Inhaled pulmonary vasodilators: a narrative review

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Abstract: Pulmonary hypertension (PH) is a severe disease that affects people of all ages. It can occur as an idiopathic disorder at birth or as part of a variety of cardiovascular and pulmonary disorders. Inhaled pulmonary vasodilators (IPV) can reduce pulmonary vascular resistance (PVR) and improve RV function with minimal systemic effects. IPV includes inhaled nitric oxide (iNO), inhaled aerosolized prostacyclin, or analogs, including epoprostenol, iloprost, treprostinil, and other vasodilators. In addition to pulmonary vasodilating effects, IPV can also be used to improve oxygenation, reduce inflammation, and protect cell. Off-label use of IPV is common in daily clinical practice. However, evidence supporting the inhalational administration of these medications is limited, inconclusive, and controversial regarding their safety and efficacy. We conducted a search for relevant papers published up to May 2020 in four databases: PubMed, Google Scholar, EMBASE and Web of Science. This review demonstrates that the clinical using and updated evidence of IPV. iNO is widely used in neonates, pediatrics, and adults with different cardiopulmonary diseases. The limitations of iNO include high cost, flat dose-response, risk of significant rebound PH after withdrawal, and the requirement of complex technology for monitoring. The literature suggests that inhaled aerosolized epoprostenol, iloprost, treprostinil and others such as milrinone and levosimendan may be similar to iNO. More research of IPV is needed to determine acceptable inclusion criteria, long-term outcomes, and management strategies including time, dose, and duration.

Keywords: Pulmonary hypertension (PH); nitric oxide; epoprostenol; iloprost; treprostinil

Introduction

Pulmonary hypertension (PH) is a severe disease that affects people of all ages that can occur as an idiopathic disorder at birth or as part of a variety of cardiovascular and pulmonary disorders. PH is considered when the mean pulmonary artery pressure (PAP) is greater than 25 mmHg measured through the right heart catheter (1). Severe acute PH may develop or worsen of right ventricular (RV) failure. RV failure and PH may reduce left ventricular (LV) filling, LV diastolic and systolic pressures, result in reduction of cardiac output and hypotension (2,3). In the clinical management with PH, optimizing RV afterload and RV performance is an important physiological goal. Inhaled pulmonary vasodilators (IPV) can reduce pulmonary vascular resistance (PVR), improve RV function, and with minimal systemic effects. It is including inhaled nitric oxide (iNO), inhaled aerosolized prostacyclin, or analogs including epoprostenol, iloprost, treprostinil, and other vasodilators. In addition to pulmonary vasodilating effects, IPV can also be used to improve oxygenation, reduce inflammation, and protect cell. However, evidence supporting the inhalational

administration of these medications is limited, inconclusive, and controversial regarding their safety and efficacy.

This review seeks to: review the clinical use and updated evidence of IPV, explore possible directions in future research. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4895).

Methods

We conducted a search for relevant papers published up to May 2020 in four databases: PubMed, Google Scholar, EMBASE and Web of Science. Search terms and phrases included "pulmonary hypertension", "pulmonary vasodilators", "nitric oxide", "prostacyclin", "epoprostenol", "iloprost", "treprostinil", "milrinone", "levosimendan". Case reports, abstracts, review articles, and original research articles were reviewed.

Discussion

Inhaled nitric oxide (iNO)

NO is a colorless, odorless gas, and only slightly soluble in water. It was first identified by Joseph Priestley in 1774, and discovered accidentally to relax vascular smooth muscle by Palmer and colleagues in 1987 (4). In 1991, iNO as a selective pulmonary vasodilator was recommend in models of PH (5). In 1999, the FDA approved iNO for neonatal patients (>34 weeks gestation) in hypoxic respiratory failure patients with PH (6). Currently, iNO is widespread in the daily clinical practice for kinds of cardiopulmonary disorders.

Biochemistry and physiological actions

NO will react with oxygen, other free radical species, various amino acids, and transition metals, with a potential for nitrogen dioxide (NO_2), peroxynitrite, and methemoglobin (7,8). Therefore, medical-grade NO gas is produced under carefully controlled conditions, thinned with pure nitrogen, and saved in oxygen-free environment. NO exerts its effects via activation of guanylate cyclase, which enhances cyclic guanosine monophosphate (cGMP), resulting in relaxation of smooth muscle (9). When NO is preferentially inhaled into well-ventilated alveoli, the consequences of selective pulmonary vasodilation resulting in reduced mean PAP, PVR, and RV afterload improve ventilation-perfusion (V/Q) distribution, reduce shunting, and improve oxygenation (9).

In addition to its pulmonary vasodilating effects, NO down-regulates leukocyte responses, reduces platelet aggregation, promotes neurotransmission, enhances bronchodilation, and reduce inflammatory responses caused by interference such as ischemia and reperfusion (10).

Clinical use

In contrast to intravenously infused vasodilators, iNO produces selective pulmonary vasodilation in patients with PH, without systemic vasodilation and severe systemic hypotension (11). In addition, most clinical trials have claimed that iNO has relatively few systemic side effects, and without significant toxicities. Therefore, iNO is widely used in neonates, pediatrics, and adults with different cardiopulmonary diseases. Depending on the clinical target, iNO is in a range of 1–80 ppm. The limitations of iNO include high cost, flat dose-response, risk of significant rebound PH after withdrawal, and the requirement of complex technology for monitoring. More evidence is needed for the clinical use of iNO, and further translational research is required.

Persistent pulmonary hypertension of the newborn (PPHN)

PPHN is the result of failed pulmonary vascular transition at birth. It will lead to PH with severe hypoxemia, which may eventually lead to circulatory failure and finally life-threatening (12). PPHN remains a major problem occurring as many as 1−2 per 1,000 in live births. It is a frequent cause for admission to the intensive care unit, with high mortality of 10−20% (13). Oxygen supplementation, avoidance of hypothermia, agitation, and acidosis are included in treatments of reduce PVR. Further deterioration in hemodynamics may require iNO, tropic support, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation (ECMO) (14). A few studies and case series showed that iNO sustains improved in arterial oxygenation and systemic hemodynamics in neonates, reduces the need for ECMO and seems to reduce rebound hypoxemia and production of toxic byproducts (15-19). However, the dosing of iNO remains a more complex question. In many centers, initiate dose of iNO is 20 ppm, and easy to wean. Furthermore, minimizing the dose and monitoring for met-hemoglobinemia is essential in the utilization of iNO if neonates are involved.

Bronchopulmonary dysplasia (BPD)

BPD is now defined as arrested lung growth with reduced

alveolarization and dysmorphic vasculature. Consequently, lung development is markedly impaired, which can affect lung function and is associated with prolonged hospitalization (20). Early studies reported that iNO increased angiogenesis and alveolarization in animal models (21,22). However, previous clinical trials among premature newborns with respiratory failure, revealed that early routine use of iNO does not improve survival without BPD, and the effect of later use of iNO to prevent BPD is likely small (23-30). Several previous studies did not support iNO to prevent BPD in preterm infants requiring respiratory support (31-34). However, a meta-analysis claimed that the race effects of iNO should be considered for preterm African American infants at high risk for BPD, interpreted as genetic variation related to lung development, drug metabolism, and immune response (35,36). More studies are needed to investigate the off-label use of iNO as a rescue therapy in the future.

Congenital cardiac disease

PH is one of the most challenging complications in congenital heart surgery and is exacerbated by cardiopulmonary bypass (CPB). CPB may be responsible for postoperative dysfunction of pulmonary endothelial cells and may contribute to postoperative PH in children. After CPB, iNO is use as a selective pulmonary vasodilator and without systemic circulatory effects (37). Routine use of iNO after congenital heart surgery can directly reduce PVR, lessen the risk of PH crises, and shorten the postoperative course, without toxic effects (38-41). However, there are no differences in several clinical outcomes, including long-term mortality and neurodevelopmental outcome. More studies are needed to confirm its role (42).

Cardiothoracic surgery

PH often increases the difficulty in the care of cardiac surgery patients, and increases morbidity and mortality. The selective pulmonary vasodilators are frequently administered in these patients to prevent or reverse RV failure and cardiogenic shock. iNO has proven effective in reducing PAP without systemic arterial hypotension, supplying cardioprotective effects during CPB, improving oxygenation with vasodilation in well-ventilated areas, and maintaining a very low incidence of adverse effects (43-48). Furthermore, iNO was reported to have a kidney-protective effect by decreasing the incidence of acute kidney injury (49-51). However, the clinical outcomes of iNO were of no or minimal benefit; large randomized trials are needed

to assess its effect on major clinical outcomes and its cost-effectiveness (52,53). iNO also has been used to treat PH and hypoxemia that occurs in thoracic surgery during one-lung ventilation, postpneumonectomy pulmonary edema, and lung transplantation (54,55).

Left ventricular assist devices (LVAD)

RV failure after implantation of LVAD increases postoperative morbidity and mortality (56). Treatments that have been used include optimizing volume status, intravenous inotropes, vasodilators, and right ventricular assist devices (RVAD). When the PVR >3 Wood units, or transpulmonary gradient >12 mmHg, iNO is the preferred initial treatment, aimed at minimizing systemic effects directly to the lung (57). iNO results in decreased PVR, decreased RV distension, increased RV ejection, promoted LV filling, and improved LVAD performance (58-60). However, iNO does not achieve significance for a reduction in RVAD. Similarly, iNO after LVAD placement provides no significant improvement in mechanical ventilation time, reduction in hospital or intensive care unit stay and need of RVAD (61).

ECMO

ECMO is used as rescue therapy in severe cardiopulmonary disease. In routine clinical practice, patients frequently receive iNO during ECMO for PH treatment. iNO into the ECMO circuit is safe and could potentially reduce ischemia-reperfusion injury, even reduce the need of mechanical support in end-organ dysfunction (62). A large observational study evaluated the benefits of iNO use among patients during ECMO, showing that it was not associated with any survival benefits (63).

Cardiac arrest (CA)

Sudden CA is a main cause of death in the world. The poor outcomes are mainly owing to post-CA syndrome, including cerebral and myocardial dysfunction after a pronounced inflammatory response (64). iNO may improve post-CA outcomes in animal models and patients. In adult male mice, iNO after CA reduce water diffusion abnormality, caspase-3 activation, cytokine induction in the brain, and increase serum nitrate/nitrite levels, show the protective effects on the outcome (65). Following 10 minutes CA in rats, 40 ppm iNO improve seven-day neurological outcomes and survival, and 20 ppm iNO with mild therapeutic hypothermia had similar results (66,67). iNO during CPR and with a percutaneous LVAD can improve transpulmonary blood

flow, and clinical neurological outcomes in pigs (68). However, human trials are still lacking.

Ischemia-reperfusion injury (IRI)

IRI is a complex series of events, involving intracellular injury and causing inflammatory responses, which can lead to vital organ injury and even failure. In the feline mesentery, a role for iNO for IRI of distal microvascular beds was first demonstrated in 1998 (69). In mice models subjected to 60-minute left anterior descending artery ligation followed by reperfusion, iNO, iNO + H_2, or iNO with phosphodiesterase 5 (PDE5)-specific inhibitor tadalafil has superior efficacy to decrease myocardial infarction size, reduce damage following reperfusion, and improve LV function (70-74). Rats underwent thoracotomy with clamps used to create left lung ischemia, iNO protective at 4 hours of reperfusion, with reversal of postischemic lung hypoperfusion and reduction of lung neutrophil (75). In a canine model with selectively embolizing blood clots to an intended right lower lobar pulmonary artery, iNO improved PaO_2/FiO_2, decreased the mean PAP and PVR (76). For kidney IRI, iNO and corticosteroids started 30 minutes before alternatively suprarenal aortic cross-clamping for 90 minutes in pigs, improved hemodynamic parameters, oxygenation, and reduced the systemic inflammatory response and protected kidney (77). These animal models claimed that iNO might protect IRI in the heart and other organs. However, more human studies are needed.

Transplantation

iNO was preferred by 48% in perioperative care of lung transplants (78), may ameliorate IRI, improving perioperative pulmonary function, diminish ventilatory support requirements, and improve survival. iNO reduces PVR, attenuates apoptosis, reduces neutrophil extravasation, decreases capillary leak, reduces wet-to-dry lung, increases lung compliance, and improves oxygenation in animal models (79-86). There is some controversy in lung transplant patients. Some studies claimed that iNO may be an effective drug to prevent and treat hypoxemia and/or PH, decrease RV dysfunction, and avoid ECMO after lung transplant (87,88). Prolonged use of iNO is associated with worse survival dependency (89,90). However, in other studies, there is no significant effect of iNO on physiologic variables or outcomes (91-93). Recipient PH after heart transplantation (HT) is a main cause of RV dysfunction. Before HT, vasodilator challenge with iNO is

safe undergoing right heart catheterization in candidates, it produces a reasonably predictable hemodynamic response (94). iNO also a useful adjunct in the postoperative treatment protocol, selectively reduces PVR, enhances RV output, reduces the risk of RV dysfunction, and improves survival in HT patients with PH (95-98). In liver transplantation patients, iNO was claimed to be safe, decrease hepatic injury and improve allograft function (99). In addition, iNO is a potential rescue therapy for severe hypoxemia, PH, and persistent hepatopulmonary syndrome after liver transplantation (100-102). Further powered studies are required to define the effect, dose, and timing of iNO in transplantation patients.

Acute respiratory distress syndrome (ARDS)/ hypoxemic respiratory failure

ARDS is a clinical syndrome characterized by a refractory hypoxemia due to non-cardiogenic pulmonary edema with bilateral chest radiograph opacities. The major beneficial effect of iNO appears to improve oxygenation by improving V/Q, matching results from selective vasodilation of residual ventilated lung regions, rather than a reduction in PAP (103,104). The sufficient concentrations of iNO can be in the range of 100–2,000 ppb, positive end expiratory pressure and the baseline level of PVR determined improvement in arterial oxygenation and pulmonary vascular effects (105-107). Recommendations suggest an indication of iNO when the PaO_2 <100 mmHg with 100% FiO_2 or oxygen index (OI = mean airway pressure × FiO_2 × 100/PaO_2) ≥25. In hypoxemic term and near-term infants, iNO appears to have improved outcomes by reducing the risk of death or use of ECMO. However, mortality was not affected (108-115). Similar, evidence is insufficient to support iNO for ARDS in children and adults. It results in an improvement in oxygenation, however, no reduction of mortality and even may be harmful by increasing renal impairment (116-122). In recent guidelines of the ARDS, iNO corresponded to a level of proof that were expert opinions (123). Worthy of attention, iNO is being explored as an interventional rescue therapy for COVID-19-induced ARDS (124,125).

Chronic obstructive pulmonary disease (COPD)

PH is a common complication of severe COPD and worsens prognosis. V/Q mismatch results in hypoxemia in patients with advanced disease, possibly because of a high degree of vasodilation. In some studies, iNO

does not seem to improve either RV function or arterial oxygenation in patients with severe COPD or acute exacerbation of COPD (126,127). However, iNO was claimed to prevent the exercise-associated decrease of PaO$_2$, make the patient feel better, and be safe and effective in severe COPD patients with long term oxygen, in other studies (128-131).

Sickle cell disease (SCD)

In SCD patients, occlusion of the small blood vessels presents as episodes of severe pains that called vaso-occlusive crisis (VOC), which damage to the vital organs. Some patients develop acute chest syndrome (ACS), a major cause of death in SCD (132). iNO has positive effect in the pathophysiological and therapeutic in case series of ACS patients (133). However, randomized controlled trials showed that in SCD patients with VOC or mild to moderate ACS, iNO did not significantly improve time to crisis resolution compared to placebo and did not significantly reduce the rate of treatment failure (134-136). Therefore, we need large, long-term trials to provide more evidence in iNO for SCD patients (137).

Inhaled aerosolized vasodilators

Successful clinical use of iNO prompted the search of other more cost-effective alternatives. Aerosolization of systemic vasodilators is less expensive than iNO and was expected to minimize their systemic effects (138). The literature suggests that inhaled aerosolized prostacyclin or analogs, including epoprostenol, iloprost, treprostinil and others such as milrinone and levosimendan may be similar to iNO for PH patients (139-142).

Prostacyclin or Analogs

Prostacyclin is a prostaglandin member of the eicosanoid family of lipid molecules. It is a naturally occurring prostaglandin produced primarily by the endothelial cells of the vascular intima, and is well known as antiplatelet aggregation, potent vasodilator, cytoprotective effects. Inhaled prostacyclin or analogs can be offered as an alternative treatment option for PH patients, and include epoprostenol (Flolan, Veletri), iloprost (Ventavis), and treprostinil (Tyvaso) in clinical use (143,144).

Epoprostenol

Epoprostenol is a synthetic prostacyclin that mimics the actions of natural prostacyclin. Intravenous infusion epoprostenol was approved by the FDA for PH treatment but has adverse effects, including systemic hypotension and an increase of intrapulmonary shunts (145). Previous studies reported that inhaled epoprostenol (iEPO) in cardiopulmonary disease patients has a similar efficacy as iNO. It is effective in reducing pulmonary pressures and increasing oxygenation by improving V/Q matching, and has minimal adverse events (146-149). More importantly, depending on the institution's contracted price, the use of iEPO is associated with significant savings, and there is no difference between Flolan and Veletri (150,151). In mechanical ventilation patients, the nebulizer placed at the humidifier inlet or outlet in a ventilator with bias flow results in the highest amount of mean epoprostenol deposition (152). For iEPO through noninvasive routes of ventilator support system, Li *et al.* demonstrated iEPO feasibility via high-flow nasal cannula (HFNC) in improving oxygenation, and these improvements were more significant when gas flow was titrated (153,154). iEPO initiated by the transport team is suggested as optimizing oxygenation and improving transport safety (155,156). However, the significance of iEPO effects in improving clinical outcomes, such as survival and ventilator-free days, remains unknown. More studies are needed to determine the role. Inhaled epoprostenol has been reported that it can produce mild acute sterile tracheitis in animal model, however, recent novel toxicology program showed no drug related airway or lung inflammation (157,158).

Iloprost

Iloprost is a synthetic analog of the endogenous prostacyclin; it has an analog pharmacologically like epoprostenol. Aerosolized iloprost is regarded as a potential alternative and/or adjuvant to iNO in the management of PH patients. The "AIR" trial demonstrated that monotherapy with aerosolized iloprost has significant improvement in New York Heart Association (NYHA) classification, quality of life, and dyspnea beneficial effects for patients with PH (159). The "STEP" trial demonstrated that aerosolized iloprost with oral bosentan therapy may be a safe and effective treatment approach (160). Improved outcomes in these studies, such as hemodynamics, exercise tolerance and quality of life, have established a position of aerosolized iloprost treatment in PH patients including children (160-163). Furthermore, aerosolized iloprost is claimed to improve RV function and reverse established RV fibrosis partially (164,165). Interestingly, aerosolized iloprost has been shown to be a safe and well-tolerated agent

for PH in the first three months after diagnosis, and should be combined with other drugs if used for a prolonged time (166,167). Aerosolized iloprost also had a favorable efficacy and safety profile compared to iNO for the treatment of perioperative PH (168,169). Recently, aerosolized iloprost has been reported to improve oxygenation, lung mechanics, and cardiac function in thoracic surgery (170,171). The use of modern nebulizers for aerosolized iloprost ensures the dose required for pulmonary deposition and systematically minimizes side effects (172). There are limited data on the adverse reactions of aerosolized iloprost. There are reported cases of dizziness, diarrhea, bronchospasm, and wheezing (162).

Treprostinil

Treprostinil is a synthetic analog of prostacyclin and is used to diminish symptoms associated with exercise in PH patients with NYHA class II–IV symptoms. It is available in intravenous, subcutaneous, inhaled, and oral form (173,174). In clinical trials, inhaled treprostinil is a safe, well-tolerated, efficacious treatment with improvements in exercise capacity, functional class, pulmonary hemodynamics, quality of life, and clinical status in symptomatic patients with PH who remain symptomatic on bosentan or sildenafil (175-179). Long-term inhalation of treprostinil has sustained benefit in PH patients who have been treated for 24 months (180-182). Moreover, transitioning from inhaled iloprost, intravenous treprostinil, or subcutaneous treprostinil to inhaled treprostinil demonstrated safety and acceptability in patients with PH (183-185). For group 1 PH patients, inhaled treprostinil changed clinical assessments of disease severity and improved the overall risk assessment in most (186). Because of its short half-life (20–30 min) and fast elimination time (30 min to 1 hour), inhaled treprostinil must be used 6 to 9 times daily. The most common adverse events include cough, headache, nausea, pharyngolaryngeal pain, chest pain, and vomiting (180).

Milrinone

Milrinone, a phosphodiesterase three inhibitor that works to increase the heart's contractility and decrease PVR. It is commonly used as therapy for PH and is often combined with other medications, such as sildenafil. The administration of milrinone through inhalation in cardiac surgical patients with PH was reported to have a protective effect, including minimizing CPB related inflammation, preventing pulmonary endothelial dysfunction, and facilitating weaning from CPB (187-190). In addition, routine use of inhaled milrinone and iloprost before initiation of CPB and at chest closure is associated with reduced postoperative iNO trope use (191). And aerosolized milrinone with mesh nebulization improved with almost a 3-fold higher deposition compared to jet nebulization (192). Furthermore, inhaled milrinone after LVAD implantation proved to be well-tolerated, feasible, improved hemodynamics, pharmacokinetics, and was less expensive (193).

Levosimendan

Levosimendan is not a vasopressor, but a new calcium sensitizer with positive inotropic and vasodilating properties. The potential usefulness of inhaled levosimendan for PH treatment is the absence of enough evidence to date. Just a single pilot randomized double-blind study claimed that inhaled levosimendan is effective as milrinone in reducing PAP and has a longer duration of action (194). Large, randomized clinical trials are needed to support inhalational levosimendan for PH treatment (195,196).

Conclusions

PH is a life-threatening condition and commonly treated with IPVs such as iNO and less frequently with epoprostenol, iloprost, treprostinil and other drugs, such as milrinone and levosimendan. IPV drug selection always depends mostly on hospital rules and regulations, doctors' experience and preferences, and patients' expenses. Off-label use of IPV is common in daily clinical practice. However, limited, and inadequate studies have reported a mortality benefit of IPV in different patients. These are summarized in *Figure 1*. More research of IPV is needed to determine acceptable inclusion criteria, long-term outcomes, and management strategies including time, dose, and duration.

Figure 1 IPV. IPV, inhaled pulmonary vasodilators; iNO, inhaled nitric oxide; PVR, pulmonary vascular resistance; PPHN, persistent pulmonary hypertension of the newborn; BPD, bronchopulmonary dysplasia; ECMO, extracorporeal membrane oxygenation; CA, cardiac arrest; IRI, ischemia-reperfusion injury; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; SCD, sickle cell disease.

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Footnote

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