

Development of a Time-Cycled Volume-Controlled Pressure-Limited Respirator and Lung Mechanics System for Total Liquid Ventilation

Juan Luis Larrabe*, Francisco J. Alvarez, Elena Gastiasoro Cuesta, Adolf Valls-i-Soler, Luisa F. Alfonso, Arantzazu Arnaiz, M. Begoña Fernández, Begoña Loureiro, Nelson G. Publicover, Lourdes Roman, Jose A. Casla, and Miguel A. Gómez

Abstract—Total liquid ventilation can support gas exchange in animal models of lung injury. Clinical application awaits further technical improvements and performance verification. Our aim was to develop a liquid ventilator, able to deliver accurate tidal volumes, and a computerized system for measuring lung mechanics. The computer-assisted, piston-driven respirator controlled ventilatory parameters that were displayed and modified on a real-time basis. Pressure and temperature transducers along with a lineal displacement controller provided the necessary signals to calculate lung mechanics. Ten newborn lambs (<6 days old) with respiratory failure induced by lung lavage, were monitored using the system. Electromechanical, hydraulic, and data acquisition/analysis components of the ventilator were developed and tested in animals with respiratory failure. All pulmonary signals were collected synchronized in time, displayed in real-time, and archived on digital media. The total mean error (due to transducers, analog-to-digital conversion, amplifiers, etc.) was less than 5% compared with calibrated signals. Components (tubing, pistons, etc.) in contact with exchange fluids were developed so that they could be readily switched, a feature that will be important in clinical settings. Improvements in gas exchange and lung mechanics were observed during liquid ventilation, without impairment of cardiovascular profiles. The total liquid ventilator maintained accurate control of tidal volumes and the sequencing of inspiration/expiration. The computerized system demonstrated its ability to monitor *in vivo* lung mechanics, providing valuable data for early decision making.

Index Terms—Data acquisition, newborn lamb, perfluorocarbon, pressure-limited, total liquid ventilation, ventilator, volume-controlled.

Manuscript received November 13, 2000; revised June 27, 2001. This work was supported in part by the Basque government under Grant P.I. 1997-26 and in part by the Spanish Ministry of Health under Grant FIS 98/0767 and Grant FIS 98/0905. This work was presented at the 3rd International Symposium on Neonatology: Problems in Respiratory Therapy, Bilbao, Spain, October 1998. Asterisk indicates corresponding author.

*J. L. Larrabe is with the Department of Navigation Sciences, Engineers and Shipbuilders, High Technical School of Maritime Studies, Maria Diaz de Haro, 62, E-48920 Portugalete, Bizkaia, Spain (e-mail: cnplabaj@lg.ehu.es).

F. J. Alvarez, E. Gastiasoro Cuesta, A. Valls-i-Soler, L. F. Alfonso, A. Arnaiz, M. B. Fernández, B. Loureiro, and L. Roman are with the Research Unit on Experimental Pulmonary Physiology and Neonatal Intensive Care Unit, Department of Pediatrics, Hospital of Cruces, Basque Country School of Medicine, E-48920 Portugalete, Bizkaia, Spain.

N. G. Publicover is with the Biomedical Engineering Program, Department of Physiology and Cell Biology, University of Nevada, Reno, NV 89507 USA.

J. A. Casla, and M. A. Gómez are with the Department of Navigation Sciences, Engineers and Shipbuilders, High Technical School of Maritime Studies, E-48920 Portugalete, Bizkaia, Spain.

Publisher Item Identifier S 0018-9294(01)08278-7.

I. INTRODUCTION

LIQUID ventilation is a promising technique that might prove useful in the management of severe human lung diseases. Partial liquid ventilation, a relatively simple technique, has been evaluated in preterm and pediatric clinical trials [1], [2], but currently, a multicenter study of adult respiratory distress syndrome has completed the recruitment patients and the results will be published shortly. Tidal or total liquid ventilation is more complex, but offers significant physiological advantages to enhance gas exchange and lung mechanics. Several total liquid ventilators have been reported, but none has been able to simultaneously deliver accurate preset tidal volumes and control ventilation during real-time monitoring of lung mechanics. Such features are essential in gas respirators to optimize ventilation processes [3], [4]. Moreover, only a limited number of total liquid prototypes have been tested in lung injury studies, or developed with safety and reliability checks that are essential in a clinical setting.

The primary forces that oppose the gaseous inflation of mammalian lungs are: 1) resistance to airflow in the tubular airways, and 2) surface tension in the alveoli. During normal expiration, gas leaves the lungs passively, moved by its elastic recoil to overcome airway resistance. When a liquid with a low surface tension is introduced into the lungs (e.g., perfluorocarbon), surface tension is lowered, but airway resistance is greatly increased due to the dynamic viscosity and density of the liquid [5]. During total liquid ventilation, in order to maintain a low airway resistance, the velocity of the liquid must be kept low using prolonged inspiration and expiration durations, and low cycling frequencies. These approaches tend to decrease the efficiency of gas exchange; however, the low gas diffusion coefficient and high capacity of perfluorocarbon to dissolve respiratory gases, make this ventilatory strategy possible [6].

Studies in immature lambs managed on total liquid ventilation have demonstrated that liquid ventilation can maintain an adequate gas exchange at pressures lower than those used in gas ventilation [7], [8]. Early devices were simply gravity-driven [9]–[11], with control of perfluorocarbon flows implemented either manually [10] or by automatically operated valves [9], [11]. In the former type, control of inspiratory and expiratory times was difficult to achieve, particularly if volumes had to be measured by graduated vessels. Automatic valves usually achieved

higher precision over inspiratory and expiratory times and frequencies, but the problem of controlling tidal volume remained. Volumes have been measured by scales (based on weight) or displacement transducers [9]. These devices are subject to artifacts since movement and forces generated by attached devices (e.g., tubing, wires, monitors, etc.) are difficult to avoid.

In more advanced liquid ventilators, pumps drive fluids and automatic valves regulate ventilation settings. This is particularly advantageous for large animals [12], [13]. In some systems, pumps regulated inlet and outlet perfluorocarbon flows [12] while in others, gravity has been used for expiration [13]. Volumes were obtained by integrating pulsatile flows, but had to be verified by weight. Thus, the problem of regulating tidal volumes remained.

To date, the most accurate volume-controlled ventilators use linear actuator pumps [14]–[17], in which volume is *controlled* by integrating the displacement of the actuator (taking into account piston cross section). However, gravity drain during expiration does not insure an accurate assessment of expiratory volumes and thus, of volumes remaining in lungs [15]. Moreover, these systems do not evaluate lung mechanics or other parameters that are useful to monitor and optimize ventilation. In addition, the respiratory medium (perfluorocarbon) has not been isolated from mechanical components (solenoid valves, bellows, reservoirs, etc.). In a *clinical* setting, replacement of hydraulic components from patient to patient would not be feasible.

In this study, our aims were to: 1) develop a electromechanical liquid ventilator prototype with easily removable hydraulic components, to accurately deliver preset tidal volumes of perfluorocarbon; 2) develop a computerized system to measure lung mechanics able to acquire, calculate and continuously display measurements to provide operator feedback to better control ventilation; and 3) test the usefulness of the ventilator and lung mechanics-measuring system in small animals with acute lung *injury*. We show that lung mechanics can be accurately monitored using total liquid ventilation in real-time under physiological and acute injury conditions.

II. MATERIALS AND METHODS

A. Ventilator System

The ventilator is a time-cycled, volume-controlled, pressure-limited system with multiple rigid cylinder-piston devices on a sliding platform moved by a linear actuator with an electric synchronous motor (Fig. 1). The motor (OSY71STH, Sew Eurodrive, Bilbao, Spain) was controlled by applying a “resolver” with 4096 steps/revolution. It was possible to select the type of movement (e.g., linear ramps, square waves, and sinusoidal oscillations) as well as speed (and acceleration) by adjusting the step rate to the motor.

To push and pull pistons, the rotary movement of the motor was transformed into linear displacement of the platform using a lead screw and recirculating ball nut. Ball adjustments could be made to avoid backlash and the effects of wear between pistons and the motor. Pistons with known cross-sections were attached to the sliding platform, so that displacement could be precisely determined by the angular position of the motor. With the motor

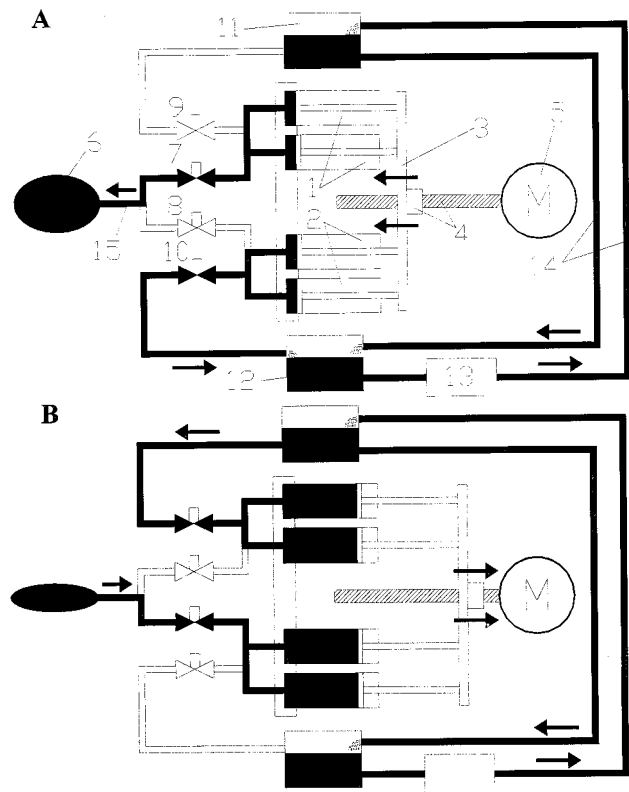


Fig. 1. Ventilator scheme. Components of the ventilator include: (1) inspiratory piston-cylinder, (2) expiratory piston-cylinder, (3) piston push-pull platform, (4) lead screw and recirculating ball nut, (5) synchronous electric motor, (6) lung, (7) inspiratory valve, (8) expiratory valve, (9) valve from inspiratory reservoir, (10) valve to expiratory reservoir, (11) inspiratory reservoir, (12) expiratory reservoir, (13) warmer and oxygenator feedback circuit, (14) tubes, and (15) endotracheal tube. In (A) Inspiration sequence, valves (7) and (10) are open while (8) and (9) are closed. Both piston-cylinders empty their contents, resulting in an expanded lung volume. (B) Expiration sequence, valves (8) and (9) are open, while (7) and (10) are closed. Both piston-cylinders expand their volume while lung volume becomes smaller.

step resolution described above and a screw pitch of 5 mm, the precision in piston movement was $1.2 \mu\text{m}$ (i.e., per step). The speed of piston displacement was directly proportional to the flow of perfluorocarbon in the hydraulic circuit. Linear actuator movement was managed by a ventilator controller (Movidyn, SEW Eurodrive, Bilbao, Spain). This device regulated the speed and angular position of the motor as well as the synchronization of valves.

During inspiration, pinch valves (Z110A, Sirai, Milan, Italy) were used to drive flows from the inspiratory reservoir to the lungs. During the expiratory cycle, perfluorocarbon flows were driven from the lungs to the expiratory reservoir. Reservoirs, valves and tubing were all placed at the same level to avoid the introduction of parasitic hydrostatic forces (other than those produced by the linear actuator).

Perfluorocarbon was recirculated in a feedback circuit from an auxiliary reservoir through a heat exchanger (ECMO-Therm, Avecor, Plymouth, MN) and a membrane oxygenator (0800A, Avecor, Plymouth, MN) by means of a roller pump (10-150, Stockert, Munchen, Germany). In order to maintain temperature and oxygenation of the perfluorocarbon liquid, a temperature proportional-integral-derivative controller (Precisterm, JP Selecta, Barcelona, Spain) and a source of oxygen were attached

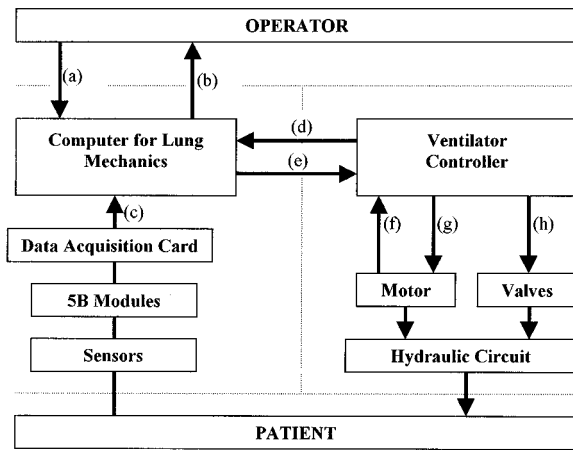


Fig. 2. Signal flows between the ventilator, lung mechanics system, patient, and operator. Signals between components include: (a) patient weight (kg), diameter of cylinders (mm), total volume of cylinders (ml), I:E ratio, tidal volume ($\text{mL}\cdot\text{kg}^{-1}$), ventilatory frequency ($\text{breath}\cdot\text{min}^{-1}$), standardized functional residual capacity ($\text{mL}\cdot\text{kg}^{-1}$), and data sampling ($\text{data}\cdot\text{s}^{-1}$). (b) Circuit pressure (cmH_2O), instantaneous lung volume (mL), tracheal pressure (cmH_2O), chart with tracheal pressure versus lung volume, chart with circuit pressure versus lung volume, instantaneous perfluorocarbon flow ($\text{L}\cdot\text{min}^{-1}$), perfluorocarbon temperature ($^\circ\text{C}$), and patient body temperature ($^\circ\text{C}$). (c) Electrical signals (V) proportional to endotracheal pressure, alveolar pressure, and perfluorocarbon temperature. (d) Instantaneous motor angular position (number of steps). (e) Motor speed during inspiration and expiration processes (rpm), angular position (steps), functional residual capacity, and tidal volume. (f) Motor angular position (steps). (g) Electric current (A) in the motor. (h) Digital signals to drive valves.

to these devices. With an eye toward applications in clinical settings, the ventilator was designed to facilitate the exchange and disposal of those elements containing the perfluorocarbon in contact with the patient (i.e., piston cylinders, tubing, fittings, etc.). The ventilator contains multiple and equal numbers of cylinder-pistons in each inspiratory and expiratory branch. Standard plastic cylinder-pistons of different volumes were used.

Operator control of ventilatory processes was performed via a graphic interface. Settings that were selected at the start of liquid ventilation included: patient body weight (bw; kg), inspiratory–expiratory ratio (I:E), ventilatory frequency (f; $\text{cycles}\cdot\text{min}^{-1}$), standardized tidal volume (V_T ; $\text{mL}\cdot\text{kg}^{-1}$), standardized functional residual capacity (FRC; $\text{mL}\cdot\text{kg}^{-1}$). In order to control delivered volumes from different cylinder-pistons, volume (mL), and diameter (mm) must be also set. All settings could subsequently be adjusted as needed.

B. Lung Mechanics System

Fig. 2 summarizes the major components and signal flows between the total liquid ventilator controller, computer for lung mechanics, patient, and operator. Signals from the patient and perfluorocarbon circuit were acquired via pressure transducers (Transpac IV, Abbot Lab., Sligo, Ireland) and temperature sensors (Pt100, Maikontrol, Barakaldo, Spain), and acquired by full bridge strain gauge and resistance temperature detector input modules (5B38 and 5B34, Analog Devices, Norwood, MA, respectively). These devices conditioned and amplified analog input signals to a standard voltage range (0–5 V). All voltages were then converted by a data acquisition card (MIO6040E, National Instruments, Austin, TX) to 12-bit digital

signals. These were subsequently buffered on a first-in/first-out (FIFO) basis in order to reduce timing constraints during data acquisition by the computer.

The angular position of the synchronous motor was sent from the ventilator controller ($10\text{ samples}\cdot\text{s}^{-1}$) to the computer for lung mechanics. This computer was interfaced using a peripheral component interconnect with an extension for instrumentation (PXI-8156, National Instruments, Austin, TX; Fig. 2). A program (Labview Ver. 5.1, Austin, TX) developed by the authors was used to transform the raw input data stream into a real-time displays of classic signals used to assess pulmonary function (volume, airway pressure, I:E flows, I:E temperature of respiratory fluid and time). All results were displayed graphically and archived on a hard drive in a format that is compatible with standard spreadsheet programs.

In order to reduce electrical noise, shielded cables and grounded junction boxes isolated all signals. According to the Nyquist sampling theorem [18], the system must be able to sample at least twice the rate of the maximum frequency component in the signal to prevent aliasing. Since the fundamental frequency of signals was 0.167 Hz ($10\text{ cycle}\cdot\text{min}^{-1}$) and waveforms were devoid of sharp (i.e., high frequency) transitions, the acquisition frequency for all signals was selected as 10 Hz . Signals were over-sampled at 1 kHz , and a median filter averaged groups of 100 data points in order to achieve this rate.

Pulmonary mechanics measurements were calculated on a breath-by-breath basis. Breath-by-breath data were used to calculate derived pulmonary parameters including: minute ventilation (\dot{V}_E), mean airway pressure ($\overline{P_{AW}}$), quasi-static peak inspiratory pressure (PIP), quasi-static positive end expiratory pressure (PEEP), mean airway resistance (R_{AW}), dynamic lung compliance (C_{dyn}), and work of breathing (W_R). Since the sampling rates of all signals were constant, each respiratory cycle had a number of samples (n) that was related to respiratory frequency (>100 points in all cases).

Mean airway pressure ($\overline{P_{AW}}$), expressed in cmH_2O , was calculated as the mean value of airway pressure during one breath

$$\overline{P_{AW}} = \frac{1}{n} \sum_{i=1}^n P_{aw_i} \quad (1)$$

Standardized tidal volume, expressed in $\text{mL}\cdot\text{kg}^{-1}$, was the normalized volume of one breath.

Quasi-static PIP and quasi-static positive end-expiratory pressure (PEEP), expressed in cmH_2O , were calculated as the mean pressure at the end of the inspiratory and expiratory cycles by a proximal airway occlusion for 500 ms. These were determined when sample-to-sample increments of instantaneous lung volume were less than 0.01 mL (i.e., perfluorocarbon flow was close to zero and airway pressure was considered equal to alveolar pressure). If n' and n'' are the number of pressure samples during inspiration and expiration, respectively, then PIP and PEEP can be computed as

$$\text{PIP} = \frac{1}{n'} \sum_{i=1}^{n'} P_{aw_i} \quad (2)$$

$$\text{PEEP} = \frac{1}{n''} \sum_{i=1}^{n''} P_{aw_i} \quad (3)$$

Standardized dynamic lung compliance (C_{dyn}), expressed in $\text{mL}\cdot\text{cmH}_2\text{O}^{-1}\cdot\text{kg}^{-1}$, was calculated as maximum difference in volume normalized by the pressure difference and body weight [19]

$$C_{dyn} = \frac{\Delta V}{\Delta P \cdot bw} = \frac{V_{\max} - V_{\min}}{(PIP - PEEP) \cdot bw}. \quad (4)$$

The airway resistance (R_{AW}), expressed in $\text{cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$ was calculated at different levels of inflation volume using the method of Mead and Whittenberger [20] as

$$R_{AW} = \frac{P_{\text{ins}} - P_{\text{exp}}}{\dot{V}_{\text{ins}} + |\dot{V}_{\text{exp}}|}. \quad (5)$$

The pressure difference between inspiratory pressure (P_{ins}) and expiratory pressure (P_{exp}) was obtained for each step of volume change from the P-V loop. Inspiratory (\dot{V}_{ins}) and expiratory flows ($|\dot{V}_{\text{exp}}|$) were measured at the same level of volume.

Standardized work of breathing (W_R), expressed in $\text{g}\cdot\text{cm}\cdot\text{kg}^{-1}$, was calculated for each breath using the following [3]:

$$W_R = \frac{\int P_{aw} dV}{bw} = \frac{\int P_{aw} (dV/dt) dt}{bw} = \frac{\int P_{aw} \dot{V} dt}{bw}. \quad (6)$$

This value is the area enclosed by the hysteresis loop formed by plotting pressure versus volume.

C. Calibrations

Circuit compliance (C_{circuit}) was determined in the hydraulic components (i.e., piston cylinders, tubing, fittings, etc.) of the ventilator at constant volume increments (1 mL). Determinations of C_{circuit} were repeated ten times.

Calibrations of volume, pressure and temperature were performed at atmospheric pressure and room temperature (25°C and 101.4 ± 0.7 kPa). Under these conditions, the perfluorocarbon (FC-75, 3M, St. Paul, MN) used in this study has the following physical and chemical properties: 157 mL $\text{CO}_2 \cdot 100$ mL, 52 mL $\text{O}_2 \cdot 100$ mL, surface tension 0.015 N $\cdot\text{m}^{-1}$, vapor pressure 7.87 kPa, and dynamic viscosity $8 \cdot 10^{-4}$ Pa $\cdot\text{s}$.

The accuracy of measuring delivered volumes was assessed using 5-, 10-, and 50-mL glass syringes (Hispano ICO SA, Barcelona, Spain). In each case, the cylinder-piston device of the ventilator was serially connected to calibration syringes in which the measured volumes were recovered, and later compared with volumes established by the computer for lung mechanics (5, 10, 20, 30, 40, and 50 mL).

Pressure signals were calibrated with a U-tube water manometer (3T294, Fisher Scientific, Chicago, IL). Atmospheric pressure was considered a zero reference point. Upper and lower pressures were expressed as relative values (-30 , -20 , -10 , 10 , 20 , and 30 cmH_2O).

Temperature signals were compared with digital thermometers with a resolution of 0.1°C (Digi-Sense, Cole-Parmer Instr. Co., Chicago, IL) at 25 , 37 , and 45°C .

The accuracy of time-dependent ventilatory settings (i.e., inspiratory and expiratory times, I:E ratio and frequency) was compared using traces recorded by a polygraph (7P, Grass

Instr., Quincy, MA). Computerized and polygraph records were closely examined over five consecutive respiratory cycles ($n=5$). To calibrate I:E ratios (3:1, 2:1, 1:1, 1:2 and 1:3) and inspiratory (T_I) and expiratory (T_E) times (3–12 s), physiological V_T (15 $\text{mL}\cdot\text{kg}^{-1}$), animal weight (4 kg) and frequency (5 $\text{cycles}\cdot\text{min}^{-1}$) were maintained constant. Conversely, in order to calibrate frequency (1, 2, 5, 8, and 10 $\text{cycles}\cdot\text{min}^{-1}$); V_T (15 $\text{mL}\cdot\text{kg}^{-1}$), animal weight (4 kg), I:E ratio (1:1) were maintained constant.

The absolute ($\Delta\text{Value} = \text{Value}_{\text{measured}} - \text{Value}_{\text{reference}}$) and percent relative errors ($\delta\text{Value} = 100 \cdot \Delta\text{Value}/\text{Value}_{\text{reference}}$) were determined at each increment of volume, pressure, temperature and time [21]. A mean calibration error was calculated for each set of values.

D. In Vivo Experiments

Experimental protocols met all regulations for animal research (EU Directive 86/609) and were approved by the Institutional Experimental Research Committee. The study was carried out on ten healthy newborn lambs less than six days old with a mean \pm SD of 3.21 ± 0.75 kg.

Lambs were sedated, anesthetized and paralyzed as previously described [22]. A tracheotomy was performed and animals were placed on a conventional gas ventilator. Rectal temperature was monitored and kept constant with a radiant warmer. Catheters were placed in the left femoral and pulmonary arteries to determine pH, partial pressures of oxygen (PaO_2) and carbon dioxide (PaCO_2), systemic arterial and pulmonary artery pressures, and cardiac output computed from a mean of three random determinations [23].

Lung lavage was performed as previously reported [24] to obtain a severe and stable respiratory failure with $\text{PaO}_2 < 100$ mmHg, $\text{PaCO}_2 > 50$ mmHg, $\text{pH} < 7.2$, 50% decrease in C_{dyn} and 50% increase in pulmonary artery pressure. At least 30 min were allowed to ensure that additional substantial changes in physiological parameters did not occur. Baseline levels were determined at this point (i.e., post-injury). After lung lavage, lambs received an intratracheally instilled volume of 30 $\text{mL}\cdot\text{kg}^{-1}$ as perfluorocarbon FRC, and then placed on liquid ventilation for three hours. All series of parameters were recorded every 30 min.

During gas ventilation, C_{dyn} , R_{AW} , $\overline{P_{AW}}$, and \dot{V}_E were calculated by a computerized system (PEDS, MAS, Hatfield, PA), as previously described [22]. During total liquid ventilation, lung mechanics parameters were determined using the computerized system and equations described above. All pulmonary mechanics studies during gas and liquid ventilation were performed on ten consecutive breaths over a period when there were no changes in ventilation strategy (i.e., constant f , V_T , I:E ratio, etc.).

E. Statistical Analyses

All values are given as mean \pm SD. Simple linear regression analyses were performed to describe the relationship between calibrated and monitored signals (e.g., temperature, frequency) and to describe relative errors. Comparisons of physiological data were tested with one-factor analysis of variance with Bonferroni–Dunn’s correction as function of time (StatView

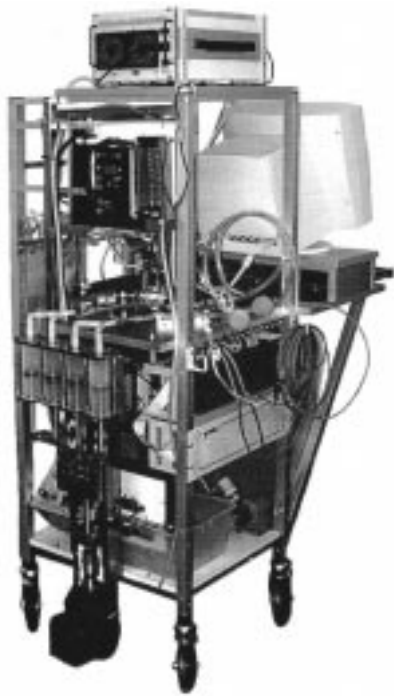


Fig. 3. Photograph of the time-cycled, volume-controlled, and pressure-limited ventilator. The system can be transported for use and is completely self-contained except for a supply of electrical power.

SE+Graphics; Abacus Concepts Co., Orlando, FL). A p -value < 0.05 was accepted as significant.

III. RESULTS

A. Ventilatory Performance

The respirator prototype was assembled on a portable and compact frame that could be easily managed and that facilitated making correct connections with animals (Fig. 3). During ventilation, accessibility by the operator was made as convenient as possible to enable the checking and management of circuit components as well as to respond quickly to warning signals. Tubing, fittings and cylinder-piston seals did not show perfluorocarbon leakage over physiological ranges of pressures (-20 to 50 cmH_2O) and temperatures (25 $^\circ\text{C}$ to 45 $^\circ\text{C}$).

When the total liquid ventilator is turned on, the computer positions cylinder-pistons and valves in the inspiratory phase, avoiding the generation of potentially harmful pressures. This is maintained until operator commands are entered to begin respiratory control.

During inspiratory cycles [Fig. 1(a)], the motor pushes a platform that is a common housing for inspiratory and expiratory pistons using a lead screw. The pistons have equal diameter, so they each move the same amount of liquid. The lung inspiratory valve opens, allowing perfluorocarbon to flow through the lungs. The expiratory cylinder places its contents in the expiratory reservoir through the (open) expiratory reservoir valve. The other two valves in the perfluorocarbon circuit are closed.

During the expiration cycle [Fig. 1(b)], the inspiratory reservoir and lung expiratory valves open. The motor pulls both pistons at the same time, resulting in the movement of oxygenated perfluorocarbon from the inspiratory reservoir to the inspiratory

cylinder and (reduced oxygen) perfluorocarbon from the lung to the expiratory cylinder.

The respirator system incorporates adjustable airway pressure safety limits for inspiration (50 cmH_2O) and active expiration (-20 cmH_2O). During the expiration cycle, if the lower airway pressure limit is reached, the current respiratory cycle is automatically stopped and a new inspiration started. Similarly, during inspiration, if upper airway pressure is achieved, the input flow into the lungs is arrested and an expiration cycle initiated. However, typical maximum inspiratory and minimum expiratory pressures were between ten and 25 cmH_2O , and between -5 and -15 cmH_2O , respectively.

B. Calibration Assays of Signals

A primary advantage of total liquid ventilation is the relative incompressibility of the fluids and solid structures on the ventilator side of the pulmonary circuit. Since the compliance of the hydraulic component is negligible compared with other elastic elements (i.e., the lungs), volume variations within the ventilator pistons are directly transmitted to the lungs. The hydraulic circuit compliance was $8.3 \cdot 10^{-3} \pm 0.7 \cdot 10^{-3}$ $\text{ml} \cdot \text{cmH}_2\text{O}^{-1} \cdot \text{kg}^{-1}$.

Pressure signals were measured over a range from -20 to 50 cmH_2O during *in vivo* studies involving ten newborn lambs. The system is capable of monitoring a range from -543 to 650 cmH_2O . Calibration experiments involving pressure signals resulted in a mean error of $-1.0 \pm 0.8\%$. No single measurement produced a pressure error greater than 4% .

The delivered volume signal was varied over the range from 0 to 120 mL during *in vivo* studies. The system is capable of delivering and monitoring a range from 0 to 320 mL . Calibration procedures demonstrated a mean error in delivered volumes of $0.9 \pm 1.7\%$.

Temperature signals had a physiological range of 25 $^\circ\text{C}$ to 45 $^\circ\text{C}$ during *in vivo* studies. The system is capable of measuring a range from near 0 $^\circ\text{C}$ to 100 $^\circ\text{C}$. The regression coefficient between electrical signals provided by the temperature probes and its conversion to degrees Celsius was $R^2 = 0.999$ ($p < 0.001$). Therefore, the error in temperature measurement was considered negligible.

The ability of the computerized system to make temporal measurements was assessed by having the system take readings from well-defined control signals. Mean absolute and relative errors of T_I and T_E at different I:E ratios are summarized in Table I. Errors from manually derived data using polygraph traces showed higher mean values than those obtained with computerized calibrations. In all cases, the absolute and relative errors compared with polygraph determinations were less than 100 ms and 2.56% . Computerized measurements demonstrated the lowest mean errors (100 ms and -1.66%).

Similar series of experiments were performed to assess the accuracy of frequency measurements (Table II). Both polygraph and computerized measurement errors were never greater than $\pm 2\%$. Linear regression between applied and measured frequencies showed a good correlation ($R^2 = 0.975$, $p < 0.005$ with polygraph method and $R^2 = 0.999$, $p < 0.001$ with computer method).

TABLE I
TEMPORAL ERRORS IN POLYGRAPH TRACES VERSUS COMPUTERIZED
ASSESSMENT OF INSPIRATORY AND EXPIRATORY TIMES WITH
DIFFERENT I : E RATIOS

	I:E ratio	3:1 {9:3 s}	2:1 {8:4 s}	1:1 {6:6 s}	1:2 {4:8 s}	1:3 {3:9 s}
Polygraph	T _I (abs)	0.01±0.01 s	0.01±0.01 s	0.02±0.00 s	-0.01±0.01 s	-0.02±0.01 s
	(rel)	0.06±0.12 %	0.17±0.08 %	0.41±0.06 %	-0.26±0.17 %	-0.77±0.20 %
Polygraph	T _E (abs)	0.08±0.00 s	-0.01±0.00 s	0.03±0.00 s	0.02±0.01 s	0.10±0.00 s
	(rel)	2.56±0.11 %	-0.24±0.11 %	0.47±0.07 %	0.30±0.07 %	1.12±0.02 %
Computer	T _I (abs)	0.07±0.05 s	-0.02±0.05 s	0.00±0.00 s	-0.05±0.06 s	-0.06±0.05 s
	(rel)	0.83±0.55 %	-0.31±0.62 %	0.00±0.00 %	-1.25±1.44 %	-1.66±1.92 %
Computer	T _E (abs)	-0.02±0.05 s	0.00±0.00 s	0.00±0.00 s	0.02±0.05 s	0.10±0.00 s
	(rel)	-0.83±1.66 %	0.00±0.00 %	0.00±0.00 %	0.31±0.62 %	1.11±0.00 %

Data are shown as mean ± SD. T_I: inspiratory time; T_E: expiratory time; (abs): absolute error; (rel): relative error.

TABLE II
TEMPORAL ERRORS IN POLYGRAPH TRACES VERSUS COMPUTERIZED
ASSESSMENT OF FREQUENCY

f {interval}	1 {60 s}	2 {30 s}	5 {12 s}	8 {7.5 s}	10 {6 s}	
Polygraph	(abs)	0.83±0.02 s	0.23±0.01 s	0.05±0.00 s	0.00±0.01 s	-0.04±0.02 s
	(rel)	1.38±0.04 %	0.76±0.04 %	0.44±0.04 %	0.02±0.08 %	-0.63±0.40 %
Computer	(abs)	0.26±0.01 s	0.10±0.01 s	0.00±0.00 s	-0.03±0.01 s	-0.04±0.01 s
	(rel)	0.44±0.41 %	0.33±0.15 %	0.00±0.00 %	-0.40±0.20 %	-0.66±0.82 %

Data are shown as mean ± SD. f: frequency (cycles·min⁻¹); (abs): absolute error; (rel): relative error.

C. Lung Mechanics System

Displays of raw signals, P-V loops and lung mechanics calculations were presented on a breath-by-breath basis (Fig. 4). The system had three windows: ventilatory configuration, unprocessed (raw signals) and integrated (P-V loops) data, and dynamic lung parameters derived from (4)–(6). All displays were available at any time during an experiment in a summarized window (Fig. 4) with partial data from prior pages.

The system can calculate dynamic compliance (C_{dyn}) from raw signals (volume and pressure) using (4), with a range from near 0 to 100 ml·cmH₂O⁻¹·kg⁻¹. In the 30 procedures performed (three/animal, after 1, 2, and 3 hours), a physiological range of 1.04±0.02 to 2.68±0.01 ml·cmH₂O⁻¹·kg⁻¹ was measured. Scatter of C_{dyn} for each procedure (dispersion) showed a maximum range of 16.68% (−7.37 to 9.31%) and minimum of 0.84% (−0.55 to 0.29%). The maximum standard deviation expressed as a percentage was 4.83% [Fig. 5(a)].

The system can calculate airway resistance (R_{AW}) from raw signals (pressure and flow) using (5), with a range from 0 to 11 500 cmH₂O·L⁻¹·s⁻¹. The physiological range during *in vivo* studies involving ten newborn lambs was 107±4 to 1659±21 cmH₂O·L⁻¹·s⁻¹. Scatter of R_{AW} for each study had a maximum range of 15.18% (−8.56 to 6.62%) and minimum of 2.42% (−1.47 to 0.95%). The maximum standard deviation was 5.00% for all studies [Fig. 5(b)].

The system can calculate standardized work of breathing (W_R) from raw signals (pressure, volume) using (6), with a range from 0 to 12 300 g·cm·kg⁻¹. The physiological range during *in vivo* studies involving ten newborn lambs was 62±1

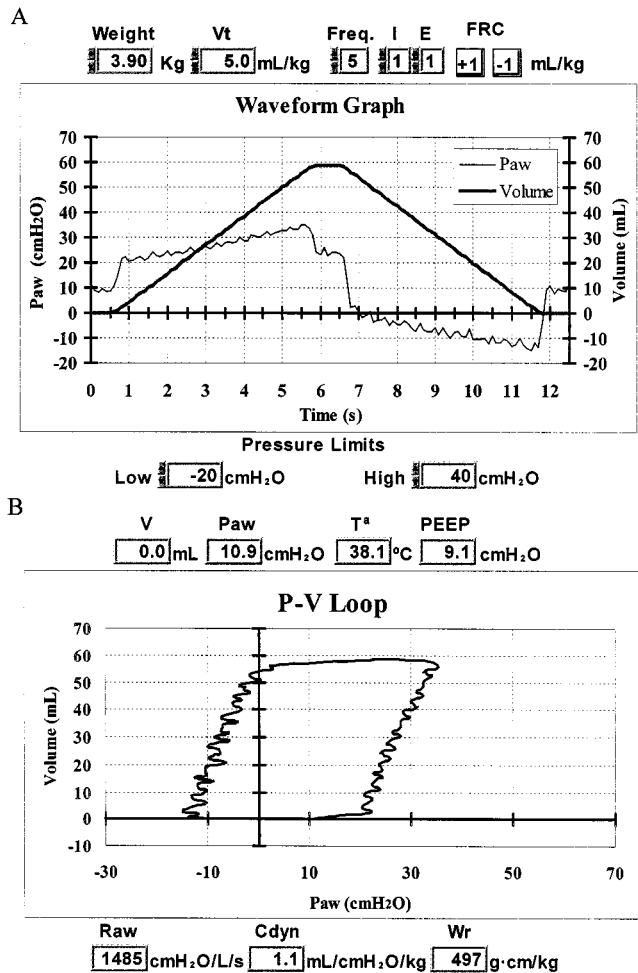


Fig. 4. Operator screens. (A) Example of a screen indicating input parameters: animal weight, tidal volume, frequency, I:E ratio and functional residual capacity adjustment. Airway pressures and lung volume waveforms are also shown. (B) Example of a screen during breath-by-breath analysis. Pulmonary parameters that were calculated include: mean airway pressure, quasi-static positive end expiratory pressure, standardized respiratory work, standardized dynamic compliance and airway resistance through P-V loops.

to 1177±40 g·cm·kg⁻¹. Scatter of W_R for each study had a maximum range of 14.10% (−8.49 to 5.61%) and minimum of 1.03% (−0.46 to 0.57%). The maximum standard deviation was 4.91% for all studies [Fig. 5(c)].

Traces of lung mechanics measurements (C_{dyn}, R_{AW}, W_R) were displayed continuously (e.g., Fig. 6). Stable values were observed in the absence of changes in ventilatory settings. In addition, real-time displays of $\overline{P_{AW}}$, quasi-static PIP and PEEP were generated. During ventilation, it was possible to change the physiological characteristics of the pulmonary load, for example by manually perturbing FRC. The pulmonary consequences of such disturbances could be detected by the system and corrective actions taken.

D. In Vivo Experiments

Pulmonary lavage during gas ventilation produced a significant decrease of arterial pH and oxygenation, and an increase in PaCO₂ levels (Table III). Tachycardia (increased heart rate) and pulmonary hypertension were associated with the lavage procedure, but no effects were observed on either cardiac output

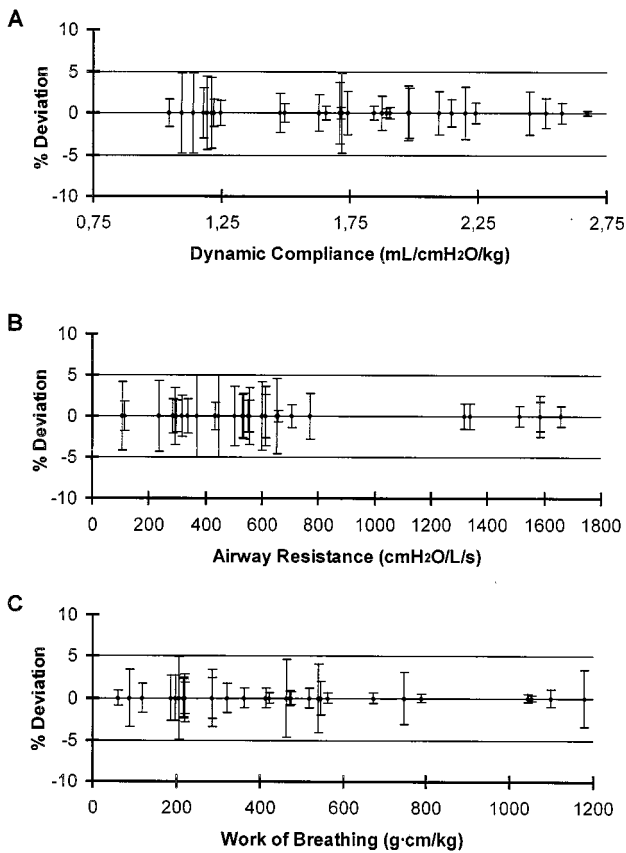


Fig. 5. Range of computed lung mechanics parameters. Measurements were performed during ten consecutive breaths (repeated three times/animal using ten animals). Values for dynamic compliance (A) ranged from 1.04 to 2.68 $\text{mL}\cdot\text{cmH}_2\text{O}^{-1}\cdot\text{kg}^{-1}$, airway resistance (B) from 107 to 1659 $\text{cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$ and work of breathing (C) from 62 to 1177 $\text{g}\cdot\text{cm}\cdot\text{kg}^{-1}$.

or systemic arterial pressure. The procedure did, however, compromise the elastic properties of the lung as indicated by a decrease in C_{dyn} (1.7 ± 0.5 versus 0.4 ± 0.2 $\text{mL}\cdot\text{cmH}_2\text{O}^{-1}\cdot\text{kg}^{-1}$, $p < 0.05$) and an increase in R_{AW} (28 ± 10 versus 50 ± 11 $\text{cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$, $p < 0.05$) and \bar{P}_{AW} (Table III).

After the start of total liquid ventilation, a twofold increase in arterial oxygenation and an improvement of ventilation with a significant reduction in carbon dioxide were observed. In addition, arterial pH demonstrated an upward trend while heart rate, pulmonary and systemic arterial pressures, and cardiac output did not change significantly. After one hour, a fourfold improvement of C_{dyn} (2.0 ± 0.5 $\text{mL}\cdot\text{cmH}_2\text{O}^{-1}\cdot\text{kg}^{-1}$) with lower \bar{P}_{AW} and \dot{V}_{E} was observed with a large increase in R_{AW} (667 ± 525 $\text{cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$). This later finding is related to the high dynamic viscosity and density of perfluorocarbon that flows through the upper airways. During experiments, ventilatory settings were adjusted as needed and physiological data remained stable thereafter.

IV. DISCUSSION

Since the 1970s, ventilators have been developed to improve both the control and safe application of total liquid ventilation [9], [10], [13]–[17], [25], [26]. Improvements have focused mainly on the control of inspiratory-expiratory times and

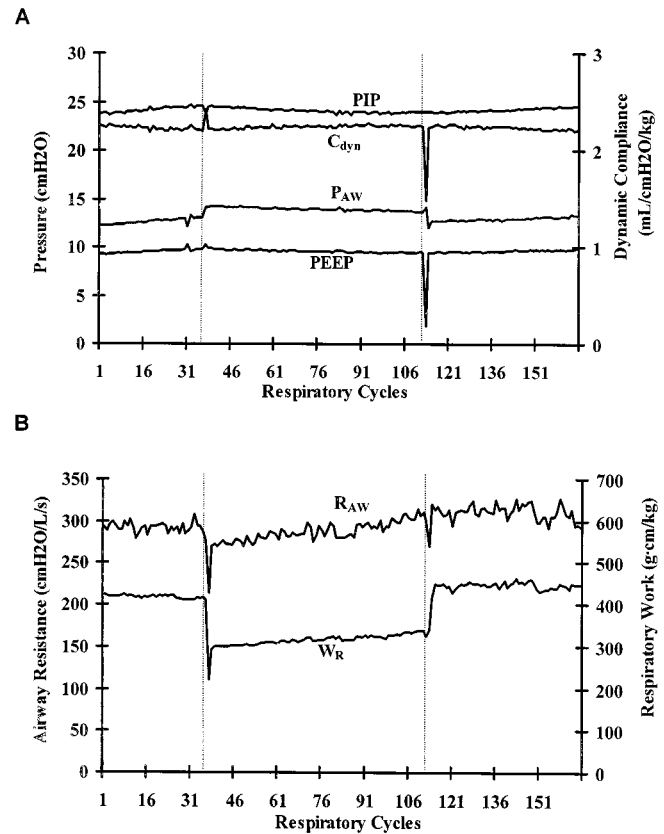


Fig. 6. Continuous monitoring during total liquid ventilation. Traces demonstrate the stability of the ventilator and how parameters vary with a change in ventilator settings through a 30 min monitoring period. The ventilator frequency was 5 breaths/min except between the dashed lines when it was 6 breaths/min. (A) Quasi-static positive end expiratory pressure, standardized dynamic compliance, mean airway pressure, and quasi-static peak expiratory pressure trends. (B) Airway resistance and respiratory work during the same monitoring period.

fluid volumes by means of forced flow mechanisms such as peristaltic pumps or linear actuators. Demand-controlled ventilators were developed to provide automated control of time and volumes by integrating pulsating flows [14], [26]. Recently, linear actuators have been employed to improve accuracy and reliability. Piston-driven ventilators have been shown to meet operational and mechanical requirements for small animals [16], [17], although the potential range of applications using this approach has not been fully developed. In this study, we describe a multiple piston-driven ventilator that includes new solutions to some previously unresolved problems.

In liquid ventilators that utilize linear actuators, volume control is obtained by determining cylinder-piston position [16], [17]. Linear potentiometers have been used to perform this function [16]. A “resolver” connected to a motor shaft can also be used to produce a high degree of accuracy. In addition, the use of a gearbox introduces backlash and the effects of wear between the motor and pistons. We prefer to directly connect the motor to the shaft-lead screw in order to avoid this problem and to maintain a high spatial resolution ($2\ \mu\text{m}$) of piston position. Although, a rapid improvement in lung compliance would make a pressure-limited, time-cycled ventilation a less aggressive strategy, the fact that the only available systems to measure liquid tidal volume is by means of weight scales, seems to be

TABLE III
MEAN PULMONARY GAS EXCHANGE PARAMETERS DURING GAS
AND LIQUID VENTILATION

	Gas Ventilation	Liquid Ventilation		
	Post-Injury	1 hour	2 hour	3 hour
PaO ₂ (mmHg)	93±19 #	201±74	202±80	202±37 *
PaCO ₂ (mmHg)	60±19 #	58±19	49±14	48±10 *
pH	7.06±0.06 #	7.11±0.10	7.16±0.09	7.20±0.15 *
Systemic arterial pressure (mmHg)	83±14	76±16	69±14	73±9
Heart rate (beats·min ⁻¹)	213±20 #	217±34	223±32	219±29
Pulmonary artery pressure (mmHg)	35±8 #	36±11	41±11	34±12
Cardiac output (mL·min ⁻¹ ·kg ⁻¹)	356±88	320±133	298±86	304±84
Quasi-static PIP (cmH ₂ O)	25.6±0.3 #	15.2±5.7	16.2±5.8	19.1±4.4 *
Mean airway pressure (cmH ₂ O)	11.1±1.0 #	7.3±3.5	10.3±2.7	9.1±1.9 *
Minute ventilation (mL·min ⁻¹ ·kg ⁻¹)	366±77 #	137±28	153±52	126±35 *

Data are shown as mean ± SD. (#) ANOVA, $p < 0.05$ vs. baseline; (*) ANOVA *post hoc* treatment, $p < 0.05$ all values versus post-injury level.

a less accurate approach, since external disturbances generated by attached devices are difficult to avoid.

Ventilatory management is generally performed at frequencies of 4 to 8 cycles·min⁻¹, I:E ratios of 1:1 to 1:3, tidal volumes of 15 to 25 mL·kg⁻¹, inspiratory pressures of 70 to 30 cmH₂O and PEEPs of -10 to 100 cmH₂O [6]–[8]. Our system readily handles these ventilatory settings. In addition, in each case, the system can perform well beyond these ranges in order to handle pathophysiological situations.

In order to determine the accuracy of our ventilator, we performed an extensive check of errors introduced by each component (volume-delivered linear actuator, pressure transducer, temperature sensor, etc.). This is the first time such quality controls have been reported in the development of total liquid ventilators. In summary, we observe a low mean error in all calibrated signals (pressure: -1.0%, delivered volume: 0.9%, temperature: 0%, T_I: -1.66%, T_E: 2.56%, f: 1.38%). The low error in raw signals suggests that computed pulmonary parameters (compliance, resistance, work of breathing, etc.) accurately represent the physiological state of the lungs. In most cases, errors can be considered negligible. In all cases, measurement errors are sufficiently low that they should not significantly alter the selection of appropriate ventilatory therapies.

Conventional gas ventilators have progressively incorporated servo-control limits to prevent pulmonary damage. Particular attention has been paid to limit pressure, volume and T_I-T_E. As demonstrated in animal models [9], [27]–[29], total liquid ventilators may prove effective in the management of critical

respiratory patients if it can be demonstrated that similar safety measures are in place.

In our design, steps have been taken to implement such safety measures. The ventilator motor is regulated by three nested feedback loops. First, a speed feedback loop provides control over frequency, I:E ratio, T_I, T_E and acceleration ramps. The measurement resolution of this feedback loop is less than 3% in T_I-T_E durations and -0.66% in frequency. Second, a positioning feedback system regulates tidal volume and variation of FRC by means of exact synchronization of valves and the linear displacement of the cylinder-piston. Error in mean delivered volume is less than 0.9%. Third, a pressure feedback loop limits airway pressure between upper and lower limits. The integration of these feedback loops produces a high degree of security superimposed with the following mechanisms: 1) high-low pressure alarms and volume/pressure cut-off limits to prevent lung injury due to excessive volumes or pressures, and moreover, prevents the expiratory airway collapse, the incomplete emptying of the lungs and the possibility to hyperinflation of the lung at the next inspiratory cycle; 2) manual/automatic servo control of priming volumes with changing FRCs to preset PEEPs in order to optimize alveolar expansion and improve gas exchange; and 3) starting ventilation in the inspiratory phase to avoid dangerous airway collapse and hemorrhagic shock.

Computerized respirator systems with on-line displays have been developed to test lung function during spontaneous and/or conventional mechanical ventilation [3]. A primary goal using these techniques is to develop optimum ventilatory therapies for patients under different conditions [4], [20]. Total liquid ventilation is an active ventilatory technique using forced inspiration and expiration cycles that require continuous monitoring on a breath-by-breath basis. Liquid ventilation must be performed using a dedicated, computerized system in order to obtain reliable measurements without extensive training (beyond that available in a typical clinical setting), and real-time calculations of lung mechanics [33]. Changes in our ventilatory strategy (e.g., frequency, tidal volume, I:E ratio, etc.) produced immediate alterations in lung function (compliance, resistance, work of breathing, etc.). As shown in Fig. 6, following such changes, stable trends in pulmonary values suggest that the system accurately reflects physiological conditions in the lungs. This finding is also corroborated by the low variance of calculated values (Fig. 5).

Some of the analysis protocols during total liquid ventilation utilize the assumption that liquids are relatively incompressible. Under this condition, volume changes in the cylinder-piston produce an equivalent displacement of volume through a closed circuit to the lungs. A way to test the validity of this assumption is to determine whether C_{circuit} is negligible compared with the measured minimum C_{dyn}. If C_{circuit} were in the same range as C_{dyn}, then the accurate measurement of lung compliance becomes much more difficult. In our ventilator, C_{dyn} was 570 times higher than C_{circuit}, suggesting that an accurate measure of lung compliance can be obtained.

As in any ventilatory system, problems can arise if there are the leaks between different components. During total liquid ventilation, the cylinder-piston gasket is one of the most problematic areas. This is exacerbated by both the characteristics

of perfluorocarbon compounds and high hydraulic pressures present in the cylinder-piston region. Leakage can be resolved through decreased applied pressures by limiting piston speed. Adequate flows can be maintained by connecting multiple parallel cylinder-pistons to sustain total cross sectional area. The multiple cylinder-piston arrangement in the current design can handle animals similar in size to human neonates (3 kg at $25 \text{ mL} \cdot \text{kg}^{-1}$). The system should be able to handle (without adding cylinders) an infant patient up to 12 kg ($V_T = 300 \text{ mL}$).

In lung-injured newborn lambs, our ventilator prototype¹ was able to maintain precise control of delivered tidal volume for at least 3 hours. The depletion of the surfactant by lung lavage induced an acute respiratory failure, characterized by severe hypoxia and acidosis, low lung compliance and high airway resistance [30]. These findings closely simulate those found in respiratory distress syndrome, a serious problem in preterm babies. Total liquid ventilation has proven its efficacy in the treatment of preterm (rabbit, lamb) [12], [31] and lung-injured animals [13], [32].

Our gas exchange data during liquid ventilation demonstrate an improvement in gas exchange parameters similar to those described by others. We observed a 200% increase in oxygenation and a significant decrease in hypercarbia (carbon dioxide levels) and acidosis (pH) that was maintained throughout the total liquid ventilation period (three hours). Moreover, some animals were sustained for up to 6 hours and cardiopulmonary status were maintain ($n = 3$; PaO_2 : $202 \pm 6 \text{ mmHg}$; PaCO_2 : $45 \pm 4 \text{ mmHg}$; systemic arterial pressure: $71 \pm 14 \text{ mmHg}$; cardiac output: $347 \pm 78 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), without the appearance of adverse clinical symptoms (i.e., incidence of perflurothoraces, cardiovascular instability, etc.). Also, our measurements of lung mechanics are closely similar to those previously described during total liquid ventilation [8], [27], [29].

In summary, the use of a multiple piston-driven liquid ventilator in animals with acute lung injury induced by repeated lung lavage produced an adequate gas exchange without compromising cardiovascular function. The ventilator was tested with different set-points of tidal volume, f , I:E ratio and flow profiles. The monitoring of pulmonary mechanics and the on-line control of the respirator settings facilitated the ventilatory management of a group of ten animals. The system has demonstrated an adequate range of ventilatory management that should be applicable to critically ill, newborn patients up to 12 kg. With appropriate modifications (multiple cylinder-pistons), adult patients could also be treated. The system permits the safe use of total liquid ventilation and facilitates clinical measurements of pulmonary function. Specifically, our systems have the following advantages: 1) precise control of delivered liquid tidal volume; 2) high accuracy of acquired signals (mean error <3%); 3) introduction of three nested feedback loops (safety servocontrol limits) for time, volume and pressure; 4) real time display of measured and calculated pulmonary parameters; and 5) PFCs isolation in the respiratory circuit from the mechanical components that could be disposable.

¹The ventilator prototype described in this paper was patented E9901420, June 25, 1999.

ACKNOWLEDGMENT

The authors would like to thank J. M. Sainz de la Maza (SEW Eurodrive), R. Murias, I. Aparicio, M. C. Rey-Santano, and B. Acc. Maquina y Herramienta for their excellent technical assistance supporting experiments and their collaboration.

REFERENCES

- [1] C. L. Leach, J. S. Greenspan, S. D. Rubenstein, T. H. Shaffer, M. R. Wolfson, J. C. Jackson, R. DeLemos, B. P. Furhman, and Liquevent Study Group, "Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome," *N. Eng. J. Med.*, vol. 335, no. 11, pp. 761–767, 1996.
- [2] J. S. Greenspan, W. W. Fox, S. D. Rubenstein, M. R. Wolfson, S. S. Spinner, T. H. Shaffer, and Liquevent Study Group, "Partial liquid ventilation in critically ill infants receiving extracorporeal life support," *Pediatrics*, vol. 99, no. 1, p. e2, 1997.
- [3] V. K. Bhutani, "Pulmonary function profile: computer analysis and pulmonary graphics," in *Neonatal Pulmonary Function Testing: Physiological, Technical and Clinical Considerations*, 1st ed, V. K. Bhutani, T. H. Shaffer, and D. Vidyasagar, Eds. Ithaca, NY: Perinatology, 1988, pp. 13–33.
- [4] V. K. Bhutani, E. M. Sivieri, S. Abbasi, and T. H. Shaffer, "Evaluation of neonatal pulmonary mechanics and energetics: A two factor least mean square analysis," *Pediatr. Pulmonol.*, vol. 4, pp. 150–158, 1988.
- [5] V. K. Bhutani and T. H. Shaffer, "Effect of liquid ventilation on preterm lamb tracheal mechanics," *Biol. Neonate*, vol. 44, pp. 257–263, 1983.
- [6] P. A. Koen, M. R. Wolfson, and T. H. Shaffer, "Fluorocarbon ventilation: Maximal expiratory flows and CO₂ elimination," *Pediatr. Res.*, vol. 24, no. 3, pp. 291–296, 1988.
- [7] M. R. Wolfson, J. S. Greenspan, K. S. Deoras, S. D. Rubenstein, and T. H. Shaffer, "Comparison of gas and liquid ventilation: Clinical, physiological, and histological correlates," *J. Appl. Physiol.*, vol. 72, no. 3, pp. 1024–1031, 1992.
- [8] S. E. Curtis, B. P. Furhman, and D. F. Howland, "Airway and alveolar pressures during perfluorocarbon breathing in infants lambs," *J. Appl. Physiol.*, vol. 68, no. 6, pp. 2322–2328, 1990.
- [9] W. H. Matthews, R. H. Balzer, J. D. Shelburne, P. C. Pratt, and J. A. Kylstra, "Steady-state gas exchange in normothermic, anesthetized, liquid-ventilated dogs," *Undersea Biomed. Res.*, vol. 5, no. 4, pp. 341–354, 1978.
- [10] D. B. Kimless-Garber, M. R. Wolfson, C. Carlsson, and T. H. Shaffer, "Halothane administration during liquid ventilation," *Respir. Med.*, vol. 91, no. 5, pp. 255–262, 1997.
- [11] A. Valls-i-Soler, M. A. Gomez, E. Gastiasoro, and F. J. Alvarez, "Perfluorocarbon liquid ventilation," in *Proc. XV Eur. Cong. Perinatal Medicine*, 1996, pp. 250–256.
- [12] M. R. Wolfson, N. Tran, V. K. Bhutani, and T. H. Shaffer, "A new experimental approach for the study of cardiopulmonary physiology during early development," *J. Appl. Physiol.*, vol. 65, no. 3, pp. 1436–1443, 1988.
- [13] R. B. Hirschl, S. I. Merz, P. Montoya, A. Parent, M. W. Wolson, T. H. Shaffer, and R. H. Bartlett, "Development and application of a simplified liquid ventilator," *Crit. Care Med.*, vol. 23, no. 1, pp. 157–163, 1995.
- [14] T. H. Shaffer and G. D. Moskowitz, "Demand-controlled liquid ventilation of the lungs," *J. Appl. Physiol.*, vol. 36, no. 2, pp. 208–213, 1974.
- [15] Y. Baba, Y. Taenaka, H. Akagi, T. Nakatani, T. Masuzawa, E. Tatsumi, Y. Wakisaka, K. Toda, K. Eya, K. Tsukahara, and H. Takano, "A volume-controlled liquid ventilator with pressure-limit mode: Imperative expiratory control," *Artif. Organs*, vol. 20, no. 9, pp. 1052–1056, 1996.
- [16] K. M. Sekins, L. Nugent, M. Mazzoni, C. Flanagan, L. Neer, A. Rozenberg, and J. Hoffman, "Recent innovations in total liquid ventilation system and component design," *Biomed. Instrum. Technol.*, vol. 33, pp. 277–284, 1999.
- [17] J. P. Meinhardt, M. Quintel, and R. B. Hirschl, "Development and application of a double-piston configured, total-liquid ventilatory support device," *Crit. Care Med.*, vol. 28, no. 5, pp. 1483–1488, 1999.
- [18] H. Nyquist, "Regeneration theory," *Bell Syst. Tech. J.*, vol. 11, pp. 126–147, 1932.
- [19] S. Z. Turney, T. C. McAslan, and R. A. Cowley, "The continuous measurement of pulmonary gas exchange and mechanics," *Ann. Thorac. Surg.*, vol. 13, pp. 229–242, 1972.
- [20] W. Nikischin, T. Gerhardt, R. Everett, and E. Bancalari, "A new method to analyze lung compliance when pressure-volume relationship is nonlinear," *Amer. J. Respir. Crit. Care Med.*, vol. 158, pp. 1052–1060, 1998.

- [21] K. Roske, B. Foitzik, R. R. Wauer, and G. Schmalisch, "Accuracy of volume measurements in mechanically ventilated newborns: A comparative study of commercial devices," *J. Clin. Monit.*, vol. 14, pp. 413–420, 1998.
- [22] E. Gastiasoro, F. J. Alvarez, A. Arnaiz, B. Fernandez, J. Lopez-Heredia, L. F. Alfonso, and A. Valls, "Transient response to inhaled nitric oxide in meconium aspiration in newborn lambs," *Pediatr. Res.*, vol. 43, no. 2, pp. 198–202, 1998.
- [23] M. Sydow, H. Burchardi, E. Ephraim, S. Zielmann, and T. A. Crozier, "Long-term effects of two different ventilatory modes on oxygenation in acute lung injury," *Amer. J. Respir. Crit. Care Med.*, vol. 149, pp. 1550–1556, 1994.
- [24] F. J. Alvarez, L. F. Alfonso, E. Gastiasoro, J. López-Heredia, A. Arnaiz, and A. Valls-i-Soler, "The effects of multiple small doses of exogenous surfactant on experimental respiratory failure induced by lung lavage in rats," *Acta Anaesthesiol. Scand.*, vol. 39, pp. 970–974, 1995.
- [25] L. C. Clark and F. Gollan, "Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure," *Science*, vol. 152, pp. 1755–1756, 1966.
- [26] T. H. Shaffer and G. D. Moskowitz, "An electromechanical demand regulated liquid breathing system," *IEEE Trans. Biomed. Eng.*, vol. 22, pp. 412–417, May 1975.
- [27] T. H. Shaffer, P. R. Douglas, C. A. Lowe, and V. K. Bhutani, "The effects of liquid ventilation on cardiopulmonary function in preterm lambs," *Pediatr. Res.*, vol. 17, pp. 303–306, 1983.
- [28] R. Foust, N. N. Tran, C. Cox, T. F. Miller, J. S. Greenspan, M. R. Wolfson, and T. H. Shaffer, "Liquid assisted ventilation: An alternative ventilatory strategy for acute meconium aspiration injury," *Pediatr. Pulmonol.*, vol. 21, no. 5, pp. 316–322, 1996.
- [29] R. B. Hirschl, A. Parent, R. Tooley, M. McCracken, K. Johnson, T. H. Shaffer, M. W. Wolson, and R. H. Bartlett, "Liquid ventilation improves pulmonary function, gas exchange, and lung injury in a model of respiratory failure," *Ann. Surg.*, vol. 221, no. 1, pp. 79–88, 1995.
- [30] B. Lachmann, B. Robertson, and J. Vogel, "In vivo lung lavage as an experimental model of the respiratory distress syndrome," *Acta Anaesthesiol. Scand.*, vol. 24, pp. 231–236, 1980.
- [31] T. H. Shaffer, D. Rubenstein, G. D. Moskowitz, and M. Delivoria-Papadopoulos, "Gaseous exchange and acid-base balance in premature lambs during liquid ventilation since birth," *Pediatr. Res.*, vol. 10, pp. 227–231, 1976.
- [32] R. B. Hirschl, R. Tooley, A. Parent, K. Johnson, and R. H. Bartlett, "Evaluation of gas exchange, pulmonary compliance, and lung injury during total and partial liquid ventilation in the acute respiratory distress syndrome," *Crit. Care Med.*, vol. 24, no. 6, pp. 1001–1008, 1996.
- [33] J. L. Heckman, J. Hoffman, T. H. Shaffer, and M. R. Wolfson, "Software for real-time control of a tidal liquid ventilator," *Biomed. Instrum. Technol.*, vol. 33, no. 3, pp. 268–276, 1999.

Juan Luis Larrabe was born in 1969. He received the B.S. degree in electrical engineering from the University of the Basque Country, Bilbao, Spain, in 1993.

Since 1994, he is Professor of Electrical Engineering in the same university. His main research activities include design of new biomedical devices, lung mechanics, and predictive maintenance in electric devices.

Francisco J. Alvarez was born in 1962. He received the B.S. degree in biological sciences in 1985 from the University of the Basque Country, Bilbao, Spain.

He worked in the Service of Laboratory Animal Care and Husbandry in the same university (1986–1988). He was a Fellow in Biomedical Science (1991–2000). Currently, he is a Biologist in the Research Unit on Experimental Pulmonary Physiology in the Hospital of Cruces, Basque Country Health's Service, Spain. His main research activities are focused on lung physiology and development, gas and liquid ventilatory support, and biomedical engineering.

Mr. Alvarez received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.

Elena Gastiasoro Cuesta was born in 1962. She received the M.D. degree in 1987 from the University of the Basque Country, Bilbao, Spain.

She is a Fellow in Biomedical Science (1990–2001) and works in the Research Unit on Experimental Pulmonary Physiology, Hospital of Cruces, Basque Country Health's Service, Bilbao, Spain. Her main research activities are focused on lung physiology, pulmonary mechanics, and gas and liquid ventilatory support.

Dr. Gastiasoro Cuesta received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.

Adolf Valls-i-Soler was born in 1942. He received the M.D. degree in 1967 from the University of Barcelona, Barcelona, Spain, and the Ph.D. degree in 1989 from the University of the Basque Country, Bilbao, Spain.

Since 1975, he works as Neonatologist in the Neonatal Unit, Hospital of Cruces, Basque Country Health's Service, Bilbao, and Professor of Pediatrics at the Faculty of Medicine, University of the Basque Country. He is director of the Laboratory of Experimental Lung Physiology at the Research Unit, Hospital of Cruces. His current research interests include intensive care medicine, gas and liquid ventilatory support, and lung physiology.

Dr. Valls-i-Soler received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.

Luisa F. Alfonso was born in 1954. She received the B.S. degree from the University of Salamanca, Salamanca, Spain, in 1977, and was credited as pediatric surgeon in 1980.

Since 1986, she works as a Pediatric Surgeon in the Hospital of Cruces, Basque Country Health's Service, Bilbao, Spain. Her main research activities are focused on pathophysiological lung diseases, hypoplasia, and lung immaturity.

Dr. Alfonso received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.

Arantzazu Arnaiz was born in 1962. She received the B.S. degree in 1987 from the University of the Basque Country, Bilbao, Spain.

She worked in the Service of Laboratory Animal Care and Husbandry in the same university (1987–1993). She is a Fellow in Biomedical Science (1994–2001) working in the Research Unit on Experimental Pulmonary Physiology, Hospital of Cruces, Basque Country Health's Service, Bilbao, Spain. Her main research activities are focused on lung physiology and development, pulmonary hypoplasia, and ventilatory support.

Dr. Arnaiz received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.

M. Begoña Fernández was born in 1964. She received the M.D. degree in 1993 from the University of the Basque Country, Bilbao, Spain.

She is a Fellow in Biomedical Science (1994–1999) working in the Osteoba, Basque Country Health's Service, Galdakao, Spain. Her main research activities are focused on lung physiology, epidemiology, and ventilatory support.

Dr. Fernández received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.

Begoña Loureiro was born in 1970. She received the M.D. degree in 1994 from the University of Basque Country, Bilbao, Spain, and was credited as pediatrician in 1998.

Since 1999, she is a Neonatologist in the Neonatal Unit, Hospital of Cruces, Basque Country Health's Service, Bilbao, Spain. Her main research activities are focused on critical care medicine, lung physiology, and ventilatory support.

Nelson G. Publicover received the B.S. degree in engineering physics in 1976 and the M.S. degree in physics in 1977 from Dalhousie University, Halifax, Canada. He received the Ph.D. degree in biomedical engineering in 1982 from McGill University, Montreal, Canada.

He is currently a Professor in the departments of Physiology and Cell Biology, and Electrical Engineering at the University of Nevada School of Medicine, Reno. He is also Director of the Graduate Program in Biomedical Engineering and director of the Applied Research Facility at the same university. His current research interests include biomedical instrument design, electrophysiology, biosensors, and various modalities of imaging (fluorescence, X-ray, high-rate).

Lourdes Roman was born in 1958. She received the M.D. degree from the University of the Basque Country, Bilbao, Spain, in 1981, and was credited as pediatrician in 1986.

Since 1987, she is a Neonatologist in the Neonatal Unit, Hospital of Cruces, Basque Country Health's Service, Bilbao. Her main research activities are focused on critical care medicine, lung immaturity, and gas and liquid ventilatory support.

Jose A. Casla was born in 1937. He received the B.S. degree in 1971 and the Ph.D. degree in 1993 on electrical engineering from the University of the Basque Country, Bilbao, Spain.

Since 1969, he is a Professor at High Technical School of Navigation and Naval Machines, University of the Basque Country. He is also director of Department of Naval Sciences and Techniques, Naval Machines and Construction at the University of Basque Country, Bilbao. His main research activities are predictive maintenance, electrical machines, and hydraulic devices.

Miguel A. Gómez was born in 1961. He received the B.S. degree in naval engineering from the University of the Basque Country, Bilbao, Spain, in 1986.

He worked in Freighter Marine for seven years. Since 1994, he is a Professor at High Technical School of Navigation and Naval Machines, University of the Basque Country, Bilbao. His main research activities are focused on biomedical engineering, electrical modeling, and system's simulation.

Dr. Gómez received the Research Group's Award "ORDESA" in 1995 for Pediatric Research on perfluorocarbon liquid ventilation.