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A Liquid Ventilator Prototype for Total Liquid Ventilation Preclinical Studies

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1. Introduction

1.1 Context

Mechanical ventilation is a life-saving procedure used for treating acute respiratory distress, when the respiratory system is no longer capable of regulating blood gases via pulmonary gas exchange. While conventional mechanical ventilation (CMV) is often sufficient to transiently replace lung function until recovery, the most severe respiratory distress syndromes must be treated either by non conventional mechanical ventilation such as high frequency ventilation or even non ventilator strategies such as extracorporeal gas exchange (Raoof et al., 2010).

Large literature data suggest a radical change in ventilator support by replacing the traditional gas mixture with a breathable liquid. This method, called liquid assisted ventilation, leads to the replacement of the air-liquid interface in the alveoli by a liquid-liquid interface. Since the 70s, perfluorocarbon liquids (PFC) have been identified as the best candidates to be used in liquid ventilation due to their high oxygen and carbon dioxide solubility (Wolfson & Shaffer, 2005). In addition, they are biochemically stable and bio-inert molecules, available as medical grade products including for respiratory use. Liquid assisted ventilation can be performed either as partial or total liquid ventilation. During partial liquid ventilation, only a fraction of the lungs are filled with perfluorocarbon liquid and a conventional mechanical gas ventilator ensures lung ventilation. In contrast, during total liquid ventilation (TLV), the lungs are completely filled with perfluorocarbon liquid while a dedicated device, called a liquid ventilator, must be used to periodically renew a liquid tidal volume in the lungs. A large number of preclinical studies involving various animal models of acute respiratory distress syndrome have demonstrated clear benefits from total liquid ventilation as compared to all other tested ventilation strategies, including partial liquid ventilation, conventional and high frequency gas ventilation (Hirschl et al., 1996; Wolfson et al., 2008). Among its several theoretical advantages over CMV, TLV is considered less aggressive for the lungs, due to lower positive inspiratory pressures and lower respiratory rates. This is felt to be beneficial in both pediatric and adult respiratory distress syndromes, where repeated alveolar overdistension during CMV contributes to

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acute and chronic lung injury (Chan et al., 2007; Hayes et al., 2010; Speer, 2009). Moreover, it offers a new means to clean the lung of inflammatory debris (Richman et al., 1992; Foust et al., 1996 Avoine et al., 2011). Consequently, a round table discussion of experts in liquid ventilation has unanimously recommended that a liquid ventilator must be developed for clinical applications (Costantino et al., 2009).

1.2 Problem

In TLV, minute ventilation has been previously reported to be a significant limiting factor for gas exchange (Bull et al., 2009; Matsuda et al., 2003), due to choked flows during expiration, which severely impede lung emptying and greatly decrease tidal volume (Koen et al., 1988; Baba et al., 2004; Robert et al., 2009). Even if the mechanical stresses of the collapses on the airway are not significant (Bagnoli et al., 2007), a decrease in minute ventilation can affect arterial blood gases. Previously, we have shown that the use of a pressure controlled mode prevents choked flows (Robert et al., 2010) and allows maximizing V_{min}. The location of the pressure sensor in the trachea is motivated by the fact that the expiratory collapses can occur in the first airway (Robert et al., 2009) or close to the carina (Bull et al., 2005). Hence, the pressure controlled mode maintains a constant acceptable negative pressure in the trachea during the expiratory flow, such that the limiting phenomena of collapse can be avoided (Robert et al., 2010). It is important to note that such control mode is new in TLV because all previously published liquid ventilator prototypes were controlled in volume (Baba et al., 1996; Corno et al., 2003; Hirschl et al., 1995; Polhmann et al., 2011; Sekins et al., 1999). However, the insertion of a pressure sensor in the mouth can be problematic in a clinical context, thus the main issue is to adapt this pressure controlled mode without a pressure sensor in the trachea.

Many efficient demonstrations of TLV have been performed with different prototypes (Corno et al. 2003; Cox et al. 2003; Degraeuwe et al., 2000a; Hirschl et al., 1995; Larrabe et al., 2001; Meinhardt et al., 2000; Parker et al., 2009; Pohlmann et al., 2011; Sekins et al., 1999; Tredici et al., 2004). With O_2 saturated PFC and limited to low minute ventilations (comparatively to CMV), they obtained acceptable ventilation. However, the use of O_2 saturated PFC has never been questioned, despite the fact that high concentrations of O_2 in the lungs are a well-known factor contributing to acute and chronic lung injury (Hayes et al. 2010; Speer 2009; Tasake et al., 2008). In addition, the use of O_2-saturated PFC during TLV often results in hyperoxia. This is particularly deleterious in neonatal medicine in which even a transitory hyperoxia can result in so-called neonatal oxygen radical disease. This disease affects multiple organs including lung, retina, gut and brain and results in acute and chronic morbidities with potential lifelong consequences (Bitterman, 2009; Dorfman et al., 2010; Gitto et al., 2009). Hence, an efficient liquid ventilator with a pressure regulated mode capable of reaching high V_{min} must include a device to control the oxygenation.

1.3 Objective

For the liquid ventilator prototype to reach the readiness level for clinical applications, the objective is dual. From an engineering perspective, it must ensure both targeted minute ventilation and oxygenation. From a medical perspective, it must resemble other conventional ventilators to be operated by clinicians in intensive care units.

Consequently, two distinct objectives are targeted:

i. Implement a pressure regulation mode, but with a pressure sensor located at the mouth and not in the trachea. Moreover, the proposition is to translate what has been done in

CMV to liquid ventilators: inspiration and expiration should be controlled in pressure (Simon et al., 2000). Finally, a control algorithm must prevent large lung volume which may compromise the cardiovascular system or induce a perfluorothorax (rupture of the lungs).

ii. Control the O_2 concentration in the inspired PFC, similarly to what is done in CMV with the control of oxygen concentration in inspired air (FiO_2).

2. Description of Inolivent-4

2.1 The prototype Inolivent-4

Following years of research in liquid ventilator development for animal experiments, this study presents the most advanced prototype of liquid ventilator, Inolivent-4 (figure 1). Its design is based on fundamental concepts developed for our third prototype, Inolivent-3 (Robert et al., 2006) and by including the most recent knowledge on flow dynamics in liquid ventilation (Bossé et al., 2010). Inolivent-3 comprises two independent piston pumps and an oxygenator unit which regroups the heating system, buffer reservoir and condenser (used to recuperate the PFC vapors emanating from the oxygenator columns). These concepts have demonstrated their efficiency during animal experiments and were maintained for our following prototype, Inolivent-4. The latter, compared to its predecessors, includes different ventilation control modes like those found on conventional ventilators (Robert et al., 2007b; Robert et al., 2010). From a clinician's point of view, volume controlled ventilation (VCV) during inspiration and pressure controlled ventilation (PCV) during expiration, greatly simplifies the use of liquid ventilator and minimizes the risk of incorrect ventilation parameter selection which could induce systematic airway collapses and lead to oxygen deprivation.

Parameter	Description	Unit
Fr	Respiratory frequency	RPM
V_t	Tidal volume	ml
$F_{gas}O_2$	Fraction of oxygen in the gas bubbled	%
T_i	Inspiration time	s
T_{eip}	End inspiration pause time	%
T_{eep}	End expiration pause time	%
$P_{ref,e}$	Expiration reference pressure	cmH_2O
$P_{ref,i}$	Inspiration reference pressure	cmH_2O
$P_{LIM,H}$	Upper inspiration limit pressure	cmH_2O
$P_{LIM,L}$	Lower expiration limit pressure	cmH_2O
$PEEP_{ref}$	Reference PEEP	cmH_2O

Table 1. Ventilation parameters available on the user interface.

The table 1 presents the basic ventilator parameters accessible on the touch screen user interface. A schematic of the ventilator circuit (figure 1) represents the PFC flow path. Its operation can be described by considering a typical liquid ventilation cycle. The cycle starts when the valve 1 is opened and the valve 2 is closed; a tidal volume of PFC is pumped from the buffer reservoir by the inspiration pump. When the inspiratory pump is ready, the valve 1 is closed, the valve 2 is opened. Then, the inspiratory pump pushes the tidal volume of PFC into the lungs. When the active inspiration phase is completed, the valve 2 is closed.

The inspiration pause is when both valves 2 and 4 are closed. Valve 4 is then opened and the active expiration starts: the expiratory pump removes the tidal volume of PFC from the lungs. Finally, the valve 4 is closed to operate the expiration pause. Simultaneously, the valve 3 is opened and the expiration pump pushes the PFC inside the filter which goes to the oxygenator. By overflow, the oxygenated PFC travels to the buffer reservoir. The time parameters (Fr and Ti) and the tidal volume serve as cycle limits. The end inspiration and expiration pauses are used to measure the positive-end inspiratory pressure (PEIP) and positive-end expiratory pressure (PEEP). The duration is proportional (in percentage) to the length of each phase. The upper and lower pressure limits stop the corresponding phase, in case the airway pressure goes beyond these values. The reference PEEP is used by the PEEP controller to correct the inspired or expired volume (see section *PEEP controller*).

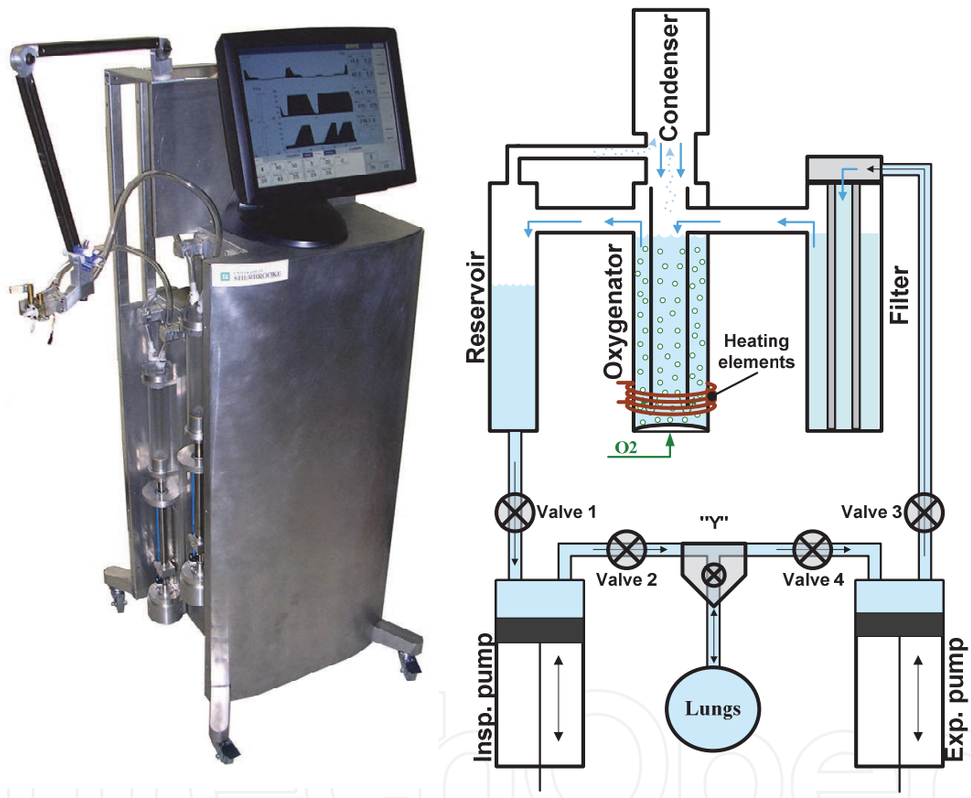

Fig. 1. Picture of Inolivent-4 (left) and the schematic of the ventilator circuit (right).

The "Y" piece (figure 2) is connected to the endotracheal tube (ET). It includes a mechanical 3 way valve to select the CMV port, the TLV circuit or the closed position. An airway pressure sensor can be located in the ET tube (via an epidural catheter inserted into the Y-piece) to monitor the tracheal pressure. A pressure sensor located in the Y-piece is used to measure the mouth pressure (*Py*). The new pressure controller regulates *Py* both during the inspiration and expiration phases.

All actuators and sensors are connected to a real-time control unit composed of a PC with two analog input boards (PCI-DAS1602, Measurement Computing, USA) and one analog output board (PCI-DAC6703, Measurement Computing, USA). The user interface is a touch screen PC which communicates with the real-time control unit.

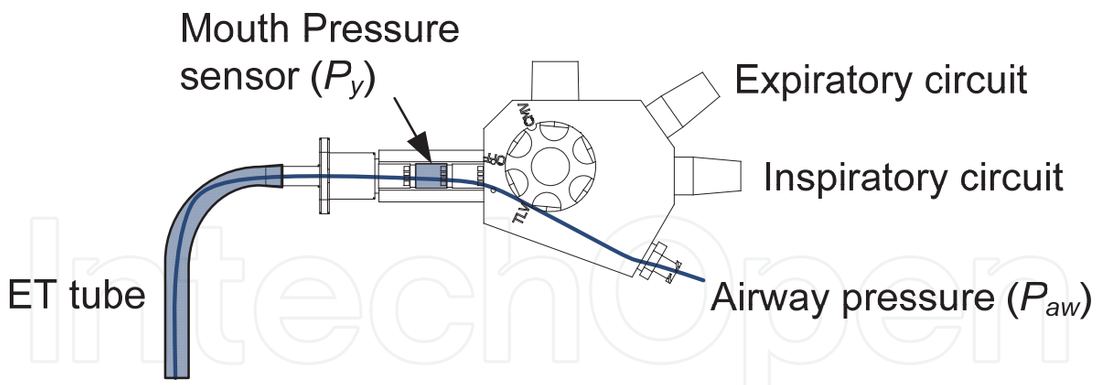

Fig. 2. "Y"-piece connected to the endotracheal tube.

2.2 Oxygenator description

Research teams in TLV have mainly used bubble oxygenators (Parker et al., 2009; Sekins et al., 1999; Tissier et al., 2009), commercial membrane oxygenators (Corno et al. 2003; Larrabe et al., 2001; Hirschl et al., 1995; Wolfson et al., 1999, 2008) or have developed membrane oxygenators specifically for TLV (Tredici et al., 2004). However, the requirements for extracorporeal blood oxygenation appear irrelevant in TLV, since there is no mechanical stress to the blood (hemolysis) or bubble infusion in the blood (Iwahashi et al., 2004). Hence, a bubble oxygenator seems acceptable for a clinical use.

The bubble oxygenator of Inolivent-4 is composed of 2 translucent, polycarbonate cylinders, which communicate with each other at the bottom of the inner cylinder (figure 3). When the PFC retrieved from the lung is pumped into the inner cylinder, an equivalent volume of PFC overflows into the outer cylinder and to the buffer reservoir. In this manner, the PFC coming from the lungs is not in direct contact with the PFC going to the lungs. Therefore the PFC residence time in the oxygenator is maximized. The gas to be bubbled flows through a perforated santoprene™ rubber membrane (McMaster, USA) at the bottom of the oxygenator. The latter has approximately 470 perforations made with a 1.2 mm diameter needle, (all equally spaced with a rounded pattern over the entire membrane surface) which generate bubbles into both cylinders (Beaudry, 2009). The stainless steel base contains three 100-watt cartridge heaters (Watlow, St-Louis, USA), which maintain the PFC at the targeted temperature. A condenser on top of the oxygenator liquefies the PFC vapors to minimize evaporative losses.

2.3 Oxygen concentration control

To control the O_2 concentration in the bubbled gas ($F_{gas}O_2$), medical air is blended with O_2 using a gas mixer system. The latter is composed of two proportional valves (ET-P-10-6025, Clippard, USA) controlled by two solenoid drives (B5950, Canfield Connector, USA). Each proportional valve controls the air and O_2 flow, measured by distinct flowmeter (41211, 41212, TSI, USA). The reference flow for each bubbled gas is computed based on the required $F_{gas}O_2$ and on the total gas flow requested by the user. These references and the measured flows are used by two separate feedback controllers (one for both gases), which were programmed using Simulink (MathWorks, MA, USA) and implemented with xPC target (MathWorks, MA, USA). An O_2 gas sensor (KE-25, Figaro, Japan) measures the $F_{gas}O_2$, allowing the latter to be modulated from 21% to 100%. Pressure regulators (MMR-1N-P60,

Clippard, USA) decrease line pressure while gas filters (C-02917-00, Parker, USA) remove unwanted particles, which could impair flowmeter measurements.

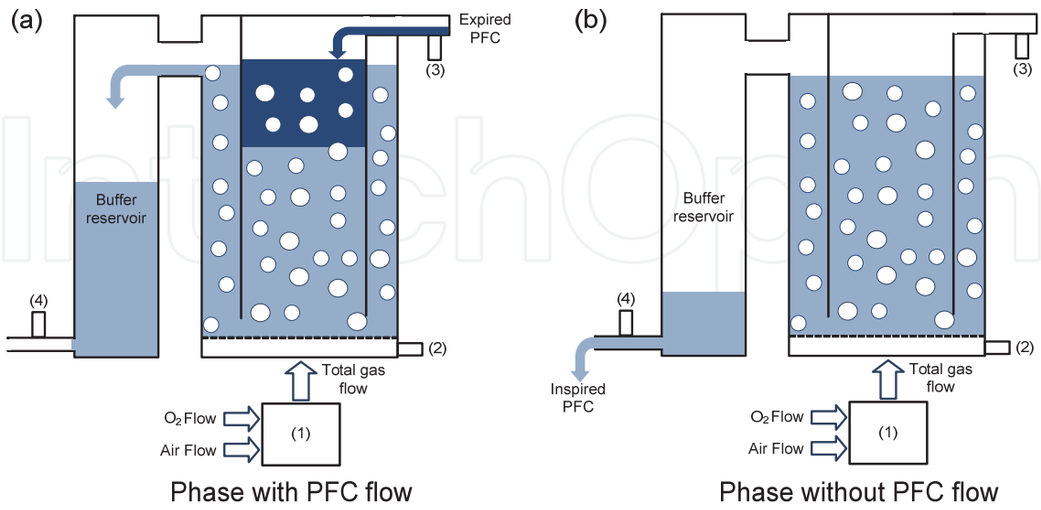

Fig. 3. Sketch of the oxygenator and the buffer reservoir with PFC flow (left) and without PFC flow (right). (1) Gas mixer system with O_2 gas sensor to measure $F_{gas}O_2$, (2) gas mixing chamber with a rubber membrane to generate bubbles, (3) circuit of the expired PFC with O_2 liquid sensor, (4) circuit of the expired PFC with O_2 liquid sensor, (a) when the expired PFC is inserted there is an overflow of PFC from the oxygenator to the buffer reservoir, (b) the inspired PFC is pumped from the buffer reservoir

In order to measure oxygen fraction concentration, a fluorescence sensor (Fibox 3 LCD, PreSens Precision Sensing GmbH, Germany) was used to determine the O_2 fraction in the PFC liquid, at the inspiratory ($Fi_{PFC}O_2$) and expiratory ($Fe_{PFC}O_2$) circuit alternately. Data were recorded with the software provided by PreSens (LCDPST3 V1.16, PreSens Precision Sensing GmbH, Germany). The 90th percentile response time of the sensor is 40 s and was measured in-vitro in our laboratory (Beaudry, 2009).

2.4 The pressure controller

2.4.1 The targeted pressure

The pressure controller commands the pumps during the inspiration and expiration to track desired pressure (figure 4) measured at the mouth, with the pressure sensor in the "Y-piece".

Before the inspiration, the airway pressure is equal to the PEEP which depends on the end-expiratory lung volume (V_{EELV}). At the start of the inspiration, the pressure (P_y) must increase from the PEEP level to the inspiratory reference pressure ($P_{ref,i}$) in less than 1 second. The pressure regulator regulates the inspiratory flow to maintain P_y within ± 1 cmH_2O of $P_{ref,i}$. When the tidal volume $V_{t,i}$ is completely inserted in the lungs or when the inspiration time T_i is reached, the inspiration is stopped. During the end inspiratory pause, the airway pressure is equal to the PEIP which depends on the end-inspiratory lung volume (V_{EILV}).

At the start of the expiration, P_y must decrease from the PEIP to the expiratory reference pressure ($P_{ref,e}$). The pressure regulator controls the expiratory flow which maintains P_y

within ± 1 cmH_2O of ($P_{ref,e}$). When the tidal volume $V_{t,e}$ is completely removed from the lungs or when the expiratory time T_e is reached, the expiration is stopped. During the end-expiratory pause, the airway pressure must reach the desired PEEP, called $PEEP_{ref}$. If not, modifications are done on the volume to be inspired or expired in order to correct the PEEP. Those modifications are made by the PEEP follower.

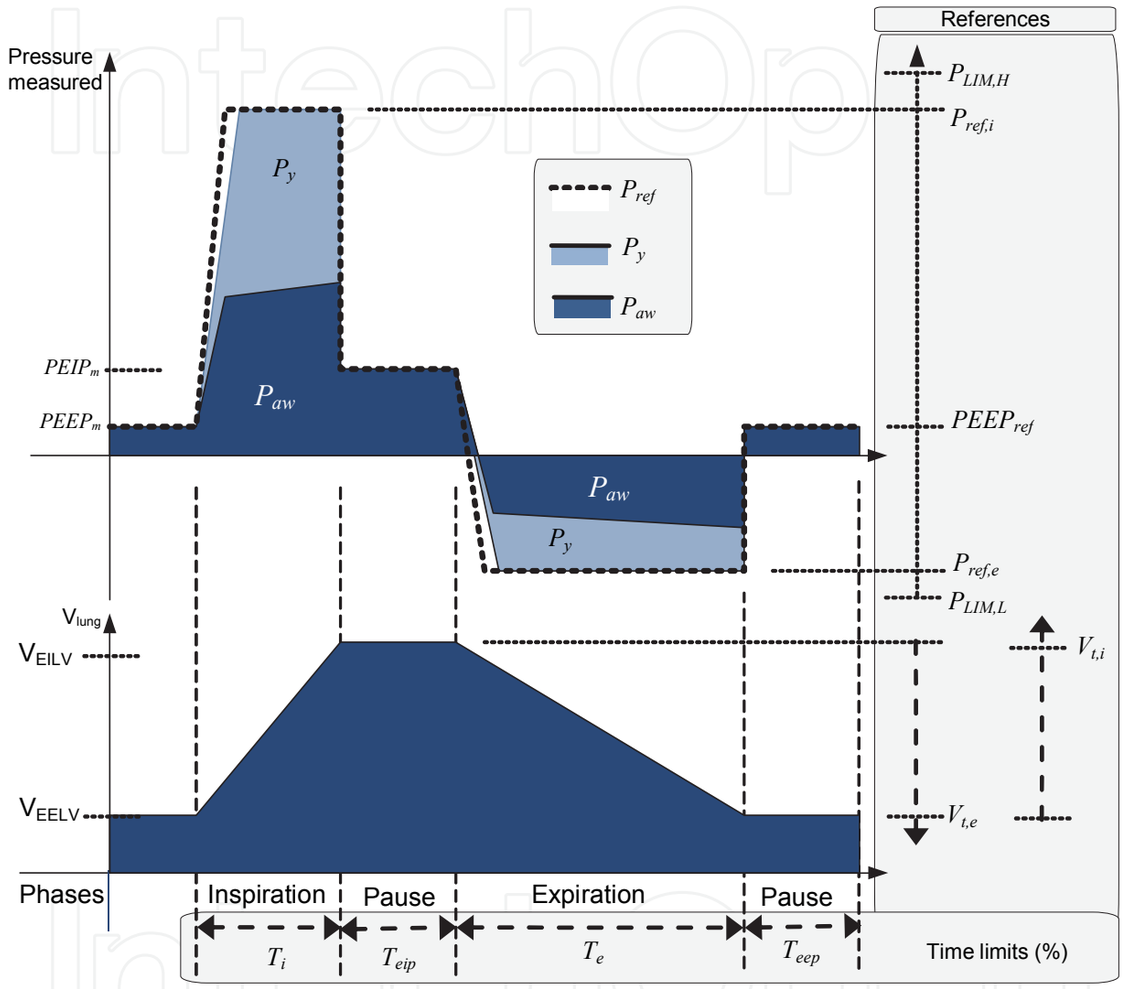

Fig. 4. Reference respiratory cycle in pressure regulated mode

2.4.2 The controller

Based on the work presented in a previous publication (Robert et al., 2010), the objective is to insert or remove the PFC liquid from the lungs at a specified pressure reference, $P_{ref,e}$ during expiration phase and $P_{ref,i}$ during inspiration. In control terms, the problem is to implement a feedback loop to command the pump, U, as a function of the error between the pressure reference, P_{ref}, and the Y pressure P_y as illustrated in figure 5.

The design of the pressure regulator for the inspiration and expiration was done by loop shaping, using the robust design toolbox of Matlab (Mathworks, USA). The pressure

regulator bandwidths were set at 2 Hz. The controller design follows a pole placement procedure where the process plant *P(s)* with a regulator *C(s)* leads to an open loop transfer function, chosen to be an integrator with a low pass filter at 100 rad/s.

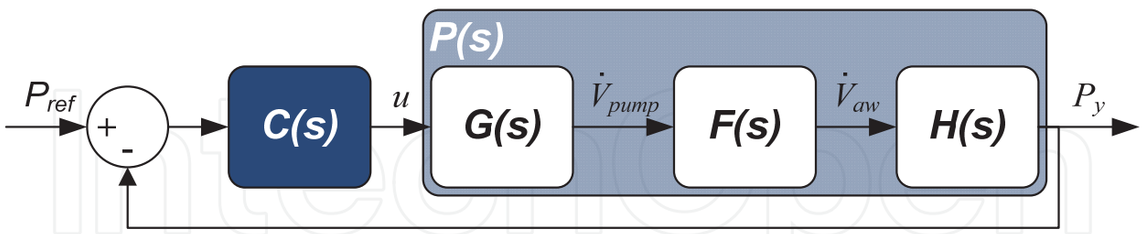

Fig. 5. Block diagram of the control system. C: Controller; G: Pump model; F: Tube dynamic; H: Lung model; P: Plant.

The robust control toolbox gave a lag filter coupled with a notch filter. The lag filter cancels the pole and zero of the motor, lungs and ET tube. The notch filter compensates for the tube resonance. Thus, the form of the controller is;

$$C(s) = K_c\left(\frac{1+\tau_c s}{1+\beta\tau_c s}\right)K_f^2\left(\frac{s^2+2/c\omega_f s+\omega_f^2}{s^2+2K_f d/c\omega_f s+K_f^2\omega_f^2}\right) \quad (1)$$

Where β and τ_c cancel the pole and zero of the lung, motor and ET tube, K_c is set to achieve the desired bandwidth, the gain K_f adjusts the filter gain in higher frequency (2.0), ω_f is the notch filter frequency (15 rad·s-1), c and d are the filter parameters (5.5). Gain scheduling was done in order to take into consideration all the ET tube diameters (from 4 to 6 mm) and different fluid properties (PFOB and PFDEC).

2.5 The PEEP controller

2.5.1 The specifications

The PEEP controller acts on the inspiration and expiration tidal volumes from cycle to cycle. It monitors the volumes inspired, the volume expired and the pressure measured during the end-expiration pause (PEEP). All these measures coupled with the PEEP reference set by the clinician ($PEEP_{ref}$), are used by the PEEP controller to adjust from cycle to cycle the volume pumped. In the end, the lung volume is corrected and the reference PEEP is tracked.
It is important to note the difference between the PEEP and the $P_{ref,e}$. In conventional mechanical ventilation, the PEEP set on the user interface is the pressure reference maintained in the airway by the pressure regulator. In TLV, the $P_{ref,e}$ is much lower than the PEEP in order to maximize the ventilation frequency. Since the PEEP is a clinical setting on all mechanical ventilators, a control scheme was developed for the liquid ventilator

2.5.2 The algorithm

PEEP regulation can be obtained by controlling the end-expiratory lung volume V_{EELV} with a supervisor (Robert et al., 2007a). Cycle after cycle, the balance between inserted and retrieved PFC volume can be used to increase or decrease V_{EELV}. The PEEP estimate takes into consideration the pumping errors that could occur during the expiration. The PEEP controller removes these volume errors from the PEEP measured during the expiratory pause ($PEEP_m$), since it is corrected by the supervisor.

As in a conventional mechanical ventilator, the clinician specifies a required PEEP ($PEEP_{ref}$). This value is compared to the PEEP estimated ($PEEP_{est}$) during the end-expiratory pause of the k^{th} cycle. The step of increasing or decreasing V_{EELV} (the volume correction ΔV) is proportional to the PEEP error (limited to avoid too large variations and/or instabilities) and expiratory volume error E_e:

$$\Delta V[k] = K_{PEEP}\left(PEEP_{est}[k] - PEEP_{ref}[k]\right) + E_e[k] \tag{2}$$

A limit is imposed on the estimated PEEP variation but not on the expiratory volume error. The equation 3 is used to estimate the PEEP.

$$PEEP_{est}[k] = PEEP_m[k] - \frac{E_e[k]}{K_{PEEP}} \tag{3}$$

Where K_{Peep} is a gain and $E_e[k]$ is the volume error measured during the expiration. Theoretically, the product of lung elastance $E_L = C_L^{-1}$ ($cmH_2O \cdot ml^{-1}$) and expiratory volume error E_e provides an exact estimate of the PEEP. However, for improved robustness, K_{Peep} was fixed. If the volume correction is negative, the volume to be inspired for the next cycle ($V_{t,i}[k+1]$) is lower than the tidal volume V_t in order to increase the lung volume

$$V_{t,i}[k+1] = \begin{cases} V_t & if \quad \Delta V \geq 0 \\ V_t + \Delta V[k] & if \quad \Delta V < 0 \end{cases} \tag{4}$$

If the volume correction is positive, the volume to be expired for the next cycle is lower than the tidal volume V_t in order to decrease the lung volume

$$V_{t,e}[k+1] = \begin{cases} V_t - E_i[k+1] & if \ \Delta V \leq 0 \\ V_t - E_i[k+1] - \Delta V[k] & if \ \Delta V > 0 \end{cases} \tag{5}$$

Where $E_i[k+1]$ is the inspiratory volume error for the $[k+1]^{th}$ cycle.

3. Validation of the oxygenator

3.1 Oxygenator time-constant measurement

The oxygenator is modeled as a first order system characterized by a time constant, τ. To measure the oxygenator time constant, the method consisted to perform a step time test: $F_{PFC}O_2(t)$ was recorded when the oxygen concentration in the bubbled gas is abruptly switched from $F_{gas}O_2(t)=0$ for $t \leq 0$ to $F_{gas}O_2(t)=100\%$ for $t>0$, at null initial condition ($F_{PFC}O_2(0)=0\%$). To generate this system excitation, pure CO_2 was first bubbled in order to retrieve all dissolved O_2 from the PFC. Once $P_{PFC}O_2$ reached less than 5 mmHg, the gas brought under the membrane was switched to pure O_2 at a fixed flow rate. The $P_{PFC}O_2$ was recorded at a sampling time of 1 second (figure 6 presents a typical measured time response) to compute off-line the $F_{PFC}O_2$.

The data was fed to the System Identification Toolbox of Matlab (Mathworks, USA) to identify the time constant values (by selecting a first order linear system) and its 95% confidence interval. The procedure was repeated for different oxygen flows by using incremental values of 0.5, 1, 2, 4, 6 and 8 L/min at a PFC temperature of 39°C. As can be

seen in the table 2, the smallest time constant was 14 seconds at an O_2 flow of 8 L/min. Thus, in the worst case scenario when there is no oxygen in the PFC, the concentration reaches 95% of the $F_{gas}O_2$ after 42 seconds. Fortunately, this case will not happen, since the expired PFC will always contain a certain amount of oxygen. A theoretical development can mathematically quantify this fact with the index α .

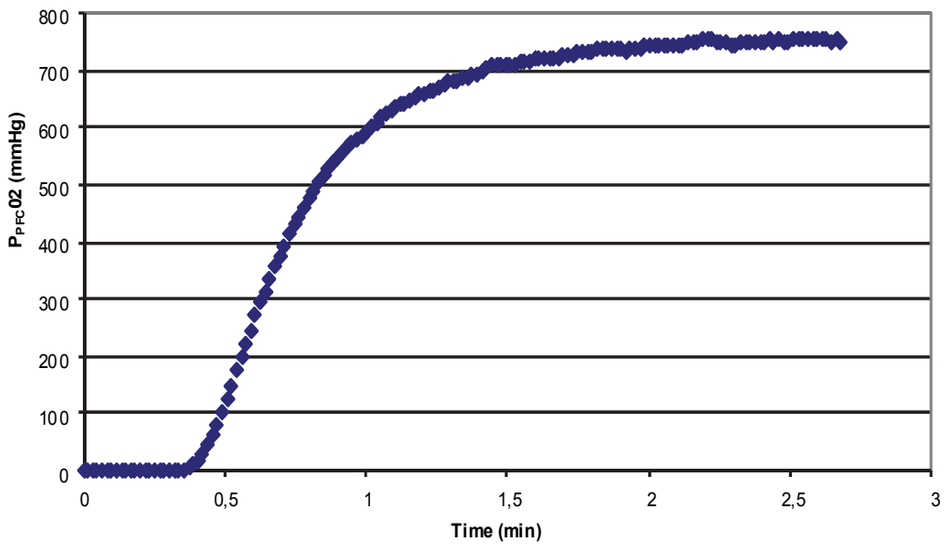

Fig. 6. Typical O_2 partial pressure variation measured in the PFC versus time at a flow rate of 6 l/min.

O_2 flow (L/min)	τ (s)	α (%)
0.5	167	38
1	77	58
2	41	73
4	22	85
6	17	89
8	14	91

Table 2. Identified time constants (in seconds) for different O_2 flow rates (L/min) at 39°C. The 95% confidence interval was equal or inferior to 1 second for all values. The α values are computed with equation (9) for t_c=10s and a=10%.

3.2 An index to evaluate the oxygenator efficiency

To quantify oxygenator efficiency throughout all of the experiments, the following index is computed:

$$\alpha = \left(Fi_{PFC}O_2 - Fe_{PFC}O_2\right) / \left(F_{gas}O_2 - Fe_{PFC}O_2\right) \tag{6}$$

An α equal to 0 signifies an inefficient oxygenator since $Fi_{PFC}O_2$ = $Fe_{PFC}O_2$. Conversely, an α equal to 1 signifies a perfect oxygenator since $Fi_{PFC}O_2$ = $F_{gas}O_2$.

Considering the dynamic response of the oxygenator as a first order system, it is possible to write the index of efficiency (6) as a function of the time constant and the ventilator parameters. In the following demonstration, the initial time refers to the instant when the tidal volume V_t is expired from the lungs and mixed with the PFC volume already present in the oxygenator. Considering the oxygenator as a first order system characterized by a time constant, τ, the initial oxygen concentration is assumed equal to the expired PFC mixed proportionally with the PFC volume in the oxygenator. Thus,

$$F_{PFC}O_2(0) = aFe_{PFC}O_2 + (1-a)Fi_{PFC}O_2 \tag{7}$$

where $a=V_t/V_0$ is the volume ratio, V_0 is the PFC oxygenator volume and the PFC tidal volume, V_t. The final cycle time, $t=t_c$, is when a V_t goes through the oxygenator to the buffer reservoir by overflow (when the tidal volume of PFC expired from the lungs is pushed into the oxygenator). Since the PFC in the buffer reservoir will be pumped to the lungs during the next cycle, the inspired oxygen concentration $Fi_{PFC}O_2=F_{PFC}O_2(t_c)$. Considering these assumptions, it is obvious that:

$$Fi_{PFC}O_2 = \alpha F_{gas}O_2 + (1-\alpha)Fe_{PFC}O_2 \tag{8}$$

Where the index defined by (6) is:

$$\alpha = \frac{1-\exp(-\frac{t_c}{\tau})}{1-\exp\left(-\frac{t_c}{\tau}\right)(1-a)} \tag{9}$$

An α equal to 0 occurs if the cycle time t_c is much smaller than the time constant ($t_c/\tau \rightarrow 0$). On the other hand, an α equal to 1 signifies a perfect oxygenator since $Fi_{PFC}O_2=F_{gas}O_2$. This case occurs if the tidal volume is smaller than the oxygenator volume ($V_t/V_0 \rightarrow 0$). Finally, an α superior to 90% indicates that the oxygenator is almost independent of expired PFC gas concentration since the contribution of $Fe_{PFC}O_2$ to $Fi_{PFC}O_2$ is inferior to 10%.

3.3 In-vivo validation of the oxygenator

3.3.1 In-vivo protocol

The experimental protocol was approved by our institutional Ethics Committee for Animal Care and Experimentation. For the in vivo protocol, five healthy newborn lambs (<4 days old, 2.5-3.6 kg) were intubated, anaesthetized and paralyzed as detailed previously (Robert et al., 2010). The lambs were premedicated by intramuscular injection, orally intubated with a 5.0 or 5.5 mm cuffed endotracheal tube (Mallinckrodt, St. Louis, MO) and restrained in supine position under radiant heat to maintain a central temperature of 39±1°C. The lambs were ventilated with a conventional mechanical ventilator (Servo 300 ventilator, Siemens-Elema AB, Solna, Sweden) in pressure-regulated, volume controlled mode (positive end-expiratory pressure (PEEP) = 4 cmH_2O, V_t = 10 ml/kg, FiO_2 = 100%, respiratory frequency (Fr) = 50 breaths/minute, inspiratory time on expiratory time ratio (I:E) = 1:2). The baseline parameters were recorded after 30 minutes. Inolivent-4 was then used to initiate and perform TLV. Lungs were first filled (25 ml/kg) with warmed (39.0 ± 0.5°C) and pre-oxygenated perfluorodecalin with a PEEP of 7 cmH_2O. TLV was then initiated (Fr =

5.35/minute, V_t = 20 ml/kg, I:E = 1:3, $F_{gas}O_2$ = 100%) (Robert et al. 2010). Fifteen minutes after reaching each new setting, the PFC partial pressure of oxygen, $P_{PFC}O_2$, was measured with the liquid sensor (Fibox 3 LCD, PreSens, Germany) in both the expired ($Pe_{PFC}O_2$) and inspired ($Pi_{PFC}O_2$) PFC. An arterial blood sample was also drawn for PaO_2 and $PaCO_2$ measurements.

Three different settings were tested using the following parameters. First a reduction in minute ventilation (V_{min}) from 180 to 120 ml/min/kg at an $F_{gas}O_2$ = 100% and constant gas flow of 6 l/min. Second, a reduction in gas flow from 8 to 0.5 l/min at an $F_{gas}O_2$ = 100% and constant V_{min} = 180 ml/min/kg. Finally, a reduction in $F_{gas}O_2$ from 100 to 65% at constant gas flow of 8 l/min and V_{min} = 180 ml/min/kg.

Prior to each experiment, the maximum O_2 partial pressure value in the PFC, $P_{PFC}O_{2,100\%}$, was noted in order to calculate both the O_2 concentration in the inspired PFC ($Fi_{PFC}O_2$=$Pi_{PFC}O_2$/$P_{PFC}O_{2,100\%}$) and the O_2 concentration in the expired PFC ($Fe_{PFC}O_2$=$Pe_{PFC}O_2$/$P_{PFC}O_{2,100\%}$). This value was obtained by bubbling pure O_2 in the oxygenator, during the TLV preparation phase (which is a closed-loop circulation of the PFC in the liquid ventilator). After 10 minutes, the measured O_2 partial pressure in the PFC was invariant and close to the atmospheric pressure. This measured value was noted as $P_{PFC}O_{2,100\%}$. The atmospheric pressure was measured with a precision dial barometer (4199, Control Company, USA).

Statistical values were obtained with the Statistics Toolbox provided with Matlab (Mathworks, USA). Statistical significance was assumed at $p < 0.05$. The Shapiro-Wilk test was first applied to each group to verify sample normality. The paired Student-t test was used to test a significant difference between two paired groups, after verification that homoscedacity was respected with the two samples F-test. The relationship between PaO_2 and $Fi_{PFC}O_2$ was established by using linear regression statistics (Seber, 1989) in order to compute the regression coefficients R^2. An F-test was finally performed on the slope.

3.3.2 In-vivo results

Upon transfer from conventional gas ventilation (V_{min} =602 ± 50 ml/min/kg; FiO_2=100%) to total liquid ventilation (V_{min}=180 ± 3 ml/min/kg; $F_{gas}O_2$=100%), blood gases were not significantly different (CMV: PaO_2=285 ± 87 mmHg, $PaCO_2$=39 ± 3 mmHg, pH=7.35 ± 0.05; TLV: PaO_2 = 217 ± 76 mmHg, $PaCO_2$=43 ± 5 mmHg, pH=7.25 ± 0.07).

Decreasing pure O_2 flow from 8 to 4 l/min (table 3) did not lead to a significant decrease in $Fi_{PFC}O_2$ and $Fe_{PFC}O_2$, the oxygenator efficiency index remaining in the range 80 to 73%. On the contrary, a significant decrease in $Fi_{PFC}O_2$ was observed for O_2 flow below 4 l/min. Despite this decrease in $Fi_{PFC}O_2$, no significant decrease in PaO_2 was observed for all O_2 flows tested and PaO_2 was maintained above 100 mmHg. Meanwhile, $PaCO_2$ and pH were significantly altered for pure O_2 flow at 0.5 l/min. Finally, the oxygenator efficiency index dramatically dropped at 54% for O_2 flow at 0.5 l/min, showing the inability of the oxygenator to saturate the PFC with O_2 at this flow level.

When $F_{gas}O_2$ was reduced from 100 to 65% (table 4), $Fi_{PFC}O_2$ decreased from 96 to 64% and $Fe_{PFC}O_2$ decreased from 80% to 31%. Between each decrement of $F_{gas}O_2$, significant differences were observed both in $Fi_{PFC}O_2$ and $Fe_{PFC}O_2$, although no significant differences were observed in oxygenator efficiency, which remained in the range of 96 to 80%. No significant differences were observed for either $PaCO_2$ or pH with the various $F_{gas}O_2$ tested. As expected, PaO_2 simultaneously decreased from 217 to 99 mmHg, a significant correlation being observed between PaO_2 and $Fi_{PFC}O_2$ (and the oxygenator efficiency index) in the 5 newborn lambs tested (Slope = 350 mmHg with R^2=0.37, Fisher test $p<0.05$).

	O_2 gas flow (l/min)					
	8	**6**	**4**	**2**	**1[1]**	**0.5[1]**
$Fi_{PFC}O_2$ (%)	96±1	96±1	95±2	94±1	93±2	88±2
$Fe_{PFC}O_2$ (%)	80±2	80±2	80±3	78±3	77±3	74±4
α (%)	80±7	77±4	77±9	73±7	69±7	54±7
PaO_2 (mmHg)	217±76	234±64	213±57	232±54	188±59	177±41[2]
$PaCO_2$ (mmHg)	43±5	41±3	44±5	47±4	50±6	60±10
pH	7.25±0.07	7.28±0.05	7.26±0.06	7.26±0.05	7.22±0.06	7.14±0.06

Table 3. In vivo results obtained in 5 newborn lambs while varying gas flow and maintaining $F_{gas}O_2$ at 100% and V_{min}=180 ml/min/kg. Data are presented as mean ± SD with underbraces indicating statistical significance ($p<0.05$). $Fi_{PFC}O_2$, oxygen fraction of inspired PFC; $Fe_{PFC}O_2$, oxygen fraction of expired PFC; α, oxygenator efficiency index; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of CO_2 in arterial blood; pH, arterial blood pH. [1]Data obtained with 4 lambs. [2]Measurements did not pass the Shapiro-Wilk normality test and were excluded from the significance test

	$F_{gas}O_2$ (%)					
	100	**90**	**80**	**75[1]**	**70[1]**	**65[1]**
$Fi_{PFC}O_2$ (%)	96 ± 1	89 ± 2	78 ± 1	74 ± 1	69 ± 1	64 ± 1
$Fe_{PFC}O_2$ (%)	80 ± 2	72 ± 5	61 ± 3	57 ± 3	52 ± 2	46 ± 4
α (%)	80 ± 7	96 ± 13	91 ± 7	93 ± 5	95 ± 5	95 ± 4
PaO_2 (mmHg)	217 ± 76	153 ± 53	133 ± 63	149 ± 53	100 ± 39	99 ± 47
$PaCO_2$ (mmHg)	43 ± 5	45 ± 6	44 ± 3[2]	43 ± 4	44 ± 5	45 ± 3
pH	7.25±0.07	7.23±0.07	7.25±0.05	7.25±0.06	7.26±0.06	7.25±0.06

Table 4. In vivo results obtained in 5 newborn lambs while varying $F_{gas}O_2$ at a constant gas flow of 8 l/min and V_{min} =180 ml/min/kg. Data are presented as mean ± SD with underbraces indicating statistical significance ($p<0.05$). V_{min}, minute ventilation; $Fi_{PFC}O_2$, oxygen fraction of inspired PFC; $Fe_{PFC}O_2$, oxygen fraction of expired PFC; a, oxygenator efficiency index; PaO_2, Partial pressure of oxygen in arterial blood; $PaCO_2$, Partial pressure of CO_2 in arterial blood; pH, arterial blood pH. [1]Data obtained with 4 lambs. [2]Measurements did not pass the Shapiro-Wilk normality test and were excluded from the significance test.

3.4 Discussion regarding the oxygenator

Results in the present and previous (Avoine et al., 2011; Beaudry 2009; Robert et al. 2010) studies show that our custom-designed bubble oxygenator can oxygenate PFC at a level up to $Fi_{PFC}O_2$=96%, which is similar to previously published data obtained with a silicone hollow fiber membrane oxygenator in rabbits (93%, when considering a standard atmospheric pressure of 760 mmHg) (Tredici et al., 2004) or commercial membrane oxygenator (84%) (Cox et al., 2003; Stavis et al., 1998). In addition, the maximal PaO_2 of 234 mmHg obtained herein is similar to the PaO_2 value of 201 mmHg previously reported in healthy newborn lambs by others (Hirschl et al., 1995; Larrabe et al., 2001; Stavis et al., 1998,

Cox et al. 2003). Beyond their low cost and simplicity of use, the present study clearly shows that bubble oxygenators can be highly efficient during TLV.

Our results highlight elevated PaO_2 values, which can be obtained in TLV in the presence of an O_2-saturated PFC, when minute ventilation is maximized. The present results show that it is possible to control PaO_2 during total liquid ventilation without altering alveolar ventilation or oxygenator efficiency. The PaO_2 can be controlled by adjusting the O_2 fraction in the gas flowing into the oxygenator, thus mimicking the method used in conventional gas ventilation. Reduction of gas flow to the oxygenator decreases the oxygenator efficiency index, with the most undesirable effect being the deterioration of the CO_2 removal before any effect on PaO_2 reduction. Similar results, on the high flow rate requirement in order to achieve an efficient CO_2 removal, were previously reported with a hollow-fiber oxygenator in a rabbit model (Tredici et al., 2004).

Finally, as expected, our method based on the control of $F_{gas}O_2$ with a gas mixer enabled us to adjust $Fi_{PFC}O_2$ and consequently to control PaO_2 down to safer values without significantly altering $PaCO_2$ and pH. The use of this particular method, which reproduces the manner in which FiO_2 is controlled in all existing conventional gas ventilators, has never been reported for TLV.

This study could be deemed as being limited to a specific PFC, a perfluorodecalin (PFDEC), since another PFC, the perfluoroctylbromide (PFOB), is usually considered as the PFC of choice for TLV. It was used in clinical studies I/II on partial liquid ventilation (Kacmarek et al., 2006; Hirschl et al., 1998, 2002). However, the conclusions should be the same, regardless of the PFC type, since the oxygenator is able to control the gas concentration, reach the desired oxygen fraction in the inspired PFC ($Fi_{PFC}O_2$) and remove the CO_2.

4. Validation of the pressure controller

4.1 In-vivo protocol

The experimentations were obtained with 10 healthy anaesthetized and paralyzed newborn lambs (age < 5 days, weight < 4 kg, 1 hours TLV trial with PFOB or PFDEC). The experimental protocol was approved by our institutional Ethics Committee for Animal Care and Experimentation. The lamb was placed in a supine position and an epidural catheter was inserted in the Y-piece such that the extremity extended 1 centimeter before the ET tube ending. The other end of the catheter was connected to a pressure sensor located at the same height as the ET tube in the trachea. The pressure sensor (Model 1620, Measurement Specialties, Hampton, VA) was used to measure airway pressure P_{aw} in the trachea.

After randomization, the lungs were filled at functional residual capacity (25 ml/kg) with warmed and oxygenated PFDEC or PFOB. After PFC instillation, total liquid ventilation was initiated in volume-controlled mode (during the first minute) at a rate of 5.35 breaths/minute and a V_t = 40 ml with an $F_{gas}O_2$ of 100%. Then, the ventilation modes were switched rapidly to pressure regulated modes for both inspiration and expiration and the pressure references $P_{ref,i}$ and $P_{ref,e}$ were adjusted to reach the desired tidal volume (25 ml/kg) at a frequency around 6.4 rpm.

4.2 In-vivo results

Figure 7 presents typical results for the pressure regulators during TLV using PFDEC and PFOB. The controllers were able to reach the pressure references, without oscillations. The airway pressure P_{aw} was much lower that the Y pressure P_y during the inspiration, since the

ET tube added a significant pressure loss in the fluid circuit. Those losses were highly influenced by the inside diameters of the ET tube (considered in the design of the controllers).

There was no airway collapse during the expiration even if the airway pressure was below −10 cmH_2O. The airway pressure decreased proportionally during the expiration. This can be explained as the pressure losses in the ET tube decrease with the flow which in turn, decreases exponentially with time, thus resulting in a proportional decrease of the airway pressure over time. The pressure references used during TLV with the PFOB are lower, because the PFOB viscosity is lower compared to the PFDEC, which affects directly the ET tube pressure losses.

The measured PEEP offset can be explained by looking closely at the volumes pumped in the lungs. With PFDEC, the requested tidal volume V_t was 2.5 ml/kg over the volume inspired $V_{t,i}$. This difference was directly reflected on the expiration volume error E_e (2.43 ± 0.69 ml/kg). The figure 8 presents typical results for the Peep controller during TLV using PFDEC and PFOB. For both PFC the $PEEP_{est}$ was near the $PEEP_{ref}$. There was a slight offset since the gain K_{Peep} used was not equal to the dynamic compliance measured. The table 5 indicates that the mean error between the $PEEP_{ref}$ and the $PEEP_{est}$ was around 0.3 ± 0.1 cmH_2O (PFDEC) and 0.4 ± 0.1 cmH_2O (PFOB). The measured PEEP was 2.7 ± 0.7 cmH_2O over the reference for the PFDEC and 1.4 ± 1.1 cmH_2O for the PFOB, once the ventilation parameters were stabilized. For both PFC, the PEEP controller was stable.

Using equation 3, it becomes obvious that an error on the expired volume will cause a PEEP offset. Since the PFOB is less viscous, it is easier to reach the requested tidal volume V_t. In consequence, the expiration error and the PEEP offset are smaller.

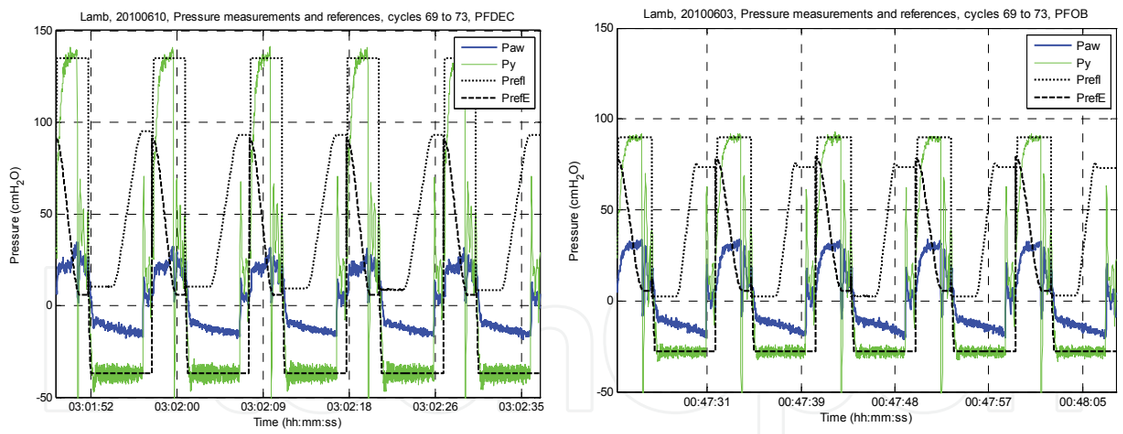

Fig. 7. Left graphic: Airway pressure (P_{aw}) and Y pressure (P_y) versus time for $P_{ref,i}$ = 135 cmH_2O and $P_{ref,e}$ = -37 cmH_2O using PFDEC. Right graphic: Airway pressure (P_{aw}) and Y pressure (P_y) versus time for $P_{ref,i}$ = 90 cmH_2O and $P_{ref,e}$ = -28 cmH_2O using PFOB

The table 5 presents the numerical results obtained on 5 newborn lambs (< 4 days old) per PFC group (PFOB and PFDEC). The inspired and expired volume for both groups were similar, but the frequency reached using PFOB was higher, even if the pressure reference and PEEP measured were lower. Again, the viscosity of the PFDEC is the explanation behind these observations. Adequate gas exchange and normal acid-base equilibrium were maintained during TLV.

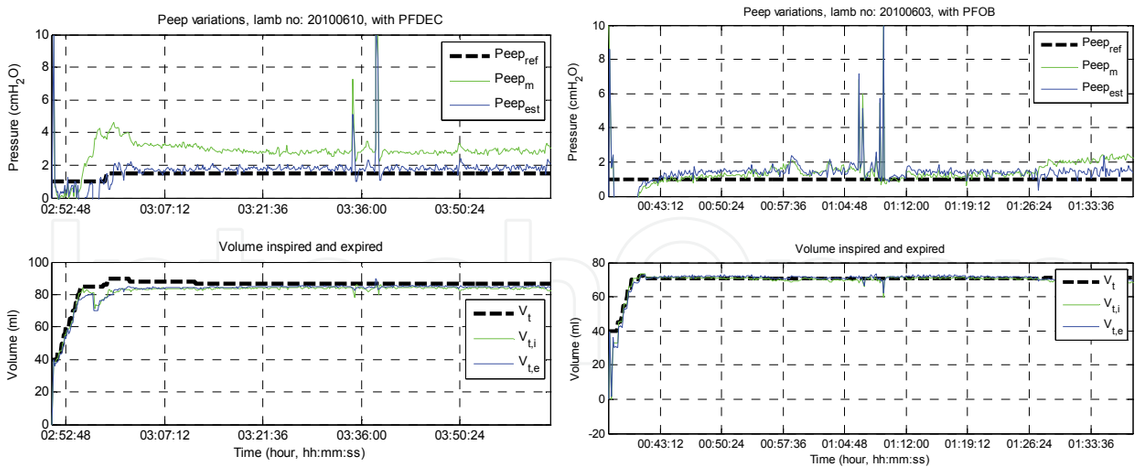

Fig. 8. Left top graphic: typical evolution of the PEEP measured ($PEEP_m$), estimated ($PEEP_{est}$) and reference ($PEEP_{ref}$) over a complete experiment with PFDEC. Left bottom graphic: typical evolution of the inspired ($V_{t,i}$) and expired volume ($V_{t,e}$) versus the tidal volume (V_t) for PFDEC. Right top graphic: typical evolution of the PEEP measured ($PEEP_m$), estimated ($PEEP_{est}$) and reference ($PEEP_{ref}$) over a complete experiment with PFOB. Right bottom graphic: typical evolution of the inspired ($V_{t,i}$) and expired volume ($V_{t,e}$) versus the tidal volume (V_t) for PFOB. References are shown in bold for the $PEEP_{ref}$ and V_t.

	PFDEC		**PFOB**	
V_t (ml/kg)	26.9	± 0.6	25.9	± 0.9
$V_{t,i}$ (ml/kg)	24.4	± 0.7	24.9	± 0.4
$V_{t,e}$ (ml/kg)	24.6	± 0.6	25.2	± 0.4
E_i (ml/kg)	-0.14	± 0.51	-0.41	± 0.05
E_e (ml/kg)	2.43	± 0.69	1.07	± 1.00
$P_{ref,i}$ (cmH_2O)	152.7	± 46.3	111.5	± 17.3
$P_{ref,e}$ (cmH_2O)	-39.1	± 8.02	-32.9	± 5.6
Fr (rpm)	6.14	± 0.13	6.43	± 0.08
V_{min} (ml/min/kg)	149.7	± 5.9	160.3	± 3.3
$PEEP_{ref}$ (cmH_2O)	1.8	± 0.6	1.0	± 0.1
$PEEP_{est}$ (cmH_2O)	2.1	± 0.7	1.3	± 0.2
$PEEP_m$ (cmH_2O)	4.5	± 1.0	2.3	± 1.1
PaO_2 (mmHg)	285.0	± 67.0	288.3	± 91.4
$PaCO_2$ (mmHg)	52.9	± 10.9	37.2	± 10.2
pH	7.29	± 0.11	7.39	± 0.11
$F_{gas}O_2$	1.0	± 0.0	1.0	± 0.0

Table 5. Results of 5 healthy newborn lambs for each TLV group (< 4 days old). (mean ± standard deviation)

4.3 Discussion regarding the PEEP-controller

The proposed PEEP controller manages directly the end-expiratory alveolar pressure (by controlling the PEEP) and all the measurable volume errors. However, all measurable volume errors do not include sensor non-linearities, machining tolerances and analog input precisions, so the lung volume can derive positively or negatively, if and only if such volume derivatives have no impact on the alveolar pressure. In the normal case, the control of the end-expiratory alveolar-pressure is equivalent to the control of the end-expiratory lung volume (EELV) because there is a direct relationship between these two variables (Degraeuwe et al., 2000b; Parker et al., 2009).

5. Conclusion

The oxygenator presented at the beginning of this chapter shows that we can control the oxygen fraction of the inspired PFC and removal of all the CO_2 contained in the expired liquid. This control of the oxygen concentration, $Fi_{PFC}O_2$, permits the adjustment of the arterial partial pressure of oxygen PaO_2 without any consequence on the arterial partial pressure of CO_2, $PaCO_2$. A decrease in the oxygen flow rate through the oxygenator is not a suitable solution, since they it compromises the $PaCO_2$, before any effect on PaO_2 reduction.

The choice of a bubble oxygenator could be seen as a limitation, since most research groups use membrane oxygenators with TLV (Corno et al. 2003; Cox et al. 2003; Hirschl et al., 1995; Larrabe et al., 2001; Parker et al., 2009; Pohlmann et al., 2011; Tredici et al., 2004). On the contrary, we strongly believe that bubble oxygenators are quite suitable for TLV. Beyond their low cost and simplicity of use, the present study shows that they can be highly efficient during TLV.

The presented pressure controlled ventilation modes seem similar to those used in conventional gas ventilators, although there are some differences. The PEEP follower maintains the end-expiratory alveolar pressure constant by commanding volume corrections based on the end-expiratory pressure. The pressure references $P_{ref,i}$ and $P_{ref,e}$ are higher compared to CMV. The pressure controlled mode eliminates the airway collapses and favors higher minute ventilation. Thus, it can be implemented successfully on liquid ventilators during the inspiration and expiration phases. When used in conjunction with the oxygenator presented, the arterial blood gases can be maintained in a normal range throughout the liquid ventilation. As for the PEEP controller, the latter compensates all the volume errors (measurable and non-measurable) from cycle to cycle, which secures the TLV by avoiding lung overdistension.

There is still room for improvement, as the observed results do not fully comply with the defined specifications. The PEEP controller is able to estimate quite well the real PEEP, but the measured PEEP can increase since the expired volume is not reached. Modifications will be performed to improve PEEP tracking. In some ventilation cycles, the volume expired is not achieved. Thus, the pressure limit $P_{ref,e}$ could be adapted from cycle to cycle to increase the expired volume. Nevertheless, the pressure regulators and PEEP controller have greatly improved the ventilation efficiency and simplified the interaction with the liquid ventilator, since all the volumes and errors are managed by controllers from cycle to cycle.

In the ultimate objective of transferring liquid ventilators into intensive care units (Costantino et al., 2009), we strongly recommend the addition of a gas mixer to the oxygenator (to adjust the O_2 concentration) coupled with pressure controlled ventilation mode as two efficient means to maintain normal blood gases during TLV.

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