

A prototype of a liquid ventilator using a novel hollow-fiber oxygenator in a rabbit model

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Objective: A functional total liquid ventilator should be simple in design to minimize operating errors and have a low priming volume to minimize the amount of perfluorocarbon needed. Closed system circuits using a membrane oxygenator have partially met these requirements but have high resistance to perfluorocarbon flow and high priming volume. To further this goal, a single piston prototype ventilator with a low priming volume and a new high-efficiency hollow-fiber oxygenator in a circuit with a check valve flow control system was developed.

Design: Prospective, controlled animal laboratory study.

Setting: Research facility at a university medical center.

Subjects: Seven anesthetized, paralyzed, normal New Zealand rabbits

Interventions: The prototype oxygenator, consisting of cross-wound silicone hollow fibers with a surface area of 1.5 m² with a priming volume of 190 mL, was tested in a bench-top model followed by an *in vivo* rabbit model. Total liquid ventilation was performed for 3 hrs with 20 mL·kg⁻¹ initial fill volume, 17.5–20 mL·kg⁻¹ tidal volume, respiratory rate of 5 breaths/min, inspira-

tory/expiratory ratio 1:2, and countercurrent sweep gas of 100% oxygen.

Measurements and Main Results: Bench top experiments demonstrated 66–81% elimination of CO₂ and 0.64–0.76 mL·min⁻¹ loss of perfluorocarbon across the fibers. No significant changes in PaCO₂ and PaO₂ were observed. Dynamic airway pressures were in a safe range in which ventilator lung injury or airway closure was unlikely (3.6 ± 0.5 and -7.8 ± 0.3 cm H₂O, respectively, for mean peak inspiratory pressure and mean end expiratory pressure). No leakage of perfluorocarbon was noted in the new silicone fiber gas exchange device. Estimated *in vivo* perfluorocarbon loss from the device was 1.2 mL·min⁻¹.

Conclusions: These data demonstrate the ability of this novel single-piston, nonporous hollow silicone fiber oxygenator to adequately support gas exchange, allowing successful performance of total liquid ventilation. (Crit Care Med 2004; 32:2104–2109)

KEY WORDS: total liquid ventilation; liquid ventilation; perfluorocarbons; fluorocarbons; mechanical ventilation; ventilator

Total liquid ventilation (TLV) has been explored as a potential therapy for acute respiratory failure; to perform this technique, a “liquid ventilator” that allows adequate control of liquid tidal volume and flow profile over time is essential. Despite its great potential as a form of lung-protective ventilation and its ability to provide effective treatment of severe respiratory failure as suggested by several studies (1–9), the clinical application of TLV requires that the technical challenges currently met by gas ventilators also be overcome for liquid ventila-

tors. A successful device should oxygenate and remove CO₂ efficiently from the liquid (perfluorocarbon, PFC), provide low resistance to flow, minimize heat and liquid loss, have a low priming volume, and avoid drainage flow limitation. Moreover, issues such as material compatibility and the use of disposable components to prevent cross-contamination between patients must be considered (10). To date, the most advanced liquid ventilators use a dual-piston pump, where each piston and cylinder unit is dedicated either to inspiration or expiration with pinch valves controlling the direction of flow. Commercial membrane oxygenators or bubble gas exchangers have been employed because commercially available hollow fibers allow leakage of the low surface tension PFCs into the gas phase of the device (10–14). However, the recent advent of new solid-silicone membrane technology has offered a hollow fiber option for use in a TLV system. To evaluate the ability of this type of fiber to sustain gas exchange during TLV, a pro-

totype simplified low-priming volume “liquid ventilator” was built and tested both on the bench top as well as in an *in vivo* rabbit model (15).

MATERIALS AND METHODS

Total Liquid Ventilation System. The liquid ventilation system consisted of a single piston and cylinder unit connected to the new prototype oxygenator and a heat exchanger in series. An expiratory bypass to the piston with a bubble-sputum trap, in line with the system, completed the circuit configuration. Check valves (PP-Viton 3/8 in., United States Plastic, Lima, OH) were used to control the direction of the flow (Fig. 1).

The prototype oxygenator was handmade specifically for TLV by our laboratory with a silicone hollow fiber provided by Fuji Systems Corporation (Tokyo, Japan). The silicone hollow fibers have a 300-μm outer diameter, a 50-μm wall thickness, and a mechanical strength tenfold higher than conventional silicone rubber. The hollow fibers were cross-wound around the core of the membrane oxygenator and packed with a density of 40% in a polycarbonate cylindrical case. The total ex-

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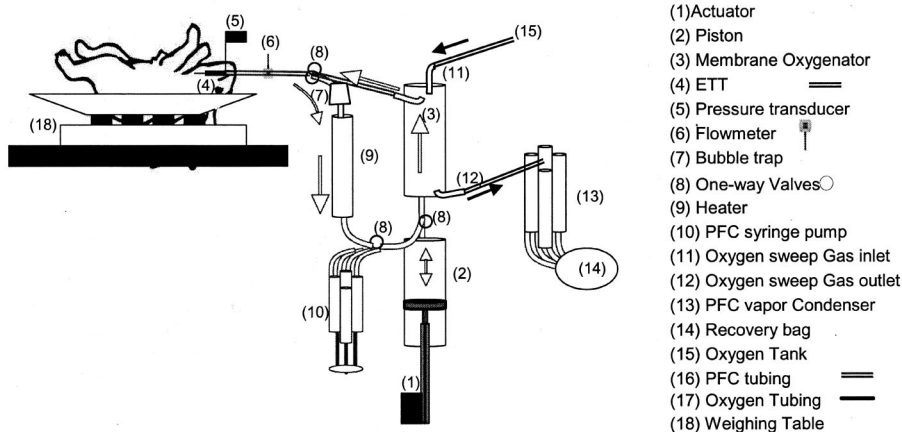


Figure 1. Schematic diagram of the liquid ventilator used in this study. Perfluorocarbon (PFC) is pumped by the actuator (1) from the piston (2) through the oxygenator (3) and then directly to the animal via the endotracheal tube (ETT) (4). During the expiratory phase, PFC is actively drained from the animal back to the piston, passing through a bubble trap (7) and heat exchanger (9). One-way valves (8) are used to control the direction of flow (PFC flow direction is indicated by the unfilled arrows). Additional PFC volume is added to the system by a syringe pump system (10) connected to the expiratory limb. PFC vapor exhaled from the oxygenator is condensed by a cooler coil (13) and collected in a recovery bag (14). Countercurrent sweep gas flow (indicated by filled arrows), 5 L·min⁻¹ of 100% of oxygen from an oxygen tank (15) is passed through the oxygenator from the gas inlet (11), sited on the top of the oxygenator, to the gas outlet (12) at the bottom. PFC tidal volume and end-expiratory and end-inspiratory volume are recorded by a scale (18).

changing surface area was 1.5 m², and the total priming volume was 190 mL. The device parameters were chosen to facilitate its use in TLV on larger animals in addition to rabbits. A Smart Bug actuator (1720 series, Ultramotion LLC, Long Island, NY) was used to drive the single piston. The Smart Bug actuator is a linear motion control system that allows easily configured high-precision flow while providing a force of up to 1335 N at 7.6 cm·sec⁻¹. To maintain body temperature, a heating system was placed in the circuit, which consisted of an extracorporeal stainless steel heat exchanger (HE-3, Gish Biomedical, Rancho Santa Margarita, CA) connected to a water warmer system. Finally, a PFC vapor condensing system was connected to the gas outlet port of the oxygenator to recover PFC lost by evaporation through the oxygenator. A continuous infusion of PFC into the circuit was required to match evaporative loss through the oxygenator. The total priming volume of the system was 450 mL.

Bench-Top Gas Exchange Evaluation. Before testing the device *in vivo*, we performed bench-top studies to evaluate CO₂ removal efficiency and evaporative loss. The liquid ventilator described previously without a heat exchanger was tested *in vitro* with a bubble deoxygenator simulating the lungs. Therefore, these experiments were performed at room temperature. Tidal volume was 60 mL with five breaths performed per minute (to approximate the liquid ventilator settings in the rabbit experiments described here, based on an animal weight of 3 kg), thus generating a mean PFC flow rate of 300 mL·min⁻¹. Oxygen sweep flow rates through the gas exchange

device started at 1 L·min⁻¹ and were increased sequentially up to 15 L·min⁻¹ in increments of 2 L·min⁻¹. As described later in outcome measures, the efficiency of CO₂ removal was calculated after maintenance of each gas sweep flow for 20 mins by measuring partial pressures of CO₂ in the FC77 before and after the gas exchange device.

In similar studies, an FC77-filled beaker, which simulated the lungs, was situated on a scale (TR-4101, Denver Instruments, Denver, CO) with an accuracy of 0.1 g. Oxygen sweep gas flow rates of 0, 3, 6, and 9 L·min⁻¹ were applied while the PFC flow rate was maintained at 0.3 L·min⁻¹. The weight of the FC77-filled beaker, with a layer of water on top of the PFC to prevent evaporation of PFC from the surface, was monitored for change in weight to assess loss of PFC vapor across the fibers as a function of sweep gas flow rate.

Animal Model and Intervention. The study was approved by the University of Michigan institutional committee on the use and care of animals; the National Institutes of Health guidelines for animal use and care were followed. A total of seven adult New Zealand White rabbits (mean body weight of 3.2 ± 0.2 kg) of either gender were used for these studies. Performance of this study in seven animals allowed us to appropriately use parametric testing since a normal distribution of the data could be demonstrated. All animals were anesthetized with xylazine hydrochloride (5 mg·kg⁻¹ intramuscularly) and ketamine hydrochloride (20 mg·kg⁻¹ intramuscularly). After cannulation of the right ear vein with a 22-gauge angiocath, a continuous infusion of lactated Ringer's solution was started at 60

mL·hr⁻¹. The trachea was isolated, and an uncuffed, handmade, metal endotracheal tube (4 mm inner diameter) was inserted and secured with a suture. The use of a thin-walled metal tube allows us to effectively seal the trachea around it without narrowing its diameter. After administration of pancuronium 0.2 mL·kg⁻¹, conventional mechanical gas ventilation was initiated using a volume-controlled ventilator (Inspira 55-7058, Harvard Apparatus, Holliston, MA). The right carotid artery was cannulated with a 16-gauge angiocath for pressure monitoring. Anesthesia was maintained during the study with continuous intravenous administration of 5 mg·kg⁻¹·hr⁻¹ of ketamine and intermittent administration of 0.2 mg·kg⁻¹·hr⁻¹ of pancuronium. The lungs were then slowly filled with 20 mL·kg⁻¹ preoxygenated FC77. The PFC was preoxygenated by circulating the FC77 through the device as oxygen was infused through the gas exchanger. The endotracheal tube was then connected to the liquid ventilation device. TLV was then initiated with the inspiratory phase. The ventilation parameters were set by prescribing the ventilator piston motion. The tidal volume was maintained in all animals at 17.5–20 mL·kg⁻¹ with a respiratory rate of five cycles per minute and an inspiratory/expiratory ratio of 1:2 by using a square wave flow pattern during both phases of ventilation. These ventilation parameters are typical for TLV (16–18). To avoid flow limitation, it is necessary to have a slower expiration than in gas ventilation. This requires a higher tidal volume to maintain an adequate minute-ventilation. The material properties of PFC allow a high tidal volume without development of high peak inspiratory pressure.

In all animals, the weight was followed using a metal platform supported by three LCAB-20 load cells over a period of 3 hrs to assess the rate of FC77 loss from the system and to provide an evaluation of the delivered tidal volume in each cycle based on the animal weight variation. The load cell outputs were assessed by a processor that was connected to a digital display model DP41-U (all components from Omega Engineering, Stamford, CT) that read to the nearest gram. The platform was calibrated to within 2 g of a known test load applied anywhere within a defined area of the table surface. The rabbit was placed within this area during each study. Based on preliminary estimates, a continuous infusion of FC77 into the sideport of the endotracheal tube was performed at a rate of 1.2 mL·min⁻¹ with additional PFC administered on an as-needed basis to compensate for the evaporative loss of PFC and to avoid the development of choked flow. After completion of a 3-hr period of TLV, animals were killed and a macroscopic evaluation of the chest cavity was performed to examine for fluorothorax.

Outcome Measures. Perfluorocarbon samples were collected in the bench-top studies 20 mins after each change in sweep flow rate and in the *in vivo* studies at initiation of TLV and

then at 60-min intervals for the 3 hrs of TLV to assess the efficiency of carbon dioxide (CO₂) removal by the prototype oxygenator. The CO₂ removal efficiency was calculated by the equation $[P_{PFC}CO_{2out} - P_{PFC}CO_{2in}]/[P_{GAS}CO_{2in} - P_{PFC}CO_{2in}]$, where $P_{PFC}CO_2$ is the partial pressure of carbon dioxide in PFC, $P_{GAS}CO_2$ is the partial pressure of carbon dioxide in the gas phase of the oxygenator, and "in" and "out" are respectively the inlet and outlet side of the gas exchange device (19). The $P_{PFC}CO_{2in}$ and the $P_{PFC}CO_{2out}$ were measured using an ABL505 blood gas machine (Radiometer America, Westlake, OH). The assumption was made that $P_{GAS}CO_{2in}$ was zero since the in flow gas was oxygen.

During the *in vivo* studies, the pulmonary gas exchange as well as mean arterial pressure, heart rate, dynamic peak inspiratory airway pressure, and dynamic end-expiratory pressure were recorded at initiation of TLV and at time 10 and 20 mins and then every 20 mins during TLV. Delivered tidal volume was measured by assessing weight change in the animal over the course of the ventilatory cycle (4, 20, 21) and compared with the tidal volume set on the ventilator.

Peak inspiratory airway pressure and end-expiratory pressure were measured by a PFC-filled transducer attached to PE tubing with side holes lying just beyond the tip of the endotracheal tube. The Marquette monitor was used to measure these pressures in units of mm Hg, which were then converted to cm H₂O.

The mean rate of PFC loss from the ventilating system was determined for the bench-top studies and an average rate of loss calculated. In the *in vivo* studies, the FC77 loss rate was calculated based on the change in weight of the animal minus both the weight of FC77 and intravenous fluids administered over time. Any urine or feces were contained on the load transducer platform. No correction for insensible loss of the rabbit was included in the calculation.

Assessment of leak was performed hourly, by checking the transparent oxygenator casing and the gas tubing for presence of liquid PFC. The outlet of the sweep gas was maintained at the lowest point so that any liquid that leaked out of the fibers could be identified in the tubing, which formed a trap leading from the sweep flow outlet. In our early device development, we could easily identify leak from the fibers as accumulation of PFC inside the casing or in the trap formed by the tubing at the sweep gas outlet.

Data Analysis. All data are reported as mean \pm SEM. One-way analysis of variance with *post hoc* Bonferroni test was used to assess for differences over time. Values of $p < .05$ were considered significant.

RESULTS

Bench-Top Evaluation of Gas Exchanges. Figure 2 demonstrates the ef-

fect of sweep flow on CO₂ elimination from the gas exchange device. Because PFC flow remained constant at 60 mL·min⁻¹, the gas exchange device ventilation/perfusion ratio evaluated ranged from 3 to 50. CO₂ removal efficiency did not appear to increase above oxygen sweep flow rates of 3–5 L·min⁻¹. As such, for our *in vivo* studies, we applied oxygen sweep flow rates of 5 L·min⁻¹. Figure 3 reveals the rate of FC77 loss from the system as a function of oxygen sweep gas flow.

Animal Model. Based on the animal weight measurements, delivered tidal volume was 19 \pm 0.5 mL·kg⁻¹. The agreement between the set and delivered tidal volumes was close with a difference <5% at each cycle. The maximum dynamic peak inspiratory pressure was 5.6 cm H₂O with an average value of 3.6 \pm 0.5 cm H₂O, and the minimum dynamic end-expiratory pressure was -9.6 cm H₂O with an average value of -7.8 \pm 0.3 cm H₂O.

No significant changes in PaO₂ and PaCO₂ (407 \pm 3.5 and 44 \pm 0.6 torr,

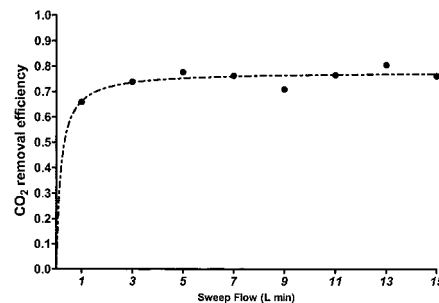


Figure 2. Gas exchanger device CO₂ removal efficiency vs. sweep gas flow, during the *in vitro* evaluation with a constant perfluorocarbon flow of 0.3 L·min⁻¹ (ventilation/perfusion ratio ranged from 3 to 50). The best fit curve (*dashed line*) was forced to pass through the origin because it was assumed that no sweep gas flow corresponds to no CO₂ removal.

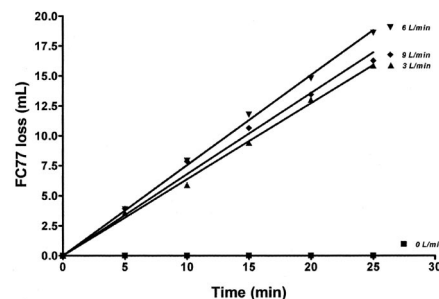


Figure 3. Perfluorocarbon (FC77) loss from the system vs. time, at sweep flow rates of 3, 6, and 9 L·min⁻¹ during the *in vitro* evaluation.

respectively) were observed for the duration of the experiment (Figs. 4 and 5). No acidosis was observed: The mean animal pH was 7.39 \pm 0.01. As can be seen in Figure 6, the movement of PFC liquid in and out of the lungs had a significant effect on blood pressure (82 \pm 1 and 66 \pm 1 for mean arterial pressure at end-expiration and mean arterial pressure at end-inspiration, respectively; Student's *t*-test $p < .001$). However, no significant variations in heart rate or end-inspiratory or end-expiratory mean arterial pressure were noted during the period of total liquid ventilation (Figs. 6 and 7).

There was no requirement for vasoactive drug or sodium bicarbonate administration during this study. Body temperature remained stable (mean 36.6 \pm 0.04°C, $p = 1.0$ repeated-measures analysis of variance) over the duration of TLV.

The mean *in vivo* carbon dioxide (CO₂) removal efficiency of the prototype gas exchange device was 78.0% \pm 0.1% with a sweep gas flow of 5 L·min⁻¹ of oxygen (Fig. 8). Mean inspiratory PFC oxygen was 707 \pm 9 torr (94.3 kPa). Mean in-

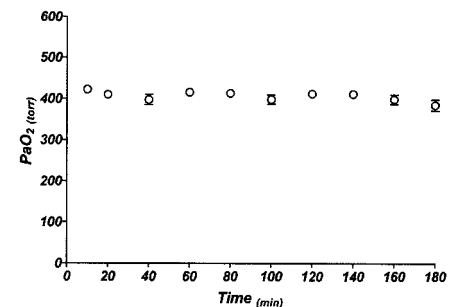


Figure 4. PaO₂ vs. time during the 3-hr period of total liquid ventilation. No significant changes in PaO₂ were observed. Sweep gas flow was 100% oxygen at 5 L·min⁻¹. Data are expressed as mean \pm SEM.

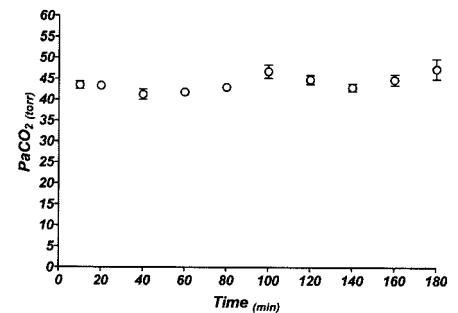


Figure 5. PaCO₂ vs. time during the 3-hr period of total liquid ventilation; No deviations from the physiologic range were observed. Sweep gas flow was 100% oxygen at 5 L·min⁻¹. Data are expressed as mean \pm SEM.

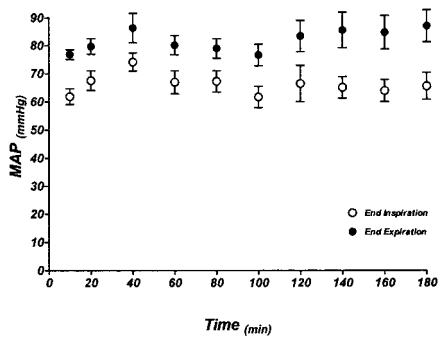


Figure 6. Mean arterial pressure (*MAP*) vs. time during the 3-hr period of total liquid ventilation. A sinusoidal pattern of mean arterial pressure related to the ventilator phase was observed during total liquid ventilation: Solid circles represent values at the end of the expiratory phase and open circles values at the end of inspiratory phase. Data are expressed as mean \pm SEM.

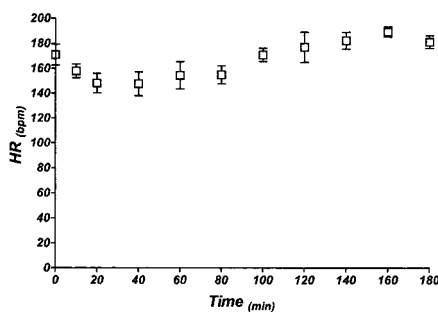


Figure 7. Heart rate (*HR*) during the 3-hr period of total liquid ventilation.

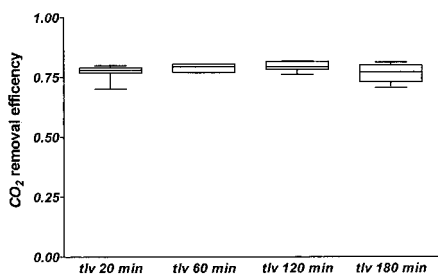


Figure 8. Box plots of the CO_2 efficiency removal during total liquid ventilation (*tlv*). Data are presented as median, maximum, minimum, and 25th and 75th percentiles at time 20, 60, 120, and 180 mins.

spiratory CO_2 was 4.8 ± 0.5 torr (0.64 kPa). Figure 9 demonstrates the loss rate of PFC from the liquid ventilating system over time. The slope of the best fit model line for that data was 1.2 ± 0.02 , which suggested a PFC loss rate of $1.2 \text{ mL}\cdot\text{min}^{-1}$. No leak of PFC across the fibers into the gas phase was noted.

No lung injury or evidence of fluorothorax was observed at gross necropsy at

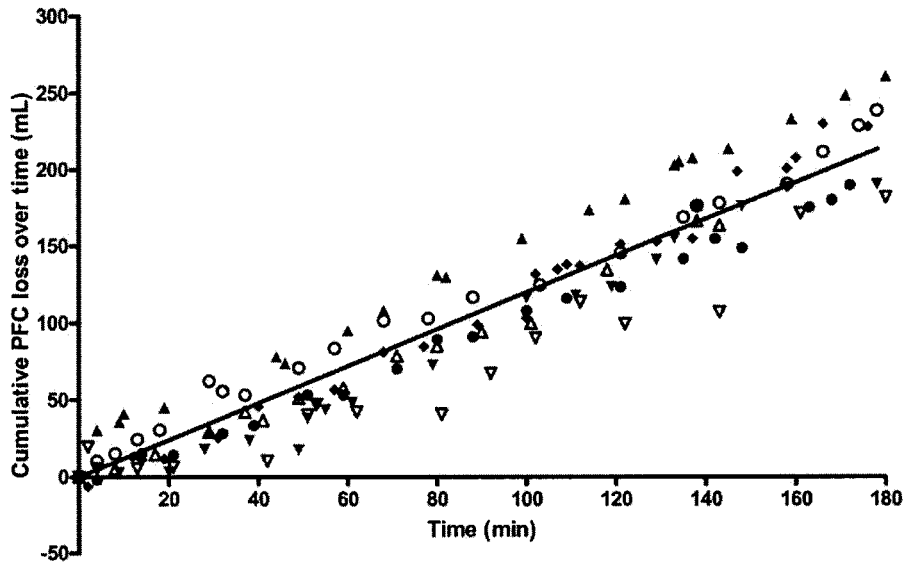


Figure 9. Perfluorocarbon (PFC) evaporative loss vs. time in the animal experiments. This loss was calculated by conservation of mass, accounting for fluids and PFC infusion. Each symbol corresponds to an individual animal. The line indicates the linear regression, and its slope indicates the average PFC loss rate, $1.2 \text{ mL}\cdot\text{min}^{-1}$.

the end of the TLV period. No hemorrhagic areas or evidence of atelectasis or air trapping was observed on surface assessment of the lung.

DISCUSSION

The results of this study demonstrate the following: a) TLV with a single-piston pump can be successfully used to support gas exchange over a 3-hr period in a normal rabbit model; b) a hollow-fiber gas exchange device in combination with a heat exchanger provides adequate oxygenation, carbon dioxide removal, and maintenance of body temperature; and c) silicone hollow fibers may be used with PFCs without evidence of leak into the gas phase of the gas exchange device.

Although we have previously demonstrated that a double-piston pump system significantly improves the control of liquid ventilation, this approach requires a high priming volume (11). The availability of nonporous silicone hollow fibers has allowed us to decrease the system priming volume to 450 mL. We hope that such a device will make the transition of TLV to the clinical setting feasible and affordable. Although direct performance comparisons with bubble gas exchangers have not been performed, the CO_2 removal efficiency in the current device under study was similar to that described by Meinhardt et al. (11) for the bubble gas exchange device used in similar-sized animals. Moreover, the ability of the sili-

cone hollow fiber to oxygenate the PFC is comparable in these two studies (hollow fibers = 707 ± 9 torr [94.3 kPa]; bubble gas exchanger = 668 ± 28 torr [89.1 kPa]). However, it should be noted that the ventilation/perfusion ratio of the gas exchange device was approximately 17, which is elevated and indicates the need for a relatively high sweep flow rate. Unlike with blood oxygenators in which CO_2 levels of approximately 40 mm Hg at the outlet are acceptable, higher oxygen sweep flow rates and ventilation/perfusion ratios are required to achieve the CO_2 levels <10 mm Hg required to optimally perform liquid ventilation.

The lack of liquid PFC leak through the silicone hollow fibers is remarkable given the low surface tension of FC77 ($15 \text{ dynes}\cdot\text{cm}^{-1}$ at 25°C) and suggests great potential for these fibers in the application of total liquid ventilation. However, with the ventilator settings used in these experiments, an estimated loss rate of $1.2 \text{ mL}\cdot\text{min}^{-1}$ was observed, which is equivalent to $0.38 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in these rabbits of weight 3.2 ± 0.2 kg. This is a substantial amount over time. During our bench-top tests, we estimated that the loss of PFC was approximately $0.6 \text{ mL}\cdot\text{min}^{-1}$, which was lower than the estimated loss rate *in vivo* at similar oxygen sweep flow rates. One reason for the observed difference between the two was the fact that the bench-top studies were performed at room temperature, whereas

These data demonstrate the ability of this novel single-piston, nonporous hollow silicone fiber oxygenator to adequately support gas exchange, allowing successful performance of total liquid ventilation.

the *in vivo* tests were at body temperature. The loss rate of PFC usually depends on the size of the animal, the total surface area of the fibers, the gas flow, the physical properties of the PFC, and the liquid minute ventilation. As such, for an adult with a larger tidal volume and PFC minute volume and an increased fiber surface area, the PFC loss will be much greater. Means for efficiently recovering PFC, therefore, are critical to successful performance of TLV, although Libros et al. (22) demonstrated that a reclamation system can only provide recovery rates of 60–80%.

The hollow fiber gas exchange devices have low resistance to flow, making them a better choice than the commercial blood-circuit membrane oxygenators previously used as gas exchange devices during liquid ventilation studies (1, 4, 6, 23). The low resistance to the flow in combination with the simple design and the ability to precisely control tidal volume and flow provides a ventilator that allows maintenance of the dynamic airway pressures in a range in which both ventilator-induced lung injury and flow limitation or choked flow are unlikely (23, 24). In this study, we were able to avoid the high dynamic airway pressures that may result in hemodynamic impairment or acidosis as described by other authors during TLV (25–37). The only hemodynamic abnormality observed in the current study was a sinusoidal pattern of mean arterial pressure related to the ventilator phase (20, 21, 38). The sinusoidal variation of mean arterial pressure that we observed during total liquid ventilation is likely a result of the large tidal volumes ($19 \pm 0.5 \text{ mL}\cdot\text{kg}^{-1}$) used in this study. Such sinusoidal variations may have an effect on

hemodynamics and even result in changes in cerebral blood flow. These sinusoidal changes in systemic pressure have been recognized previously, but the relationship to the safety of total liquid ventilation needs to be explored further.

Although this study demonstrated the potential of the silicone hollow fibers for use as gas exchange devices in performing liquid ventilation, this TLV device requires further development from several aspects before clinical application. First, pressure-limiting functions (either pop-off valves or electromechanical servo regulation) need to be added to prevent application of excessive positive and negative airway pressures. Second, easier means for monitoring PFC inventory in the lung (i.e., liquid FRC) and device during TLV are required. Finally, we need to enhance our understanding of various aspects of the mechanics of liquid ventilation, such as the optimal waveforms and flow patterns, which should be used during TLV, especially during drainage of PFC from the lungs.

Although this liquid ventilator appears to be effective, we have not examined its use in the setting of lung injury, nor have we assessed histology or histomorphometry of the lung following TLV with this device. In addition, essential experiments investigating the efficacy and benefits of total liquid ventilation with this device compared with partial liquid ventilation and conventional gas ventilation have yet to be performed. Finally, the superiority of total liquid ventilation compared with gas ventilation, in terms of patient and financial outcomes, yet awaits clinical evaluation. However, this study demonstrates the ability of this novel single-piston, nonporous hollow silicone fiber oxygenator to adequately support gas exchange allowing successful performance of TLV, thus opening this technique to further study.

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