



Original Articles

Safety and efficacy of perflubron-induced lung growth in neonates with congenital diaphragmatic hernia: Results of a prospective randomized trial



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ABSTRACT

Background: Mechanical transduction has been shown to promote fetal lung growth. We examined the safety and efficacy of perflubron-induced lung growth (PILG) in neonates with congenital diaphragmatic hernia (CDH) requiring extracorporeal membrane oxygenation (ECMO).

Methods: Infants with left-sided CDH requiring ECMO were eligible. Exclusion criteria included active air leak, intracranial hemorrhage, major congenital anomalies, and oxygenation index >25 for 24 hours. Perflubron was instilled endotracheally and continuous positive airway pressure was applied without ventilation. Survival to discharge was the primary outcome. Daily chest radiographs were used to quantify lung size (the secondary outcome). Midway through the study our institutional practice shifted toward earlier repair of CDH.

Results: Eight infants were randomized to each arm. In the conventional-ventilation arm, six survived to discharge (75%). In the perflubron arm, four survived (50%); the others succumbed to suprasystemic pulmonary hypertension. No adverse events related to perflubron occurred. Within the perflubron group, 4/8 patients had "late repair" (15–19 days of life [DOL]) and 4 had "early repair" (2–3 DOL). "Early repair" patients had similar total lung growth, but accelerated growth and shorter ECMO runs.

Conclusion: PILG is safe in CDH and doubles the total lung size on average (accelerated with early repair). Despite amelioration of pulmonary hypoplasia with PILG, pulmonary hypertension persists.

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Congenital diaphragmatic hernia (CDH) is a devastating birth defect that occurs in approximately 1 in every 3000 deliveries. Although survival has improved in select centers, overall survival remains only 65% [1]. The major morbidity and mortality of CDH result from pulmonary hypoplasia and pulmonary hypertension. Severe CDH patients continue to accrue a disproportionate burden of the mortality and morbidity. Despite advances in extracorporeal membrane oxygenation (ECMO) technology and management, the survival of CDH patients requiring ECMO remains only 50–60%, with significant morbidity among survivors [2,3]. A novel strategy for promoting lung growth could substantially improve the survival of newborns with severe CDH. Prenatal strategies include fetoscopic tracheal occlusion (FETO), which is being evaluated in a large prospective randomized clinical trial (the Tracheal Occlusion To Accelerate Lung Growth [TOTAL] Trial for Severe Pulmonary Hyperplasia) [4].

Perflubron is capable of carrying large amounts of oxygen (53 mL/dL) and carbon dioxide (210 mL/dL) [5,6]. Surface tension is also low (18 dynes/cm) and, as such, the presence of the liquid in the lungs

appears to enhance pulmonary function in newborns with CDH. Previous laboratory studies have examined partial liquid ventilation (PLV), in which the lungs are filled with perflubron and then gas-ventilated using a standard mechanical ventilator. PLV demonstrated increases in pulmonary compliance and gas exchange when compared to gas ventilation in newborn lambs with CDH and respiratory failure [7,8]. As well, more than 400 patients have been treated with PLV in various trials and have tolerated it well; while no cumulative survival benefit has been found, perflubron itself has been well-tolerated [9].

A related but distinct technique, perflubron-induced lung growth (PILG), involves intratracheal instillation of perflubron to transduce mechanical force to the alveolar spaces, thereby expanding them permanently and stimulating new lung growth. In the case of PILG, the perflubron is not used as a gas exchange medium, but is used solely for pressure transduction. We previously performed a prospective, randomized pilot study evaluating PILG in newborns with CDH on ECMO for up to one week at six medical centers [10]. A survival of 6 of 8 (75%) was observed in the PILG group and 3 of 5 (60%) in the conventional mechanical ventilation (CMV) group in that study. Strong evidence from the laboratory indicates that up to 3 weeks are necessary to achieve maximal lung growth using the PILG strategy [11]. Therefore, the purpose of this study was to perform a prospective, randomized clinical trial comparing PILG versus CMV in newborns with left CDH

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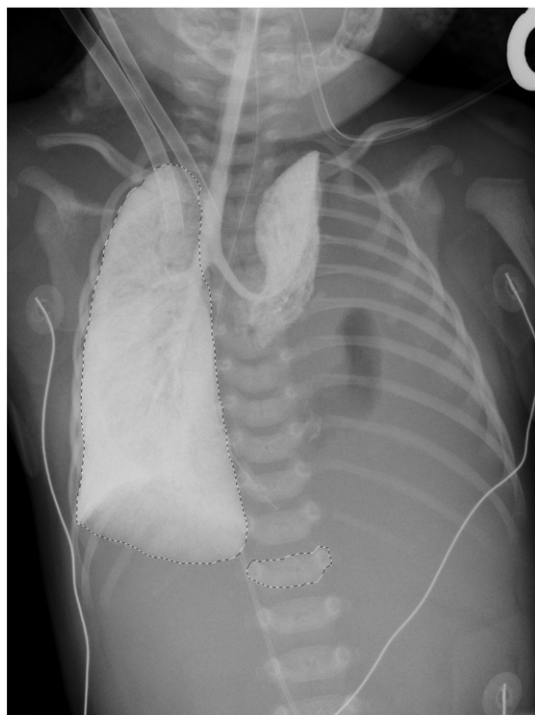


Fig. 1. Chest radiograph of an infant with CDH on ECMO with perflubron instilled; area of left lung and L1 vertebral body selected for analysis.

who require ECMO. The hypothesis underlying the study was that PILG would result in 1) increased area in the hypoplastic lungs of these patients and 2) increased survival to hospital discharge.

1. Methods

This was a single center, open label, prospective, randomized trial involving 16 patients with left CDH who required ECMO at the University of Michigan from October 2006 to March 2011. This study was approved by the University of Michigan Institutional Review Board (IRB). An Investigational New Drug (IND) application (#44,628) was approved by the United States Food and Drug Administration (FDA) for the use of perflubron for up to 3 weeks of PILG in infants with CDH who require ECMO.

Inclusion criteria included left CDH requiring ECMO. Exclusion criteria included: active air leak, hemodynamic instability, genetic anomalies, intracranial hemorrhage, major congenital heart defects, and age greater than 72 hours. Patients with an oxygenation index (fraction of inspired oxygen multiplied by mean airway pressure divided by arterial partial pressure of oxygen) greater than 25 for more than 24 hours prior to the initiation of ECMO were also excluded.

After informed consent was obtained, block randomization was used to assign patients to the two treatment groups: the PILG group, in which patients received intratracheal perfluorocarbon with continuous positive airway pressure (CPAP) of 8 cm H₂O applied without ventilation while on ECMO ($n = 8$), or the CMV group, in which patients received conventional mechanical ventilation while on ECMO ($n = 8$). CMV involved PEEP of 8 cm H₂O while on ECMO; after ECMO, pressure-control settings were used to keep peak inspiratory pressure <30 cm H₂O. Other interventions, such as inhaled nitric oxide, high-frequency oscillatory ventilation (HFOV), and administration of exogenous surfactant were not used during the 21-day study period. In the PILG group, the lungs were gently filled with perflubron until a meniscus was observed in the endotracheal tube, and CPAP of 8 cm H₂O (no tidal volume) was applied for up to 21 days. The endotracheal tube was checked every six hours; if a meniscus of perflubron was not visible, perflubron

was added until one was seen, and the amount was recorded. Patients were not paralyzed. The same group of surgeons was responsible for operative and perioperative care of all infants in both groups.

At baseline and on each subsequent day, static chord pulmonary compliance was assessed in triplicate in both groups by instilling gas in the lungs at CPAP = 5 cm H₂O until airway pressure equaled 30 cm H₂O. Compliance >0.24–0.48 mL/mm Hg was initially an indication for draining the perflubron and initiating a trial off ECMO after lung recruitment. However, compliance proved difficult to obtain and unreliable in completely fluid-filled lungs. After the first three patients receiving PILG did not meet this criterion but were successfully weaned from ECMO, we changed the protocol to indicate that a trial off ECMO would be initiated at 7 days if the patient met traditional clinical criteria for weaning. If the trial failed, perflubron was re-instilled for at least 48 hours before another trial was initiated.

Initially, we stipulated that CDH repair would not be performed before 14 days. Early in the trial, our institutional preference was to operate after ECMO decannulation, or at 14 days if the patient still required ECMO. In this early phase, 3 patients could not be weaned at 14 days so CDH repair was performed. We noted accelerated lung growth in this subgroup and changed our protocol to perform early repair on ECMO starting in 2009 in both groups. All protocol changes were approved by our IRB and the FDA.

Daily anteroposterior chest radiographs were taken to check the distribution of perflubron and for routine critical care purposes. Each digital radiograph from the period of perflubron instillation was also analyzed to estimate the growth of the lungs during the study. (Radiographs of patients in the control arm were taken, but could not be analyzed because their lungs were not clearly defined by the radiopaque perflubron.) Since the actual size of the lung varied between individual radiographs, the size of the first lumbar vertebral body (L1) was used as a standardizing measure. Images were analyzed in Photoshop Extended (Adobe, San Jose, CA). The area of L1 and the area of each lung were calculated from the outline of the space occupied by the radiopaque perflubron (Fig. 1). The area of each lung was divided by the area of the L1 vertebral body to yield a lung-to-L1 ratio, or standardized measure of lung area, for each lung on each radiograph. The ratios were aggregated for each patient and plotted in Excel (Microsoft, Redmond, Wash). The change in lung-to-L1 ratio over the course of the experiment was calculated for the left and right lung of each patient, which represents the overall change in lung area. Finally, dividing this percentage change by the number of days that participant was treated with perflubron yielded the rate at which each lung increased in area.

We collected data daily on hemodynamics, ventilator settings, and blood gases. Potential systemic effects of perflubron were assessed by hematologic, renal, liver and electrolyte abnormalities as well as organ dysfunction during the treatment period. Demographic characteristics of each group (age, sex, birth weight, Apgar scores) were compared using Fisher's exact test, Mann-Whitney *U* test, and Student's *t* test. Survival, ventilator-free days (of the first sixty days) and duration of ECMO were compared as well. Statistical analysis was done in R (R Foundation, Vienna, Austria).

Table 1
Characteristics of PILG and CMV groups of infants with CDH requiring ECMO.

	PILG ($n = 8$)	CMV ($n = 8$)	P-value*
Estimated gestational age (weeks)	38.7 ± 1.3	38.4 ± 1.0	.65
Birth weight	3.1 ± 0.29	3.2 ± 0.38	.53
1-minute Apgar score (median)	4	2	0.79
5-minute Apgar score	6	6	0.73
CDH study group predicted survival**	56 ± 25%	61 ± 24%	0.75
Liver in chest	4 (50%)	5 (63%)	1
Female sex	4 (50%)	2 (25%)	.36
Prenatal diagnosis of CDH	3 (38%)	3 (38%)	1
Days of life at CDH repair	11.8 ± 7.5	10.0 ± 8.1	0.66

* From Fisher's exact test, Mann-Whitney *U* test, or *t*-test.

** Incorporates 5-minute Apgar score and birth weight [12].

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