Letters

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Combining Heliox and Inhaled Nitric Oxide as Rescue Treatment for Pulmonary Interstitial Emphysema

In the December 2008 issue of RESPIRATORY CARE, Phatak and associates[1] reported a case where they used heliox in combination with inhaled nitric oxide (NO) as rescue treatment for a preterm infant with pulmonary interstitial emphysema. They reported that this novel and innovative intervention was instituted because of the progression of severe cardiorespiratory compromise despite several conventional treatments.

My group reported a very similar case in abstract form in 1999.[2] The case report from Phatak et al is therefore more likely the second documented case in which the combination of heliox and inhaled NO appeared to improve ventilation and oxygenation in a preterm infant with pulmonary interstitial emphysema and critical gas-exchange defects that were refractory to conventional interventions.

A major difference in the way heliox and inhaled NO were simultaneously delivered in those 2 reports should be pointed out. Phatak et al[1] used a bleed-in system whereby an 80% helium/20% oxygen mixture was added to the ventilator circuit (Babylog, Dräger, Lübeck, Germany), distal to the injector module of the NO delivery device (INOVent, INO Therapeutics, Clinton, New Jersey). That setup could result in inaccuracies in the gas-concentration measurements and limit the maximum inspired helium concentration that could be delivered before the ventilator would not function.[1]

My group used an Infrasonics InfantStar ventilator (Tyco-Mallinckrodt, Carlsbad, California) with 80% helium/20% oxygen instead of compressed air, so the INOVent injector module would measure circuit flow comprised of a blended helium-oxygen gas mixture through the ventilator.[2] At the initial fraction of inspired oxygen (F_{IO_2}) of 0.80, a set dose of 5.4 ppm NO was required to deliver a dose of 10 ppm NO. This effect is caused by the physical properties of helium, which has a higher thermal conductivity than nitrogen, oxygen, or air.[3] Heliox more rapidly cools the heated-wire element in the INOVent's injector module, resulting in a higher calculated flow rate than is actually delivered. This causes the INOVent to inject a larger volume of NO. This effect increases proportional to the concentration of helium in the gas mixture and results in a higher inhaled NO dose delivery at any set dose. To maintain a constant inhaled NO dose delivery, any changes in F_{IO_2}, and therefore the helium concentration, require an adjustment in the set inhaled NO dose.[2]

We studied this effect in a bench-top laboratory experiment with an infant test lung, in which we assessed the functioning of the INOVent and the inhaled NO dose delivery at various heliox concentrations and minute ventilations, by changing the respiratory rate and peak inspiratory pressure. The set dose to deliver a 10-ppm dose of inhaled NO was 9.5–9.4 ppm at a helium concentration of 5%, versus 0.8–0.7 ppm at a helium concentration of 75% (Fig. 1). We found no effects on the formation of nitrogen dioxide, and the INOVent otherwise functioned normally.

The 2 cases[1,2] have striking similarities. Both involved preterm infants $<$ 1,200 g with respiratory distress syndrome followed by the development of pulmonary interstitial emphysema, early use of surfactant, failure of conventional and high-frequency ventilation, use of steroids, and initiation of heliox ventilation followed by combined heliox plus NO. In both cases F_{IO_2} was reduced from approximately 80% to 60% soon after the initiation of heliox plus NO, because of improved oxygenation. This reduction in F_{IO_2} allowed delivery of a higher fraction of inspired helium, which in turn improved CO_2 elimination and permitted lower ventilator pressures. This effect on gas exchange, F_{IO_2}, and ventilation pressures may have helped to attenuate the cycle of progression of pulmonary interstitial emphysema in these infants. Both infants were subsequently weaned off heliox, then weaned off inhaled NO, and extubated.

Heliox reduces gas trapping,[4] improves the distribution of ventilation and CO_2 clearance,[5,6] functions as a carrier gas for better penetration of inhaled NO to distal gas-exchange units,[7,8] and reduces lung inflammation,[9] all of which may have benefited these critically ill infants with pulmonary interstitial emphysema.

In low-birth-weight infants, pulmonary interstitial emphysema is a complication of mechanical ventilation and is associated with chronic respiratory insufficiency and bronchopulmonary dysplasia.[10,11] As stated 2 decades ago,[10] in regards to the treatment of premature infants with respiratory distress syndrome and the prevention of bronchopulmonary dysplasia, "it would be prudent to use all methods to reduce the concentration and duration of the inspired supplemental oxygen and to reduce peak ventilator pressures and their duration as much as possible." This holds true today as much as it did then, as pulmonary interstitial emphysema and bronchopulmonary dysplasia continue to be clinically important problems in the neonatal intensive care unit. For that reason the combined use of heliox and inhaled NO may be a means of accomplishing these treatment goals in infants with pulmonary interstitial emphysema who continue to deteriorate despite aggressive conventional interventions.

Betit's editorial[12] on the case report from Phatak et al[1] identified several important technical issues, questioned the safety of the combined therapy, and raised the ethical dilemma of using unproven therapies. The effect of heliox on the functional and performance characteristics of many mechanical ventilators has been determined.[3,13] Several ventilators suitable for infant ventilation now have heliox compatibility, which eliminates some of the technical and safety issues cited by Betit.[12] We found no effect on nitrogen-dioxide formation, and our delivery method allows a more stable titration and control of the heliox mixture and the inhaled NO dose delivered.[2]

Therefore, given the above solutions for the major technical and safety issues stated by Betit,[12] the more important question is whether the combined use of heliox and inhaled NO made a difference in outcome. This can only be determined by further innovation, technical refinement, and clinical study of this potentially beneficial treatment for pulmonary interstitial emphysema.

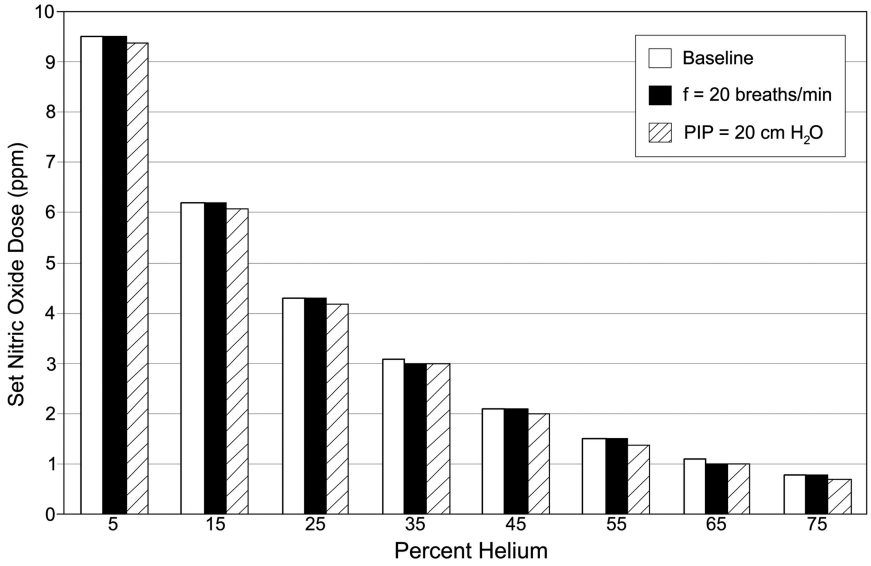

Fig. 1. The effects of helium concentration, change in respiratory rate (f), and change in peak inspiratory pressure on the set dose to deliver 10 ppm inhaled nitric oxide. The baseline settings were: respiratory rate 44 breaths/min, peak inspiratory pressure (PIP) 33 cm H_2O, and positive end-expiratory pressure 4 cm H_2O. The next ventilation settings (black bars) were the same as the baseline settings except we decreased f to 20 breath/min. The final ventilation settings (hatched bars) were the same as the baseline settings except we decreased the peak inspiratory pressure to 20 cm H_2O.

These case reports[1,2] may be the catalyst needed to stimulate that process.

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The author has disclosed no conflicts of interest.

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The authors respond:

We read with interest the case report from Siobal and colleagues of the simultaneous use of heliox and inhaled NO in an infant with pulmonary interstitial emphysema, pulmonary hypoplasia, and pulmonary hypertension,[1] and we appreciate Mark Siobal's comments on our paper.

In the case we described we also operated the ventilator (Babylog, Dräger, Lübeck, Germany) with 80% helium/20% oxygen, as described by Siobal et al, but the infant was so unstable that even that change was not tolerated. Thus, we used the bleed-in method and gradually increased the heliox added to the ventilator circuit. The infant tolerated this gradual increase in helium. An in-line oxygen sensor measured delivered oxygen. We acknowledged that this would not have given us the exact concentration of helium inspired, and we used clinical observation and noninvasive and invasive measurements to assess respiratory function. A

sensor in the inspiratory limb measured the delivered NO concentration (in ppm).

There have been no documented adverse effects in the pediatric use of helium in the past 35 years.[2] We agree that the technical issues in the delivery of heliox with inhaled NO need further research, and that further work on the utility of heliox in the treatment of air-trapping disease in neonates would be beneficial.

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Dr Phatak and Dr Klonin have disclosed relationships with BOC Gases/Linde Group. Dr Charles Pairaudeau, Dr Peter Pairaudeau, and Dr Smith have disclosed no conflicts of interest.

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CORRECTION

In the article "Airway humidification during high-frequency percussive ventilation" by Allan PF et al (Respir Care 2009;54[3]:350–358), the units of measurement for absolute humidity are in error. The correct units for absolute humidity are mg/L, not g/L.

We regret the error.