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# Effect of Viscosity on Instilled Perfluorocarbon Distribution in Rabbit Lungs

*The effect of viscosity on the distribution of perfluorocarbon instilled into the lungs for liquid ventilation was investigated. Perfluorocarbon (either perfluorodecalin or* FC-3283*) was instilled into the trachea during ventilation at a constant infusion rate of* 40 ml/min *and radiographic images were obtained at* 30 frames/s. *Image analysis was performed and the homogeneity index of the distribution was computed for images at the end of inspiration of each breath to evaluate the evolution of perfluorocarbon distribution during filling. The higher viscosity perfluorocarbon (perfluorodecalin) resulted in a more homogeneous distribution. This was attributed to perfluorodecalin's higher propensity to form liquid plugs in large airways and to those plugs leaving behind a thicker liquid layer as they propagated through the lungs.* [DOI: 10.1115/1.2354214]

*Keywords: liquid ventilation, surfactant replacement therapy, liquid bolus*

## Introduction

There are many clinical situations in which liquids are instilled into the lungs. Examples include surfactant replacement therapy (SRT) [1,2], lung lavage, pulmonary delivery of medications and genetic material [3,4], and liquid ventilation [5]. This study is primarily motivated by liquid ventilation, but is relevant to these other liquid delivery situations. There are two liquid ventilation methodologies currently under investigation: partial liquid (PLV), in which the lungs are partially filled with perfluorocarbon (PFC) and ventilated with a gas tidal volume, and total liquid ventilation (TLV), in which the lungs are totally filled with PFC and ventilated with a liquid tidal volume [5–7]. PFCs, which have low surface tension and high oxygen and carbon dioxide solubilities, have been shown to improve gas exchange and lung mechanics in animal models of lung injury [5,7,8]. PLV has shown promise in treating newborns with congenital diaphragmatic hernia by inducing lung growth [9]. A uniform distribution of instilled PFC is desired in both PLV and TLV to avoid gas trapping and over inflation of the lungs, and PFC distribution influences PFC elimination, gas exchange, and respiratory compliance [10].

The various clinical protocols in the literature for filling the lungs for liquid ventilation have been developed primarily through trial and error. Most studies on delivery of surfactant [11–13] or PFC [10,14] to the lungs have focused on the final distribution rather than the dynamics and mechanisms of distribution. Our prior studies demonstrated that instillation technique [15] and respiratory rate [16] can cause significant differences in the resulting distribution of surfactant in the lungs. Typical dose sizes for SRT are 2–5 ml/kg of body weight [2], significantly smaller than the 20–40 ml/kg typical of liquid ventilation. Our previous work on filling the lungs with PFC showed that instillation rate and posture affect the distribution dynamics during the filling and the final homogeneity [17]. Although it was shown that supine posture results in a more homogenous distribution of perflubron [17], it may be desirable to use an upright posture to minimize reflux of liquid from the lungs, and to potentially increase the strain in the gravity dependent part of the lung to induce growth in treating diaphragmatic hernia [9]. We hypothesized that PFC viscosity affects the distribution dynamics of liquid instilled into the lungs, and examined these effects in this study by comparing the behavior of two commercially available PFCs of similar density and surface tension, but different viscosity.

## Methods

**Experiments.** The experimental procedure was similar to the procedure we used previously to investigate posture and instillation rate effects [17], and we summarize it here, highlighting differences. Two PFCs with different viscosities were used. One group of animals was instilled with perfluorodecalin (PFDEC) (F2 Chemicals, Preston, England), which has a relatively high kinematic viscosity (2.90 cSt). PFDEC has been used in previous liquid ventilation studies [18], and in clinical trials in Europe [19]. The other group of animals was instilled with FC-3283 (3M Specialty Materials, St. Paul, MN) plus barium (Sigma, St. Louis, MO). Since FC-3283 alone was not sufficiently radio-opaque to be easily observed in the video images without adjusting the image contrast with software, barium was added. A solution of 5 ml barium and 500 ml FC-3283 had the same optical density, as measured in a series of experiments on sample mixtures, as the PFDEC. The viscosity and surface tension of the FC-3283+Ba mixture were measured using an Oswalt bulb viscometer and a ring tensiometer, respectively, both of which we have used in previous work [20,21]. The kinematic viscosity of FC-3283+Ba (1.09 cSt) is approximately that of perflubron which has been used in clinical trials of PLV [9] and our previous study [17]. The density and surface tension of PDEC and FC-3283 are very similar, but the viscosity is much different (see Table 1), allowing investigation of viscous effects.

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**Table 1 Physical properties of the PFDEC and FC-3283+Ba**

| | PFDEC | FC-3283+Ba |
|---|---|---|
| Chemical formula | $C_{10}F_{18}$ | $C_9F_{21}N$ |
| Molecular weight | 462 | 521 |
| Density, $\rho$, $\mathrm{kg/m^3}$ | 1930 | 1820 |
| Kinematic viscosity, $\nu=\mu/\rho$, cS | 2.90 | 1.09 |
| Surface tension, $\sigma$, dyn/cm | 19 | 16 |

This experimental protocol was reviewed and approved by the University Committee on Use and Care of Animals. New Zealand white rabbits (3.1±0.2 kg) were anesthetized (Xylazine, 5 mg/kg, and Ketamine, 20 mg/kg). A tracheotomy was performed and an endotracheal tube (3/16 in. diameter) was placed. Heparin (100 units/kg) was administered intravenously and allowed to circulate prior to euthanizing the rabbit by an IV dose of Beuthanasia (Schering-Plough Animal Health, Union, NJ) (0.5 ml/kg). Previous studies suggest that there is minimal change in behavior of the lungs of intact rabbits within one hour of euthanasia [22,23]. All experiments in this study were, therefore, performed within 40 min of euthanasia. The rabbit was ventilated by a small animal ventilator (Inspira ASV, Harvard Apparatus, Holliston, MA) with ambient air using a tidal volume of 24 ml, a respiratory frequency of 40 breaths/min, and an inspiratory-to-expiratory ratio of 1:1. We did not vary the tidal volume or frequency between rabbits, so that the gas velocity within the endotracheal tube was the same for each animal. We considered a pressure of 30 cm $H_2O$ to be excessive (and potentially damaging to the rabbit's lungs) and limited the peak inspiratory pressure to $\leqslant 27$ $\mathrm{cmH_2O}$ via a one-way, by pass valve in the circuit. The animal was placed in upright position prior to PFC instillation and a continuous sequence of X-ray images of the lung during ventilation were obtained at a rate of 30 frames/s by a high resolution fluoroscopy machine (Philips portable c-arm, Phillips Medical Systems, Amsterdam, The Netherlands) and recorded to digital video tape. After acquiring liquid-free images to use for image subtraction, we acquired a sequence of lung images during the instillation of 60 ml of PFC through the endotracheal tube at a constant infusion rate of 40 ml/min from a syringe pump (PHD 2000 Programmable, Harvard Apparatus Inc., Holliston, MA). This instillation rate corresponds to the middle instillation of our previous study [17], and was chosen as a representative example of instillation rates that might be used clinically. The instillation was performed in five animals for each PFC, and the data for each PFC were averaged for the five animals.

**Analysis.** We viewed the X-ray videos of PFC filling the lungs and made qualitative observations regarding the homogeneity of the liquid distribution. Our previous image analysis techniques [17] were used to quantify the homogeneity of the liquid distribution, and are summarized as follows. The digital video was transferred to a Pentium 4 computer (OptiPlex Dell, Round Rock, TX) and converted to a series of images using Adobe Premier (Adobe Systems Incorporated, San Jose, CA). Noting that lung size is minimum at end-expiration and that the respiration rate was 40 breaths/min, we used image processing to determine the time during the ventilation cycle of each breath [17] that corresponded to each image. Images at end-expiration of each breath (60 breaths occurred over the 1.5 min instillation period) were selected for analysis to produce a time sequence of images. Each image was read into MATLAB (Mathworks, Natick, MA) as a double precision matrix whose elements correspond to the intensity, $I^*(x,y)$, of individual pixels. In these two-dimensional images, $I^*(x,y)$ ranged from 0 (black) to 255 (white). The images were then rescaled so that $I=255\times[\text{ones matrix}]-I^*$, where $I$ ranges from 0 (white) to 255 (black) and [ones matrix] is a matrix in which every entry has the value 1.

We used image subtraction (using Beer's law) to produce an image of the instilled PFC by itself. Beer's law relates the illumination of radiopaque material in an X-ray to the path length through the radiopaque material [24]. Applying Beer's law to the lung tissue with and without PFC, and subtracting element-by-element yields the scaled intensity matrix, $\hat{I}$. The matrix $\hat{I}$ was then cropped using a border mask (constructed from the unsubtracted image of the unfilled lung at end-inspiration) to include only the lung portion of the image. The images were sectioned into quadrants, as defined by the centerline of the trachea and a line half way between the superior and inferior edges of the lungs. A pixel in the image was considered to have been reached by liquid if $\hat{I}$ at that location was greater than a threshold value, $\hat{I}=0.2\times\hat{I}_{\max}$. As in our previous studies [15–17], this threshold value was specified based on the amplitude of noise in lung images without liquid and the intensity when a minimal thickness of liquid was present. The sensitivity of the results to the threshold value was assessed to ensure that the threshold was not set artificially high. The number of pixels reached by PFC in each quadrant was calculated, and the fraction of the quadrant that was reached by PFC was computed, as a measure of the liquid distribution. The homogeneity index HI which is defined as the ratio of the highest fraction reached to the lowest fraction reached, was calculated as a gross-scale indicator of how homogenous the lungs are filled. The value of HI can range from 0 to 1.

**Theory.** To examine how PFC viscosity influences distribution, we considered a theoretical model of a single liquid plug that is blown through a single straight tube. Although airway branching is ignored in this model, it is intended to provide insight into the transport of a single liquid plug during the inspiration phase of a single breath. Halpern et al. [25,26] approximated liquid plug motion by a semi-infinite bubble in a tube and determined the dimensionless trailing film thickness, $f$, as a function of capillary number, Ca, to be

$$f=h/a=f(\mathrm{Ca})=0.36\left[1-e^{-2\mathrm{Ca}^{(0.523)}}\right] \tag{1}$$

where $a$ is the tube radius and capillary number, $\mathrm{Ca}=\mu U/\sigma$, is the ratio of viscous force to surface tension force. Fluid viscosity and surface tension denoted by $\mu$ and $\sigma$, respectively, and $U$ is the speed of the liquid plug. The volume density, center of mass of the liquid distribution, and the time, $T_f$, at which the plug ruptures were calculated from conservation of mass based on $f$. Time, $t$, was nondimensionlized as $\hat{T}=t/T_f$. Ca was higher for PFDEC, resulting in different values of $f$ and $\hat{T}$ for each PFC, so we use subscripts to indicate the PFC. The dimensionless position (scaled by initial plug length) of the leading edge of the plug is $\hat{\lambda}=\hat{T}(1-2f)/2f+1$ for $0\leqslant\hat{T}\leqslant 1$. Because dimensionless time is therefore different for each PFC, we rescaled $\hat{T}_{\mathrm{PFDEC}}$ to obtain the corresponding dimensionless time based on $T_f$ for FC-3283, e.g., $T=\hat{T}_{\mathrm{FC\text{-}3283}}=\hat{T}_{\mathrm{PFDEC}}\cdot f_{\mathrm{FC\text{-}3283}}/f_{\mathrm{PFDEC}}$. The theoretical distribution of liquid was also calculated from the film thickness distribution, such that the volume density of the liquid, $\rho(x,t)$, is approximated by

$$\rho(x,t)=\left\{\begin{array}{ll} 2\pi a^2 f, & 0\leqslant x\leqslant x_T(t) \\ \pi a^2, & x_T(t)\leqslant x\leqslant x_T(t)+L_p(t) \end{array}\right\} \tag{2}$$

where $x_T$ is the position of the trailing meniscus of the liquid plug and $L_p$ is the length of the plug. Note that $x_T+L_p$ is the dimensional position of the leading edge of the liquid plug. This theoretical distribution of liquid was then integrated to calculate its center of mass at various times.

## Results

For the experiments, time was normalized by the time of instillation, $T_{\mathrm{instill}}=60\ \mathrm{ml}/(40\ \mathrm{ml/min})=1.5$ min, to result in a dimen-

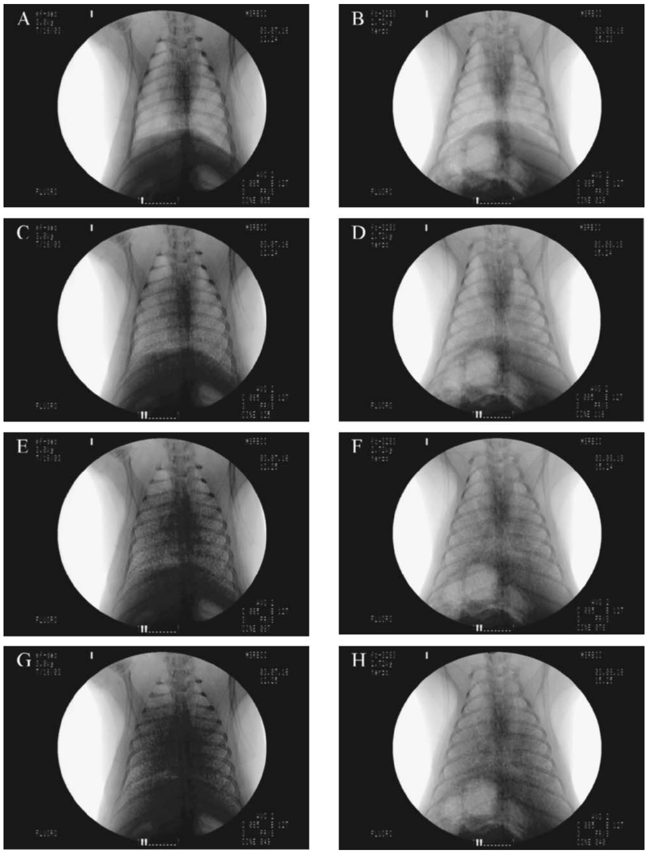

**Fig. 1 Lung images at various times: (*a*) PFDEC and (*b*) FC-3283 at *t*=0, the start of instillation; (*c*) PFDEC and (*d*) FC-3283 at *t*=0.33, when 1/3 of the PFC is instilled; (*e*) PFDEC and (*f*) FC-3283 at *t*=0.67, when 2/3 of the PFC is instilled; and (*g*) PFDEC and (*h*) FC-3283 at *t*=1, when all 60 ml of the PFC has been instilled. Note that time is scaled by infusion time, so that time indicates the fraction of total PFC that has been instilled.**

sionless time that ranged from $t=0$ at the initiation of PFC instillation to $t=1$ at the end of PFC instillation. This dimensionless time also an indicator of the fraction of the total PFC that has been instilled at that particular instant, e.g., half of the PFC had been instilled when $t=0.5$. The data from all animals in a PFC group were averaged at each time instant and the standard error of the mean was calculated. The results are presented as mean ± standard error. A sequence of lung images during the filling process is shown in Fig. 1. The images on the left side of Fig. 1 are during filling with PFDEC and the ones on the right are during filling with FC-3283. Images are shown for $t=0$, 0.33, 0.67, and 1. Initially, there was no PFC in the lungs, and as time progressed the lungs filled. The lungs filled with PFDEC appeared more homogenous than those filled with FC-3283. The images correspond to end-inspiration, which was used for the analysis. Liquid plugs could be observed in airway generations 0–2 for PFDEC and in slightly smaller airways (generations 3 and 4) for FC-3283 during inspiration. The fraction reached increased in time for both PFCs (Fig. 2), and was higher in each quadrant at a given time for PFDEC compared to FC-3284. The difference between the fraction reached in the upper and lower quadrants was smaller for lungs filled with PFDEC (more viscous) than for lungs filled with FC-3283 (less viscous). Similarly, the difference in the fraction of the right and left quadrants reached by PFDEC is smaller than the corresponding difference in FC-3283. Both PFCs reached more of the lower quadrants compared to the upper quadrants. HI was generally higher for PFDEC (more viscous) than FC-3283 (Fig. 3). At early times, there was a high variability in HI, with little difference between the two liquids. HI was 1 at $t=0$ because an unfilled lung is homogeneous. As liquid entered through the endotracheal tube, the value of HI became zero (since at very early times the lower regions are unfilled). Once PFC reached the lower lung regions, this initially high variability decreased and the two liquids began to behave differently. HI increased more rapidly and reached higher levels for PFDEC than for FC-3283. The maximum value of HI for FC-3283 was 0.5, while for PFDEC the maximum value was greater than 0.8, indicating a fairly homogeneous distribution (the maximum possible HI is 1).

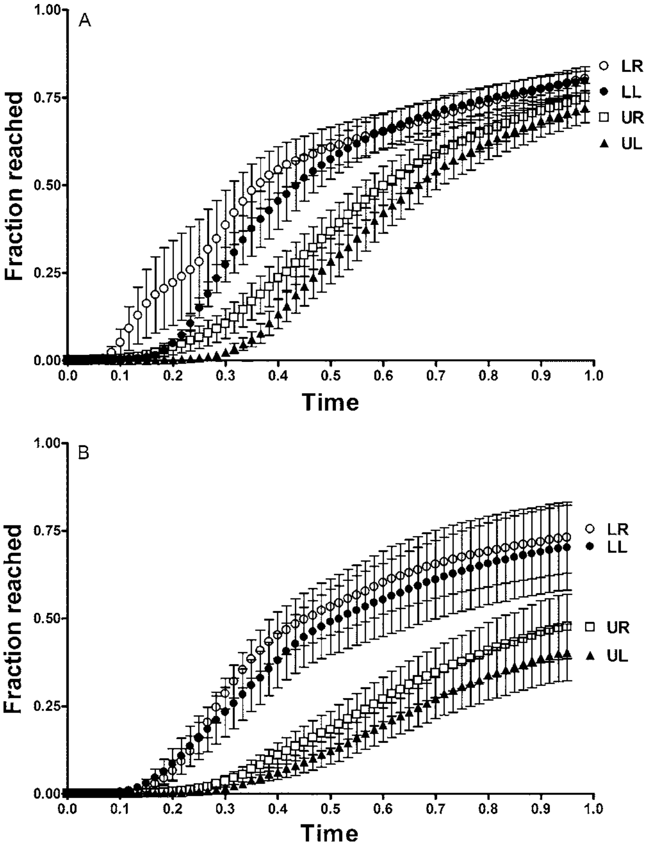

**Fig. 2 Fraction reached versus time for each of the four lung quadrants when filled with (a) PFDEC and (b) FC-3283. Each graph contains the fraction reached for the upper left (UL), lower left (LL), upper right (UR), and lower right (LR) quadrants.**

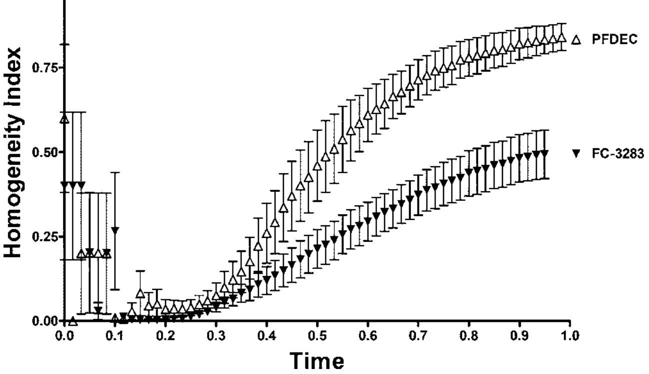

**Fig. 3 Homogeneity index, HI, versus time, *t*, for PFDEC and FC-3283**

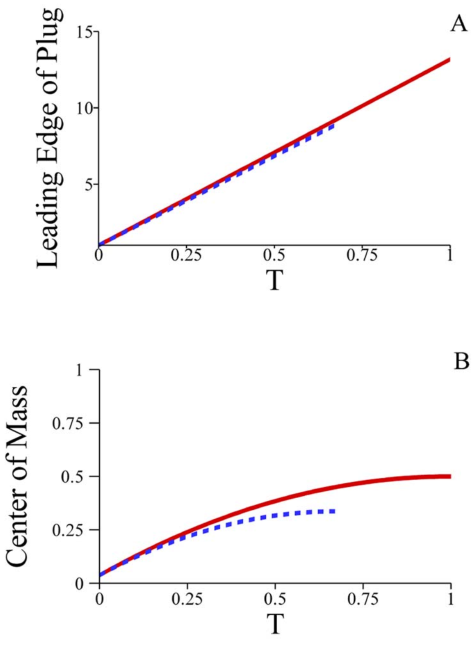

**Fig. 4** (***a***) **Leading edge of liquid plug versus T, and (*b*) center of mass versus T, for PFDEC (dashed line) and FC-3283 (solid line)**

The theoretical results for the motion of a single liquid plug through a single tube are shown in Fig. 4, where time is scaled by the time required for an idealized plug of FC-3283 to rupture and position is scaled by the initial plug length. The lines stop at the time corresponding to plug rupture. The FC-3283 plug propagates further than the PFDEC plug before rupturing (Fig. 4(*a*)). The center of mass moves further for FC-3283 than for PFDEC (Fig. 4(*b*)), corresponding to further propagation into the lungs.

## Discussion

The results demonstrate that a more viscous liquid can result in a more homogeneous distribution in the lungs. In fact the HI obtained by PFDEC is slightly higher than the maximum obtained in our previous study [17] for supine posture, which yielded a more uniform distribution than upright posture in that study. This appears to be due to the dynamics of liquid plugs, which occurred in larger airways for animals instilled with the more viscous PFC (PFDEC), and deposition of liquid by them. The theory provides some insights into the deposition of PFC by the plugs. As indicated by Eq. (1), film thickness increases with Ca. For the same $U$, which is determined by the ventilation waveform, and $\sigma$ values, a more viscous fluid leads to a higher Ca and a thicker film behind the liquid plug. Note that $\mathrm{Ca}_{\mathrm{PFDEC}} \sim 3\mathrm{Ca}_{\mathrm{FC\text{-}3283}}$ for the same $U$ and $\sigma$. As the liquid plug propagates along the airway tree, it splits as it passes through airway bifurcations and shortens in length as liquid is left behind. Ca is smaller in small airways where velocities are smaller due to the airway area expansion, reducing the thickness of the deposited liquid. When the plug length, $L_p$, decreases to zero, the plug ruptures and the liquid is then transported due to surface tension gradients [20,21] and gravitational drainage. Less viscous plugs leave behind less liquid and propagate further into the lungs before rupturing (Fig. 4), leading to a less homogeneous distribution of liquid. The theoretical predictions of the propagation of the leading edge of the liquid plug indicate that the FC-3283 plug will propagate approximately 1/3 farther into the model airway before rupturing than the PFDEC plug will (Fig. 4(*a*)). Likewise, the center of mass of liquid delivered by a single plug of FC-3283 is predicted to be approximately 50% further into the model airway (Fig. 4(*b*)). These theoretical results suggest that the less viscous liquid, when it does form a liquid plug within the airway, will be delivered more distally than the more viscous liquid. The liquid deposited by each plug during each breath contributes to the overall liquid distribution dynamics that are quantified by the experiments. Repeated delivery of the majority of instilled liquid to the inferior region of the lungs during each breath leads to a less homogeneous overall liquid distribution as time progresses, as was the case for FC-3283 in the experiments (Figs. 2 and 3).

Although no prior studies have examined the effects of viscosity on the homogeneity of instilled liquids, the influence of liquid plug dynamics in this study is consistent with our previous study [17] in which a more homogeneous PFC distribution was attained when liquid plugs formed in the large airways. When liquid plugs do not form in the trachea, the instilled liquid drains by gravity into smaller airways where plugs then form [15]. Less viscous liquids are less likely to form liquid plugs in the trachea, as was demonstrated in a glass tube model of the trachea [27]. Previous studies on liquid distribution in PLV have suggested that a more viscous PFC results in a less homogeneous distribution because the higher viscosity provides higher resistance to transporting the PFC [10]. In that study, two different PFCs were used and the distribution of PFC following instillation in rabbits was more homogeneous for the less viscous one. The dynamics of the instillation process were not investigated in that study. The different results are likely due to different filling protocols. In the current study, the animals were positioned upright rather than supine, and the instillation rate was faster with ~20 ml/kg delivered in 1.5 min compared to ~17 ml/kg over 5 min in the PLV study [10]. It is unlikely that the very slow instillation in that study [10] lead to liquid plug formation, but the presence of liquid plugs during lung filling was not assessed in that study. If liquids are instilled slowly enough, their transport in large airways is driven primarily by gravitational drainage [15,17,25]. In that transport mode, viscous dissipation of momentum opposes transport of the liquid, producing the less uniform final liquid distribution noted in that study [10].

The findings of the present study suggest that low viscosity PFCs may be useful for targeting the gravity dependent regions of the lungs for liquid delivery. Along with the previously demonstrated effects of posture, instillation rate [17], instillation technique [15], and ventilation rate [16], viscosity could potentially be selected to obtain the desired distribution of an instilled liquid. Previous studies have demonstrated that PFCs can be mixed to produce a PFC with engineered properties [28]. However, the optimal PFC properties for TLV are yet to be determined. Although more viscous PFCs might be preferred for the relatively homogenous liquid distribution they provide, less viscous PFCs may be advantageous to other aspects of TLV, such as preventing the occurrence of expiratory airway collapse [29]. PFC viscosity is one of many PFC properties; e.g., density, interfacial tension, and gas solubility; and distribution homogeneity is one criterion that should be considered in the engineering of PFC properties to optimize TLV efficacy.

While this study provides important information regarding the effects of viscosity on liquid delivery to the lungs, which was its aim, it has a number of limitations. Only two PFCs were compared, because of practical limitations on the availability of PFCs with similar properties except viscosity. These two were selected because of their large differences in viscosity. Although there are many parameters related to ventilation and instillation that could conceivably be varied during the filling process, this study did not investigate the effects of them. Future work should consider the effects of tidal volume, breathing frequency, functional residual capacity, filling volume, and instillation rate in order to fully optimize delivery of PFC for particular treatment modalities. The two-dimensional images do not provide information regarding the homogeneity of liquid in the direction normal to the plane of the image. The use of euthanized animals in this study likely did not change the distribution dynamics since previous investigations demonstrated little change in the mechanical properties of rabbit lungs within one hour following euthanasia [22,23]. This did, however, preclude investigating the effects of liquid distribution on gas exchange. The animals in this study were positioned upright rather than supine, and care should be used in applying these findings to the supine posture. The choice of posture was motivated by potential advantages that might be provided by an upright posture or by elevating the patient's head. The length of the rabbit lung is relatively small compared to that of an adult human, and, based on elevation differences, the gravitational effects in a supine adult human are likely at least as significant as those in an upright rabbit. This suggests that plug formation and higher PFC viscosities might be advantageous for even filling in adult humans. The length scale of a neonatal lung is similar to that of the rabbit lung considered here, and, even though the lung morphometry is different, the findings of this study may be applicable to neonatal humans. The desired distribution of PFC in the neonatal lung will depend on the primary goal of treatment, which might be for treating respiratory distress syndrome or for treating diaphragmatic hernia [9]. Distending the inferior regions of the lung and inducing growth there might potentially benefit from a distribution of liquid that favors that region, whereas a uniform distribution might be beneficial for enhancing gas exchange.

In conclusion, our study demonstrates that PFDEC can lead to a more uniform liquid distribution compared to the less viscous FC-3283. This was attributed to PFDEC liquid plugs leaving behind a thicker liquid layer, resulting in a more uniform distribution, and to the propensity for PFDEC to form liquid plugs in the larger airways during instillation. Liquid viscosity is a parameter that may potentially be selected to either target specific regions of the lung or achieve a homogeneous liquid distribution.

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## References

[1] Grotberg, J. B., 1994, "Pulmonary Flow And Transport Phenomena," Annu. Rev. Fluid Mech., **26**, pp. 529–571.

[2] Jobe, A. H., 1993, "Pulmonary Surfactant Therapy," N. Engl. J. Med., **328**(12), pp. 861–868.

[3] Smith, D. J., Gambone, L. M., Tarara, T., Meays, D. R., Dellamary, L. A., Woods, C. M., and Weers, J., 2001, "Liquid Dose Pulmonary Instillation of Gentamicin PulmoSpheres (R) Formulations: Tissue Distribution and Pharmacokinetics in Rabbits," Pharm. Res., **18**(11), pp. 1556–1561.

[4] Weiss, D. J., Strandjord, T. P., Jackson, J. C., Clark, J. G., and Liggitt, D., 1999, "Perfluorochemical Liquid-Enhanced Adenoviral Vector Distribution and Expression in Lungs of Spontaneously Breathing Rodents," Exp. Lung Res., **25**(4), pp. 317–333.

[5] Shaffer, T. H., Wolfson, M. R., and Clark, L., Jr., 1992, "State of the Art Review: Liquid Ventilation," Pediatr. Pulmonol., **14**(2), pp. 102–109.

[6] Clark, L. C., Jr., and Gollan, F., 1966, "Survival of Mammals Breathing Organic Liquids Equilibrated With Oxygen at Atmospheric Pressure," Science, **152**, pp. 1755–1756.

[7] Hirschl, R. B., Grover, B., McCracken, M., Wolfson, M. R., Shaffer, T. H., and Bartlett, R. H., 1993, "Oxygen Consumption and Carbon Dioxide Production During Liquid Ventilation," J. Pediatr. Surg., **28**(4), pp. 513–518.

[8] Hirschl, R. B., Conrad, S., Kaiser, R., Zwischenberger, J. B., Bartlett, R. B., Booth, F., and Cardenas, V., 1998, "Partial Liquid Ventilation in Adult Patients With ARDS: A Multicenter Phase I–II Trial," Ann. Surg., **228**(5), pp. 692–700.

[9] Hirschl, R. B., Fox, W., Glick, P. L., Greenspan, J., Smith, K., Thompson, A., Wilson, J., and Adzick, N. S., 2003, "A Prospective, Randomized Pilot Trial of Perfluorocarbon-Induced Lung Growth in Newborns With Congenital Diaphragmatic Hernia," J. Pediatr. Surg., **38**(3), pp. 283–289.

[10] Miller, T. F., Milestone, B., Stern, R., Shaffer, T. H., and Wolfson, M. R., 2001, "Effects of Perfluorochemical Distribution and Elimination Dynamics on Cardiopulmonary Function," J. Appl. Physiol., **90**(3), pp. 839–849.

[11] Merritt, T. A., Kheiter, A., and Cochrane, C. G., 1995, "Positive End-Expiratory Pressure During KL4 Surfactant Instillation Enhances Intrapulmonary Distribution in a Simian Model of Respiratory Distress Syndrome," Pediatr. Res., **38**(2), pp. 211–217.

[12] Ueda, T., Ikegami, M., Rider, E. D., and Jobe, A. H., 1994, "Distribution of Surfactant and Ventilation in Surfactant-Treated Preterm Lambs," J. Appl. Physiol., **76**(1), pp. 45–55.

[13] Greenspan, J. S., Fox, W. W., Rubenstein, S. D., Wolfson, M. R., Spinner, S. S., and Shaffer, T. H., 1997, "Partial Liquid Ventilation in Critically Ill Infants Receiving Extracorporeal Life Support," Pediatrics, **99**(1), pp. E21–E25.

[14] Hirschl, R. B., Overbeck, M. C., Parent, A., Hernandez, R., Schwartz, S., Dosanjh, A., Johnson, K., and Bartlett, R. H., 1994, "Liquid Ventilation Provides Uniform Distribution of Perfluorocarbon in the Setting of Respiratory Failure," Surgery (St. Louis), **116**(2), pp. 159–167.

[15] Cassidy, K. J., Bull, J. L., Glucksberg, M. R., Dawson, C. A., Haworth, S. T., Hirschl, R. B., Gavriely, N., and Grotberg, J. B., 2001, "A Rat Lung Model of Instilled Liquid Transport in the Pulmonary Airways," J. Appl. Physiol., **90**, pp. 1955–1967.

[16] Anderson, J. C., Molthen, R. C., Dawson, C. A., Haworth, S. T., Bull, J. L., Glucksberg, M. R., and Grotberg, J. B., 2004, "Effect of Ventilation Rate on Instilled Surfactant Distribution in the Pulmonary Airways of Rats," J. Appl. Physiol., **97**(1), pp. 45–56.

[17] Bull, J. L., Tredici, S., Komori, E., Brant, D. O., Grotberg, J. B., and Hirschl, R. B., 2004, "Distribution Dynamics of Perfluorocarbon Delivery to the Lungs: An Intact Rabbit Model," J. Appl. Physiol., **96**(5), pp. 1633–1642.

[18] Andrade, C. F., Martins, L. K., Tonietto, T. A., Koefender, C., Anflor, L. C., da Silva, N. B., Felicetti, J. C., Camargo, J. D., Fortis, E. A. F., and Cardoso, P. F. G., 2004, "Partial Liquid Ventilation With Perfluorodecalin Following Unilateral Canine Lung Allotransplantation in Non-Heart-Heating Donors," Nurse Anesth., **23**(2), pp. 242–251.

[19] Walker, G. M., Kasem, K. F., O'Toole, S. J., Watt, A., Skeoch, C. H., and Davis, C. F., 2003, "Early Perfluorodecalin Lung Distension in Infants With Congenital Diaphragmatic Hernia," J. Pediatr. Surg., **38**(1), pp. 17–20.

[20] Bull, J. L., Nelson, L. K., Walsh, J. T., Glucksberg, M. R., Schurch, S., and Grotberg, J. B., 1999, "Surfactant-Spreading and Surface-Compression Disturbance on a Thin Viscous Film," ASME J. Sol. Energy Eng., **121**(1), pp. 89–98.

[21] Bull, J. L., and Grotberg, J. B., 2003, "Surfactant Spreading on Thin Viscous Films: Film Thickness Evolution and Periodic Wall Stretch," Exp. Fluids, **34**, pp. 1–15.

[22] Meinhardt, J. P., Ashton, B. A., Annich, G. M., Quintel, M., and Hirschl, R. B., 2003, "The Dependency of Expiratory Airway Collapse on Pump System and Flow Rate in Liquid Ventilated Rabbits," Eur. J. Med. Res., **8**(5), pp. 212–220.

[23] Foley, D. S., Brah, R., Bull, J. L., Brant, D. O., Grotberg, J. B., and Hirschl, R. B., 2004, "Total Liquid Ventilation: Dynamic Airway Pressure and the Development of Expiratory Flow Limitation," ASAIO J., **50**(5), pp. 485–490.

[24] Skoog, D. A., and West, D. M., 1965, *Analytical Chemistry*, Holt, Rinehart, and Winston, New York.

[25] Halpern, D., Jensen, O. E., and Grotberg, J. B., 1998, "A Theoretical Study of Surfactant and Liquid Delivery Into the Lung," J. Appl. Physiol., **85**(1), pp. 333–352.

[26] Halpern, D., and Gaver, D. P., 1994, "Boundary Element Analysis of the Time-Dependent Motion of a Semi-Infinite Bubble in a Channel," J. Comput. Phys., **115**(2), pp. 366–375.

[27] Espinosa, F. F., and Kamm, R. D., 1998, "Meniscus Formation During Tracheal Instillation of Surfactant," J. Appl. Physiol., **85**(1), pp. 266–272.

[28] Gabriel, J. L., Miller, T. F., Wolfson, M. R., and Shaffer, T. H., 1996, "Quantitative Structure-Activity Relationships of Perfluorinated Hetero-Hydrocarbons as Potential Respiratory Media—Application to Oxygen Solubility, Partition Coefficient, Viscosity, Vapor Pressure, and Density," ASAIO J., **42**(6), pp. 968–973.

[29] Bull, J. L., Reickert, C. A., Tredici, S., Komori, E., Frank, E. L., Brant, D. O., Grotberg, J. B., and Hirschl, R. B., 2005, "Flow Limitation in Liquid-Filled Lungs: Effects of Liquid Properties," ASME J. Biomech. Eng., **127**(4), pp. 630–636.