EDITORIAL VIEWS

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Phenylephrine and Inhaled Nitric Oxide in Adult Respiratory Distress Syndrome

When Are Two Better than One?

ADULT respiratory distress syndrome (ARDS), originally defined 30 yr ago, is now a major cause of morbidity and mortality. In the absence of definitive therapy, management involves supportive care using mechanical ventilation with increased inspired oxygen concentrations and positive end-expiratory pressure (PEEP). Because hypoxemia in patients with ARDS is primarily a result of alveolar collapse, which results in intrapulmonary shunting, patients may remain hypoxemic despite such therapy. In 1993, Rossaint *et al.* showed that inhaled nitric oxide (INO) improves oxygenation and decreases pulmonary hypertension in patients with ARDS,[1] a finding subsequently confirmed by multiple other investigators.[2-5] Using the multiple inert gas elimination technique, Rossaint *et al.* showed that INO improves oxygenation by decreasing blood flow to areas of intrapulmonary shunting and increasing blood flow to areas with normal ventilation-perfusion ratios.[1] The ability of INO (and other inhaled vasodilators, such as prostacyclin[6,7]) to improve oxygenation is a result of the inhaled as opposed to the intravenous route of administration. As an inhaled vasodilator, INO only reaches alveoli with good ventilation and thereby produces pulmonary vasodilation only in these areas. A corollary to this concept is that INO should be effective only when there is increased vascular tone in well-ventilated areas; such increased tone may be the result of humoral vasoconstrictor mediators in patients with ARDS.

Studies of INO in patients with ARDS show that many patients have no response or only a minor response to INO,[1-5,8,9] resulting in interest in therapies that might be alternative, additive, or synergistic to INO. Almitrine bismesylate stimulates peripheral chemoreceptors and increases hypoxic pulmonary vasoconstriction (HPV).[10] Almitrine improves oxygenation but worsens pulmonary hypertension in some but not all patients with ARDS, and the combination of almitrine and INO has additive effects in improving oxygenation with no increase (and frequently a decrease) in pulmonary hypertension.[11,12] Because of toxicity with long-term use, almitrine is not clinically available, so an alternate therapy that improves oxygenation in patients with ARDS would be valuable.

During the past decades, Dr. Marshall *et al.* have advanced our understanding of the pulmonary circulation. In 1994, they used an elegant mathematical model of the pulmonary circulation to discuss the role of HPV in pulmonary gas exchange and blood gas distribution in normal and abnormal lungs.[13,14] The results showed that INO should improve oxygenation only in patients who have a diffuse increase in pulmonary arterial or venous tone. They predicted that the combination of an intravenous pulmonary vasoconstrictor and INO could produce additive beneficial effects on oxygenation. In this issue of ANESTHESIOLOGY, the article by Doering *et al.* from this group confirms this prediction.[15]

Doering *et al.* studied 12 patients with moderate-to-severe ARDS. Each patient received three therapies in randomized order: phenylephrine infusion to increase systemic blood pressure by 20%, 40 ppm INO, and the combination of phenylephrine and INO. Phenylephrine improved Pa_{O2} by 15 mmHg; INO improved Pa_{O2} by 45 mmHg, and the combination improved Pa_{O2} by 48 mmHg. Eleven of the 12 patients responded to INO as defined by an improvement in Pa_{O2} by at least 10 mmHg. In contrast, only 6 of 12 patients responded to phenylephrine. In the phenylephrine responder group, phenylephrine increased Pa_{O2} by 27 mmHg; INO increased Pa_{O2} by 33 mmHg, and the combination additively increased Pa_{O2} by 55 mmHg. In this phenylephrine responder group, PAP increased with phenylephrine but not with combination therapy. In the group that did not respond to phenylephrine, INO increased Pa_{O2} by 56 mmHg, and the combination increased Pa_{O2} by 43 mmHg. Thus, the combination of phenylephrine plus INO was superior to INO alone only when phenylephrine by itself improved oxygenation.

The ability to improve oxygenation with phenylephrine plus INO may be useful for two reasons. With improved oxygenation, patients may be ventilated with

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lower inspired oxygen concentrations and lower peak, mean, and PEEP airway pressures, thereby decreasing oxygen toxicity, barotrauma, and ventilator-induced lung injury. A large phase II study of INO in ARDS suggested that 5 ppm INO improves oxygenation, allows a decreased intensity of mechanical ventilation, and may decrease the duration of mechanical ventilation in patients with ARDS.[16] The ability of phenylephrine infusion to further increase oxygenation could increase the ability of INO to improve outcome.

The second potential application of combined phenylephrine plus INO therapy involves patients who remain hypoxemic with INO alone. However, the article provides few data relevant to this population. Only one patient was frankly hypoxemic, and that patient responded to INO but did not respond to phenylephrine. Of the five patients with Pa_{O2} less than 80 mmHg, one patient had a borderline response to phenylephrine, and four patients had no response. A study focusing on the patients with the most severe gas exchange abnormalities will be needed.

In addition to showing a new therapeutic combination, the study by Doering *et al.* provides insights into the underlying pathophysiology of patients with ARDS. The ability of phenylephrine to improve oxygenation confirms that the degree of HPV present in those with ARDS does not produce maximal vasoconstriction to areas with alveolar hypoxia. In theory, phenylephrine and INO could worsen oxygenation — phenylephrine could vasoconstrict areas with adequate ventilation and INO could vasodilate areas with low but not zero ventilation - perfusion ratios. The results of this study suggest that these effects do not occur and that INO is able to reverse phenylephrine-induced vasodilation in well-ventilated areas.

As in other studies, INO had a variable effect. Although 11 of 12 patients responded to INO, the proportion of responders may vary with the definition of a response so that up to one third of patients are considered nonresponders in most studies. Patients who do not respond to INO presumably have little if any vasoconstriction in well-ventilated areas. In theory, use of phenylephrine to enhance vasoconstriction throughout the lung (in atelectatic and well-ventilated areas) may result in converting an INO nonresponder into a responder. Again, additional studies of larger numbers of such patients will be required.

The reasons why some but not all patients respond to phenylephrine are unknown, but the data provide some fascinating trends. Patients who do not respond to phenylephrine appear to have worse gas exchange (Pa_{O2}, Pa_{CO2}, shunt fraction, dead space), more pulmonary hypertension (pulmonary artery pressure, pulmonary vascular resistance), and a greater response to INO. Unfortunately, because of the small number of patients (six per group), these differences did not reach statistical significance. However, such trends suggest a group of patients who already have maximal pulmonary vasoconstriction, so that phenylephrine is unable to further decrease blood flow to atelectatic areas. This concept is reinforced by the findings that INO decreased pulmonary artery pressure only in this group of patients and that phenylephrine produced statistically significant increases in pulmonary artery pressure only in the phenylephrine responders. Further studies will be needed, particularly because the absolute increase in pulmonary artery pressure was greater in the nonresponders than in the responders (but reached statistical significance only in the responders) and because PVR did not increase with phenylephrine in the responder group.

Although studies have suggested use of INO in patients with ARDS, neonatal respiratory failure, perioperative pulmonary hypertension, and chronic pulmonary hypertension, INO does not yet have any Food and Drug Administration (FDA) approved indication and is therefore limited in the United States to experimental use. The ongoing Ohmeda-sponsored trial comparing 5 ppm INO to placebo may provide a definitive answer on the use of INO in patients with ARDS, but results will not be available until 1998. However, two recently published randomized trials have shown a significant reduction in the need for extracorporeal membrane oxygenation (ECMO) therapy in neonates with respiratory failure.[21,22] These and other data on this patient population may be sufficient for FDA approval of INO. If so, physicians will then have the option to use INO in selected patients with ARDS. The study by Doering *et al.* may extend the population of patients with ARDS who benefit from such therapy and may allow us to develop better combination therapy in the future.

Ronald G. Pearl, M.D., Ph.D.
Department of Anesthesia
Stanford University School of Medicine
Stanford, CA 94305-5117
Electronic mail: RGP@leland.stanford.edu

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