dependent H_2S production [305], which activates ATP-dependent vascular potassium channels by S-sulfhydration, causing smooth muscle hyperpolarization, resulting in vasodilation [300,306]. H_2S also increases NO bioavailability, another mechanism contributing to its vasodilatory activity; H_2S upregulates eNOS activity by S-sulfhydration, increasing eNOS dimerization, promoting eNOS activation by phosphorylation through several kinases (Akt/PKB, AMPK, PKA, PKC, PKG, and CaMK-2) [307], and countering NO-mediated inhibition of eNOS [136]. CSE-dependent H_2S production is crucial to endothelium function, and CSE knockout mice exhibit hypertension and markedly reduced endothelium-dependent vasorelaxation [293]. H_2S also acts as an antioxidant both by acting as reactive species scavenger, including peroxynitrite [308] and upregulating glutathione (GSH) and superoxide dismutase (SOD) [48]. Other functions of H_2S include effects on mitochondrial function and cAMP-dependent activation of NMDA receptors to play a role in long-term potentiation in the nervous system [24].

Like NO, the effects of H_2S are concentration-dependent - whereas, at lower concentrations, H_2S may be protective, excessive H_2S contributes to cytotoxicity, including inhibition of cytochrome C oxidase, halting mitochondrial respiration [24,309]. H_2S has been observed to inhibit leukocyte adhesion to the endothelium, reduce the expression of adhesion molecules, attenuate the production of pro-inflammatory agents such as monocyte chemoattractant protein 1 (MCP-1) and TNF-α, inhibit the NF-κB pathway, and increase the release of anti-inflammatory cytokine IL-10 [310–314]. On the other hand, pro-inflammatory actions of H_2S have also been reported with the use of H_2S-releasing salts such as NaHS, which increases the pro-inflammatory markers TNF-α and MPO activity [315]. Notably, high H_2S concentrations have also been reported in septic shock patients [315].

12. Dysregulation of H_2S

H_2S concentration is an important determinant of the body's defense against disease. Dysregulation of H_2S levels has been described in the pathogenesis of various conditions ranging from cardiovascular diseases to septic shock [316,317]. Reduced H_2S levels are proposed as a contributor to the pathogenesis of asthma, and rescue with exogenous H_2S was found to alleviate asthma severity in two separate animal models [318,319]. Similarly, serum H_2S was reduced by 36% among patients with community-acquired bacterial pneumonia compared with healthy controls [320]. In contrast, elevated H_2S levels are seen in septic and endotoxic shock and are associated with adverse outcomes, with improvements upon H_2S inhibition [315,317,321,322]. Viral infection at different stages and severities can be characterized by different H2S concentrations, with excessive H_2S as seen in sepsis and depleted H_2S resulting in increased susceptibility to the consequences of infection. In one study, RSV infection was found to reduce H_2S production and CSE mRNA and protein expression in airway epithelial cells 24 h after infection [323]. Among COVID-19 patients, both increased and decreased H_2S levels have been observed, although the number of studies is limited.

Among a group of 74 COVID-19 pneumonia patients admitted to the hospital for lower respiratory infection, Renieris et al. investigated the association between serum H_2S levels and mortality, finding that 28-day survivors had higher serum H_2S levels on days 1 and 7 of admission, compared to non-survivors, with day 1 total sulfide pool (representing H_2S levels) lower than a cutoff of 150.44 μM having 11.11 times the odds of 28-day mortality [324]. Furthermore, decreases of greater than 36% in serum H_2S levels between day 1 and 7 was associated with more significant 28-day mortality [324]. These findings suggest depletion of H_2S during a SARS-CoV-2 infection as an indication of greater infection severity.

A study with COVID-19 viral pneumonia patients who had received a positive COVID-19 test within the past 14 days found a significantly reduced plasma sulfide pool [149]. Moreover, monitoring the change in the sulfide pool in a control patient who later contracted SARS-CoV-2 and recovered revealed a corroborative decrease in total sulfide levels upon infection followed by an increase to original levels; this corresponded to a reduction in symptoms and recovery [149]. Depletion of total sulfide levels (a representation of H_2S concentration [325]) during infection was observed here. In contrast with the findings by Renieris et al. [323], however, this study also found an opposing trend between mortality and H_2S levels; non-survivors had increased levels of H_2S compared to survivors, and similarly, severe COVID-19 illness was associated with significantly increased levels of H_2S compared to mild to moderately severe cases [149]. Unlike the first study, however, there is no clear indication of the point in time when mortality was monitored.

The reason for the contradictory results between the two studies is unclear. Timeline regarding monitoring the infection and mortality and categories of patients chosen for comparative analyses may explain some differences. More studies are needed to understand the changes in H_2S availability at different times and severities of viral infection. Despite discrepancies, previously documented dysregulation of H_2S in infectious and non-infectious conditions and dysregulation described in these two studies indicate that regulation of H_2S levels, either through restoration or reduction, may be a way to alleviate SARS-CoV-2 infection.

13. H_2S as an antiviral: therapeutic potential in early-stage therapy

Compared to NO, research on the antimicrobial properties of H_2S is relatively limited. Numerous studies conducted with organosulfur molecules, including garlic polysulfides and compounds isolated from medicinal plants, found these to have antiviral properties; only later were these compounds discovered as H_2S donors [326]. Since then, the use of known H_2S donors has verified the antiviral actions of H_2S against multiple viruses and suggests their use in early-stage viral infections.

13.1. H_2S as an antiviral against a range of viruses

The first line of defense provided by H_2S enhances the ability of the body to remove harmful particles that have not yet had the opportunity to inflict damage. In addition, H_2S increases mucociliary clearance, an important defense against airborne pathogens, by increasing the clearance of harmful particles through the disruption of sulfide bonds [327,328] and stimulation of electrolyte absorption to reduce mucus viscosity [329,330] (Fig. 4). H_2S also acts as a more direct antiviral agent against

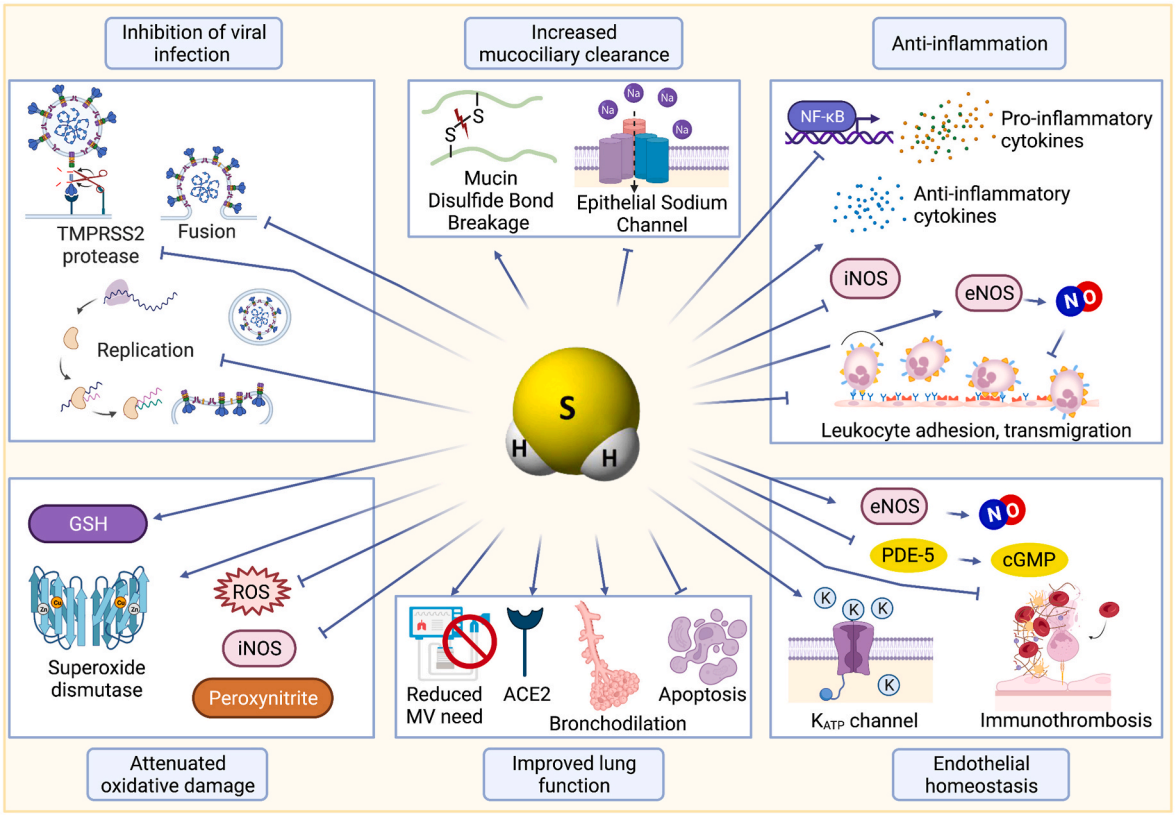

Fig. 4. Role of H_2S in COVID-19. H_2S inhibits viral entry by downregulating host TMPRSS2 which prevents S protein activation, and may prevent binding to the ACE2 receptor through disruption of ACE2 disulfide bonds. Additionally, H_2S inhibits genome and protein replication, assembly, and release of several viruses likely including SARS-CoV-2. H_2S increases mucociliary clearance as a host defense against respiratory pathogens by reducing mucus viscosity and increasing mucus hydration, by breaking mucin disulfide bonds and inhibiting Na^+ reabsorption through epithelial Na^+ channels, respectively. During later stages of infection, H_2S serves a protective role by inhibiting pro-inflammatory transcription factor NFκB, reducing the release of proinflammatory cytokines while increasing anti-inflammatory cytokines and promoting inflammation resolution. H_2S inhibits iNOS while upregulating eNOS, and inhibits leukocyte adhesion and transmigration. In the endothelium, in addition to increasing eNOS function, H_2S also inhibits PDE5, increasing NO bioavailability and its anti-inflammatory, anti-thrombotic, and vasorelaxant effects. H_2S directly induces vasorelaxation through K^+ channel stimulation and exerts anti-thrombotic effects. In the lungs, H_2S reduces apoptosis, improves ventilation and perfusion through broncho- and pulmonary vaso-dilation, respectively, protects against Ang II-induced lung injury by upregulating ACE2, and reduces the need for MV, reducing MV-related lung injury. H_2S also upregulates antioxidant machinery including GSH and SOD, directly scavenges peroxynitrite and ROS, and inhibits iNOS and the production of ROS.
Abbreviations: ACE2, angiotensin converting enzyme 2; Ang II, angiotensin II; eNOS, endothelial nitric oxide synthase; GSH, glutathione; H_2S, hydrogen sulfide; iNOS, inducible nitric oxide synthase; K^+, potassium ion; MV, mechanical ventilation; Na^+, sodium ion; NFκB, nuclear factor kappa light chain enhancer of activated B cells; NO, nitric oxide; PDE5, phosphodiesterase 5; ROS, reactive oxygen species; S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome 2; SOD, superoxide dismutase; TMPRSS2, transmembrane serine protease 2.

a range of enveloped RNA viruses by inhibiting viral replication. In vitro administration of GYY4137, a slow-releasing H_2S donor, has been found to dose-dependently inhibit viral replication of multiple viruses, including strains of influenza A and B, Crimean-Congo hemorrhagic fever virus (CCHFV), Rift Valley fever virus (RVFV), Recombinant Zaire Ebola Virus (EBOV), Far-eastern tick-borne flavivirus (RSSEV), as well as paramyxoviruses, which include (RSV, human metapneumovirus (hMPV), and Nipah virus (NiV) [331,332]. Conversely, inhibition of CSE by dl-propargylglycin (PAG) led to a 3- to 4-fold increase in the formation of RSV viral infectious particles, providing evidence for the antiviral actions of endogenously produced H_2S [332]. A separate study using the cysteine-based H_2S donor XM-01 confirmed inhibition of NiV, HSV-1, RSV, a strain of influenza, and vesicular stomatitis (VSV) by inhibiting membrane fusion through disruption of the viral membrane; these effects were much more potent than seen with NaHS and GYY4137 [333].

The antiviral actions of H_2S donors were confirmed in vivo using mouse models of RSV. In one study, CSE knockout mice had a 50% increase in RSV viral titer compared to wild-type mice with functional CSE, and administration of GYY4137 to these mice attenuated the exacerbation of the infection [334]. Another study with a thiol-activated *gem*-dithiol-based H_2S donor, TAGDD-1, which releases H_2S in the presence of thiols such as glutathione, was found to reduce RSV replication in vitro significantly and in mice through intranasal delivery [335].

The mechanism through which H_2S can inhibit viral infection is diverse and may vary according to the identity of the virus. In one study, the H_2S donor XM-01 disrupted the viral membrane without impacting the host cell, inhibiting membrane fusion and, therefore, viral entry [333]. In addition to inhibiting access, H_2S also inhibits viral replication (Fig. 4). Downregulation of viral mRNA, RNA, and protein expression has been seen in some viruses, suggesting genome and protein replication inhibition as one antiviral mechanism [331,332]. However, downregulation of viral genomic material and proteins were not seen in all the viruses treated with H_2S donors, suggesting a different antiviral mechanism; further investigation revealed GYY4137 to inhibit virus syncytium formation and likely affect viral assembly/release [332]. H_2S is also responsible for upregulating GSH levels [336], an antioxidant with antiviral actions that extend beyond its function as a ROS scavenger [337]. Antiviral effects of H_2S against HSV type 1 (HSV-1) [338] and Sendai virus [339] are documented in vitro and mouse models of influenza [340].

Despite the broad range of antiviral activity that has been demonstrated throughout various studies, the antiviral actions of H_2S may not extend to all viruses. For example, in one study, XM-01 was unable to inhibit infection by rotavirus, suggesting that H_2S is unable to target non-enveloped viruses [333]. This is consistent with the finding that XM-01 inhibits infection by inhibiting membrane fusion [333]; unlike enveloped viruses, non-enveloped viruses cannot use membrane fusion to enter the host [341–343], therefore H_2S would be unequipped to inhibit infection from non-enveloped viruses. Considering the tremendous antiviral actions against enveloped viruses, however, H_2S therapy is promising for translation to SARS-CoV-2, an enveloped RNA virus.

13.2. H_2S as an antiviral defense against COVID-19

Indeed, H_2S has also demonstrated direct antiviral activity against SARS-CoV-2 through interference with viral entry using the ACE2 and TMPRSS2 machinery. In bronchial and pulmonary epithelial cells, using both fast-releasing and slow-releasing H_2S donors, NaHS and GYY4137, respectively, induced down-regulation of TMPRSS2 mRNA and protein expression (Fig. 4) without any significant effects on ACE2 expression [344]. NaHS was further found to reduce TMPRSS2 mRNA and protein levels in human nasal primary epithelial cells and human alveolar cells, indicating that H_2S will work as an antiviral in the upper and lower respiratory tracts [344]. Additionally, reported disruption of disulfide bonds, for example, in mucin and activation of vascular endothelial growth factor receptor 2, has provided the basis for suggesting that H_2S may also disrupt sulfides of the host ACE2 receptor and impair binding and internalization of the virus [345].

Upregulation of GSH by H_2S [336] may be another mechanism for inhibiting SARS-CoV-2 infection. Using high-throughput artificial intelligence-based binding affinity, GSH has been predicted to interact with and possibly inhibit ACE2 and TMPRSS2, inhibiting SARS-CoV-2 entry into the host [346]. N-acetylcysteine (NAC), which generates both GSH and H_2S [347,348], has been suggested as a therapy for COVID-19 [48]. One study found that NAC was unable to inhibit cell fusion; however, NACA, a more potent derivative of NAC, was, in fact, successful in inhibiting S protein binding to ACE2, syncytia formation, cell fusion, and viral entry in vitro, and demonstrated similarly promising results in infected mice transfected with human ACE2 and TMPRSS2 [349].

Studies of H_2S and COVID-19 are currently limited and complicated by concerns about delivery platforms and potential toxicities. However, from the antiviral properties that have been demonstrated against other enveloped viruses and some preliminary studies that have been done with COVID-19, it appears that H_2S holds promise with the need for more research in this arena.

14. H_2S for management of hyperinflammation

In addition to acting as an antiviral, H_2S protects against inflammatory and oxidative damage, making it of interest in later-stage therapy of viral infections characterized by hyperinflammation. Consistent with the anti-inflammatory functions of H_2S, serum H_2S has been found to negatively correlate with inflammatory marker CRP among individuals with community-acquired lower respiratory tract infection and chronic obstructive pulmonary disease (COPD) [320]. As discussed previously, H_2S inhibits leukocyte adhesion to the endothelium, reduces the expression of adhesion molecules, inhibits the NF-κB pathway, attenuates the production of pro-inflammatory agents, and increases the release of anti-inflammatory cytokines [310–314,350,351] (Fig. 4). As eluded to above, it also contributes to oxidant neutralization through scavenging of NO derivative peroxynitrite [308,352,353], upregulation of antioxidant machinery like GSH [336], superoxide dismutase [354, 355], and reduction of superoxide anion production [356] (Fig. 4).

Several studies have demonstrated that H_2S reduces experimentally induced inflammation. For example, in a rat model of aspirin-induced leukocyte adhesion in mesenteric venules, adhesion and infiltration into a rat pouch were promoted by CSE inhibition, whereas NaHS and Na_2S inhibited both adhesion and infiltration [312]. Accordingly, in TNF-α-induced human umbilical vein endothelial cells (HUVEC), treatment with NaHS showed marked suppression of leukocyte adhesion molecules ICAM-1, VCAM-1, and E-selectin [357]. The anti-inflammatory and antioxidant properties of H_2S have also been demonstrated in several animal models. In experimentally induced states of oxidative stress and inflammation, H_2S donors attenuated tissue inflammation, reduced production of IL-6, TNF-α, ROS, macrophage infiltration, and neutrophil transmigration through the endothelial barrier, and decreased cell apoptosis. At the same time, it increased IL-10, overall ameliorating disease severity [334,351,358–362].

The anti-inflammatory effects of H_2S are partially attributable to crosstalk with iNOS. The expression of iNOS is induced by some toxins and pro-inflammatory cytokines, which activate the transcription factor NF-κB [363]. As previously mentioned, excessive iNOS activity during hyperinflammation can lead to increased production of NO, superoxide anions, and the formation of damaging derivatives, resulting in inflammatory damage and reduced NO bioavailability. H_2S inhibits NF-κB, reducing iNOS expression [313,314] (Fig. 4). This effect has been demonstrated in vitro and in vivo and is a significant aspect of inflammation resolution. Administration of L-cysteine to LPS-stimulated macrophages significantly repressed iNOS expression and iNOS-derived NO production, which was reversed upon CSE inhibition [314]. The addition of NaHS or a solution prepared by bubbling pure H_2S in distilled water to the same system also inhibited iNOS expression and iNOS-derived NO production; however, CSE inhibition in this system had minimal effects [314]. A similar finding was reported in a mouse model; iH_2S (80 ppm for 6 h) decreased inflammatory cytokine production, reduced neutrophil infiltration, and attenuated NO metabolite levels that were increased by the LPS challenge, and improved survival [364]. In a murine model of lung injury induced by cotton smoke inhalation, inhalation of H_2S at 80 ppm for 6 h reduced iNOS expression [365]. In addition to reducing iNOS expression, H_2S donors have been found to restore NO to the endothelium by upregulating eNOS activity [360], reinstating the anti-inflammatory defense of NO in the vasculature (Fig. 4). These studies provide extensive evidence of H_2S as an anti-inflammatory, an antioxidant mediator that scavenges oxidants, upregulates defense machinery and curtails any excessive iNOS activity that may be elicited in an uncontrolled inflammatory response.

It is noteworthy that several studies have noted pro-inflammatory actions of H_2S; in fact, NaHS was used to induce pulmonary inflammation in mice [366]. In LPS-induced inflammatory response, administration of NaHS increased lung inflammation, neutrophil infiltration, and TNF-α levels in mice; in contrast, CSE inhibition resulted in marked anti-inflammatory activity [315]. The contradictory findings are potentially due to the nature of the H_2S donors; when administered to LPS-treated murine macrophages, the slow-releasing H_2S donor GYY4137 dose-dependently and consistently inhibited the release of pro-inflammatory mediators. The fast-releasing donor NaHS exerted a biphasic effect, suppressing pro-inflammatory mediators at lower concentrations and doing the opposite at higher concentrations [367]. Indeed, when comparing studies reporting anti-inflammatory vs. pro-inflammatory properties of H_2S donors, studies using fast-releasing H_2S donors have mainly reported pro-inflammatory actions, whereas studies with newer, slow-releasing GYY4137 have mostly found H_2S to exert anti-inflammatory effects, further details are provided in Ref. [368].

Regarding cytokine storm described in some COVID-19 cases, H_2S therapy might be promising for resolving inflammation, pending more rigorous investigation with SARS-CoV-2. In the Renieris et al. study, which found low H_2S levels to be associated with greater COVID-19 mortality, H_2S was also negatively correlated with pro-inflammatory markers procalcitonin, IL-6, and CRP, all of which were found elevated in non-survivors compared to survivors [324]. Following these

findings, higher IL-6 levels are associated with greater COVID-19 severity [369], and two separate retrospective studies conducted in Wuhan, China, found IL-6 to be higher in non-survivors compared to survivors of COVID-19 [74,370]. These findings suggest that the IL-6 receptor antagonist tocilizumab to combat cytokine storm in COVID-19 [371]. The same rationale may support H_2S use in COVID-19 patients. In one study, intravenous administration of NAC, known to increase both H_2S and GSH levels, to 10 COVID-19 patients on a respirator, including one patient with glucose 6 phosphate dehydrogenase deficiency, allowed removal of the respirator and decreased inflammatory markers in all patients [372]. The anti-inflammatory properties of H_2S also promise to ameliorate respiratory and cardiovascular complications of viral infections by reducing inflammation in these systems.

15. H_2S for management of respiratory complications

Respiratory compromise is often induced by viral infections and is one of the critical points of intervention to prevent mortality. Cytokine storm, as described in several viral infections, frequently causes lung injury characterized by neutrophil infiltration and chronic collagen deposition resulting in fibrosis [12]. Being an antiviral, anti-inflammatory, and bronchodilating agent, H_2S therapy may be important for conditions characterized by pulmonary damage (Fig. 4). In a mouse model of RSV infection, administration of GYY4137 reduced pulmonary inflammation and viral load, combining its antiviral and anti-inflammatory effects as a defense of the pulmonary system [334]. The protective effect was further demonstrated in CSE-knockout mice with increased sensitivity to methacholine challenge and showed increased airway resistance and symptom severity; these were rescued by GYY4137 administration [334].

H_2S has also demonstrated improvement in lung pathology in ALI models induced by non-infectious sources, underscoring its protective effects apart from its antiviral activity. For example, in a murine model of burn and smoke-induced ALI, parenteral post-treatment with NaHS decreased pro-inflammatory interleukins, increased anti-inflammatory IL-10 (a known inhibitor of iNOS [131]), reduced oxidative damage, and histological analysis showed improved lung condition – increasing median survival time and reducing mortality overall [310]. Additionally, in rat models of oleic acid-induced ALI, a widely used model that resembles human ARDS [373], treatment with NaHS significantly increased PaO2 levels, attenuated alveolar epithelial cell apoptosis and proapoptotic Fas protein expression, reduced pulmonary wet/dry weight ratio, and alleviated the magnitude of ALI [362,374].

Reducing the need for MV by reducing pulmonary damage, and lessening VILI in cases where MV is necessary, is another major point of interest in infection-induced respiratory compromise. Pre- and post-treatment with H_2S (NaHS, iH_2S) attenuated VILI in mice and rats, decreased pulmonary inflammation, oxidative stress, autophagy, and ER stress, and improved oxygenation [375–378]. Studies have demonstrated that the protective effects of H_2S against VILI are mediated through multiple pathways, including induction of cyclooxygenase-2 and its product prostaglandin J2 and their downstream effects [379]; activation of the Akt/PI3K pathway, and resulting GSH induction [380]; and inhibition of the pro-inflammatory transcription factor NF-κB [381]. H_2S also downregulates genes that promote inflammation and oxidative stress while increasing anti-inflammatory and antiapoptotic genes such as suppressor of cytokine signaling 3 (Socs3), activating transcription factor 3 (Atf3), and growth arrest and DNA-damage-inducible 45 alpha (Gadd45a) [382]. Furthermore, a study reported that NaHS prevent MV-induced diaphragmatic dysfunction, which results in challenges in weaning patients from MV [383].

While studies of H_2S use with COVID-19 are lacking due to its relative under-exploration compared to NO, and questions about its safety remain primarily unanswered, positive results from past studies may indicate its potential in reducing infection and VILI in SARS-CoV-2 as well. Considering reports of reduced H_2S levels in COVID-19 patients [149] and decreases in H_2S levels being associated with higher mortality [324], restoration of H_2S may rescue patients as it has with RSV-infected CSE knockout mice [334]. Besides its anti-inflammatory and antiviral actions in protecting the lungs, H_2S has an additional feature relevant particularly to SARS-CoV-2 infection; H_2S upregulates the ACE2 protein that is of central importance in COVID-19. As discussed earlier, SARS-CoV-2 enters the host using the ACE2 receptor [42,43] that is widely expressed throughout the body including in the respiratory tract [46]. Upon infection, the ACE2 receptor is downregulated by SARS-CoV-2, contributing to increased pro-inflammatory and vasoconstrictive mediators and related lung injury [49,51], and restoration of ACE2 has demonstrated the ability to lessen lung injury [52]. Interestingly, H_2S upregulated ACE2 expression in atherosclerotic mice [384], suggesting its potential as a post-infection respiratory therapy for COVID-19.

While direct H_2S donor molecules or iH_2S have not been used in the management of COVID-19 patients, multiple studies with promising results have used compounds that have elsewhere demonstrated H_2S-boosting properties. The most extensive of these is NAC. Liu et al. describe the successful management of a critical COVID-19 pneumonia patient with NAC inhalation after progressive deterioration despite therapy with antibiotics, antivirals, and respiratory support, followed by endotracheal intubation and MV; with persisting refractory hypercapnia after initiation of MV, NAC inhalation was utilized as a rescue therapy [385]. The patient gradually improved and was discharged from the hospital [385]. Other studies with NAC in COVID-19 patients have reported increases in oxygenation, reduction in lung damage and inflammatory markers, removal from the respirator and veno-venous ECMO, and overall clinical improvement [372,386].

Additionally, sildenafil, a PDE5 inhibitor that prolongs NO effects, has shown promising results in COVID-19 patients. Among COVID-19 patients admitted to the emergency department with perfusion abnormalities as indicated by CT scan, treatment with sildenafil 25 mg thrice daily for seven days was associated with decreased use of IMV and duration of hospital stay [251]. Sildenafil has also shown a dose-dependent increase in H_2S production in the human bladder dome that is reversed by CSE and CBS inhibitors [387].

16. H_2S for management of vascular complications

H_2S has a protective function in the vascular endothelium, making it important in viral infections associated with vascular complications arising from endothelial dysfunction. As indicated, H_2S acts as a vasodilator by S-sulfhydration of ATP-dependent potassium channels [300,306] and increases NO bioavailability through upregulation of eNOS activity [136] (Fig. 4). H_2S also inhibits leukocyte and platelet adhesion in the basal state. These functions designate H_2S as a crucial molecule for the maintenance of the endothelium, disruptions in H_2S bioavailability can lead to endothelial dysfunction much the same way as NO depletion does.

Experimental models of H_2S deficiency show impaired endothelium-dependent vasodilator actions and hypertensive states corresponding to endothelial dysfunction. For example, CSE knockout mice treated with L-NAME and indomethacin exhibited a 60% reduction in cholinergic vasorelaxation of the mesenteric arteries. However, NOS/COX contributes only 20–25% of cholinergic vasorelaxation in the mesenteric arteries [306]. In another study, CSE deficient mice displayed impaired endothelium-dependent vasorelaxation and developed hypertension despite functional eNOS, whereas exogenously administered NaHS exerted dose-dependent decreases in blood pressure [293]. These studies demonstrate that H_2S deficiency impairs endothelial response to stimuli independent of NO levels.

Similarly, a study with 14 hypertensive adults and 15 controls found markedly reduced H_2S production and CSE and 3-MPST expression in hypertensive patients; correspondingly, H_2S-mediated vasodilation was absent in the hypertensive patients, and exogenous administration of

Na_2S restored vasodilator activity [262]. These findings suggest a beneficial role in restoring H_2S to a damaged endothelium; in a mouse model of Ang II-induced hypertension, administration of NaHS restored H_2S bioavailability, reduced the rise in blood pressure, and reversed the reduction of endothelium-dependent vasodilator response [356]. A separate study showed that both exogenous and endogenous upregulation of H_2S levels could reverse damage to the endothelium; NaHS supplementation and overexpression of CSE ameliorated endothelial cell damage in vitro in hydrogen peroxide-treated endothelial cells [388]. Whereas H_2S contributes to endothelial function independent of NO, extensive crosstalk between the two gasotransmitters is also responsible for maintaining vascular homeostasis. CSE knockout mice have been found to have not only the expected reduction in H_2S levels but also reduced eNOS-NO levels; supplementation with H_2S donor diallyl trisulfide increased eNOS activation and NO bioavailability [389]. Restoration of H_2S to the endothelium using NaHS was also seen to restore NO bioavailability to the endothelium in a mouse model of Ang II-induced hypertension [356]. This crosstalk allows both gasotransmitters to contribute to the endothelium's health simultaneously.

H_2S increases endothelial NO bioavailability (Fig. 4) through multiple pathways: by stabilizing eNOS through S-sulfhydration [136], increasing eNOS activation by PI3K/Akt mediated phosphorylation [390], and decreasing NO consumption by reducing aortic superoxide anion production [356]. Indeed, the fast-releasing H_2S donor, NaHS, restored constitutive NOS coupling and induced aortic vasorelaxation in the isolated aorta of old rats [391]. Furthermore, H_2S inhibits the activity of phosphodiesterases, preventing the breakdown of cGMP and allowing prolonged effects of NO [392]. In addition to increasing NO production, reducing its consumption by superoxide anions, and inhibiting phosphodiesterase activity – multiple ways of increasing NO bioavailability and function, H_2S administration also exerts redox regulation on NO receptor sGC, enhancing its response to NO donors and NO-dependent vasorelaxation, especially in conditions of oxidative stress which alter the function of sGC [393]. An additional level of feedback regulation exists here; NO can also induce increased CSE-dependent H_2S levels, such that the usage of H_2S to restore NO to the endothelium will induce further H_2S production and reinforce the cycle [394]. Therefore, H_2S administration will cause combined restoration of the vasodilator, anti-adhesive, anti-inflammatory, and anti-thrombotic properties of both H_2S and NO.

Multiple studies have demonstrated critical anti-thrombotic properties of H_2S. Thrombosis and endothelial damage are associated with reduced expression of CSE mRNA and protein, and restoration of H_2S reduces thrombosis [388] (Fig. 4). In addition, the H_2S donor GYY4137 reduced platelet-leukocyte aggregation, leukocyte count, and platelet activation in whole human blood stimulated with thrombin-receptor activating peptide [395]. The anti-thrombotic actions of H_2S have been verified in several animal models, administration of various H_2S donors reversed CSE downregulation and endothelial cell apoptosis, reduced and delayed thrombus formation to an extent comparable with the use of *anti*-P-selectin antibodies, attenuated P-selectin distribution, prolonged tail-vein bleeding time, and increased thrombolysis [357,388,395,396].

There are multiple mechanisms through which these anti-thrombotic actions are mediated. Gao et al. report that an H_2S-releasing aspirin derivative, as well as NaHS, inhibited ADP- or thrombin-induced platelet aggregation and P-selectin expression. In contrast, these actions were reversed by administering a gap junction-stabilizing modifier that improved channel conductance, suggesting H_2S functions through gap junction activity depression [397]. Additionally, H_2S also seems to demonstrate anti-thrombotic properties that stem from the crosstalk with NO; the anti-thrombotic effects of H_2S are partly due to the upregulation of NO production by H_2S; in a mouse model of phototoxicity-induced thrombus formation, treatment with Na_2S significantly delayed thrombus formation, and immunohistochemical analysis showed upregulation of eNOS and iNOS compared with placebo controls [398]. Treatment with L-NAME partly reversed the anti-thrombotic action of Na2S and drastically reduced both eNOS and iNOS function [398].

Despite a dearth of studies on viral infection-induced thrombosis, the endothelial function-restoring and anti-thrombotic properties of H_2S make it a potential therapy for prothrombotic states in viral infections, including COVID-19.

17. H_2S donors

The actions of H_2S are biphasic or bell-shaped, making its mode of delivery crucial as a therapeutic agent. Ideal delivery mechanisms will allow for sustained release of H_2S to minimize toxicity. Inorganic sulfide salts such as NaHS and Na_2S have been widely used in research; however, their therapeutic use is limited by their release kinetics, which results in a sharp increase followed by a rapid decrease in H_2S levels [399,400]. These traditional fast H_2S donors have demonstrated both protective and toxic effects in vivo [367]. GYY4137, a slow-releasing alternative, closely mimics endogenous H_2S production [399] and consistently has modulated protective parameters in vivo [368]. Synthetic H2S donors that release H_2S under various conditions are constantly being developed, giving more control over release [399]. Examples include hydrolysis-triggered H_2S donors, thiol-triggered H_2S donors, light- and enzyme-triggered H_2S donors, and engineered H_2S delivery platforms, reviewed in Ref. [401]. Additionally, multiple existing drugs have been coupled to H_2S-donating moieties generating chimeras that combine the therapeutic effects of the parent drug with the novel actions of H_2S. ACS14, an H_2S-releasing derivative of aspirin, is an agent that has shown promising antithrombotic effects both in vitro and in vivo [402].

H_2S inhalation provides more targeted effects to the respiratory system and bypasses issues with systemic administration. However, inhalation of H_2S gas still poses many difficulties, including handling and toxicity concerns. Thus, determining proper dosage becomes critical; erring on the side of caution can lead to an inadequate dose with mild or no effects, whereas higher concentrations may be toxic and, in some cases, fatal. Demonstrating this point, a study of VILI in mice found that inhalation of H_2S at 1–5 ppm was ineffective in alleviating injury, whereas 60 ppm accelerated VILI; on the other hand, IV injection of NaHS was protective [403]. Multiple animal studies using H_2S inhalation therapy have yielded positive results, but human studies are limited for safety reasons [404]. Limited human studies with low H_2S concentrations have shown minimal efficacy [404]. An alternative H_2S inhalation therapy using H_2S-containing thermal waters has demonstrated 'healing' properties, although these have not been verified by more extensive, high-powered studies [404].

Naturally occurring H_2S donors, including garlic, onions, and cruciferous vegetables, are rich in organosulfur compounds and can provide beneficial boosts to H_2S levels that can be of therapeutic value, for example, in lowering blood pressure [399]. Importantly, these natural compounds require the presence of reduced glutathione to release H_2S [405]. Further studies are needed to assess the full therapeutic potential of dietary H_2S sources. Overall, the clinical application of the promising results of various studies with H_2S for use with viral infections, including COVID-19, requires further investigation into methods and delivery timing.

18. Crosstalk between NO and H_2S in Covid-19

As evident by the preceding discussions of NO and H_2S, these gasotransmitters have overlapping functions and engage in significant levels of crosstalk. Synergistic interactions between NO and H_2S have been reported regarding vasorelaxant effects [406], where inhibiting the endogenous production of NO reduces the vasorelaxant activity of H_2S donor molecules and vice versa [407]. There is also evidence of antagonism between the two signaling molecules [408]. The opposing

findings may result from methodological differences, including the timeline for measurement of the effects, release kinetics of the donor molecules, and concentrations used. For instance, H_2S has biphasic effects on the vasculature, causing vasoconstriction at low concentrations and vasorelaxation at higher concentrations [409,410]. Thus, consistency across experiments would be crucial for evaluating the trends and potential application within COVID-19 management.

There are multiple levels of interaction between NO and H_2S, including mutual effects on production, modulation of downstream signaling pathways, and reactions to form new molecules. A clear understanding of these interactions and knowledge of COVID-19-induced dysregulation in NO and H_2S levels will help inform management approaches for using these gasotransmitters in COVID-19.

Multiple studies with NO demonstrate its ability to modulate H_2S bioavailability. For example, the administration of various NO donors was found to increase H_2S levels [394,411] by increasing CSE expression and activity (Fig. 5) [300,412,413], whereas L-NAME was shown to inhibit CSE expression [414]. Yet, in a murine model of LPS-induced endotoxic shock, the NO-releasing nonsteroidal anti-inflammatory drug, nitroflurbiprofen, reduced H_2S formation in the liver and kidney [415]. The reason for these discrepancies is not entirely apparent. Still, it is possible that NO donors interact differently with H_2S in the endotoxic shock model, where it serves to curtail rather than augment H2S production. Additionally, while the effects of NO on CBS are not as extensively explored as those on CSE, NO has been reported to bind and inhibit CBS activity (Fig. 5) [416,417]. As CBS is a major H_2S producer within the liver and the kidney [418], it is also possible that NO-mediated inhibition of this enzyme decreased H_2S production in the endotoxic shock model. It is reasonable to venture that exogenous administration of H_2S in the COVID-19 model may also have varying interactions with NO depending on the severity and stage of the illness.

The effects of H_2S upon NO signaling have been much more extensively documented. A range of H_2S donors have demonstrated the ability to increase NO bioavailability [356,389], whereas reduced NO bioavailability and impaired vasorelaxant effects of NO donors were seen with CSE silencing [389,390]. One mechanism through which H_2S modulates NO bioavailability is its impact on NO production by eNOS and iNOS (Fig. 5). In murine models, sulfide salts increased eNOS expression [398,413]. H_2S also increased eNOS activation by inducing intracellular Ca^{2+} release from the endoplasmic reticulum [419] and/or Akt-mediated phosphorylation at the active site of eNOS [360,420,421]. Additionally, there may be competition between NO and H_2S for *S*-nitrosylation and *S*-sulfhydration, respectively, of the same proteins, giving each a role in regulating the actions of the other [422]. Indeed, one in vitro study reported that the administration of NaHS led to *S*-sulfhydration of eNOS, preventing NO-mediated *S*-nitrosylation and preserving eNOS dimerization and activity [136]. Correspondingly, CSE knockout mice had increased *S*-nitrosylated eNOS [136] and significantly lower eNOS active site phosphorylation levels. Based on these studies, exogenous H_2S administration to restore both H_2S and eNOS-derived NO holds double promise for combatting extensive endothelial dysfunction and the resulting thrombotic complications that may arise in severe COVID-19. Yet there is also some evidence that suggests H_2S inhibits eNOS [410,423]. The dual effects of H_2S on vascular tone may be due to the biphasic actions of H_2S.

H_2S has also demonstrated the ability to curtail iNOS expression and iNOS-derived NO production by inhibiting NF-κB [313,314,364,365,381,424–426], which may prove helpful when combatting COVID-19 cases that have progressed to a hyper-inflammatory state. However, there are also reports that NaHS, H_2S, or L-cysteine upregulate iNOS [398] or do not affect iNOS levels [423]. Interestingly, both results were seen in one study, demonstrating that H_2S administration may produce

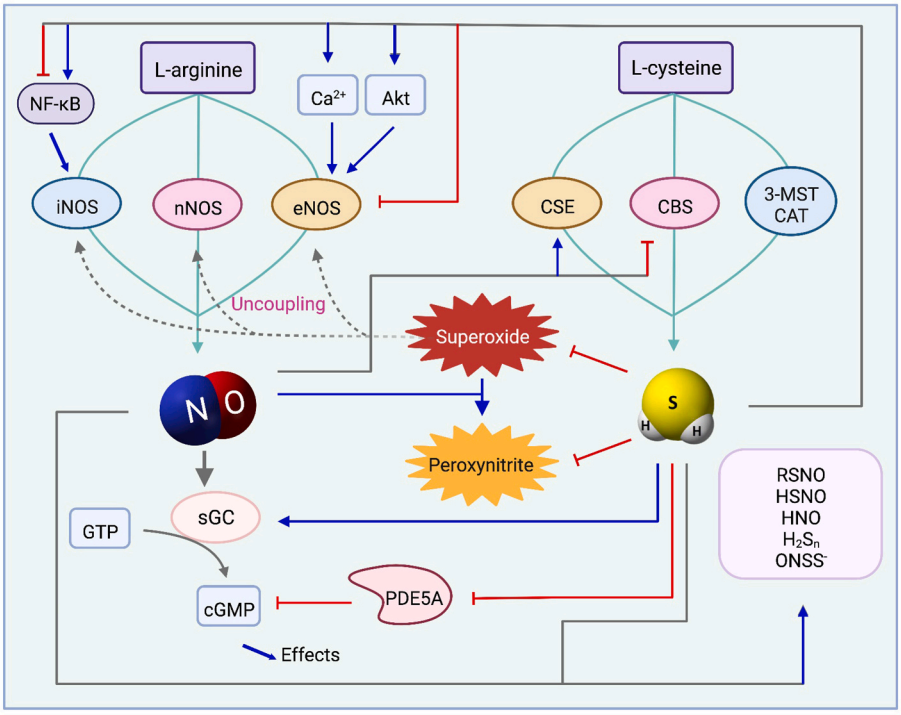

Fig. 5. NO and H_2S crosstalk. NO, and H_2S interact at multiple levels to mutually impact production and downstream signaling and create new reaction products. NO – enzymatically produced from L-arginine by nNOS, eNOS, and iNOS mediates most of its downstream effects through the sGC-cGMP pathway. Superoxide reduces NO production by causing NOS uncoupling and consumes NO to form peroxynitrite. NO signaling is terminated by PDE5A, which degrades cGMP. H_2S is produced enzymatically by CBS, CSE, and 3-MST in conjunction with CAT. NO upregulates CSE expression and, in a cell-free system, inhibits CBS activity. H_2S has a dual effect on eNOS activity and expression that may be dependent on the release kinetics of donor molecules, concentration, and other factors; it may either inhibit eNOS or increase eNOS activity via intracellular Ca^{2+} release or Akt-mediated phosphorylation. Similar biphasic effects are noted upon NF-κB, the transcription factor for iNOS. H_2S also reduces superoxide production, thereby reducing NO consumption to produce peroxynitrite; additionally, H_2S is a scavenger of peroxynitrite as well. H_2S augments downstream signaling of NO by increasing sGC activity and inhibiting PDE5A. NO and H_2S may also combine to form new species such as RSNO, HNO, and HSNO, which produce different effects than either gasotransmitter alone.

Abbreviations: 3-MST, 3-mercaptopyruvate sulfurtransferase; Ca^{2+}, calcium ion; CAT, cysteine aminotransferase; CBS, cystathionine β-synthase; cGMP, cyclic guanosine monophosphate; CSE, cystathionine γ-lyase; eNOS, endothelial nitric oxide synthase; H_2S, hydrogen sulfide; HNO, nitroxyl; HSNO, thionitrous acid; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; PDE5A, phosphodiesterase type 5A; RSNO, nitrosothiol; sGC, soluble guanylyl cyclase; RSNO, nitrosothiol; HSNO, thionitrous acid; H_2S_n, polysulfide; HNO, nitroxyl; $ONSS^-$, nitropersulfide.

varying effects in physiological vs. pathological states; although NaHS and L-cysteine increased iNOS expression and NO production by enhancing IL-1β-induced NF-κB activation, it did not affect NO production or iNOS expression when IL-1β stimulation was absent [427]. There is also evidence emphasizing the importance of donor release kinetics and concentration. While GYY4137 a slow H_2S donor, significantly reduced nitrite concentration and inhibited LPS-induced NF-κB activation, the sulfide salt NaHS increased NF-κB activity at lower concentrations (100–200 μM) and inhibited activity at higher concentrations (1000 μM) [367]. These results underscore the biphasic anti-inflammatory and pro-inflammatory effects of H_2S. Thus, using different donors at different concentrations across studies may be responsible for opposing trends and indicates that slow-release compounds, which are a better model for endogenous production, are a superior option for any therapeutic needs.

In addition to affecting NO production, H_2S has multiple downstream interactions with NO signaling. As an antioxidant, H_2S serves to modulate NO bioavailability by reducing the production of superoxide anions (Fig. 5) [356], thus decreasing NO consumption and conversion to peroxynitrite and restoring NOS enzyme uncoupling [391]. In addition, H_2S can also scavenge peroxynitrite and inhibit related cell toxicity [308]. H_2S also has a wide range of downstream effects that amplify the NO signaling pathway. For example, H_2S enhances the response of sGC to NO through redox regulation of sGC (Fig. 5) [393]. In addition, it inhibits the activity of PDE5A [392], thereby allowing prolonged effects of NO by preventing the breakdown of cGMP [392], and correspondingly, CSE knockout mice had reduced levels of cGMP [389].

In addition to mutually regulating production and downstream signaling, NO and H_2S may also chemically react to form new species with different effects than either of the two gasotransmitters individually (Fig. 5) [291]. H_2S and its anionic form (HS^-) can act as potent reducing agents that can react with NO, nitrate, nitrite, and other oxidized forms to yield nitrosothiols (RSNO), thionitrous acid (HSNO), polysulfides (H_2Sn), nitroxyl (HNO), and nitropersulfide (ONSS-), which may decompose to yield NO at physiological pH [291,428–431]. Incubation of NO donors with NaHS has provided evidence of nitrosothiol formation and decreased cGMP accumulation, suggesting that nitrosothiol formation may be important in regulating the effects of endogenous NO and H_2S [432]. Another study demonstrated that a mixture of NO and H_2S donors eliminated the vasorelaxant actions of either one, both in vitro and in vivo [433], suggesting that the administration of both donors simultaneously may be problematic. Yet HNO formation has also been demonstrated by mixing sulfide salts with NO donors such as GSNO and SNP, with the ability for enhanced effects compared to either gasotransmitter alone [434,435]. In fact, HNO is important in improving cardiac function, reducing oxidative stress, and preventing thrombosis [436–438].

NO, and H_2S each individually hold promise as antiviral, anti-inflammatory, and anti-thrombotic agents in managing COVID-19. Additionally, understanding the extensive crosstalk between the two gasotransmitters may inform the targeted use of either one to augment the beneficial activity of the other. However, further investigation is required in this arena to characterize these interactions and their implications more fully.

19. Conclusions and perspectives

Regarding SARS-CoV-2 infection, it appears that a robust immune response and unchecked inflammation may lead to severe illness, complications that lead to multisystem organ failure, and death. Pro-inflammatory cytokines increase, including IL-1β, IFN-γ, IFN-γ-inducible protein 10, IL-6, granulocyte-colony stimulating factor, MCP-1, macrophage inflammatory protein 1-α, and TNF-α, may be the driving forces in severe COVID-19 [439–441]. Of note, NO has demonstrated promise in modulating inflammation in many respiratory disease models and may have utility in treating COVID-19. Thus, exogenous NO therapy geared toward the right population at the optimal stage of the infection may be a compelling option for patients [441]. In the same vein, H_2S may be effective in managing COVID-19 by suppressing the immune response and inflammation development, especially in high-risk populations with underlying conditions such as cardiovascular diseases and diabetes. Furthermore, both NO and H_2S may block SARS-CoV-2 entry into the host cells by interfering with ACE2 and TMPRSS2; moreover, they can inhibit SARS-CoV-2 replication by attenuating syncytium formation and virus assembly and release. Although many NO-donors can be evaluated against SARS-CoV-2, this space requires the development of stable and slow-releasing H_2S-donors with further studies directed towards its molecular targets.

Eicosanoids, which include prostaglandins, thromboxanes, and leukotrienes, are derived from arachidonic acid (AA) and have a role in the inflammatory process. In addition, they are also critically involved in the resolution phase of inflammation by initiating the host defense mechanisms [442]. But not all eicosanoids are pro-inflammatory as arachidonic acid, and related fatty acids are also metabolized into anti-inflammatory and pro-resolution docosanoids [443,444]. Thus, the balance between the pro-inflammatory and anti-inflammatory eicosanoids and pro-resolution lipid mediators during the initiation and resolution of infection can regulate the cytokine storm [445]. Therefore, it has been hypothesized that SARS-CoV-2 may trigger a temporal production of an eicosanoid storm, including an imbalance of both pro-inflammatory and proresolution mediators [446].

Apart from being a substrate for the cyclooxygenases and lipoxygenases pathways, AA is also a substrate for the cytochrome P450 pathway leading to either hydroxyeicosatetraenoic acids through w-hydroxylases or epoxyeicosatrienoic acids (EETs: 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET) through epoxygenases [444,447]. The latter is involved in regulating inflammation and is chiefly produced in the endothelium. The epoxides of EETs are rapidly converted into dihydroxyeicosatrienoic acids by the enzyme soluble epoxide hydrolase (sEH). Inhibitors of this enzyme raise endogenous EET levels and exhibit potent anti-inflammatory activity. Stabilizing the anti-inflammatory, pro-resolving EETs using sEH inhibitors (sEHIs) has shown therapeutic application in various preclinical models and human trials, including sepsis, cardiovascular disease, neuroinflammatory disease, and cancer [444,448,449]. Thus, the role of EETs, sEH, and sEHIs in COVID-19 should be explored.

Authorship contributions

KK – formulated the general concept of this review, PPO and KK researched the literature and wrote the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

Supported in part by the National Institutes of Health [R24 DA018055; R01GM123508] and the Professional Staff Congress-City University of New York (PSC-CUNY) [TRADB-49-271]. Figs. 1–4 were Created with BioRender.com.

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