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Liquid Ventilation Improves Pulmonary Function, Gas Exchange, and Lung Injury in a Model of Respiratory Failure

Ronald B. Hirschl, M.D., Alan Parent, B.S., Richard Tooley, M.D., Michael McCracken, B.S., Kent Johnson, M.D.,* Thomas H. Shaffer, Ph.D.,† Marla R. Wolfson, Ph.D.,† and Robert H. Bartlett, M.D.

From the Department of Surgery and Pathology, the University of Michigan, Ann Arbor, Michigan; and the Departments of Pediatrics and Physiology,† Temple University School of Medicine, Philadelphia, Pennsylvania*

Objective

The authors evaluated gas exchange, pulmonary function, and lung histology during perfluorocarbon liquid ventilation (LV) when compared with gas ventilation (GV) in the setting of severe respiratory failure.

Background

The efficacy of LV in the setting of respiratory failure has been evaluated in premature animals with surfactant deficiency. However, very little work has been performed in evaluating the efficacy of LV in older animal models of the adult respiratory distress syndrome (ARDS).

Methods

A stable model of lung injury was induced in 12 young sheep weighing 16.4 ± 3.0 kg using right atrial injection of 0.07 mL/kg of oleic acid followed by saline pulmonary lavage and bijugular venovenous extracorporeal life support (ECLS). For the first 30 minutes on ECLS, all animals were ventilated with gas. Animals were then ventilated with either 15 mL/kg gas (GV, n = 6) or perflubron ([PFC], LV, n = 6) over the ensuing 2.5 hours. Subsequently, ECLS was discontinued in five of the GV animals and five of the LV animals, and GV or LV continued for 1 hour or until death.

Main Findings

Physiologic shunt (Q_{ps}/Q_t) was significantly reduced in the LV animals when compared with the GV animals (LV = 31 ± 10%; GV = 93 ± 4%; $p < 0.001$) after 3 hours of ECLS. At the same time point, pulmonary compliance (C_T) was significantly increased in the LV group when compared with the GV group (LV = 1.04 ± 0.19 mL/cm H_2O/kg; GV = 0.41 ± 0.02 mL/cm H_2O/kg; $p < 0.001$). In addition, the ECLS flow rate required to maintain the PaO_2 in the 50- to 80-mm Hg range was substantially and significantly lower in the LV group when compared with that of the GV group (LV = 14 ± 5 mL/kg/min; GV = 87 ± 15 mL/kg/min; $p < 0.001$). All of the GV animals died after discontinuation of ECLS, whereas all the LV animals demonstrated effective gas exchange without extracorporeal support for 1 hour ($p < 0.01$). Lung biopsy light microscopy demonstrated a marked reduction in alveolar hemorrhage, lung fluid accumulation, and inflammatory infiltration in the LV group when compared with the GV animals.

Conclusion

In a model of severe respiratory failure, LV improves pulmonary gas exchange and compliance with an associated reduction in alveolar hemorrhage, edema, and inflammatory infiltrate.

Various interventions, including positive end-expiratory pressure, extracorporeal life support (ECLS), differential lung ventilation, and inverse ratio ventilation have been used in an attempt to allow resolution of lung injury and to improve pulmonary function and gas exchange in those patients with severe acute respiratory failure (ARF).[1] However, these methods of "lung management" have had little impact on the 50% mortality observed in those pediatric and adult patients with ARF.[2] Specifically, there are no available lung management techniques that directly affect the pathophysiology of respiratory failure. Therefore, the interventions that currently are used are, in general, supportive, but not therapeutic.

Recent studies have demonstrated the regional nature of respiratory failure, with the majority of the disease process isolated to the dependent regions of the lungs.[3] In fact, compliance, which serves as a barometer for lung injury and function, is directly proportional to the amount of remaining nondependent, aerated lung as assessed by computer tomographic scanning.[4] Intra-alveolar exudate accumulation, atelectasis, and consolidation in the dependent regions of the lung appear to contribute substantially to the reduction in gas exchange and pulmonary function observed with ARF.

Additional studies have demonstrated the ability of perfluorocarbon liquid ventilation (LV) to provide adequate gas exchange in full-term and premature, newborn lambs and other animals, with or without lung injury.[5] Tidal volume ventilation with perfluorocarbons has the potential to reduce alveolar surface tension and remove and replace alveolar exudate from the dependent regions of the lung with perfluorocarbons, which may carry out gas exchange. Alveolar recruitment and ventilation/perfusion matching may, therefore, be enhanced in the setting of ARF. In addition, evacuation of exudate and reinflation of alveoli may have a direct salutary effect on pulmonary pathology and pathophysiology. The purpose of this study, therefore, was to evaluate whether lung management with LV would allow improvement in pulmonary function and gas exchange and amelioration of lung injury in a model of severe ARF.

METHODS

Twelve sheep weighing 16.4 ± 3.0 kg were anesthetized with a mixture of 50 g guaifenesin/liter (Sigma Chemical Co., St. Louis, MO) and 1 g ketamine/liter (Aveco Co., Inc., Fort Dodge, IA), 1 mL/lb administered for initial anesthesia with titration to effect. A midline neck incision was performed and the trachea isolated and cannulated with a 9-mm inner diameter jet ventilation endotracheal tube (Mallinckrodt, Inc., St. Louis, MO). The right carotid artery and both internal jugular veins were identified. An 18-gauge angiocatheter (Becton Dickinson Vascular Access, Sandy, UT) was placed into the carotid artery and advanced approximately 3 cm and anchored in place. A 5-French balloon-tipped catheter (Opticath, Abbott Laboratories, North Chicago, IL) was advanced into the pulmonary artery under transduced pressure guidance via the right femoral vein. All pulmonary and arterial blood pressure measurements were assessed using Sorenson Transpac II pressure transducers (Abbott Laboratories, North Chicago, IL) and Hewlett-Packard signal analysis and output (Hewlett Packard Medical Division, Andover, MA). Pancuronium 0.1 mg/kg was administered intravenously, and gas mechanical ventilation was initiated. An anesthetic infusion of the guaifenesin/ketamine mixture was started at a rate of 1 mL/lb/hr using an IVAC 565 infusion pump (IVAC Corporation, San Deigo, CA). An orogastric tube was placed to reduce abdominal distension. Animals remained in the supine position throughout all studies. Baseline physiologic data were assessed.

Technique of Extracorporeal Life Support

Heparin 100 units/kg were administered intravenously. A 23-French venous drainage cannula (Medtronics/Bio-Medicus, Eden Prairie, MN) was placed via the left internal jugular vein into the right atrium and anchored in place. An 18-French reinfusion cannula (Medtronics/Bio-Medicus, Eden Prairie, MN) was placed into the right internal jugular vein and anchored in place. A standard device described previously by our group was used for ECLS.[6] The bypass circuit was first saline- and then blood-primed. The blood prime was recirculated, warmed, and oxygenated. Calcium and bicarbonate levels of the blood prime were assessed and ad-

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Perflubron provided by the Alliance Pharmaceutical Corporation, San Diego, California.

Address reprint requests to Ronald B. Hirschl, M.D., L2110 Maternal and Child Health Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0245.

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justed to maintain the calcium ≥ 1.0 and the calculated base deficit ≥ −4.0 mEq/L. Venovenous bypass was initiated at a flow rate of 10 mL/kg/min and slowly increased to approximately 100 mL/kg/min over 15 minutes to avoid hypotension. The membrane lung remained capped at this point in the protocol. Therefore, blood circulated through the extracorporeal device, but no contribution to gas exchange took place (ECLS-NO GE). Physiologic data, including systemic and pulmonary pressure, pulmonary compliance, ventilator pressure, and blood gas data, were assessed after extracorporeal blood flow rate had been increased to 100 mL/kg/min. Extracorporeal life support blood flow was assessed with a Transonics flow meter (Transonic Systems Inc., Ithaca, NY) and a ¼-inch tubing flow probe placed on the infusion limb of the extracorporeal circuit.

Induction of Lung Injury

Oleic acid ($C_{18}H_{34}O_2$, Mallinckrodt, St. Louis, MO) 0.07 mL/kg were added to 6 mL of heparinized blood withdrawn from the ECLS circuit into a 10-mL syringe. The oleic acid was emulsified in the blood by vigorous shaking. This blood with emulsified oleic acid was then injected, with continued shaking, into the right atrium through the proximal port of the pulmonary artery catheter over a 5-minute period. This was followed by instillation of normal saline 35 mL/kg into the endotracheal tube as lung lavage was performed three times at 5-minute intervals. Two liters/minute of oxygen sweep flow through the membrane lung were initiated to facilitate pulmonary saline lavage. This membrane lung sweep flow was discontinued immediately after the 15-minute period of saline pulmonary lavage.

Experimental Protocol

After induction of lung injury, the FiO_2 was increased to 1.0, and ventilator pressures were adjusted to maintain the 35 mm Hg ≤ $PaCO_2$ ≤ 45 mm Hg. Maximum ventilator settings included a peak inspiratory pressure of 50 cm H_2O, a positive end-expiratory pressure of 4 cm H_2O, and a respiratory rate of 30 breaths/minute. Ventilator pressures were assessed using a Sechrist Model 400 airway pressure monitor (Sechrist Industries Inc., Anaheim, CA.) attached to the carinal pressure port of the endotracheal tube. Physiologic data were assessed every 15 minutes. The presence of arterial hypoxemia (PaO_2 < 50 mm Hg with FiO_2 = 1.0) and an increased alveolar-arterial oxygen gradient ([A-a]DO_2 ≥ 610), which are clinical indicators of severe respiratory failure and predictive of high mortality, were used to indicate the need for ECLS.[7] Therefore, a sweep flow of oxygen at 2 L/min was initiated through the membrane lung so that gas exchange support (ECLS-GE) was taking place. Once on ECLS-GE, physiologic data were assessed every 30 minutes. The venovenous extracorporeal blood flow rate in all groups was adjusted to maintain the arterial blood gas values with a PaO_2 = 50–80 mm Hg and the membrane lung ventilating gas flow rate adjusted to maintain the $PaCO_2$ = 35–45 mm Hg. Extracorporeal life support blood flow rate was maintained ≥ 10 mL/kg/min to avoid circuit thrombosis. For the first 30 minutes on ECLS-GE, all animals remained gas ventilated. After 30 minutes of ECLS-GE, animals were randomized to management with gas (n = 6) or liquid (n = 6) ventilation. Heparin 100 units/kg and pancuronium 0.1 mg/kg were administered intravenously every hour. Extracorporeal life support with gas exchange was continued for an additional 150 minutes. At conclusion of 3 hours of ECLS-GE, blood flow through the extracorporeal device was discontinued in five animals in each group. The GV animals were continued on gas mechanical ventilation, which was increased to the maximum ventilator settings, as described previously. The LV animals were continued on the same tidal volume liquid ventilation settings except that the tidal volume was increased as necessary to 20 mL/kg. Gas or perfluorocarbon ventilation was continued with assessment of physiologic data every 15 minutes or until death of the animal. Those animals surviving for the proscribed 1 hour were killed with 1 mL/5 kg high-dose pentobarbital.

Gas Ventilation

Six animals were supported with ECLS-GE. A Bennett MA-1 ventilator was used to provide gas ventilation at a tidal volume of 15 mL/kg, a positive end-expiratory pressure of 4 cm H_2O, and a rate of 10 breaths/minute. The FiO_2 was maintained at 1.0. Ventilator tidal volume settings were calibrated by spirometer to a demonstrated accuracy of ±6%. End-expiratory pressures and ventilator rates were monitored by the Seachrist airway pressure monitor, with an accuracy of pressure measurement of ±3 cm H_2O.

Perfluorocarbon Liquid Ventilation

Six animals were supported with ECLS-GE. The lungs were filled with perflubron (Liquivent, Alliance Pharmaceutical Corp., San Diego, CA) 35 mL/kg with the animal in the supine, reverse Trendelenburg position. The lungs were degassed by manipulation of position and light compression of the chest. The liquid ventilator, which has been described previously and is depicted in

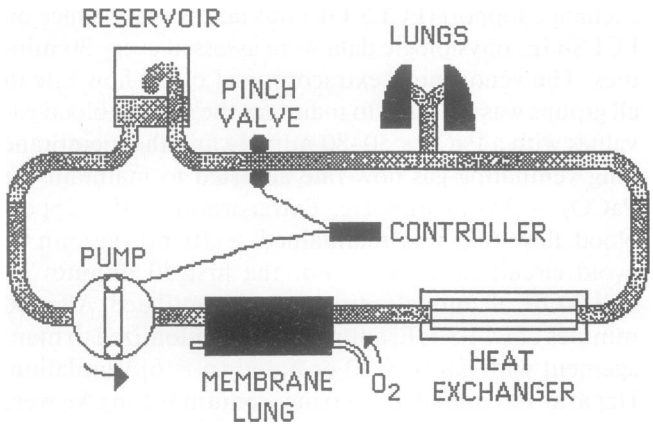

Figure 1. A ventilator developed for tidal volume perfluorocarbon liquid breathing. During inspiration, the pinch valve occludes the expiratory limb at the same time that the pump perfuses perflubron through the membrane lung, through the heat exchanger, and into the lungs. During expiration, roller pump function is discontinued, which leads to occlusion of the inspiratory limb of the circuit. Simultaneously, the pinch valve releases and perfluorocarbon drains by siphon pressure from the lungs into the reservoir.

Figure 1, was attached to the endotracheal tube, and the animal was placed supine.[8] Liquid ventilation at a tidal volume of 15 mL/kg and a rate of 5 breaths/minute with an inspiratory time of 4 seconds and an expiratory time of 8 seconds was instituted. The perfluorocarbon reservoir was suspended from an LCDA-50 load cell transducer (Omega Engineering Inc., Samford, CT) with amplified signal readout using a Grass Model 7D Polygraph recorder (Grass Instruments Co., Quincy, MA) with a 15-Hz low pass filter. Load cell accuracy was ±7 g, and the strip chart readout was calibrated by injection of 50 mL of perfluorocarbon into the reservoir before initiation and after discontinuation of LV.

Reservoir perfluorocarbon volume measurement reproducibility and accuracy were assessed over a range of 50 to 400 mL. The mean measurement reproducibility was 2.8%, with a range of 2.0% to 4.9%, and mean measurement accuracy was 1.0 mL, with a range of 0.3 to 2.7 mL. The FiO_2 of the gas sweep flow through the membrane lung of the liquid ventilator was 1.0.

Pulmonary Function

Static total lung inflation and deflation compliance (C_T) during GV was assessed by sequential endotracheal tube injections and then removal of 4 mL/kg of air with 5-second intervals between injections, to a maximum of 20 mL/kg starting at end-expiratory pressure of 0 cm H_2O. A Collins 1-L syringe (Warren E. Collins Inc., Braintree, MA) with 10-ml calibrations was attached to the endotracheal tube and used to instill and then remove the 4 mL/kg volumes of room air. Air trapping was tolerated to within 10% of the volume of gas injected, or the compliance measurement was repeated. Static airway pressure measurements were assessed by a Cobe CDX III transducer (Cobe, Lakewood, CO) attached directly to the carinal port of the jet endotracheal tube with signal amplification and readout performed by the Grass polygraph. The polygraph was calibrated before and at the end of each experiment to a pressure of 30 cm H_2O. Static airway pressure measurement accuracy and reproduciblity were assessed over a range of 10 to 40 cm H_2O. Mean airway pressure measurement reproducibility was 2.5%, with a range of 2.0% to 11.2%, and mean measurement accuracy was 0.6 mm Hg, with a range of 0.3 to 1.0 mm Hg.

During LV compliance assessment, the end-expiratory pressure was set at O cm H_2O by placement of the expiratory drainage tube within the reservoir at the level of the endotracheal tube. Compliance measurements starting, therefore, at end-expiratory pressure of O cm H_2O were obtained by occluding the expiratory limb of the liquid ventilator while infusing perfluorocarbon into the lungs in 4-mL/kg increments with 5-second intervals between infusions, to a total of 20 mL/kg. The volume infused was measured by calibrated change in weight of the perfluorocarbon reservoir using the load cell transducer and Grass polygraph as described previously. Airway pressure measurements were evaluated by a Cobe CDX III transducer (Cobe, Lakewood, CO) connected directly to the carinal port of the jet endotracheal tube. Signal amplification and readout were provided by the previously calibrated Grass polygraph. After inflation to a 20-mL/kg volume, the expiratory limb occlusion was partially and intermittently released as deflation was performed at 4-mL/kg increments with 5-second intervals between until 20 mL/kg perfluorocarbon had been evacuated and a return to baseline end-expiratory pressure of O cm H_2O was assured.

Blood Gas Data

Arterial and venous blood was drawn into heparin-coated syringes and assessed immediately by an ABL blood gas analyzer (Radiometer, Copenhagen, Denmark) and an OSM-3 co-oximeter calibrated for sheep blood (Radiometer, Copenhagen, Denmark).

Lung Biopsy Assessment

All lungs were inflated to 10 cm H_2O constant pressure, and the endotracheal tubes were clamped. The lungs were excised en bloc and examined. Approximately 5-g samples from the anterior and posterior aspects of the lungs were ligated with a 2-0 suture *in situ,*

excised, and placed into formalin. Routine histologic preparation of the specimens with hematoxylin and eosin staining and light microscopic analysis were performed. This allowed an estimate of the degree of intra-alveolar hemorrhage, intra-alveolar edema, and infiltration of inflammatory cells present.

Data Analysis

Baseline transpulmonic shunt fraction (Q_{ps}/Q_t) and alveolar-arterial oxygen gradient ([A-a]DO_2) were calculated based on assessment of arterial O_2 content, mixed venous (pulmonary artery catheter) O_2 content, alveolar end-capillary O_2 content, and $PaCO_2$ using the following equations:

$$Q_{ps}/Q_t = (CiO_2 - CaO_2)/(CiO_2 - CvO_2)$$

where Q_{ps} = physiologic shunt; Q_t = cardiac output; CaO_2 = O_2 content of arterial blood; CvO_2 = O_2 content of mixed venous blood; and CiO_2 = O_2 content of the blood draining from the ideal alveolus ventilated with gas (FiO_2 = 1.0) or perfluorocarbon as derived from the alveolar gas equation and the O_2 dissociation curve; and

$$(A\text{-}a)DO_2 = PAO_2 - PaO_2$$

where PAO_2 = [(barometric pressure × FiO_2) − 47] − $PaCO_2$. Perfluorocarbon PiO_2 was assessed by an ABL blood gas analyzer and the result used to calculate the PAO_2 during LV by using the following equation:

$$PAO_2 = PiO_{2(pfc)} - PaCO_2.$$

Venovenous bypass allowed measurement of Q_{ps}/Q_t despite the influence of extracorporeal support on gas exchange.

All data throughout this proposal were evaluated by Student t test, chi-square analysis, or analysis of variance, where appropriate, and are reported as mean ± SD. All studies were reviewed and approved by the University Committee on the Care and Use of Animals and National Institutes of Health guidelines for animal use and care were followed throughout.

RESULTS

Physiologic data for the GV and LV animals are presented in Table 1. Data for the GV animals after discontinuation of ECLS are not reported because of instability and impending death in most animals within minutes of discontinuation of ECLS.

The calculated physiologic shunt (Q_{ps}/Q_t) is demonstrated in Figure 2. Physiologic shunt was approximately 15 ± 6% at baseline and increased to 68 ± 9% in the GV animals and 65 ± 8% in the LV animals after induction of lung injury. After 30 minutes on ECLS, both animal groups remained gas ventilated. With initiation of liquid ventilation significant and sustained, reductions in physiologic shunt were noted that continued for the duration of the 3 hours that the animals were supported with ECLS. After 3 hours on ECLS, the physiologic shunt in the GV animals was 93 ± 4% and in the LV group was 31 ± 10% ($p < 0.001$).

Initiation of LV resulted in a significant reduction in the required ECLS flow rate (Fig. 3). During GV, the PaO_2 always was maintained in the 50- to 80-mm Hg range. However, during LV, the ECLS blood flow rate could frequently be reduced to the previously dictated minimum of 10 mL/kg/min. Therefore, PaO_2 always was > 50 mm Hg and often > 80 mm Hg in the LV animals, despite minimal ECLS blood flow rate (Table 1). Required ECLS flow rate after 3 hours of extracorporeal support was 14 ± 5 mL/kg/min in the LV group, which was substantially less than the 87 ± 15 mL/kg/min flow rate required in the GV group ($p < 0.001$).

Inflation and deflation pulmonary compliance curves developed for GV and LV animals with instillation of 4-mL/kg increments of gas or perfluorocarbon volume, respectively, after 3 hours on ECLS, are demonstrated in Figure 4. Compliance was increased significantly at each incremental point ($p < 0.001$) except at the 4 mL/kg and 8 mL/kg volume point during deflation ($p = 0.055$ and 0.38, respectively). Compliance at the 20 mL/kg inflation was 0.41 ± 0.02 mL/cm H_2O/kg in the GV animals and 1.04 ± 0.19 in the LV animals ($p < 0.001$).

The pulmonary compliance as measured at 20 mL/kg inflation volume over time is demonstrated in Figure 5. Baseline compliance was 1.30 ± 0.27 mL/cm H_2O/kg in the GV group and 1.26 ± 0.28 mL/cm H_2O/kg in the LV group. After induction of lung injury, the compliance at 20 mL/kg inflation volume in the GV group decreased to 0.51 ± 0.07 mL/cm H_2O/kg and to 0.51 ± 0.1 mL/cm H_2O/kg in the LV group. At 30 minutes on ECLS, both groups of animals remained gas ventilated. The compliance after 3 hours on ECLS was 0.41 ± 0.02 mL/cm H_2O/kg in the GV group and 1.04 ± 0.19 mL/cm H_2O/kg in the LV animals ($p < 0.001$).

After discontinuation of ECLS, all five GV animals died, most within 5 to 30 minutes, demonstrating profound hypoxemia, hypercarbia, and acidosis with subsequent development of refractory hypotension. All of the five LV animals survived the proscribed 1 hour after discontinuation of ECLS, demonstrating effective gas exchange during LV (Table 1). Survival in the LV group was significantly improved when compared with that of the GV group ($p < 0.01$).

Gross autopsy specimens demonstrated severe consolidation, atelectasis, and pulmonary hemorrhage, especially in the posterior, or dependent, regions of all GV lungs, as demonstrated in Figure 6. In contrast, all LV

Table 1. PHYSIOLOGIC DATA

	Baseline	After Injury	On ECLS 30′	60′	90′	120′	150′	180′	Off ECLS
MSAP (mmH)									
GV	90 ± 14	54 ± 28	59 ± 22	57 ± 26	54 ± 23	54 ± 30	54 ± 22	52 ± 20	
LV	109 ± 11*	78 ± 11	71 ± 23	79 ± 23	82 ± 26	73 ± 27	69 ± 25	67 ±3 1	58 ± 26
MPAP (mmH)									
GV	25 ± 15	24 ± 7	25 ± 9	27 ± 5	30 ± 6	30 ± 4	32 ± 6	32 ± 5	
LV	17 ± 9	24 ± 8	22 ± 5	22 ± 3*	24 ± 7	26 ± 8	26 ± 7	29 ± 7	29 ± 5
TEMP (°C)									
GV	38.0 ± 0.1	37.7 ± 0.1	37.7 ± 0.1	37.7 ± 0.1	37.8 ± 0.1	37.8 ± 0.1	37.7 ± 0.2	37.8 ± 0.1	
LV	37.9 ± 0.0	37.6 ± 0.6	37.7 ± 0.3	37.7 ± 0.2	37.7 ± 0.3	37.7 ± 0.1	37.7 ± 0.3	37.6 ± 0.5	37.8 ± 0.1
pH									
GV	7.42 ± .08	7.24 ± .13	7.40 ± .10	7.38 ± .05	7.39 ± .05	7.38 ± .08	7.37 ± .05	7.35 ± .08	
LV	7.45 ± .08	7.35 ± .11	7.46 ± .05	7.39 ± .07	7.33 ± .11	7.36 ± .04	7.38 ± .02	7.36 ± .09	7.29 ± .07
$PaCO_2$ (mmHg)									
GV	37.3 ± 7.7	51.6 ± 17.0	33.2 ± 8.0	33.3 ± 5.8	31.2 ± 6.3	34.9 ± 7.3	34.3 ± 6.9	34.8 ± 8.1	
LV	33.9 ± 4.8	46.8 ± 16.3	31.0 ± 3.5	34.3 ± 3.7	49 ± 30.2	37.7 ± 1.3	40.1 ± 4.8	37.1 ± 7.5	52.3 ± 8.2
PaO_2 (mmHg)									
GV	478 ± 63	48 ± 9	54 ± 8	61 ± 12	61 ± 18	69 ± 17	77 ± 26	72 ± 31	
LV	515 ± 65	46 ± 5	68 ± 21	177 ± 20†	155 ± 45†	177 ± 47†	163 ± 67*	179 ± 85*	135 ± 49
SaO_2 (%)									
GV	99 ± 1	61 ± 13	76 ± 11	80 ± 10	80 ± 10	86 ± 7	86 ± 6	82 ± 10	
LV	99 ± 1	64 ± 4	88 ± 5*	99 ± 2†	97 ± 2†	98 ± 1†	97 ± 2†	96 ± 4†	94 ± 5

Physiologic data observed in gas-ventilated (GV) and perfluorocarbon liquid-ventilated (LV) animals at baseline, after induction of lung injury, at 30-minute intervals while on extracorporeal life support (ECLS), and after discontinuation of ECLS. MSAP = mean systemic arterial blood pressure; MPAP = mean pulmonary arterial pressure; TEMP = core temperature.

* $p < 0.05$, † $p < 0.01$.

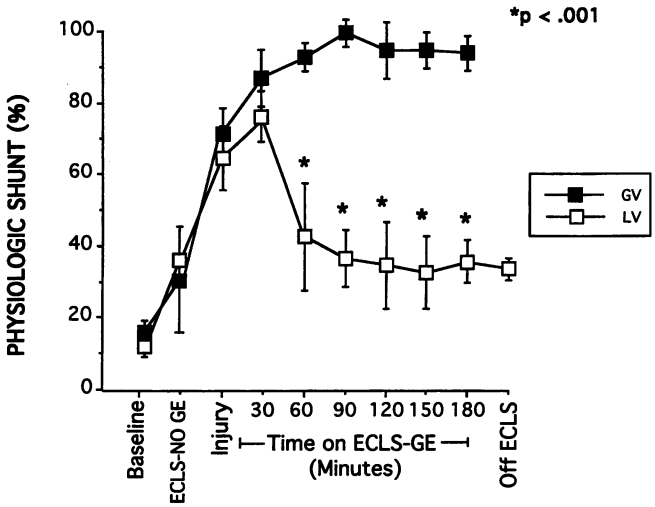

Figure 2. Calculated pulmonary physiologic shunt at baseline; on extracorporeal life support but without membrane lung gas exchange (ECLS-NO GE); after lung injury; for 3 hours while on extracorporeal life support with membrane lung gas exchange (ECLS-GE); and after discontinuation of extracorporeal life support (ECLS). Animals underwent gas ventilation (GV) or liquid ventilation (LV) while on ECLS and after discontinuation of ECLS, although all animals underwent GV for the first 30 minutes while on ECLS-GE. (*$p < 0.001$)

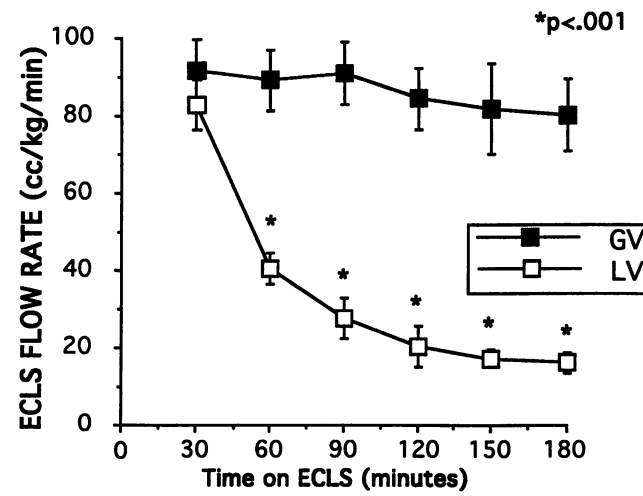

Figure 3. Extracorporeal life support flow rate required to maintain PaO_2 between 50–80 mm Hg while on ECLS with membrane lung gas exchange (ECLS-GE). Animals underwent gas ventilation (GV) or liquid ventilation (LV) for 3 hours, although all animals underwent GV for the first 30 minutes while on ECLS-GE. During LV, the ECLS blood flow rate frequently could be reduced to the previously determined minimum of 10 mL/kg/min. Therefore, PaO_2 often was >80 mm Hg during LV despite minimal ECLS blood flow rate. (*$p < 0.001$)

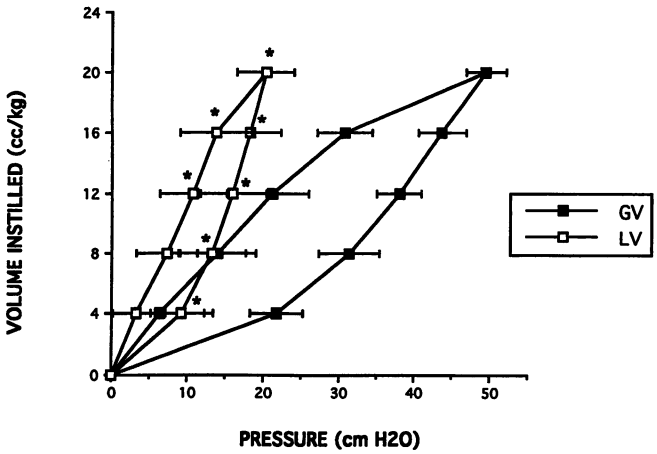

Figure 4. Inflation and deflation pulmonary compliance curves developed for gas-ventilated (GV) and perfluorocarbon liquid-ventilated (LV) animals with instillation of 4 mL/kg increments of gas or perfluorocarbon volume, respectively, after 3 hours on extracorporeal support. (*p < 0.001 when static airway pressure generated at each volume during GV and LV are compared)

lungs demonstrated a paucity of consolidation and atelectasis, although mild pulmonary hemorrhage was evident. Light microscopic assessment of GV biopsy specimens revealed substantial pulmonary vascular congestion, alveolar hemorrhage, alveolar proteinaceous fluid accumulation, and inflammatory infiltration, all consistent with adult respiratory distress syndrome ([ARDS], Fig. 7). Liquid-ventilated biopsy specimens, however, demonstrated a paucity of these pulmonary vascular and alveolar findings with a distinct absence of an inflammatory infiltrate.

DISCUSSION

Pulmonary gas exchange using liquid breathing has been investigated during the past 3 decades.[5] Initial studies explored the efficacy of hyperbaric saline ventilation in providing adequate gas exchange.[9] However, the subsequent recognition of the excellent oxygen-carrying capacity of fluorocarbons led to the investigation of a number of such compounds as blood substitutes and as liquids to support respiration.[10,11] The physiology and toxicology of perfluorocarbon liquid breathing, along with the mechanical and technical aspects, have been explored and defined during the last few years.[5,12] In addition, the role of perfluorocarbon liquid ventilation in the setting of surfactant deficiency has been assessed.[13] Studies have demonstrated the efficacy of ventilation with liquid perfluorocarbons in improving gas exchange and pulmonary function in premature animals. In 1989, the first human trials of perfluorocarbon ventilation were performed in premature newborns.[14] These studies documented the ability of LV to adequately support gas exchange and demonstrated an improvement in compliance in moribund premature human neonates.

The pathophysiology of respiratory failure in premature newborns with surfactant deficiency is distinctly different from that observed in older patients. The major causative factors of respiratory failure in the non-neonatal population include ARDS and various forms of pneumonia.[15] However, it appears that the common mechanism of pulmonary insufficiency in these patients involves the production of alveolar exudate and the development of atelectasis predominantly in the dependent portions of the lung.[3] The presence of both airspace fluid and atelectasis contributes significantly to the ventilation mismatch, the physiologic shunt, and the inability to provide adequate gas exchange. The improved efficacy of liquid ventilation, when compared with gas ventilation in newborn lambs with acute respiratory failure secondary to intravenous oleic acid injection, has been demonstrated.[16] Little work has been performed evaluating the ability of perfluorocarbon liquid ventilation to improve pulmonary function and gas exchange and reduce lung injury in older models of severe ARDS.

There are multiple reasons to expect that perfluorocarbon liquid ventilation would enhance pulmonary function and gas exchange in the setting of ARF. First, the alveolar surface tension in the perfluorocarbon-filled lung is approximately half that of normal lungs filled with air.[17] We previously have demonstrated that alveolar re-expansion is enhanced during perfluorocarbon

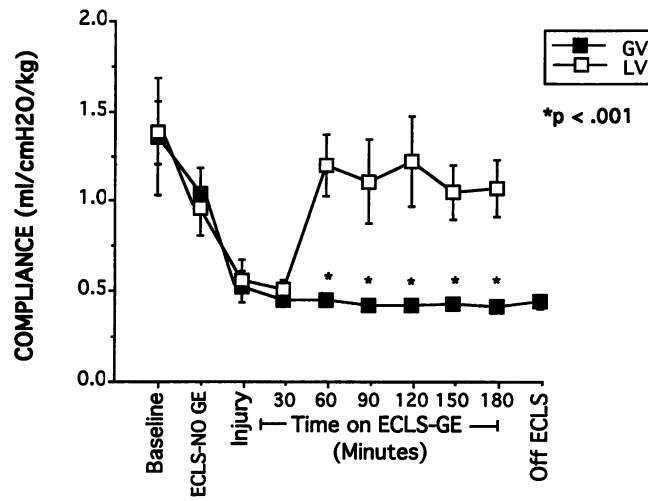

Figure 5. Pulmonary compliance with inflation to 20 mL/kg gas or perfluorocarbon at baseline; on extracorporeal life support but without membrane lung gas exchange (ECLS-NO GE); after lung injury; for 3 hours while on extracorporeal life support with membrane lung gas exchange (ECLS-GE); and after discontinuation of extracorporeal life support (ECLS). Animals either underwent gas ventilation (GV) or liquid ventilation (LV) while on ECLS and after discontinuation of ECLS, although all animals underwent GV for the first 30 minutes while on ECLS-GE. (*p < 0.001)

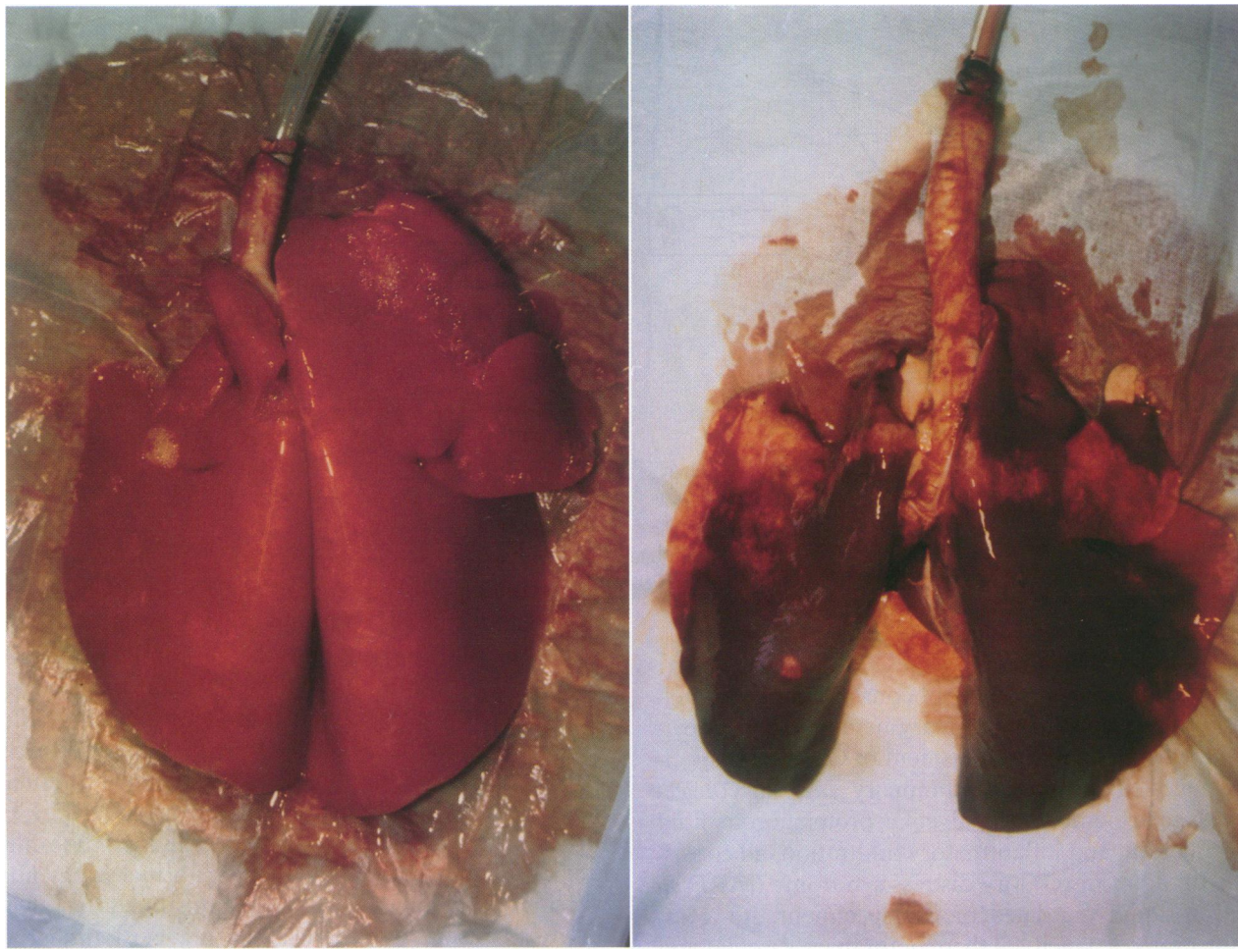

Figure 6. Posterior (dependent) view of representative noninflated lungs after completion of the protocol and at the time of autopsy in a liquid-ventilated (LV) (left) and a gas-ventilated (GV) (right) animal. Substantial reduction in pulmonary consolidation, atelectasis, and hemorrhage in the LV lungs is noted.

when compared with gas ventilation in the setting of lobar atelectasis.[18] In addition, LV appears to be especially effective at recruiting dependent atelectatic/consolidated lung in an animal model of ARDS, which may result in an improvement in ventilation/perfusion matching and, therefore, gas exchange.[19]

Secondly, tidal volume ventilation with perfluorocarbons may provide a lavage effect with removal of exudate, especially in the dependent regions of the lungs. This may be accompanied by replacement with a liquid that has the capability of effecting gas exchange. Substantial volumes of exudate were observed floating on the perfluorocarbon in the reservoir of the liquid ventilator during each of the experiments. In addition, lung biopsies from the dependent regions of the perfluorocarbon-ventilated lungs demonstrated a paucity of intra-alveolar exudate and hemorrhage. This effect likely plays an important role in the observed improvement in lung function.

Third, in the setting of ARDS, physiologic shunt is increased substantially because the majority of pulmonary blood flow perfuses the dependent regions of the lungs, which are consolidated and which contribute minimally to alveolar ventilation.[20] In healthy animals, pulmonary blood flow is re-distributed to nondependent lung regions during perfluorocarbon ventilation.[21] This redistribution of pulmonary blood flow to nondependent regions of the lung may enhance ventilation/perfusion matching with an associated reduction in physiologic shunt. Whether this effect actually occurs during LV in the setting of ARDS has not been evaluated.

Finally, there was a conspicuous absence of inflammatory infiltrate in the injured, perfluorocarbon-ventilated lungs. The etiology for this finding remains unclear. Previous studies on reperfusion of ischemic myocardial regions with perfluorocarbons have demonstrated a reduction in the subsequent inflammatory infiltrate observed in those areas.[22] One can only speculate whether

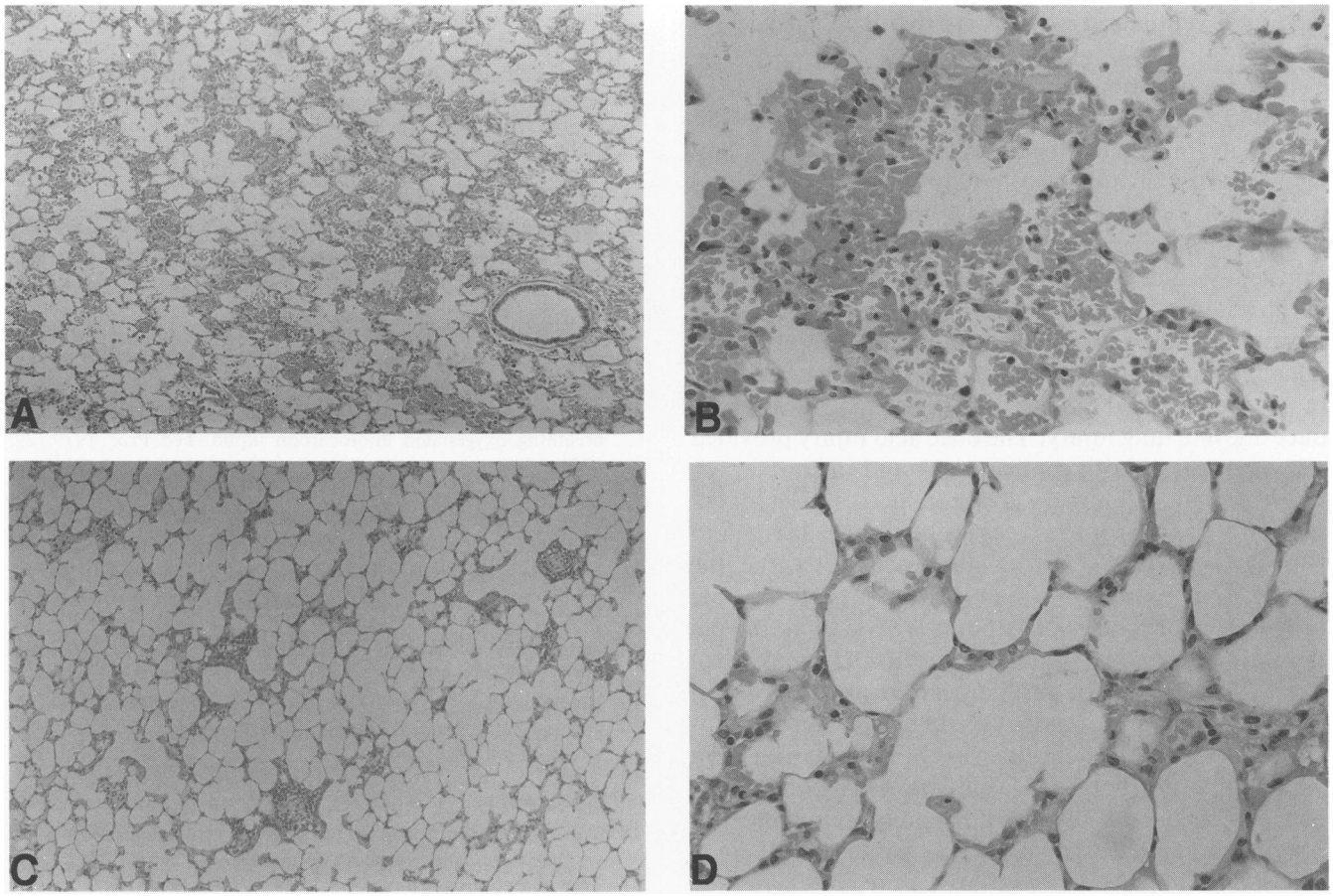

Figure 7. 10× and 40× view of a biopsy from the lower (dependent) region of the injured lung after completion of the protocol in a representative (A),(B) gas-ventilated (GV) and (C), (D) liquid-ventilated (LV) animal. Reductions in pulmonary vascular congestion, alveolar hemorrhage, alveolar proteinaceous fluid accumulation, and inflammatory infiltration are noted in the LV specimen.

the paucity of inflammatory infiltrate observed in the LV lungs is the result of a direct anti-inflammatory effect of perfluorocarbons or the evacuation of intra-alveolar exudate and associated inflammatory mediators.

The use of extracorporeal support during these studies allowed evaluation of both techniques of pulmonary ventilation in a severe but stable model of lung injury. The observation that pulmonary compliance and physiologic shunt deteriorated at onset of bypass, before lung injury, is consonant with the clinical observation that diffuse radiologic pulmonary opacification occurs at initiation of extracorporeal support.[23] The etiology of this phenomenon is unclear, but is likely a complement and cytokine-mediated effect. In this study, both the GV and LV groups were exposed equally to the detrimental pulmonary effects of ECLS. Therefore, no differential effect in either group would be expected.

Pulmonary compliance was improved substantially in the perfluorocarbon-filled lungs when compared with the gas-ventilated lungs. This may be a direct effect of the reduction in surface tension in the perfluorocarbon-filled lung as discussed previously.[17] Alternatively, evacuation of substantial volumes of exudate with associated alveolar recruitment may result in an increase in the volume of lung available for ventilation. Finally, the differences in compliance between the GV and LV groups may be related directly to the medium that was used for compliance measurements. Previous studies in patients with ARDS have revealed that pulmonary compliance is directly proportional to the volume of aerated lung available for ventilation.[4] These studies suggest, therefore, that compliance may reflect the volume available for distribution of gas in the injured lung. It may be that the volume available for distribution of infused perfluorocarbon in the injured perfluorocarbon-filled lung is much greater than that for gas in the partially gas-filled, injured lung, resulting in a difference in compliance measurement. If so, this would have important implications regarding the uniformity of lung ventilation and avoidance of overdistension of isolated lung regions dur-

ing liquid ventilation when compared with gas ventilation.

The model used in this study was an acute preparation, and therefore, gas exchange capabilities were evaluated only for 1 hour after discontinuation of ECLS. Previous studies have demonstrated the efficacy of liquid ventilation for up to 30 hours in healthy animals (T. Shaffer, Ph.D., personal communication, March 1994). Further studies will be required to delineate the effectiveness of LV for longer periods in the setting of lung injury and to assess gas exchange in the injured lung after return to gas ventilation. This preparation combined two accepted models of respiratory failure to produce a severe lung injury. The oleic acid injury provided a component of both capillary leak and inflammation, whereas saline pulmonary lavage induced surfactant deficiency.[16,24,25] All of these components are observed in patients with ARDS. One can only speculate whether the observations made while studying this model of acute lung injury for a number of hours will apply to the patient with respiratory failure developed over a number of days. Clinical trials of perfluorocarbon ventilation will be required and are underway. In the meantime, this study documents the effectiveness of lung management with perfluorocarbon liquid ventilation in reducing alveolar pathology and inflammatory infiltration while improving pulmonary function and gas exchange in a model of acute, severe respiratory failure.

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