Journal of Pediatric Surgery

VOL 28, NO 4 APRIL 1993

Oxygen Consumption and Carbon Dioxide Production During Liquid Ventilation

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● **Liquid ventilation with perfluorocarbon (PFCV) has advantages over conventional gas ventilation (GV) in premature and lung-injured newborn animals. Indirect calorimetric measurement of both oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) during PFCV has not been previously performed. In addition, comparison to indirect calorimetric measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ during GV has not been evaluated. Ten fasted normal cats weighing 2.6 to 3.9 kg were anesthetized with pentobarbital and pancuronium. Tracheostomy was performed. Gas exchange was measured across the native lung during GV and across the membrane lung of the liquid ventilator during PFCV. $\dot{V}O_2$ was measured using a modification of a previously described, indirect, closed-circuit, volumetric technique. $\dot{V}CO_2$ was analyzed by capnographic assay of the mixed-expired closed-circuit air. The $\dot{V}CO_2/\dot{V}O_2$ ratio (RQ) was calculated. There was no change in $\dot{V}O_2$, $\dot{V}CO_2$, or RQ during PFCV when compared with GV ($\dot{V}O_2$: GV = 5.7 ± 0.3 mL/kg/min, PFCV = 5.6 ± 0.5 mL/kg/min [P = NS]; $\dot{V}CO_2$: GV = 4.9 ± 1.1 mL/kg/min, PFCV = 4.8 ± 0.9 mL/kg/min [P = NS]; RQ: GV = 0.85 ± 0.21, PFCV = 0.86 ± 0.21 [P = NS]). During GV the PaO_2 was higher than during PFCV (PaO_2: GV = 335 ± 70 mm Hg, PFCV = 267 ± 83 mm Hg [P = .04]), as is expected because of the relative reduction in the inspiratory PiO_2 of the perfluorocarbon during liquid ventilation. There was no significant change in the $PaCO_2$ ($PaCO_2$: GV = 37.3 ± 2.2 mm Hg, PFCV = 40.4 ± 5.3 mm Hg [P = NS] or the pH (pH: GV = 7.34 ± 0.04, PFCV = 7.35 ± 0.06 [P = NS]). This study demonstrates the efficacy of measuring $\dot{V}O_2$ and $\dot{V}CO_2$ during gas and liquid ventilation using an indirect calorimetric technique. The data demonstrate that $\dot{V}O_2$ and $\dot{V}CO_2$ do not change during liquid ventilation and that excellent gas exchange can be accomplished through PFCV.**

INDEX WORDS: Liquid ventilation.

PULMONARY gas exchange utilizing perfluorocarbon liquid ventilation (PFCV) has been investigated over the past 25 years.[1-4] Efficacy of gas exchange in normal animals has been established.[5] In addition, numerous studies in newborn premature animals have demonstrated efficacy in providing reduction of surface tension at the air-liquid interface in the PFC-filled lung with associated improvement in compliance, improvement in ventilation/perfusion matching, and reduction in ventilator airway pressure requirements.[6-9]

Although the goal of PFCV is to provide gas exchange, few studies have actually measured $\dot{V}O_2$ and $\dot{V}CO_2$ during liquid ventilation.[8,10,11] Those that have evaluated gas exchange during PFCV indicate that there is a reduction in the metabolic rate, the etiology of which remains unclear. In these studies, $\dot{V}O_2$ and/or $\dot{V}CO_2$ during gas and liquid ventilation were compared in different animals, under different conditions, or by methods with potential for significant measurement inaccuracy. The purpose of this study, therefore, is to relate gas exchange in comparison during PFCV and gas ventilation (GV) in the same animals under the same conditions by an indirect, calorimetric technique which allows accurate measurement of $\dot{V}O_2$ and $\dot{V}CO_2$.[12,13]

MATERIALS AND METHODS

Ten healthy cats weighing 2.6 to 3.9 kg were anesthetized with pentobarbital, 25 mg/kg. A midline neck incision was performed and the trachea as well as the right carotid artery and internal jugular vein were isolated. A tracheostomy tube was advanced into the trachea to a point above the carina and anchored in place. A jet ventilation endotracheal tube (Mallinckrodt, Inc, Argyle, NY) was utilized in order to allow measurement of carinal airway pressure. An 18-gauge catheter was placed in the carotid artery and a 4F

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Presented at the 23rd Annual Meeting of the American Pediatric Surgical Association, Colorado Springs, Colorado, May 13-16, 1992.

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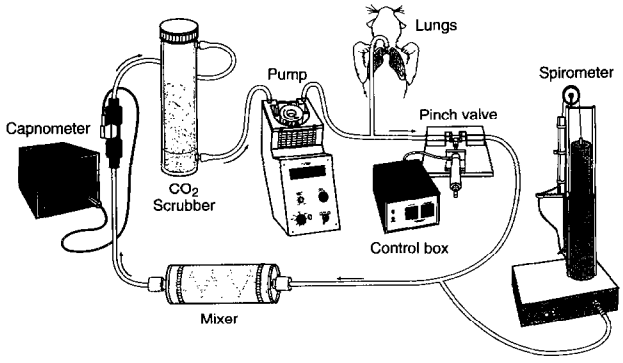

Fig 1. A flow-limited, time-cycled device that provides ventilation while simultaneously measuring $\dot{V}O_2$ and $\dot{V}CO_2$ during GV. The control box allows variation in the frequency and duration of pinch valve closure. This, along with variation in the gas flow rate, establishes the respiratory rate and TV.

venous Oximetrix catheter (Oximetrix, Inc, Mountain View, CA) was advanced into the right atrium via the right internal jugular vein and anchored in place. Mechanical ventilation was instituted and pancuronium bromide, 0.1 mg/kg, was administered intravenously at this point and hourly thereafter. Subsequent anesthesia was administered in the form of pentobarbital (10 mg/kg/h) intravenous infusion in 5% dextrose/Ringer's lactate solution at a maintenance rate of 4 mL/kg/h.

Measurement of $\dot{V}O_2$ and $\dot{V}CO_2$

A previously described device was adapted as a flow-limited, time cycled ventilator which allowed measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ during gas ventilation (Fig 1).[13] This device consists of a Cobe occlusive roller pump (Cobe Cardiovascular, Inc, Arvada, CO), which induces continuous gas flow at a prescribed rate through a closed circuit. The roller pump, the endotracheal tube, and a pinch valve are connected in series. A controller box allows alteration in inspiratory (IT) and expiratory time (ET) through variation of the duration of pinch valve closure. Tidal volume (TV), therefore, is dependent on gas flow rate (GFR) and inspiratory time. The appropriate gas flow rate for each desired number of breaths per minute, inspiratory and expiratory times, and desired tidal volume may be calculated using the equation:

$$GFR = BPM * (IT + ET)/IT * \text{Desired TV}$$

Additional components in the closed circuit included a mixing chamber and an HP-47210A (Hewlett-Packard, Inc, Waltham, MA) or a Novametrix 1260 (Novametrix Medical Systems, Inc, Wallingford, CT) capnometer. CO_2 in the circuit was measured via the capnometer and then deleted via a CO_2 scrubber.

Measured CO_2 beyond the CO_2 scrubber was documented to be less than 0.4 mm Hg during each experiment. The coefficient of variation for $\dot{V}CO_2$ measurement utilizing this device was documented to be 0.7 ± 0.1.[14] The pump flow rate was calibrated and the pressurized closed-circuit tested for leaks at the beginning of each study. The barometric pressure was ascertained daily. Stability of the $PaCO_2$ at ±5 mm Hg between individual $\dot{V}CO_2$ measurements was documented. $\dot{V}CO_2$ was calculated based on the following equation:

$$\dot{V}CO_2 \text{ (mL/kg/min)} = \text{Circuit } PCO_2 \text{ (mm Hg)} \times \text{pump flow rate (mL/min)/barometric pressure (mm Hg)/weight of animal (kg)}$$

Oxygen consumption was evaluated by measurement of volume loss from a spirometer in the closed circuit. Since carbon dioxide is deleted from the circuit by the CO_2 scrubber, volume loss in the leak-free circuit is only secondary to oxygen consumption. A linear-variable differential transformer (LVDT) was adapted to a 1-L spirometer (Collins, Inc, Braintree, MA), which was used to continuously measure oxygen consumption during each period of the study. Calibration of the LVDT was performed utilizing a secondary spirometer, which demonstrated a conversion of 5.8 mL of oxygen consumed per milivolt change in the LVDT. The coefficient of variation for $\dot{V}O_2$ measurement utilizing this device was 0.4 ± 0.1.[14]

A correction factor (CF_G) for $\dot{V}O_2$ and $\dot{V}CO_2$ at standard temperature and pressure dry (STPD) was applied to all data obtained during gas ventilation and was derived from the following formula:

$$CF_G = [273°K/(273° + T)] + [(Atm - P_{H_2O})/Atm]$$

where T = the room temperature for $\dot{V}O_2$ measurements and the circuit temperature at the capnometer site for $\dot{V}CO_2$ evaluation, Atm = atmospheric pressure, and PH_2O = water vapor pressure.

$\dot{V}O_2$ and $\dot{V}CO_2$ measurements during liquid ventilation were assessed utilizing a similar apparatus as seen in Fig 2. The pinch valve and endotracheal tube are deleted and replaced by the 4.5 m^2 membrane lung (Avecor, Minneapolis, MN) in the closed circuit. The roller pump provides a continuous sweep flow through the membrane lung as gas exchange occurs between the PFC and the closed circuit across the silicone membrane. $\dot{V}O_2$ and $\dot{V}CO_2$ measurements were evaluated by similar capnometric and closed-circuit, volumetric techniques as described above. However, a correction factor (CF_L), incorporating a factor for the effect of liquid vapor pressure (P_{pfc}) during PFCV upon gas exchange measurements, was applied to $\dot{V}O_2$ and $\dot{V}CO_2$ measurements:

$$CF_L = [273°K/(273° + T)] + (Atm - P_{H_2O} - P_{pfc})/Atm$$

Gas Ventilation

GV was performed utilizing the ventilator depicted in Fig 1. Use of this ventilator allowed assessment of $\dot{V}O_2$ and $\dot{V}CO_2$ during GV. The ventilator settings included IT = 1 second, ET = 2 seconds, TV = 15 mL/kg/breath, rate of 20 breaths/min, and circuit FiO_2 = 1.0.

Liquid Ventilation

A flow-limited, time-cycled perfluorocarbon liquid ventilator was developed and used as seen in Fig 3. This ventilator consists of an adaptation of an extracorporeal life support circuit. The inspiratory and expiratory limbs are "Y'd" at the endotracheal

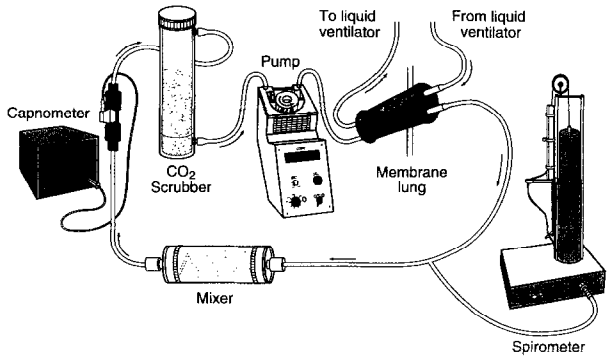

Fig 2. Incorporation of the membrane lung of the liquid ventilator into the closed-circuit calorimeter described in Fig 1 allows continuous measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ during PFCV. The roller pump serves to provide a continuous sweep flow of ventilating gas through the membrane lung.

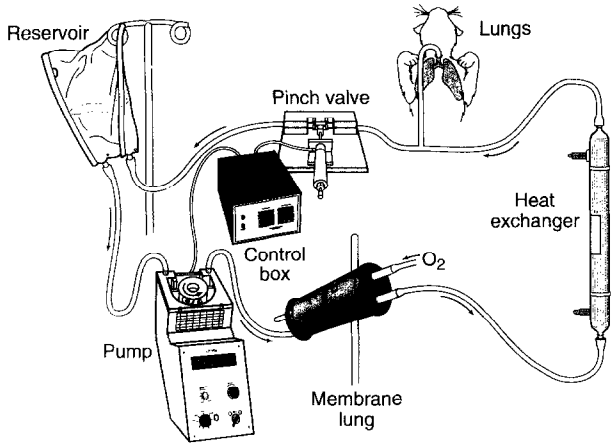

Fig 3. A flow-limited, time-cycled device for liquid ventilation. The control box allows variation in IT and ET. During inspiration, the pinch valve is occluded and the pump functional such that a tidal volume is generated. During expiration, pump function is discontinued which occludes the inspiratory limb. Simultaneously, the pinch valve releases, which allows drainage of PFC into the reservoir.

tube. A pinch valve is present on the expiratory limb followed in series by a reservoir, a roller pump, a membrane lung, and a heat exchanger. A controller box induces pinch valve closure simultaneously with onset of roller pump function during inspiration. This provides occlusion of the expiratory limb during inspiration as perfluorocarbon is perfused through the membrane lung and heat exchanger and a pulmonary tidal volume is produced. During expiration, roller pump activity is discontinued which provides occlusion of the inspiratory limb as the pinch valve opens allowing drainage of perfluorocarbon from the lungs into the reservoir. Initial ventilator settings included an IT of 4 seconds, an ET of 8 seconds, a rate of 5 breaths/min, a TV of 15 to 20 mL/kg/breath, and a membrane lung sweep flow of 2 L/min of oxygen with an FiO_2 = 1.0. The partial pressure of oxygen in the PFC exiting the membrane lung ($PiO_{2(pfc)}$) was 380 ± 102 mm Hg.

Animals were hyperoxygenated and hyperventilated prior to institution of liquid ventilation. Warmed, oxygenated PFC (Rimar-101, density 1.76 g/mL; Miteni SPA, Milano, Italy) 35 mL/kg was then instilled into the endotracheal tube (ETT) and the lungs debubbled. The ETT was then attached to the liquid ventilator and PFCV performed. After liquid ventilation was instituted the membrane lung was incorporated into the device used for measurement of O_2 consumption and CO_2 production as described above (Fig 2). This allowed measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ during liquid ventilation.

Measurement of Gas Exchange

Once stable after performance of tracheostomy and line placement, the animal was placed on the gas ventilator described previously. $\dot{V}O_2$ was then assessed over three consecutive 10-minute periods. Capnometric data were collected at the end of each of the three 10-minute periods. Liquid ventilation was then instituted as described above. Once stable on the liquid ventilator, the membrane lung was incorporated into the gas exchange measurement device. $\dot{V}O_2$ and $\dot{V}CO_2$ data were then collected, as during GV, over three consecutive 10-minute periods.

Pancuronium bromide, 0.1 mg/kg, was administered immediately prior to each series of gas exchange measurements during GV and liquid ventilation in order to provide pharmacological paralysis. Rectal temperature was maintained at 37.5°C ± 0.5°C at all times. The $PaCO_2$ was maintained at ±10 mm Hg from the original $PaCO_2$ at onset of GV. Anesthesia was administered by continuous infusion of pentobarbital, 10 mg/kg, throughout each study.

Arterial blood gas data were assessed utilizing an ABL 30 Blood Gas Analyzer (Radiometer A/S, Copenhagen, Denmark). Blood oxygen saturation data were evaluated using an OSM 3 co-oximeter (Radiometer A/S).

Data Analysis

$\dot{V}O_2$ and $\dot{V}CO_2$ data collected during each of the 10-minute periods were averaged and ±SD determined for GV and PFCV for all animals. Arterial blood gas data collected from all animals after 1 hour of either GV or PFCV were averaged and ±SD determined. The $\dot{V}CO_2/\dot{V}O_2$ ratio (RQ) was calculated, averaged, and ±SD determined for GV and PFCV. The paired Student's *t* test was applied for statistical comparison of data.

Approval for this study was obtained from the committee on university laboratory animal medicine at the University of Michigan Medical Center and all animal care guidelines followed. Animals were euthanized at completion of the study.

RESULTS

As seen in Fig 4, there was no change in $\dot{V}O_2$, $\dot{V}CO_2$, or RQ during PFCV when compared to GV ($\dot{V}O_2$: GV = 5.7 ± 0.3 mL/kg/min, PFCV = 5.6 ± 0.5 mL/kg/min [*P* = NS]; $\dot{V}CO_2$: GV = 4.9 ± 1.1 mL/kg/min, PFCV = 4.8 ± 0.9 mL/kg/min [*P* = NS]; RQ: GV = 0.85 ± 0.21, PFCV = 0.86 ± 0.21 [*P* = NS]).

Arterial blood gas data (Fig 5) after 1 hour of GV or liquid ventilation demonstrated that the PaO_2 was higher during GV than during PFCV (PaO_2: GV = 335 ± 70 mm Hg, PFCV = 267 ± 83 mm Hg [*P* = .04]). This is expected because of the relative reduction in the inspiratory partial pressure of oxygen in PFC [$PiO_{2(pfc)}$] during liquid ventilation. There was no significant change in the $PaCO_2$ ($PaCO_2$: GV = 37.3 ± 2.2 mm Hg, PFCV = 40.4 ± 5.3 mm Hg [*P* = NS]) or the pH (pH: GV = 7.34 ± 0.04, PFCV = 7.35 ± 0.06 [*P* = NS] [Fig 6]).

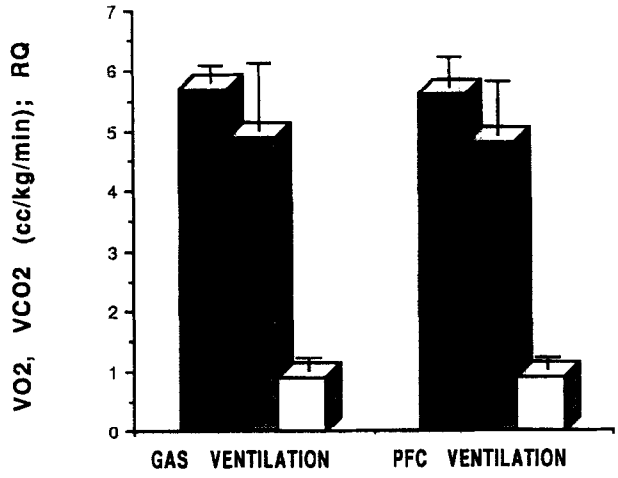

Fig 4. Oxygen consumption ($\dot{V}O_2$ [■]), carbon dioxide production ($\dot{V}CO_2$ [▨]), and the $\dot{V}CO_2/\dot{V}O_2$ ratio (RQ [□]) during GV and PFCV.

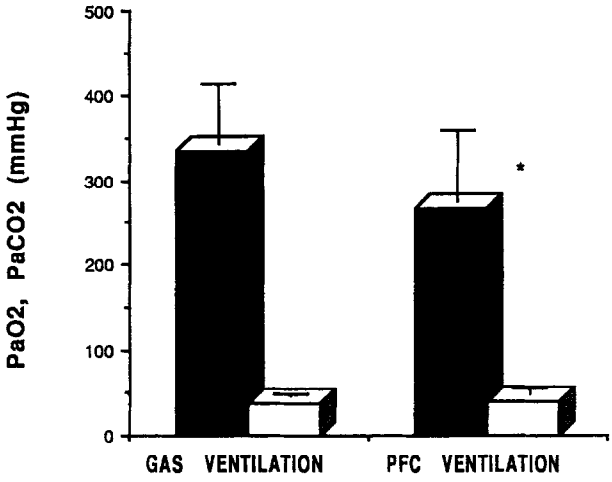

Fig 5. PaO_2 (■) and $PaCO_2$ (□) during GV and PFCV. *P < .05.

There was no significant change in heart rate (HR) or mean systemic blood pressure (MAP) when GV and PFCV were compared (MAP: GV = 102 ± 20 mm Hg, PFCV = 101 ± 14 mm Hg [P = NS]); HR: GV = 129 ± 21 beats/min, PFCV = 147 ± 29 beats/min [P = NS]).

DISCUSSION

This study documents that oxygen consumption and carbon dioxide production remain unchanged during liquid ventilation when related in comparison to that during GV. In addition, provision of adequate gas exchange utilizing PFCV in normal animals is demonstrated.

The concept of liquid ventilation extends back to the early 1920s when the efficacy of saline as a means of altering the physiologic effects of the pulmonary gas-liquid interface was investigated.[5] However, because of the limited solubility of oxygen in saline (approximately 2 mL O_2/dL at PO_2 = 700 mm Hg), adequate oxygenation could not be provided during saline liquid ventilation except under hyperbaric conditions.[15] Interest in the pulmonary applications of perfluorocarbon liquids, which incorporated properties of low surface tension and high oxygen solubility, began in 1966.[1] At that time, the ability of the perfluourocarbon FX-80 to provide adequate gas exchange in the spontaneously breathing mouse and cat was demonstrated. Since then, a variety of perfluorocarbons have been developed and used, with the most recent generation incorporating and enhancing such desirable properties as low surface tension, high gas solubility, low viscosity to decrease airway resistance, and relatively high vapor pressure so that the perfluorocarbon might evaporate from the airways after conversion from liquid to gas ventilation.[16] Subsequent studies have demonstrated improved survival, enhanced gas exchange, and increased compliance in premature newborn animals, full-term lambs with meconium aspiration, and in animals with experimentally induced lung injury.[5,17,18] In addition, the first human trials of liquid ventilation in three neonates have demonstrated feasibility of gas exchange utilizing liquid ventilation.[19]

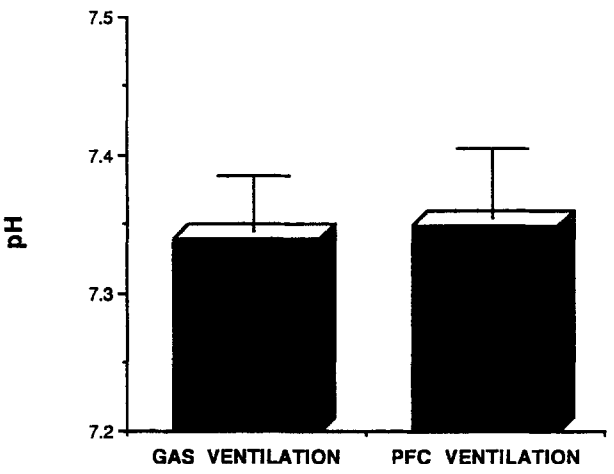

Fig 6. pH during GV and PFCV.

Although the efficacy of gas exchange during liquid ventilation has been assessed in numerous studies, measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ has rarely been evaluated. Among the studies that have investigated gas exchange during perfluorocarbon ventilation include those by Sivieri et al[10] in 1981 and Harris et al[11] in 1983. In the former, $\dot{V}O_2$ in spontaneously gas-breathing animals was compared to that during liquid ventilation as measured by a spirometric, volume-loss technique similar to the method utilized in this study. $\dot{V}O_2$ was found to decrease 18.6% after initiation of liquid ventilation. In the second study, Harris et al evaluated $\dot{V}O_2$ and $\dot{V}CO_2$ in animals undergoing liquid ventilation by measuring the oxygen tension in inspired (P_IO_2) and expired (P_EO_2) PFC and the carbon dioxide tension in inspired (P_ICO_2) and expired (P_ECO_2) PFC and calculating gas exchange based on the following equations:

$$\dot{V}O_2 = \dot{V}_E (P_IO_2 - (P_EO_2) * \alpha O_2$$

$$\dot{V}CO_2 = \dot{V}_E (P_ECO_2 - P_ICO_2) * \alpha CO_2$$

where αO_2 and αCO_2 are the solubility coefficients for oxygen and carbon dioxide, respectively, in PFC and $\dot{V}_E$ is the minute volume ventilation with PFC. The derived values of $\dot{V}O_2$ and $\dot{V}CO_2$ were then compared to values obtained in similar fashion from another group of animals during GV. $\dot{V}O_2$ and $\dot{V}CO_2$ were reduced in this study after application of liquid ventilation by 42% and 35%, respectively. Therefore, in both of these studies, gas exchange appeared to be reduced during liquid ventilation, although the under-

lying physiology accounting for this finding remained unclear.

In the current study, gas exchange during liquid ventilation remained unchanged in comparison to that noted during GV. We believe that our study differs from those of others for the following reasons:

1. $\dot{V}O_2$ and $\dot{V}CO_2$ were evaluated by methods which allowed accurate measurement of gas exchange. In the study by Harris et al, evaluation of gas exchange was based on measurements of oxygen and carbon dioxide tensions in inspired and expired perfluorocarbon in order to calculate $\dot{V}O_2$ and $\dot{V}CO_2$. The authors, in discussing their results, note that the calculations for $\dot{V}O_2$ and $\dot{V}CO_2$ are dependent on solubility coefficients for these gases in PFC and that a variety of differing solubility coefficients have been determined, which may induce up to a 20% to 30% variation depending on the coefficient used. In contrast, the present study used an indirect, closed-circuit calorimetric technique that allowed accurate measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ without need for application of a gas solubility coefficient.
2. In the study by Sivieri et al, animals were spontaneously respiring during gas breathing, but were pharmacologically paralyzed and ventilated during liquid breathing. In normal animals, the resting energy expenditure from breathing is approximately 1% to 5% of overall oxygen consumption and is even greater during periods of hyperventilation.[20] In addition, pharmacological paralysis may result in an 11% reduction in $\dot{V}O_2$.[21] Mechanical ventilation and pharmacological paralysis, therefore, could account for the reduction in oxygen consumption noted in the study by Sivieri et al. In contrast, in the present study, animals were pharmacologically paralyzed and mechanically ventilated when gas exchange measurements were performed during both GV and PFCV.

The accuracy of the closed-circuit, indirect calorimetric technique for evaluating $\dot{V}O_2$ and $\dot{V}CO_2$ has been previously documented.[12,13] The efficacy of a modification of this technique for the measurement of gas exchange during liquid ventilation has been demonstrated in this study. A number of factors, however, may affect the metabolic rate or the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$. For instance:

1. Gas exchange could potentially have been altered because of variation in the $PaCO_2$ and pH. The metabolic rate has been shown to increase with a rising pH and diminishing $PaCO_2$. This change in $\dot{V}O_2$ has been demonstrated to increase approximately 7% for each 10 mm Hg decrease in $PaCO_2$.[22] $PaCO_2$ values during this study were, therefore, maintained at ± 10 mm Hg from the initial $PaCO_2$.
2. The metabolic rate may be altered with temperature, level of sedation, and paralysis. Therefore, all of these were carefully controlled throughout this study.
3. Stability of the $\dot{V}CO_2$ and $PaCO_2$ are required for accurate assessment of $\dot{V}CO_2$. However, $\dot{V}CO_2$, as measured by the method used in this study, would not have been affected by the absolute $PaCO_2$ value as long as that value was relatively stable. A stable $PaCO_2$ (± 5 mm Hg between gas exchange measurements) was ensured during all measurements of $\dot{V}CO_2$. Therefore, any differences in $PaCO_2$ seen between gas and liquid ventilation would not have affected the measured $\dot{V}CO_2$.

Excellent gas exchange capabilities were documented during perfluorocarbon ventilation. The slight, but significant, reduction in the PaO_2 during PFCV when compared to GV is expected because of the relative reduction in inspiratory partial pressure of oxygen in PFC ($PiO_{2(pfc)}$) during liquid ventilation ($PiO_{2(pfc)} = 380 \pm 102$ mm Hg) in comparison to the PiO_2 of the closed circuit during GV ($FiO_2 = 1.0$, PiO_2 = approximately 700 mm Hg). If adequate time is allowed, the partial pressure of oxygen in PFC will equilibrate with the partial pressure of oxygen in the gas to which the PFC is exposed. Therefore, this reduction in $PiO_{2(pfc)}$ and PaO_2 is a reflection of minor limitations in the liquid ventilator device utilized, rather than being inherent to the liquid ventilation technique itself.

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Discussion

F.J. Rescorla (Indianapolis, IN): Liquid ventilation with the use of perfluorcarbons has been studied for the past 25 years. Recent advances in the development of these compounds takes advantage of the low surface tension, high gas solubility, and low viscosity allowing delivery of oxygen and elimination of CO_2 in a low-pressure system. Animal models using liquid ventilation to treat meconium aspiration and other experimental lung injuries have noted increased compliance, enhanced gas exchange, and improved survival. Liquid ventilation has also been shown to extend the limits of viability of immature lambs presumably by eliminating the dependency on surfactant. The recent initial human studies have demonstrated the feasibility of the model in premature babies. However, the very viable nature of the initial subjects that being a pH of 6.77 to 7.22 and short term survival and 19 hours at the maximum prevents determination of therapeutic benefits. Dr Hirschl and his colleagues have made a significant contribution to the field of liquid ventilation. They have demonstrated the efficacy of measuring oxygen consumption and carbon dioxide production during liquid ventilation using an indirect calorometic technique. They have shown that oxygen consumption and CO_2 production do not change during liquid ventilation and that excellent gas exchange can be accomplished due to fluorocarbon ventilation. My questions are as follows. In your model, the inspiratory partial pressure of oxygen in PFCV was 380 ± 102 mm Hg compared to approximately 700 mm Hg in the GV system. I understand from the manuscript that this is limited by your present system. Therefore, do you have plans to change your system to allow a higher partial pressure of oxygen in perfluorocarbon? Second, what do you foresee as the clinical application of this therapy? Will it be limited initially to prematures as in the initial clinical trial? Will it increase the viability of the fetus to a lower gestational age? Could this modality be used in the older infants and children with acute insults such as inhalation injuries and severe respiratory distress of other causes? And, finally, how can you avoid the situation experienced by other new therapies in which only the sickest and probably unsalvageable children are offered the new therapy. This appears to be the situation in the initial clinical trial. What do you foresee as the future for this modality?

W.J. Chwals (Winston-Salem, NC): Hirschl, in as much as the difference between ventilation conventionally and PFCV may be due to a difference in muscle tone in terms of energy expenditure, is the fact that your model involved paralysis not likely to reduce any differences which may be seen in conventional ventilation versus the PFCV model? In previous studies, the ventilatory mode when conventional ventilation was used is seldom complemented by paralysis.

R.B. Hirschl (response): Yes, the PiO_2, the inspiratory partial pressure of oxygen, was decreased with the liquid ventilator. We have already made changes in this system. These include allowing continuous flow of perfluorocarbon through the membrane lung which will alter the PiO_2 of the perfluorocarbon and which should improve the arterial oxygenation. With regard to possible clinical applications, I think that there is potential for wide-spread use not just in premature newborns, but in other neonates, children, and adults. The key benefit of PFCV is the elimination of the alveolar air-fluid interface with a reduction in alveolar surface tension. That's true especially with surfactant deficiency which is often present in the setting of respiratory failure. In addition, in situations where the alveoli are filled with fluid, perfluorocarbons may replace that fluid, allowing gas exchange to take place. These advantages of PFCV in the setting of respiratory failure will likely make this new modality applicable to all age groups. With regard to fetal application, there is a lot of speculation. It goes all the way to the point where you could imagine a premature baby submerged in the perfluorocarbon with gas exchange, in some fashion, being accomplished via the perfluorocarbon. However, there is a point where the lung is not adequately developed and ventilation with perfluorocarbons would not be applicable below that level. PFCV is at a point where evaluation in nonmoribund newborns is required. Our plan is to try to implement and explore this new modality on ECMO because it provides a safe setting for doing so. In addition, we are performing studies right now to evaluate whether PFCV will actually improve gas exchange and pulmonary function in newborns on ECMO. The pulmonary opacification that we observe after onset of bypass may be due to atelectasis and may actually be improved by PFCV. In addition, lavage with perfluorocarbons may allow removal of meconium from the lungs in the setting of the meconium aspiration syndrome. This has been shown to be true in animal models, with associated improvement in pulmonary function. With regard to the use of paralysis in this study, a previous study was done in which spontaneously breathing animals were compared to mechanically liquid ventilated animals. As would be expected, an increase in oxygen consumption in the spontaneously breathing animals was noted. We chose, therefore, to investigate whether there was a primary increase in baseline oxygen consumption and carbon dioxide production from the modality itself. I think that the best way to do that was to maintain control of all factors of oxygen consumption, which included the use of paralysis for both groups.