Are Inhaled Vasodilators Useful in Acute Lung Injury and Acute Respiratory Distress Syndrome?

Mark S Siobal RRT FAARC and Dean R Hess PhD RRT FAARC

Introduction
Inhaled Pulmonary Vasodilators
  Inhaled Nitric Oxide
  Inhaled Prostacyclins
Pro: Inhaled Vasodilators Are Useful in Acute Lung Injury and Acute Respiratory Distress Syndrome
  Rescue Treatment for Refractory Hypoxemia
  Treatment of Acute Right Heart Failure
  Other Benefits
  Summary of the Pro Position
Con: Inhaled Vasodilator Should Not Be Used in Acute Lung Injury and Acute Respiratory Distress Syndrome
  Lack of Outcome Benefit
  Toxicity
  Delivery System
  Cost
  Summary of the Con Position
Summary

In patients with acute respiratory distress syndrome (ARDS), inhaled vasodilator can result in important physiologic benefits (eg, improved hypoxemia, lower pulmonary arterial pressure, and improved right-ventricular function and cardiac output) without systemic hemodynamic effects. Inhaled nitric oxide (INO) and aerosolized prostacyclins are currently the most frequently used inhaled vasodilators. Inhaled prostacyclins are as effective physiologically as INO and cost less. Randomized controlled trials of INO in the treatment of ARDS have shown short-term physiologic benefits, but no benefit in long-term outcomes. No outcome studies have been reported on the use of prostacyclin in patients with ARDS. There is no role for the routine use of inhaled vasodilators in patients with ARDS. Inhaled vasodilator as a rescue therapy for severe refractory hypoxemia in patients with ARDS may be reasonable, but is controversial. Key words: acute lung injury; acute respiratory distress syndrome; inhaled nitric oxide; prostacyclin; pulmonary hypertension. [Respir Care 2010;55(2):144–157. © 2010 Daedalus Enterprises]
Introduction

Inhaled vasodilators have a localized effect in the lung, known as selective pulmonary vasodilation. This means that they dilate the pulmonary vasculature in well ventilated areas of the lungs, which reduces pulmonary arterial pressure and pulmonary vascular resistance, and improves ventilation-perfusion matching and oxygenation (Fig. 1). The short half-life of inhaled vasodilators minimizes the systemic effects, compared to intravenous, subcutaneous, or oral administration. Pulmonary selectivity has been reported in adult patients with acute respiratory distress syndrome (ARDS) in studies that compared the effects of inhaled nitric oxide (INO) and intravenous and inhaled prostacyclin (alprostadil prostaglandin E-1 [PGE1]). INO and either inhaled or intravenous prostacyclin had similar effects on pulmonary arterial pressure, pulmonary vascular resistance, cardiac output, and right-ventricular (RV) ejection fraction. However, in contrast to INO and inhaled prostacyclin, intravenous prostacyclin caused systemic vasodilation, which lowered mean systemic arterial pressure and worsened arterial oxygenation (Fig. 2). This deleterious effect on gas exchange was a result of non-selective reversal of hypoxic pulmonary vasoconstriction, which increases perfusion to non-ventilated alveoli.

ARDS is characterized by lung inflammation, which induces alveolar microvascular permeability, pulmonary edema, and surfactant inactivation. Clinically, this results in atelectasis, decreased lung compliance, hypoxemia, and pulmonary hypertension. Pulmonary vascular obstruction from thromboemboli in ARDS increases pulmonary arterial pressure and alveolar dead space, which can lead to a cascade of events that further aggravate lung injury (Fig. 3). The elevated pulmonary arterial pressure early in ARDS can worsen RV function and lead to RV failure, particularly in patients with preexisting pulmonary hypertension and RV pathology (Fig. 4). In patients with ARDS, inhaled vasodilators such as INO and prostacyclin can increase PaO2 and decrease pulmonary arterial pressure, but the use of inhaled vasodilators in patients with ARDS is controversial. On one hand, inhaled vasodilators improve gas exchange and hemodynamics. On the other hand, inhaled vasodilators can be expensive, and a survival benefit has not yet been reported. We will review the available research, debate the pros and cons, and provide some practical advice about inhaled pulmonary vasodilators.

Inhaled Pulmonary Vasodilators

Vasodilators that have been administered via inhalation, clinically and experimentally, include oxygen, nitric oxide, milrinone, nitroglycerin, prostacyclins, nitroprusside, nitric oxide donors, phosphodiesterase inhibitors, endothelin receptor antagonists, and agonists of soluble guanylate cyclase. INO and inhaled prostacyclins are the most frequently used inhaled vasodilators. Inhaled vasodilators reduce pulmonary arterial pressure and redistribute pulmonary blood flow to ventilated lung regions, with little or no systemic hemodynamic effect, so INO and inhaled prostacyclins are selective pulmonary vasodilators.

Inhaled Nitric Oxide

INO was the first selective pulmonary vasodilator used in humans. Soon after its mechanism was described experimentally it was introduced in clinical trials. In hypoxic term newborns with pulmonary hypertension, INO decreases pulmonary hypertension, increases PaO2, and decreases the need for extracorporeal life support. This led to Food and Drug Administration approval of INO for newborns in 1999. According to the label, INO, “in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (> 34 weeks) neonates with hypoxic respiratory failure.
associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (www.inomax.com/pdf/prescribing_information.pdf). For this disorder, INO is standard accepted practice. A Cochrane review concluded that it is reasonable to use INO in an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have diaphragmatic hernia.33

INO has also been used for various off-label indications, including hypoxemia and pulmonary hypertension associated with ARDS. Because of INO’s cost, required delivery system, and potential toxicity, inhaled prostacyclins are more attractive than INO for pulmonary vasodilation.

Inhaled Prostacyclins

The vasodilator effects of the inhaled prostacyclins, epoprostenol (prostaglandin I-2 [PGL2]) and alprostadil (PGE1), are nearly identical to INO. Several comparisons have found similar2,30 or better31,32 physiologic effects (improved $P_{\text{a}O_2}$, reduced pulmonary arterial pressure) with prostacyclins than with INO in patients with ARDS. In infants with pulmonary hypertension following cardiac surgery, intravenous epoprostenol was 6–10 times more potent than alprostadil in reducing pulmonary vascular resis-
In ranked order of ability to improve gas exchange after experimentally induced pulmonary hypertension in perfused rabbit lungs, inhaled epoprostenol appeared to have a greater effect than did alprostadil. Inhaled alprostadil was also found to be less effective than inhaled epoprostenol in reducing experimental pulmonary hypertension in sheep. Additionally, a low concentration of epoprostenol (10 ng/mL) prevented localized thrombosis in rats following microvascular anastomosis (10% vs 37% in controls), whereas a higher concentration of alprostadil (250 ng/mL) was not effective (67% vs 33% for controls). These findings suggest different effects between inhaled epoprostenol and inhaled alprostadil. Whether the differences in physiologic response, potency, and anti-thrombotic properties translate into better efficacy with inhaled epoprostenol than with inhaled alprostadil in the treatment of ARDS remains unknown.

The dose range for inhaled epoprostenol, 10–50 ng/kg/min, is based on dose-response trials and comparisons to INO. Predicted body weight is used to calculate the dose, so that it is based on lung size and not on body mass. The rationale for calculating dose in this manner is that it appears to achieve the desired physiologic effect in the lungs while avoiding unnecessary higher doses that may cause systemic adverse effects. The common starting dose is 50 ng/kg/min, which has maximum benefit without systemic effects, and then to wean down as appropriate. Epoprostenol requires reconstitution with a specific diluent to maintain stability. The drug solution is stable for 8 hours at room temperature (48 h with refrigeration) and must be discarded thereafter. Epoprostenol is also photosensitive and must be protected from direct sunlight to prevent decomposition.

Iloprost is a longer-acting, more stable PGI2 analog. It is currently the only prostacyclin that is Food and Drug Administration approved for inhalation. In a randomized controlled trial (RCT) with ambulatory patients with pulmonary hypertension, periodic inhalation of 2.5–5.0 μg f iloprost 6–9 times per day improved exercise tolerance and quality of life. Several studies have found that inhaled iloprost is a more potent pulmonary vasodilator than INO. In intubated patients, inhaled iloprost was used in the acute-care setting for pulmonary hypertension following pulmonary endarterectomy, with aerosol doses of 25 μg given over 15 min. The duration of pulmonary-artery-pressure reduction from this single dose of iloprost was as long as 2 hours. In comparison to the shorter half-life of INO and inhaled epoprostenol, the longer action of inhaled iloprost makes it suitable for intermittent dosing regimens.

In 2 dose-comparison trials, the comparable equipotent dose ratio of iloprost versus epoprostenol was approximately 1 to 5. The aerosolized dose of 9–21 μg of iloprost was found to be equivalent to 52–112 μg of epoprostenol. When given via intravenous infusion the equipotent dose was 1.2 ± 0.5 ng/kg of iloprost versus 7.2 ± 3.4 ng/kg of epoprostenol. Therefore, an equivalent dose of con-
continuous inhaled iloprost of 2–10 ng/kg/min, versus 10–50 ng/kg/min of epoprostenol, may provide a more stable therapy for severe hypoxemia and acute RV failure. Unlike epoprostenol, iloprost does not require special preparation or handling. The reconstituted solution of iloprost and 0.9% saline is stable at room temperature for 5 days, can be stored refrigerated for 30 days, and is comparable in cost to epoprostenol.44

Pro: Inhaled Vasodilators Are Useful in Acute Lung Injury and Acute Respiratory Distress Syndrome

Rescue Treatment for Refractory Hypoxemia

Inhaled vasodilator can be a life-saving intervention by preventing cardiopulmonary collapse in patients with ARDS, severe hypoxemia, and acute RV failure (Fig. 6). Although death from hypoxemia is rare in patients with ARDS, rescue treatment with inhaled vasodilator may significantly improve oxygenation and allow time to institute other definitive therapies.

In patients with acute lung injury (ALI) and ARDS, INO improves oxygenation for at least 24 hours after initiation of therapy (Fig. 7).45-54 and there is some evidence of a more prolonged effect.45 INO is a valid option for life-threatening refractory hypoxemia, defined as a ratio of $P_{\text{aO}_2}/F_{\text{IO}_2} < 100$ mm Hg, in conjunction with other supportive therapies.35-61 INO is useful as a short-term adjunct to cardiopulmonary support in patients with acute hypoxemia and/or life-threatening pulmonary hypertension.9 The physiologic response to inhaled prostacyclins, when compared to an equivalent dose response to INO, is nearly identical.2,31,62 Approximately 60% of patients with ARDS have an acute improvement with INO48,52,63 or inhaled prostacyclin,31,39,64 defined as a ≥ 20% increase in $P_{\text{aO}_2}/F_{\text{IO}_2}$ or a ≥ 20% decrease in pulmonary arterial pressure.

Inhaled vasodilator for treatment of severe hypoxemia may be lung-protective in patients whose oxygenation might otherwise depend on potentially injurious ventilator management. It has been suggested that the survival benefit from lung-protective ventilation is due to a decrease in RV failure, from the reduction in lung hyperinflation and RV afterload.65-68 By improving oxygenation with an inhaled vasodilator, higher settings of PEEP, which can lead to alveolar over-distention69 and can increase RV afterload, may be avoided.70 Inhaled vasodilator may prevent RV failure if increases in afterload from high levels of ventilatory support can be avoided. Correction of severe hypoxemia may also allow a decrease in $F_{\text{IO}_2}$, which may prevent further acute inflammatory lung injury.71 The use of other rescue measures, such as neuromuscular blockade, prone positioning, high-frequency ventilation, and extracorporeal membrane oxygenation, may also be avoided if a severe oxygenation defect responds to inhaled vasodilator treatment.

---

**Fig. 5.** Pulmonary vasodilator site of action in the endothelial and smooth-muscle cell. NO = nitric oxide. PGI$_2$ = prostaglandin I-2. PGE$_1$ = prostaglandin E-1. R = receptor. NOS = nitric oxide synthase. L-arg = L-arginine. PCS = prostacyclin synthase. AA = arachidonic acid. ET-A = endothelin type A receptor. ET-B = endothelin type B receptor. GC = guanylate cyclase. AC = adenylyl cyclase. GTP = guanosine triphosphate. cGMP = cyclic guanosine monophosphate. ATP = adenosine triphosphate. cAMP = cyclic adenosine monophosphate. PDE = phosphodiesterase. PKG = protein kinase G. PKA = protein kinase A. LC = light-chain. (Adapted from Reference 28.)
Treatment of Acute Right Heart Failure

ARDS is a common cause of acute RV failure secondary to pulmonary hypertension. Pulmonary hypertension due to hypoxic pulmonary vasoconstriction and thromboembolic occlusion of the pulmonary microcirculation is a characteristic of ARDS. Pulmonary hypertension and elevated pulmonary vascular resistance occur in the early phase of ARDS, correlate with the severity of lung injury, and remain elevated in non-survivors.

Fig. 6. Case of a 51-year-old male, status after exploratory laparotomy for intra-abdominal abscess that developed sepsis, abdominal compartment syndrome, and severe acute respiratory distress syndrome. Transesophageal echocardiogram revealed a dilated right ventricle, evidence of increased pulmonary arterial pressure, and low right-ventricular ejection fraction. Global hemodynamic failure persisted despite fluid resuscitation and titration of dopamine up to 20 μg/kg/min and phenylephrine up to 200 μg/min. Rescue treatment with inhaled epoprostenol at a dose of 50 ng/kg/min profoundly improved oxygenation and hemodynamic function, and reduced pulmonary arterial pressure. Baseline blood gas and hemodynamic measurements were done, and repeated after 30 min, 15 min after inhaled epoprostenol was initiated. The ratio of $P_aO_2$ to fraction of inspired oxygen ($FIO_2$) increased from 44 mm Hg to 98 mm Hg (123% increase). Mean arterial pressure increased from 51 mm Hg to 81 mm Hg (59% increase). Mean pulmonary arterial pressure decreased from 45 mm Hg to 36 mm Hg (20% decrease).

Fig. 7. Effect of nitric oxide on the ratio of $P_aO_2$ to fraction of inspired oxygen at 24 hours. (Adapted from Reference 45.)

<table>
<thead>
<tr>
<th>First Author</th>
<th>Number of Patients</th>
<th>Nitric Oxide</th>
<th>Control</th>
<th>Ratio of Means (95% CI)</th>
<th>Ratio of Means 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day $^6$</td>
<td>11</td>
<td>10</td>
<td></td>
<td>0.95 0.64–1.42</td>
<td></td>
</tr>
<tr>
<td>Schweber $^7$</td>
<td>9</td>
<td>10</td>
<td></td>
<td>1.20 0.94–1.54</td>
<td></td>
</tr>
<tr>
<td>Delling $^8$</td>
<td>120</td>
<td>57</td>
<td></td>
<td>1.27 1.14–1.41</td>
<td></td>
</tr>
<tr>
<td>Michael $^9$</td>
<td>16</td>
<td>16</td>
<td></td>
<td>1.28 1.01–1.62</td>
<td></td>
</tr>
<tr>
<td>Troncy $^{10}$</td>
<td>15</td>
<td>15</td>
<td></td>
<td>1.14 0.94–1.39</td>
<td></td>
</tr>
<tr>
<td>Dobyns $^{11}$</td>
<td>49</td>
<td>50</td>
<td></td>
<td>0.94 0.77–1.15</td>
<td></td>
</tr>
<tr>
<td>Lundis $^{12}$</td>
<td>78</td>
<td>66</td>
<td></td>
<td>1.05 0.93–1.19</td>
<td></td>
</tr>
<tr>
<td>Mehta $^{13}$</td>
<td>8</td>
<td>6</td>
<td></td>
<td>1.20 0.82–1.75</td>
<td></td>
</tr>
<tr>
<td>Park $^{14}$</td>
<td>11</td>
<td>6</td>
<td></td>
<td>1.03 0.70–1.51</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>312</td>
<td>236</td>
<td></td>
<td>1.13 1.04–1.23</td>
<td></td>
</tr>
</tbody>
</table>
Acute RV failure (cor pulmonale)\(^72,67,68\) is the result of an increase in pulmonary arterial pressure and pulmonary vascular resistance (RV afterload). Unlike the thick-walled left ventricle, RV myocardial size prevents increased contractility against a high afterload.\(^78\) As RV afterload increases, RV dilation occurs. RV dilation and an increase in RV end-diastolic volume cause a load stress on the right heart, which increases oxygen demand and myocardial oxygen consumption, decreases coronary artery perfusion pressure, causes subendocardial ischemia, depresses RV contractility, and worsens RV ejection fraction.\(^78,79\) The elevated pulmonary arterial pressure secondary to hypoxic pulmonary vasoconstriction that develops early in ARDS can lead to worsening RV function and RV failure, particularly in patients with preexisting pulmonary hypertension and RV pathology. This reduction in RV output causes a restriction in the preload volume to the left heart and contributes to a decrease in cardiac output and systemic hypotension. As RV end-diastolic volume increases, the interventricular septum is displaced toward the left-ventricular cavity during diastole, due to the restriction imposed by the pericardial sac.\(^72,80\) The leftward shift of the interventricular septum impedes LV end-diastolic volume (Fig. 8), which further decreases cardiac output and coronary artery perfusion. The vicious cycle of acute RV failure can eventually lead to hemodynamic collapse\(^72\) despite adequate fluid resuscitation and vasopressor support.\(^82\)

The recognition of the pivotal role of the right ventricle in hemodynamic function in patients with ARDS makes the case for RV afterload reduction with inhaled vasodilator as an important treatment option.\(^60,61,72,73,78,81,83,87,88\) In patients with severe ARDS, with profound hypoxemia and acute RV failure, RV afterload reduction with inhaled vasodilators results in important physiologic benefits in pulmonary gas exchange, systemic circulation, and oxygen transport, so inhaled vasodilator is an appropriate therapy.

Other Benefits

Other potential benefits of inhaled prostacyclin for ARDS include the inhibition of platelet aggregation,\(^36\) anti-inflammatory properties,\(^89,90\) and potential anti-thrombotic and thrombolytic effects.\(^91\) The anti-platelet effects of prostacyclin in humans are well known.\(^36,92,93\) Decreased platelet aggregation and inhibition of neutrophil and macrophage activation can affect the inflammatory response.\(^94\) Prostacyclins demonstrate both pro-inflammatory and anti-inflammatory effects,\(^89,90\) and their complexity is highlighted by the diverse and often opposing effects on the inflammatory process.\(^95\) Anti-thrombotic and thrombolytic properties of prostacyclins have been demonstrated in animal\(^98\) and laboratory\(^91\) studies. Thrombolysis with fibrinolytic infusion improves hemodynamics and oxygenation in patients with ARDS,\(^96\) so inhaled prostacyclins may attenuate the local inflammatory process and ameliorate pulmonary vascular obstruction.

Sepsis is a common cause of ARDS.\(^55\) Intravenous prostacyclin in patients with sepsis\(^97\) and respiratory failure\(^98,99\) increases gastric intramucosal pH\(^97\) and improves oxygen delivery and oxygen uptake,\(^98,99\) suggesting improved splanchnic and visceral organ perfusion. The increase in cardiac output with inhaled vasodilator may explain why INO improves hepatic microcirculation in patients with RV failure.\(^100\) Also, spillover of inhaled prostacyclin to the systemic circulation may improve splanchnic perfusion and tissue oxygenation in patients with pulmonary hypertension and septic shock.\(^101\) Reducing pulmonary vascular resistance with intravenous prostacyclin increases cardiac output but worsens pulmonary shunt fraction; however, there is a net benefit of improved oxygen transport.\(^102\) A benefit of using inhaled vasodilator to improve oxygenation and intrapulmonary shunt, while increasing systemic oxygen transport and splanchnic microcirculation, may be underappreciated.\(^103\)
Summary of the Pro Position

Inhaled drugs such as INO and prostacyclin are selective pulmonary vasodilators that improve arterial oxygenation and reduce pulmonary hypertension without affecting systemic blood pressure, which is important in patients with ARDS and refractory hypoxemia. The decrease in pulmonary arterial pressure is important to reduce pulmonary edema formation and RV afterload.

Con: Inhaled Vasodilator Should Not Be Used in ALI/ARDS

To begin the discussion of the con position, it should be noted that no inhaled pulmonary vasodilator is approved by the Food and Drug Administration for administration via inhalation in intubated mechanically ventilated patients with ALI or ARDS. Thus, use of these drugs in this manner is an off-label use.

Lack of Outcome Benefit

Although inhaled vasodilator may produce acute physiologic benefits, evidence is lacking that this translates into a meaningful outcome benefit. RCTs of INO versus placebo in patients with ALI or ARDS found no benefit in mortality or ventilator-free days. Dellinger et al.48 in a phase-2 study, evaluated the safety and physiologic response of INO in patients with ARDS. This was a prospective multicenter randomized double-blind placebo-controlled study. Patients (n = 177) were randomized to receive placebo or INO at 1.25, 5, 20, 40, or 80 ppm. An acute INO response (P\textsubscript{A\textsuperscript{O}2} increase ≥ 20%) was seen in 60% of the patients receiving INO, compared with 24% of placebo patients. The increase in P\textsubscript{A\textsuperscript{O}2} translated into an F\textsubscript{I\textsuperscript{O}2} reduction over the first day, and in the intensity of mechanical ventilation over the first 4 days of treatment, as measured by the oxygenation index. There were no differences between INO and placebo with respect to mortality rate or the number of days alive and off mechanical ventilation.

In a RCT by Michael et al, INO was compared to placebo in 40 patients with ARDS.49 Compared to placebo, INO was associated with an acute increase in P\textsubscript{A\textsuperscript{O}2}/F\textsubscript{I\textsuperscript{O}2}. However, beyond 24 hours, the 2 groups had an equivalent improvement in P\textsubscript{A\textsuperscript{O}2}/F\textsubscript{I\textsuperscript{O}2}. Patients treated with INO were no more likely to improve so that they could be managed with a persistent decrease in F\textsubscript{I\textsuperscript{O}2} ≥ 0.15 during the 72 hours following randomization. The mortality rate was 55% in the 20 patients who received INO and 45% in the 20 patients who received conventional therapy.

Troncy et al.50 randomized 30 patients with ARDS to receive INO or usual care. During the first 24 hours of therapy there was a significant improvement in P\textsubscript{A\textsuperscript{O}2} in the group that received INO (P = .02). After the first day of therapy, however, no further INO benefits were detected. In the INO patients, 40% were alive and free of mechanical ventilation within 30 days after randomization, compared to 33% in the control group (P = .83). The 30-day mortality rate was similar in the 2 groups.

To determine whether INO can increase the frequency of reversal of ALI, Lundin et al.52 conducted a prospective randomized trial with 268 patients with early ALI. Responders were defined as patients in whom P\textsubscript{A\textsuperscript{O}2} increased by > 20% with INO. Responders were randomly assigned to conventional therapy with or without INO. The frequency of ALI reversal was no different between the INO patients (61%) and the controls (54%), but the development of severe respiratory failure was lower in the INO group (2.2%) than in the controls (10.3%). The 30-day mortality was 44% in the INO patients, 40% in the control patients, and 45% in non-responders.

Gerlach et al.104 conducted an RCT with 40 patients with ARDS, randomized to conventional treatment or INO at 10 ppm. After 4 days, the dose-response curve of the INO-treated patients was left-shifted, with a peak response at 1 ppm. At higher doses (10 and 100 ppm), oxygenation deteriorated, and the response to INO disappeared in several patients. INO had no effect on duration of mechanical ventilation or ICU stay.

Taylor et al.105 conducted a multicenter randomized placebo-controlled blinded study with 385 patients with moderately severe ALI. Patients were randomly assigned to placebo or INO at 5 ppm. INO did not increase the number of days alive or off assisted breathing. Mortality was similar between the groups. This lack of effect on clinical outcomes was seen despite a statistically significant increase in P\textsubscript{A\textsuperscript{O}2}.

Sokol et al.106,107 conducted a systematic review and meta-analysis of RCTs on INO for ALI and ARDS in children and adults. Their analysis included 5 RCTs, which included 535 patients. There were no differences in ventilator-free days between the treatment and placebo groups, and no specific dose of INO was more advantageous than any other. INO had no effect on mortality (relative risk 0.98, 95% confidence interval [CI] 0.66–1.44).

Adhikari et al.45 conducted a systematic review and meta-analysis on the effect of INO on oxygenation and mortality in patients with ALI. They selected RCTs with parallel groups that compared INO to control. They identified 12 studies, which included 1,237 patients. Overall methodological quality was good. On treatment day 1, INO increased P\textsubscript{A\textsuperscript{O}2}/F\textsubscript{I\textsuperscript{O}2} (13%, 95% CI 4–23%) and decreased the oxygenation index (14%, 95% CI 2–25%). Some evidence suggested that the oxygenation improvement persisted until day 4 of mechanical ventilation, but INO had no significant effect on hospital mortality (risk ratio 1.10, 95% CI 0.94–1.30) (Fig. 9).45,48-50,52-54,104,105,108 duration
of ventilation, or ventilator-free days. There was no effect on mean pulmonary arterial pressure. Adhikari et al. concluded that INO is associated with limited improvement in oxygenation in patients with ALI or ARDS, but confers no mortality benefit; they do not recommend routine use of INO in these severely ill patients. Moreover, Adhikari et al. suggested that the trend toward higher mortality in the INO patients, which was highly consistent across the trials, and the finding of potential adverse effects of INO, such as renal failure, raise concern about the use of INO in patients with ALI.

There have been no studies of the effects of inhaled prostacyclins on important outcomes. Seven studies of alprostadil have enrolled 697 patients, with predominantly ARDS, although 3 restricted enrollment to those with trauma, surgery, or sepsis as a risk factor. Those studies differed with respect to method of medication administration: 4 used continuous infusion, and 3 used intermittent boluses. The pooled analysis showed no statistically significant effect of alprostadil on early mortality (relative risk 0.95, 95% CI 0.77–1.17). Individual trials reported more adverse events, leading to study-drug discontinuation in the alprostadil group. These adverse events were primarily cardiopulmonary (hypotension, dysrhythmias, hypoxia) and neurological (agitation). Admittedly, none of these studies used inhaled prostacyclin, but this is the best available evidence, as outcomes studies of inhaled prostacyclin have not been done.

Toxicity

Inhaled vasodilators are not without toxicity. This is well recognized for INO, as has been previously reviewed. Although platelet inhibition may be beneficial, as discussed above, it could also be harmful in a patient with a bleeding disorder. Reducing pulmonary arterial pressure might worsen pulmonary edema in patients with left heart failure. Methemoglobinemia can occur, particularly with high doses. Abrupt discontinuation can result in rebound hypoxemia and pulmonary hypertension. At high concentrations, INO can have direct toxic effects in the lungs. When nitric oxide mixes with oxygen in the delivery system, nitrogen dioxide is produced, which is toxic at high concentrations. Nitric oxide reacts with oxygen free radicals in the lungs to produce peroxynitrite, which has important toxicities. Nitric oxide and peroxynitrite can damage pulmonary surfactant.

Data from 4 large trials, representing nearly 75% of all patients in a meta-analysis, showed an increased risk of renal dysfunction in patients receiving INO (Fig. 10). This is a concern despite that it was the result of a post hoc analysis and is potentially subject to publication bias. The mechanisms of the renal effects of INO include inhibition of mitochondrial and enzymatic function and damage to deoxyribonucleic acid and membranes. This also raises concerns that, although the vasodilatory effects of INO are selective to the lungs, other effects of INO may manifest systemically.

INO has been delivered to hundreds of patients with ALI/ARDS in clinical trials that assessed, among other things, toxicity and adverse effects. So the safety profile of INO is relatively well known, but inhaled prostacyclins have not been subjected to such rigorous investigation. Thus, toxicity data do not exist and the safety profile of inhaled prostacyclins in mechanically ventilated patients with ALI/ARDS is largely unknown.

Delivery System

The one INO delivery system that is commercially available in North America has a long (> 10 years) history.
of safe INO delivery. It is important that clinicians use that system and not jury-rig their own INO systems, which could result in inaccurate INO dosing and the delivery of toxic nitrogen dioxide.\(^{120-123}\)

There is no standard approved delivery system for prostacyclin to mechanically ventilated patients. Theoretically, any nebulizer that provides an acceptable particle size and output can be used. In the United States, iloprost is intended to be delivered with either the I-neb (Respironics, Murrysville, Pennsylvania) or the Prodose (Profile Therapeutics, West Sussex, United Kingdom). The I-neb is used almost exclusively for this purpose, but it is intended for use with spontaneously breathing patients and it cannot be adapted for intubated patients. The I-neb is a third-generation adaptive aerosol delivery system that uses the mesh aerosol-generation technology.\(^{124}\) It is unknown whether other mesh nebulizers are suitable for use during mechanical ventilation or could be used to deliver iloprost or other prostacyclins. A nebulizer system for iloprost delivery during mechanical ventilation has been studied in vitro,\(^ {125}\) but no in vivo data are available. A method for continuous aerosolization of epoprostenol with a pneumatic nebulizer for intubated patients has been described.\(^ {39,126,127}\)

To assure consistent, reliable, reproducible and accurate delivery, only nebulizers that have been thoroughly characterized and shown to be suitable for inhaled prostacyclin should be used. Currently used systems for prostacyclin delivery are by and large jury-rigged, based on our knowledge of bronchodilator delivery during mechanical ventilation. It may be difficult to deliver a precise dose because of the many factors that affect aerosol delivery during mechanical ventilation.\(^ {128-132}\) Most important, it should not be assumed that all aerosol delivery systems for inhaled prostacyclins are equally effective. Claims of benefit with any system should be supported by in vivo evidence of clinical effectiveness. The dosing with one delivery system might be quite different from that with another system.

A pneumatic nebulizer can interfere with ventilator function and result in variable dose delivery.\(^ {16}\) A pneumatic nebulizer with an external flow source increases the tidal volume, affects the accuracy of exhaled tidal volume measurement, increases ventilator circuit pressures, can adversely affect patient-initiated triggering, and can alter the F\(_{2}\)O\(_{2}\) if an external oxygen blender is not used. A pneumatic nebulizer with a built-in nebulizer-driver function on a ventilator also affects the delivered dose over time with various ventilation settings, such as respiratory rate and inspiratory time. Dose can also be affected by the bias flow rate and the position of the nebulizer in the ventilator circuit. Any continuous nebulizer system can potentially clog expiratory filters and affect expiratory-valve function, which raises additional safety concerns.

**Cost**

The cost of INO has raised much concern among clinicians and administrators. Presently, the cost of INO is $137.50 per hour, capped at $13,200 per month, which includes the costs of the INO and the delivery system. The off-label use of INO costs some hospitals a million dollars per year. The search for less costly alternatives has increased the use of inhaled prostacyclin in patients with ALI. The drug cost of inhaled epoprostenol is about $275 per day, which does not include the cost of the delivery system. However, it is important to recognize that the use of inhaled prostacyclin in intubated adult patients with respiratory failure is off-label, as is INO. Whether one chooses INO or inhaled prostacyclin, evidence is lacking for any improved outcome benefit. Value is defined as benefit divided by cost. If the benefit of INO or inhaled prostacyclin is low, then its value will be low regardless of its cost.

**Summary of the Con Position**

Use of inhaled vasodilators is off-label in intubated patients with ALI/ARDS, and an outcome benefit has not been reported. Delivery systems for aerosolized prostacyclins are jury-rigged, because no commercially available
system exists for use during mechanical ventilation. The cost of these drugs may prohibit widespread use.

Summary

Given that the best available evidence suggests no survival advantage and possible higher mortality and renal dysfunction with INO, routine use of INO cannot be recommended for ALI/ARDS. However, INO may be considered as a rescue treatment in patients with ARDS and severe life-threatening refractory hypoxemia. Because of the challenges of enrolling patients with refractory hypoxemia into large trials, definitive data supporting or refuting INO in such situations are unlikely to be forthcoming, so we must base the decision on lower-level evidence, such as physiologic response. Given the reported physiologic effects of inhaled prostacyclin, and the cost of INO, it is reasonable to consider inhaled prostacyclin as an alternative to INO. However, there is no evidence of an outcome benefit from INO or inhaled prostacyclin, so inhaled vasodilator should be discontinued if a physiologic benefit is not obtained after a short clinical trial.

REFERENCES

ARE INHALED VASODILATORS USEFUL IN ALI/ARDS?


64. Bein T, Metz C, Keyl C, Sendtner E, Pfeifer M. Cardiovascular and pulmonary effects of aerosolized prostacyclin administration in se-
75. Leeman M. Pulmonary hypertension in acute respiratory distress syndrome. Monaldi Arch Chest Dis 1999;54(2):146-149.
ARE INHALED VASODILATORS USEFUL IN ALI/ARDS?


Discussion

Moores: I think we can all agree that these adjunctive therapies don’t have a lot of data showing benefit, but physiologically they make sense. You like it, you understand it, it makes sense, and you can see an oxygenation improvement. I wonder if it’s reasonable to use these adjunctive therapies to stay within the lung-protective ventilation parameters? If I’m having trouble oxygenating the patient and I’m afraid I’m going to go too high on PEEP or pressure to meet the oxygenation goals, is it worthwhile to use an inhaled vasodilator to meet the low pressure ventilation goals?

Hess: I don’t think we know. In fact, one of the criticisms of INO trials for ARDS is that they may have allowed or promoted ventilation strategies that were not lung-protective. In a couple of the INO studies, if you got an improvement in oxygenation, it actually encouraged you to decrease PEEP, for example. I don’t think it has been stud-
ied, but I think we have to be careful about being seduced by improvements in physiologic variables. I come back again to the ARDS Network trials where improvements in physiology did not translate to improvements in outcome.

**Gentile:** A lot of this discussion concerns cost. If these agents were as inexpensive as oxygen, I doubt we’d have the same debate.

**Hess:** Well, if you look at my last point, regardless of the cost, if the benefit is zero, the value remains zero.

**Siobal:** I’d point out that the benefit of inhaled prostacyclin has not been unproven. It’s definitely been proven that INO does not have a mortality benefit. They have similar physiologic effects, but they are different. The point is, inhaled prostacyclin hasn’t been unproven, and in some patients it gives physiologic benefit, and it’s cheaper than INO.

**MacIntyre:** It seems to me you’re making an argument for a good clinical trial rather than this uncontrolled, “Let’s use whatever seems to be a good idea today.”

**Siobal:** Yes, definitely.

**Gay:** I think this obsession with oxygenation has overlooked another surrogate that maybe we should start thinking about when we’re using these agents, and that’s RV dysfunction, which is sometimes prominent in these patients. And to the extent that the patient Mark mentioned was worsened by a high-dose alpha agonist or dopamine needs to be considered. Concentrating on how that choice really may have been deleterious to that patient is important. More profound RV dysfunction should have been a better focus early on. Finally, when the patient gets a little better oxygenation, you could relax, but I would bet the best thing that they really did was change their vasopressor management and improve right-heart function.

**Fessler:** If the goal is to unload the right ventricle, there’s an even less expensive way to do that, which is prone positioning. A 2007 paper in *Chest* showed that patients with ARDS who had signs of RV overload reversed their RV load after 18 hours of prone positioning. So, even if we look for other physiologic end points, there may be better ways to get there.


**Talmor:** I take issue with the contention that improving oxygenation is injurious. That’s exactly the wrong message to take from the ARDS Network trial. Improving oxygenation by increasing tidal volume to 10–12 mL/kg is injurious, but oxygenation in and of itself is a good thing. I don’t think we should so rapidly dismiss trials that improve oxygenation, particularly since that may allow us to get the patient over the hump and give them time to get better.

**Epstein:** Mark, you mentioned the mechanisms of action of epoprostenol, prostacyclin, and iloprost, and said something about the anti-thrombotic effect. It seems to me that the reduction in pulmonary artery pressure you would see in ARDS is probably more related to the relief of hypoxia and hypoxic vasoconstriction, because, if you take the analogy from idiopathic pulmonary hypertension or human-immunodeficiency-virus-related pulmonary hypertension or portopulmonary hypertension, the anti-thrombotic and anti-proliferative effects unfold over weeks and weeks, and probably aren’t relevant to this population. We also know from those studies that, at least in idiopathic pulmonary hypertension, only 10% of patients respond to an inhaled vasodilator with a reduction in pulmonary artery pressure.

**Siobal:** The anti-thrombotic effect is a theoretical benefit. It has not been proven or studied. We need an RCT of inhaled prostacyclin.

**MacIntyre:** The history of inhaled vasodilators at Duke is fascinating. For many years we could make it ourselves for less than $100 a tank, so it was used without much control. When it suddenly became tens of thousands of dollars per tank, everybody stood up and took notice. We now use inhaled iloprost in postoperative cardiac surgery patients and lung transplant patients. It’s interesting because our indication is only that “the surgeon wants INO.”

**Hess:** So how did you figure out dosing and what delivery device to use and whether it’s safe?

**MacIntyre:** We started with the approved dose of iloprost. I realize that dose was approved only for the iNeb and that there are issues about the iNeb’s efficiency compared to other aerosol devices we might use in the ventilator circuit. However, taking into account that we have an intubated patient, which impacts delivery into the tracheobronchial tree, we’ve come up with a dosing schedule that starts at the recommended dose and drops from there. Dean, you can criticize me all you want, because there’s little supportive data.

**Hess:** I’m merely curious.

**MacIntyre:** There are multiple reasons to criticize me. You know this is kind of made up stuff, but it’s a reasonable starting point and seems to give us the effects we want without adverse effects. Mike, do you want to elaborate?

**Gentile:** Giving it to the intubated patient is a little easier than continu-
ing it in a patient who’s going to the floor, and we’re wrestling with that a bit more. It was by trial and error, like everything else.

This is outside the scope of ARDS, but INO is like crack cocaine to thoracic surgeons, and they use it for everything—perceived pulmonary hypertension—and they have a very good argument that they want to get the patient off the pump and out of the operating room, and how much does it cost per hour? They have a very good argument, which is that the operating room costs are probably a lot more than your INO costs. Our number-one use of INO is in the patient coming out of thoracic surgery, so we’ve moved on to other inhaled agents that are as effective and less expensive.

**MacIntyre:** We almost never use INO for lung injury, and I don’t think we’ve used it for ALI or ARDS in recent memory.

**Gentile:** Not in 5 years.

**MacIntyre:** It’s solely for severe hypoxemia, pulmonary hypertension, and RV overload, usually after cardiothoracic surgery.

**Hess:** We’re trying to convert the cardiothoracic surgeons from use of NO in the operating room. I am bothered that we may be substituting one unproven therapy for another. Maybe it’s the best that we can do, but I guess that in my gut that doesn’t seem right.

**MacIntyre:** I can’t disagree with you, but I’d rather lose $100,000 a year than $1,000,000 a year.

**Hess:** I understand; we’re faced with the same thing.

**Moores:** It’s interesting when you look at the different disease-modifying agents that we’re using for patients with pulmonary hypertension. The prostacyclins are different than other inhaled vasodilators, and are the only class that has good evidence of a mortality benefit. I think that most people feel that it has nothing to do with any vasodilatation, but with the anti-inflammatory and anti-fibrotic properties. So that’s intriguing when you think about lung injury and ARDS and whether those effects might make it different than INO. I agree we don’t have the data yet, but I think it’s intriguing that there might be another mechanism that might make this class of drugs different.

**Siobal:** I agree. We use the AeroNeb Solo [Aerogen, Galway, Ireland], which has a continuous mode and gives you better control over the aerosol particle size and dose delivery, so it’s really an infusion pump for the lung. But even with that better delivery device there’s still no evidence that it’s doing any good. In terms of what Neil’s doing at Duke—giving iloprost continuously—somebody needs to do a dose-response study to find the continuous inhaled dose at which you start getting systemic vasodilation. If we knew that, we could do an RCT.

**Sessler:** Since cardiac surgeons’ use is probably the highest, are there data to support its use in the operating room? Or in the immediate post-operative period?

**Gentile:** There are negative data from the lung-transplantation population, but it doesn’t matter to them. We’re still giving it to a variety of thoracic patients, but for a shorter period of time. But, again, we still hear “ka-ching” because somebody’s ringing the cash register. It’s not just lung-transplant patients; it’s anybody who has a thoracotomy.

**Sessler:** In a meta-analysis, INO was associated with higher risk of developing renal insufficiency. That was the only statistically significant finding other than oxygenation benefit. Do we just not believe that’s real, or do we not understand mechanistically how it could happen, so we don’t know what to think about it?


**Hess:** I don’t think I know what to make of it. I would also point out that those findings in the 3 trials were found retrospectively. In none of the studies did they look specifically for that as the trial was being conducted. So I’m not sure I know what to make of it.

**Epstein:** Dean, you mentioned 3 potential down sides. Any comments about peroxynitrate as a toxic oxygen radical? That was discussed a lot when we were using a lot of INO.

**Hess:** Actually, 10 years ago we did a Journal Conference on INO and my talk was on toxicity. I talked about peroxynitrate and so forth, and it’s been investigated in animal models. It has been shown in animal models—at least in big doses—to be an issue. I don’t know that there are any confirming data in humans. There may be, but I’m not aware of them.

1. Inhaled nitric oxide: part I. Respir Care 1999;44(2):129-240.

**Gentile:** I think that went away when the INO dose went from 100 ppm down to 20 ppm or 5 ppm. So did concern about methemoglobin.

**Siobal:** Another issue is that in a really sick patient an inhaled vasodilator may allow you to reduce the FiO₂ and thus lower the risk of oxygen toxicity. I’ve heard attendings say that once the lung is inflated it’s less prone to oxygen injury, but I’ve never seen...
any studies on that. Does anybody know of any data on that?

Moore: I looked at that a little while ago and didn’t find anything. The data on oxygen toxicity came from normal lungs, and I don’t think we know about abnormal lungs. I don’t think we can say that there isn’t oxygen toxicity.

Hess: I think Dr Durbin did a Journal article about that. I’m grateful to Neil for his charismatic way of phrasing the lowest PaO2 of telling us that the patients who had oxygen toxicity were grateful.

Durbin: The concept is permissive hypercapnia, and now, if you will, permissive hypoxemia, the operative word there is permissive. People used to ask me, “Neil, if you do permissive hypercapnia, how far do you want to drive the CO2 up?” To that I said no, no, you’ve got it all wrong. You are simply allowing CO2 to rise because it’s an effect of providing something beneficial (ie, smaller tidal volume and lower plateau pressure).

I think the same thing holds true of hypoxemia. The idea of pushing up the PEEP to get the PaO2 into the hundreds and to get the shunt fraction back to normal is misguided, because clearly we are paying too big a price for that with the high pressures required, and so we’ll let the PO2 fall. I agree with Dan; we don’t want people dying of hypoxemia, for crying out loud, but I think a PaO2 in the 60s or 70s is probably fine, as opposed to applying the ventilation pressures required to drive PaO2 up to 100 mm Hg. The ARDS Network’s table focuses on a PaO2 of 55–80 mm Hg. A lot of people focus on 55; I sort of focus on 80 as an interesting boundary.

I would like to comment about the oxygen issue in ARDS trials. I’m grateful to Neil for his charismatic way of telling us that the patients who had the lowest PaO2 in the ARDS Network trials had the best survival. This now seems to be the mantra around this table, and that’s an interesting observation, but none of those patients were dying of hypoxemia. On average, or even in the extremes of the ARDS Network trial, those patients were not critically hypoxic. So it isn’t a patient with a PaO2 in the 30s or 40s where you’re saying, “Don’t worry about them.” The ARDS Network survivors had PaO2 in the 80s, as opposed to the 90s.

I don’t think the message should be that oxygen delivery and oxygen partial pressure in the blood are not concerning in a patient who’s dying. I think the therapies we’ve talked about in these last 2 sessions really are life-saving, and you have to use PaO2, as your marker. A patient whose PaO2 is 30 mm Hg or lower for a long time is probably not going to survive, but if inhaled prostacyclin gets the PaO2 up to 40 or 50 mm Hg, then at least there’s a chance of survival.

MacIntyre: The fact is permissive hypercapnia, and now, if you will, permissive hypoxemia, the operative word there is permissive. People used to ask me, “Neil, if you do permissive hypercapnia, how far do you want to drive the CO2 up?” To that I said no, no, you’ve got it all wrong. You are simply allowing CO2 to rise because it’s an effect of providing something beneficial (ie, smaller tidal volume and lower plateau pressure).

I think the same thing holds true of hypoxemia. The idea of pushing up the PEEP to get the PaO2 into the hundreds and to get the shunt fraction back to normal is misguided, because clearly we are paying too big a price for that with the high pressures required, and so we’ll let the PO2 fall. I agree with Dan; we don’t want people dying of hypoxemia, for crying out loud, but I think a PaO2 in the 60s or 70s is probably fine, as opposed to applying the ventilation pressures required to drive PaO2 up to 100 mm Hg. The ARDS Network’s table focuses on a PaO2 of 55–80 mm Hg. A lot of people focus on 55; I sort of focus on 80 as an interesting boundary.

Siobal: In some patients I call using the ARDS Network table the PEEP/F1O2 rollercoaster, because lowering the PEEP and derecruitment can happen several times: bring the PEEP down too much and the patient crashes, and then the next day it’s up again.
MacIntyre: Then use the higher table!

Siobal: I like to use no table and just do free-form PEEP.

MacIntyre: Free-form PEEP sounds like a free fall.

Siobal: I just mean don’t only follow the table, but instead look at what’s happening with the patient. If they’re getting better and they’ve been stable, then consider lowering the PEEP. You mentioned a \( P_O_2 \) of 60 mm Hg. We’d all be happy with a \( P_O_2 \) of 60, but if they’re on 100% oxygen and they have a \( P_O_2 \) of 60, that bothers me, because I think we’re causing lung injury with the oxygen.

MacIntyre: So you’ve got one injury there and you’re talking about using a therapy that—who knows—might poison other organs from ventilator-induced lung injury. I don’t know.

Hess: To get back to Charlie’s point, and others have made it, I think if there’s any place for inhaled pulmonary vasodilator therapies in patients with ARDS, it is probably in the patient with refractory hypoxemia. Unfortunately, I don’t think we’ll ever be able to study that. I can’t imagine putting together a trial in that patient population and getting it through an IRB [institutional review board], first of all, and then enrolling enough patients to be able to answer the question.

Branson: Dean, I want to echo that, but also to say it should be reversible hypoxemia.

Hess: Correct: you need to be able to demonstrate a response.

Branson: Or at least refractory hypoxemia in a patient with reversible disease, because not everybody needs INO before they die. That’s a very expensive way of sending people out through the basement. That’s what we’ve done: limit it to patients with severe trauma and severe hypoxemia and who we think might survive their injuries, not in patients who have hepatorenal syndrome, who have 100% mortality.