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## PARTIAL LIQUID VENTILATION WITH PERFLUBRON IN PREMATURE INFANTS WITH SEVERE RESPIRATORY DISTRESS SYNDROME

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### ABSTRACT

**Background** The intratracheal administration of a perfluorocarbon liquid during continuous positive-pressure ventilation (partial liquid ventilation) improves lung function in animals with surfactant deficiency. Whether partial liquid ventilation is effective in the treatment of infants with severe respiratory distress syndrome is not known.

**Methods** We studied the efficacy of partial liquid ventilation with perflubron in 13 premature infants with severe respiratory distress syndrome in whom conventional treatment, including surfactant therapy, had failed. Partial liquid ventilation was initiated by instilling perflubron during conventional mechanical ventilation to a volume approximating the functional residual capacity. Infants were considered to have completed the study if they received partial liquid ventilation for at least 24 hours.

**Results** Ten infants received partial liquid ventilation for 24 to 76 hours. In the other three infants, partial liquid ventilation was discontinued within four hours in favor of high-frequency ventilation, which was not permitted by the protocol, and the data from these infants were excluded from the analysis. Within one hour after the instillation of perflubron, the arterial oxygen tension increased by 138 percent and the dynamic compliance increased by 61 percent; the mean ( $\pm$ SD) oxygenation index was reduced from  $49 \pm 60$  to  $17 \pm 16$ . Chest radiographs showed symmetric filling, with patchy clearing during the return from partial liquid to gas ventilation. There were no adverse events clearly attributable to partial liquid ventilation. Infants were weaned from partial liquid to gas ventilation without complications. Eight infants survived to 36 weeks' corrected gestational age.

**Conclusions** Partial liquid ventilation leads to clinical improvement and survival in some infants with severe respiratory distress syndrome who are not predicted to survive. (N Engl J Med 1996;335:761-7.)

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**S**URFACTANT therapy has substantially improved the survival of premature infants with respiratory distress syndrome<sup>1</sup> but is not uniformly effective. Ventilation with perfluorocarbon liquids improves lung function in conditions involving surfactant deficiency and dysfunction, including respiratory distress syndrome,<sup>2-4</sup> congenital diaphragmatic hernia,<sup>5,6</sup> and adult respiratory distress syndrome.<sup>7,8</sup> Perfluorocarbon liquids have low surface tension (14 to 18 dyn per centimeter) and high density (1.7 to 1.9 mg per milliliter), and at atmospheric pressure, large amounts of oxygen and carbon dioxide dissolve in them. Replacement of the gas functional residual capacity by perfluorocarbon liquid eliminates the alveolar-membrane air-liquid interface, reduces surface tension in the surfactant-deficient lung, and physically keeps the alveoli open. In one technique (total liquid ventilation), oxygenated perfluorocarbon liquid is instilled into the lungs, and the liquid-filled lungs are then ventilated with liquid tidal volumes.<sup>3,9</sup>

Partial liquid ventilation, also known as perfluorocarbon-associated gas exchange, is a modified approach in which perfluorocarbon liquid is instilled into the lungs during continuous positive-pressure

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gas ventilation, and the liquid-filled lungs are ventilated with the use of tidal breaths of gas delivered by a standard positive-pressure gas ventilator.<sup>10</sup> The perfluorocarbon liquid lost through evaporation is periodically replaced to maintain a liquid lung volume that is less than or equal to the functional residual capacity throughout the treatment period.

We report a trial of the safety and efficacy of partial liquid ventilation with perflubron (LiquiVent, Alliance Pharmaceutical Corporation, San Diego, Calif.) in premature infants with severe respiratory distress syndrome refractory to other treatments.

## METHODS

### Study Design

This multicenter study was performed under a phase 1–2 study as part of a corporate-sponsored Investigational New Drug application. The protocol was approved by the investigational review board at each center, and all the parents consented to the enrollment of their infants.

### Infants

We studied 13 premature infants (gestational age, 24 to 34 weeks; birth weight, 600 to 2000 g) with severe respiratory distress syndrome who were less than 5 days old and were considered to have a high risk of morbidity or death on the basis of the lack of a sustained response to surfactant therapy<sup>11</sup> and the continued requirement for a high level of supplemental oxygen and ventilator support. Because premature infants have an increased risk of intracranial hemorrhage and the small size of their vessels poses technical limitations, these infants were not eligible for extracorporeal life support.

All 13 infants had values for arterial oxygen tension that were less than 60 mm Hg or values for arterial carbon dioxide tension that were greater than 60 mm Hg on two consecutive determinations and required oxygen therapy with a fraction of inspired oxygen of 1.0 and a mean airway pressure of more than 10, 12, and 14 cm of water for birth weights of 600 to 1000 g, 1001 to 1500 g, and 1501 to 2000 g, respectively. Two neonatologists confirmed the risk assessment for each infant.

Infants were ineligible for the study if they had conditions that would have interfered with the interpretation of end points or rendered medical intervention futile. These conditions included concomitant lethal anomalies, congenital heart disease, congenital diaphragmatic hernia, hydrops fetalis, confirmed bacterial or viral sepsis, bronchopleural fistula, severe intracranial hemorrhage, diffuse pulmonary interstitial emphysema, and seizures refractory to treatment with anticonvulsant drugs.

### Protocol

After informed consent had been obtained, the infant was reintubated with an endotracheal tube and placed on a conventional, time-cycled, pressure-limited ventilator (Infant Star; Nellcor, Puritan, and Bennett, San Diego, Calif.). Partial liquid ventilation was initiated by instilling perflubron at a rate of 1 ml per kilogram of body weight per minute through the side port of the endotracheal tube without interrupting mechanical gas ventilation, maintaining a positive end-expiratory pressure of 4 cm of water, until a column of fluid welled up in the endotracheal tube during momentary disconnection from the ventilator. The volume of perflubron required to produce this meniscus represented the infant's liquid functional residual capacity. Pulse oximetry and gas tidal-volume monitoring (Bear Tidal Volume Monitor NVMI, Bear Medical by Allied Health Care, Riverside, Calif.) were performed

continuously, and the ventilator setting or the rate of instillation of perflubron was adjusted to reflect the changing lung mechanics and to maintain the tidal volume between the base-line value and 10 ml per kilogram of body weight. The level of the perflubron meniscus in the endotracheal tube was checked hourly, and perflubron was added as needed to replace liquid lost through evaporation and to maintain the liquid functional residual capacity throughout the treatment period.

Partial liquid ventilation was to be conducted for a minimum of 24 hours. Because it was difficult to predict the ongoing need for partial liquid ventilation with improved lung function, after 48 hours perflubron was no longer added, in an attempt to return to gas ventilation. These periods were chosen on the basis of maturational responses of the lungs to other interventions.<sup>12</sup> If the oxygenation index increased to a value that was 30 percent higher than the value when partial liquid ventilation was stopped, partial liquid ventilation could be resumed by reestablishing the liquid functional residual capacity for a maximal cumulative treatment period of 96 hours.<sup>13</sup>

### Outcome Measures

The primary end points were safety (assessed on the basis of the heart rate, blood pressure, chest films, cranial ultrasonographic studies, and clinical laboratory values), the presence or absence of new medical conditions, and developmental progress. Secondary end points included changes in arterial oxygen tension, arterial carbon dioxide tension, dynamic compliance, ventilatory requirements and oxygenation index, and survival. The oxygenation index was calculated as follows: (fraction of inspired oxygen  $\times$  mean airway pressure  $\times$  100)  $\div$  arterial oxygen tension. The dynamic compliance was calculated as follows: (tidal volume  $\div$  kilograms of body weight)  $\div$  (positive inspiratory pressure – positive end-expiratory pressure).<sup>14</sup> Blood perflubron concentrations were measured in 250- $\mu$ l aliquots of blood equilibrated in a head-space autosampler (Tekmar 7000, Tekmar–Dörhmann, Cincinnati) by gas chromatography (5890 Series II; Hewlett–Packard, Avondale, Pa.).

### Statistical Analysis

We performed an analysis of variance with repeated measures to test for significant changes over time in the group of infants who completed the trial. The results during partial liquid ventilation and during gas ventilation were compared with the use of paired two-tailed t-tests with a Bonferroni–Dunn correction.<sup>15</sup> Safety and demographic data were analyzed for all 13 infants. All results are expressed as means  $\pm$  SD, except in the figures.

## RESULTS

Thirteen infants with a mean gestational age of  $28 \pm 3$  weeks and a mean weight of  $1057 \pm 362$  g were enrolled in the study (Table 1). The infants had numerous other conditions in addition to severe respiratory distress syndrome. Three infants who had required high-frequency ventilation for refractory hypercapnia before enrollment had recurrent hypercapnia during partial liquid ventilation with the use of a conventional ventilator, despite some improvement in lung function. They were withdrawn from the trial less than four hours after enrollment. Two of these infants continued to have improved lung function; the third infant died. Ten infants completed the trial, having received partial liquid ventilation for  $42 \pm 5$  hours (range, 24 to 76). The drugs administered before, during, or after partial liquid ventilation included tolazoline, nitric oxide, dexamethasone, indomethacin, pressors, and antibiotics.

**TABLE 1.** CLINICAL CHARACTERISTICS OF 13 INFANTS WITH SEVERE RESPIRATORY DISTRESS SYNDROME TREATED WITH PARTIAL LIQUID VENTILATION.

CHARACTERISTIC	VALUE*
Gestational age — wk	28±3 (24–33)
Birth weight — g	1057±362 (635–1760)
Age — hr	44±41 (6–164)
Apgar score	
At 1 min	4±3 (1–8)
At 5 min	6±3 (1–9)
Sex — M/F	8/5
Race — white/black	10/3
Surfactant — no. of doses	3±1 (1–4)
Additional conditions	
— no. of infants	
Shock requiring pressor support	10
Pulmonary hypertension	3
Periventricular ischemia	3
Patent ductus arteriosus	3
Sepsis and pneumonia†	2
Acute renal failure	2
Metabolic acidosis	2
Perinatal asphyxia	2
Intracranial hemorrhage	2
Grade I	1
Grade II	1
Pulmonary interstitial emphysema	2
Pulmonary hemorrhage	1
Intrauterine growth retardation	1

\*Plus-minus values are means ±SD, and values in parentheses are ranges.

†After enrollment, group B streptococcus was confirmed in one infant, and *Escherichia coli* in the other.

### Lung Function

The initial volume of perflubron instilled was  $15 \pm 4$  ml per kilogram. This liquid functional residual capacity was established over a period of  $25 \pm 23$  minutes. During partial liquid ventilation, additional perflubron was given at a rate of  $3.3 \pm 0.9$  ml per kilogram per hour. Figure 1 shows chest radiographs in a representative infant at base line (during gas ventilation) and one hour after the initiation of partial liquid ventilation. The base-line radiograph shows a diffuse ground-glass appearance with air bronchograms and low lung volumes. During partial liquid ventilation, the radiopaque perflubron created symmetric radiodensities.

Gas exchange and lung mechanics were markedly improved in the infants during partial liquid ventilation. At base line, with a fraction of inspired oxygen of 1.0, the arterial oxygen tension was  $60 \pm 34$  mm Hg (Fig. 2). Within one hour after the initiation of partial liquid ventilation, the arterial oxygen tension had increased to  $143 \pm 99$  mm Hg ( $P = 0.02$ ). The fraction of inspired oxygen was reduced to less than 0.6 over a period of 24 hours ( $P < 0.001$ ), and the arterial carbon dioxide tension became normal within 4 hours ( $P = 0.03$ ). The dynamic compliance

increased during the first hour by more than 60 percent (from  $0.18 \pm 0.12$  ml per centimeter of water per kilogram during gas ventilation to  $0.29 \pm 0.12$  ml per centimeter of water per kilogram during partial liquid ventilation) and continued to increase throughout the first 24 hours. The mean airway pressure decreased by 29 percent (from  $17 \pm 3$  to  $12 \pm 2$  cm of water) in the first 24 hours, despite an increase in the tidal volume from  $5.0 \pm 3.4$  ml per kilogram during gas ventilation to  $7.8 \pm 3.4$  ml per kilogram during partial liquid ventilation ( $P < 0.001$ ). The oxygenation index, which was markedly elevated at base line ( $49 \pm 60$ ), decreased to  $17 \pm 16$  within 1 hour after the start of partial liquid ventilation and to  $9 \pm 7$  at 24 hours ( $P = 0.02$ ) (Fig. 3).

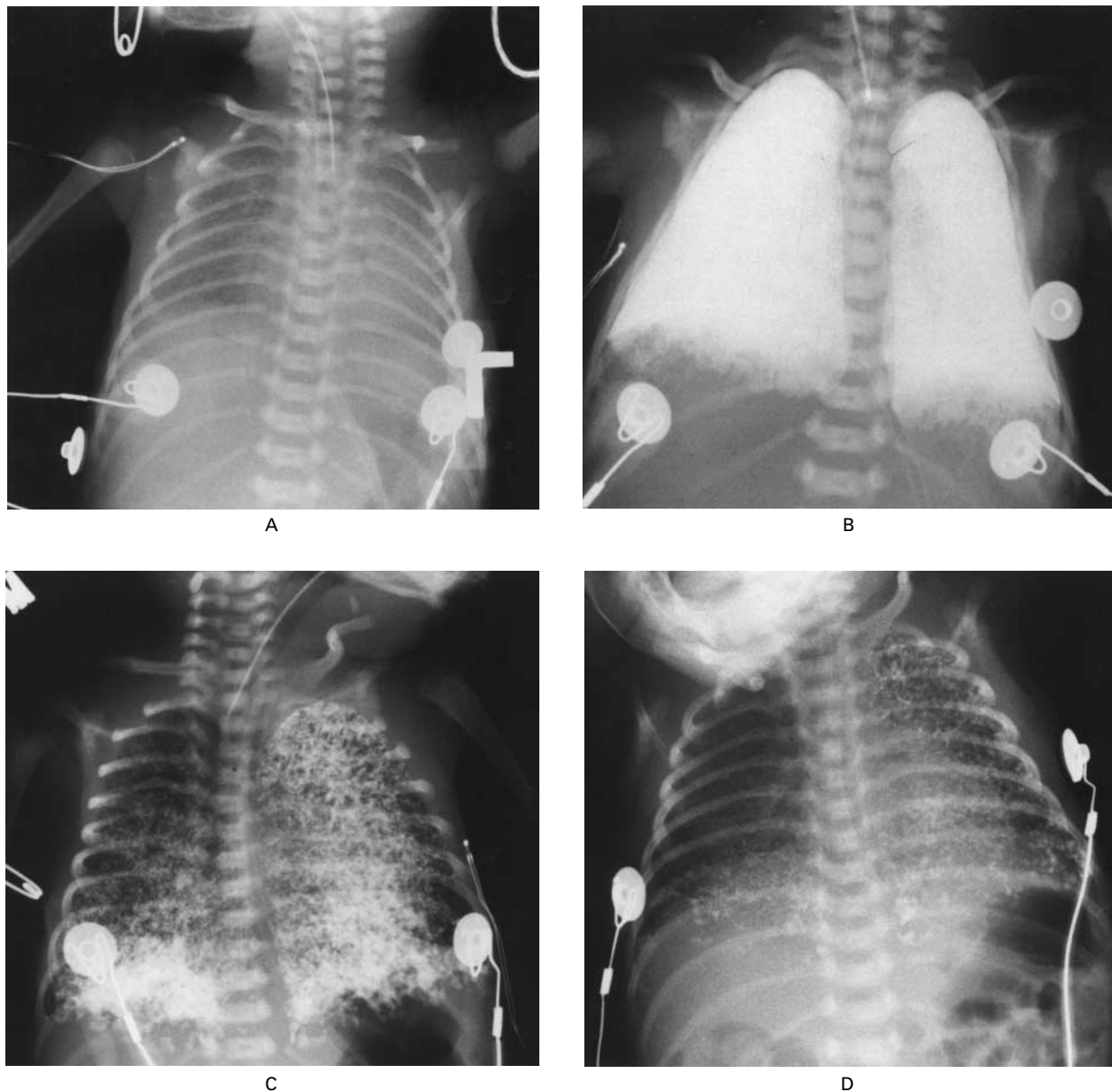
### Returning to Gas Ventilation

Overall, the oxygenation index remained low during the return to gas ventilation (Fig. 3). Three infants met the criteria for the resumption of partial liquid ventilation. In one infant, partial liquid ventilation was resumed within minutes after an attempt to return to gas ventilation, but the lung function continued to worsen during the next 24 hours of partial liquid ventilation, and the infant died. Gas ventilation was continued in the other two infants. In one, the deterioration resolved with the treatment of a patent ductus arteriosus. The other infant remained dependent on high-frequency ventilation, which ruled out the resumption of partial liquid ventilation; this infant also died.

Chest radiography 48 hours and 3 weeks after the last dose of perflubron showed largely gas-filled lungs with some residual perflubron (Fig. 1). The volume of residual perflubron, as suggested by the pattern of radiodensities, varied among the infants. In several infants, radiographs showed only scant traces of perflubron within 48 hours after the return to gas ventilation; in others, the radiographs showed patchy radiodensities consistent with the presence of residual perflubron for up to 7 days; a few radiographs showed residual perflubron several weeks after the last dose.

### Safety Measures and Outcome

Partial liquid ventilation was well tolerated in these severely ill infants. The core body temperature, heart rate, and mean arterial pressure did not change during partial liquid ventilation; the need for pressor support decreased. The adverse events noted during and after partial liquid ventilation are shown in Table 2. Endotracheal-tube obstruction and transient hypoxic episodes may have been related to the partial liquid ventilation; intracranial hemorrhage, pneumothorax, and upper gastrointestinal hemorrhage were considered typical complications of prematurity. The mean blood perflubron concentration in eight infants who received partial liquid ventilation

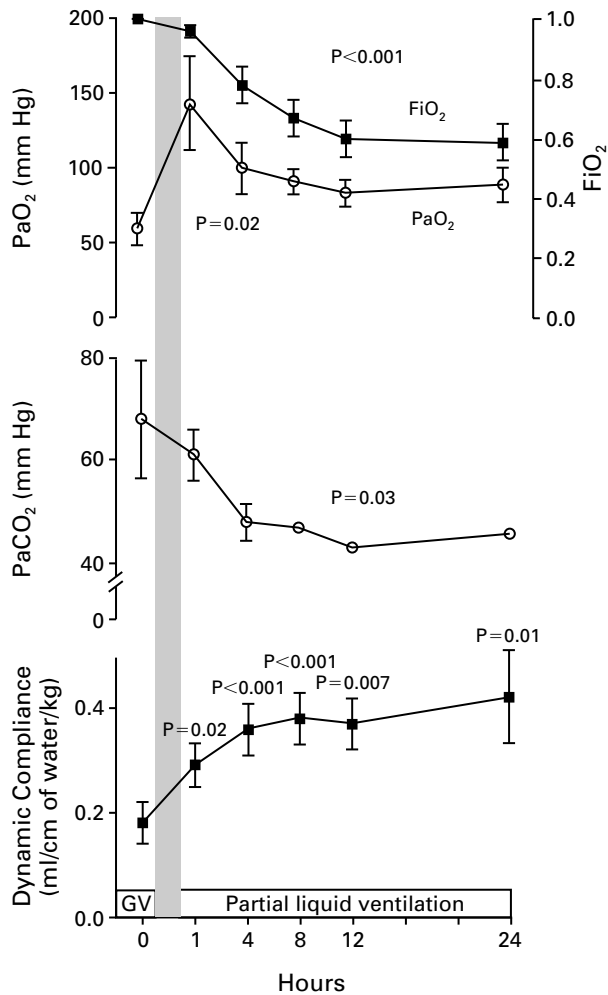


**Figure 1.** Chest Radiographs in One Infant during Treatment with Gas Ventilation (Panel A), 1 Hour after the Initiation of Partial Liquid Ventilation with Perflubron (Panel B), and 48 Hours (Panel C) and 3 Weeks (Panel D) after the Last Dose of Perflubron.

for 24 hours or longer was  $9.8 \pm 6.7 \mu\text{g}$  per milliliter after 4 hours of partial liquid ventilation,  $17.2 \pm 16.7 \mu\text{g}$  per milliliter after 24 hours, and  $2.7 \pm 2.4 \mu\text{g}$  per milliliter 20 to 28 days after the last dose of perflubron.

Eight of the 13 infants, including 2 withdrawn from the trial, survived to a corrected gestational age (gestational age plus chronologic age after birth) of 36 weeks (Table 2). Three of these infants were breathing room air, four required low-flow supplemental oxygen (and were weaned to room air within

60 days), and one continued to require mechanical ventilation. In seven infants, neurodevelopmental follow-up at 4 months of age showed normal hearing and vision, with mental and psychomotor development appropriate for the adjusted age in six of the infants and a slight delay in one (which resolved at 12 months); none of these infants had cerebral palsy. The infant who remained dependent on a ventilator died at five months from severe lung disease of unknown cause. Among the five infants who died before 36 weeks, the cause of death was pneu-



**Figure 2.** Mean ( $\pm$ SE) Values for Arterial Oxygen Tension ( $\text{PaO}_2$ ), Arterial Carbon Dioxide Tension ( $\text{PaCO}_2$ ), the Fraction of Inspired Oxygen ( $\text{FiO}_2$ ), and Dynamic Compliance during Gas Ventilation (GV) and the Initial 24 Hours of Partial Liquid Ventilation in the 10 Infants Who Completed the Study.

P values are for the comparisons between partial liquid ventilation and gas ventilation. The gray bar denotes the period during which the liquid functional residual capacity was established.

monia and sepsis in one, severe intracranial hemorrhage in two, and severe respiratory distress syndrome in two.

## DISCUSSION

These results demonstrate that partial liquid ventilation can be performed safely in critically ill premature infants with severe respiratory distress syndrome. Possible causes of a limited response to surfactant therapy in such infants include an uneven distribution of surfactant in those with established lung disease<sup>16,17</sup>; underinflation of the lungs; and

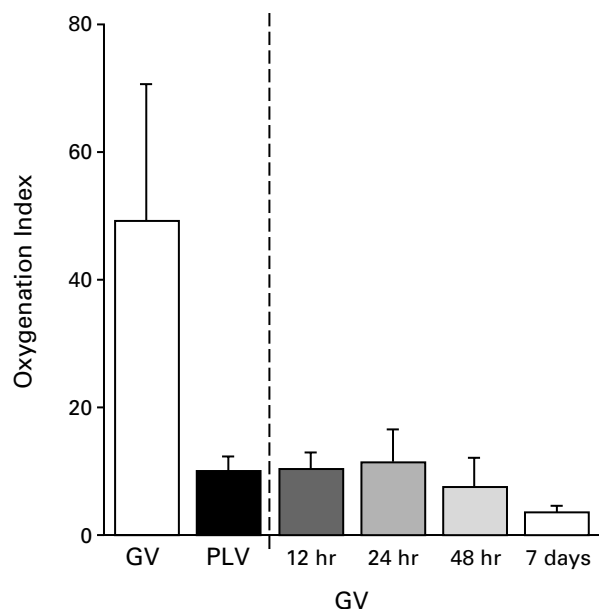
coexisting sepsis, acidosis, or patent ductus arteriosus.<sup>11,14,18,19</sup>

Several mechanisms may contribute to the improvement in lung function with partial liquid ventilation in these infants. Replacement of the alveolar-membrane gas-liquid interface with a liquid-liquid interface reduces interfacial or surface tension.<sup>20</sup> Perflubron is not inactivated by protein and thus will reduce surface tension in a proteinaceous alveolar environment less responsive to surfactant.<sup>14,19</sup> Furthermore, the incompressible perflubron largely replaces the gas functional residual capacity. The positive end-expiratory pressure exerted by the liquid stabilizes the alveolar architecture so that alveoli are recruited and functional residual capacity increases.<sup>21</sup> The improved compliance permits ventilation with increased tidal volumes, resulting in increased gas exchange, and the redistribution of blood flow in lungs filled with perfluorocarbon liquid may contribute to improved ventilation-perfusion matching.<sup>22</sup> Finally, endogenous surfactant production may increase during partial liquid ventilation, as observed in healthy animals<sup>23</sup> and those with surfactant deficiency.<sup>24</sup>

The rate of supplemental administration of perflubron reflects several factors in addition to the replacement of evaporated liquid. These factors include a loss or gain of functional residual capacity due to an increase in or resolution of pulmonary infiltrates, intrapulmonary redistribution of liquid, and changes in airway and alveolar surface tension. The three infants with pulmonary hypertension had a response to partial liquid ventilation, corroborating studies demonstrating that partial liquid ventilation is not contraindicated in patients with pulmonary hypertension<sup>25</sup> and may improve pulmonary hypertension associated with combined parenchymal and pulmonary vascular disease.<sup>5</sup>

Our ability to identify complications of partial liquid ventilation is limited by the uncontrolled design of our study and the small number of infants. These infants were selected for their poor prognosis, and multiple complications of prematurity were expected. Intracranial hemorrhage occurred in the setting of preexisting conditions associated with intracranial hemorrhage during conventional management: hypotension, hypercapnia, asphyxia, acidosis, sepsis, respiratory distress syndrome, and prematurity.<sup>26</sup> Several infants had episodic endotracheal-tube obstruction with mucoid material. This material was viscous, tenacious, and greater in amount than that present during gas ventilation and could be removed by suctioning with saline. The material may have been a preexisting deep exudate, endogenous surfactant or previously administered exogenous surfactant mobilized by perflubron, or a newly formed airway or alveolar exudate. In all the infants who died, the cause of death appeared to be unrelated to partial liquid ventilation.

Perflubron, a biochemically inert molecule, is not



**Figure 3.** Mean (+SE) Values for the Oxygenation Index during Gas Ventilation (GV), at the Completion of Partial Liquid Ventilation (PLV), and during the Return to Gas Ventilation in the Nine Infants Switched from Partial Liquid to Gas Ventilation. P=0.02 for the change in the index over time, and P=0.01 for the comparison between the oxygenation index during partial liquid ventilation and the index on day 7 after the last dose of perflubron. The broken line denotes the completion of partial liquid ventilation.

**TABLE 2.** ADVERSE EVENTS AND OUTCOME IN THE 13 PREMATURE INFANTS.

VARIABLE	VALUE
<b>Adverse events (no. of events)</b>	
During partial liquid ventilation	
Endotracheal-tube obstruction	5
Hypoxic episode	2
Intracranial hemorrhage — grade IV	1
After partial liquid ventilation	
Intracranial hemorrhage	
Grade III	1
Grade IV	1
Pneumothorax	1
Upper gastrointestinal hemorrhage	1
<b>Outcome (no. of infants)</b>	
Survival at 36 weeks' corrected gestational age*	
Breathing room air	3
Requiring oxygen through a nasal cannula	4
Requiring mechanical ventilation	1†
Death	
Due to respiratory distress syndrome	2
Due to intracranial hemorrhage	2
Due to pneumonia and sepsis	1

\*The corrected gestational age is the gestational age plus the chronologic age after birth.

†This infant died from severe lung disease of unknown cause at five months.

metabolized and is eliminated intact almost exclusively by exhalation (Flaim SF, Alliance Pharmaceutical Corporation: personal communication). The low but detectable blood and tissue concentrations of perflubron during partial liquid ventilation in animals indicate a transfer between alveoli and pulmonary vessels and between systemic vessels and organs, reflecting passive diffusion through the lipid compartment.<sup>27</sup> Studies in animals and in adult patients receiving intravenous doses of an emulsion of perflubron resulting in blood concentrations several orders of magnitude higher than after partial liquid ventilation suggest that the minor systemic uptake of perflubron during partial liquid ventilation has few toxic effects.

Overall, the process of switching from partial liquid ventilation to gas ventilation was uncomplicated, with sustained improvement in gas exchange and lung function — results also reported in animal studies.<sup>13,28</sup> Although the rate of perflubron supplementation suggests that evaporation should have been complete within 24 hours, chest radiographs in some infants showed residual perflubron as long as 28 days later. This finding may be the result of several factors. Evaporation of perflubron is influenced by surface area, minute ventilation, liquid volume, and segmental alveolar ventilation.<sup>29</sup> It is also possible that delayed clearance was due to areas of hypoventilation or accumulation of perflubron in the lung parenchyma.

Although the interpretation of these results is limited by the uncontrolled design of our study, the improvement in lung function was nevertheless associated with the initiation of partial liquid ventilation. We conclude that partial liquid ventilation leads to clinical improvement and survival in some infants with severe respiratory distress syndrome who are not expected to survive.

Supported in part by a grant from Alliance Pharmaceutical Corporation. Drs. Leach, Shaffer, Wolfson, Jackson, and Fuhrman are consultants to the Alliance Pharmaceutical Corporation, makers of LiquiVent.

## APPENDIX

Other members of the LiquiVent Study Group include Michael Antunes, M.D., Chantal Lecart, M.D., F.C. Morin, III, M.D., Ramanathan Rangasamy, M.D., and Peter Tarczy-Hornoch, M.D.

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## CORRECTION

**Perflubron in Infants with Severe Respiratory Distress Syndrome**

*To the Editor:* Leach et al. report (Sept. 12 issue)<sup>1</sup> that partial liquid ventilation with perfluorocarbons in premature infants may be an effective therapy for severe respiratory distress syndrome. Their conclusion that such treatment prevented oxygen toxicity, reduced the incidence of barotrauma due to improved dynamic compliance, and improved ventilation — each of which is a highly desirable goal of therapy in neonates with this often fatal syndrome — may not be supported by the results.

Each neonate was reintubated at entry into the study, but the authors do not mention the size of the new tube and whether retained occlusive secretions were present. Improved air flow from either an unobstructed or enlarged lumen could have accounted for the increase in dynamic compliance as well as the improved ventilation.

More important is the issue of improved oxygenation. To the clinician, perhaps the measure of oxygenation that best guides the tapering of potentially toxic levels of inspired oxygen is the arterial oxygen content. This value is dependent on the percentage of oxygen saturation of hemoglobin, which accounts for nearly 99 percent of the oxygen carriage in blood. The reader cannot determine the effect of partial liquid ventilation on the percentage of oxygen saturation of hemoglobin despite the fact that this value is usually reported with the partial pressure of arterial oxygen during blood gas analysis. One would hope the improvement in oxygenation was as beneficial as the improvements in compliance and ventilation.

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**References**

1. Leach CL, Greenspan JS, Rubenstein SD, et al. Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 1996;335:761-767.

The authors reply:

*To the Editor:* We appreciate the opportunity to clarify several points. The patients were reintubated with the same-size endotracheal tube, and it was after this that base-line values for gas exchange and lung mechanics were obtained. The protocol was designed to permit direct comparison of pulmonary function during gas ventilation with that during partial liquid ventilation.

Oxygen saturation is one indicator of oxygenation. The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen has also been used as an indicator of the severity of lung dysfunction.

We chose to report data on the partial pressure of arterial oxygen and fraction of inspired oxygen to enable the reader to assess lung function using that ratio. Moreover, the success of this intervention can be gauged by the ability of the investigators to reduce the level of supplemental oxygen from 100 percent to less than 60 percent while documenting improved partial pressure of arterial oxygen at the same time.

Our disclosure statement should have stated that Drs. Fuhrman, Shaffer, and Wolfson are inventors; patents related to their inventions, filed by several universities, are currently licensed by Alliance Pharmaceutical Corporation, which manufactures LiquiVent, the perflubron used in our study.

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