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Effect of Low Isoflurane Concentrations on the Ventilation–Perfusion Distribution in Injured Canine Lungs

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Background: **Rapid recovery and weaning from ventilatory support and cardiovascular stability are suggested advantages of isoflurane inhalation, in concentrations ranging from 0.1 to 0.6 vol%, for long-term sedation in mechanical ventilated patients. This study was designed to determine whether isoflurane in low concentrations impairs pulmonary gas exchange by increasing ventilation and perfusion ($\dot{V}_A/\dot{Q}$) mismatch during lung injury.**

Methods: **Fourteen anesthetized dogs received in random order 0, 0.25, or 0.5 vol% end-tidal isoflurane before and after induction of lung injury with oleic acid. Gas exchange was assessed by blood gas analysis and by estimating the $\dot{V}_A/\dot{Q}$ distributions using the multiple inert gas elimination technique.**

Results: **Administration of oleic acid produced a lung injury with severe $\dot{V}_A/\dot{Q}$ mismatch and 38 ± 4% intrapulmonary shunting of blood. During lung injury, isoflurane accounted for a dose-related increase in blood flow to shunt units from 38 ± 4 to 42 ± 3 (0.25 vol%) and 48 ± 4% (0.5 vol%) ($P < 0.05$), dispersion pulmonary blood flow distribution from 0.94 ± 0.07 to 1.01 ± 0.09 (0.25 vol%) and 1.11 ± 0.11% (0.5 vol%) ($P < 0.05$), and a decrease in perfusion of normal $\dot{V}_A/\dot{Q}$ units from 58 ± 5 to 55 ± 4 (0.25 vol%) and 50 ± 4% (0.5 vol%) ($P < 0.05$) (mean ± SE). Isoflurane decreased arterial oxygen partial pressure from 72 ± 4 to 62 ± 4 mmHg (0.25 vol%) and 56 ± 4 mmHg (0.5 vol%) ($P < 0.05$) and oxygen delivery from 573 ± 21 to 529 ± 19 ml · kg^{-1} · min^{-1} (0.25 vol%) and 505 ± 22 ml · kg^{-1} · min^{-1} (0.5 vol%) ($P < 0.05$). Gas exchange, perfusion of shunt and normal $\dot{V}_A/\dot{Q}$ units, and pulmonary blood flow distribution was similar in absence of lung injury with and without isoflurane. Isoflurane 0.5 vol% lowered cardiac output during all conditions ($P < 0.05$).**

Conclusions: **Inhalation of low concentrations of isoflurane contributed to increased $\dot{V}_A/\dot{Q}$ mismatch and decreased systemic blood flow and oxygen delivery in mechanically ventilated animals with injured lungs.**

ACUTE lung injury causes alveolar collapse with a decrease in lung compliance and resting lung volume, resulting in a mismatch between ventilation and perfusion ($\dot{V}_A/\dot{Q}$).[1] The $\dot{V}_A/\dot{Q}$ mismatch accounts entirely for the severe arterial hypoxemia observed during acute lung injury.[2]

The volatile anesthetic isoflurane has been used in low concentrations of 0.1–0.6 vol% as a sedative to facilitate mechanical ventilation in critically ill patients.[3–10] Faster recovery and weaning from ventilatory support,[4,5,8,10] cardiovascular stability,[3,6,10] and effective bronchodilation[11] have been suggested as an advantage of isoflurane inhalation, compared with midazolam infusion for long-term sedation. Previous investigations indicate that inhalation of 1.4–3.5 vol% isoflurane inhibits hypoxic pulmonary vasoconstriction in intact animals[12–15] and humans[16–18] during one-lung ventilation. These observations suggest that isoflurane contributes to arterial hypoxemia by inhibiting hypoxic pulmonary vasoconstriction in a dose-dependent manner.[12] Therefore, even low concentrations of isoflurane may increase $\dot{V}_A/\dot{Q}$ mismatch and impair pulmonary gas exchange during acute lung injury.

We hypothesized that low concentrations of isoflurane would augment $\dot{V}_A/\dot{Q}$ mismatching during acute lung injury. To test this hypothesis, we examined changes in the continuous $\dot{V}_A/\dot{Q}$ distributions during inhalation of low concentrations of isoflurane in dogs with and without oleic acid–induced lung injury.

Materials and Methods

Instrumentation

After we obtained approval from the Laboratory Animal Care and Use Committee of the University of South Florida, 14 mongrel dogs weighing 20–26 kg (22.2 ± 2.0 kg, mean ± SD) were anesthetized with intravenous sodium pentobarbital, a 12-mg/kg bolus dose, followed by infusion of 20 μg · kg^{-1} · min^{-1}, and paralyzed with intravenous pancuronium bromide (0.1 mg/kg). Animals were placed supine, and their tracheas were intubated with a 9-mm ID cuffed endotracheal tube (Mallinckrodt, Argyle, NY). Dogs then were mechanically ventilated (Servo 900D; Siemens, Schaumburg, IL) with 40% oxygen in nitrogen, a tidal volume of 10 ml/kg, and ventilator frequency adjusted to maintain arterial blood carbon dioxide tension ($Paco_2$) between 35 and 45 mmHg. A catheter was inserted into a femoral artery, and a 7-French, thermistor-tipped, triple-lumen pulmonary artery catheter (93A-131-7F; Baxter Edwards Critical Care, Irvine, CA) was placed through a femoral vein.

Cardiovascular Measurements

Systemic blood pressure, central venous pressure, pulmonary artery pressure, and pulmonary artery occlusion pressure were transduced (Transpac® II; Abbott Critical Care, Chicago, IL) and recorded (TA 2600; Statham Gould, Oxnard, CA). A horizontal plane through the shoulder was taken as zero reference point for blood pressure measurements. Cardiac output (CO) was mea-

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sured with a thermal dilution technique (Oximetrix® 3; Abbott Critical Care). Ten milliliters of iced 5% dextrose solution was used as the indicator, and three determinations were performed at random moments during the ventilatory cycle and averaged.

Ventilatory Measurements

Gas flow was measured at the proximal end of the endotracheal tube with a heated pneumotachograph (3791; Hans Rudolph, Kansas City, MO), connected to a differential pressure transducer (DP 1030871; Validyne, Northridge, CA). Tidal volume was derived from the integrated gas flow signal. Expiratory minute ventilation ($\dot{V}_E$) was measured for control with a calibrated Wright respirometer at the outlet of the gas mixing chamber, which was connected to the expiratory port of the ventilator. Airway pressure was measured at the proximal end of the endotracheal tube with a differential gas-pressure transducer (MP45-871; Validyne). Esophageal pressure was measured with a balloon catheter (Mallinckrodt) connected to a differential pressure transducer (MP45-871, $\pm$35 cm H_2O; Validyne) as described by Baydur *et al.*[19] Transpulmonary pressure was obtained by subtracting esophageal pressure from airway pressure. End-inspiratory pressures were measured following a 5-s end-inspiratory occlusion,[20] and intrinsic positive end-expiratory pressures following a 5-s end-expiratory occlusion of the airway, as described previously.[21] Static lung compliance was obtained by dividing expiratory tidal volume by the difference between end-inspiratory transpulmonary pressure and intrinsic positive end-expiratory pressure. Pulmonary resistance (R_L) was calculated by dividing the difference between maximal and end-inspiratory transpulmonary pressure by the preceding gas flow.[20]

Blood Gas Analysis

Arterial and mixed venous P_{O_2} and P_{CO_2} and *p*H were determined immediately after sampling with standard blood gas electrodes (Model 1303; Instrumentation Laboratories, Lexington, MA). Oxygen saturation of arterial and mixed venous blood, and total hemoglobin were determined by spectrophotometry with a CO-oximeter (Model 282; Instrumentation Laboratories). Fractions of inspired oxygen (F_{IO_2}) and mixed expired oxygen (F_{EO_2}), carbon dioxide, and end-tidal isoflurane were determined with a Raman scattering gas analyzer (Rascal® II; Ohmeda, Louisville, CO).[22]

Inert Gas Analysis

Six inert gases (sulfur hexafluoride, ethane, cyclopropane, enflurane, diethyl ether, and acetone) were dissolved in lactated Ringer's solution and infused into a peripheral vein with a constant rate set at about 0.05% of $\dot{V}_E$ for at least 40 min.[23,24] Arterial and mixed venous blood samples were collected during stable conditions confirmed by constancy of $\dot{V}_E$, F_{EO_2}, F_{ECO_2}, and CO. Expired gas samples were collected after the blood samples with a time delay equal to the transit time of the gas through the mixing chamber.[24] Inert gases were extracted, their concentrations were measured with a gas chromatograph (HP 5890; Hewlett-Packard, Waltham, MA), and their blood gas partition coefficients were determined.[25] To provide adequate separation of the inert gases and isoflurane, temperature programming was used as has been described in detail by Dueck *et al.*[26]

Data Analysis

Arterial to mixed venous (retention) and mixed expired to mixed venous (excretion) concentration ratios of the inert gases were used to obtain retention and excretion solubility curves.[23,24] By formal mathematical analysis with enforced smoothing, these relations were transformed into a 50-compartment distribution plot of blood flow and ventilation against $\dot{V}_A/\dot{Q}$.[23,27] Intrapulmonary shunt was defined as the fraction of pulmonary blood flow ($\dot{Q}_T$) perfusing essentially nonventilated alveoli ($\dot{V}_A/\dot{Q} < 0.005$), low $\dot{V}_A/\dot{Q}$ as the fraction of $\dot{Q}_T$ perfusing poorly ventilated lung areas ($0.005 < \dot{V}_A/\dot{Q} < 0.1$), high $\dot{V}_A/\dot{Q}$ as the fraction of $\dot{V}_E$ ventilating poorly perfused lung areas ($10 < \dot{V}_A/\dot{Q} < 100$), and dead space as fraction of $\dot{V}_E$ ventilating nonperfused lung areas ($\dot{V}_A/\dot{Q} > 100$). Mean $\dot{V}_A/\dot{Q}$ ratio of perfusion ($\dot{Q}$) and ventilation ($\dot{V}$), and logarithmic SDs of perfusion ($logSD_Q$) and ventilation ($logSD_V$) were derived from the 50-compartment model. Predicted values for P_{aO_2} were calculated from the recovered $\dot{V}_A/\dot{Q}$ distributions as previously described.[24]

Transmural central venous pressure, pulmonary artery pressure (Ppa_{tm}), and pulmonary artery occlusion pressure (Pao_{tm}) were derived by subtracting esophageal pressure from the measured vascular pressures. Systemic vascular resistance was calculated as

$$(\text{mean Psa} - \text{mean Pcv}) \times 80/\text{CO},$$

and pulmonary vascular resistance was calculated as

$$(\text{mean } Ppa_{tm} - Pao_{tm}) \times 80/\text{CO}.$$

Oxygen content for arterial blood (Cao_2) was calculated as

$$(1.34 \times S_{O_2} \times \text{Hb}) + (0.0031 \times P_{O_2}),$$

oxygen delivery (Do_2) was calculated as

$$Cao_2 \times \text{CO},$$

and oxygen consumption ($\dot{V}_{O2}$) was calculated as[28]

$$(\dot{V}_I \times F_{IO_2}) - (\dot{V}_E \times F_{EO_2}).$$

Alveolar arterial oxygen difference was calculated as

$$F_{IO_2} \times (P_B - P_{H2O}) - (Paco_2 \times R) - Pao_2,$$

Table 1. Ventilatory and Pulmonary Mechanics Variables

	Before Lung Injury			After Lung Injury		
	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*
P_{pe} (cm H_2O)	17 ± 5	17 ± 5	17 ± 5	25 ± 5†	26 ± 3†	27 ± 5†
P_{pl} (cm H_2O)	15 ± 4	15 ± 4	15 ± 4	23 ± 4†	23 ± 3†	24 ± 4†
$PEEP_i$ (cm H_2O)	0.6 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	1.2 ± 0.3	1.0 ± 0.2	1.1 ± 0.3
RR (breaths/min)	10 ± 2	10 ± 2	10 ± 2	10 ± 2	10 ± 2	10 ± 2
$\dot{V}_E$ (L/min)	4.5 ± 1.1	4.5 ± 1.2	4.5 ± 1.2	4.5 ± 1.1	4.5 ± 1.0	4.5 ± 1.0
R_L (cm $H_2O \cdot {}^{-1} \cdot s^{-1}$)	3.9 ± 1.1	3.9 ± 1.1	3.9 ± 1.1	4.7 ± 1.1	4.6 ± 1.1	4.6 ± 1.1
C_L (ml/cm H_2O)	30 ± 2	30 ± 2	30 ± 2	19 ± 2†	18 ± 2†	18 ± 2†

Values are mean ± SE.

* Tested on a randomized basis. † $P \leq 0.05$ compared with 0 vol% isoflurane before lung injury.

P_{pe} = peak airway pressure; P_{pl} = plateau airway pressure; $PEEP_i$ = intrinsic positive end-expiratory pressure; RR = respiratory rate; $\dot{V}_E$ = minute volume; R_L = pulmonary resistance; C_L = static lung compliance.

where P_B is barometric pressure, P_{H2O} is the pressure of the water vapor at body temperature, and R is the respiratory quotient.

Experimental Procedure

Dogs remained supine after instrumentation. Body temperature was kept between 37 and 38°C with a heating pad. Adequate hydration and energy supply (25 kcal $\cdot$ $kg^{-1} \cdot d^{-1}$) was ensured with an infusion of 5% dextrose and lactated Ringer's solution to achieve an Pao_{tm} of 8 mmHg. After 90-min stabilization, measurements reflecting the noninjured state were obtained.

Acute lung injury was induced by injection of 0.08 ml/kg purified oleic acid (J. T. Baker Inc., Phillipsburg, NJ) into the right atrial catheter over 15 min. Additional 0.2-ml increments of oleic acid were administered every 30 min until Pao_2 was less than 75 mmHg. Lung injury was allowed to stabilize for 90 min until measurements were repeated.

The dogs received, in random order, 0, 0.25, and 0.5 vol% end-tidal isoflurane concentrations before and after induction of oleic acid lung injury. Isoflurane was administered with a calibrated vaporizer (isoflurane vaporizer 952; Siemens). Forty minutes of equilibration was allowed for each intervention before measurements. Following each measurement, dogs were ventilated without isoflurane for at least 30 min until $\dot{V}_E$, FEO_2, $FECO_2$, CO, Ppa_{tm}, systemic blood pressure, Pao_2, and $PaCO_2$ returned to baseline values before or after induction of lung injury (± 5%). To reopen unspecific atelectasis, animals' lungs were inflated manually to an airway pressure of 30 cm H_2O for 10 s after each measurement, before changing the isoflurane concentration.

Statistical Analysis

Results are expressed as mean ± SEM (SE). Data were analyzed using a repeated two-way analysis of variance. When a significant F ratio was obtained, differences between the mean values were isolated with the Scheffé multiple range test. The relation between measured and predicted Pao_2 was assessed with a linear regression analysis. $P < 0.05$ was considered statistically significant.

Results

Administration of oleic acid produced a lung injury with severe $\dot{V}_A/\dot{Q}$ mismatch, which decreased Pao_2 from 163 ± 8 to 72 ± 4 mmHg during mechanical ventilation with 40% oxygen. Following induction of lung injury, an average of 38 ± 4% of the CO perfused shunt ($\dot{V}_A/\dot{Q} < 0.005$), 3.7 ± 1.3% low $\dot{V}_A/\dot{Q}$ ($0.005 < \dot{V}_A/\dot{Q} < 0.1$), and 58 ± 5% normal $\dot{V}_A/\dot{Q}$ areas ($0.1 < \dot{V}_A/\dot{Q} < 10$). Dead space ventilation ($\dot{V}_A/\dot{Q} > 100$) comprised 46 ± 4% of the total ventilation, and another 5.4 ± 2.3% was distributed to high $\dot{V}_A/\dot{Q}$ areas ($10 < \dot{V}_A/\dot{Q} < 100$).

The effects of isoflurane and oleic acid–induced lung injury on pulmonary mechanics are shown in table 1. Static lung compliance decreased ($P < 0.05$) and airway pressures increased ($P < 0.05$) following induction of lung injury. Inhalation of isoflurane did not affect lung compliance, R_L, or intrinsic positive end-expiratory pressure in the presence or absence of lung injury. Ventilatory rate and $\dot{V}_E$ remained unchanged throughout the study.

Changes in cardiovascular variables are shown in table 2. Inhalation of 0.5 vol% isoflurane decreased systemic vascular resistance both in presence and absence of lung injury ($P < 0.05$). CO was lowest during 0.5 vol% isoflurane ($P < 0.05$). Elevated mean Ppa_{tm} and pulmonary vascular resistance decreased with 0.25 and 0.5 vol% isoflurane during lung injury ($P < 0.05$). Heart rate, transmural central venous pressure, and Pao_{tm} remained unchanged.

Despite inhalation of isoflurane, Pao_2, alveolar arterial oxygen difference, Do_2, and $P\bar{v}o_2$ remained unchanged in absence of lung injury. Inhalation of 0.25 and 0.5 vol% isoflurane was associated with a decrease in Pao_2, Do_2, and $P\bar{v}o_2$ ($P < 0.05$) and an increase in alveolar arterial

Table 2. Cardiovascular Variables

	Before Lung Injury			After Lung Injury		
	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*
HR (beats/min)	125 ± 4	126 ± 2	129 ± 3	127 ± 3	128 ± 4	128 ± 4
Psa (mmHg)	100 ± 5	95 ± 5	86 ± 6†	95 ± 6	85 ± 4‡	76 ± 4‡
Ppa_{tm} (mmHg)	22 ± 2	20 ± 2	21 ± 2	26 ± 2	24 ± 2‡	22 ± 2‡
Pcv_{tm} (mmHg)	7 ± 2	8 ± 2	8 ± 2	7 ± 2	7 ± 2	7 ± 2
Pao_{tm} (mmHg)	9 ± 2	8 ± 2	9 ± 2	9 ± 2	9 ± 2	9 ± 2
CO (l/min)	4.4 ± 1.5	4.2 ± 1.2	4.0 ± 1.3†	4.3 ± 1.4	4.0 ± 1.1	3.9 ± 1.2‡
SVR ($dyn \cdot s \cdot cm^{-5}$)	1,691 ± 107	1,652 ± 101	1,560 ± 86†	1,633 ± 107	1,560 ± 118‡	1,419 ± 128‡
PVR ($dyn \cdot s \cdot cm^{-5}$)	239 ± 31	225 ± 29	215 ± 34	316 ± 36	287 ± 27§‡	247 ± 29‡

Values are mean ± SE.

* Tested on a randomized basis. † $P \leq 0.05$ compared with 0 vol% isoflurane before lung injury. ‡ $P \leq 0.05$ compared with 0 vol% isoflurane after lung injury.

HR = heart rate; Psa = mean blood pressure; Ppa_{tm} = transmural mean pulmonary artery pressure; Pcv_{tm} = transmural central venous pressure; Pao_{tm} = transmural mean pulmonary artery occlusion pressure; CO = cardiac output (thermodilution); SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

oxygen difference during lung injury (table 3). Arterial *p*H, $Paco_2$, and $\dot{V}o_2$ remained unchanged during all tested conditions.

Changes reflecting the distribution of ventilation and perfusion are summarized in table 4 and figure 1. Patterns of blood flow and ventilation distributions were unimodal in 11 animals and modestly bimodal in the 3 remaining animals. During lung injury, inhalation of 0.5 vol% isoflurane accounted for a 10 ± 2% increase ($P < 0.05$) in blood flow to shunt units ($\dot{V}_A/\dot{Q} < 0.005$) and an 8 ± 1% decrease ($P < 0.05$) in the fraction of CO to units with normal $\dot{V}_A/\dot{Q}$ ratios ($0.1 < \dot{V}_A/\dot{Q} < 10$). In the absence of acute lung injury, inhalation of 0.5 vol% isoflurane did not affect pulmonary blood flow distribution. Blood flow distribution curves were centered, with $\dot{Q}$ ranging from 0.83 ± 0.09 to 1.02 ± 0.16, and their dispersions were increased ($logSD_Q > 0.6$). Highest $logSD_Q$ was observed during inhalation of 0.5 vol% isoflurane in acute lung injury ($P < 0.05$). Ventilation distributions were shifted to the right with $\dot{V}$ ranging from 1.75 ± 0.16 to 2.90 ± 0.46, while dispersions of the curves were above the upper normal limit ($logSD_V >$ 0.6). Changes in dead space, $\dot{Q}$, and $logSD_V$ were not statistically significant.

Predicted Pao_2 was close to measured Pao_2 for all tested conditions (table 5). Mean residual sum of squares indicated acceptably small experimental error for all inert gas measurements.

Discussion

This study was designed to evaluate the effect of low isoflurane concentrations on pulmonary gas exchange in subjects with acute lung injury. We found that inhalation of 0.25 and 0.5 vol% isoflurane worsened $\dot{V}_A/\dot{Q}$ mismatch during acute lung injury, as reflected by increases in intrapulmonary shunt and $logSD_Q$. Inhalation of isoflurane caused systemic vasodilation and reversed pulmonary vasoconstriction induced by lung injury.

Sedation is used in critically ill patients to minimize discomfort and allow effective ventilatory support.[7,29] However, sedatives have adverse effects and the potential to prolong duration of ventilatory support and length

Table 3. Physiologic Gas Exchange

	Before Lung Injury			After Lung Injury		
	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*
Flo_2	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0
Pao_2 (mmHg)	163 ± 6	154 ± 8	156 ± 9	72 ± 4†‡	62 ± 4†‡§	56 ± 4†‡§
$AaDo_2$ (mmHg)	89 ± 4	98 ± 3	95 ± 3	180 ± 7	191 ± 8	197 ± 7
$Paco_2$ (mmHg)	41 ± 2	40 ± 2	41 ± 2	41 ± 2	41 ± 3	43 ± 2
pHa, units	7.32 ± 0.02	7.34 ± 0.02	7.32 ± 0.02	7.32 ± 0.02	7.32 ± 0.03	7.30 ± 0.02
$P\bar{v}o_2$ (mmHg)	45 ± 1	44 ± 1	43 ± 1	42 ± 2	41 ± 3	40 ± 3
Do_2 $ml \cdot kg \cdot min^{-1}$	622 ± 25	593 ± 27	565 ± 28	573 ± 21	529 ± 19†‡§	505 ± 22†‡§
$\dot{V}o_2$ $ml \cdot min^{-1}$	155 ± 19	145 ± 21	149 ± 24	158 ± 21	145 ± 26	150 ± 22

Values are mean ± SE.

* Tested on a randomized basis. † $P \leq 0.05$ compared with 0 vol% isoflurane before lung injury. ‡ $P \leq 0.05$ compared with 0.5 vol% isoflurane before lung injury. § $P \leq 0.05$ compared with 0 vol% isoflurane after lung injury.

Flo_2 = inspiratory fraction of oxygen; Pao_2 = arterial oxygen tension; $AaDO_2$ = alveolar arterial oxygen difference; $Paco_2$ = arterial carbon dioxide tension; $P\bar{v}o_2$ = mixed venous oxygen tension; DO_2 = oxygen delivery; $\dot{V}O_2$ = oxygen consumption.

Table 4. Inert Gas Data

	Before Lung Injury			After Lung Injury		
	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*
RSS	2.7 ± 0.4	2.2 ± 0.3	2.3 ± 0.4	1.9 ± 0.4	2.5 ± 0.5	2.5 ± 0.5
Shunt ($\dot{V}_A/\dot{Q}<0.005$; $\%\dot{Q}_T$)	5.9 ± 0.9	6.1 ± 1.2	6.3 ± 1.1	38.3 ± 4.0†‡	42.2 ± 3.3†‡	48.2 ± 4.3†‡§
$0.005 < \dot{V}_A/\dot{Q} < 0.1$ ($\%\dot{Q}_T$)	0.6 ± 0.3	0.7 ± 0.3	0.8 ± 0.4	3.7 ± 1.3†‡	2.2 ± 0.9	1.6 ± 0.7
$0.1 < \dot{V}_A/\dot{Q} <10$ ($\%\dot{Q}_T$)	93.5 ± 1.7	93.1 ± 1.4	92.9 ± 1.4	58.0 ± 4.9†‡	55.6 ± 3.5†‡	50.2 ± 3.5†‡§
$10 < \dot{V}_A/\dot{Q} < 100$ ($\%\dot{V}_E$)	1.2 ± 0.6	1.2 ± 0.8	1.4 ± 0.7	5.4 ± 2.3†‡	6.1 ± 2.2	6.4 ± 3.2
Dead space ($\dot{V}_A/\dot{Q} > 100$; $\%\dot{V}_E$)	44.2 ± 2.7	45.1 ± 2.3	45.7 ± 2.7	45.8 ± 4.5	47.0 ± 3.7	48.0 ± 4.9
$\bar{Q}$	0.83 ± 0.09	0.85 ± 0.02	0.87 ± 0.02	1.02 ± 0.16	0.88 ± 0.14	0.98 ± 0.14
Log SD_Q	0.62 ± 0.07	0.67 ± 0.07	0.65 ± 0.05	0.94 ± 0.07†‡	1.01 ± 0.09†‡	1.11 ± 0.11†‡
$\bar{V}$	1.75 ± 0.16	1.93 ± 0.15	1.97 ± 0.19	2.67 ± 0.34†‡	2.75 ± 0.56†‡	2.90 ± 0.46†‡
Log SD_V	0.73 ± 0.12	0.79 ± 0.10	0.81 ± 0.12	0.84 ± 0.11	0.92 ± 0.17	0.94 ± 0.17

Values are mean ± SE.

* Tested on a randomized basis. † $P \leq 0.05$ compared with 0 vol% isoflurane before lung injury. ‡ $P \leq 0.05$ compared with 0.25 or 0.5 vol% isoflurane before lung injury. § $P \leq 0.05$ compared with 0 vol% isoflurane after lung injury.

RSS = residual sum of squares; $\dot{V}_A/\dot{Q}$ = ventilation to perfusion ratio; $\dot{Q}_T$ = pulmonary blood flow; $\dot{V}_E$ = expired volume per unit time; $\bar{Q}$ = mean $\dot{V}_A/\dot{Q}$ of blood flow; Log SD_Q = logarithm of the standard deviation of perfusion distribution; $\bar{V}$ = mean $\dot{V}_A\dot{Q}$ of ventilation; Log SD_V = logarithm of the standard deviation of ventilation.

of intensive care unit stay.[30] Faster emergence and weaning from ventilatory support,[4–6,8,10] cardiovascular stability,[3,10] and bronchodilation[11,31] have been suggested an advantages of isoflurane inhalation over midazolam or propofol infusions for prolonged sedation. Ostermann *et al.*[7] recommended further investigations because isoflurane is currently used infrequently for sedation. Although isoflurane in low concentrations has been shown to be useful for sedation of ventilated patients with mild pulmonary dysfunction without causing adverse effects on cardiorespiratory, hepatic, renal, or adrenal function, its effects on gas exchange in acute lung injury are unknown.[4,8,9] Furthermore, effects of low isoflurane concentrations on gas exchange may also be important during recovery from general anesthesia.

When comparing our results with those of previous human and animal studies, it should be emphasized that our observations were made in anesthetized dogs with oleic acid–induced lung injury. However, although pathophysiologically different, oleic acid–induced lung injury is a well-established animal model of human acute lung injury.[32] The essentially unimodal $\dot{V}_A/\dot{Q}$ distribution with 38 ± 4% of the pulmonary blood flow perfusing shunt units indicated severe lung injury in our dogs and is consistent with previous observations in the canine oleic acid model.[32,33] Distributions of $\dot{V}_A/\dot{Q}$ ratios observed in dogs with oleic acid–induced lung injury[32,33] are essentially comparable to those in humans with acute lung injury, where blood flow is distributed to either shunt or normal $\dot{V}_A/\dot{Q}$ units.[2] The slightly elevated dispersion of the pulmonary blood flow ($logSD_Q$) indicated mild $\dot{V}_A/\dot{Q}$ mismatch in our dogs in the absence of lung injury and is consistent with previous observations in anesthetized and mechanically ventilated subjects.[34] Anesthesia with sodium pentobarbital in our animals may have had a minor effect on $\dot{V}_A/\dot{Q}$ matching from inhibition of hypoxic pulmonary vasoconstriction,[35] but a constant sodium pentobarbital infusion could not have been responsible for the observed changes in the $\dot{V}_A/\dot{Q}$ distributions at different end-tidal isoflurane concentrations.

Previous experimental and clinical studies corroborated findings regarding the $\dot{V}_A/\dot{Q}$ matching during anesthesia with isoflurane. Carlsson *et al.*[17] observed no change in $\dot{V}_A/\dot{Q}$ matching with 1.0 and 1.5 vol% isoflurane in healthy patients during one-lung ventilation. In contrast, Kellow *et al.*[18] observed a threefold increase intrapulmonary shunt with 1.5–2.0 vol% isoflurane when compared with propofol infusion in patients undergoing thoracic surgery. Our results appear to be in contrast with those of Domino *et al.*,[12] who observed in dogs that 1.4–3.5 vol% isoflurane inhibits hypoxic pulmonary vasoconstriction in a dose-dependent manner during one-lung ventilation. This dose–response curve suggests that low concentrations of isoflurane have little adverse effect on hypoxic pulmonary vasoconstriction and thereby on $\dot{V}_A/\dot{Q}$ matching.[12] However, all previous studies have involved subjects in which 0.5 vol% isoflurane was administered before and after oleic acid–induced lung injury. Therefore, our results reflect the effect of low isoflurane concentrations on $\dot{V}_A/\dot{Q}$ mismatching in diffuse lung injury.

Inhalation of 0.25 and 0.5 vol% isoflurane during induced lung injury consistently resulted in a marked increase in blood flow to shunt units, without creating increase in low $\dot{V}_A/\dot{Q}$ areas. Because the normal mean $\dot{V}_A/\dot{Q}$ of the distribution of pulmonary blood flow and its dispersion ($logSD_Q$) remained unchanged, some essentially nonventilated lung units became better perfused. These observations support the contention that isoflurane increases intrapulmonary shunting by inhibiting hypoxic pulmonary vasoconstriction.[12–15,18,36] In addition, absence of changes in mean $\dot{V}_A/\dot{Q}$ of the alveolar

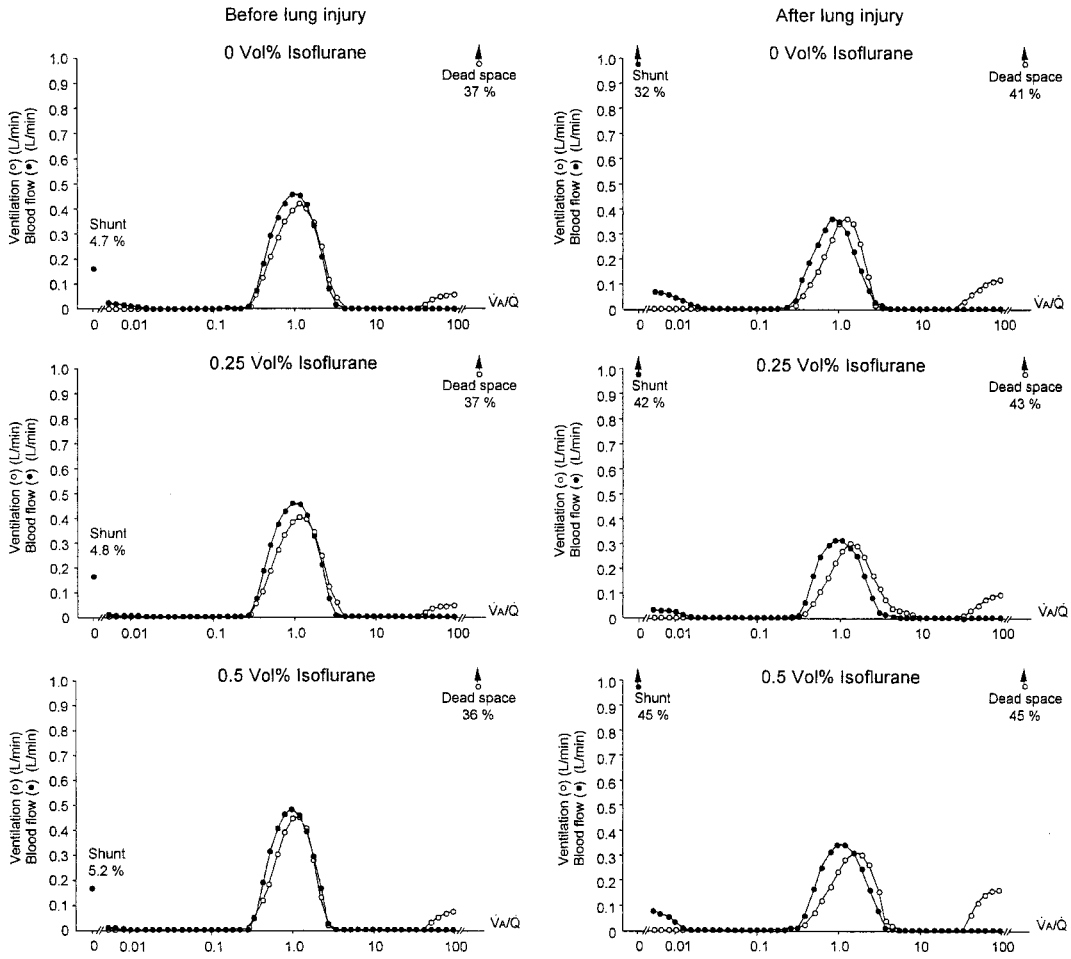

Fig. 1. Continuous distributions of ventilation and blood flow plotted *versus* the ventilation to perfusion ($\dot{V}_A/\dot{Q}$) ratio for a representative animal ventilated with 0, 0.25, and 0.5 vol% end-tidal isoflurane before and after oleic acid–induced lung injury.

ventilation distribution, its dispersion ($logSD_V$), dead space ventilation, and lung compliance indicate that alveolar collapse and decreased ventilation of well-perfused lung regions did not occur. Because in current study pulmonary vascular resistance was not measured at constant pulmonary blood flow, our results do not allow direct conclusions on hypoxic pulmonary vasoconstriction. Our observations are in contrast to a study by Kleinsasser *et al.*,[37] who report that inhalation of 2.0 vol% sevoflurane but not of 1.15 vol% isoflurane increased blood flow to shunt units and low $\dot{V}_A/\dot{Q}$ areas and decreased arterial blood oxygenation in pigs with pneumoperitoneum-induced deterioration in gas exchange. The mechanism by which sevoflurane but not isoflurane affects pulmonary blood flow distribution could not be explained on the basis of these data.[37] The apparent discrepancy to our results may be attributed to the lung injury model used, the degree of the preexisting $\dot{V}_A/\dot{Q}$ mismatch, and species-related differences. Increase in intraabdominal pressure during pneumoperitoneum will result in alveolar collapse caused by a cephalad shift of the diaphragm most evident in dependent lung areas, whereas the well-ventilated lung units have to be considered healthy. The corresponding intrapulmonary shunt of 9–14% indicates mild pulmonary dysfunction when compared with our dog with an intrapul-

Table 5. Predicted *versus* Measured Arterial Oxygen Tension

	Before Lung Injury			After Lung Injury		
	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*	0 vol% Isoflurane*	0.25 vol% Isoflurane*	0.5 vol% Isoflurane*
Measured Pa_{O_2} (mmHg)	163 ± 8	154 ± 8	153 ± 8	72 ± 4	62 ± 4	56 ± 4
Predicted Pa_{O_2} (mmHg)	158 ± 6	151 ± 6	156 ± 9	69 ± 3	60 ± 3	54 ± 3
r^2	0.90	0.91	0.92	0.92	0.92	0.93

Values are mean ± SE. Relationship between measured and predicted arterial oxygen tension (Pa_{O_2}) was assessed with linear regression analysis.

monary shunt of 38–41%.[38] Intrapulmonary shunting ranging up to 12% in healthy subjects during anesthesia has been found to correlate directly with the formation of nonaerated tissue observed by computed tomography in dependent lung regions adjacent to the diaphragm.[34] Experimental[39] and clinical[17,38,40,41] observations indicate that isoflurane concentrations between 0.5 and 2.0 vol% have only a small effect on venous admixture and gas exchange during one-lung ventilation. In contrast to observations in healthy subjects during one-lung ventilation or during increased intraabdominal pressure, oleic acid causes a direct lesion to the pulmonary vasculature, resulting in a diffuse but not homogeneous lung injury with increased pulmonary vascular permeability, intrapulmonary shunting, and arterial hypoxemia.[42] Furthermore, release of endogenous vasodilators, including metabolites of the cyclooxygenase pathway, *e.g.*, prostacyclin, have been shown to oppose hypoxic pulmonary vasoconstriction in animals with lung injury.[43] Isoflurane may attenuate hypoxic pulmonary vasoconstriction by increasing production of vasodilator metabolites of the cyclooxygenase pathway.[14] Observations in a dog model showed that isoflurane-induced attenuation of hypoxic pulmonary vasoconstriction is abolished by cyclooxygenase inhibition.[14] Recently, isoflurane has been found to induce release of other vasodilator mediators during inflammation.[44] Thus, release of endogenous vasodilators may have aggravated the increase in blood flow to shunt units in our dogs with injured lungs.

Small differences between Pa_{O_2} predicted from the recovered $\dot{V}_A/\dot{Q}$ distribution and the measured Pa_{O_2} indicate that alveolar end-capillary equilibration was complete. Thus, observed changes in gas exchange can be attributed to the measured $\dot{V}_A/\dot{Q}$ mismatch. Corresponding to the increase in $\dot{V}_A/\dot{Q}$ mismatch, Pa_{O_2} decreased during 0.25 and 0.5 vol% isoflurane in the presence of acute lung injury. Extrapulmonary factors with potential effects on Pa_{O_2}, such as alveolar ventilation and acid-base status, did not change significantly.[45]

Changes in CO have been reported to positively correlate with the intrapulmonary shunt fraction.[46] In our study, isoflurane decreased pulmonary blood flow and directed it preferentially to nonventilated lung units. Consequently, decreased CO was associated with significantly larger intrapulmonary shunting of blood, lower Pa_{O_2}, and markedly reduced D_{O_2}. Therefore, changes in CO cannot explain the increase in intrapulmonary shunting of blood with isoflurane during lung injury.[46] Inhalation of 0.5 vol% isoflurane lowered the elevated mean Ppa_{tm} and pulmonary vascular resistance during induced lung injury. Isoflurane in concentrations between 0.3 and 1.4 vol% has previously been shown to produce pulmonary vasodilation in subjects with pulmonary hypertension.[47,48] Inhalation of isoflurane reduced mean systemic blood pressure and systemic vascular resistance in our dogs, a well-documented effect at these isoflurane concentrations.

Intrapulmonary shunting of blood and reduction in lung compliance results from alveolar collapse during lung injury. Higher intrapulmonary shunt with unchanged lung compliance during inhalation of isoflurane indicates augmented perfusion of essentially nonventilated lung units. An increase in R_L is a known feature of human acute lung injury; this phenomenon was observed in the current study as well.[49] Decrease in R_L with isoflurane inhalation during induced bronchoconstriction and in patients with asthma has been reported previously, albeit with some inconsistency.[11,31] In contrast, R_L was unaffected by inhalation of isoflurane in our dogs, a finding in agreement with a study by Pesenti *et al.*,[49] which demonstrated no change in elevated R_L during intravenous β_2-agonist infusion in patients with acute lung injury.

Previous reports have recommended inhalation of isoflurane in low concentrations as a sedative agent to facilitate mechanical ventilation in critical ill patients. The results of this study demonstrate that even 0.25 to 0.5 vol% of isoflurane may increase $\dot{V}_A/\dot{Q}$ mismatching by inhibiting hypoxic pulmonary vasoconstriction in experimental lung injury. Controlled clinical trials and long-term investigations are warranted to evaluate the validity of these results in critically ill patients.

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