

Heliox With Inhaled Nitric Oxide: A Novel Strategy for Severe Localized Interstitial Pulmonary Emphysema in Preterm Neonatal Ventilation

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We describe the combined use of inhaled nitric oxide and heliox (79% helium and 21% oxygen) as a rescue therapy for a critically ill infant with localized interstitial pulmonary emphysema and pulmonary hypertension. Conventional interventions were ineffective, not feasible, or unlikely to take effect in time, during this infant's acute critical illness. We added heliox based on its known pulmonary effects, and inhaled nitric oxide to improve oxygenation, after echocardiographic evidence of high right-ventricular pressure. The infant made a full recovery. To our knowledge this is the first case report of heliox and inhaled nitric oxide used simultaneously in localized interstitial pulmonary emphysema. Key words: helium, inhaled nitric oxide, newborn, respiratory distress syndrome, localized interstitial pulmonary emphysema, pulmonary hypertension. [Respir Care 2008;53(12): 1731–1738. © 2008 Daedalus Enterprises]

Introduction

Pulmonary interstitial emphysema is one of a group of air-leak syndromes, characterized by air in pulmonary tissue in which it is not normally present.¹ Pulmonary interstitial emphysema can be transient or persistent, with a diffuse or localized pattern, and arises from alveolar air leaks or small airways that allow gas to enter and become trapped in the pulmonary parenchyma, resulting in splinting of the lungs and decreased compliance.^{2–8} Air trapped in the perivascular spaces compromises the pulmonary circulation by compressing blood vessels.^{2,9} Compression of remaining healthy lung areas causes atelectasis and impairs gas

exchange, leading to overall ventilation-perfusion mismatch.² The degree of air-trapping and requirement for high ventilation pressure affect systemic venous return and right-ventricular outflow.^{9–11} Pulmonary hypertension then contributes to impaired oxygenation.¹

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Pulmonary interstitial emphysema is usually seen in preterm infants as a complication of neonatal respiratory distress syndrome, and is a risk factor for pneumothorax, intraventricular hemorrhage, and bronchopulmonary dysplasia.^{2–4} Mortality is highest in those with the lowest gestational ages, birth weight < 1,500 g, and requirement for high ventilation pressure in the first 2 weeks of life.⁵

Various strategies for managing unilateral severe pulmonary interstitial emphysema have been described, including respiratory manipulations, patient positioning, dex-amethasone, and various drainage techniques, but their merits are unclear (Table 1).^{2,4,7,12–19} We describe the strategy we used with an infant with severe cardiorespiratory compromise, and discuss our rationale. The patient was in the neonatal intensive care unit at Women and Children's Hospital, Hull Royal Infirmary, East Yorkshire, United Kingdom, and the patient's mother gave consent for submission for publication.

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Both Drs Phatak and Klonin have had a relationship with BOC Gases/Linde Group, Guildford, United Kingdom. The authors report no other conflicts of interest related to the content of this paper.

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Table 1. Case Reports and Series on Treatment of Localized Pulmonary Interstitial Emphysema

First Author, Year, Country	Number of Cases/Study Type	Type of Lesion	Mean Gestational Age	Time of Development	Treatment	Age at Treatment	Results	Time to Resolution
Stocker ² 1977 United States	22 cases Retrospective case review	10 localized, 12 generalized	All except 2 were premature	Localized developed at 19 d Generalized developed at 14 d	Oxygen Respiratory therapy 7 surgical removal	Various	No survival in generalized group 7 with surgery were discharged well 3 with localized interstitial pulmonary emphysema died Some complicating factors found	Not stated
Greenough ¹ 1984 United Kingdom	41 cases Retrospective case review	14 unilateral	28 wk	1.7 d	Fast-rate ventilation in 12 infants Neuromuscular paralysis in 9	Not stated	Fewer pneumothoraces in fast-rate group No other improvement in outcomes	Not stated
Levine ¹² 1981 United States	4 cases Retrospective case review	Focal unilateral	34 wk	Day 1. Only one example described	Surgical pleurotomy decompression	9 d	3 improved 1 death	Extubated 2 d after surgery in case described 5.3 d
Cohen ¹³ 1984 United States	9 cases Prospective study	Focal	28.9 wk	4.3 d	Lateral decubitus position	11.6 d	2 deaths 1 death delayed 7 had partial or complete resolution	7 d
Fitzgerald ¹⁴ 1998 Canada	10 cases Retrospective case review	7 unilateral	25.8 wk	7.5 d	Dexamethasone	8.5 d	9 survived 1 death	Several days of suction
Fox ¹⁵ 1998 United States	1 case report	Focal	Full-term	Not stated	Computerized-tomography-guided percutaneous drainage	Not stated	Improved	Improved
Messineo ¹⁶ 2001 Italy	1 case report	Focal	38 wk	Birth	Resection and lung reduction	3 wk and 6 wk	Improved	Weaned from ventilator 3 d after lung reduction
Donnelly ⁷ 2003 United States	17 cases Retrospective case note and computerized tomography review	6 bilateral	Premature	8 d	11 had surgical resection	9 surgical resection before 1 y 2 had surgical resections after 1 y	Nonsurgical 7 had at least partial resolution 2 went to surgery later 1 lesion enlarged but stable	Diagnosis to surgical resection or last follow-up, 179 d
Holzk ¹⁷ 2003 Germany	3 cases Retrospective case review	Focal	2 term 1 premature	3-4 wk after term in 2 infants 4 d in 30-wk-gestation infant	Contralateral selective intubation	On presentation	2 elective surgery, days later 1 resolved	Hours
Staden ¹⁸ 2004 Germany	1 case report	Focal	27 wk	10 d	Extubation	17 d	Improved	2 d
Chalak ¹⁹ 2007 United States	1 case report	Focal	24 wk	4 d	Left main-bronchus intubation	2 wk	Improved	2 d

Table 2. Sequential Arterial Blood Gas Values and Ventilatory Measurements Over the First 18 Hours of Treatment.

Time (h:min)	Day 14				Day 15			
	13:20	14:50	16:50	20:16	00:20	01:00	04:45	08:00
pH	7.18	7.19	7.30	7.26	7.20	7.26	7.29	7.33
P _{aCO₂} (mm Hg)	60	70	46	51	61	55	49	38
P _{aO₂} (mm Hg)	61	46	59	62	60	63	55	81
HCO ₃ (mEq/L)	20	23	22	21	21	23	22	21
F _{IO₂}	76	78	99*	64	63	62	60	58
Maximum inspiratory pressure (cm H ₂ O)	38	29	26	26	26	28	28	26
PEEP (cm H ₂ O)	2.9	3.3	2.5	2.5	2.4	2.5	2.5	2.5
Respiratory rate (breaths/min)	40	50	50	44	45	50	50	50
Oxygenation index [†]	15	19	NA‡	10	10	12	13	8
Heliox (L/min)	NA§	12	7	10	10	10	9	9
Inhaled nitric oxide concentration (ppm)	0	0	ND	6	3.7	3.8	5.1	4.4

* During circuit-change for inhaled nitric oxide, transient fraction of inspired oxygen (F_{IO₂}) increase to 100%

† Oxygenation index = F_{IO₂} × mean airway pressure × 100/P_{aO₂}

‡ NA = not applicable because the oxygen concentration went up to 100% during circuit change

§ NA = not applicable because this was prior to adding helium-oxygen mixture (heliox).

|| ND = No data recorded at time of circuit change

PEEP = positive end-expiratory pressure

Case Report

The patient was a surviving twin male infant, born at 25 weeks plus 3 days gestation, via spontaneous vaginal delivery, with a birth weight of 822 g. He was electively intubated with a 3.0-mm inner-diameter endotracheal tube, ventilated at birth, and received 120 mg of surfactant (Po-ractant Alfa, Trinity, London, United Kingdom) via the ETT, at 7 min, 6-h, and 12 h of age.

Initially we used volume-controlled synchronized intermittent ventilation with volume guarantee (Babylog, Dräger, Lübeck, Germany). The maximum inspiratory pressure (MIP) to achieve a target tidal volume of 4–5 mL/kg was 15–17 cm H₂O. The fraction of inspired oxygen (F_{IO₂}) was 0.22–0.3 between day 2 and day 9 of life. Arterial blood gas values on day 9 included pH 7.33, P_{aCO₂} 48 mm Hg, and P_{aO₂} 50 mm Hg. Chest radiographs on days 5 through 9 of life were consistent with resolving respiratory distress syndrome and gradually developing pulmonary interstitial emphysema.

The patient developed an increasing oxygen requirement and associated hypercarbia from day 9, which necessitated high ventilation pressure. On day 13 his respiratory status markedly worsened. He required F_{IO₂} of 0.80 and MIP of 38 cm H₂O at the highest, to achieve an adequate tidal volume and satisfactory oxygenation. Arterial blood gas values were P_{aO₂} 60 mm Hg, P_{aCO₂} 60 mm Hg, and pH 7.18 (Table 2).

At this stage, chest radiograph showed an over-inflated right lung and localized interstitial pulmonary emphysema, and an under-inflated left lung (Fig. 1). Echocardiogram showed elevated right-ventricular pressure.

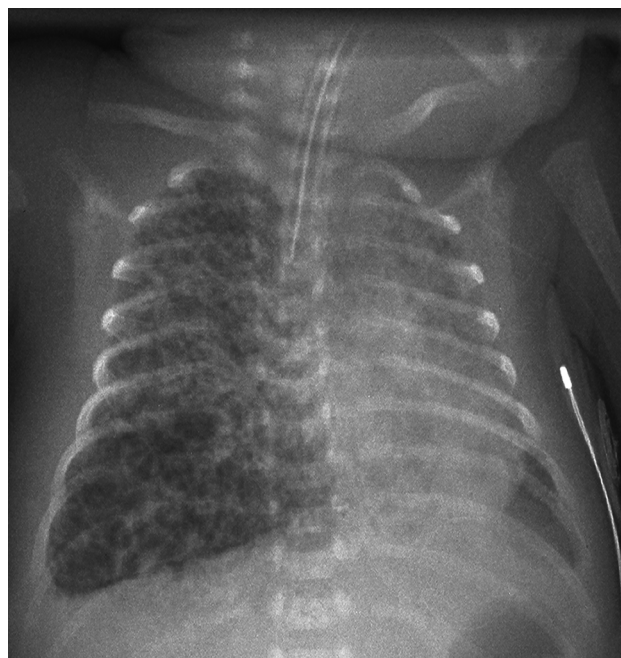


Fig. 1. Day 13 chest radiograph shows an over-inflated right lung with severe localized pulmonary interstitial emphysema, and an under-inflated left lung.

We attempted mechanical ventilation over a range of positive end-expiratory pressure (PEEP) values (3–5 cm H₂O) and respiratory rates (40–50 breaths/min).

We then initiated high-frequency oscillatory ventilation (3100A, SensorMedics, Yorba Linda, California) with a mean airway pressure (\bar{P}_{aw}) of 12–15 cm H₂O and 100% oxygen. Initially on high-frequency oscilla-

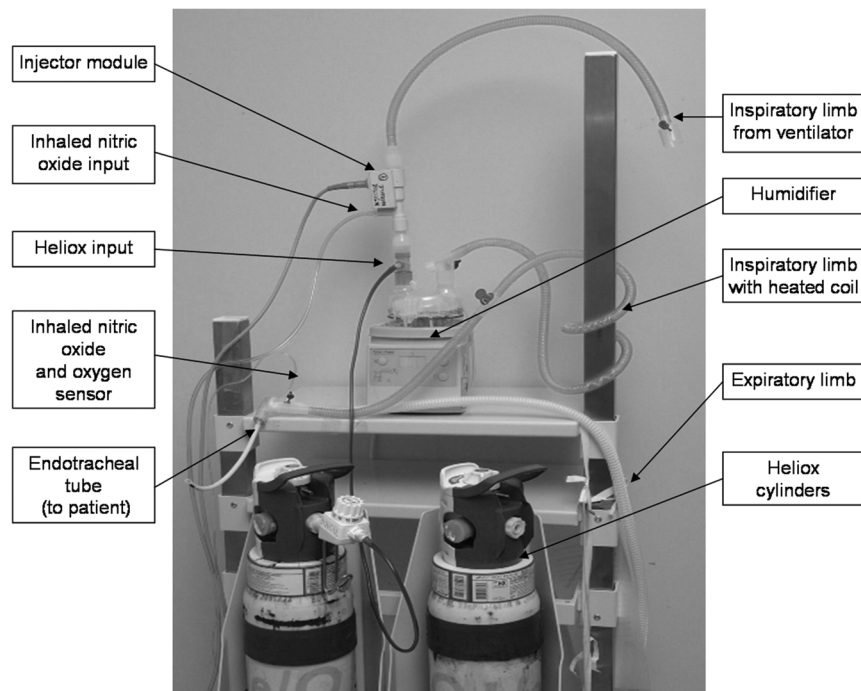


Fig. 2. Circuit configuration for delivering helium-oxygen mixture (heliox) and inhaled nitric oxide.

tion his oxygen saturation went up to 91%, but then dropped again. We again tried a lower mean airway pressure (12 cm H₂O), which resulted in a saturation drop to 79%. We abandoned high-frequency oscillation after approximately one hour.

The patient also decompensated with attempts to move him to the lateral decubitus position. On day 14 we commenced dexamethasone at 100 µg/kg/d for 3 days, followed by 50 µg/kg/d for 4 days.

We added heliox (79% helium, 21% oxygen) (BOC Gases/Linde Group, Guilford, United Kingdom) to the circuit concurrently with the first dose of dexamethasone, as a strategy to control the rising P_{aCO₂} and acidosis. To ensure accurate tidal-volume delivery we inserted a pressure-differential pneumotachometer (CO₂SMO Plus, Respirationics, Wallingford, Connecticut) calibrated for the presence of helium into the ventilator circuit. To improve oxygenation we added inhaled nitric oxide (INO) (Ino Therapeutics, Clinton, New Jersey) at 6 ppm, which is the lowest dose that maintained adequate oxygen saturation. Figure 2 shows the circuit configuration.

After initiating heliox and INO, we adjusted PEEP to 3 cm H₂O. The MIP required to obtain a tidal volume of 4–5 mL/kg dropped immediately with heliox, and 2-hours after that the P_{aCO₂} had improved by 34%. As INO was introduced, we lowered F_{IO₂} from 0.78 to 0.64.

Figure 3 shows the course of the MIP, F_{IO₂}, pH, P_{aCO₂}, and P_{aO₂} before and after we added INO and heliox.

A chest radiograph taken 5 hours after adding heliox showed decreased right-lung air-trapping and expansion of much of the left lung (Fig. 4). We decreased the F_{IO₂} over 12 h, because the patient had a sustained improvement in oxygenation index, from 18 to 11. Oxygenation index is calculated as:

$$\bar{P}_{aw} \times F_{IO_2} \times (100/P_{aO_2})$$

Heliox flow was approximately 10–12 L/min. Heliox flow > 12 L/min caused the “leak in hose system” ventilator alarm.

After the first 12 hours, no further weaning took place for 24 hours, and the patient continued to receive heliox at approximately 11 L/min. Thereafter we gradually weaned the heliox, by 1.8 L/min every 4 h, until completely off after 55 h. Weaning of INO was commenced after 48 h and took place over 24 hours. He was successfully extubated to pressure-support ventilation via an infant flow driver (Viasys Healthcare, Warwick, United Kingdom) with a MIP of 8 cm H₂O, a PEEP of 5 cm H₂O, and F_{IO₂} of 0.3 after a further 24 hours, on day 18 of life. The day after extubation, his hospital course was complicated by a colonic perforation that required surgery, for which he remained ventilated for 4 days, after which he was uneventfully extubated. Resolution of pulmonary hypertension was confirmed by a normal echocardiogram in the patient's third month. Chest radiographs taken 5 months after birth showed

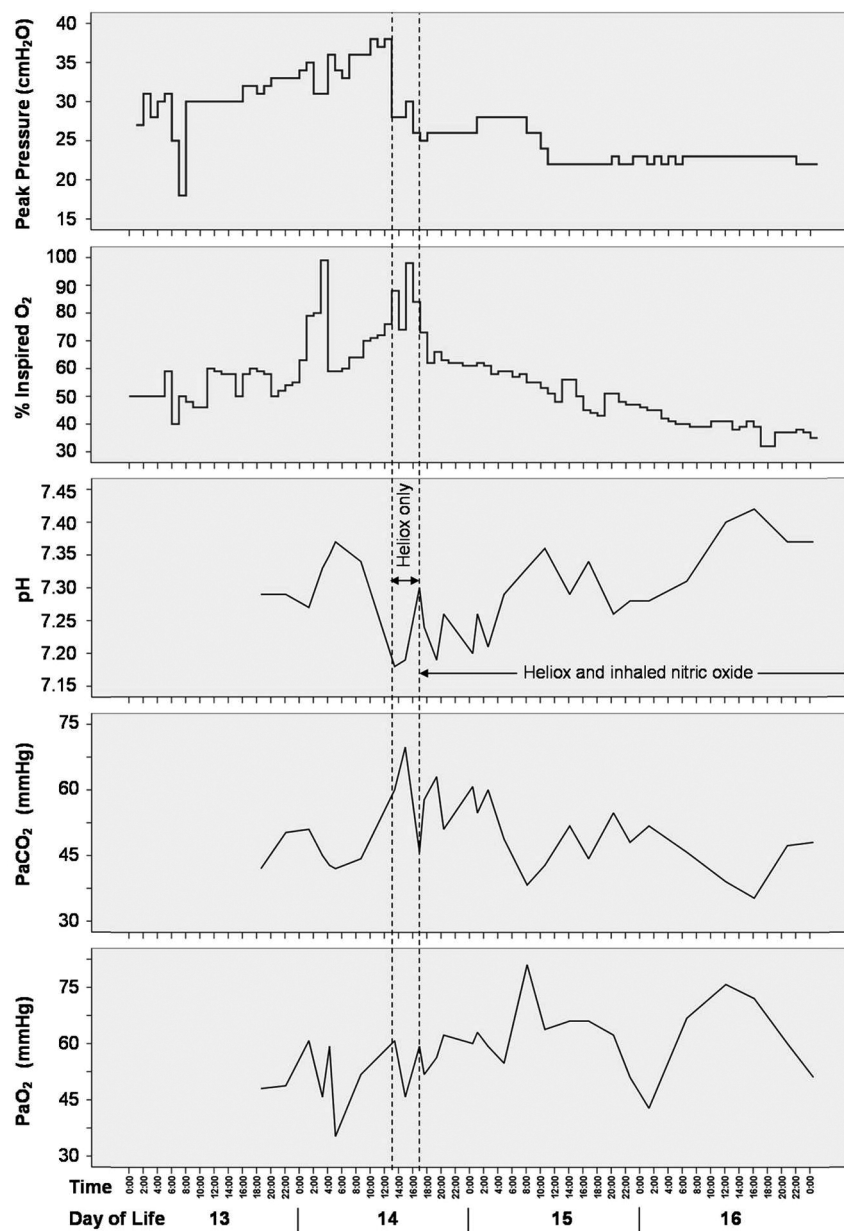


Fig. 3. Maximum inspiratory pressure, fraction of inspired oxygen, pH, P_{aCO_2} , and P_{aO_2} before and after addition of inhaled nitric oxide and helium-oxygen mixture (heliox).

complete resolution of pulmonary interstitial emphysema, although there remained background changes suggestive of bronchopulmonary dysplasia. He had a prolonged hospital stay, due to difficulties establishing nutrition, and was discharged home at 6 months of age.

He did not require home oxygen or inhaled bronchodilators, and at 1 year of age his development was normal.

Discussion

As far as we know, this is the first reported use of heliox plus INO as adjunct therapy for a critically ill infant with

localized interstitial pulmonary emphysema and pulmonary hypertension.

Table 1 describes management strategies previously reported for localized interstitial pulmonary emphysema.^{2,4,7,12-19} Those case reports and series had various outcomes. The most successful therapy for pulmonary interstitial emphysema has been high-frequency jet ventilation, by Keszler et al, but they did not state whether any of the infants had unilateral pulmonary interstitial emphysema.²⁰ For unilateral pulmonary interstitial emphysema, dexamethasone appeared to be associated with a successful outcome, but clinical resolution took 7 days. Other than

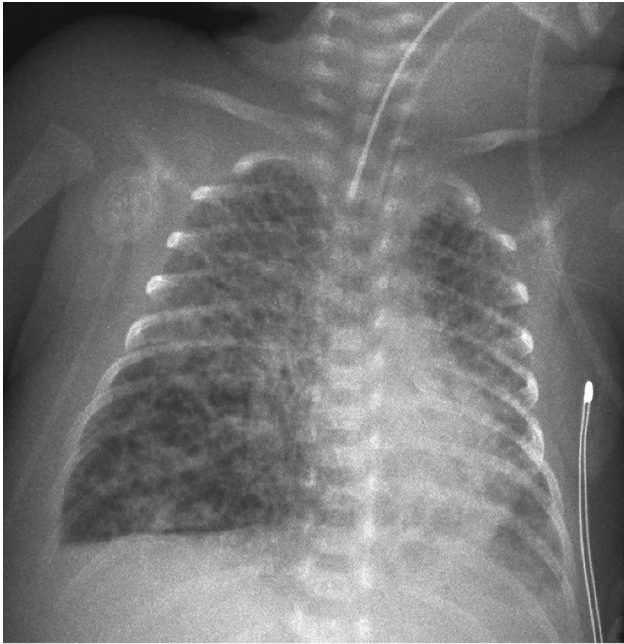


Fig. 4. Chest radiograph taken 5 hours after instituting helium-oxygen mixture (heliox) shows decreased right-lung air-trapping and expansion of the left lung. The endotracheal tube appears higher but had not been adjusted.

dexamethasone, none of the therapies appeared to be easily applicable to our patient, who was extremely small for extracorporeal membrane oxygenation or major thoracic surgery, and whose instability would have made transportation to the operating theater or tomography room difficult and potentially unsafe.^{2,7,12,15,16} Selective intubation of the left main bronchus to provide unilateral mechanical ventilation would have been challenging in an acidotic, hypoxic, 822-g baby.¹⁹ Manipulation of ventilatory variables and a trial of lateral decubitus positioning were not successful in our patient.^{4,13,21,22} It may have been possible to attempt to decompress the right lung by needle thoracocentesis, but there was no obvious localized area to treat, and the patient decompensated even with routine minor nursing procedures.¹⁵ After conventional and oscillatory ventilation failed, we used heliox and INO to attempt to relieve the acute life-threatening gas-exchange problem.

The rationale for adding heliox was that in neonatal medicine heliox has been used in stridor and laryngotracheal problems, has reduced the oxygen requirement and the duration of ventilation in respiratory distress syndrome, and has improved lung mechanics in bronchopulmonary dysplasia.²³⁻²⁶ Heliox's low density (compared to air) increases flow in regions where turbulent flow predominates, and it promotes lower-resistance laminar flow.²⁶⁻²⁸

Mechanical ventilation with heliox may also be beneficial in pulmonary interstitial emphysema, because nitro-

gen is absent from the inspired gas, which allows nitrogen wash-out from the circulation, which facilitates re-absorption of trapped interstitial gas. For that reason, pure oxygen has been suggested for treatment of pulmonary interstitial emphysema.² Although we are unaware of any evidence to support this effect of heliox in pulmonary interstitial emphysema, in a model of pneumothorax, resolution was faster with heliox or pure oxygen than with air.²⁹ During mechanical ventilation heliox is associated with reduced inadvertent PEEP and improved hemodynamics, presumably because it increases gas flow and lung-emptying.^{28,30} This effect on gas-trapping may partly explain the improvement in our patient. Heliox shortens the time for alveolar emptying, reduces hyperinflation, enhances mechanical efficiency, and reduces discomfort.^{24,25,31} There was a dramatic drop in MIP with heliox, even at a concentration of only 20–30%. We speculate that this may reflect the position of both lungs on unfavorable portions of the pressure-volume curve.³² Hence, even a small decrease in hyperinflation of the right lung and increase in volume of the left lung may effect a large pressure drop.

We are unaware of any detailed studies on how heliox is distributed to the airway during mechanical ventilation with a variable-flow ventilator. Helium may accumulate at various points in the ventilatory cycle, and the actual delivered dose may change. It may be that, due to its lower density, flow of helium is preferentially distributed to the narrow airways, allowing a higher concentration to reach the small airways and start to open them, decreasing air trapping and allowing opening of collapsed airways, reversing the pathophysiology. The lower MIP observed in this case on the introduction of heliox may result in less barotrauma.³³ It is possible that dexamethasone was beneficial, but the cases so far described took days to resolve.¹⁴ However, dexamethasone may have been a factor in the longer-term resolution of this illness.

Although heliox appeared to improve ventilation, hypoxia remained a problem. We used INO because the infant had evidence of pulmonary hypertension, which contributed to the inability to wean the F_{IO_2} . INO has been used in neonatal intensive care as a pulmonary vasodilator.³⁴ Molecular diffusion is increased with heliox, which increases carriage of oxygen and nitric oxide and favors carbon-dioxide exchange.^{27,31,35-40} It may be that this improved the effectiveness of INO in our patient. Infants with pulmonary interstitial emphysema may require higher doses of INO and have poor outcomes because diffusion is impaired by the trapped interstitial gas and fluid.^{40,41} In our patient a low INO concentration was effective, and the heliox may have allowed the INO to be more efficiently distributed in the lungs.^{36,39} There has been little research on the safety, efficacy, and effectiveness of combining air, oxygen, helium, and INO. The problems of adequate assessment are increased by the difficulty in obtaining mon-

itors that can simultaneously measure the concentrations of each gas. In this case we customized the equipment to monitor the variables and patient response, but for further research it would be valuable to have dedicated helium and oxygen sensors in the inspiratory limb.

As ventilation strategies with lower MIP are increasingly used, it may be that severe pulmonary interstitial emphysema associated with barotrauma will become less common and the ability to perform large-scale randomized trials will decrease.^{33,42} Despite this, pulmonary interstitial emphysema still occurs and can be life-threatening. There is an increasing body of clinical, experimental, and physiologic evidence that heliox may have benefits at both the airway and alveolar levels.^{26,33,43,44} Our patient appeared to benefit from the addition of heliox and nitric oxide, without complications, which allowed time for other modalities to take effect, and we hypothesize as to how this benefit may have taken place. However, additional investigation is needed before the combination of heliox and nitric oxide could be recommended outside the experimental setting.

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