World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:1, No:3, 2007

# Computer-Assisted Piston-Driven Ventilator for Total Liquid Breathing

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***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, A/D conversion, amplifiers, etc.) was less than 5% compared to calibrated signals. 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.

***Keywords*—**Immature lamb, perfluorocarbon, pressure-limited, total liquid ventilation, ventilator; volume-controlled.

## I. Introduction

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 finish to recruit 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.

Different 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 [5], [6]. Early devices were simply gravity-driven [7]-[9], with control of perfluorocarbon flows implemented either manually [8] or by automatically operated valves [7], [9]. 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 [7]. 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 [10], [11]. In some systems, pumps regulated inlet and outlet perfluorocarbon flows [10] while in others, gravity has been used for expiration [11]. Volumes were obtained by integrating pulsatile flows, but had to be verified by weight. Thus, the problem of regulating tidal volumes remained.

The aims of the present study were to: i) develop a electromechanical liquid ventilator prototype with easily removable hydraulic components, to accurately deliver pre-set tidal volumes of perfluorocarbon; ii) develop a computerized system to measure lung mechanics able to acquire, calculate and display measurements to provide operator feedback to better control ventilation; and iii) 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.

This work has been supported in part by grants from the Basque government P.I. 1997-26, Spanish Ministry of Health: FIS 98/0767, FIS 98/0905, and from the Basque Country University: 9/UPV00077.327-15330/2003. The ventilator prototype described is patented E9901420, 1999.

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## II. Materials and Methods

### A. Liquid Ventilation System

#### 1. Ventilator Design

The ventilator prototype was mounted on a compact portable structure easy to handle and connect to animals simulated patients (Fig. 1). The prototype was designed to facilitate the inspection and the handling of the ventilator components, in order to obtain an early answer of the operator to the alarm signals. Tubes, seals, and connections between the cylinder and piston were selected and thought to avoid the possibility of perfluorocarbon leakages.

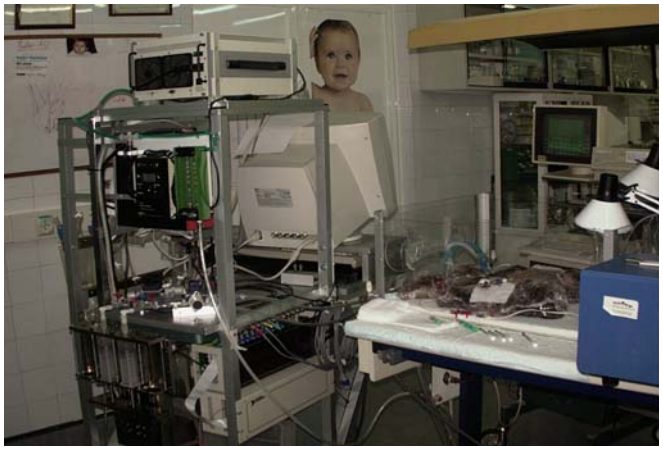

Fig. 1 Time-cycled, volume-controlled, pressure-limited ventilator prototype. The prototype was mounted on a compact portable structure easy to handle and connect to animals, except for electrical supply

To achieve and easy quick and automatic purging in any gas phase of the circuit, the cylinders were placed vertically, delivering the perfluorocarbon from the top. The electro-pinch valves and the endotracheal tube were placed at the same hydrostatic level.

The ventilator was designed to make easier the change of the disposable items in contact with the patient and also of the perfluorocarbon, having in mind the clinical applications, (eg. the assemble cylinder-piston, tubes, accessories, etc). For each inspiration and expiration branches, we considered a ventilator with the capability of being connected in parallel to a multiple and equivalent number of cylinder-piston assemblies. Further to this, in order to meet the particular tidal volume requirements of each patient standard plastic cylinder-piston assemblies with different volumes were used.

#### 2. Perfluorocarbon Pumping System

The ventilator used was limited in pressure, with controlled volume and time-cycled with many elements of the cylinder-piston assembly rigidly built. (Patent E9901420, June 25,1999). The piston was screwed to a sliding platform driven by a lineal actuator, synchronous motor and permanent magnets (Fig. 2). The motor (OSY71STH, Sew Eurodrive, Bilbao, Spain) speed and position was controlled by a resolver which was providing a resolution of 4096 pulses per revolution, making possible 4096 different stops for each axe turn. It was also possible to select the type of movement (eg. lineal ramp, square wave, and sinusoidal profile) the speed and the consequent acceleration by adjusting the velocity ratio [12].

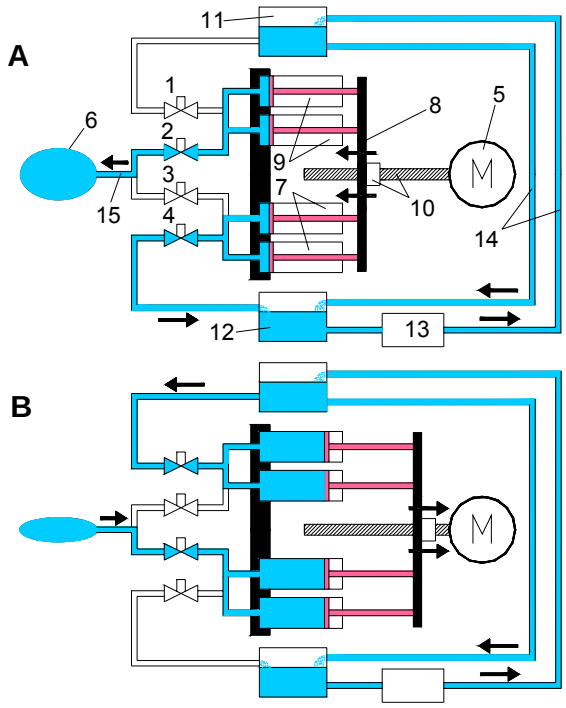


Fig. 2 Liquid ventilator scheme. The ventilator is composed by: (1) valve of the inspiratory reservoir, (2) inspiratory valve, (3) expiratory valve, (4) valve of the expiratory reservoir, (5) synchronous motor, (6) lungs, (7) expiratory cylinder-pistons, (8) sliding platform, (9) inspiratory cylinder-pistons, (10) threaded rod and nut assembly, (11) inspiratory reservoir, (12) expiratory reservoir, (13) feedback circuit, heat exchanger and membrane oxygenator, (14) tubes and (15) endotracheal tube. (A) During the inspiration, the valves 2 and 4 are opened, while the valves 1 and 3 remain closed. The cylinder-piston emptied the perfluorocarbon tidal volume to the lungs. (B) During expiration, the valves 1 and 3 are opened, while the valves 2 and 4 remain closed. The cylinder-pistons drew in the perfluorocarbon tidal volume from the lungs

To push and pull the pistons, the rotary movement of the motor was turned into a linear displacement by a device consisting in a threaded rod and a nut assembly, in order to prevent any sway and perfect adjustment between the pistons and the axe of the motor some bearings were placed. Pistons of known sections were fixed to the sliding platform so that their linear displacement could be found out through the angular position of the motor. Being constant the pistons section, their displacement speed was directly proportional to the flow of perfluorocarbon in the hydraulic circuit.

The movement of the linear actuator was controlled by the processor and controller of the ventilator (Movidyn, Sew Eurodrive, Bilbao, Spain) (Fig. 3). This device regulated the speed and the angular position of the motor, and also the synchronisation of the inspiration and expiration valves.

During the inspiration process, pinch valves were used (Z110A, Sirai, Milan, Italy), to properly lead the flow from the inspiration reservoir to the lungs. During the expiration cycle,

the circulation of the perfluorocarbon was lead from the lungs to the expiratory reservoir by properly opening and closing the four pinch valves (Fig. 2). The trachea, the valves, and the overflow level of both reservoirs were placed at the same hydrostatic level in order to avoid the presence of parasite pressures different to those exerted by the linear actuator (Fig. 4).

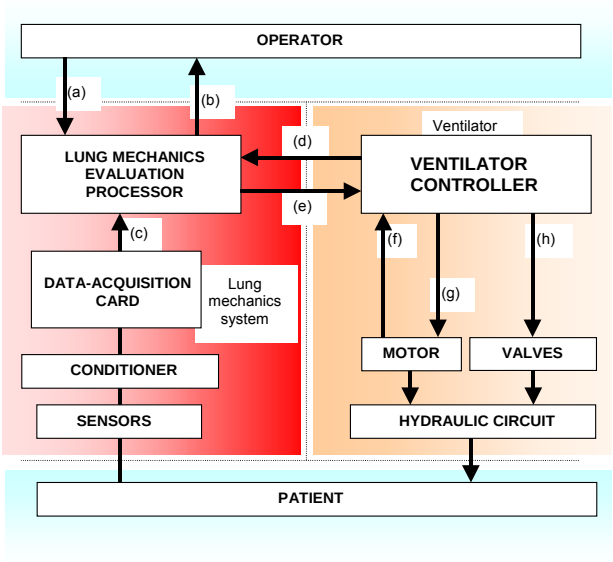


Fig. 3 Flow diagram. Signal between the components include: (a) patient weight (kg), diameter of the cylinders (mm), total volume of the cylinders (ml), *I:E* ratio, standardized tidal volume (ml·kg$^{-1}$), respiratory frequency (cycles·min$^{-1}$), standardized functional residual capacity (ml·kg$^{-1}$), sample rate (data·s$^{-1}$). (b) circuit pressure ($cmH_2O$), instant lung volume (ml), tracheal pressure ($cmH_2O$), pressure-volume curve, graph of circuit pressure vs. lung volume, instant perfluorocarbon flow (l·min$^{-1}$), perfluorocarbon temperature (°C), patient temperature (°C). (c) signals (volts) from endotracheal and alveolar pressures and perfluorocarbon temperature. (d) instant angular position of the motor (4096 steps per revolution). (e) lineal velocity of the motor during inspiration and expiration (rpm), angular position (steps), functional residual capacity and tidal volume. (f) instant angular position of the motor (steps). (g) alternative current (A) on the motor. (h) digital signals to valve control

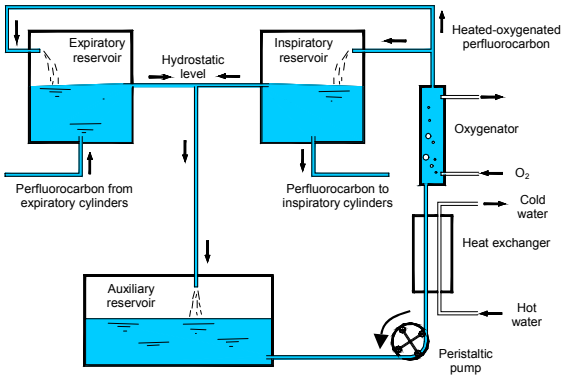


Fig. 4 Feedback circuit. Both inspiratory and expiratory reservoirs and trachea were placed at same hydrostatic level to avoid parasitic pressure gradients

## 3. Recirculating Circuit Design

The perfluorocarbon was constantly recirculated (Fig. 4) from the expiratory to the inspiratory reservoir trough an auxiliary reservoir and a feedback circuit which consisted in a heat-exchanger (ECMO-Therm, Avecor, Plymouth MN, USA), a membrane oxygenator (0800, Avecor, Plymouth Mn, USA) and a peristaltic pump (10-50, Stockert, Munchen, Germany).

In order to maintain the same hydrostatic level in the inspiratory and expiratory reservoirs regardless of the amount of flow in the hydraulic circuit at any moment of the respiratory phase, a low auxiliary reservoir was incorporated (Fig. 4).

The maintenance of temperature and the oxygenation of the perfluorocarbon were achieved by a temperature regulator PID (Precisterm, JP Selecta, Barcelona, Spain) and connecting an oxygen source to the oxygenator formerly described.

## 4. Valves Sequence and Pressure Alarms

On connecting the breather to the electricity supply, this started performing the reference finding procedure (Figs. 5 and 6A). Once the limit of the stroke was selected, the motor remained standing by, waiting for the configuration of the equipment by the operator, that is to say, diameter, maximum capacity, and number of cylinders installed. Once known the data, the ventilator controller processor positioned the pistons, in relation to the reference point or the end of the stroke, that is to say, the position of maximum cylinder capacity (Figs. 5 and 6B). After that, the ventilator was ready to supply a residual functional volume or to start the cycle, delivering the corresponding tidal volume.

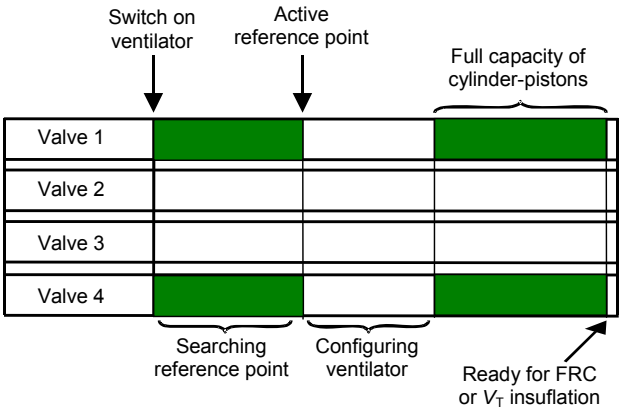


Fig. 5 Valve operation mode during the ventilator switch on. Green rectangles represent opened phase of valves

On starting the process of total liquid ventilation, the control system secured the position of the cylinder-pistons and of the valves in the inspiration phase position, thus, avoiding the generation of potential harmful pressures. This stage was kept until the operator entered the order to initiate the respiratory process.

For the inspiratory cycle, the engine pushed all the pistons using a platform as a common coupling. The rotary movement was turned into lineal through a system of threaded rod and nut plus adjustment by bearings, avoiding wear and sway. All

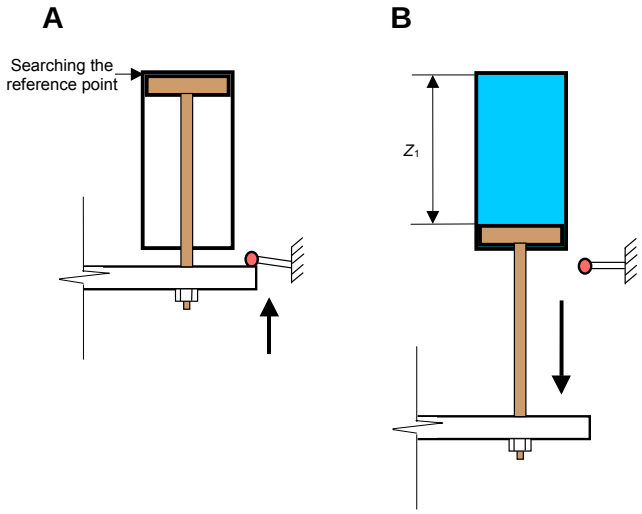


Fig. 6 (A) After to switch on the ventilator, the pistons attached to the sliding platform run to reach the reference point. An end-run interrupter stops the movement of platform and the angular position of the threaded rod was used as reference. (B) After ventilator configuration, the pistons attached to sliding platform load the maximum adjusted volume into the cylinders ($Z_1$)

the pistons were of equal diameter, thus, moving exactly the same amount of liquid. The inspiration valve (Fig. 2A) was opened allowing the flow of perfluorocarbon towards the lungs, at the same time, the expiratory cylinders deposited their content in the expiratory reservoir through the valve 4. The other two valves 1 and 3 of the circuit remained closed.

During the expiratory cycle (Figs. 2B and 7), the valve 1 of the inspiratory reservoir and the expiratory valve 3 of the lung remained opened. The motor drawn the pistons at the same time, generating a flow of oxygenated perfluorocarbon from the inspiratory reservoir to the inspiratory cylinder-piston and taking the perfluorocarbon processed in the lungs (reduced in oxygen and increased in carbon dioxide) to the expiratory cylinder-piston. Fig. 7 also shows how at the final stage of the inspiration and expiration the ventilator remained stationary for the respective pause time, with all the valves closed.

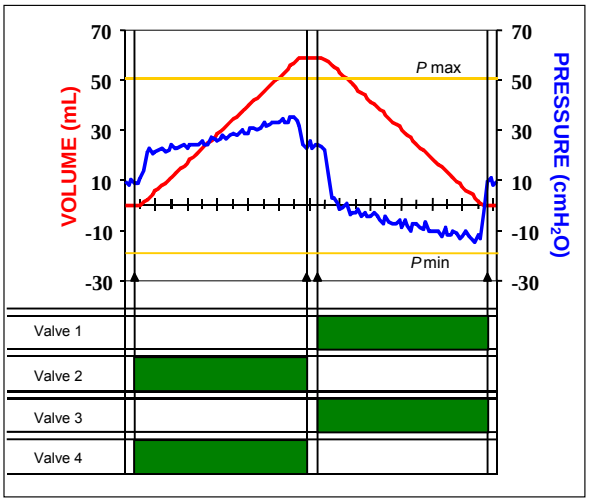


Fig. 7 Valve operation mode during one assisted breath. Green rectangles represent opened phase of valves

The breathing system incorporated two adjustable pressure limits for the airway, one during the inspiratory process (normally 50 $cmH_2O$) and another active expiration (typically -20 $cmH_2O$). When during the expiratory cycle, the lower pressure limit in the airway was reached, the cycle was automatically detained, starting a new inspiration with the valves sequence shown in Fig. 8.

Similarly, if the upper limit was reached during the inspiration, the coming flow to the lungs was detained and a new expiratory cycle started, with the valves sequence shown in Fig. 9.

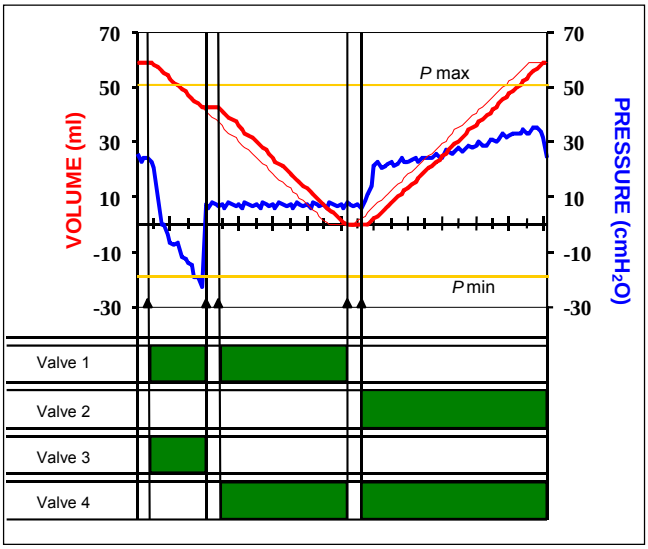


Fig. 8 Valve operation mode during low-pressure alarm. Green rectangles represent opened phase of valves. Thin and thick red lines show hypothetical and real changes of the tidal volume, respectively

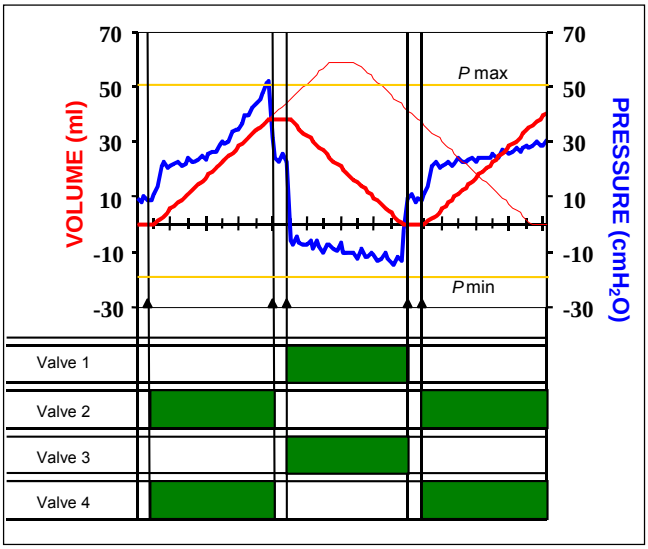


Fig. 9 Valve operation mode during high-pressure alarm. Green rectangles represent opened phase of valves. Thin and thick red lines show hypothetical and real changes of the tidal volume, respectively

5. Breather Control System

The operator´s control of the ventilation process was done in a graphic computer monitor. The software for this application was designed on a graphic software support (Labview Ver 5.1, Austin TX, USA). All the parameters were standardised by the patient weight ($m_p$, kg). In addition to this, on starting the process of liquid ventilation, the following parameters were adjusted: inspiratory-expiratory ratio (*I:E*), respiratory frequency ($f_R$, cycles·min$^{-1}$), standardised tidal volume ($V_T$, ml·kg$^{-1}$) and standardised functional residual capacity (FRC, ml·kg$^{-1}$). In order to control the volumes delivered by the different types of cylinder-piston, we had to specify their volumes (ml) and the diameters (mm). Consequently, all the parameter could be varied in according with needs.

6. Calculus of the Velocity of the Ventilator Motor

On this paragraph the mathematical processes followed by the ventilation parameters are described (standardised tidal volume, respiratory frequency and inspiratory-expiratory ratio), all these processes were handled by the operator until turning them into an speed turning requirement to move the pistons.

Both semicycles represented in Fig. 2 were determined by the following parameters:

For inspiration:

**$\alpha_{VT}$ [rev]:** Total angular displacement of the motor axe to deliver the required volume for the inspiration. The value of this parameter was determined by the geometric features of the different cylinder-piston used (stroke and diameter) and for the tidal volume for each complete breath.

**$\beta$ [rpm·s$^{-1}$]**: Constant motor acceleration

**$\beta$' [rpm·s$^{-1}$]**: Constant motor deceleration

***n*$_I$ [rpm]**: Maximum angular speed during the inspiration. The value of this parameter was determined by the respiratory frequency and the *I:E* ratio.

***t*$_{up}$ [s]**: Motor acceleration time from 0 to maximum speed during the inspiration.

***t*$_{down}$ [s]**: Instant time when the motor started the deceleration.

***t*$_{pI}$ [s]**: Instant when the respiratory pause started. Also was expressed the period of time in which the motor was moving during the inspiration.

***t*$_{pau,I}$ [s]**: Period of time which lasted the inspiratory pause.

***t*$_I$ [s]**: Time employed by the ventilator in an inspiration.

For expiration:

The origin of the time (t=0 s) started with the expiration.

**$\alpha_{VT}$ [rev]:** Angular position from which the motor axe returned to the initial angular position (e = 0 rev). With this manoeuvre, the same amount of perfluorocarbon that was delivered in the inspiration was withdrawn from the lungs. The value of this parameter was determined by the geometrical features of the different cylinder-pistons used (diameter and stroke) and for the tidal volume for each complete breath.

**$\beta$ [rpm·s$^{-1}$]**: Constant acceleration of the motor.

**$\beta$' [rpm·s$^{-1}$]**: Constant deceleration of the motor.

***n*$_E$ [rpm]**: Maximum angular speed of the motor during expiration. The value of this parameter was determined by the respiratory frequency and the *I:E* ratio.

***t*$_{up}$ [s]**: Time employed by the motor in accelerating from 0 to the maximum speed during the expiration.

***t*$_{down}$ [s]**: Time instant in which motor deceleration started

***t*$_{pE}$ [s]**: Instant in which started the respiratory pause. Time in which the motor was running during the expiration.

***t*$_{pau,E}$ [s]**: Period of time which lasted the expiration pause.

***t*$_E$ [s]**: Time employed by the ventilator in an expiration.

The inspiratory ($t_I$) and the expiratory ($t_E$) times depended on the respiratory frequency and the *I:E* ratio in according with the following formulae:

$$t_I = \frac{60}{f_R} \cdot \frac{I}{I+E} \ [s]$$

$$t_E = \frac{60}{f_R} \cdot \frac{E}{I+E} \ [s]$$

$$t_{pI} = t_I - t_{pau,I}$$

$$t_{pE} = t_E - t_{pau,E}$$

Times $t_{pau,I}$ and $t_{pau,E}$ remained constant and equal among themselves

$$t_{pau,I} = t_{pau,E} = 500 \ ms$$

The stroke or lineal displacement to be made by the pistons ($Z_{VT}$) in function of the standardised tidal volume ($V_T$), interior diameter of the cylinders ($d$; mm) and simulated patient weights ($m_p$) were given by:

$$V_T \cdot m_p = \frac{d^2 \cdot \pi}{4000} \cdot Z_{VT} \ [cm^3]$$

$$Z_{VT} = \frac{4000 \cdot V_T \cdot m_p}{d^2 \cdot \pi} \ [mm]$$

$Z_{VT}$ was related with the angular displacement of the motor ($\alpha_{VT}$; rev) via the threaded rod pitch ($Ph$ = 5 mm·rev$^{-1}$):

$$\alpha_{VT} = \frac{Z_{VT}}{Ph} = \frac{4000 \cdot V_T \cdot m_p}{d^2 \cdot \pi \cdot Ph} \ [rev]$$

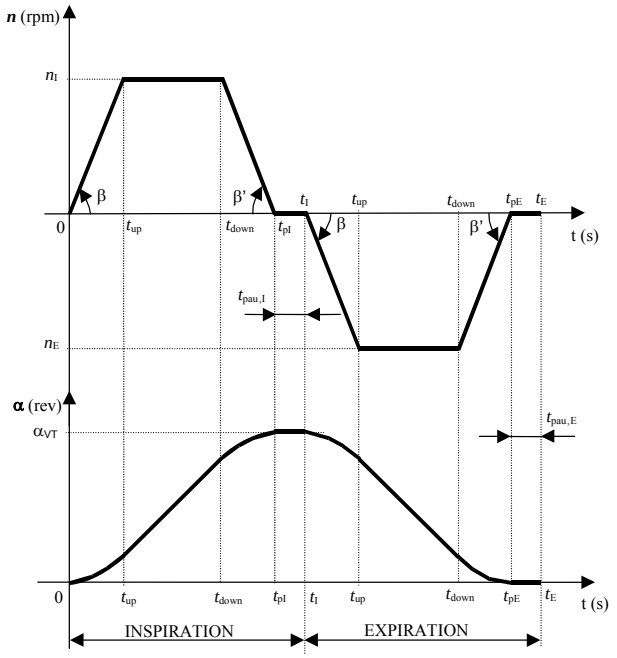


Fig. 10 Start-stop manoeuvre of the motor to perform a breath at *I:E* ratio = 1:1

On this particular case for the used motors, β and β' were calculated as follows (Figure 10):

$$\beta = \frac{3000}{t_{R,up}} \quad \left[\frac{rpm}{s}\right]$$

$$\beta' = \frac{3000}{t_{R,down}} \quad \left[\frac{rpm}{s}\right]$$

$t_{R,up}$ and $t_{R,down}$: established the required time to accelerate the motor from 0 to 3000 rpm and decelerate from 3000 to 0 rpm respectively. Both parameters, although being individually adjustable, were kept constant and equal between themselves in all the experiments.

$$t_{R,up} = t_{R,down} = 7{,}5\ [s] \Rightarrow \beta = \beta' = 400\ \left[\frac{rpm}{s}\right] = 24000\ \left[\frac{rpm}{min}\right]$$

From Fig. 10, it can be deducted that $\alpha_{VT}$ corresponds with the area enclosed in the positive trapezoid of the speeds graphic.

$$\alpha_{VT} = \frac{2 \cdot t_{up} \cdot n_I}{2} + \left(t_{pI} - 2 \cdot t_{up}\right) \cdot n_I \Rightarrow n_I = \frac{\alpha_{VT}}{\left(t_{pI} - t_{up}\right)}$$

Substituting $t_{up}$ in the function $n_I$ and β:

$$n_I = \beta \cdot t_{up} \ [rpm] \Rightarrow n_I = \frac{\alpha_{VT}}{\left(t_{pI} - \frac{n_I}{\beta}\right)}$$

$$\frac{1}{\beta} \cdot n_I^2 - t_{pI} \cdot n_I + \alpha_{VT} = 0$$

$$n_I = \frac{t_{pI} \pm \sqrt{t_{pI}^2 - \frac{4 \cdot \alpha_{VT}}{\beta}}}{\frac{2}{\beta}}$$

Analogically for the expiratory phase is obtained:

$$n_E = \frac{t_{pE} \pm \sqrt{t_{pE}^2 - \frac{4 \cdot \alpha_{VT}}{\beta}}}{\frac{2}{\beta}}$$

Finally, and substituting the different parameters the consigned value of the maximum speed for the inspiration was obtained, in function of the physiological constants of the experiment (standardised tidal volume, respiratory frequency, inspiration pause length of time and inspiratory-expiratory ratio), and the inherent constants to the ventilator as the constant acceleration of the motor, and the diameters of pistons and pitch of the threaded rod.

$$n_I = \frac{\left(\frac{60}{f_R} \cdot \frac{I}{I+E} - t_{pau,I}\right) \pm \sqrt{\left(\frac{60}{f_R} \cdot \frac{I}{I+E} - t_{pau,I}\right)^2 - \frac{4 \cdot \frac{4000 \cdot V_T \cdot m_p}{d^2 \cdot \pi \cdot Ph}}{\beta}}}{\frac{2}{\beta}} \ [rpm]$$

Equally for the expiration:

$$n_E = \frac{\left(\frac{60}{f_R} \cdot \frac{E}{I+E} - t_{pau,E}\right) \pm \sqrt{\left(\frac{60}{f_R} \cdot \frac{E}{I+E} - t_{pau,E}\right)^2 - \frac{4 \cdot \frac{4000 \cdot V_T \cdot m_p}{d^2 \cdot \pi \cdot Ph}}{\beta}}}{\frac{2}{\beta}} \ [rpm]$$

The two former equations have two solutions, but only was satisfactory the one obtained from the positive square root. The ventilator processor controller only admitted entire units for speed and angular position of the motor.

7. Calculus of the Angular Position of the Motor

The ventilator for total liquid breathing was designed to guarantee patients with the safest possible connection. Therefore, it was established a starting procedure as the one described below.

On connecting the ventilator to the electricity source, the processor controller of the ventilator was programmed to turn the motor till the position in which the platform that controlled the piston would reach the top of its displacement (Fig. 6A). At this instant, the motor stopped and the processor controller of the ventilator took the angular position of the threaded rod as a reference, in order to know the position of the pistons in future manoeuvres.

Once the operator inserted the parameters in the equipment, that is, entered the values of the piston diameters, maximum capacity of each cylinder-piston and the number of cylinder-pistons used, the system calculated the angular position (pulses quantity at a ratio of 4096 per revolution) at which the motor had to rotate and to achieve the maximum inside capacity of the cylinder-pistons (Fig. 6B). Only after this moment, and after the order of the operator, the ventilator was capable of starting the delivery of the functional residual capacity or tidal volume of perfluorocarbon to the patient.

The perfluorocarbon amount contained in the cylinder-pistons, or what is the same, the position of the pistons in relation to the movement reference established by the end of the stroke, was known through the number of pulses delivered by the resolver attached to the motor axe (4096 pulses per revolution) and the pitch of the threaded rod ($Ph$= 5 mm·rev$^{-1}$), changing the rotary movement into a lineal one of the pistons.

The cylinder-pistons were vertically placed to make easier the automatic purging of the hydraulic circuit. T represent the movement and the position of the pistons a three dimensional Cartesian system of axes XYZ was chosen, being Z the vertical axe in which were done the different translations. Further up, as the movements were below the end of the reference stroke, that is to say, the reference point for 0 movement (Fig. 6A), all the positions got by the pistons were of a negative sign.

The stroke or linear displacement ($Z_1$; mm) to be made by the pistons to position at the maximum capacity point inside the cylinders (Fig. 6B) was calculated in function of the diameter of the pistons ($d$; mm) and the total capacity of the cylinders ($V_{CYL}$; mL):

$$V_{CYL} = \frac{d^2 \cdot \pi}{4000} \cdot (-Z_1) \ [ml] \Rightarrow Z_1 = -\frac{4000 \cdot V_{CYL}}{d^2 \cdot \pi} \ [mm]$$

$Z_1$ was related to the angular position of the motor ($\alpha_1$; rev) via the pitch of the threaded rod ($Ph$ = 5 mm·rev$^{-1}$):

$$\alpha_1 = \frac{Z_1}{Ph} = -\frac{4000 \cdot V_{CYL}}{d^2 \cdot \pi \cdot Ph} \ [rev]$$

As previously referred, the motor resolution was of 4096 different stops, evenly spaced per each revolution. On passing by each stop position, the ventilator processor controller obtained a pulse (4096 pulses per revolution). With this data,

the consignment of the angular position of the motor, measured in number of pulses since the reference was fixed as follows:

$$\alpha_1 = -4096 \cdot \frac{4000 \cdot V_{CYL}}{d^2 \cdot \pi \cdot Ph} \ [\text{pulses}]$$

To deliver and amount of perfluorocarbon equivalent to the residual functional capacity, the pistons were moved from the position $Z_1$ to $Z_2$ (Fig. 11). As $Z_1$ and $\alpha_1$ had a negative sign, $Z_{FRC}$ and $\alpha_{FRC}$ were magnitudes with a positive sign. The position $\alpha_2$, expressed in the number of pulses from the reference point, was found out in function of the standardised functional residual capacity (ml·kg$^{-1}$), simulated patient weight ($m_p$; kg), cylinder volumes ($V_{CYL}$; ml), piston diameters ($d$; mm)·and threaded rod pitch ($Ph$ = 5 mm·rev$^{-1}$):

$$Z_2 = Z_1 + Z_{FRC} \Rightarrow \alpha_2 = \alpha_1 + \alpha_{FRC}$$

$$\alpha_2 = -4096 \cdot \frac{4000 \cdot V_{CYL}}{d^2 \cdot \pi \cdot Ph} + 4096 \cdot \frac{4000 \cdot FRC \cdot m_P}{d^2 \cdot \pi \cdot Ph} \ [\text{pulses}]$$

$$\alpha_2 = 4096 \cdot \frac{4000}{d^2 \cdot \pi \cdot Ph} \cdot (-V_{CYL} + FRC \cdot m_P) \ [\text{pulses}]$$

The *set point* ($\alpha_3$; pulses), for introducing into the lungs the pre-set tidal volumes (Fig. 12), was worked out as in the case of the FRC previously described, being the final expression:

$$\alpha_3 = 4096 \cdot \frac{4000}{d^2 \cdot \pi \cdot Ph} \cdot (-V_{CYL} + V_T \cdot m_P) \ [\text{pulses}]$$

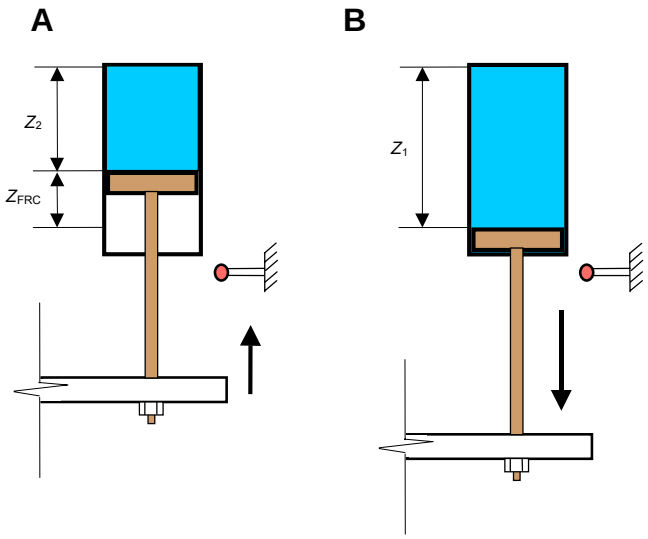


Fig. 11 (A) The cylinder-piston inflates the lungs with a pre-set functional residual capacity (FRC). (B) After delivery the FRC, the cylinder-piston returns to maximum adjusted volume ($Z_1$)

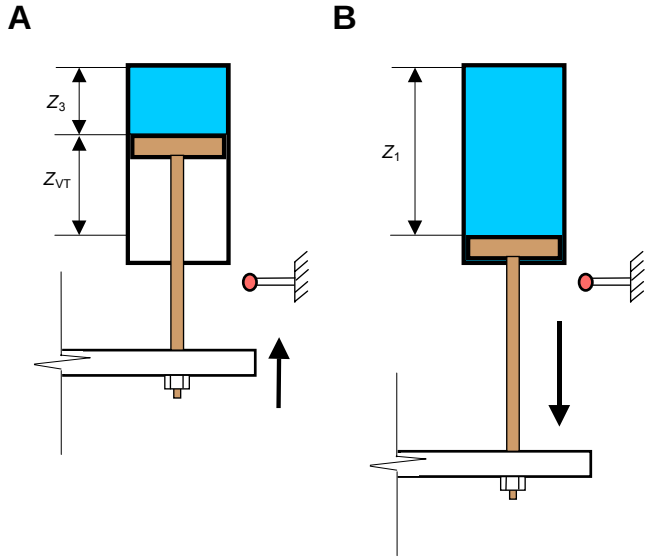


Fig. 12 (A) The cylinder-piston runs to $Z_{VT}$ to inflate the lungs with the pre-set tidal volume. $Z_3$ piston position corresponds with the $\alpha_3$ angular position of the motor. (B) The piston-cylinder returns to the initial position $Z_1$ after the delivery of the tidal volume

### B. *Mechanic Pulmonary System*

Fig. 3 summarizes most of the breather components, as much as the flow of signals between the processor which controls the ventilator, the processor for the pulmonary mechanics, the patient and the operator. The temperature and pressure signals from the patient and the perfluorocarbon circuit were conveyed by means of pressure transducers (Transpac IV, Abbot Lab., Sligo, Ireland) and sensors (Pt100 (Maikontrol, Baracaldo, Spain), an later modulated by a complete Wheatstone bridge and a resistance variation detector, placed in their respective entry devices with each insulation (5B38 and 5B34, Analog Devices, Norwood, MA, USA). These devices rectified and amplified the analogic input signals to a standardized voltage in the rank of (0-5 V). Forthwith, these voltages were turned into 12-bite digital through a data acquisition card (MIO 6040E, National Instruments, Austin, TX, USA). This digital data was stored in a memory and operated by a buffer system first in–first out (FIFO) all this in order to reduce the processor in charge data acquisition time period.

The angular position of the synchronous motor was sent from the ventilator controlling processor to the computer dedicated to the pulmonary mechanics (10 samples·s$^{-1}$) to be used in future different calculations. This computer, to be connected to the process, was provided with a peripherical component with and extension for instrumentation (PXI-8156, National Instrument, Austin TX, USA). Specific software was developed on a graphic program base (Labview Ver 5.1, Austin TX, USA) through which the entering digital data was transformed in the numerical parameters required for the functioning of the breather and the calculations of the pulmonary mechanics (tidal volume, airway pressures, inlet and outlet flow). In and out temperatures of the respiratory fluid and time. All results were graphically shown to the operator and filed on data support devices in a compatible format with the standard Excel program.

In order to reduce the electromagnetic noise, all cables were screened and all connection boxes earthen, isolating all the signals. The theorem of Nyquist [13] about the signals testing and with the aim of prevent the overlapping states that a data acquisition system must be capable of checking at least two times faster than the component of the signal with the highest frequency. On this particular case, knowing that the basic frequency of the signal to be used had a highest frequency of

0.167 Hz (10 cycles·min$^{-1}$) and that the shape of the waves were peakless (components of high frequency during the transition periods), the checking time for all the signals was fixed in 10 Hz. Due to this, the signals were initially received at 1 kHz, and for each 100 units of data received was applied an arithmetical mean filter in such a way that the mention checking time were achieved.

With the data gathered all along each respiration process the derived pulmonary parameters were worked out, by monitoring at the end of each respiratory cycle: standardised minute ventilation ($V'_E$; ml·min$^{-1}$·kg$^{-1}$), mean airway pressure ($\overline{P_{aw}}$), quasi-static peak inspiratory pressure (PIP), quasi-static positive end expiratory pressure (PEEP), airway resistance ($R_{aw}$), dynamic lung compliance ($C_{L,dyn}$), work of breathing ($W_{OB}$). As the checking periods of all the signals were constant, each respiratory cycle has a number of samples (n) related to the respiratory frequency (n > 100 in all cases).

The mean airway pressure ($\overline{P_{aw}}$), expressed in cm$H_2O$, was calculated as the mean value of the airway pressure during a breath:

$$\overline{P_{aw}} = \frac{1}{n}\sum_{i=1}^{n}(P_{aw})_i$$

where $(P_{aw})_i$ represent the instant different values in the airway acquired during one respiratory cycle.

The standardised tidal volume ($V_T$), was the normalised volume of one breath taking expressed in ml·kg$^{-1}$.

The quasi-static peak inspiratory (PIP) and positive end-expiratory (PEEP) pressures, expressed in cm$H_2O$, were calculated as the mean pressure at the end of the inspiration and expiration cycles respectively. Both were determined when the volume increase was less than 0.01 ml between consecutive samples. In these conditions, it was considered that the perfluorocarbon flow through the airway was close enough to 0, and thus the pressure of the airway equal to the alveolar one. If n' and n'' are the number of pressure samples fulfilling the conditions already mentioned during one inspiration and expiration respectively, PIP and PEEP are calculated as follows:

$$\mathrm{PIP} = \frac{1}{n'}\sum_{i=1}^{n'}(P_{aw})_i$$

$$\mathrm{PEEP} = \frac{1}{n''}\sum_{i=1}^{n''}(P_{aw})_i$$

The standardised dynamic lung compliance ($C_{L,dyn}$), expressed in ml·cm$H_2O^{-1}$·kg$^{-1}$, is calculated as the maximum difference in volume between the difference in pressure and the weight of the patient [14]:

$$C_{L,dyn} = \frac{\Delta V}{\Delta P \cdot m_P} = \frac{V_T\max - V_T\min}{(\mathrm{PIP} - \mathrm{PEEP}) \cdot m_P} \quad (1)$$

The airway resistance ($R_{aw}$), expressed in cm$H_2O$·l$^{-1}$·s$^{-1}$, was worked out at different levels of tidal volume using the method of Mead & Whittenberger [15]:

$$R_{aw} = \frac{P_{ins} - P_{esp}}{V'_{ins} + |V'_{esp}|} \quad (2)$$

The difference between the inspiration pressure ($P_{ins}$) and the expiration pressure ($P_{esp}$) was obtained in each step of volume change during the *P-V* cycle. Both pressures were measured at the end of the endotracheal tube as close as possible of the carina. The inspiration ($V'_{ins}$) and expiration ($|V'_{exp}|$) flow were measured at the same pulmonary volume level already described.

The standardised work of breathing ($W_{OB}$), expressed in g·cm·kg$^{-1}$, was calculated for each breath using the following equation [3]:

$$W_{OB} = \frac{\int P_{aw}\,dV_T}{m_p} = \frac{\int P_{aw}\,dV_T/dt\,dt}{m_p} = \frac{\int P_{aw}V'\,dt}{m_p} \quad (3)$$

This value is the area enclosed by the hysteresis composed by the graphic of the airway pressure in relation with the pulmonary volume.

### *C. Calibrations*

Previous to start the experiences, some calibrations were programmed and made in order to test the accuracy of the system in relation with data acquisition and functioning. With this procedure in mind, were valued the intrinsic features inherent to the nature of the breather which could affect or disturb the final results with the patient. The calibrated signals were, the compliance of the whole hydraulic circuit, perfluorocarbon delivered volume, pressure, temperature, inspiratory and expiratory times, *I:E* ratio and respiratory frequency.

The compliance of the whole hydraulic circuit was measured ($C_{cir}$), considering the whole assembly of tubes, cylinder-pistons, catheters, etc at constant volume increases (1 ml). The tests to determine the $C_{cir}$ were made 10 times and a mean value was calculated.

The volume, pressure and temperature measuring calibrations were made at atmospheric pressure and ambient temperature (101.4±0.7 kPa and 25°C). Under these conditions, The used perfluorocarbon (FC-75, 3M, St. Paul, MN, USA) has the following physic-chemical properties: $CO_2$ solubility: 157 ml gas/100 ml PFC liquid, solubility $O_2$: 52 ml gas/100 ml PFC liquid, surface tension: 0.015 N·m$^{-1}$, vapour pressure: 7.87 kPa and dynamic viscosity: $8\cdot10^{-4}$ Pa·s.

The accuracy of the measures delivered by the ventilator was checked using glass syringes (Hispano ICO SA, Barcelona, Spain) of 5, 10 and 50 ml. On each case, the cylinder-piston assembly of the ventilator was series-connected to the syringes, where were recovered the displaced volume and later compared with pre-established ones in the pulmonary mechanics processor, the calibration points were: 5, 10, 20, 30 and 40 ml.

The pressure signals were calibrated with a water manometer tube (3T294, Fisher Scientific, Chicago IL, USA). The reference value of atmospheric pressure was taken as zero. The pressures higher or lower than the reference were expressed as relative pressures or manometer pressures. The calibration points taken were: -30, -20, -10, 10, 20 and 30 cm$H_2O$.

The temperature signals were match with the digital thermometers with a resolution of 0.1°C (Digi-Sense, Cole-Parmer Instr. Co., Chicago IL, USA). The calibration points were taken at intervals considered to be regular of: 3.9; 22.2; 38.2; 51.6 and 79.3 °C.

The precision of the ventilation parameters depended upon time, that is, inspiratory time, expiratory time, *I:E* ratio and respiratory frequency. It was obtained by measuring and comparing the graphics drawn by the polygraph (7P, Grass Instr., Quincy MA, USA) and those of the computerised data acquisition of the breather. Considering 5 consecutive cycles (n=5) the obtained registers were analysed by the computerised system and the polygraph. For the calibration the *I:E* ratios (3:1, 2:1, 1:1, 1:2 and 1:3), inspiratory times ($t_I$) and expiratory times, ($t_E$) (3-12 s), the following parameters were kept constant inside the normal physiological ranges: $V_T$=15 ml·kg$^{-1}$, simulated patient weight=4 kg, respiratory frequency: 5 cycles·min$^{-1}$. On the opposite, to calibrate the respiratory frequency (1, 2, 5, 8 and 10 cycles·min$^{-1}$), were taken: $V_T$=15 ml·kg$^{-1}$, simulated patient weight=4 kg and I:E ratio of 1:1.

The absolute error ($\Delta$Value = Value $_{measured}$ - Value $_{reference}$) and the percentage of the residual error ($\delta$Value = 100·$\Delta$Value / Value $_{reference}$) were determined for each increase of volume, pressure and time [16]. The mean calibration error was calculated for each group 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 10 healthy newborn lambs less than 6 days old with a mean bw (± SD) of 3.21±0.75 kg.

Lambs were sedated, anaesthetized and paralyzed as previously described [17]. 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 ($P_{aO2}$) and carbon dioxide ($P_{aCO2}$), systemic arterial and pulmonary artery pressures, and cardiac output computed from a mean of three random determinations [18].

Lung lavage was performed as previously reported [19] to obtain a severe and stable respiratory failure with $P_{aO2}$<100 mmHg, $P_{aCO2}$>50 mmHg, pH<7.2, 50% decrease in $C_{L,dyn}$ and 50% increase in pulmonary artery pressure. At least 30 minutes 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 ml·kg$^{-1}$ as perfluorocarbon FRC, and then placed on liquid ventilation for 3 hours. All series of parameters were recorded every 30 min.

During gas ventilation, $C_{L,dyn}$, $R_{aw}$, $\overline{P_{aw}}$ and $\dot{V}_E$ were calculated by a computerized system (PEDS, MAS, Hatfield PA, USA), as previously described [17]. 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 10 consecutive breaths over a period when there were no changes in ventilation strategy (i.e. constant $f_R$, $V_T$, *I:E* ratio, etc).

### E. Statistical Analyses.

Values are expressed as mean ± 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 SE+Graphics; Abacus Concepts Co., Orlando FL, USA). A *p*-value <0.05 was accepted as significant.

## III. Results

### A. Ventilatory Performance

The ventilator prototype was assembled on a portable and compact frame that could be easy managed and that facilitated making correct connections with animals. 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 cm$H_2O$) and temperatures (25 to 45°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.

The respirator system incorporates adjustable airway pressure safety limits for inspiration (50 cm$H_2O$) and active expiration (-20 cm$H_2O$). During the expiration cycle, if the lower airway pressure limit is reached, the current 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 10 and 25 cm$H_2O$, and between -5 and -15 cm$H_2O$, 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 to 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 $10^{-3}$ ± 0.7·$10^{-3}$ ml·cm$H_2O^{-1}$·kg$^{-1}$.

Pressure signals were measured over a range from -20 to 50 cm$H_2O$ during in vivo studies involving 10 newborn lambs. The system is capable of monitoring a range from -543 to 650 cm$H_2O$. Calibration experiments involving pressure signals resulted in a mean error of -1.0±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±1.7%.

Temperature signals had a physiological range of 25-45 °C during in vivo studies. The system is capable of measuring a range from near 0 to 100 $cmH_2O$. The regression coefficient between electrical signals provided by the temperature probes and its conversion to °C was $R^2$=0.999 ($p<0.001$). Therefore, the temperature error 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 error of $T_I$ and $T_E$ at different *I:E* ratios are summarized in Fig. 13. 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 to polygraph determinations were less than 100 ms and 2.56 %. Computerized measurements demonstrated the lowest mean errors (100 ms and -1.66%).

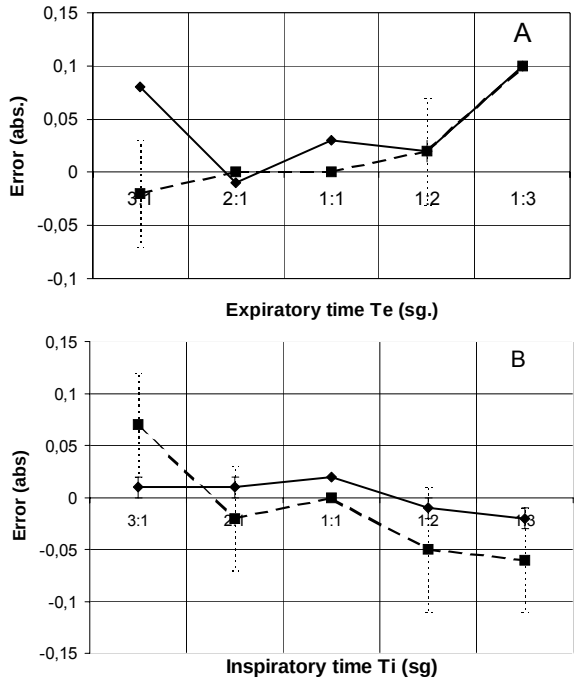


Fig. 13 Temporal errors in polygraph traces (♦) versus computerized (■) assessment of expiratory (A) and inspiratory (B) times with different I:E ratios. Mean ± SD. Te: expiratory time, Ti: inspiratory time, (abs.): absolute error

### C. Lung Mechanics System

The system can calculate dynamic compliance ($C_{L,dyn}$) from raw signals (volume and pressure) using equation (1), with a range from near 0 to 100 $ml \cdot cmH_2O^{-1} \cdot kg^{-1}$. In the 30 procedures performed (3 per animal, after 1, 2 and 3 hours), a physiological range of 1.04±0.02 to 2.68±0.01$ml \cdot cmH_2O^{-1} \cdot kg^{-1}$ was measured. Scatter of $C_{L,dyn}$ 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. 14A).

The system can calculate airway resistance ($R_{aw}$) from raw signals (pressure and flow) using equation (2), with a range from 0 to 11500 $cmH_2O \cdot l^{-1} \cdot s^{-1}$. The physiological range during *in vivo* studies involving 10 newborn lambs was 107±4 to 1659±21 $cmH_2O \cdot l^{-1} \cdot s^{-1}$. 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. 14B).

The system can calculate standardized work of breathing ($W_{OB}$) from raw signals (pressure, volume) using equation (3), with a range from 0 to 12300 $g \cdot cm \cdot kg^{-1}$. The physiological range during in vivo studies involving 10 newborn lambs was 62±1 to 1177±40 $g \cdot cm \cdot kg^{-1}$. Scatter of $W_{OB}$ 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. 14C).

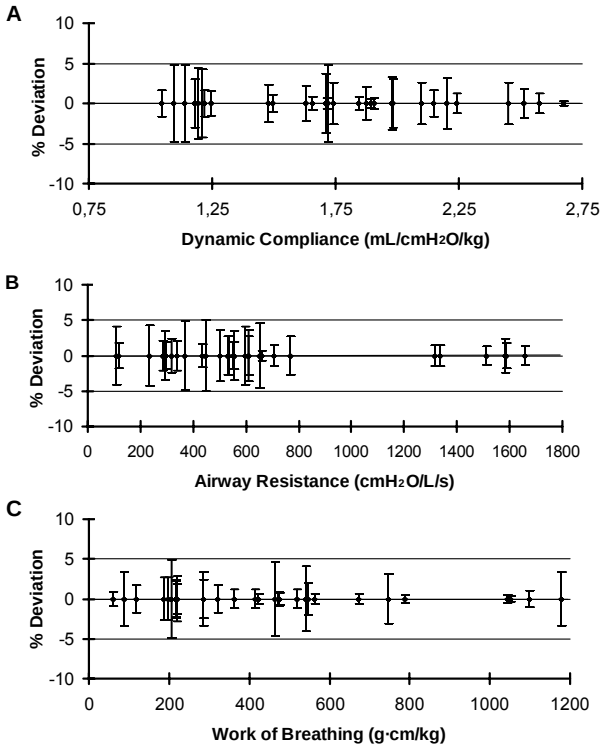


Fig. 14 Range of computed lung mechanics parameters. Values for $C_{L,dyn}$ (A) ranged from 1.04 to 2.68 $ml \cdot cmH_2O^{-1} \cdot kg^{-1}$, $R_{aw}$ (B) from 107 to 1659 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ and $W_{OB}$ (C) from 62 to 1177 $g \cdot cm \cdot kg^{-1}$

### D. In Vivo Experiments

Pulmonary lavage during gas ventilation produced a significant decrease of arterial pH and oxygenation, and an increase in $P_{aCO2}$ levels (Fig. 15). Tachycardia (increased heart rate) and pulmonary hypertension were associated with the lavage procedure, but no effects were observed on either cardiac output or systemic arterial pressure. The procedure, however, compromised the elastic properties of the lung decreasing $C_{L,dyn}$ (1.7±0.5 vs. 0.4±0.2 $ml \cdot cmH_2O^{-1} \cdot kg^{-1}$, $p<0.05$) and increasing in $R_{aw}$ (28±10 vs. 50±11 $cmH_2O \cdot l^{-1} \cdot s^{-1}$, $p<0.05$) and $\overline{P_{AW}}$ .

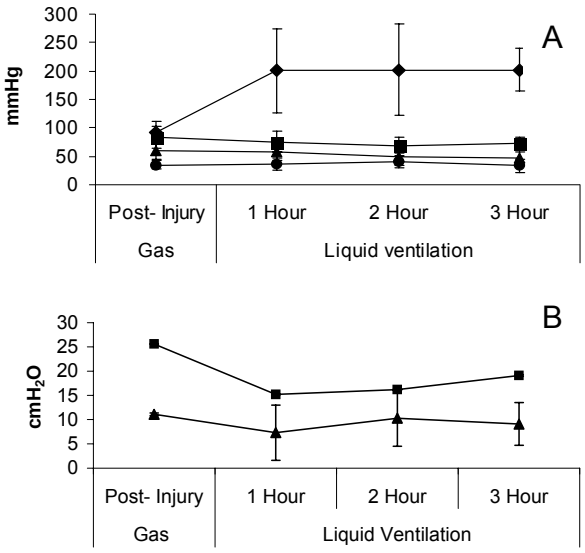


Fig. 15 Mean pulmonary gas exchange parameters during gas and liquid ventilation. Data are shown as mean ± SD. (#) ANOVA, $p<0.05$ vs. baseline; (*) ANOVA *post hoc* treatment, $p<0.05$ all values versus post-injury level. (A) $P_{aO2}$ (♦),$P_{aCO2}$ (■), Systemic arterial pressure (▲) and Pulmonary arterial pressure (●). (B) Quasi-static PIP (■) and mean airway pressure (▲)

After the start of total liquid ventilation, a 2-fold 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 4-fold improvement of $C_{L,dyn}$ ($2.0\pm0.5$ ml·cm$H_2O^{-1}$·kg$^{-1}$) with lower $\overline{P_{AW}}$ and $\dot{V}_E$ was observed with a large increase in $R_{aw}$ ($667\pm525$ cm$H_2O$·l$^{-1}$·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

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 cm$H_2O$ and PEEP's of -10 to 100 cm$H_2O$ [5], [6], [20]. 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%, $f_R$: 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.

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], [15]. 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 [21]. 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.), which suggest that the system accurately reflects physiological conditions in the lungs. This finding is also corroborated by the low variance of calculated values (Fig. 14).

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 to the measured minimum $C_{L,dyn}$. If $C_{circuit}$ were in the same range as $C_{L,dyn}$, then the accurate measurement of lung compliance becomes much more difficult. In our ventilator, $C_{L,dyn}$ was 570 times higher than $C_{circuit}$, suggesting that an accurate measure of lung compliance can be obtained.

Our ventilator prototype was able, in lung injured newborn lambs, 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 [22]. 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) [10], [23] and lung injured animals [11], [24].

The gas exchange data during liquid ventilation in our study 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 (3 hours). Moreover, some animals were sustained for up to 6 hours and cardiopulmonary status were maintain (n=3; $P_{aO2}$: $202\pm6$ mmHg; $Pa_{CO2}$: $45\pm4$ mmHg; systemic arterial pressure: $71\pm14$ mmHg; cardiac output: $347\pm78$ ml·min$^{-1}$·kg$^{-1}$), without the appearance of adverse clinical symptoms (i.e. incidence of perfluorothoraces, cardiovascular instability, etc…). Also, our

measurements of lung mechanics are closely similar to those previously described during total liquid ventilation [6], [25], [26].

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. 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) PFC's isolation in the respiratory circuit from the mechanical components that could be disposable.

## ACKNOWLEDGMENT

Authors are grateful to Mr. Jose Manuel Sainz de la Maza (SEW Eurodrive), Mr. Ricardo Murias, Miss Idoia Aparicio, Miss Mª Carmen Rey-Santano and BEN 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 Liquivent Study Group, "Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome," *N. Engl. J. Med.*, vol. 335, pp. 761-767, 11. 1996.

[2] J. S. Greenspan, W. W. Fox, S. D. Rubenstein, M. R. Wolfson, S. S. Spinner, T. H. Shaffer and Liquivent Study Group, "Partial liquid ventilation in critically ill infants receiving extracorporeal life support," Pediatrics, vol. 99, pp. e2, 1. 1997.

[3] V. K. Bhutani, "Pulmonary function profile: computer analysis and pulmonary graphics," in *Neonatal Pulmonary Function Testing: Physiological, Technical and Clinical Considerations*, V. K. Bhutani, T. H. Shaffer and D. Vidyasagar, Ed., 1st ed. Ithaca, N.Y.: Perinatology Press, 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] 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, pp. 1024-1031, 3. 1992.

[6] S. E. Curtis, B. P. Fuhrman and D. F. Howland, "Airway and alveolar pressures during perfluorocarbon breathing in infants lambs," *J. Appl. Physiol.*, vol. 68, pp. 2322-2328, 6. 1990.

[7] 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, pp. 341-354, 4. 1978.

[8] D. B. Kimless-Garber, M. R. Wolfson, C. Carlsson and T. H. Shaffer, "Halothane administration during liquid ventilation," *Respir. Med.*, vol. 91, pp. 255-262, 5. 1997.

[9] A. Valls-i-Soler, M. A. Gomez, E. Gastiasoro and F. J. Alvarez, "Perfluorocarbon liquid ventilation," in *Proc. XV European Congress of Perinatal Medicine*, 1996, pp. 250-256.

[10] 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, pp. 1436-1443, 3. 1988.

[11] 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, pp. 157-163, 1. 1995.

[12] J.L. Larrabe, F.J. Alvarez, E. Gastiasoro, L.F. Alfonso, A. Arnaiz, M.B. Fernandez, B. Loureiro, A. Valls-i-Soler, N.G. Publicover, L. Roman, J.A. Casla, M.A. Gomez. "Development of a time-cycled, volume-controlled respirator and lung mechanics system for total liquid ventilation". *IEEE Tran. Biomed. Eng*., vol. 48, pp. 1134-1144, 2001

[13] H. Nyquist. "Regeneration theory," Bell System Tech. J., vol 11, pp. 126-147, 1932.

[14] 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.

[15] W. Nikischin, T. Gerhardt, R. Everett and E. Bancalari, "A new method to analyze lung compliance when pressure-volume relationship is nonlinear," *Am. J. Respir. Crit. Care Med.*, vol. 158, pp. 1052-1060, 1998.

[16] 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.

[17] 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, pp. 198-202, 2. 1998.

[18] M. Sydow, H. Burchardi, E. Ephraim, S. Zielmann and T. A. Crozier, "Long-term effects of two different ventilatory modes on oxigenation in acute lung injury," Am. J. Respir. Crit. Care Med., vol. 149, pp. 1550-1556, 1994.

[19] 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.

[20] P. A. Koen, M. R. Wolfson and T. H. Shaffer, "Fluorocarbon ventilation: maximal expiratory flows and CO2 elimination," *Pediatr. Res.*, vol. 24, pp. 291-296, 3. 1988.

[21] 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, pp. 268-276, 3. 1999.

[22] 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.

[23] 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.

[24] 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, pp. 1001-1008, 6. 1996.

[25] 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.

[26] 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, pp. 79-88, 1. 1995.