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.

Journal of Critical Care 69 (2022) 153988

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Inhaled pulmonary vasodilators in severe COVID-19: Don't hold your breath

Swapnil S. Pawar,, MD, FCICM, CHSE [a,b], M. Elizabeth Wilcox,, MD, PhD [c,d], Frank M.P. van Haren,, MD, PhD, FCICM [a,b,e,*]

[a] Intensive Care Unit, St George Hospital, Sydney, Australia
[b] University of New South Wales Medicine and Health, Sydney, Australia
[c] Department of Medicine, Toronto Western Hospital, Toronto, Canada
[d] Interdepartment Division of Critical Care Medicine, University of Toronto, Toronto, Canada
[e] Australian National University, College of Health and Medicine, Canberra, Australia

Respiratory failure requiring hospitalisation, oxygen treatment and in severe cases, mechanical ventilation, is a devastating complication of SARS-CoV-2 infection. Although the combination of severe hypoxaemia with relatively preserved lung mechanics is not unique to COVID-19 Acute Respiratory Distress Syndrome (ARDS), and has also been described in non-COVID-19 ARDS, there are likely pathophysiological differences [1]. Pneumonitis, endotheliitis, microvascular thrombosis and lung perfusion dysregulation are induced by a significant cytokine release and coagulopathy in response to viral infection, and are thought to be responsible for the degree of severe hypoxaemia seen with COVID-19 ARDS [2-6]. Hypoxia-induced pulmonary vasoconstriction further worsens ventilation-perfusion mismatch as blood flow is restricted to poorly ventilated lung segments, resulting in increased alveolar dead space and severe hypoxaemia. Lastly, hypoxia-induced pulmonary vasoconstriction and the use of non-selective vasopressors may increase pulmonary vascular resistance leading to greater pulmonary hypertension and worsened right ventricular function. Clinical consideration of adjuvant therapeutic strategies aimed at pulmonary vasoconstriction may reverse these physiological changes and may therefore play a role in managing severe COVID-19 induced hypoxaemia [7-9].

The most used pulmonary vasodilators for refractory hypoxaemia are inhaled prostacyclins and inhaled nitric oxide (iNO). Inhaled prostacyclins, such as epoprostenol (iEpo), treprostinil, and iloprost, are potent systemic and pulmonary vasodilators, that act as endogenous inhibitors of platelet aggregation [10]. Their anti-thrombotic effect is attributed to the activation of intracellular adenylate cyclase and increased cyclic adenosine monophosphate in platelets. Inhaled NO is a selective pulmonary vasodilator with additional anti-inflammatory properties attributed to its inhibitory effect on neutrophil activation [11,12]. Previously, inhaled pulmonary vasodilators have demonstrated no mortality benefit in ARDS and therefore are not recommended in routine practice [7,8,11,13]. They may be used however as a rescue therapy.

Preliminary data suggest uncertain effects of inhaled pulmonary vasodilators in patients with COVID-19 ARDS. This data comes from several small retrospective single-centre studies [14-19]. These studies have reported conflicting results regarding the effects on oxygenation. It appears that up to 50% of patients may show a modest increase (10%) in the PaO2/FiO2 ratio, which is of uncertain clinical relevance. No specific factors have been identified to predict which patients may show improved oxygenation when treated with inhaled pulmonary vasodilators. A recent conference abstract reporting a systematic review and meta-analysis that included seven studies ($n = 211$ patients; studies investigating iEpo [$n = 140$] and iNO [$n = 71$]) showed a benefit in oxygenation with iEpo, whereas such a benefit was not seen with iNO administration [20].

In this issue of the Journal of Critical Care, three studies are published investigating the effect of iEpo and/or iNO on both oxygenation, carbon dioxide elimination, and echocardiographic indices in patients with COVID-19 pneumonia requiring either invasive mechanical ventilation or oxygen by high flow nasal canula (HFNC). (JCRC-D-21-01499 (Bonizzoli et al), JCRC-D-21-00672_R1 (Lubinsky et al), JCRC-D-21-01091_R1 (Chiles et al)) In the studies by Bonzzoli et al. and Lubinsky et al. the effects of inhaled pulmonary vasodilators are investigated in adult patients requiring mechanical ventilation. (JCRC-D-21-01499 (Bonizzoli et al), JCRC-D-21-00672_R1 (Lubinsky et al), JCRC-D-21-01091_R1 (Chiles et al)) Comparing the effects of iNO ($n = 69$) and iEpo ($n = 15$), Lubinsky and colleagues report no significant change in any of the measured primary outcomes (PaO2/FiO2, oxygenation index or ventilatory ratio) with administration. Further, the lack of effect was consistent over a 5-day period of drug administration. The median time to administration, left to the discretion of the treating clinician, was 6 days post-intubation and was continued for a median duration of 106 h in the iNO group and 7 days post-intubation and continued for 53 h in the iEpo group. Substantial dropout due to death challenge any conclusion of benefit, nonetheless minimal adverse events were reported in survivors. Consistent findings of no benefit are also reported by Bonizzoli et al., where 12 consecutive patients received iNO as a rescue therapy early in their ICU course. Serial echocardiographic evaluations at baseline, 12 and 24 h showed that half of patients present with right ventricular dilation and varying degrees of right ventricular dysfunction. Further, the mean pulmonary arterial pressure at presentation was 54 ± 7 mmHg. Echocardiogram

https://doi.org/10.1016/j.jcrc.2022.153988

determination of pulmonary hypertension was not improved with the administration of iNO. These findings were consistent with the absence of an effect of iNO on measured oxygenation indices.

Lastly, the use of iEpo in patients with moderate to severe symptoms of COVID-19 but not yet invasively ventilated but receiving high flow nasal oxygen (HFNC) was reported. (JCRC-D-21-01091_R1 (Chiles et al)) In this single centre retrospective study, fifty patients were enrolled, and it was shown that it was feasible to administer iEpo non-invasively. Just over half of patients required invasive ventilation during their ICU stay; one in four patients died in the ICU. Residual confounding of the study design limits any conclusions as to the benefit of iEpo administration early in the disease course of COVID-19. Because there was no control group, it is not possible to determine whether iEpo administration influenced intubation rates. There was no improvement in oxygenation after administration of iEpo as assessed by SpO2/FiO2 ratio, which may question whether the drug was ineffective or perhaps not delivered successfully. More precise measures of drug administration to pulmonary vasculature may prove to be of future benefit in determining any advantage to therapy in this patient population.

Although none of these studies are definitive with regards to the benefit or the lack thereof, of inhaled prostacyclins or iNO, several randomised controlled trials are actively enrolling [21-23]. Whilst we wait for the results of these studies, data from observational cohorts demonstrating variability in clinical response with the use of inhaled pulmonary vasodilators in patients with COVID-19 hypoxaemia leave bedside clinicians with more questions than answers. Is there a role for the use of inhaled pulmonary vasodilators in COVID-19? If so, what is the optimal timing of iEPO or iNO initiation, early or as rescue therapy? How does one titrate to the "best" dose of pulmonary vasodilators? How does illness severity influence response rates (i.e., additional organ failure risk)? Further, are there specific pulmonary vascular effects due to COVID-19 itself that influence the variability in response? And is there a subgroup of patients with COVID-19 most likely to benefit?

In conclusion, the results of the 3 studies published in the Journal may stimulate discussion at the bedside of the potential benefits of pulmonary vasodilators in severe COVID-19 but are unlikely to change current practice. There is no current evidence to support the routine use of inhaled pulmonary vasodilators for severe COVID-19. Similarly to the practice in non-COVID ARDS, some clinicians may continue to consider inhaled pulmonary vasodilators as rescue therapy for patients with COVID-19 hypoxaemia who failed other therapies.

Declaration of Competing Interest

All authors declare no conflict of interest.
No funding was obtained for this work.

References

[1] Panwar R, Madotto F, Laffey JG, Van Haren FMP, Investigators LS, the ETG. Compliance phenotypes in early ARDS before the COVID-19 pandemic. Am J Respir Crit Care Med. 2020;202(9):1244–52.
[2] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46:1099–102.
[3] Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA. 2020;323:2329–30.
[4] Li H, Liu SM, Yu XH, Tang SL, Tang CK. Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents. 2020;55:105951.
[5] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417–8.
[6] van Haren FMP, Page C, Laffey JG, Artigas A, Camprubi-Rimblas M, Nunes Q, et al. Nebulised heparin as a treatment for COVID-19: scientific rationale and a call for randomised evidence. Crit Care. 2020;24:454.
[7] Afshari A, Brok J, Møller AM, Wetterslev J. Aerosolized prostacyclin for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev. 2010:Cd007733.
[8] Fuller BM, Mohr NM, Skrupky L, Fowler S, Kollef MH, Carpenter CR. The use of inhaled prostaglandins in patients with ARDS. Chest. 2015;147:1510–22.
[9] Moezinia CJ, Ji-Xu A, Azari A, Horlick S, Denton C, Stratton R. Iloprost for COVID-19-related vasculopathy. Lancet Rheumatol. 2020;2:e582–3.
[10] Searcy RJ, Morales JR, Ferreira JA, Johnson DW. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis. 2015;9:302–12.
[11] Adhikari NK, Dellinger RP, Lundin S, Payen D, Vallet B, Gerlach H, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med. 2014;42:404–12.
[12] Ichinose F, Roberts Jr JD, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. Circulation. 2004;109:3106–11.
[13] Wright BJ. Inhaled pulmonary vasodilators in refractory hypoxemia. Clin Exp Emerg Med. 2015;2:184–7.
[14] DeGrado JR, Szumita PM, Schuler BR, Dube KM, Lenox J, Kim EY, et al. Evaluation of the efficacy and safety of inhaled Epoprostenol and inhaled nitric oxide for refractory hypoxemia in patients with coronavirus disease 2019. Crit Care Explor. 2020;2:e0259.
[15] Longobardo A, Montanari C, Shulman R, Benhalim S, Singer M, Arulkumaran N. Inhaled nitric oxide minimally improves oxygenation in COVID-19 related acute respiratory distress syndrome. Br J Anaesth. 2021;126:e44–6.
[16] Lotz C, Muellenbach RM, Meybohm P, Mutlak H, Lepper PM, Rolfes CB, et al. Effects of inhaled nitric oxide in COVID-19-induced ARDS - is it worthwhile? Acta Anaesthesiol Scand. 2021;65:629–32.
[17] Sonti R, Pike CW, Cobb N. Responsiveness of inhaled Epoprostenol in respiratory failure due to COVID-19. J Intensive Care Med. 2021;36:327–33.
[18] 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 pneumonia. Crit Care. 2020;24:508.
[19] Tsareva NA, Avdeev SN, Kosanovic D, Schermuly RT, Trushenko NV, Nekludova GV. Inhaled iloprost improves gas exchange in patients with COVID-19 and acute respiratory distress syndrome. Crit Care. 2021;25:258.
[20] Beran Beran A, Mhanna M, Srour O, Ayesh H, Sajdeya O, Ghazaleh S, et al. Inhaled pulmonary vasodilator treatment for COVID-19: a systematic review and META-analysis. CHEST. 2021;160:A558.
[21] Franco V. Venta prost in subjects with COVID-19 requiring mechanical ventilation. ClinicalTrialsgov Identifier: NCT04452669. 2020.
[22] Kharma N. Inhaled iloprost for suspected COVID-19 respiratory failure. ClinicalTrialsgov Identifier: NCT04445246. 2020.
[23] Johansson PI, Bestle M, Soe-Jensen P, Kristiansen KT, Stensballe J, Clausen NE, et al. The effect of prostacyclin (Iloprost) infusion at a dose of 1 ng/kg/min for 72 hours compared to placebo in mechanically ventilated patients with COVID-19: a structured summary of a study protocol for a randomized controlled trial. Trials. 2020;21:746. https://doi.org/10.1186/s13063–020-04696-2.