

Clinical Manifestation of Endotheliitis in COVID-19 along with Flow-Mediated Vasodilation Study

Kazumi Fujioka*

Department of Radiology, Nihon University School of Medicine, Tokyo, Japan

ABSTRACT

The emerging Coronavirus Disease 2019 (COVID-19) by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a worldwide outbreak and still has spread relentlessly and recrudescence due to the new mutant's occurrence. The respiratory failure from Acute Respiratory Distress Syndrome (ARDS) presents the major cause of mortality and multi-organ failure represents other causes of mortality in patients with COVID-19. The author previously described a link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19 and cutaneous manifestation and vasculitis of COVID-19 in dermatology, suggesting that COVID-19 may be a systemic endothelial disease or a multi-organ disease especially in the severe stage. In this review, the author emphasizes that COVID-19 represents a systemic endothelial disease and/or a multi-organ disease based on the current evidences. The author also suggests that Flow Mediated Vasodilation (FMD) test should be assessed for the risk stratification and therapy effects in follow up study in COVID-19. As COVID-19 is a pathophysiological systemic and complex disease including the endotheliitis, hypercoagulability, and cytokine storm, thereby therapeutic strategy is complicated especially in severe stage. Based on the current evidences therapeutic strategy to improve endothelial dysfunction such as Renin Angiotensin System (RAS) inhibitors or statins might be helpful to prevent and control systemic complications in patients with SARS-CoV-2 infection. In addition to antiviral and anti-inflammatory drugs, a novel therapeutic of Nitric Oxide (NO) use may be a potential prevention and treatment in COVID-19.

Keywords: Endotheliitis; Flow-mediated vasodilation; Nitric oxide; RAS inhibitors; COVID-19

INTRODUCTION

The emerging COVID-19 still has spread relentlessly and recrudescence due to the new mutants occurrence. The author previously described a link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19 [1] and cutaneous manifestation and vasculitis of COVID-19 in dermatology [2], suggesting that COVID-19 may be a systemic endothelial disease or a multiorgan disease especially in the severe stage. In this article, the current knowledges of clinical manifestation of endotheliitis in COVID-19 along with flow-mediated vasodilation study have been reviewed. The author also described a new therapeutic strategy focusing on the endothelial dysfunction.

ENDOTHELIAL DYSFUNCTION AND DAMAGE IN COVID-19

The expression of Angiotensin Converting Enzyme 2 (ACE2) which serves as an essential role in Renin Angiotensin System (RAS) was recognized in the respiratory epithelium, vascular endothelium, and other cell types. It has been also regarded as a primary mechanism of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) entry and infection processes. Hoffmann et al. [3] suggested that SARS-CoV-2 infection depends on ACE2 and type 2 Transmembrane Serine Protease (TMPRSS2) as host cell factors. The author previously described a link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19 [1] and cutaneous manifestation and vasculitis of COVID-19 in dermatology [2]. It

Correspondence to: Kazumi Fujioka, Department of Radiology, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho Itabashi-ku, Tokyo, Japan, Tel: +81-3-5732-1241; Fax: +81-3-5732-1234; E-mail: spbk2xq9@ninus.ocn.ne.jp

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has been proposed that Flow Mediated Vasodilation (FMD) and Nitroglycerin Mediated Vasodilation (NMD) in the brachial artery is a potential procedure for evaluating vascular endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis status [4]. The author has described several reports on the diseases of migraine, Cardiovascular Disease (CVD), Chronic Kidney Disease (CKD), dyslipidemia, and aging liver [5-16] of FMD and NMD studies. The Working Group on Atherosclerosis and Vascular Biology, and the Council of Basic Cardiovascular Science of the European Society of Cardiology provided a position paper in the endothelial dysfunction of COVID-19 [17]. The statement described the evidences that a link between endothelial cells and SARS-CoV-2 infection including the expression and function of its receptor Angiotensin Converting Enzyme 2 (ACE2) in the vasculature. It also suggests that FMD test should be considered for the follow-up of convalescent COVID-19 patients for early detection of long-term cardiovascular complications [17].

ASSOCIATION BETWEEN ENDOTHELIAL DAMAGE AND HYPERCOAGULABILITY IN COVID-19

Nitric oxide (NO) prevents leucocyte and platelet adhesion, inflammatory cell migration, vascular smooth muscle cell proliferation and suppresses apoptosis and inflammation status. As a result of SARS-CoV-2 infection, the host cell loses ACE2 activity leads to decreased conversion to angiotensin. Raised angiotensin II stimulate vascular constriction and reduced angiotensin suppresses NO production which causes increased thrombogenicity and vasoconstriction [18,19]. With respect to the mechanisms of clot formation in COVID-19, SARS-CoV-2 infects monocyte/macrophage and vascular endothelial cell. The infected monocyte/macrophage expresses tissue factor on the surface and initiates coagulation cascade. While the infected vascular endothelial cell due to the release of factor VIII and Von Willebrand Factor (VWF) from Weibel-Palade body promotes coagulation. It is known that two mechanism including the activated macrophage and endothelial injury induce the vicious cycle of the thrombus formation. The typical coagulopathy in COVID-19 shows increased D-dimer, fibrinogen, and VWF levels. While, the relatively normal Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), and platelet count were demonstrated [19].

ENDOTHELIAL DAMAGE AND IMMUNE DYSREGULATION IN COVID-19

It is well known that the endothelium regulates the control of homeostasis, fibrinolysis, vascular tone or vasomotion, inflammation, oxidative stress, vascular permeability, and structure [1,20]. Activated endothelial cells promote localized inflammation by inducing pro-inflammatory gene expression, attracting immune cells, promoting recruitment of inflammatory cells to injured or infected tissues, vascular leak by increasing endothelial permeability, and altering the thrombotic

potential of the local intimal surface. It has been described that impaired endothelial barrier function and IL-stimulation sequentially lead to a cytokine storm and aggravation of the ARDS in patients with COVID-19. Regarding the pathophysiological mechanism of a cytokine storm, IL-1 induces its own gene expression and that of other pro-inflammatory cytokines including TNF- α and IL-6. In result, the induction of IL-6 which is produced by IL-1 provides another amplification loop, leading to the cytokine storm [1,20]. Endothelial cells damage is also compounded by Toll-Like Receptor (TLR) activation by viral RNA recognition, leading to increased Reactive Oxidative Species (ROS) [21]. With respect to the heightened innate immune response and a pro-thrombotic states elicited by innate immune mediators. In result, increased cascade of these pathways, leading to micro and macrovascular endothelial cell injury such as hyper-inflammatory syndrome similar to Kawasaki disease shock syndrome [22]. The author suggests that COVID-19 is a pathophysiological systemic and complex disease including endotheliitis, hyper-coagulability, and immune dysregulation (cytokine storm) thereby therapeutic strategy is complicated especially at severe stage.

CLINICAL MANIFESTATION OF ENDOTHELIITIS IN COVID-19

Libby et al. [20] described that SARS-CoV-2 induces the protean clinical manifestations, affecting the multiple organ systems. Position paper statement described that the presence of a vasculitis such as Kawasaki disease-like syndrome, and endotheliitis as evidence of endothelial cell infection in fatal COVID-19 patients [17]. Monteil et al. [23] demonstrated that SARS-CoV-2 directly infects neojunctional human blood vessel and kidney organoids through human recombinant soluble ACE2 (hrsACE2) and their result showed that hrsACE2 can block early stages of SARS-CoV-2 infections. Ackermann et al. have described pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19, indicating the presence of pulmonary intussusceptive angiogenesis and other pulmonary vascular features in the lungs [24]. Verga et al. [25] described the direct SARS-CoV-2 viral invasion of vascular endothelial cell and diffuse endothelial inflammation, suggesting that the virus can invade into human vascular and induce vasculitis. The report by Menter et al. [26] noted that postmortem examination of COVID-19 patients showed diffuse alveolar damage with severe capillary congestion and variegated features in lungs and other organs suggesting vascular dysfunction. With respect to the dermatologic field, Colmenero et al. [27] indicated that lymphocytic vascular damage was the appearance in patients with COVID-19-associated chilblains. The author has described cutaneous manifestation and vasculitis of COVID-19 in dermatology and suggested that COVID-19 represents an endothelial disease and may be a systemic disease or a multi-organ disease based on the vasculitis in microvasculature [2]. As the endotheliitis have been recognized in multi-organs based on the evidences, the author also emphasizes that COVID-19 represents an endothelial disease and a systemic disease or a multi organ disease especially in severe stage.

ENDOTHELIAL BIOMARKERS AND FUNCTION STUDIES IN COVID-19

Position paper statements also recommend that the endothelial biomarkers and function such as flow-mediated vasodilation (FMD) should be assessed for their usefulness of the risk stratification in patients with COVID-19 [17]. It also suggests that FMD study should be considered for the follow-up of convalescent COVID-19 patients for early detection of long-term cardiovascular complications. It is known that circulating endothelial cell (CEC) are stressed cells detached from injured vessels. CEC counts have increased in various diseases of inflammatory, infectious, or ischemic origin. Guervilly et al described that increased CEC counts show a direct proof of endothelial damage and a clinically informative of biomarker of disease severity [28]. Khider et al. [29] noted that patients had significantly more CECs at admission than COVID-19-negative ones. While, it is known that endothelin-1, endoglin, sE-selectin, thrombomodulin, soluble vascular cell adhesion molecule 1 (sVCAM-1), and vWF are considered as endothelial dysfunction biomarker. Sega et al. [30] have reported time course of endothelial dysfunction markers and mortality in COVID-19 and described the changes over time of sVCAM-1 seem to be strongly associated with mortality. Regarding FMD study, Riou et al. [31] described that FMD was lower in COVID-19 patients as compared to controls and half of the hospitalized COVID-19 survivors showed a decreased FMD<8% at three months of COVID-19 onset. They concluded that impaired FMD is not related to COVID-19 severity three months after hospitalization for SARS-CoV-2 infection. Similar to FMD study, position statements recommend that arterial stiffness as an endothelial marker should be monitored in studies of COVID-19 outcome and therapy effects [17]. Ratchford et al. [32] have reported that significantly lower systemic vascular function and higher arterial stiffness evident weeks after testing positive for SARS-CoV-2 among young adults compared with controls. Siddiqi et al. described SARS-CoV-2-mediated endothelial injury leading to multi-system dysfunction in COVID-19 [33].

THERAPEUTIC STRATEGY FOR COVID-19

With regard to the therapeutic strategy for COVID-19, the statement by position paper described the data from ongoing clinical trials to test recombinant ACE2 may be instrument. It also suggested that statins and beta-blockers on endothelial response to SARS-CoV-2 should be examined [17]. It is known that the ACE converts angiotensin (Ang) to Ang II which promotes vasoconstriction, hypertension, and vascular inflammation. In general, antihypertensive drugs have been developed to reduce the production [ACE inhibitors (ACEIs)] or downstream effects [Ang II receptor blockers (ARBs)] of Ang II [17]. It has been suggested that ACEIs and ARBs do not increase the risk of COVID-19 or disease severity in population-based study [34,35]. As the interaction between the SARS viruses and ACE2 has been proposed as a potential factor in their infectivity [3]. Based on the available evidences, Vaduganathan et al. mentioned that RAAS inhibitors should be continued in

patients in otherwise stable condition who are at risk for, being evaluated for, or with COVID-19 [36]. It is known that the renin-angiotensin-aldosterone system is the mainstay in COVID-19 pathophysiology and Quinaglia et al. [37] described that ACE inhibitors, ATII receptor blockers, and statins are among the most cited. Lopes et al. studied effect of discontinuing versus continuing ACE inhibitors and AT II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19 in a randomized clinical trial. Their results do not support routinely discontinuing ACEIs or ARBs among patients hospitalized with mild to moderate COVID-19 [38]. While Zoufaly et al. described that intravenous delivery of hrsACE2 could have an important effect on blocking the systemic spread of the virus from the lung to other organs in a case report, suggesting a plausible potential effect of the recombinant ACE2 [39]. With regard to statin therapy, Quinaglia et al. described that it improves peripheral NO-mediated arterial relaxation and offset the effects of SARS-CoV-2 [37]. Nagele et al. [40] described that focusing therapies on prevention and improving endothelial dysfunction improve outcomes in patients with COVID-19. Based on the evidence, they recommend continuing RAS inhibitors and statins in patients with COVID-19. With respect to the prevention, according to the current guidelines they recommend that patients with a cardiovascular indication should be prescribed RAS inhibitors and statins. It is putative that eNOS activity and NO production may influence viral infection of endothelial cells by altering TMPRSS2 activity by a position paper statement [17]. The recent study by Hoffmann et al. [3] suggested that Camostat mesylate as TMPRSS2 inhibitor decreases SARS-CoV-2-spike-driven entry into lung epithelial cells. As the ectodomain shedding of ACE2 is required for viral entry and peptidase activity of enzymes, ADAM17 and TMPRSS2 are associated with ectodomain shedding of ACE2 thereby suggesting that blocking the ectodomain shedding of ACE2 provide a treatment opportunity in patients with COVID-19 [41]. While inhibition of SARS-CoV-2's own peptidases such as 3C-like protease (3CLpro) and papain-like protease (PLpro) is also essential aspect of treatment targets against SARS-CoV-2 and α -ketoamide inhibitor which inhibits SARS-CoV-2 RNA synthesis has been also identified [42]. The study suggested that NO level and bioavailability decreased in patients with COVID-19, indicating exogenous supplementation of NO might assist prevention and therapeutic of infection [43]. As a large number of studies have been carried out the treatment effects of iNO in COVID-19 [44], it is plausible that the inhaled NO may provide a potential prevention and therapy in COVID-19 in near future.

CONCLUSION

The author emphasizes that COVID-19 represents a systemic endothelial disease and/or a multi-organ disease based on the current evidences. The author also suggests that FMD test should be evaluated for the risk stratification and therapeutic effects in follow up study in COVID-19.

As COVID-19 is a pathophysiological systemic and complex disease including the endotheliitis, hypercoagulability, and

cytokine storm, thereby therapeutic strategy is complicated especially in severe stage. Based on the current evidences, therapeutic strategy to improve endothelial dysfunction such as RAS inhibitors or statins might be helpful to prevent and control systemic complications in patients with SARS-CoV-2 infection. In addition to antiviral and anti-inflammatory drugs, a novel therapeutic of nitric oxide use may be a promising prevention and treatment in COVID-19.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

REFERENCES

1. Fujioka K. A link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19. *CPQ Med.* 2021;11(4):01-08.
2. Fujioka K. Cutaneous manifestation and vasculitis of COVID-19 in dermatology. *Acta Sci Med Sci.* 2021;5(6):16-19.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-280.
4. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39(2):257-265.
5. Fujioka K, Oishi M, Nakayama T, Fujioka A. Correlation between vascular failure (endothelial dysfunction) and fibrosis markers. *Jpn Med Ultrasonics.* 2016;43:S458.
6. Fujioka K. Association between endothelial dysfunction and aspartate aminotransferase to platelet ratio index in patient without hepatic-related disease. *Angiol Open Access.* 2021.
7. Fujioka K, Oishi M, Fujioka A, Nakayama T. Increased nitroglycerin-mediated vasodilation in migraineurs without aura in the interictal period. *J Med Ultrason.* 2018;45:605-610.
8. Fujioka K. Reply to: Endothelium-dependent and -independent functions in migraineurs. *J Med Ultrason.* 2019;46:169-170.
9. Fujioka K, Oishi M, Nakayama T, Fujioka A. Association of brachial artery measures with estimated GFR >60 mL/min/1.73m² in a cross-sectional study of the community-based women. *Angiol Open Access.* 2019;7:231.
10. Fujioka K. Propensity to the vascular smooth muscle cell abnormality in migraine without aura and vasospastic angina along with a genome-wide association studies. *J Carcinog Mutagene.* 2019;10:334.
11. Fujioka K, Oishi M, Fujioka A, Nakayama T, Okada M. Interrelationship among lipid profiles, arterial stiffness, and nitroglycerin-mediated vasodilation in the community-based setting of Japanese women. *Angiol Open Access.* 2019;7:235.
12. Fujioka K. Effect on microRNA-92a in atherosclerosis along with flow-mediated vasodilation study. *J Cancer Oncol.* 2020;4(1):000153.
13. Fujioka K. A novel biomarker microRNA 92a-3p as a link between cardiovascular disease and chronic kidney disease. *J Carcinog Mutagene.* 2020;11(2):1000345.
14. Fujioka K. Association between chronic liver disease and atherosclerosis: an inflammation as common pathway. *J Clin Trials.* 2021;11(1):444.
15. Fujioka K. NAFLD/NASH-related hepatocellular carcinoma: along with the role of genetics. *J Cancer Oncol.* 2020;4(2):000165.
16. Fujioka K. Current genetic advances in NAFLD/NASH: Related hepatocellular carcinoma along with characteristic clinical manifestations. *J Carcinog Mutagene.* 2021;12(S17):1000001.
17. Evans PC, Rainger GE, Mason JC, Guzik TJ, Osto E, Stamataki Z, et al. Endothelial dysfunction in COVID-19: A position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res.* 2020;116(14):2177-2184.
18. Verdecchia P, Ca vallini C, Spanevello A, Angeli F. COVID-19: ACE2centric infective disease? *Hypertension.* 2020;76(2):294-299.
19. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. *Inflamm Res.* 2020;69:1181-1189.
20. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J.* 2020;41:3038-3044.
21. To EE, Vlahos R, Luong R, Halls ML, Reading PC, King PT, et al. Endothelial NOX2 oxidase exacerbates virus pathogenicity and is a target for antiviral therapy. *Nat Commun.* 2017;12(8):69.
22. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395:1607-1608.
23. Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahi M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissue using clinical-grade soluble human ACE2. *Cell.* 2020; 181:905-913.
24. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-128.
25. Varga Z, Flamer AJ, Steiger P, Habereker M, Andermatt R, Zinkemagel AS, et al. Endothelial cell infection and endothelitis in COVID-19. *Lancet.* 2020;395:1417-1418.
26. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology.* 2020;77:198-209.
27. Colmenero I, Santonja C, Alonso-Riano M, Noguera-Morel L, Hernandez-Martin A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: Histopathological, immunohistochemical and ultrstructural study of seven paediatric cases. *Br J Dermatol.* 2020;183:729-737.
28. Guervilly C, Burtsey S, Sabatier F, Cauchois R, Lano G, Abdili E, et al. Circulating endothelial cells as a marker of endothelial injury in severe COVID-19. *J Infect Dis.* 2020;222(11):1789-1793.
29. Khider L, Gendron N, Goudot G, Chocron R, Hauw-Berlemont C, Cheng C, et al. Curative anticoagulation prevents endothelial lesion in COVID-19 patients. *J Thromb Haemost.* 2020;18:2391-2399.
30. Sega FVD, Fontini F, Spadaro S, Ronzoni L, Zucchetti O, Manfrini M, et al. Time course of endothelial dysfunction markers and mortality in COVID-19 patients: a pilot study. *Clin Transl Med.* 2021;11(3):e283.
31. Riou M, Oulehri W, Momas C, Rouyer O, Lebourg F, Meyer A, et al. Reduced flow-mediated dilatation is not related to COVID-19 severity three months after hospitalization for SARS-CoV-2 infection. *J Clin Med.* 2021;10:1318.
32. Ratchford SM, Stickford JL, Province VM, Stute N, Augenreich MA, Koontz LK, et al. Vascular alterations among young adults with SARS-CoV-2. *Am J Physiol Heart Circ Physiol.* 2021;320:H404-H410.
33. Siddiqi HK, Libby P, Ridker PM. COVID-19 a vascular disease. *Trends Cardiovasc Med.* 2021;31(1):1-5.
34. Mehra MR, Desai SS, Kuy SR, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. *N Engl J Med.* 2020;382(25):e102.
35. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. *N Engl J Med.* 2020;382(25):2431-2440.

36. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382 (17):1653-1659.
37. Quinaglia T, Shabani M, Breder I, Silber HA, Lima JAC, Sposito AC. Coronavirus disease-19: the multi-level, multi-faceted vasculopathy. *Atherosclerosis*. 2021;322:39-50.
38. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Dos Santos TM, Mazza L, et al. Effect of discontinuing vs. continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: A randomized clinical trial. *JAMA*. 2021;325(3): 254-264.
39. Zoufaly A, Poglitsch M, Aberle J, Hoepler W, Seitz T, Traugott M, et al. Human recombinant soluble ACE2 in severe COVID-19. *Lancet Respir Med*. 2020;8(11):1154-1158.
40. Nagele MP, Haubner B, Tanner FC, Ruschizka F, Flammer AJ. Endothelial dysfunction in COVID-19: Current findings and therapeutic implications. *Atherosclerosis*. 2020;314:58-62.
41. Amraei R and Rahimi N. COVID-19, renin-angiotensin system and endothelial dysfunction. *Cells*. 2020;9:1652.
42. Zhang L, Lin D, Sun X, Curth U, Drosten C, Sauerhering L, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Sci*. 2020;368:409-412.
43. Fang W, Jiang J, Su L, Shu T, Liu H, Lai S, et al. The role of NO in COVID-19 and potential therapeutic strategies. *Free Radic Biol Med*. 2021;163:153-162.
44. Tavazzi G, Pozzi M, Mongodi S, Dammassa V, Romito G, Mojoli F. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19. *Crit Care*. 2020;24:508.