

Use of Inhaled Vasodilators in ARDS Patients: A Review Article

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a severe lung injury leading to bilateral lung opacities and severe hypoxemic respiratory failure. It results from acute inflammation, endothelial dysfunction, and disruption of the alveolar-capillary membrane. ARDS management encompasses lung-protective supportive care such as lung-protective ventilation strategies. Inhaled pulmonary vasodilators show potential as adjunctive therapies for refractory hypoxemia and hold promise in improving oxygenation and reducing pulmonary vascular resistance in severe ARDS. However, their impact on mortality remains uncertain, and current evidence supports their role as rescue therapies. Prudent consideration and assessment of potential benefits and risks are crucial when integrating these agents into clinical practice.

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INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a critical condition that causes severe lung injury and ultimately leads to acute hypoxemic respiratory failure. The rapid development of severe hypoxemia, bilateral pulmonary opacities on chest radiography, and respiratory distress without left atrial hypertension are the hallmarks of (ARDS). Many conditions, including sepsis, pneumonia, trauma, aspiration, and acute pancreatitis, can result in (ARDS), a complicated illness. 10% of patients hospitalized in critical care units are thought to have ARDS, which is linked to a death rate of up to 40% [1].

The pathogenesis of ARDS involves a complex interplay between acute inflammation and endothelial dysfunction, leading to the accumulation of fluid and proteinaceous material in the alveolar space and impaired gas exchange. The inflammatory response in ARDS is characterized by the activation of immune cells, such as neutrophils and macrophages, which release cytokines and chemokines that recruit more inflammatory cells to the lungs. This leads to the destruction of lung tissue and the formation of hyaline membranes. Endothelial dysfunction is also a key feature of ARDS, with increased pulmonary vascular permeability and the formation of microthrombi leading to increased dead space and worsening hypoxemia [2].

Targeted therapies to address the underlying cause of the illness are combined with supportive care such as hydration management and mechanical ventilation to effectively manage (ARDS). Mechanical ventilation is a cornerstone of ARDS management, but it can also lead to further lung injury if not used appropriately. Therefore, lung-protective ventilation strategies are recommended, including the use of low tidal volumes (6-8 ml/kg ideal body weight) and appropriate titration of positive end-expiratory pressure (PEEP) to prevent lung overdistension (barotrauma) or atelectasis (atelectotrauma) [3]. The use of corticosteroids in early ARDS is controversial, as studies have shown conflicting results. This can be partly explained by the significant heterogeneity of ARDS. Steinberg et al. conducted a study evaluating methylprednisolone for 14 days in patients with ARDS for at least 7 days. This study demonstrated more ventilator-free days in the steroids group, but no difference in 60-day mortality was noted [4]. Similarly, Tongyoo et al. evaluated hydrocortisone in patients with sepsis-associated ARDS within 12 hours of diagnosis; no difference in mortality was observed with corticosteroids [5].

However, corticosteroids have been shown to provide a survival benefit in a randomized, placebo-controlled trial of moderate-severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 200$) and in other studies involving COVID-19 ARDS [6, 7]. Based on the available evidence, corticosteroids appear to be beneficial in ARDS caused by eosinophilic pneumonia, organizing pneumonia, pneumocystis pneumonia, severe bacterial pneumonia, and coronavirus disease 2019 (COVID-19).

Measures to treat refractory hypoxemia in moderate to severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) include prone positioning to improve homogeneity of ventilation (distribution of blood and airflow more evenly), use of muscle relaxants to decrease oxygen consumption (and improve arterial hemoglobin saturation) and minimize patient-ventilator dyssynchrony, and extracorporeal membrane oxygenation (ECMO). Furthermore, because inhaled pulmonary vasodilators can increase oxygenation and lower pulmonary vascular resistance, they have been studied as a possible treatment for refractory hypoxemia. The rationale for this approach is the selective vasodilation of pulmonary vessels which increases pulmonary blood flow in the better-ventilated lung units [8].

INHALED PULMONARY VASODILATORS

MECHANISM OF ACTION

Inhaled pulmonary vasodilators are drugs that cause selective vasodilation of the pulmonary arteries that supply well-ventilated alveoli, leading to improved oxygenation by redirecting blood to healthy alveoli. In ARDS, inhaled vasodilators can also reverse the normal vasoconstriction caused by low oxygen levels in the pulmonary blood vessels of healthy alveoli. ARDS increases pulmonary vascular resistance through various mechanisms, such as vasoconstriction due to alveolar hypoxia, lung consolidation resulting in compression of the pulmonary vasculature, and atelectasis. This process increases pulmonary blood pressure and increases right ventricular (RV) afterload [9]. These agents reduce the resistance in the pulmonary vasculature and RV afterload, improving RV function.

Individuals who have COVID-19 Acute Respiratory Distress Syndrome (CARDS) are prone to experiencing platelet hyperactivity, which may account for the elevated occurrence of microvascular thrombi that contain elevated levels of platelets in the systemic and pulmonary circulations [10]. The delivered prostaglandins by

inhalation have a specific inhibitory effect on platelet activation, thereby reducing the risk of microthrombi formation. This action could potentially provide additional advantages in the management of CARDS [11]. Nitric oxide (iNO) inhaled has been demonstrated to have an in-vitro anti-viral activity on SARS-CoV2.

TYPES OF INHALED PULMONARY VASODILATORS

Inhaled Pulmonary Vasodilators (IPV) encompass a range of medications, such as inhaled nitric oxide (iNO), inhaled aerosolized prostacyclins such as epoprostenol, iloprost, treprostinil, and other vasodilators that are delivered directly to the lungs.

INHALED NITRIC OXIDE (iNO) - The discovery of nitric oxide (NO) as a critical factor responsible for the relaxation of endothelium was first reported in 1987 [12]. Three different isoforms of nitric oxide synthase (NOS) are found in mammalian cells, namely endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). While nNOS and eNOS produce NO that has a transient duration, iNOS generates substantial amounts of NO in response to an infection, and the effect persists for an extended period [13]. The action of NO involves the stimulation of soluble guanylate cyclase, which leads to the overproduction of cyclic guanine monophosphate (cGMP); cGMP then triggers the activation of protein kinase G, resulting in the relaxation of smooth muscles in both vascular and nonvascular tissues, achieved by multiple downstream pathways that reduce intracellular calcium levels [14].

INHALED EPOPROSTENOL - Epoprostenol is a prostacyclin that is a metabolite of arachidonic acid and prostaglandin I₂ (PGI₂), one of many natural prostaglandins. [15, 16, 17]. This substance is synthesized in vascular tissues, particularly in endothelial and smooth muscle cells. It has important effects in patients with ARDS. In a dose-dependent manner, epoprostenol has a vasodilation effect on pulmonary and systemic vasculature [18]. By taking this action, it is possible to reduce the lungs' vasoconstriction and subsequently lower microvascular pressure. Furthermore, it also can inhibit platelet aggregation, therefore stopping platelets from adhering to the vascular endothelium [19]. Finally, during the inflammatory response, epoprostenol is known to inhibit the activation of leukocytes and monocytes, leading to a decrease in the release of lysosomal enzymes. Essentially, epoprostenol can contribute to the reduction of inflammation associated with ARDS [20, 28].

BENEFITS AND RISKS OF USING INHALED PULMONARY VASODILATORS IN ARDS

INHALED NITRIC OXIDE - In patients with severe ARDS (PaO₂: FiO₂ ratio <100), a modest dosage of iNO (e.g., 5–20 ppm) has been shown to increase arterial oxygenation [21]. iNO selectively dilates the pulmonary blood vessels [22], which reduces pulmonary pressure [23] and pulmonary transvascular albumin flux [24], leading to improved oxygenation [21].

Amid the COVID-19 outbreak, elevated systolic pressure in the pulmonary arteries has been linked to a potentially fatal hemodynamic parameter. [25]. These findings suggest the use of RV failure prevention interventions as therapeutic targets (i.e., RV protective measures) in addition to the proven lung-protective ventilation strategy [26, 27]. SARS-CoV2 viral load could be reduced by iNO while decreasing intrapulmonary inflammation, alveolar dead space, and ventilation-perfusion efficiency could be improved.

Despite its beneficial effects, iNO is not routinely used in ARDS treatment; however, it has been proposed as one of the “rescue” strategies for severe hypoxemia. This is because its effects are transient, and there is no evidence that it improves survival or other clinical outcomes (such as ventilator-free days, VFDs, or the length of stay in the intensive care unit). [28, 29, 30].

Nitric oxide (NO) plays a significant role in regulating both glomerular function and renal vascular tone. A suggestion has been made that alterations in NO production may lead to acute renal failure by affecting the function of mitochondria, enzymes, DNA, and membranes [31, 32]. High levels of inhaled NO can cause direct tissue toxicity. High NO exposure (>500–1000 ppm) can result in an immediate formation of nitrogen dioxide (NO₂), which can induce hypoxemia, pulmonary edema, alveolar hemorrhage, serious methemoglobinemia, and even death. [33, 34].

INHALED EPOPROSTENOL (iEPO) - Similar to iNO, iEPO delivers more blood to zones with active ventilation by causing vasodilation of pulmonary vascular beds [35]. When studying the effects of prostacyclins on inflammatory cytokines, it has been discovered by researchers that prostacyclin inhibits the production of tumor necrosis factor (TNF) α in activated monocytes [36]. The production of inflammatory cytokines can significantly decrease the release of prostacyclin in the pulmonary vasculature. This shift in balance may lead to a proinflammatory response

[37]. Due to the proinflammatory condition of ARDS and the high level of IL-6, IL-1, IL-10-a, and TNF expression, supplementing prostacyclin could potentially provide benefits. Lastly, prostacyclin may reduce the thrombo-occlusive state of ARDS due to their ability to inhibit platelet function [38, 39]. Only intravenous prostacyclin has been shown to have an antiplatelet impact; results employing iEPO have not confirmed this observation [40].

Recently, iEPO has been proposed as a substitute for iNO because it has comparable effectiveness, fewer systemic side effects, is easier to administer, and is significantly less expensive [36]. The most significant possible side effects of PGI₂ are systemic hypotension and bleeding because it potently vasodilates and inhibits platelet aggregation. An effective dose range based on dose-response studies is 5–50 ng/kg/min [36, 40, 41, 42, 43, 44, 45, 46, 47], which does not cause systemic hypotension. One patient experienced systemic hypotension when they received an aerosolized dose of over 200 ng/kg/min [48]. Additionally, a group of 5 healthy male volunteers experienced hypotension after inhaling around 700 ng/kg/min [49]. Similar to iNO, abrupt cessation of inhaled PGI₂ can cause burst pulmonary vasoconstriction, acute V/Q mismatch, hypoxemia, pulmonary hypertension, and right ventricular failure. However, the risk of such negative consequences may be lower with aerosolized PGI₂ as opposed to iNO, as a result of PGI₂'s prolonged half-life and lasting effect (20–25 min as opposed to 5 min for iNO) [41]. Weaning off gradually can help reduce the likelihood of a relapse. There is no statistically significant difference in mortality or other clinical outcomes, even in the presence of enhanced oxygenation [50, 51].

PRACTICAL CONSIDERATIONS FOR THE USE OF INHALED PULMONARY VASODILATORS IN ARDS

The use of inhaled pulmonary vasodilators in patients with ARDS remains controversial. Many practical aspects of its use are taken into consideration when deciding the optimal therapeutic strategy for implementation.

Regarding morbidity and mortality, one systematic review evaluating ARDS patients' response to the administration of inhaled nitric oxide has revealed that transient improvement in oxygenation can be observed but with no overall reduction in mortality. Although significant advancement was found in the signs of severe acute hypoxaemic respiratory failure (AHRF), including the ratio of PaO₂/FiO₂ and oxygenation index at 24 hours, inhaled nitric oxide was

not found to significantly decrease mortality or the length of stay in the intensive care unit (ICU) or hospital. In fact, it appears that inhaled nitric oxide could lead to impairment of renal function among adults. The study concluded that evidence is insufficient to recommend the usage of iNO in any category of critically ill patients with AHRF [52]. Moreover, a systematic review and meta-analysis conducted by Fuller et al. in 2023 investigated the association of inhaled prostaglandins and mortality in ARDS patients along with changes in pulmonary physiology. The results of the study demonstrated an improvement in oxygenation and a decrease in pulmonary artery pressure, however, it was unclear that any benefit regarding mortality is derived, and long-term clinical benefit is limited [53].

Regarding the administration of inhaled pulmonary vasodilators for the treatment of right ventricular dysfunction (RVD) in ARDS, a scoping review evaluated 17 studies and found that 11 of the 15 studies exploring inhaled nitric oxide showed a reduction in oxygenation parameters, while 6 failed to establish statistically significant results. On the other hand, only two studies reported reduced mortality in patients who were treated with inhaled nitric oxide [54].

Furthermore, in the COVID-19 pandemic, the use of inhaled vasodilators in the management of COVID-19 patients with ARDS has been evaluated. One multicenter study investigated the outcome of utilizing high-dose inhaled nitric oxide in the treatment of non-intubated spontaneously breathing COVID-19 patients and identified that an improvement of respiratory rate and systemic oxygenation was observed in tachypneic and hypoxemic patients medicated with inhaled nitric oxide at 160 ppm for 30 min twice daily [55]. Another recent study assessed the role of inhaled pulmonary vasodilators in COVID-19 patients and concluded that PaO₂/FiO₂ ratios before inhalation of pulmonary vasodilators were significantly lower compared to ratios after inhalation of pulmonary vasodilators. Nonetheless, similar results were observed between the inhaled pulmonary vasodilators and standard therapy group in terms of mortality rates, need for endotracheal intubation, and hospital length of stay (LOS) [56]. Furthermore, the study of Al Sulaiman et al. concluded that under the effect of inhaled pulmonary vasodilators, benefits may be regarded in the oxygenation status of COVID-19 patients with moderate-to-severe ARDS but not in mortality [57].

In conclusion, further studies are needed to evaluate inhaled pulmonary vasodilators as a therapy for ARDS, and clinical use of inhaled vasodila-

tors should be supported with more robust evidence. To this date, research suggests that the use of inhaled vasodilators is better used as a rescue therapy and as a bridge to more definitive measures in patients of ARDS with refractory hypoxemia.

AUTHORS' CONTRIBUTION

Hamza Alhawamleh: writing of sections 2 and 3 (Inhaled Pulmonary Vasodilators and Benefits and risks of using inhaled pulmonary vasodilators in ARDS). Sadeen Zein Eddin: writing of section 4 (Practical Considerations for the Use of Inhaled Pulmonary Vasodilators in ARDS). Yara Almadani: writing of section 1 (introduction). Basel Naim Alrawashdeh: writing of a paragraph in the introduction. Mazen O. Al-Qadi: supervision

DISCLOSURE

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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