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Flow Limitation in Liquid-Filled Lungs: Effects of Liquid Properties

Flow limitation in liquid-filled lungs is examined in intact rabbit experiments and a theoretical model. Flow limitation ("choked" flow) occurs when the expiratory flow reaches a maximum value and further increases in driving pressure do not increase the flow. In total liquid ventilation this is characterized by the sudden development of excessively negative airway pressures and airway collapse at the choke point. The occurrence of flow limitation limits the efficacy of total liquid ventilation by reducing the minute ventilation. In this paper we investigate the effects of liquid properties on flow limitation in liquid-filled lungs. It is found that the behavior of liquids with similar densities and viscosities can be quite different. The results of the theoretical model, which incorporates alveolar compliance and airway resistance, agrees qualitatively well with the experimental results. Lung compliance and airway resistance are shown to vary with the perfluorocarbon liquid used to fill the lungs. Surfactant is found to modify the interfacial tension between saline and perfluorocarbon, and surfactant activity at the interface of perfluorocarbon and the native aqueous lining of the lungs appears to induce hysteresis in pressure–volume curves for liquid-filled lungs. Ventilation with a liquid that results in low viscous resistance and high elastic recoil can reduce the amount of liquid remaining in the lungs when choke occurs, and, therefore, may be desirable for liquid ventilation. [DOI: 10.1115/1.1934099]

Introduction

Flow limitation, also known as "choked" flow, occurs when the expiratory flow reaches a maximum value and further increases in driving pressure do not increase the flow. This phenomenon has been studied extensively in the context of gas ventilation and in the context of vessel collapse in veins [1,2]. The flow of liquid or gas through flexible tubes, such as airways, can be described in terms of the physical properties of the tubes, and the fluids, as well as airway, alveolar, and pleural pressures. It would be expected that different perfluorocarbons (PFCs) would have different flow characteristics dependent on their density and viscosity.

In classic papers on flow limitation, Dawson and Elliot, and Shapiro [3–5] have shown that the maximum flow of a fluid medium through an elastic tube is limited at the speed of propagation of pressure pulse waves along the tube, which is defined as

$$\dot{V}_c = \left(\frac{A^3 dP/dA}{q\rho} \right)^{1/2} \quad (1)$$

where A =cross sectional area of any point along the tube, dP/dA =local stiffness of the tube, ρ =density of the fluid and q =a correctional constant for departure from blunt velocity profiles ($q=1.33$ for Poiseuille flow) [3–5]. This modeling approach has been effective in describing the local airway velocity at which flow limitation occurs in lungs and in the corresponding benchtop experiment, the Starling resistor. The flow-limited airway will collapse when the transmural pressure is equal to the buckling pressure, which depends on a variety of factors, including airway

properties, lung volume, and the buckling mode of the airway. A variation on this one-dimensional approach to include airway resistance provided good agreement with gas flow in excised dog tracheae mounted between two reservoirs [6]. Other models have approximated airway branching [7–11], and a number of theoretical and experimental studies have focused on flow limitation in the context of maximum expiratory flows [12–20]. More complicated models [21–28] of flow in flexible tubes and flow limitation have considered wall inertia, two- and three-dimensional geometries, and more complicated wall laws. The three-dimensional geometries allow for asymmetry of the tube when it buckles. Other investigations [29–32] have addressed flutter in flow limited collapsible tubes and the related wheezes and lung sounds.

Considerably less literature exists on flow limitation in liquid-filled lungs. While the mechanics of flow limitation in liquid-filled lungs are expected to be similar to those of gas-filled lungs, the higher viscosity and density of liquids may result in differences in the location of choke, maximum flow rate, and regional emptying of the lungs. Previous work has investigated flow limitation in excised lungs [33,34] and in intact animals [35], but has not investigated the effects of liquid properties on flow limitation. Total liquid ventilation (TLV) involves filling the lungs with a perfluorocarbon (PFC) liquid [36] and mechanically ventilating the lungs with a liquid tidal volume. The application of perfluorocarbon liquid to provide an adequate gas exchange when used as a ventilating fluid in animal experiments has been described [37,38]. TLV has not yet been widely implemented clinically, although TLV [39] and partial liquid ventilation (which involves partially filling the lungs with liquid and ventilating with a gas tidal volume) [40,41] have shown potential in clinical trials.

Maximal expiratory flow rates during assisted liquid expiration are 20 to 100 times lower than those in gas ventilation [35]. This is because the densities of perfluorocarbons are much greater than those of air, and, consequently, the wave speeds are much lower. To avoid flow limitation, expiratory flow rates are usually set at

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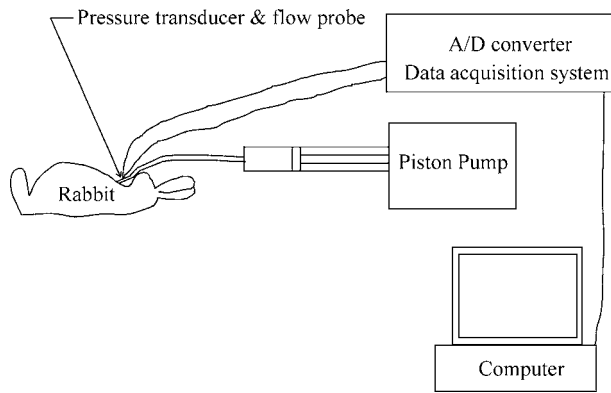


Fig. 1 Sketch of setup for flow limitation experiments. A computer-controlled piston pump provides constant flow expiration. Pressure and flow data is acquired via an A/D converter and data acquisition system.

low, constant levels in animal models of TLV. This limits respiratory rate (3–9 breaths/min), minute ventilation, and carbon dioxide clearance [35]. Understanding flow limitation in liquid-filled lungs will be essential to designing liquid ventilation strategies and for selecting optimal PFCs for TLV. In this paper we investigate the effects of liquid properties on flow limitation in liquid-filled lungs, using an intact rabbit model and a lumped-parameter, theoretical model that includes airway resistance and alveolar compliance effects.

Materials and Methods

Flow Limitation Experiments. This protocol was approved by the University of Michigan Department of Laboratory Animal Management (ULAM). New Zealand white rabbits weighing 2.5–4.5 kg were weighed and anaesthetized with intramuscular xylazine (Lloyd Laboratories, Shenandoah, IA) (5 mg/kg) and ketamine (Fort Dodge Animal Health, Fort Dodge, IA) (20 mg/kg). After ensuring adequate sedation an ear IV catheter was placed and a tracheostomy was performed. A transverse cervical incision was made and the trachea identified. A 3/16 in. steel tracheostomy tube 3 cm long was advanced into the trachea for a length of 1.5–2.0 cm and the trachea was doubly secured with silk suture to prevent fluid leak and dislodgement. The tracheostomy tube was connected to 1/4 in. Tygon (Fisher Scientific, Pittsburgh, PA) tubing by an adapter. Heparin (Elkins-Sinn, Cherry Hill, NJ) (1000 units/kg) was injected into the ear IV and the rabbit was mechanically ventilated using pure oxygen for five minutes. Because oxygen is readily absorbed by PFC, this was expected to minimize gas trapping within the lungs when they were filled with PFC, and result in lungs that were completely liquid filled. The rabbit was euthanized with Beuthanasia (Schering-Plough Animal Health, Union, NJ) (0.5 ml/kg) and connected to the experimental circuit. A schematic of the experimental setup is shown in Fig. 1. The rabbit was placed on a load cell table (Omega LCEA-5, Omega, Stamford, CT) to measure weight and the scale was zeroed. Four different PFCs were included in the study (see Table 1). These were perfluorooctylbro-

me (PFOB), perfluorodecalin (PFDEC), PP4, and FC77 (PFOB, PP4, PFDEC from F2 Chemicals, Preston, England, FC77 from 3M Specialty Materials, St. Paul, MN). The rabbit's lungs were filled to a 40 ml/kg end inspiration lung volume (EILV) of the selected PFC. The filling was by a slow, direct injection of PFC into the Tygon tubing, using gravity to distribute the PFC into the lungs. PFC was instilled into the Tygon tubing at the end of the endotracheal tube until PFC was visible in Tygon tubing following instillation. The chest of the rabbit was massaged during filling in an attempt to reduce trapped gas bubbles. The Tygon tubing was connected to the circuit (a stopcock and tubing connected to the piston pump), which was initially primed. Additional PFC was instilled into the animal's lungs through a stopcock in the circuit. The circuit was clamped between the stopcock and the rest of the circuit, such that the additional instillation of PFC entered the lungs of the rabbit. Once the lungs were filled to 40 ml/kg, the instillation was stopped. The volume of instilled PFC was carefully measured, and the animal weight change during the filling process provided a check that the instilled volume was accurately measured.

After verifying all connections, the clamp was removed and airway pressure was measured at the endotracheal tube. The servo (SmartMotor NEMA 23, Animatics Corporation, Santa Clara, CA) was programmed with specific settings that were previously determined to result in constant flow rates of 2.5, 5.0, 7.5 ml/s. An electronic control circuit was used to immediately stop pump flow when the airway pressure, measured at the exit to the endotracheal tube, dropped below -25 cm H_2O . Previous work has shown this pressure at the endotracheal tube exit to correspond with the onset of choke, usually in the trachea or at the carina, in rabbit lungs [42,43]. The computer controlling the pump piston was programmed by setting a distance to travel and a velocity for the travel (the travel distance was set to maximum of 200 cm for each trial). After 3–4 breaths at 1.25 ml/s to completely debubble the circuit, the piston position was verified at the origin position and 9 trials of exhalation were begun.

For each trial flow rate, starting airway pressure, and pump piston position at the choke point were recorded. The piston was returned to origin position at a 2.5 ml/s flow rate and the next trial was begun. The expiratory flow rate was randomized in order over the nine trials to produce three trials at each expiration rate. The motor position was converted to a volume measurement by a conversion factor that was previously determined over the range of multiple flow rates to have an accuracy of ± 0.1 ml. The volume remaining in the lungs at the point of choke, V_{ch} , was determined by subtracting the mean exhaled volume [normalized to weight (ml/kg)] at a given flow rate from the EILV (40 ml/kg). The accuracy of these volume measurements was confirmed by the instantaneous weight measurements. Each trial lasted from 10 to 40 s, with a minimal delay between trials, thus all measurements were completed within 30 min of euthanasia of the animal. Previous data from our laboratory have demonstrated that minimal effects upon parameters relative to flow limitation experiments are noted within 40–60 minutes of euthanasia in rabbits [42,44]. A necropsy was performed on each animal to assess the presence of PFC in the pleural spaces (*perfluorothorax*) and, if identified, the animal was not included in data analysis. The weight and starting airway pressures were compared between groups by ANOVA. The

Table 1 Characteristics of PFC's in this study

	PDEC	PP4	FC77	PFOB
Formula	$C_{10}F_{18}$	C_9F_{18}	$C_8F_{16}O$	$C_8F_{17}Br_1$
Molecular Weight, g/mole	462	450	415	441
Density, g/ml	1.93	1.89	1.78	1.92
Kinematic Viscosity, cS	2.90	1.20	0.80	1.10
Surface Tension (with air), dyne/cm	18	15	18	19

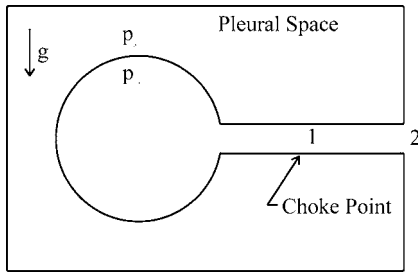


Fig. 2 Sketch of model geometry. The alveoli are modeled by a compliant sphere and the airways by a rigid tube. The thoracic cavity is modeled as a rigid box containing the pleural fluid and lungs. Gravity acts normal to the trachea as in the experiments.

V_{ch} data were compared between groups using a general linear model in SAS (SAS Institute, Inc., Cary, NC), using ANOVA and post-hoc Tukey test with a p value of <0.05 was considered significant. Data are presented as mean \pm standard deviation.

Theoretical Model. To qualitatively explain the differences in V_{ch} for different PFCs we developed a lumped-parameter model. A sketch of the model system is shown in Fig. 2. Lung compliance is assumed to be due to the compliance of the alveoli and only airway resistance is considered. In this simplified model, the alveoli are represented by a compliant element and the airway in which choke occurs by a tube. The governing equation is a modified Bernoulli equation, which accounts for viscous resistance in the airways, between an alveolus and the choke point.

$$\rho g h_{av} + p_{av} = \frac{\rho v_1^2}{2} + \rho g h_1 + p_1 + QR. \quad (2)$$

Here, the subscript av denotes alveolar, the subscript 1 denotes the choke point, ρ is density, h is height, Q is flow rate, R is resistance, g is acceleration due to gravity, and v is cross-sectionally averaged velocity. Turbulent resistance terms that scale as Q^2 are neglected because the flows here are laminar due to the high viscosity of PFC and the low rates in TLV. For these experiments, the Reynolds number in the trachea at the highest flow rate (7.5 ml/s) was estimated to be 690, 1670, 2500, and 1820 for PDEC, PP4, FC77, and PFOB, respectively. These values are below the typically assumed value of ~ 4000 for fully turbulent flow in tubes of circular cross section [45]. At the other two flow rates (2.5 and 5 ml/s), the Reynolds numbers were much lower, and were less than 2000 for all PFC's. This simplified approach ignores the fact that airway resistance is not constant and depends on lung volume. In light of the goal of explaining the reasons for the behavior observed in the experiments, we consider this to be an appropriate simplification. Alveolar pressure at a given instant in time can be related to the flow rate by

$$p_{av} - p_{pl} = \frac{V - V_{min}}{C} = \frac{V_0 - Qt - V_{min}}{C} \quad (3)$$

where p_{pl} is the pleural pressure at the alveoli, V is lung volume at time, t , V_0 is the initial lung volume, V_{min} is the lung volume corresponding to zero pressure difference across the lung wall, C is lung compliance, and Q is considered constant as is the case in the experiments. The transmural pressure at the choke point is calculated by

$$p_{tm} = p_1 - (p_{pl} + \rho_{pl}gL) \quad (4)$$

where $L = h_{av} - h_1$ is the elevation difference between the alveolus and the choke point. In this simplified model, we ignore pleural flows and assume that the pleural pressure gradient is primarily due to gravity. Combining these equations, we obtain

$$p_{tm} = \frac{V_0 - Qt}{C} - \frac{V_{min}}{C} - \rho \frac{Q^2}{2A_1^2} + \Delta\rho gL - QR \quad (5)$$

where $\Delta\rho = \rho - \rho_{pl}$, and $A_1 = Q/v_1$ is the cross-sectional area of the airway at the choke point. At choke, the liquid volume in the lung is $V = V_{ch}$, and the transmural pressure is equal to the buckling pressure of the airway, $p_{tm} = p_b$, so that

$$V_{ch} = p_b C + V_{min} - \Delta\rho gLC + RCQ + \frac{C\rho_f Q^2}{2A_1^2} \quad (6)$$

This equation can be used to estimate the volume of PFC remaining in the lungs when choke occurs, provided the values of R , C , A_1 , p_b , L , and V_{min} can be estimated. Since the goal of this model was to qualitatively explain the behavior observed in the experiments, we considered R , C , and p_b to be constants. In actuality, these quantities likely vary and a more complicated model could include those effects. The pressure, p_b , at which the airway collapses is, in general, not constant and the occurrence of airway collapse depends on a number of factors, such as the airway wall properties and lung volume. As a simplification, we have assumed it to be approximately constant here based on previous measurements of airway pressure at the choke point in liquid ventilation, in which it was found to not vary significantly with lung volume or flow rate [42,43].

Resistance and Compliance Measurements. The theoretical model requires, as inputs, airway resistance, and alveolar compliance. These were measured using the following protocol. The animals were anaesthetized, a tracheostomy was performed, and an ear IV catheter was placed as in the flow limitation experiments. The animal was instrumented and its lungs filled in the same manner as in the flow limitation experiments (previously described), with the exception that the Tygon tubing connect to a flaccid reservoir, rather than a piston pump. A stopcock in the circuit was used for the addition and removal of PFC from the lungs. We attempted to remove any gas bubbles from the lungs by unclamping the tube and allowing the reservoir to fill. The few gas bubbles that exited the lungs into the circuit were removed using a syringe connected to the stopcock. This process was repeated three times before measurements were made.

The static compliance of the rabbit's lungs was determined by measuring airway pressure at various lung volumes. This procedure started at a lung volume of 40 ml/kg, where static airway pressure was measured. Following this measurement, 5 ml/kg of PFC was removed and static airway pressure measured. Static airway pressures were measured at lung volumes between 40 ml/kg and 15 ml/kg (functional residual capacity, FRC, was assumed to be approximately 15–20 ml/kg), in 5 ml/kg increments. PFC was then instilled back into the lungs in 5 ml/kg increments and static airway pressures were measured. This process was repeated three times. Small changes in the pressure–volume relationship ($<10\%$ change in pressure at each volume) were observed between the first and second cycling of the lungs. The differences between the second and third cycles were considerably smaller and, consequently, it was assumed that any gas bubbles had been dissolved by the time the third cycle was performed. The data of the third cycle was then used to determine the compliance of the lungs. Five animals were used per PFC and the data were averaged to obtain a pressure–volume curve for that PFC. Pressure–volume curves were generated for all four PFC's used. Lung compliance values were then calculated for each PFC based on the slope of its pressure–volume curve. Because flow limitation typically occurred at low lung volumes, we used the slope of the pressure–volume in the lung volume range of 15 to 20 ml/kg as the compliance input to our model.

Following the measurement of lung compliance, the airway resistance in each animal was measured. The endotracheal tube was disconnected from the circuit and the PFC was allowed to drain due to gravity/lung elastic recoil. The flow as a function of time

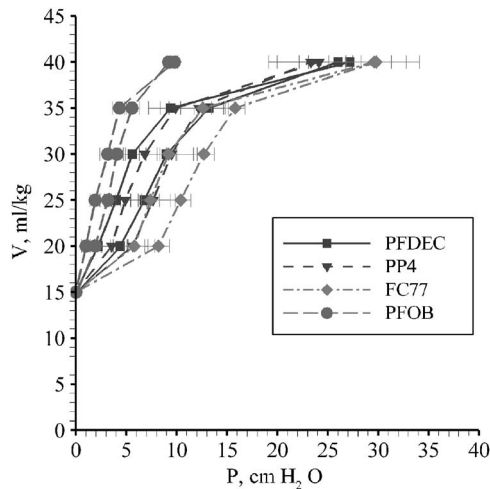


Fig. 3 Pressure–volume curves for PFC-filled lungs. The pressure was measured relative to the pressure at a lung volume of 15 ml/kg, and hence all curves pass through the point (0, 15). Hysteresis is apparent in the curves for each PFC.

was measured using a Transonics flow probe, which was connected to a flow meter and Macintosh computer equipped with Labview for data acquisition. The flow versus time data were plotted on a lognormal plot and a straight line was fit through the data. That is, exponential decay of the flow, $Q(t) = Q_0(t)e^{-R_{tot}Ct}$, was assumed and $R_{tot}C$ was calculated from the data, where Q is flow, Q_0 is the initial flow rate, R_{tot} is total resistance, and C is compliance. Since C was already determined from the static pressure–volume curves, R_{tot} could then be determined. This total resistance was assumed to be equal to the airway resistance, R , plus the resistance distal to the choke point (tracheostomy tube plus short section of trachea), R_{tube} . The value of R_{tube} was calculated, assuming fully developed pipe flow, as $R_{tube} = 32\mu \cdot (\text{tube length}) / (\pi \cdot D^4)$, where D is the tracheostomy tube diameter. Note that unlike in gas ventilation, the Reynolds number, $Re = \rho \cdot D \cdot v / \mu$, of the flow in each condition was in the laminar range ($Re \leq 2500$). The resulting value of R was then used in the theoretical model described above. Actual airway resistance is expected to vary with lung volume and is not constant. That is, even though the flow is laminar, changes in the airway cross section as the lungs empty may result in a nonlinear relation between pressure drop and flow. The constant (for a particular PFC) value of R used here can be thought of as an average resistance over the course of the lung emptying process, and is intended to facilitate the use of the theoretical model to explain the reasons for the observed behavior in the experiments.

Interfacial Tension Measurement. The lung compliance data were substantially different for PFC's with similar properties. To determine if interfacial tension between the PFC and aqueous lining of the lung could be responsible for these differences, we measured the interfacial tension between PFC and saline with Surfactant concentrations of 0 and 1.0 mg/ml using the ring tensiometer method [46–48]. Bulk surfactant concentrations in the range of 1 mg/ml are typical in the alveoli [49,50]. The PFC and saline were maintained at a constant temperature of 37°C using a thermocouple controlled heating plate. Five measurements were made for each PFC/bulk surfactant concentration combination.

Results

Lung compliance was determined from the slope of the static pressure–volume curve between 15 and 20 ml/kg (see Fig. 3). Because the change in pressure corresponding to a particular change in volume was of interest, rather than the absolute pressure

at each lung volume, the pressures were measured relative to the pressure at the 15 ml/kg lung volume. Therefore, all of the curves in Fig. 3 pass through the point $P(V=15 \text{ ml/kg})=0$. Each curve corresponds to a different PFC and the error bars indicate the standard error. The difference in the curves for PP4 and PFOB indicates that the lungs are more compliant when filled with PFOB than with PP4, and suggest that lung compliance depends on the PFC used to fill the lungs and that lung surfactant may act between PFC and the native aqueous liquid lining. Figure 4 shows a typical plot of flow versus time (shown for PFOB) with (a) a linear scale on both axes and (b) a log-linear scale. Fitting an exponential decay to the experimental data provides an estimate of RC for the experiment. Average airway resistance, R , was then determined using C , and the values of R were then averaged to provide an average resistance for each PFC. The flow limitation did not appear to occur during the experimental measurement of R . If a long drainage tube whose outlet was sufficiently lower than the animal was used, flow limitation occurred, as indicated by oscillations in $Q(t)$ and intermittent stoppage of flow at the outlet. This condition was avoided in the measurement of R by using a very short drainage tube, which minimized the siphon pressure. The values of RC , R , and C from these experiments are presented in Table 2.

Table 3 shows the interfacial tension between each PFC and saline without surfactant and with 1 mg/ml of Surfactant. With saline, the interfacial tensions of PP4 and PFOB were similar. However, when Surfactant was added to the saline, the interfacial tension was much less for PFOB. These seem logical since the lungs were the most compliant when filled with PFOB. Surfactant activity, therefore, is likely responsible for the differences in lung compliance.

Using the values of R and C determined from the animal experiments, theoretical predictions of V_{ch} were obtained. In obtaining these results, we estimated $p_b = -15 \text{ cm H}_2\text{O}$ since choke occurs at airway pressures ~ -20 to $-25 \text{ cm H}_2\text{O}$ [42,43] and rabbit pleural pressure are ~ -5 to $-10 \text{ cm H}_2\text{O}$ [51,52]. This estimate is simply the typical difference between the pleural pressure and airway pressure at choke, and represents an approximation based on previous work. No attempt to measure pleural pressures in these animals was made. In previous studies, no significant differences in the airway pressure at choke were observed between different lung volumes and expiratory flow rates for liquid-filled lungs [42,43], suggesting that the assumption of $p_b = \text{const} = -15 \text{ cm H}_2\text{O}$ is a reasonable one. L was estimated to be -1 cm , based on estimates of the elevation difference between the trachea and a typical alveolus due to the lung being filled with liquid. A_1 was taken to be $\sim 0.2 \text{ cm}^2$, approximately the cross-sectional area of the endotracheal tube since choke typically occurs in the trachea near the carina in these experiments.

Here 63 animals were used in the flow limitation experiments. Five animals in the PFDEC group were found to have perflurothorax, one the PFOB, and two in the PP4 group. All groups had similar weights, with an overall mean of $3.10 \pm 0.35 \text{ kg}$ ($p=0.99$ between groups). Theoretical values, along with the experimental values of V_{ch} , as a function of Q are shown in Fig. 5. The experimental data and theoretical predictions agree well. V_{ch} depended strongly on the PFC and Q . Increasing Q results in a larger volume of PFC being left in the lungs. For all three values of Q , V_{ch} was highest for PFDEC and lowest for PFOB. V_{ch} was lower for PP4 than for PFDEC and V_{ch} for FC77 was lower than for PP4. This V_{ch} was nearly linear in flow rate for the three flow rates considered. All groups had similar slopes ($p=0.25$) and V_{ch} varied strongly with PFC type ($p < 0.001$), as shown in Fig. 5. If PFOB is not included in the comparison, it appears that denser liquids lead to higher values of V_{ch} . The general trend that higher lung compliance results in higher V_{ch} is observed in both the theory and experimental date.

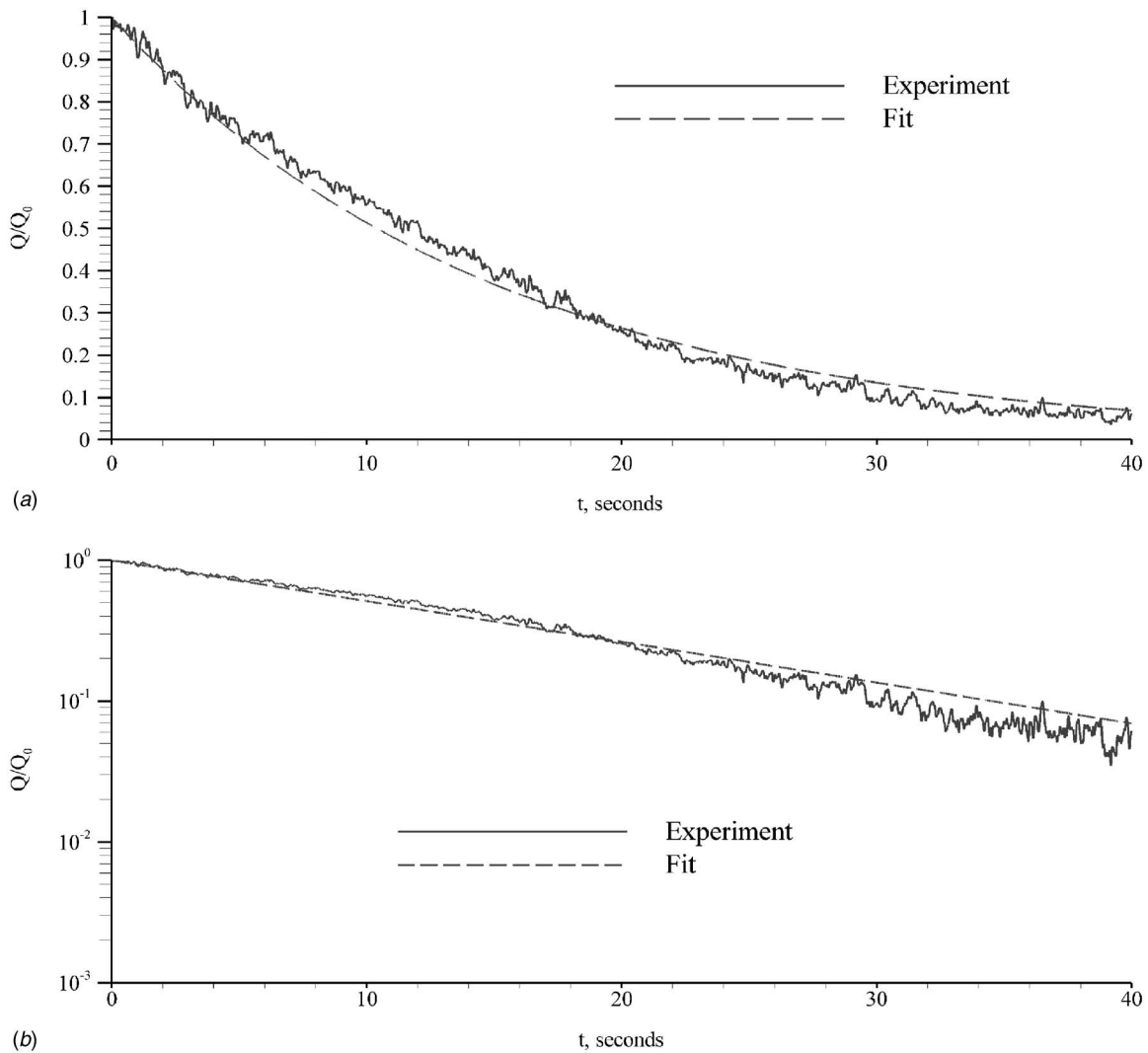


Fig. 4 Flow versus time data for the calculation of airway resistance. A typical plot is shown for PFOB. The solid line indicates the experimental data and the dotted line indicates the fit to the data. The fit to the data provides RC for the experiment, and R could be determined since C was already measured. Airway resistance, R , was calculated for each experiment and was then averaged to provide an average resistance for each PFC. (a) Plot with a linear scale on both axes; (b) log-linear plot of the same data.

Discussion

The classic theories of airway closure relate the wave speed of the wall to the speed of fluid through the airway to determine the maximum flow rate [3–5]. Once the maximum flow rate is reached, further increases in driving pressure do not increase the flow. Instead, they result in a collapse and/or oscillation of the airway wall. Decreasing lung volume is expected to increase the likelihood of flow limitation, during expiration at a constant flow rate, by decreasing airway diameters. Flow limitation will occur when the diameter of some airway has decreased enough that the flow rate there is no longer less than the maximum flow rate (and

the transmural pressure is equal to the buckling pressure). The wave speed theory of flow limitation indicates that the maximum flow rate for a given airway diameter and material properties should vary as $\rho^{-1/2}$, suggesting that denser fluids would lead to choke sooner and to higher values of V_{ch} . Surprisingly, the V_{ch} vs Q curve for PP4 lies above the curve for PFOB, despite the density, viscosity, and surface tension being very similar for the two. These two PFC's have similar properties, yet have very different values for V_{ch} . If PFOB is not included in the comparisons, the

Table 2 Measured alveolar compliance, RC time constant, and average resistance R

	C , cm ³ /cm H ₂ O/kg	RC , s	R , cm H ₂ O kg s/cm ³
PFDEC	1.8	4.7	2.61
PP4	1.8	2.5	1.72
FC77	1.0	3.1	2.5
PFOB	4.0	3.8	0.95

Table 3 Interfacial tension between PFC and saline, for both pure saline and saline with Survanta

Perfluorocarbon	Interfacial tension, dyne/cm	
	Pure saline	Saline with 1 mg/ml Survanta
PFDEC	9.05±0.41	2.99±0.56
PP4	26.53±0.87	18.99±0.80
FC77	10.44±0.38	16.12±0.44
PFOB	20.97±0.70	6.21±0.66

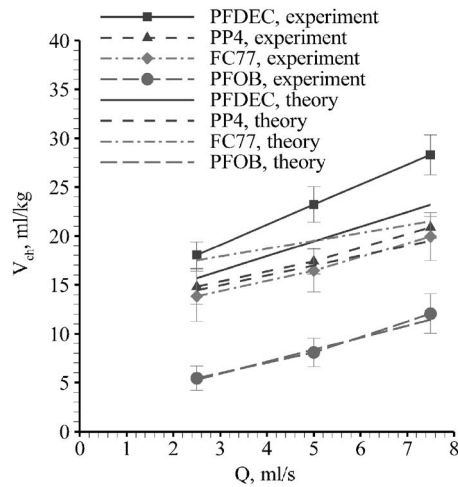


Fig. 5 The volume of PFC remaining at choke, V_{ch} , versus expiratory flow rate, Q , a comparison of theory and experiments. V_{ch} was lowest for PFOB and highest for PFDEC.

expected dependence on density and viscosity is observed in the other three fluids, i.e., denser and more viscous fluids resulted in more fluid remaining in the lungs at the onset of choke (see Fig. 5 and Table 1). Our lumped-parameter model, which includes airway resistance and lung compliance, clarifies the mechanisms responsible for the differences between the PFOB and PP4 results.

The expected behavior for V_{ch} from the theoretical model can be determined by examining Eq. (6). For typical compliance values and assuming $A_1 \sim 0.2 \text{ cm}^2$, the quadratic term is negligible and V_{ch} is essentially linear in Q , as would be expected from the experimental data. Note that the coefficient multiplying Q^2 has a maximum value ~ 0.1 for PFOB, the coefficient multiplying Q is ~ 4 , and the constants are $O(10)$ or larger. The quadratic (inertial) term was retained in the theoretical calculations, but its effects are small, as is evident from the nearly linear theory curves in Fig. 5. The data for the theoretical curves were calculated at Q increments of 0.01 ml/s . Previous studies on gas ventilation have shown that at high lung volumes density effects are primarily responsible for flow limitation, but that at low lung volumes viscous effects are more important [12,16,20]. Over the entire range of lung volumes considered in this study, viscous effects dominate due to the much lower Reynolds numbers encountered in liquid ventilation compared to gas ventilation.

From the experiments and the theoretical model, it appears that differences in airway resistance are responsible for these differences in V_{ch} . Although PFOB and PP4 have similar viscosities, the average airway resistance is lower for PFOB. This may potentially be due to smaller airway diameters as PP4 empties from the lungs, compared to the airway diameters with PFOB, or due to PFC-dependent differences in regional emptying within the lung. Decreasing airway resistance leads to a smaller pressure drop along the airways, and allows higher flow rates without the occurrence of choke. Additionally, as is evident in the pressure–volume curves (Fig. 3), the lungs are more compliant when filled with PFOB than when filled with PP4. More compliant lungs require lower pressures to inflate them. The airway pressure in lungs filled with PP4 was approximately $20 \text{ cm H}_2\text{O}$ higher for a 40 ml/kg lung volume than for a 20 ml/kg lung volume. For lungs filled with PFOB, the static pressure difference between lungs filled to 40 ml/kg and lungs filled to 20 ml/kg was approximately $10 \text{ cm H}_2\text{O}$. From Eq. (6), one can see that increasing C by itself will increase V_{ch} . Although compared to PP4 filled lungs, the alveolar compliance is higher in the PFOB-filled lungs, the airway resistance is lower, and the net result is a lower V_{ch} in PFOB-filled lungs.

The hysteresis of the pressure–volume curves suggests surfactant activity in the liquid-filled lungs, as hysteresis is not observed in saline-filled lungs [53] where there is no interface for the surfactant to affect. Previous studies have suggested that surfactant may affect lung compliance in liquid-ventilated, excised, surfactant-deficient lamb lungs, but did not examine the effects on flow limitation or the effects of using different perfluorocarbons [54]. Although we did not image the liquid inside the lungs to assess the liquid lining, the finding that lung compliance depends on the PFC filling the lungs suggests the aqueous liquid lining of the lungs may remain intact during liquid ventilation and that the instilled PFC simply fills the space that was previously occupied by gas. Regardless of whether it remains intact, it appears the aqueous liquid remains and surfactant affects the interfacial tension. We have shown that interfacial tension between perfluorocarbon and saline can be changed by the presence of Surfacta, and that the interfacial tension varies significantly depending on which PFC is used. Surfactant effects may account for the differences in lung compliance observed with different perfluorocarbons.

As expected, higher values of Q resulted in higher V_{ch} . A faster removal of liquid from the lungs results in more negative airway pressures and consequently leads to choke sooner. It appears that at higher lung volumes liquid can be removed at a faster rate without inducing flow limitation. However, as the lung volume decreases (airway diameters and alveolar transmural pressure decrease, and airway resistance increases), these higher flow rates lead to flow limitation. Based on this, we expect the flow can be sculpted (fast initially and then slower) to minimize V_{ch} , and that a higher FRC will reduce the occurrence of flow limitation.

While the theoretical model captures the trends observed in the experimental data, it significantly simplifies the physiological situation and has many limitations. For example we considered alveolar compliance to be constant, but it actually varies over the range of lung volumes. Similarly, airway resistance and diameters are known to vary with lung volume [55,56], but we have assumed them to be constant. To consider a wider range of flow rates or lower viscosities than presented here, Eq. (2) should include resistance terms that are nonlinear in Q . The perfluorocarbons were considered to be Newtonian fluids, as they are typically considered, but they may potentially exhibit non-Newtonian behavior. A more accurate estimate of L would be an improvement. The one we used was a simple estimate to account for the lung, likely distending when it is filled with PFC. Although we have assumed it to be constant, L may actually change as the lung empties. In the experiments and theoretical analysis, we have considered only constant flow expiration, as is often the case over much of the expiration phase in TLV. Additionally, the model is a lumped-parameter model and there is likely information to be gained from more complicated models that incorporate more details of lung morphometry. Nevertheless, this simplified model appears to capture the dynamics of this very complicated physiological phenomenon, indicates the reasons for the observed behavior, and is a starting point for future work. Future experimental studies on surfactant interactions with PFC's at various surfactant concentrations and their effects on lung compliance, as well as the investigation of PFC effects on airway resistance and its dependence on lung volume, will provide useful information.

In conclusion, we have shown that there are substantial differences in the volume of liquid that remains in the lungs at choke, and that this depends on the liquid properties and the rate at which the liquid is removed. Alveolar compliance and airway resistance are found to depend on the liquid used to fill the lungs. Surfactant appears to be active at the interface of perfluorocarbon and the native aqueous lining of the lungs, and induces hysteresis in lung pressure–volume curves for liquid-filled lungs. If lung compliance is the same, denser and more viscous liquids lead to higher volumes of liquid remaining in the lungs at choke. Possible strategies for ventilating liquid-filled lungs to avoid choke while maintain-

ing adequate gas transport include sculpting the expiratory flow to be fast initially and then slow, and having a high FRC with small tidal volumes and higher breathing frequencies.

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