

Effect of Increasing Perfluorocarbon Dose on $\dot{V}_A/\dot{Q}$ Distribution during Partial Liquid Ventilation in Acute Lung Injury

Chae-Man Lim, M.D., Karen B. Domino, M.D., M.P.H.,† Robb W. Glenny, M.D.,‡ Michael P. Hlastala, Ph.D.§*

Background: **Although gas exchange during partial liquid ventilation (PLV) depends on perfluorocarbon liquid, the effect of perfluorocarbon dose on the ventilation–perfusion ($\dot{V}_A/\dot{Q}$) distribution is not known. This study investigated how $\dot{V}_A/\dot{Q}$ distribution of an acutely injured lung is affected during PLV at increasing perfluorocarbon dose.**

Methods: **In eight rabbits (3.2 ± 0.1 kg), acute lung injury (ALI) was created by repeated saline lavage (arterial oxygen partial pressure/fraction of inspired oxygen, 37 ± 11 mm Hg). Three different doses of perfluorodecalin (9 ml/kg = low dose; 13.5 ml/kg = medium dose; 18 ml/kg = functional residual capacity [FRC] dose) were applied in random order during PLV. $\dot{V}_A/\dot{Q}$ distribution at different doses was evaluated by multiple inert gas elimination technique.**

Results: **Inert gas shunt (63 ± 21% at ALI) decreased with increasing perfluorocarbon dose (43 ± 21% at low dose, 29 ± 10% at medium dose, 11 ± 9% at FRC dose; $P = 0.022$). Compared with ALI (0%), the proportion of low $\dot{V}_A/\dot{Q}$ units was higher at all tested doses (19 ± 10, 25 ± 12, and 34 ± 18%, respectively; all $P < 0.05$). Compared with ALI (27 ± 14%), the proportion of normal $\dot{V}_A/\dot{Q}$ units was not increased at low or medium doses but was increased only at the FRC dose (45 ± 13% ; $P = 0.027$).**

Conclusions: **With increasing perfluorocarbon dose during PLV, shunt was reduced from a small dose. The majority shunt units were converted to units showing low $\dot{V}_A/\dot{Q}$ ratios rather than normal $\dot{V}_A/\dot{Q}$ ratios. The presence of considerable amount of low $\dot{V}_A/\dot{Q}$ units across the varying doses of perfluorocarbon suggested that additional measures are necessary during PLV to augment its effect on gas exchange.**

IN acute respiratory distress syndrome (ARDS), one of the most important aims of ventilatory support is improving oxygenation while avoiding iatrogenic lung injury. Partial liquid ventilation (PLV), a new ventilatory method for ARDS, may serve these two ends because it has shown to improve oxygenation[1–4] and to attenuate histologic injury associated with mechanical ventilation.[2,5,6] In the first description of PLV,[7] perfluorocarbon was administered until a fluid meniscus was seen at the endotracheal tube, which represents the dose of functional residual capacity (FRC). In the following studies, however, different doses of perfluorocarbon were investigated by various authors with different perspective.[8–11]

With regard to gas exchange, there have been a few studies evaluating the relation between perfluorocarbon dose and oxygenation in an acute lung injury (ALI) model.[8–10] However, there have been no studies on how the ventilation–perfusion ($\dot{V}_A/\dot{Q}$) distribution of an injured lung is affected by the perfluorocarbon dose. Because the perfluorocarbon liquid distributes preferentially to the dependent lung regions[10,12,13] where atelectasis of ARDS is most concentrated,[14] we postulated that shunt during PLV will decrease even at a small dose of perfluorocarbon. We were also curious about which proportion of $\dot{V}_A/\dot{Q}$ ratio is expanded in association with the decrease in shunt, if any.

Materials and Methods

Animal and Anesthesia

Eight New Zealand white rabbits (3.2 ± 0.1 kg) were used for this study. The following study protocol was approved by the Institutional Board of Animal Care Committee of the University of Washington, and the rabbits were cared for and handled according to the guidelines of the National Institutes of Health. The rabbits were anesthetized with 5 mg/kg xylazine intramuscularly and 30 mg/kg ketamine intramuscularly followed by an intravenous infusion of the mixture of 75 mg ketamine and 5 mg xylazine in 20 ml normal saline at the rate of 0.4–0.6 ml/min through an ear vein. Pancuronium 0.1 mg/kg was intermittently administered intravenously to prevent spontaneous respiratory movement. The rabbits were placed supine throughout the experiment on a heating blanket to maintain the core temperature at 38–39°C as measured by a thermistor catheter positioned in the descending thoracic aorta.

Mechanical Ventilation and Instrumentation

During anesthesia, a midline tracheostomy was performed in the animal, and a 3.5-mm (ID) cuffless endotracheal tube was inserted 3 cm deep into the trachea. The endotracheal tube was firmly tied around the trachea to prevent leak of gas or liquid during the experiment. Mechanical ventilation was started at tidal volume (Vt) = 8 ml/kg, frequency 50/min (adjusted to keep arterial carbon dioxide partial pressure [Pa_{CO_2}] at 35–45 mm Hg), inspiratory-to-expiratory ratio 1:1 without pause, fraction of inspired oxygen (F_{IO_2}) 1.0, positive end-expiratory pressure (PEEP) 2 cm

* Associate Professor, Division of Pulmonary and Critical Care Medicine, University of Ulsan. † Professor, Department of Anesthesiology, ‡ Associate Professor, § Professor, Division of Pulmonary and Critical Care Medicine, University of Washington.

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Address reprint requests to Dr. Lim: Asan Medical Center, Songpa PO Box 145, Seoul, Korea 138-600. Address electronic mail to: cmlim@www.amc.seoul.kr. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

H_2O (to prevent bulk movement of perfluorocarbon during PLV) using a Servo 900C (Siemens-Elema, Solna, Sweden).

The carotid artery was cut down, and a 22-gauge angiocath was inserted for blood pressure monitoring and arterial blood sampling. For sampling of mixed venous blood, a 5-French venous catheter was inserted into the right ventricle *via* the right external jugular vein under the guidance of pressure profile. The femoral artery was cut down, and a 3-French double-lumen thermodilution probe, model 94-011-3F (Baxter-Edwards Healthcare Corporation, Irvine, CA) was inserted into the aorta up to the level of the diaphragm. Cardiac output was measured with aortic thermodilution technique using an Edwards cardiac output computer (Baxter-Edwards Healthcare Corporation) using 1.5 ml cold saline injectate (computation constant 0.054).[15]

Lung Injury

Repeated saline lavage[16] was adopted to create ALI in the animal. With the endotracheal tube disconnected from the ventilator, warmed (38–39°C) normal saline at 18 ml/kg was instilled in two divided doses with the rabbit in each lateral decubitus position. With the saline residing in the rabbit lung, mechanical ventilation was resumed at the same setting as the baseline except for occasional adjustment of Vt to 6–7 ml/kg to keep peak airway pressure below 35 cm H_2O. After 30–45 s of mechanical tidal ventilation, saline was drained out of the lung by gravity using a 70-cm-long siphon. Saline lavage was performed three times 5–7 min apart, and after the third lavage the rabbit was allowed to stabilize in hemodynamics for 30 min. During the stabilization period, arterial oxygen partial pressure (Pa_{O_2}) was confirmed twice at 15 and 30 min to be less than 100 mm Hg. If Pa_{O_2} at 15 min was greater than 100 mm Hg, a fourth saline lavage was performed, and the above criteria of ALI ($Pa_{O_2} < 100$ mm Hg) was invariably met.

Partial Liquid Ventilation at Different Doses of Perfluorocarbon

For PLV, perfluorodecalin (Fluka, Buchs, Switzerland), prewarmed to 38°C, was instilled to the rabbit lung through the endotracheal tube. Three doses of perfluorocarbon were tested: 9 ml/kg (defined as low dose) = 50% of the FRC dose, 13.5 ml/kg (defined as medium dose) = 75% of the FRC dose, and 18 ml/kg = FRC dose (chosen from the authors' experience). At the application of the FRC dose, the perfluorocarbon column was visible through the endotracheal tube at end expiration. Six rabbits were randomly subjected to one of six different sequences of perfluorocarbon dosing: low–medium–FRC dose, low–FRC–medium dose, medium–low–FRC dose, medium–FRC–low dose, FRC–low–medium dose, FRC–medium–low dose. Change from a higher dose to a lower dose was accomplished by removing perfluorocarbon *via* the endotracheal tube corresponding to the difference between doses. In case the airway pressure showed an early pressure surge exceeding the end-inspiratory peak pressure, PEEP was transiently increased to push perfluorocarbon away from the central airway.[3] The pressure surge was observed mostly at the application of the FRC dose and was readily abolished by giving several tidal breaths at 4 cm H_2O of PEEP. Evaporative loss of perfluorocarbon (estimated, 1 ml/kg per 30 min) was replenished at the changing perfluorocarbon dose. The other two rabbits were observed for the stability of lung injury over 2 h corresponding to the period from ALI to the last data acquisition.

Each half of a specific dose was administered with the rabbit in the right or left lateral decubitus positions. Because of the longer equilibration time of inert gases in perfluorocarbon,[17] samples for multiple inert gas elimination technique (MIGET) were obtained at 30 min of each dose of perfluorocarbon. Perfluorocarbon was collected from the rabbit lung after the completion of the study, filtered of bronchial debris through plain gauze, and reused in the next rabbit.

Physiologic Measurements

After the rabbit was stabilized from the surgical preparation, arterial blood gases of the normal state were analyzed using an ABL 330 (Radiometer, Copenhagen, Denmark). Airway pressures, blood pressure, and heart rate were recorded on a Mark 12/DMS 1000 (Western Graphtec, Inc., Vanderbilt, Irvine, CA) with Validyne amplifiers. Hemoglobin, carboxyhemoglobin, and methemoglobin levels were measured by OSM3 Hemoximeter (Radiometer, Copenhagen, Denmark) to calculate oxygen shunt as $(Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - C\bar{v}_{O_2}) \times 100(\%)$, where Cc_{O_2}, Ca_{O_2}, and $C\bar{v}_{O_2}$ denote oxygen content of pulmonary capillary blood, arterial blood, and mixed venous blood, respectively. In calculating Cc_{O_2}, alveolar oxygen partial pressure (P_{AO_2}) was determined as $(P_B - 47) \times F_{IO_2} - Pa_{CO_2} - P_{perfluorocarbon}$, where $P_{perfluorocarbon}$ was 14 mm Hg for perfluorodecalin.

For the analysis of $\dot{V}_A/\dot{Q}$ distribution, MIGET was used as described previously.[18] Six inert gases (sulfur hexafluoride [SF6], ethane, cyclopropane, halothane, ether, acetone) in 5% dextrose water was infused at 0.7 ml/min through an ear vein. The infusion was started at least 45 min before the first sampling of inert gases, and normal saline infusion was discontinued so as not to disturb its equilibrium. The concentrations of inert gases of the expired gas, mixed venous blood, and arterial blood were measured by a gas chromatograph (Varian 3300). Five compartments of $\dot{V}_A/\dot{Q}$ were determined: 0 as venous admixture (Q_S/Q_T), 0–0.1 as low $\dot{V}_A/\dot{Q}$, 0.1–10 as normal $\dot{V}_A/\dot{Q}$, 10–100 as high $\dot{V}_A/\dot{Q}$, infinity as dead space (V_D/V_T). Mean $\dot{V}_A/\dot{Q}$ ratios of $\dot{V}_A$ and $\dot{Q}$ distributions, and log standard deviation of the $\dot{Q}$ (log $SD_{\dot{Q}}$) and log standard deviation of $\dot{V}_A$ (log $SD_{\dot{V}}$) distributions were calculated from the 50-compartment

Table 1. Hemodynamic and Respiratory Data of the Rabbits at Normal State, at Acute Lung Injury (ALI), and during Partial Liquid Ventilation at Different Doses of Perfluorocarbon

	Normal	ALI	Low Dose	Medium Dose	FRC Dose
MBP (mmHg)	73 ± 14	58 ± 18	55 ± 12	49 ± 6	48 ± 12
HR (beats/min)	202 ± 25	209 ± 32	228 ± 21*	222 ± 27*	225 ± 32*
CO (l/min)	0.33 ± 0.03	0.44 ± 0.10	0.40 ± 0.10	0.39 ± 0.10	0.32 ± 0.11*
Hemoglobin (g/dl)	10.9 ± 1.4	10.0 ± 1.0	9.8 ± 0.8	10.2 ± 1.5	9.9 ± 1.5
P_{peak} (cm H_2O)	15 ± 2	24 ± 4	23 ± 5	23 ± 6	24 ± 6
P_{mean} (cm H_2O)	8 ± 1	12 ± 2	12 ± 2	13 ± 3	14 ± 3*
P_{pause} (cm H_2O)	11 ± 2	18 ± 6	17 ± 5	18 ± 6	19 ± 6
pH	7.45 ± 0.08	7.19 ± 0.12	7.11 ± 0.12*	7.10 ± 0.17*	7.09 ± 0.17*
$Paco_2$ (mmHg)	33.4 ± 3.4	49.9 ± 7.6	58.0 ± 15.5	50.9 ± 11.3	52.6 ± 8.2
Pao_2 (mmHg)†	527 ± 17	37 ± 11	69 ± 15*	109 ± 19*‡	161 ± 36*‡
HCO_3^- (mEq/l)	22.9 ± 4.7	18.3 ± 5.5	17.5 ± 6.1	15.4 ± 6.1*	16.1 ± 6.7*
Sao_2 (%)†	100 ± 0	53 ± 25	79 ± 19*‡	93 ± 6*	97 ± 2*
Oxygen shunt	4.3 ± 1.1	64 ± 8	39 ± 9*‡	35 ± 9*	26 ± 9*

* $P < 0.05$ compared with ALI by Wilcoxon signed rank sum test. † $P < 0.05$ by analysis of variance for perfluorocarbon dose. ‡$P < 0.05$ by Tukey Honestly Significantly Different *post hoc* multiple comparisons.

FRC = functional residual capacity; MBP = mean blood pressure; HR = heart rate; CO = cardiac output; P_{peak}, P_{mean}, P_{pause} = peak, mean, and inspiratory pause airway pressures, respectively; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension; HCO_3^- = bicarbonate; Sao_2 = arterial oxygen saturation.

model. In addition, the arterial–alveolar difference [(a-A)D] area was calculated from the retention and the excretion of inert gases.[19] This index was used because it is a model-independent measure of $\dot{V}_A/\dot{Q}$ heterogeneity. (a-A)D area does not have a counterpart in the 50-compartment model. Increases in any of the aforementioned parameters are indicative of increases in $\dot{V}_A/\dot{Q}$ heterogeneity.

Respiratory data (arterial blood gases, mixed venous blood gases, airway pressures), hemodynamic data (blood pressure, heart rate, cardiac output), and samples for MIGET were obtained at the baseline (ALI) and at 30 min of PLV at different doses of perfluorocarbon.

Statistical Analysis

All data are expressed as mean ± SD unless otherwise stated. Statistical analyses were performed using StatView 4.1 (Abacus Concepts, Inc., Berkeley, CA). The statistical significance of the effect of perfluorocarbon dose was evaluated by one-way analysis of variance. Multiple pairwise comparisons were performed with Tukey Honestly Significantly Different test. Paired data were tested by Wilcoxon signed rank sum test. Because capillary-to-alveolar diffusion for SF6 was shown to be slightly hindered in the presence of perfluorocarbon,[20] the validity of shunt with SF6 during PLV was tested by Pearson correlation and by residuals of predicted shunt without SF6. P values < 0.05 were considered significant.

Results

With increasing perfluorocarbon dose, hemodynamic parameters (blood pressure, heart rate, cardiac output), and $Paco_2$ did not significantly change (table 1). In two control rabbits, oxygen shunt at ALI, 60 min, 90 min, and 120 min were 37, 39, 37, and 33%, respectively, and 69, 74, 76, and 76%, respectively. Oxygen shunt decreased with increasing perfluorocarbon dose ($P < 0.001$). Regardless of the order of perfluorocarbon dosing, the net decrease of oxygen shunt from ALI to low dose [(shunt at low dose − shunt at ALI)/shunt at low dose = 24.7 ± 13.2%] was greater than those from the low to medium dose (4.8 ± 3.2%) or from the medium to FRC dose (9.0 ± 3.5%; both $P < 0.05$).

During PLV, the inert gas shunt with SF6 was well correlated with the shunt without SF6 ($r^2 = 0.845$, $P = 0.0001$; $Y = 0.925 \times X + 0.02$), and the residuals of the predicted shunt without SF6 were within an acceptable range (fig. 1). The multiple inert gas shunt decreased with increasing perfluorocarbon dose ($P = 0.022$; fig. 2). Compared with ALI, the proportion of low $\dot{V}_A/\dot{Q}$ units was higher at all the tested doses (all $P < 0.05$). Compared with ALI, the proportion of normal $\dot{V}_A/\dot{Q}$ units was not increased at low or medium doses but was increased only at the FRC dose ($P = 0.027$). The proportion of high $\dot{V}_A/\dot{Q}$ units did not change with increasing perfluorocarbon dose. V_D/V_T decreased with increasing perfluorocarbon dose ($P = 0.016$; table 2). Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ decreased, whereas (a-A)D area increased with increasing perfluorocarbon dose ($P < 0.05$).

Discussion

The main findings of this study can be summarized as follows: (1) In the lung with ALI, a decrease of shunt during PLV occurred at a relatively small dose of perfluorocarbon (half of an FRC dose); (2) At all tested perfluorocarbon doses, shunt units (as defined by $\dot{V}_A/\dot{Q} = 0$) were mostly transformed to low $\dot{V}_A/\dot{Q}$ units ($\dot{V}_A/\dot{Q} = 0 - 0.1$).

In previous studies on PLV, the dose-dependent in-

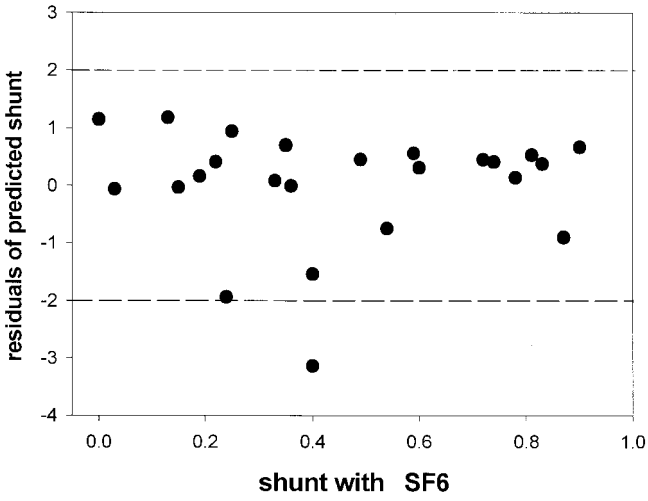

Fig. 1. Scatter plot of residuals of shunt without sulfur hexafluoride (SF6) against shunt with SF6 during partial liquid ventilation in an acute lung injury model. The values of inert gas shunt based on SF6 were within an acceptable range as compared with shunt without SF6 in our saline lavage model of acute lung injury.

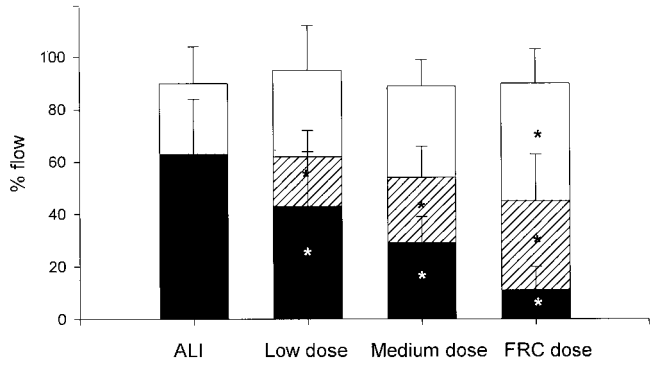

Fig. 2. Change in the proportion of inert gas shunt (*bottom*), low ventilation–perfusion ($\dot{V}_A/\dot{Q}$; *middle*), and normal $\dot{V}_A/\dot{Q}$ units (*top*) with increasing perfluorocarbon dose during partial liquid ventilation in an acute lung injury (ALI) model. Note that most of the shunt units were converted to low $\dot{V}_A/\dot{Q}$ units at all the doses. A small proportion of shunt units was converted to normal $\dot{V}_A/\dot{Q}$ units at the functional residual capacity dose. Other $\dot{V}_A/\dot{Q}$ units (high $\dot{V}_A/\dot{Q}$, V_D/V_T) are not shown in the stack bar. *$P < 0.05$ compared with ALI.

crease in oxygenation was more prominent at low doses of perfluorocarbon than at high doses.[1,21] In the study by Tütüncü *et al.*,[1] with a similar ALI model to ours, even a smaller dose of perfluorocarbon (3 ml/kg in the rabbit) was effective in reducing shunt. The current study extends these previous findings with the result of change in inert gas shunt. The significant reduction of shunt at a relatively small perfluorocarbon dose could be attributed to its chemical characteristics. Perfluorocarbon is twice as dense as water (specific gravity, 1.95 for perfluorodecalin) and thus distributes preferentially to the dependent lung.[10,12,13] Because of the preponderance of alveolar collapse in the dependent lung regions,[14] administration of perfluorocarbon even at an amount less than FRC could be translated into an application of "selective PEEP" for the dependent lung regions. Although perfluorocarbon is allegorized as liquid PEEP, this aspect contrasts with conventional PEEP, or pressure built in the proximal airway, in that the effect of the latter is devoid of regional selectivity. In our results, the net reduction of oxygen shunt during PLV was diminished with increasing perfluorocarbon dose. This aspect also contrasts with PEEP, which reduces shunt to a significant degree generally at a higher level.[22,23]

In addition to the gravity-dependent mechanism, a few nongravity effects of perfluorocarbon could probably have been involved in the reduction of shunt during PLV, *e.g.*, low surface tension or vaporized perfluorocarbon.[24] The nondependent lung units of our animal could have taken advantage of the low surface tension offered by perfluorocarbon while in the lateral decubitus position. However, it seems difficult to ascertain the relative contribution of the nongravity effects of perfluorocarbon in the reduction of shunt. At the FRC dose in the current study, cardiac output decreased compared with gas ventilation. Although a change in cardiac output may influence shunt in ARDS,[25] it certainly was not the main mechanism of the reduction in shunt seen across the varying perfluorocarbon dose in our study in view of the effectiveness of a small dose and the diminishing effect of an incremental dose.

Regarding the fate of shunt units during PLV, the current study showed that shunt units were mostly converted to units showing low $\dot{V}_A/\dot{Q}$ ratio rather than normal $\dot{V}_A/\dot{Q}$ ratio. This observation indicated that improvement of oxygenation by perfluorocarbon was not necessarily associated with a full recovery of collapsed alveoli in terms of $\dot{V}_A/\dot{Q}$ ratio. Rather, perfluorocarbon, especially at less than an FRC dose, might have recruited potential low $\dot{V}_A/\dot{Q}$ units of the dependent lung to partake in gas exchange by preventing their collapse during ventilatory cycles. The low surface tension, high spreading coefficient, and weight of perfluorocarbon all could serve this purpose, especially for the stabilization of collapsible small airways. According to Kirmse *et al.*,[21] the lower inflection point of a saline-lavaged lung (representing the pressure of small airways opening[26]) was shown shifted to the left by administration of perfluorocarbon. In support of our postulation regarding the "low dose effect" of perfluorocarbon, the decrease of the inflection point in their study was evident at one third of the FRC dose.

In that perfluorocarbon liquid alone is not sufficient to convert collapsed units to normal functioning units as shown in our study, additional measures may be necessary during PLV. In previous studies,[27–32] some of the conventional means of gas ventilation were shown to be effective during PLV. For instance, PEEP was found to be synergistic with perfluorocarbon for oxygenation and respiratory mechanics.[27–30] For PLV with a small dose of

Table 2. Gas Exchange According to Multiple Inert Gas Elimination Technique at Acute Lung Injury (ALI) during Partial Liquid Ventilation and at Different Doses of Perfluorocarbon

	ALI	Low Dose	Medium Dose	FRC Dose
Mean $\dot{V}_A/\dot{Q}$ of $\dot{Q}$*	3.32 ± 2.53	0.46 ± 0.39†‡	0.35 ± 0.24‡	0.44 ± 0.46‡
Log $SD_{\dot{Q}}$	1.41 ± 0.74	1.68 ± 0.79	2.08 ± 0.45	2.14 ± 0.54
Mean $\dot{V}_A/\dot{Q}$ of $\dot{V}$	19.93 ± 17.45	23.67 ± 18.76	20.27 ± 10.61	20.81 ± 15.08
Log $SD_{\dot{V}}$	0.97 ± 0.42	1.62 ± 0.90	1.26 ± 0.33	1.40 ± 0.47
V_D/V_T (%)*	38 ± 11	39 ± 24	21 ± 8†‡	22 ± 8
$\dot{V}$ to high $\dot{V}_A/\dot{Q}$ (%)	46 ± 20	48 ± 24	60 ± 22	60 ± 17
(a–A)D area*	0.75 ± 0.37	1.77 ± 0.39†‡	1.77 ± 0.32‡	1.75 ± 0.40‡

* $P < 0.05$ by analysis of variance. †$P < 0.05$ by Tukey Honestly Significantly Different *post hoc* multiple comparisons. ‡$P < 0.05$ compared with ALI by Wilcoxon signed rank sum test.

FRC = functional residual capacity; $\dot{V}_A/\dot{Q}$ of $\dot{Q}$ = ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) of perfusion distribution; log $SD_{\dot{Q}}$ = log standard deviation of perfusion distribution; $\dot{V}_A/\dot{Q}$ of $\dot{V}$ = $\dot{V}_A/\dot{Q}$ ratio of ventilation distribution; log $SD_{\dot{V}}$ = log standard deviation of ventilation distribution; V_D/V_T = inert gas dead space; $\dot{V}$ to high $\dot{V}_A/\dot{Q}$ = ventilation to high $\dot{V}_A/\dot{Q}$ units; (a–A)D area = arterial–alveolar difference area.

perfluorocarbon, PEEP would presumably boost the splinting effect of perfluorocarbon liquid of the small airways. In addition, more of the intrapulmonary perfluorocarbon liquid was shown to distribute to the peripheral lung ("alveolize") with the use of PEEP.[28] With PEEP set at the lower inflection point, oxygenation during PLV was secured across varying modes and inspiratory to expiratory ratios.[29] End-expiratory lung volume can also be modulated directly by PEEP.[30] As another example, sustained inflation, an alveolar recruiting maneuver, resulted in an independent effect on oxygenation during PLV.[31]

With increasing perfluorocarbon dose, (a-A)D area also increased in our result. This finding suggested a concomitant increase in $\dot{V}_A/\dot{Q}$ heterogeneity with the reduction in shunt. In view of the relatively homogenized distribution of pulmonary blood flow during PLV,[33,34] this increased dispersion of $\dot{V}_A/\dot{Q}$ ratio at a higher dose could be attributable to an increasing heterogeneity in the distribution of ventilation.[17] V_D/V_T decreased with increasing perfluorocarbon dose in our study. This finding may represent another feature of liquid PEEP as opposed to PEEP, the increasing level of which usually increases dead space.[35] Nevertheless, owing to a concomitant expansion of diffusional dead space imposed by perfluorocarbon itself,[17,20,36] a decrease in V_D/V_T at an increased perfluorocarbon dose may not necessarily translate into a reduction of $Paco_2$ level, as suggested in the insignificant change in $Paco_2$ at higher doses in the current study and in previous studies.[1,37]

Saline lavage of the lung is one of the commonly used methods for creation of ALI in the rabbit.[16] Although the oxygenation and histologic features of a saline-lavaged rabbit lung have been well characterized, there has been no information yet on the characteristics of its $\dot{V}_A/\dot{Q}$ distribution. According to our MIGET data, shunt rather than low $\dot{V}_A/\dot{Q}$ was responsible for the hypoxia of a saline-lavaged lung. In this respect, our findings may not be reproduced in other lung injury models or in human ARDS having low $\dot{V}_A/\dot{Q}$ component.[38] Regarding the stability of saline lavage injury, Kolton *et al.*[39] have shown that a 2- to 4-h period of relative stability ensued after 0.5- to 1-h stabilization period. In our control animals (though only two in number), the change in shunt over 2 h was −4% and +7 %, respectively, which could not account for the perfluorocarbon-dependent change in the study animals (approximately −38%). MIGET is a well-established method for a quantitative analysis of $\dot{V}_A/\dot{Q}$ distribution of the lung. Although the capillary-to-alveolar diffusion for SF6 was shown to be slightly hindered in the presence of perfluorocarbon,[20] the values of inert gas shunt based on SF6 were acceptable in our saline-lavaged lung.

In conclusion, during PLV in an ALI model, shunt began to decrease from a small dose of perfluorocarbon. The majority shunt units were converted to units showing low $\dot{V}_A/\dot{Q}$ ratio rather than normal $\dot{V}_A/\dot{Q}$ ratio. The presence of a considerable amount of low $\dot{V}_A/\dot{Q}$ units across the varying dose of perfluorocarbon suggested that additional measures are necessary to augment the effect of PLV on gas exchange.

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