Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Nitric Oxide 103 (2020) 4–8

Contents lists available at ScienceDirect

Nitric Oxide

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

Review

Harnessing nitric oxide for preventing, limiting and treating the severe pulmonary consequences of COVID-19

Nagasai C. Adusumilli [a], David Zhang [b], Joel M. Friedman [b,**], Adam J. Friedman [a,*]

[a] Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[b] Department of Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY, USA

ARTICLE INFO

Keywords:
Nitric oxide
COVID-19
ARDS

ABSTRACT

The ongoing outbreak of COVID-19 has quickly become a daunting challenge to global health. In the absence of targeted therapy and a reported 5.5% case fatality rate in the United States, treatments preventing rapid cardiopulmonary failure are urgently needed. Clinical features, pathology and homology to better understood pathogens suggest that uncontrolled inflammation and a cytokine storm likely drive COVID-19's unrelenting disease process. Interventions that are protective against acute lung injury and ARDS can play a critical role for patients and health systems during this pandemic. Nitric oxide is an antimicrobial and anti-inflammatory molecule with key roles in pulmonary vascular function in the context of viral infections and other pulmonary disease states. This article reviews the rationale for exogenous nitric oxide use for the pathogenesis of COVID-19 and highlights its potential for contributing to better clinical outcomes and alleviating the rapidly rising strain on healthcare capacity.

1. Introduction

Coronaviruses (CoVs) are RNA viruses that primarily infect birds and livestock [1], but when they cross the species barrier, coronaviruses have been highly infectious and lethal to humans in the severe acute respiratory syndrome (SARS) outbreak in 2002, Middle East respiratory syndrome (MERS) outbreak in 2012, and in the current coronavirus disease 2019 (COVID-19) pandemic [2,3]. Up to the submission date, Johns Hopkins Center for Systems Science and Engineering has confirmed over 8.4 million cases and 453,900 deaths worldwide, more fatalities than in the SARS and MERS epidemics combined [4]. To date no registered treatment or vaccine for the disease exists. Various general treatments, from nutritional interventions to antivirals used for other diseases, have been reviewed and proposed [5]. Recent reports suggest that ventilator therapy may be ineffective and may even increase morbidity and mortality in severely ill patients [6]. The absence of a specific treatment and the high mortality rate dictate an urgent need for therapeutics that may control the replication and rapid spread of the virus. Here we review the potential for nitric oxide in limiting the density of virus within the lungs, preventing the onset and development of COVID-19 associated acute respiratory distress syndrome (ARDS) and treating ARDS.

2. Pathophysiology of COVID-19

Symptomatic patients with SARS-CoV-2 reportedly present with fever, dry cough, shortness of breath and myalgias. The mortality stems from rapid, severe progression to acute lung injury (ALI), ARDS, respiratory failure, sepsis or cardiac arrest. Pathological reports from post-mortem assessment describe bilateral diffuse alveolar damage with edema, pneumocyte desquamation, hyaline membrane formation and massive pulmonary embolism [7,8]. These pathological features resemble the pneumonia seen with SARS and MERS [9,10]. The overall nucleotide sequence of the current virus exhibits about 79% similarity to SARS-CoV-1, and more specifically, key structural components such as binding ability to the human angiotensin-converting enzyme 2 (ACE2) receptor are shared [11,12]. The overlap of pathology and genetic structure allows parallels from more established literature about the pathophysiology of SARS-CoV-1. In addition to viral overload, animal models have illustrated apoptosis of epithelium and endothelium and an array of inflammatory and immune responses leading to a cytokine storm. Subsequent vascular permeability and abnormal T-cell and

* Corresponding author.
** Corresponding author.
E-mail addresses: joel.friedman@einsteinmed.org (J.M. Friedman), ajfriedman@mfa.gwu.edu (A.J. Friedman).

https://doi.org/10.1016/j.niox.2020.07.003
Received 5 May 2020; Received in revised form 22 June 2020; Accepted 13 July 2020
Available online 15 July 2020
1089-8603/© 2020 Elsevier Inc. All rights reserved.

macrophage responses induce ALI and ARDS [13]. Hyper-inflammatory response and compromised vasculature are increasingly shown to spur multisystem dysfunction, including in the heart, kidneys, nerves and gastrointestinal tract [14]. Therapies that can modulate the inflammatory cascade, immune response or cytokine storm may work to prevent the rapid progression to the ARDS and fulminant systemic organ failure that are driving mortality with COVID-19.

Factors that contribute to the inflammatory and immune response include the nitric oxide/reactive oxygen species (NO/ROS) ratio, the activation of M1 macrophages and red blood cell (RBC) damage. A normal NO/ROS balance is crucial for normal vascular function. NO is an endothelium-derived relaxing factor that plays key roles in vascular signaling, regulation of blood flow and host defense [15]. ROS, such as superoxide, also serve as host defense and are induced during stress, such as viral infection [16]. An excess of ROS, such as in viral overload, activates M1 macrophages, recruits neutrophils and enhances production of peroxynitrite in conjunction with NO in a potent response to the invading virus, with the collateral damage of endothelial dysfunction, permeable vessels and lipid membrane peroxidation [17]. M1 macrophages produce a large amount of highly reactive nitrogen- and oxygen-derived molecular species and proinflammatory cytokines, such as interleukin (IL)-2, IL-6, IL-8, interferon (IFN)-α/β and tumor necrosis factor (TNF)- α, that neutralize invading organisms but also compound the vascular damage [18]. Furthermore, inflammation-induced platelet activation, which can be lessened by NO, can lead to increased coagulation, an important reported consequence of the disease [19]. Lippi and Mattiuzzi recently reported evidence of SARS-CoV-2 disrupting hemoglobin in RBCs [20], likely triggering significant oxidative stress. Subsequent hemolysis can result in anemia, but more importantly it can exacerbate the inflammatory process. Cell-free hemoglobin scavenges modulators of coagulation, such as endothelial NO, while released proinflammatory heme and iron can activate platelets [21,22]. Enhanced clotting and sluggish blood flow result in systemic hypoxia in oxygen-sensitive organs such as the kidneys [23]. Repolarization of the M1 population back to M2, promoted by NO, stops the proinflammatory insult to the tissues and initiates repair processes and clearance of debris. Unchecked M1 macrophage response creates an inflammatory cascade and cytokine storm that result in a buildup of cellular debris and edema due to the leaky vasculature, presenting in the lungs as ARDS [18].

Additional processes that enhance the progression toward an inflammatory cascade include the renin angiotensin system (RAS) and reoxygenation/reperfusion. Observations that SARS-CoV-2 uses ACE2 as the receptor binding domain for its spike (S) protein, with higher affinity than measured with SARS-CoV-1, have led to postulations about the role of the RAS in the novel virus's pathophysiology [11,24–26]. The genes for viral entry and for ACE2 expression are highly enriched in nasal epithelium, implying a significant role for ACE2 in infectivity and the course of infection [27]. ACE and ACE2 serve opposing physiological functions. After ACE cleaves angiotensin (AT) I to angiotensin II, ATII binds its receptor to constrict blood vessels. ACE2 inactivates ATII and generates angiotensin 1-7 and promotes endothelial production of NO, both potent vasodilators and inhibitors of ACE [28]. Conversely, ACE inhibits NO production, promoting ROS and inflammation. The binding of SARS-CoV-2's spike protein to ACE2 likely downregulates it and contributes to unchecked downstream effects of ACE, including increased vascular permeability and decreased anti-inflammatory mediators such as NO. This mechanism of dysregulation of the NO/ROS balance has been detailed with SARS-CoV-1 and translates to a potential area for intervention in the current pandemic [29]. Hypoxia/Reoxygenation (H/R) and ischemia/reperfusion (I/R) both initiate the proinflammatory cycle through ROS- and heparinase-mediated degradation of the glycocalyx and endothelial lining [30–32]. In the setting of blood flow stagnation and microvascular emboli, ventilation and rapid restoration of blood flow to sites that were hypoxic and ischemic may contribute to pathogenesis of ARDS. Anti-inflammatory molecules such as *N*-acetylcysteine can potentially attenuate cellular damage by ROS [33], and restoring NO/ROS balance may reduce cellular damage by reoxygenation and reperfusion.

3. The rationale for nitric oxide use

Nitric oxide (NO) is a gas produced from arginine in mammalian cells by three enzymes: neuronal (nNOS), endothelial (eNOS) and inducible nitric oxide synthase (iNOS) [34]. In host cells iNOS is commonly elevated during infection by viruses, and in SARS-CoV-1 infection, NO inhibits viral replication by cytotoxic reactions through intermediates such as peroxynitrite [35]. Nitrosation of reactive thiols on the surface of RBCs and on the beta chain of the hemoglobin tetramer stabilizes against hemolysis and oxidative damage, respectively [21,22], conferring NO's potential in controlling SARS-CoV-2's RBC-associated pathogenic processes. Because SARS-CoV-2 infects endothelial cells, which are a major source of NO synthesis, the molecule is additionally well-placed to respond to viral attack. As discussed above, NO plays key roles in maintaining normal vascular function and regulating inflammatory cascades that contribute to ALI and ARDS when excessively activated in the context of declining endothelial function. Vasculature depleted of NO suffers from persistent inflammation and blunted delivery of oxygen and removal of toxic byproducts through stagnant blood flow into and out of hypoxic tissue [31,32,36]. NO supplementation under proinflammatory conditions prevents cytokine storm, restores the functional capillary density crucial for oxygen delivery and waste removal, prevents H/R injury and protects oxygen-sensitive organs such as the kidneys (Cabrales & Friedman, Kaul & Friedman, unpublished data, 2020). When ARDS is already present, NO improves arterial oxygenation and blunts pulmonary hypertension by dilating pulmonary vessels in ventilated lung parenchyma [37]. These supportive changes at the physiologic level may translate to decreased ventilator support, improved density of lung infiltrates on chest radiography and persistence of therapeutic benefits after discontinuation of NO [38]. The vulnerable populations in the current pandemic may have lower levels of endogenously produced NO. NO generated from eNOS drops off with age, and patients with chronic vascular inflammation, such as in type 2 diabetes, metabolic syndrome, chronic obstructive pulmonary disease, obesity, autoimmune disorders and hemoglobinopathies, may produce less eNOS [34,39,40]. Additionally, ACE activity relative to ACE2 activity may be elevated in patients with chronic vascular inflammation [41,42]. Older patients with vascular stressors from underlying chronic medical conditions may exhibit inadequate vascular NO levels, increasing their vulnerability to H/R and I/R injury. Consequently, exogenous NO for targeted patient populations may be a treatment that can reduce viral load in the lungs, prevent the chain of events that rapidly destabilizes patients to ARDS and promote clinical recovery from ARDS.

4. How to use NO for COVID-19

Exogenous NO has been administered with inhalation and with donor compound pro-drugs relying on enzymatic activity [43]. Inhaled NO (iNO) for treatment of active ARDS was reported by Chen and colleagues during the 2003 epidemic, but existing literature shows mixed efficacy when expanding outside the SARS-CoV-1 disease model [38,44]. Systematic review and meta-analysis of randomized controlled trials have shown that iNO, does not reduce mortality when used therapeutically in the management of ARDS [45,46]. Variations in dosing and treatment protocol may at least partly account for the differences in the literature. Additionally, the level of cellular debris and tissue damage during active ARDS may be too overwhelming to allow for NO efficacy. Donor drugs with S-nitrosothiols containing molecules (RSNOs) have demonstrated antimicrobial and anti-inflammatory activity [47]. NO delivered with *S*-nitroso-*N*-acetylpenicillamine (SNAP) inhibits the replication cycle of SARS-CoV-1 in a concentration-dependent manner and reduces the post-translational palmitoylation of the S protein,

inhibiting S protein and ACE2 receptor interaction and subsequent membrane fusion [35,48,49]. This mechanism of action suggests an additional effect of preserving host ACE2 levels that may better regulate RAS and promote endogenous NO production as described above. NO releasing nanoparticles (NO-nps) demonstrate potential in limiting inflammatory cascades and ischemia reperfusion injury [50,51]. We propose that delivering modest, persistent amounts of iNO or RSNO at the early stages of COVID-19 infection might limit the progression toward ARDS and fulminant systemic failure, particularly in vulnerable patients who may have decreased levels of endogenous NO due to increased age or comorbid conditions. This approach should decrease viral replication, downregulate ACE, prevent the onset of any hypoxia-reoxygenation/ischemia reperfusion-based inflammation, control the cytokine cascade, allow for removal of cell debris, limit lipid peroxidation and concomitant cell damage, reduce detrimental vascular permeability and maintain proper blood flow.

NO is one of several potential treatments included in the emergency expanded access program by U.S. Food and Drug Administration (FDA). Several innovators are pursuing the indication for NO in treating COVID-19. On March 30 Bellerophon Therapeutics announced the first treatment of a patient with COVID-19 using their proprietary INOpulse® inhaled nitric oxide system [52], and on May 11 the FDA accepted its Investigational New Drug application to start a Phase 3 randomized, placebo-controlled study [53]. The biotherapeutics firm currently uses INOpulse for other cardiopulmonary indications, such as pulmonary hypertension associated with pulmonary fibrosis. Portable and designed to deliver NO in outpatient settings outside of the hospital, INOpulse could aid in preserving hospital and intensive care unit (ICU) capacity as the pandemic progresses. Through expanded access the FDA also recently approved VERO Biotech's GENOSYL DS® iNO to treat patients with COVID-19 at home [54]. Currently used for persistent pulmonary hypertension of the newborn, GENOSYL is a tankless device that provides even more flexibility for healthcare resources by allowing home use of iNO. Zamanian et al. describe solely outpatient management of a patient with concomitant idiopathic pulmonary arterial hypertension and COVID-19 disease, reporting symptomatic improvement with GENOSYL DS® with no urgent care, emergency department or hospital visits [55]. Such delivery systems align with our proposal to harness NO's potential in the early stages of COVID-19 infection. As groups continue to publish more results with their respective NO platforms, dosing and protocol variations should be examined in evaluating the studies.

In addition to inhaled NO, donor compounds and nutraceuticals which boost NO production may also be possibilities in treating the novel virus. No trials with donor compounds or natural products like curcumin are currently underway, but due to the evidence of their efficacy in various models of cardiovascular dysfunction, donor compounds should absolutely be explored for early intervention in COVID-19. Curcumin upregulates gene expression for anti-inflammatory response by activating nuclear factor erythroid 2-related factor 2 (NRF2) [56–58], suggesting a reasonable avenue when exploring strategies to lessen unrestrained inflammation. Innovative delivery platforms, such as NO releasing nanoparticles, can be particularly conducive in targeting the virus's pathology in the respiratory tract before widespread systemic manifestations. Successful results would be instrumental in improving patient outcomes and curbing the inundation of health systems.

5. Conclusion

With the emergence of COVID-19 as a pandemic with the ability to overwhelm the body and the healthcare infrastructure, patients have a pressing need for effective agents that can slow down the disease in their bodies and in their communities. While the search for a vaccine and targeted drugs continues, much of medical research is actively exploring the infection's pathophysiology for points of plausible intervention. An exaggerated immune response and unchecked inflammation are likely at the root of severe illness. Nitric oxide has demonstrated promise in similar respiratory disease models in modulating the prominent inflammation, and the early reported proofs of concept urgently call for randomized control trials in treating COVID-19. Exogenous NO therapy geared toward the right population at the optimal stage of infection may be an accessible, compelling option for patients. If its efficacy is illustrated as therapeutics firms seek its indication for COVID-19, nitric oxide treatment can be pivotal in the world's fight against this immediate threat to public health.

Search strategy and selection criteria

Data for this Review were identified by searches of MEDLINE, Current Contents, PubMed, LitCovid and references from relevant articles using the search terms "nitric oxide", "SARS", "ARDS", "Angiotensin", and "COVID-19." Information about therapeutics companies and FDA indications were obtained from official press releases reported in news sources. Only articles published in English between 1993 and 2020 were included.

Declaration of competing interest

None to disclose.

Abbreviations

CoVs	coronaviruses
SARS	severe acute respiratory syndrome
NO	nitric oxide
MERS	Middle East respiratory syndrome, MERS
COVID-19	coronavirus disease 2019
ARDS	acute respiratory distress syndrome
ALI	acute lung injury
ACE2	angiotensin-converting enzyme 2
NO/ROS	nitric oxide/reactive oxygen species
RBC	red blood cell
IL	interleukin
IFN	interferon
TNF	tumor necrosis factor
RAS	renin angiotensin system
S protein	spike protein
AT	angiotensin
H/R	Hypoxia/Reoxygenation
I/R	Ischemia/Reperfusion
nNOS, eNOS and iNOS	neuronal, endothelial and inducible nitric oxide synthase
iNO	Inhaled NO
RSNO	*S*-nitrosothiols containing molecules
SNAP	*S*-nitroso-*N*-acetylpenicillamine
NO-np	nitric oxide releasing nanoparticles
FDA	Food and Drug Administration
ICU	intensive care unit
NRF2	nuclear factor erythroid 2-related factor 2

Author contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in *Nitric Oxide.*

Category 1

Conception and design of study: Joel Friedman, Adam Friedman;

acquisition of data: Nagasai Adusumilli, David Zhang, Joel Friedman, Adam Friedman; analysis and/or interpretation of data: Nagasai Adusumilli, David Zhang, Joel Friedman, Adam Friedman.

Category 2

Drafting the manuscript: Nagasai Adusumilli; revising the manuscript critically for important intellectual content: Nagasai Adusumilli, Joel Friedman, Adam Friedman.

Category 3

Approval of the version of the manuscript to be published: Nagasai Adusumilli MBA, David Zhang, Joel Friedman MD, PhD, Adam Friedman MD.

References

[1] A. Banerjee, K. Kulcsar, V. Misra, M. Frieman, K. Mossman, Bats and coronaviruses, Viruses 11 (2019) 41.

[2] D. Schoeman, B.C. Fielding, Coronavirus envelope protein: current knowledge, Virol. J. 16 (2019) 69.

[3] C. Huang, Y. Wang, X. Li, et al., Features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506.

[4] E. Dong, H. Du, L. Gardner, An interactive web-based dashboard to track COVID-19 in real time, Lancet Infect. Dis. 20 (5) (2020) 533–534 [published correction appears in Lancet Infect Dis. 2020 Jun 12;:].

[5] L. Zhang, Y. Liu, Potential interventions for novel coronavirus in China: a systematic review, J. Med. Virol. 92 (5) (2020) 479–490.

[6] S. Richardson, J.S. Hirsch, M. Narasimhan, et al., Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area, J. Am. Med. Assoc. 323 (20) (2020) 2052–2059. Published online.

[7] Z. Xu, L. Shi, Y. Wang, et al., Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (4) (2020) 420–422 [published correction appears in Lancet Respir Med. 2020 Feb 25;:].

[8] D. Wichmann, J.P. Sperhake, M. Lütgehetmann, et al., Autopsy findings and venous thromboembolism in patients with COVID-19 [published online ahead of print, 2020 May 6], Ann. Intern. Med. (2020) M20–M2003, https://doi.org/10.7326/M20-2003.

[9] B.T. Bradley, A. Bryan, Emerging respiratory infections: the infectious disease pathology of SARS, MERS, pandemic influenza, and Legionella, Semin. Diagn. Pathol. 36 (3) (2019) 152-159.

[10] K. To, J.H. Tong, P.K. Chan, et al., Tissue and cellular tropism of the coronavirus associated with severe acute respiratory syndrome: an in-situ hybridization study of fatal cases, J. Pathol. 202 (2) (2004) 157-163.

[11] R. Lu, X. Zhao, J. Li, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (2020) 565–574.

[12] D. Wrapp, N. Wang, K.S. Corbett, et al., Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation, Science 367 (2020) 1260–1263.

[13] R. Channappanavar, S. Perlman, Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology, Semin. Immunopathol. 39 (2017) 529–539.

[14] M.C. Roberts, M. Levi, R. Schilling, et al., Covid-19: a complex multisystem clinical syndrome, BMJ Opin. (2020) published online May 1, Accessed June 19, 2020.

[15] L.J. Ignarro, Nitric Oxide: Biology and Pathobiology, Academic, Cambridge, MA, 2009.

[16] T. Akaike, H. Maeda, Nitric oxide and virus infection, Immunology 101 (2000) 300–308.

[17] J. Tejero, S. Shiva, M.T. Gladwin, Sources of vascular nitric oxide and reactive oxygen species and their regulation, Physiol. Rev. 99 (1) (2019 Jan 1) 311–379.

[18] C.Y. Cheung, L. Poon, I. Ng, et al., Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis, J. Virol. 75 (2005) 7819–7826.

[19] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemostasis 18 (2020) 844–847.

[20] G. Lippi, C. Mattiuzzi, Hemoglobin value may be decreased in patients with severe coronavirus disease 2019, Hematol. Transfus. Cell Ther. 42 (2) (2020) 116–117.

[21] R. Zhang, D.T. Hess, Z. Qian, et al., Hemoglobin βCys93 is essential for cardiovascular function and integrated response to hypoxia, Proc. Natl. Acad. Sci. U.S.A. 112 (20) (2015) 6425–6430.

[22] P. Cabrales, Examining and mitigating acellular hemoglobin vasoactivity, Antioxidants Redox Signal. 18 (17) (2013) 2329–2341.

[23] Y. Cheng, R. Luo, K. Wang, et al., Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 97 (5) (2020) 829–838.

[24] Y. Chen, Q. Liu, D. Guo, Coronaviruses: genome structure, replication, and pathogenesis, J. Med. Virol. 92 (4) (2020) 418-423.

[25] M. Phadke, S. Saunik, Rapid response: use of angiotensin receptor blockers such as Telmisartan, Losartsan in nCoV Wuhan Corona Virus infections—novel mode of treatment. Response to the emerging novel coronavirus outbreak, BMJ 368 (2020) m406.

[26] D. Gurwitz, Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics, Drug Dev. Res. (2020), https://doi.org/10.1002/ddr.21656 [published online ahead of print, 2020 Mar 4].

[27] W. Sungnak, N. Huang, C. Bécavin, M. Berg, H.C.A. Network, SARS-CoV-2 Entry Genes Are Most Highly Expressed in Nasal Goblet and Ciliated Cells within Human Airways, 2020 *arXiv preprint arXiv:2003.06122*.

[28] L.J. Smyth, M. Cañadas-Garre, R.C. Cappa, A.P. Maxwell, A.J. McKnight, Genetic associations between genes in the renin–angiotensin–aldosterone system and renal disease: a systematic review and meta-analysis, BMJ Open 9 (4) (2019), e026777.

[29] E. de Wit, N. van Doremalen, D. Falzarano, V.J. Munster, SARS and MERS: Recent insights into emerging coronaviruses, Nat. Rev. Microbiol. 14 (8) (2016) 523–534.

[30] M. Antonelli, E. Azoulay, M. Bonten, et al., Year in review in Intensive Care Medicine, 2008: II. Experimental, acute respiratory failure and ARDS, mechanical ventilation and endotracheal intubation, Intensive Care Med. 35 (2) (2009) 215–231.

[31] E.P. Schmidt, Y. Yang, W.J. Janssen, et al., The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis, Nat. Med. 18 (8) (2012) 1217–1223.

[32] R. Uchimido, E.P. Schmidt, N.I. Shapiro, The glycocalyx: a novel diagnostic and therapeutic target in sepsis, Crit. Care 23 (1) (2019) 16.

[33] T.F. Lee, L.L. Jantzie, K.G. Todd, P.Y. Cheung, Postresuscitation *N*-acetylcysteine treatment reduces cerebral hydrogen peroxide in the hypoxic piglet brain, Intensive Care Med. 34 (2008) 190–197.

[34] S. Moncada, A. Higgs, The L-arginine-nitric oxide pathway, N. Engl. J. Med. 329 (1993) 2002–2012.

[35] S. Akerstrom, M. Mousavi-Jazi, J. Klingstrom, M. Leijon, A. Lundkvist, A. Mirazimi, Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus, J. Virol. 79 (2005) 1966–1969.

[36] P. Cabrales, A.G. Tsai, J.A. Frangos, M. Intaglietta, Role of endothelial nitric oxide in microvascular oxygen delivery and consumption, Free Radic. Biol. Med. 39 (9) (2005) 1229–1237.

[37] R. Rossaint, K.J. Falke, F. López, K. Slama, U. Pison, W.M. Zapol, Inhaled nitric oxide for the adult respiratory distress syndrome, N. Engl. J. Med. 328 (6) (1993) 399–405.

[38] L. Chen, P. Liu, H. Gao, et al., Inhalation of nitric oxide in the treatment of severe acute respiratory syndrome: a rescue trial in Beijing, Clin. Infect. Dis. 39 (2004) 1531–1535.

[39] H.Y. Lee, H.M.A. Zeeshan, H.R. Kim, H.J. Chae, Nox4 regulates the eNOS uncoupling process in aging endothelial cells, Free Radic. Biol. Med. 113 (2017) 26–35.

[40] B. Csoma, A. Bikov, L. Nagy, et al., Dysregulation of the endothelial nitric oxide pathway is associated with airway inflammation in COPD, Respir. Res. 20 (1) (2019) 156.

[41] M. Lopez-Sublet, L. Caratti di Lanzacco, A.H.J. Danser, M. Lambert, G. Elourimi, A. Persu, Focus on increased serum angiotensin-converting enzyme level: from granulomatous diseases to genetic mutations, Clin. Biochem. 59 (2018) 1–8.

[42] J. Wang, N. Li, F. Gao, R. Song, S. Zhu, Z. Geng, Balance between angiotensin converting enzyme and angiotensin converting enzyme 2 in patients with chronic heart failure, J. Renin-Angiotensin-Aldosterone Syst. JRAAS 16 (3) (2015) 553–558.

[43] G.R. Thatcher, An introduction to NO-related therapeutic agents, Curr. Top. Med. Chem. 5 (7) (2005) 597–601.

[44] I. Darwish, C. Miller, K.C. Kain, W.C. Liles, Inhaled nitric oxide therapy fails to improve outcome in experimental severe influenza, Int. J. Med. Sci. 9 (2) (2012) 157–162.

[45] A. Afshari, J. Brok, A.M. Møller, J. Wetterslev, Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis, Anesth. Analg. 112 (2011) 1411–1421.

[46] N.K.J. Adhikari, K.E.A. Burns, J.O. Friedrich, J.T. Granton, D.J. Cook, M.O. Meade, Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis, BMJ 334 (2007) 779.

[47] H.H. Al-Sa'doni, A. Ferro, S-nitrosothiols as nitric oxide-donors: chemistry, biology and possible future therapeutic applications, Curr. Med. Chem. 11 (20) (2004) 2679–2690.

[48] E. Keyaerts, L. Vijgen, L. Chen, et al., Inhibition of SARS-coronavirus infection in vitro by S-nitroso-N-acetylpenicillamine, a nitric oxide donor compound, Int. J. Infect. Dis. 8 (4) (2004) 223–226.

[49] S. Akerström, V. Gunalan, C.T. Keng, Y.J. Tan, A. Mirazimi, Dual effect of nitric oxide on SARS-CoV replication: viral RNA production and palmitoylation of the S protein are affected, Virology 395 (1) (2009) 1–9.

[50] M.S. Navati, A. Lucas, C. Liong, M. Barros, J.T. Jayadeva, J.M. Friedman, P. Cabrales, Reducing ischemia/reperfusion Injury by the targeted delivery of nitric oxide from magnetic-field-induced localization of S-nitrosothiol-coated paramagnetic nanoparticles, ACS Appl. Bio Mater. 2 (7) (2019) 2907–2919.

[51] P. Nacharaju, C. Tuckman-Vernon, K.E. Maier, J. Chouake, A. Friedman, P. Cabrales, J.M. Friedman, A nanoparticle delivery vehicle for S-nitroso-N-acetyl cysteine: sustained vascular response, Nitric Oxide 27 (3) (2012) 150–160.

[52] Bellerophon Therapeutics announces first patient treated with INOpulse® inhaled nitric oxide therapy for COVID-19, BioSpace (March 30, 2020). www.biospace.com/article/releases. (Accessed 1 April 2020).

[53] Bellerophon Therapeutics Announces FDA Clears Initiation of Phase 3 Study for INOpulse® Inhaled Nitric Oxide Therapy to Treat COVID-19, Globe Newswire, May 11, 2020. www.globenewswire.com/news-release. (Accessed 17 June 2020).

[54] FDA Grants Expanded Emergency Use Access for COVID-19 Nitric Oxide Treatment, PR Newswire, March 26, 2020. www.prnewsire.com. (Accessed 1 April 2020).

[55] R.T. Zamanian, C.V. Pollack Jr., M.A. Gentile, et al., Outpatient inhaled nitric oxide in a patient with vasoreactive IPAH and COVID-19 infection, Am. J. Respir. Crit.

Care Med. (2020), https://doi.org/10.1164/rccm.202004-0937LE [published online ahead of print, 2020 May 5].
[56] S.S. Boyanapalli, X. Paredes-Gonzalez, F. Fuentes, et al., Nrf2 knockout attenuates the anti-inflammatory effects of phenethyl isothiocyanate and curcumin, Chem. Res. Toxicol. 27 (12) (2014) 2036–2043.
[57] S. González-Reyes, S. Guzmán-Beltrán, O.N. Medina-Campos, J. Pedraza-Chaverri, Curcumin pretreatment induces Nrf2 and an antioxidant response and prevents hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats, Oxid. Med. Cell. Longev. 2013 (2013) 801418.
[58] A. Roy, B. Sarkar, C. Celik, et al., Can concomitant use of zinc and curcumin with other immunity-boosting nutraceuticals be the arsenal against COVID-19? Phytother Res. (2020) https://doi.org/10.1002/ptr.6766 [published online ahead of print, 2020 Jun 2].