

Selective pulmonary vasodilation in acute respiratory distress syndrome

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Acute respiratory distress syndrome (ARDS) is characterized by a marked maldistribution of pulmonary perfusion in favor of nonventilated, atelectatic areas of the lungs, and it is the main cause of pulmonary right-to-left shunting and hypoxemia. Therapeutic interventions to selectively influence pulmonary perfusion in ARDS became feasible with the introduction of inhaled nitric oxide, which provided a means not only to reduce pulmonary hypertension, but also to improve matching of ventilation to perfusion and, thus, hypoxemia. Clinical studies in ARDS subsequently demonstrated that the combination of inhaled nitric oxide with other interventions, such as positive end-expiratory pressure and prone positioning, yielded beneficial and additive effects on arterial oxygenation. Although the available randomized, controlled trials of this novel concept have so far failed to show an improved outcome in ARDS, inhaled nitric oxide is a clinically valuable option for the treatment of severe refractory hypoxemia

in ARDS, and largely promoted the concept of selective pulmonary vasodilation in intensive care practice. Currently, aerosolization of various vasodilators, in particular prostaglandins, is under evaluation in models of acute lung injury and human ARDS. Ongoing research aims to augment the effectiveness of vasodilators with specific inhibitors of phosphodiesterases or by combination with intravenous vasoconstrictors. Consequently, several alternative ways to selectively modulate pulmonary vascular tone in patients with ARDS may be available in the near future. Cost-benefit analysis of these therapeutic options will largely determine their future perspective. (Crit Care Med 2003; 31[Suppl.]:S337-S342)

KEY WORDS: acute respiratory distress syndrome therapy; almitrine; endothelin receptor antagonist; hypoxemia; inhaled nitric oxide; phosphodiesterase inhibitors; prostacyclin; pulmonary gas exchange; pulmonary hypertension; selective pulmonary vasodilation

Acute respiratory distress syndrome (ARDS) is characterized by pulmonary and endothelial inflammation, which induces permeability edema, loss and dysfunction of surfactant with atelectasis and reduction in pulmonary compliance, hypoxemia as a result of ventilation-to-perfusion mismatch associated with intrapulmonary right-to-left shunt (Qs/Qt), and pulmonary hypertension (1).

The pulmonary vascular changes in ARDS are accompanied by reduced pulmonary vasoconstriction in hypoxic shunt areas, along with vasoconstriction in well-ventilated regions, a cytokine-mediated inflammatory response, and intravascular coagulation; these may be further compounded by consequences of

therapeutic interventions, such as oxygen toxicity and barotrauma (2). Pulmonary hypertension increases inflow pressure, leading to aggravation of edema, and may impair right-ventricle loading conditions (3). Systemically administered vasodilators have been used to treat pulmonary hypertension in ARDS patients. However, their benefit on pulmonary circulation is at the cost of impaired gas exchange because the simultaneous dilation of systemic and pulmonary vessels increases Qs/Qt (4, 5).

Inhaled Nitric Oxide for Selective Pulmonary Vasodilation in ARDS

In 1987, the discovery that endothelial-derived relaxing factor was nitric oxide (NO) (6, 7) provided a rational basis for understanding the mechanism of action of nitrovasodilators. In particular, it was suggested that gaseous NO may have vasodilating properties. In experimental hypoxic pulmonary vasoconstriction, it has been demonstrated that inhaled NO (iNO) selectively vasodilates pulmonary vessels without systemic effects (8, 9). This was validated in awake healthy volunteers

(10) and in patients with chronic pulmonary hypertension (11). The selectivity of iNO to ventilated lung regions is due to its rapid inactivation on contact with hemoglobin (12).

Rossaint et al. (13) compared the effects of iNO (18 ppm) with intravenous prostacyclin (PGI₂, 4 ng/kg) in nine ARDS patients. Inhalation of NO reduced the mean pulmonary artery pressure (Ppa) from 37 ± 3 torr to 30 ± 2 torr (mean ± SE) without significant changes in the mean arterial pressure or cardiac output. Intravenous PGI₂ induced an identical reduction in Ppa but also significantly reduced mean systemic arterial pressure and increased cardiac output, indicating that the actions of intravenous PGI₂ were not selective. However, the most striking finding of this study was that inhalation of NO induced a significant increase in Pao₂ from 152 ± 15 torr to 199 ± 23 torr because of a reduction in Qs/Qt. This demonstrated a redistribution of blood flow from nonventilated to ventilated lung areas by selective vasodilation in ventilated regions.

Subsequently, it was shown that iNO is effective in conjunction with different therapeutic strategies in the treatment of

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Supported, in part, by grants DFG KA 1212/4-1 and Fa 139/4-3 from the Deutsche Forschungsgemeinschaft.

Presented, in part, at the Margaux Conference on Critical Illness, Cabo da Roca in Sintra, Portugal, November 13-17, 2002.

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DOI: 10.1097/01.CCM.0000057913.45273.1A

ARDS. Combined treatment with positive end-expiratory pressure and iNO was investigated in 21 patients with ARDS (14). In patients in whom moderate positive end-expiratory pressure induced alveolar recruitment, iNO significantly improved PaO_2 ; however, in subjects who did not respond to positive end-expiratory pressure, iNO was ineffective.

Papazian et al. (15) evaluated the effects of iNO and prone position in 14 ARDS patients. The authors demonstrated a significant and additive effect of iNO and prone position on gas exchange, and this has been confirmed in other studies (16–18). However, a synergistic action of these treatments could not be confirmed (19, 20).

Other therapeutic interventions aimed at alveolar recruitment and optimization of gas exchange have been studied in conjunction with iNO, including exogenous surfactant and partial liquid ventilation (21–23). In experimental models of acute lung injury (ALI), it was demonstrated that conditioning the lung by such means can augment the efficacy of iNO in improving gas exchange.

Response to iNO

Knowledge of the physiologic determinants of the iNO response is still incomplete. The situation is further complicated by the fact that the efficacy of iNO mainly depends on the concentration applied. Dose-response characteristics for gas exchange were found to be different from those for Ppa and pulmonary vascular resistance (24, 25). In responders to iNO, Ppa decreased steadily but in a non-linear fashion with increasing NO concentration; in contrast, the maximum effect on PaO_2 was obtained in the range of 1–10 ppm (25). This may indicate a loss of selectivity with respect to ventilated parts of the lungs at higher doses due to an increased diffusion of NO in nonventilated lung regions, with subsequent vasodilation (26).

Only a few studies have used statistical correlation analysis to identify the factors that determine responses to iNO. Data from ARDS patients inhaling various doses of NO suggest that changes in pulmonary vascular resistance, Ppa, and venous admixture (Qva/Qt) were related to the baseline values of these variables before administration of iNO (24, 27). The improvement in PaO_2 was linearly related to pretreatment values of pulmonary vascular resistance (27, 28). These findings

indicate that in ARDS, the beneficial effects of iNO on gas exchange depend on: (1) the existence of a certain degree of vasoconstriction in ventilated lung areas and (2) intrapulmonary selectivity of vasodilation to these lung regions. A third requirement is the presence of Qs/Qt . Investigations in non-ARDS patients with pulmonary hypertension provide arguments for this additional condition. Thus, iNO significantly reduced Ppa in mountaineers susceptible to high-altitude pulmonary edema at an altitude of 4559 m, but PaO_2 was only improved if edema had developed (29). Similar results were reported in patients with chronic obstructive pulmonary disease, a condition characterized by pulmonary hypertension and impaired oxygenation due to an increased fraction of low ventilation-to-perfusion ratio. In these patients, Qs/Qt was low, and iNO decreased Ppa but slightly worsened PaO_2 (30).

Blood-borne vasoactive mediators are expected to influence pulmonary vascular tone and, thus, the effects of iNO. Hyporesponsiveness to iNO in ARDS patients with septic shock (27) is considered a consequence of increased endogenous NO synthesis. Experimental models of endotoxin-induced sepsis have demonstrated increased expression of inducible NO synthase and blocking that prevented hyporesponsiveness to iNO (31, 32).

Endothelin (ET)-1 is a particularly powerful endogenous vasoconstrictor (33, 34). The lung has a high capacity for production and clearance of ET-1, and increased plasma levels of ET-1 have been measured in ARDS patients (35). Immunohistochemical analysis of lung tissue in patients who succumbed to ARDS revealed increased ET-1 levels in vascular endothelium, airway epithelium, smooth muscle cells, and alveolar macrophages when compared with lungs of patients who died without ARDS (36). It was recently demonstrated in an experimental model of ALI that improvements in PaO_2 induced by iNO were significantly related to the plasma concentration of ET-1 (37). Moreover, iNO reduced ET-1 plasma levels compared with untreated controls when applied for >2 hrs. This negative feedback mechanism may indicate that lower NO concentrations become more effective during long-term treatment with iNO because a reduced pulmonary vasoconstriction caused by lower ET-1 plasma levels requires less iNO.

Changes in dose-response characteristics during long-term inhalation of NO

were studied in a randomized, controlled, single-center trial enrolling 40 ARDS patients (38). Patients were randomized to receive long-term inhalation of 10 ppm NO or no continuous inhaled treatment. Dose-response curves ranging from 0.01 to 100 ppm iNO described hemodynamics and gas exchange at regular intervals. Initially, iNO induced comparable dose-response characteristics in both groups. However, after 4 days of treatment, the iNO group revealed a left shift in the dose-response curve, with a maximum effect on arterial oxygenation at 1 ppm as compared with 10 ppm after 2 days. This effect was not registered in the control group, and there was no difference between the groups in mortality rate, length of stay, or number of ventilator-free days. Nevertheless, the requirement for extracorporeal membrane oxygenation therapy was significantly lower in the group that received continuous iNO.

A reduced response to iNO in patients with ARDS is not a static phenomenon, and various observations indicate that patients who do not initially respond to iNO may become responders in the further treatment course (24, 39–41). In some cases, this seems to be associated with treatment modalities inducing alveolar recruitment, such as prone positioning (18) and positive end-expiratory pressure (14). It can be hypothesized that the morphologic changes due to alveolar recruitment primarily occur at the boundary layer between ventilated lung regions and consolidated shunt areas. Ongoing research may elucidate the significance of regional blood-flow redistribution along this interface for iNO responsiveness.

Randomized, Controlled Trials on iNO in Adults

Two pilot, randomized, unblinded, controlled, single-center studies with small sample sizes of $n = 40$ and $n = 30$ compared iNO treatment and conventional therapy in adult patients with ARDS (42, 43). Both investigations demonstrated only transient improvements in PaO_2 during the first 24 hrs of treatment, documented either by an increase in the $\text{PaO}_2/\text{FIO}_2$ ratio (42, 43) or by an improvement in a specific hypoxia score, and a decrease in Qva/Qt (43). No effect of iNO on mortality rate was found within these limited sample sizes.

The results of the U.S. randomized, double-blind, placebo-controlled phase II trial presented by Dellinger et al. (44)

caused widespread attention and controversy. This study aimed to investigate safety issues and physiologic effects of various iNO doses and was not powered to demonstrate a statistically significant benefit in any outcome variable. A total of 177 patients, fulfilling criteria of early ARDS in accordance with the American-European Consensus Conference criteria (45) for < 72 hrs before randomization, were enrolled in 30 hospitals. Patients were randomized to receive either iNO at concentrations of 1.25, 5, 20, 40, or 80 ppm (n = 120) or placebo gas (n = 57). No indication of adverse effects of iNO was documented, except for an increased methemoglobin concentration after application of 80 ppm and 40 ppm, a range usually not required in ARDS.

In the treatment group, ARDS patients had a 60% response rate for a change in $\text{PaO}_2/\text{FiO}_2$ of >20%. Effects on PaO_2 and hemodynamics were significant only in the initial phase of NO inhalation: the authors reported transient improvements in PaO_2 and mean Ppa during the first 24 hrs of iNO treatment and in oxygenation index during the first 4 days. Pooled data from all ARDS patients receiving iNO at any of the doses revealed no significant difference in the number of days alive and off mechanical ventilation at 28 days when compared with controls. However, according to a *post hoc* analysis, a significantly higher percentage of patients alive and off mechanical ventilation was found in the 5-ppm iNO group as compared with controls. Based on an intention-to-treat analysis, the mortality rate was 30% in both the placebo and the iNO groups.

The results of a prospective, randomized, unblinded, European, multicenter, phase III trial on iNO in ALI were reported by Lundin et al (46). The primary end point of this study was the reversal of ALI. Clinical outcome and safety were assessed as secondary objectives. Originally powered for a sample size of 600, the study was halted after the enrollment of 286 patients due to slow recruitment. After initial application of iNO (2, 10, and 40 ppm for 10 mins), responders (63%, n = 180) were randomized to either iNO at the lowest effective dose (mean iNO dose, 9 ± 8 ppm; n = 93) or to conventional treatment (n = 87) for 30 days. Besides reversal of ALI as the primary end point, a secondary end point was reached when criteria for severe respiratory failure (corresponding to extracorporeal membrane oxygenation entry criteria) were met. The hemodynamic and PaO_2 response to NO

was only reported for a single time point before randomization, and data during the further course of the study were not presented. Although reversal of ALI was not significantly different between the two arms (iNO group, 61%; controls, 54%), iNO treatment significantly reduced the frequency of severe respiratory failure (iNO group, 2.2%; controls, 10.3%; $P < 0.05$). In contrast to the U.S. phase II trial, renal failure was identified as a possible adverse effect of NO inhalation. This finding is so far unexplained and has not been confirmed in other clinical trials. Mortality rates did not differ significantly between groups at 30 days (iNO, 45%; controls, 38%; nonresponders, 45%). The following conclusions can be drawn from the randomized, controlled trials of NO treatment in ARDS: (1) iNO clearly improves PaO_2 and hemodynamics in the acute phase of its application and may allow a more lung-protective mechanical ventilation; (2) iNO does not induce clinically relevant adverse effects, with the possible exception of renal failure; (3) the effects of NO are dose-dependent and doses of ≤ 10 ppm are recommended; (4) the available randomized, controlled trials provide no evidence for a reduction in mortality with iNO in patients representing the entire range of severity of ALI and early ARDS; however, the question of whether a subgroup of severely hypoxemic ARDS patients will respond favorably to NO with an increased survival rate, more ventilator-free days, or a reduced extracorporeal membrane oxygenation frequency has not been conclusively resolved; and (5) in ARDS patients with severe and refractory hypoxemia, iNO seems to be a feasible rescue treatment. This interpretation is essentially supported by a recent meta-analysis of randomized, controlled trials on iNO therapy reported by Sokol et al. (47).

Clinical Studies in Neonates

Persistent pulmonary hypertension of the neonate is characterized by a failure of the pulmonary vascular resistance to appropriately decrease during the transition to extrauterine life. This leads to myocardial dysfunction and hypoxemia as a result of extrapulmonary right-to-left shunting across the foramen ovale and the ductus arteriosus (48).

The Neonatal Inhaled Nitric Oxide Study Group performed a randomized, double-blinded, placebo-controlled trial

enrolling 235 full-term or near-term neonates with hypoxic respiratory failure (49). Infants of <14 days of age with a mean PaO_2 of 46 torr were randomized to iNO at 20 ppm (n = 121) or to receive pure oxygen (controls, n = 114). Although mortality by 120 days of age was not different between groups (14% and 17%, respectively), significantly fewer neonates in the iNO group required extracorporeal membrane oxygenation as compared with controls (31% vs. 55%, respectively, $P < 0.0001$) (49).

Status of Licensing of iNO

Based on current evidence, iNO has been approved by the Food and Drug Administration (approval 020845, December 23, 1999) and the European Commission (EU/1/01/194/001, August 1, 2001) for the treatment of term and near-term neonates (>34 wks) with hypoxic respiratory failure associated with pulmonary hypertension. In adult ARDS patients, randomized, controlled trials have failed to consistently demonstrate that iNO reduces the necessity for extracorporeal membrane oxygenation therapy. Therefore, in adults with ARDS, iNO is currently unlicensed.

Intravenous Almitrine Combined with iNO

Almitrine bismesylate was initially described to reduce Qva/Qr by enhancement of hypoxic pulmonary vasoconstriction (50). Using multiple inert gas elimination technique in ARDS patients, Reyes et al. (51) demonstrated that almitrine redistributed pulmonary blood flow from shunt areas to lung units with normal ventilation/perfusion ratios. Almitrine is therefore considered a selective pulmonary vasoconstrictor in shunt areas. Payen et al. (52) were the first to combine iNO with intravenous almitrine in two ARDS patients. Coadministration of almitrine and iNO induced an additive effect on gas exchange, whereas increases in Ppa due to infusion of almitrine were attenuated by iNO. Accordingly, the combined use of iNO and almitrine has been proposed as an option for ARDS treatment (16).

Aerosolized Prostacyclin for Selective Pulmonary Vasodilation

Prostaglandins are endogenously produced by endothelial cells through the

cyclo-oxygenase pathway, were shown to have vasodilatory and anti-inflammatory properties, and inhibit platelet aggregation (53, 54). In ARDS, intravenously infused PGI₂ nonselectively reduces Ppa, with a concomitant increase in Qs/Qt and a deterioration in gas exchange (4, 5, 13). Inhalation of aerosolized PGI₂ at a dose of 17–50 ng·kg⁻¹·min⁻¹ was first demonstrated to selectively vasodilate the pulmonary vasculature in three ARDS patients (55).

Consequently, the efficacy of aerosolized PGI₂ on hemodynamics and gas exchange was compared with iNO in ARDS patients (56–58). In these clinical trials, aerosolized PGI₂ significantly reduced Ppa and increased oxygenation, as was the case with iNO. However, during inhalation of PGI₂, the selectivity of vasodilation is greatly dependent on the dose applied: high doses may spill over into the systemic circulation, abbreviating selectivity and possibly impairing arterial pressure and gas exchange. In contrast to iNO, the concentration of PGI₂ and the amount absorbed cannot be precisely measured. In addition, the amount of the aerosol fraction of PGI₂ that is delivered to the alveolar space is dependent on the nebulizer used (59). This has to date largely precluded explicit dose recommendations for ARDS.

Aerosolization of a stable analog of PGI₂, iloprost, in patients with pulmonary hypertension resulted in a sustained reduction of Ppa for up to 120 mins after discontinuation of the drug (60). Olschewski et al. (61) investigated iloprost for ambulant treatment of patients with chronic pulmonary hypertension and reported significant improvements in Ppa and New York Heart Association class when compared with placebo. Considering clinical applicability in ARDS, prolonged inhalation of prostaglandins yield the risk of systemic side effects. To date, there have been no randomized, controlled trials evaluating outcome variables in ARDS patients inhaling prostaglandins.

Inhibition of Cyclic Nucleotide Phosphodiesterases

NO activates soluble guanylate cyclase, generating cyclic guanosine monophosphate (cGMP), which in turn vasodilates smooth muscle cells by activating protein G-kinase and calcium-gated potassium channels (62). Various phosphodiesterases (PDEs) degrade cGMP; therefore, basal vascular tone is believed

to be influenced by the balance between cGMP production and PDE-dependent degradation (63). Of the different PDE isoforms, it is PDE-5 that specifically hydrolyzes cGMP. Inhibitors of PDE-5 have been comprehensively studied because of their ability to lower pulmonary vascular resistance, and to potentially augment NO-induced pulmonary vasodilation (64).

Dipyridamole, a PDE-5 inhibitor, has been used in combination with iNO to decrease Ppa in patients with pulmonary hypertension (65). In 11 pediatric patients with severe pulmonary hypertension, Ziegler et al. (66) compared the effects of 20 ppm iNO, 0.6 mg/kg dipyridamole, and a combined treatment with the same amounts of either drug on pulmonary and systemic hemodynamics. The authors reported an augmentation of iNO-induced pulmonary vasodilation by dipyridamole in 50% of their patients.

Sildenafil is a highly selective PDE-5 inhibitor with predictable gastrointestinal absorption (67). In healthy pigs, oral sildenafil revealed characteristics of systemic vasodilators, significantly increasing cardiac output and Qva/Qt (68). In awake lambs with pulmonary hypertension, cumulative doses of oral sildenafil (12.5, 25, and 50 mg) induced pulmonary vasodilation, with only a minor reduction in systemic arterial pressure at the lowest dose applied (69). A further experimental study in animals with acute pulmonary hypertension demonstrated that nebulization of 10 mg sildenafil alone induced selective pulmonary vasodilation and augmented the vasodilating effects of 2–5 ppm iNO during combined treatment (70).

The effects of inhaled PGI₂ and iloprost are mediated by cyclic adenosine monophosphate. Similar to cGMP, the concentration of cellular cyclic adenosine monophosphate is controlled by PDEs. PDE-2, PDE-3, and PDE-4 are cyclic adenosine monophosphate selective. The activity of PDE-2 and PDE-3 is influenced by cGMP and is therefore also indirectly dependent on the presence of the cGMP-specific PDE-5 (62). Schermuly et al. (71) investigated the effects of selective inhibitors of PDE-3, PDE-4, and PDE-5 in an experimental rabbit model of pulmonary hypertension. They reported that specific doses of all of these PDE inhibitors were effective for nonselective reduction in Ppa by about 20% and described no effects on hemodynamics and gas exchange at a ten-fold lower dose. However, coadministration of PGI₂ with PDE inhibitors

Several alternative ways to selectively modulate pulmonary vascular tone in patients with acute respiratory distress syndrome may be available in the near future.

in subthreshold doses resulted in significantly enhanced and prolonged vasodilation. These results were recently confirmed in isolated perfused rabbit lungs when PDE-3 and PDE-4 inhibitors were administered either intravenously or aerosolized in combination with inhaled PGI₂ (72).

Inhalation of Endothelin Receptor Antagonists

As stated above, endothelins were found to be increased in lungs of patients with ARDS (36). Endothelins exert their biological effects via two receptor subtypes, ET_A and ET_B (73). Whereas endothelial ET_B receptors induce the release of NO and PGI₂, stimulation of pulmonary ET_A receptors was shown to induce sustained vasoconstriction, revealing the potential of ET_A receptor antagonists to act as vasodilators (74). Endothelin receptor antagonists are usually administered intravenously or orally, and their efficacy has been shown particularly in animal models of pulmonary hypertension (75, 76). In a recent randomized, placebo-controlled trial in patients with pulmonary arterial hypertension, Rubin et al. (77) demonstrated that oral bosentan (a dual endothelin receptor antagonist) was an effective and well-tolerated therapy.

The effects of the nebulized ET_A receptor antagonist LU-135252 (Knoll, Germany) were recently studied in experimental ALI (78). Inhalation of LU-135252 (3 mg/kg) significantly reduced Qva/Qt from 58% ± 8% to 27% ± 12% (*P* < 0.05). Concomitantly, PaO₂ increased from 55 ± 12 torr to 257 ± 148 torr (*P* < 0.05) without adverse systemic effects (78). In a subsequent study, effects of short-term inhalation of a ten-fold lower dose of LU-135252 (0.3 mg/kg) were com-

pared with continuous inhalation of 30 ppm NO (79). Both treatments significantly improved gas exchange and prevented an increase of Ppa in a similar fashion without significant systemic effects when compared with controls. These results merit future clinical evaluation of the potential role of inhaled endothelin receptor antagonists for the treatment of ARDS patients.

Conclusions

Selective modulation of pulmonary blood flow in ARDS became feasible with the introduction of iNO. Clinical evaluation of this novel concept demonstrated that iNO is a clinically valuable option for the treatment of both severe hypoxemia and pulmonary hypertension in ARDS. Inhalation of various vasodilators is currently under experimental and clinical evaluation, and accordingly, the clinician will soon be offered several alternative ways to selectively modulate pulmonary vascular tone in ARDS. Efficacy and costs of these therapeutic options will determine their future use.

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