Inhaled prostacyclin analogues in COVID-19 associated acute respiratory distress syndrome: scientific rationale

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Abstract

**Background:** COVID-19 associated acute respiratory distress syndrome (CARDS) is a severe form of SARS CoV-2 infection and affects about 15–30% of hospitalized patients with a high mortality rate. Growing research and data suggest several available drugs with appropriate pharmacological effects to treat COVID-19.

**Main body:** Prostacyclin analogues are regiments for pulmonary artery hypertension. Prostacyclin analogues are expected to be beneficial in treating CARDS based on at least four rationales: (1) inhaled prostacyclin analogues improve oxygenation, V/Q mismatch, and act as an ARDS therapy alternative; (2) it alleviates direct SARS-CoV-2-related coagulopathy; (3) increases nitric oxide production; and (4) possible anti-inflammatory effect. Prostacyclin analogues are available in oral, intravenous, and inhaled forms. The inhaled form has the advantage over other forms, such as parenteral administration risks. Previously, a meta-analysis demonstrated the beneficial effects of inhaled prosta\-glan\-dins for ARDS treatment, such as improved PaO2/FiO2 and PaO2 along with reduced pulmonary artery pressure. Currently, two ongoing randomized controlled trials are evaluating inhaled epoprostenol (VPCOVID [NCT04452669]) and iloprost (ILOCOVID [NCT04445246]) for severe COVID-19 patients.

**Conclusions:** Inhaled prostacyclin could be considered in patients with refractory, life-threatening hypoxia despite standard management.

**Keywords:** ARDS, COVID-19, Epoprostenol, Prostacyclin

Background

COVID-19 caused by SARS-CoV-2 has posed enormous challenges to healthcare systems in the world. Currently, no therapeutic agent has been thoroughly proven against the disease. Growing research and clinical data regarding the virology and pathophysiology of SARS-CoV-2 suggest several reused drugs with appropriate pharmacological effects and therapeutic efficacy in treating patients with COVID-19 [1].

Most patients hospitalized for COVID-19 develop complications of acute respiratory distress syndrome (ARDS) or respiratory failure. ARDS is an acute inflammatory lung injury associated with increased pulmonary vascular permeability and loss of aerated lung tissue, affecting 23% of mechanically ventilated critically ill patients. In-hospital ARDS mortality is estimated to be between 35 and 46%, depending on the severity of ARDS [2]. However, the mortality rate in COVID-19 with ARDS seems to be higher, ranging from 13 to 73% [3].

Prostacyclin is a potent vasodilator of all vascular beds and an endogenous inhibitor of platelet aggregation. The antithrombotic effect results from the activation of intra-cellular adenylate cyclase and an increase in cyclic adenosine monophosphate (cAMP) in platelets. These agents include epoprostenol, treprostinil, and iloprost [4, 5].
Inhaled prostacyclin analogues have been used for pulmonary vasodilation for vasoreactivity testing, acute cor pulmonale, post-cardiac surgery patients, and those with ARDS [6, 7].

**Main text**

**COVID-19 associated acute respiratory distress syndrome**

COVID-19 associated acute respiratory distress syndrome (CARDS) is a severe form of SARS CoV-2 infection and affects about 15–30% of hospitalized patients. The early hypothesis stated that cytokine storm is related to CARDS development since the elevation of serum IL-6, IL-1β, and TNF-α was evident. However, a recent comparison prevailed that COVID-19 serum cytokine levels were significantly lower to sepsis and another cytokine release syndrome. Severe COVID-19 pneumonitis case definition overlaps with "classic" ARDS. Yet, CARDS is expected to have unique pathophysiological features to "classic" ARDS, namely endothelial barrier disruption followed by intravascular thrombosis, endothelial dysfunction-related hypoxic pulmonary vasoconstriction loss, and exaggerated blood flow to a collapsed lung. A post-mortem examination on CARDS patients revealed a high thrombus burden in pulmonary capillaries, indicating a thrombotic and microangiopathic vasculopathy, compared to "classic" ARDS [8, 9].

Recent multicenter studies demonstrated CARDS had the same lung morphology and respiratory mechanics of "classic" ARDS. Subsequently, CARDS patients with low static respiratory compliance and high D-dimer concentration were associated with a higher mortality rate. It is proposed that widespread pulmonary vascular thrombosis, pulmonary vascular endotheliitis, and elevated D-dimers are unique to COVID-19 patients. This intravascular pathology would increase the dead space and hypoxemia in CARDS patients [2, 10]. Besides, the widespread pulmonary vascular thrombosis could result in pulmonary hypertension (PH) and right ventricular dysfunction (RVD) [11]. Previous meta-analysis demonstrated that PH and RVD are prevalent in COVID-19 patients (19% and 22%, accordingly) and associated with higher mortality, severity, intensive care unit admission, and mechanical ventilation usage [12].

**Mechanism of action prostacyclin analogues in ARDS**

Prostacyclin analogues are the most commonly used regimens for pulmonary artery hypertension. It mimics endogenous prostacyclin (PGI2) and binds to a G-protein coupled receptor on vascular smooth muscle and platelets surface. Followingly, cyclic adenosine monophosphate (cAMP) is activated and induces pulmonary artery vasodilatation, vascular smooth muscle relaxation, and inhibits platelet aggregation. It also appears to antiproliferative and cytoprotective properties. Available forms of prostacyclin analogues are oral, inhaled, and intravenous [13].

Prostacyclin analogues potentially treat CARDS for at least four rationales. First, inhaled prostacyclin analogues improve oxygenation, V/Q mismatch, and act as an ARDS therapy alternative [13–15]. Although it has not been linked to better patient outcomes and is not commonly recommended, it can be utilized in severe, life-threatening hypoxia that is resistant to standard ARDS care, as observed in COVID-19 [13].

Second, it alleviates direct SARS-CoV-2-related coagulopathy by controlling platelet activity. Platelet aggregation is inhibited by prostacyclin at high concentrations. A routine dose of prostacyclin analogue would support platelet adherence to the damaged vascular wall and involve in vascular repair, together with thrombus formation. Prostacyclin therapy counteracts the prothrombotic effect of endothelin and may reduce the in situ thrombosis observed in PAH patients and perhaps in CARDS patients [13, 16].

Third, prostacyclin elevated nitric oxide production, leading to more antithrombotic and vasodilatation. As with inhaled nitric oxide, prostacyclin's potent endothelial effects, such as preventing vasoconstriction and platelet aggregation, may significantly affect these CARDS. Inhaled prostacyclin has the added advantage of inhaled nitric oxide because it does not necessitate the use of any specific equipment and can be administered directly through a standard ventilator (close circuit) [13].

Finally, prostacyclin and nitric oxide speculatively have essential anti-inflammatory effects, particularly on monocyte/macrophage function, which may benefit COVID-infected patients [13, 17].

**Inhaled versus other routes of administration**

Inhaled and oral prostacyclin analogues offer the benefit of avoiding concerns in parenteral administration, such as pain at the infusion site, line discharge, skin and blood infections, and other unfavorable side effects [18]. However, it remains unclear whether such agents that act on the prostacyclin pathway are equally effective whether administered orally or by inhalation. AbuHalimeh et al. [19] presented two cases in which transition from inhaled treprostinil to either oral treprostinil or selexipag, resulting in worsening clinical condition and hemodynamic profile after, subsequently the hemodynamic and clinical profile improved after switched back to inhalation. These divergent responses may reflect either impaired gastrointestinal absorption with lower systemic levels of the drug and/or a preferential (local) action of the inhaled drug specifically on the pulmonary vasculature [19, 20]. The parenteral
route of treprostinil administration of (IV, SC) is bio-
equivalent at a steady-state, while oral treprostinil
yields systemic exposure similar to that of parenteral
administration with approximately 17% bioavailability.
Inhaled treprostinil yields lower systemic concentra-
tions but with delivered locally to the lungs [21].
In general, the side effects of inhaled prostacyclin are
flushing, jaw pain, headaches, nausea, vomiting, diar-
rhrea, and dizziness [4]. In different populations, such as
heart failure, PH, RVD, or refractory hypoxemia after
cardiothoracic surgery, inhaled prostacyclin is consid-
ered safe [22, 23]. No side effects were reported in both
categories. A recent meta-analysis also stated that no
side effects such as bleeding and organ dysfunction were
reported in ARDS patients receiving inhaled prostacyclin
therapy [15].
Whereas, the potential risks and challenges of inhala-
tion therapy in COVID-19 patients include aerosolization
and blockage of bacterial/viral filters used in ventilator
circuits, particularly in epoprostenol. Therefore, place-
ment of the filter in the expiratory port of the ventilation
circuit during inhalation therapy is necessary to mini-
mize aerosolization into the room. In addition, airborne
precautions similar to those for intubation should be
taken.

Clinical evidence of inhaled prostacyclin analogue in ARDS
Clinical experience with inhaled prostacyclin for patients
with ARDS suggests that side effects are rare, although
published data are limited. Previous Cochrane review
by Afshari et al. [15] stated that nebulized iloprost and
epoprostenol reduce PaO₂/FiO₂ ratio in patients with ARDS. However, their effect on mortality reduction was
unknown. Early studies of inhaled iloprost in patients
with ARDS and pulmonary hypertension showed
improved oxygenation without adverse effects on pulmo-
nary mechanics or systemic hemodynamics [24]. Inhaled
epoprostenol may also improve oxygenation in ARDS
patients with hypotension as the most common adverse
event based on a study by Dunkley et al. [25].
A meta-analysis evaluated the potential of inhaled pros-
taglandins (including PGI₂) in ARDS management. The
review includes 25 studies consisted of 10 observational
studies, 7 case reports/series, 6 non-randomized trials,
and 2 randomized controlled trials. Improvements in
PaO₂/FiO₂ and PaO₂ were observed along with reduced
pulmonary artery pressure in inhaled prostaglandins
group. The baseline oxygenation and ARDS etiology did
not interfere with the result. Despite high heterogeneity
and risk of bias due to mixed study designs, this meta-
analysis provides evidence to support inhaled prostaglan-
dins as ARDS treatment [14].

Clinical evidence and ongoing trials of inhaled prostacyclin
analogues in COVID-19
Several retrospective studies have demonstrated the
potential benefit of prostacyclin analogues use, alone
or in combination, with better clinical outcomes in
COVID-19. A retrospective single-center study by
DeGrado et al. [26] reported that in individuals with
refractory hypoxemia due to COVID-19, inhaled epo-
prostenol and inhaled nitric oxide did not elicit mean-
ingful increases in oxygenation parameters. However,
the baseline characteristics were markedly different
and early administration of inhalation might be ben-
eficial. Sonti et al. [27] also reported clinically signif-
ificant improvement in PaO₂/FiO₂ after the initiation of

Table 1 Evidence of inhaled prostacyclin analogues for CARDS

| References          | Study design (sample size) | Regiment                  | Outcome                                                                 |
|---------------------|---------------------------|---------------------------|------------------------------------------------------------------------|
| Filippini et al. [31]| Case report (1)           | Iloprost                  | Improved SpO₂, PO₂/FiO₂, and HRCT findings                            |
| DeGrado et al. [26]  | Retrospective observational (38) | Epoprostenol or nitric oxide | No significant improvement in oxygenation metrics                      |
| Sonti et al. [27]   | Retrospective observational (80) | Epoprostenol               | Fifty percent of patients have a clinically significant improvement in PaO₂/FiO₂ after the initiation of epoprostenol |
| Li et al. [28]      | Retrospective observational (43) | Epoprostenol (some with PP) | The combination of inhaled epoprostenol and PP improved oxygenation compared to epoprostenol or PP individually |
| Franco et al. [29]  | Randomized controlled trial (actual 11) | Epoprostenol             | Respiratory and cardiac/circulatory failure, oxygenation, time to extubation, ICU days, and hospital days (ongoing) |
| Kharma et al. [30]  | Randomized controlled trial (estimated 40) | Iloprost                  | Oxygenation parameters, rates of intubation, ventilation duration, ICU and hospital LOS, rates of prone, ECMO, and mortality (ongoing) |

CARDS, COVID-19 associated acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HRCT, high resolution computed tomography; LOS, length of stay; PO₂/FiO₂, partial pressure arterial oxygen/fraction of inspired oxygen; PP, prone position; SpO₂, oxygen saturation
inhaled epoprostenol in 50% of mechanically ventilated patients. Combination use of inhaled epoprostenol and prone positioning in COVID-19 patients with mechanical ventilation with refractory hypoxemia showed improved oxygenation compared with each treatment individually [28].

To the best of the author’s knowledge, there are currently no published prospective or randomized trials on inhaled prostacyclin analogues in CARDS; however, several [29, 30] are currently being prepared or are being carried out. A randomized, double-blind controlled trial comparing the effects of inhaled epoprostenol delivered via a breath-actuated delivery system to placebo on oxygen levels and treatment outcomes in mechanically ventilated COVID-19 patients is currently on phase 2 (VPCOVID [NCT044452669]) [29]. Another inhaled prostacyclin analogue, iloprost, was also under investigation in phase 2 of a single-arm clinical trial investigating the use of inhaled iloprost 20 mcg three times daily for five days in suspected or confirmed patients COVID-19 with hypoxic respiratory failure (ILOCOVID [NCT04445246]) [30]. Evidence regarding the use of inhaled prostacyclin in CARDS is summarized in Table 1.

Conclusions
Despite the lack of high-quality evidence, the use of inhaled prostacyclin analogues is rational as an adjunctive treatment for COVID. Inhaled prostacyclin may be considered in patients with refractory, life-threatening hypoxia despite standard management. The potential benefits include enhanced perfusion preferentially to well-ventilated lung regions, reducing pulmonary pressures, antithrombotic properties, and a relatively good safety profile.

Abbreviations
ARDS: Acute respiratory distress syndrome; cAMP: Cyclic adenosine monophosphate; CARDS: COVID-19 associated acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; PH: Pulmonary hypertension; RVD: Right ventricular dysfunction.

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References
1. Wu R, Wang L, Kuo HCD, Shannar A, Peter R, Chou PJ et al (2020) An update on current therapeutic drugs treating COVID-19. Curr Pharmacol Rep 6:56–70. https://doi.org/10.1007/s40495-020-00216-7
2. Van Haren FMP, Page C, Laffey JG, Artigas A, Campuzano-Mirillas M, Nunes Q et al (2020) Nebulised heparin as a treatment for COVID-19: scientific rationale and a call for randomised evidence. Crit Care 24:1–11. https://doi.org/10.1186/s13054-020-03148-2
3. Haian SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant HA et al (2020) Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroid use: a systematic review and meta-analysis. Expert Rev Respir Med 14:1149–1163. https://doi.org/10.1080/17476348.2020.1804365
4. Searcy RJ, Morales JR, Ferreira JA, Johnson DW (2015) The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis 9:302–312. https://doi.org/10.1177/175346815599345
5. Bethesda (2012) Prostacyclin analogs. National Institute of Diabetes and Digestive and Kidney Diseases
6. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E et al (2020) Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 46:854–887. https://doi.org/10.1007/s00134-020-06022-5
7. Konstam MA, Kienan MS, Bernstein D, Bockburt B, Jacob M, Kapur NK et al (2018) Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. Circulation 137:e578-622. https://doi.org/10.1161/CIR.0000000000000560
8. Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoglu LU (2021) Severe covid-19 pneumonia: pathogenesis and clinical management. BMJ. https://doi.org/10.1136/bmj.n436
9. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S et al (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. Jama Intern Med 180:934–943. https://doi.org/10.1001/jamainternmed.2020.0994
10. Grasselli G, Tonetti T, Protti A, Maghnia D, Sabbanayagam A, Rajpal S, Lastinger LT et al (2020) Pulmonary vasodilators beyond the bounds of pulmonary arterial hypertension therapy in COVID-19. Pulm Circ 10:2045894020970369. https://doi.org/10.1177/2045894020970369
14. Fuller BM, Mohr NM, Skrupky L, Fowler S, Kollef MH, Carpenter CR (2015) The use of inhaled prostaglandins in patients with ARDS: a systematic review and meta-analysis. Chest 147:1510–1522. https://doi.org/10.1378/chest.14-3161
15. Afshari A, Bastholm Bille A, Allingstrup M (2017) Aerosolized prostacyclins for acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD007733.pub3
16. Sakamaki F, Kyotani S, Nagaia N, Sato N, Oya H, Satoh T et al (2000) Increased plasma P-selectin and decreased thrombomodulin in pulmonary arterial hypertension were improved by continuous prostacyclin therapy. Circulation 102:2720–2725. https://doi.org/10.1161/01.185.102.22.2270
17. Schroder K, Hertzog PJ, Ravasi T, Hume DA (2004) Interferon-γ: an overview of signals, mechanisms and functions. J Leukoc Biol 75:163–189. https://doi.org/10.1189/jlb.0603252
18. McLaughlin VV, Bound RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF et al (2010) Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol 55:1915–1922. https://doi.org/10.1016/j.jacc.2010.01.027
19. AbuHalimeh BJ, Parambil JG, Tonelli AR (2017) Different efficacy of inhaled and oral medications in pulmonary hypertension. Hear Lung J Acute Crit Care 46:334–337. https://doi.org/10.1016/j.hrtlng.2017.04.010
20. Mitchell JA, Almetaj-Shala B, Kirkby NS, Wright WR, Mackenzie LS, Reed DM et al (2014) Role of prostacyclin in pulmonary hypertension. Glob Cardiol Sci Pract 2014:53. https://doi.org/10.5339/gcsp.2014.53
21. Kumar P, Thudium E, Laliberté K, Zaccardelli D, Nelsen A (2016) A comprehensive review of treprostinil pharmacokinetics via four routes of administration. Clin Pharmacokinet 55:1495–1505. https://doi.org/10.1007/s40262-016-0409-0
22. Huang CY, Lee JK, ChenZW, Cheng JF, Chen SY, Lin LY et al (2020) Inhaled prostacyclin on exercise echocardiographic cardiac function in preserved ejection fraction heart failure. Med Sci Sports Exerc 52:269–277. https://doi.org/10.1249/MSS.0000000000002145
23. De Wet CJ, Affleck DG, Jacobsohn E, Avidan MS, Tymkew H, Hill LL et al (2004) Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. J Thorac Cardiovasc Surg 127:1058–1067. https://doi.org/10.1016/j.jtcs.2003.11.035
24. Sawhney E, Ellis AL, Kinasewitz GT (2013) Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. Chest 144:55–62. https://doi.org/10.1378/chest.12-2296
25. Dunkley KA, Louzon PR, Lee J, Yu S (2013) Efficacy, safety, and medication errors associated with the use of inhaled epoprostenol for adults with acute respiratory distress syndrome: a pilot study. Ann Pharmacother 47:790–796. https://doi.org/10.1345/aph.1R540
26. DiGrado JR, Szumita PM, Schuler BR, Dube KM, Lenox J, Kim EY et al (2020) 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 2:e0259. https://doi.org/10.1097/CCE.000000000000259
27. Sonti R, Pike CW, Cobb N (2021) Responsiveness of inhaled epoprostenol in respiratory failure due to COVID-19. J Intensive Care Med 36:327–333. https://doi.org/10.1177/0885066620976523
28. Li J, Fink JB, Augustynovich AE, Mirza S, Kallet RH, Dhand R (2020) Effects of inhaled epoprostenol and prone positioning in intubated coronavirus disease 2019 patients with refractory hypoxemia. Crit Care Explor 2:e0307. https://doi.org/10.1097/CCE.0000000000000307
29. Franco V (2020) Venta prost in subjects with COVID-19 requiring mechanical ventilation. ClinicalTrialsGov
30. Kharma N (2020) Inhaled iloprost for suspected COVID-19 respiratory failure. ClinicalTrialsGov
31. Filippin A, Bnà C, Bellosta R, Bazzani R, Luzzani L, Pogener MA et al (2021) COVID-19 acute respiratory distress syndrome: can iloprost have a role for the treatment? Respi Med Case Rep. https://doi.org/10.1016/j.rmcrc.2021.101358

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