J Appl Physiol 97: 1702–1708, 2004.
First published June 25, 2004; doi:10.1152/japplphysiol.01272.2003.

Soluble gas exchange in the pulmonary airways of sheep

Carmel Schimmel,[1] Susan L. Bernard,[1] Joseph C. Anderson,[1] Nayak L. Polissar,[3] S. Lakshminarayan,[1,4,*] and Michael P. Hlastala[1,2,*]

[1]*Department of Medicine;* [2]*Department of Physiology and Biophysics, University of Washington, Seattle 98195-6522;* [3]*Mountain Whisper Light Statistical Consulting, Seattle 98112-2913; and* [4]*Veterans Affairs Medical Center, Seattle Washington 98108*

Submitted 1 December 2003; accepted in final form 15 June 2004

Schimmel, Carmel, Susan L. Bernard, Joseph C. Anderson, Nayak L. Polissar, S. Lakshminarayan, and Michael P. Hlastala. Soluble gas exchange in the pulmonary airways of sheep. *J Appl Physiol* 97: 1702–1708, 2004. First published June 25, 2004; doi: 10.1152/japplphysiol.01272.2003.—We studied the airway gas exchange properties of five inert gases with different blood solubilities in the lungs of anesthetized sheep. Animals were ventilated through a bifurcated endobronchial tube to allow independent ventilation and collection of exhaled gases from each lung. An aortic pouch at the origin of the bronchial artery was created to control perfusion and enable infusion of a solution of inert gases into the bronchial circulation. Occlusion of the left pulmonary artery prevented pulmonary perfusion of that lung so that gas exchange occurred predominantly via the bronchial circulation. Excretion from the bronchial circulation (defined as the partial pressure of gas in exhaled gas divided by the partial pressure of gas in bronchial arterial blood) increased with increasing gas solubility (ranging from a mean of 4.2×10^{-5} for SF_6 to 4.8×10^{-2} for ether) and increasing bronchial blood flow. Excretion was inversely affected by molecular weight (MW), demonstrating a dependence on diffusion. Excretions of the higher MW gases, halothane (MW = 194) and SF_6 (MW = 146), were depressed relative to excretion of the lower MW gases ethane, cyclopropane, and ether (MW = 30, 42, 74, respectively). All results were consistent with previous studies of gas exchange in the isolated in situ trachea.

high-solubility gases; diffusion; bronchial circulation; aortic pouch

GAS EXCHANGE EFFICIENCY IS largely dependent on the solubility of the gas in blood (blood-air partition coefficient; λ_b). Over the past 50 years, the focus of pulmonary gas exchange research has been to characterize the exchange of gases with relatively low solubilities in blood ($\lambda_b < 10$), such as the respiratory gases O_2 and CO_2 ($\lambda_b \approx 0.7$ and 3,[1] respectively). On the basis of these results, initial models of ventilation- and perfusion-limited gas exchange to the alveolar regions were constructed with the conducting airways acting as inert conduits for movement of gas between the alveoli and ambient air. However, lungs exchange gases of solubilities ranging from low, such as He ($\lambda_b \approx 0.01$), to highly soluble, including ethyl alcohol ($\lambda_b \approx 1{,}750$) and water vapor ($\lambda_b \approx 20{,}000$–$50{,}000$). Recently, investigative attention has been directed toward the exchange of moderate to highly soluble gases common in medical and industrial applications. Toluene ($\lambda_b \approx 15$), diethyl ether ($\lambda_b \approx 12$), and methyl isobutyl ketone ($\lambda_b \approx 90$) are industrial solvents but are also used as a gasoline component, an anesthetic, and a lacquer thinner, respectively. Dimethyl ether ($\lambda_b \approx 9$) has been used as a noninvasive marker of cardiac output (11) and bronchial blood flow (10). Halothane ($\lambda_b \approx 2.5$), diethyl ether, and acetone ($\lambda_b \approx 340$) are used in the multiple inert-gas elimination technique (MIGET) to determine the efficiency of alveolar gas exchange (16). Exhaled ethanol ($\lambda_b \approx 1{,}756$) is measured to estimate blood alcohol concentration to assess the extent of intoxication (7).

Using a mathematical model of airway and alveolar gas exchange, we recently predicted that intermediately soluble gases ($10 < \lambda_b < 100$) exchange in both the airways and alveoli, whereas highly soluble gases ($\lambda_b > 100$) exchange completely in the airways (2). This model predicted that airway soluble gas exchange is significantly influenced by bronchial blood flow and diffusion of gas from the bronchial circulation to the airway lumen. These theoretical predictions are supported by experiments using an in situ isolated trachea preparation. Swenson et al. (14) showed that gas exchange from the tracheal circulation to the airway lumen is dependent on diffusion of gas through the tissue, and Souders et al. (12) confirmed that increases in tracheal blood flow increased excretion of gases from the trachea. Although these experiments provided new insights into gas exchange within the trachea, they did not investigate the importance of bronchial blood flow on gas exchange in the bifurcating generations of progressively smaller airways leading to alveolar spaces.

The present study was undertaken to extend the tracheal gas exchange measurements to the entire airway structure. To quantify inert-gas exchange in the airways, it was necessary *1*) to isolate and control the bronchial circulation for infusion of gases of varying solubility as well as the control of bronchial blood flow and *2*) to isolate gas exchange in the airways from exchange in the alveoli. We hypothesized that airway excretion of each gas would increase with increasing bronchial blood flow and increasing blood solubility.

METHODS

Animal preparation. The animal protocol was approved by the Institutional Animal Care and Use Committee at the University of Washington. Six adult sheep, 35–60 kg, were anesthetized with intravenous pentobarbital sodium (25 mg/kg), intubated, and mechanically ventilated at a tidal volume of 10 ml/kg with 5 cmH_2O positive end-expiratory pressure. The ventilation rate was adjusted to maintain normal arterial blood gases. Catheters were placed in the left and right femoral arteries. A thermodilution catheter was placed in the jugular vein (7-Fr Swan-Ganz, Baxter Healthcare, Irvine, CA) to measure cardiac output.

* S. Lakshminarayan and M. P. Hlastala contributed equally to this article.
Address for reprint requests and other correspondence: M. P. Hlastala, Division of Pulmonary and Critical Care Medicine, Box 356522, Univ. of Washington, Seattle, WA 98195-6522 (E-mail: hlastala@u.washington.edu).

[1] The blood equilibrium curves for both O_2 and CO_2 are nonlinear but can be treated as an effective linear relationship.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

A left thoracotomy was performed at the fourth intercostal space. Atelectasis was minimized by frequent hyperinflation of the lungs and maintenance of 5 cmH_2O positive end-expiratory pressure. A segment of the left carotid artery was isolated, and a 4-mm Doppler flow probe (Transonics Systems, Ithaca, NY) was placed around the vessel. The left carotid artery was catheterized (Fig. 1). The left azygous vein, which drains bronchial esophageal, dorsal intercostal, lumbar, and sometimes the costoabdominal veins, was ligated and transected. An aortic pouch was created by bypassing the segment of the aorta from which the bronchoesophageal (BE) artery originates with a 12-mm Gortex vascular graft. All vessels arising from this segment of isolated aorta with the exception of the BE artery were ligated and transected. The esophageal branch of the BE artery was ligated. The vascular graft allowed continuous perfusion to the distal aorta during the study. One end of a polyethylene tube (PE-280) was inserted into the aorta at a position that was directly across from the origin of the BE artery. The other end of the tube was connected to the carotid catheter. This tube contained a pressure transducer that provided continuous pouch pressure measurements. Once the graft and PE-280 tube were in place, the aorta was cross-clamped upstream and downstream of the origin of the BE artery, thereby forcing aortic blood to bypass the cross-clamped "pouch" section of the aorta. By cross-clamping this aortic segment, a favorable pressure gradient from the carotid artery to the pouch via the PE-280 tube was created that pushed native blood flow into the pouch (Fig. 1). The carotid flow probe measured flow of blood into the pouch. Once native flow was established, a roller pump was used to control blood flow into the pouch. Downstream from the roller pump, a mixing chamber was placed inline to administer the inert-gas solution into the perfusate. To ventilate the left and right lungs separately, a 39-Fr left Broncho-Cath (Mallinckrodt, St. Louis, MO) was carefully inserted so that the right upper lobe was not occluded. Complete separation of ventilation was checked by *1*) monitoring airway pressure and *2*) conducting a helium test. This helium test required the right lung to be ventilated with a trace amount of helium while the expired gas from the left lung was monitored to ensure that it lacked helium (and vice versa). The left pulmonary artery was then ligated.

Once the left and right lung ventilation was separated, the animal was ventilated with a dual-piston Harvard ventilator, permitting the separation of both inspiratory and expiratory circuits. The right lung ventilation was adjusted to maintain normal arterial blood gases throughout the study. The animal was repositioned in a right lateral posture, and the thoracotomy site was covered with clear plastic wrap. Blood flow from the carotid artery to the pouch without pump assistance (i.e., native blood flow) was recorded and found to be 42.0 ± 17.1 ml/min. Then, with use of the roller pump, the bronchial blood flow was adjusted randomly between 20 and 60 ml/min by using increments or decrements of 10 ml/min or greater. The animal was heparinized (500 IU/kg). The left lung was ventilated with 5% CO_2 in air, and the right lung was ventilated with 50% O_2, balance N_2. Arterial blood pressure, arterial blood gases, pulmonary arterial pressure, airway pressure (right and left lung), bronchial blood flow, and cardiac output were monitored and recorded throughout the study.

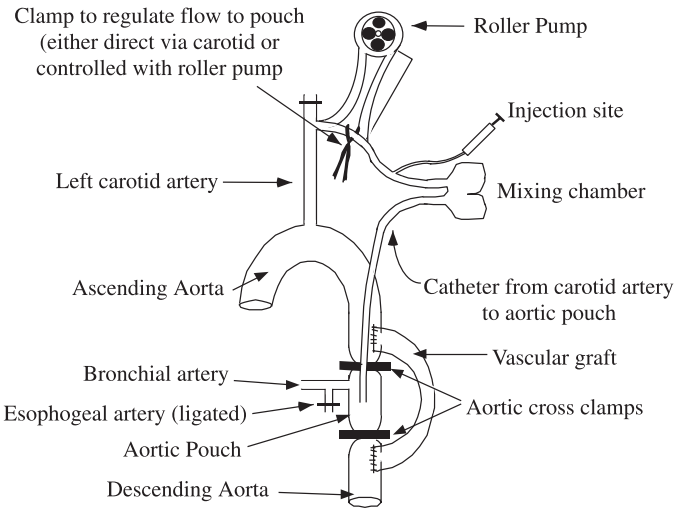

Fig. 1. Schematic of the aortic pouch preparation. The arrangement allows for the control of bronchial blood flow rate and mixing of the infused inert gases.

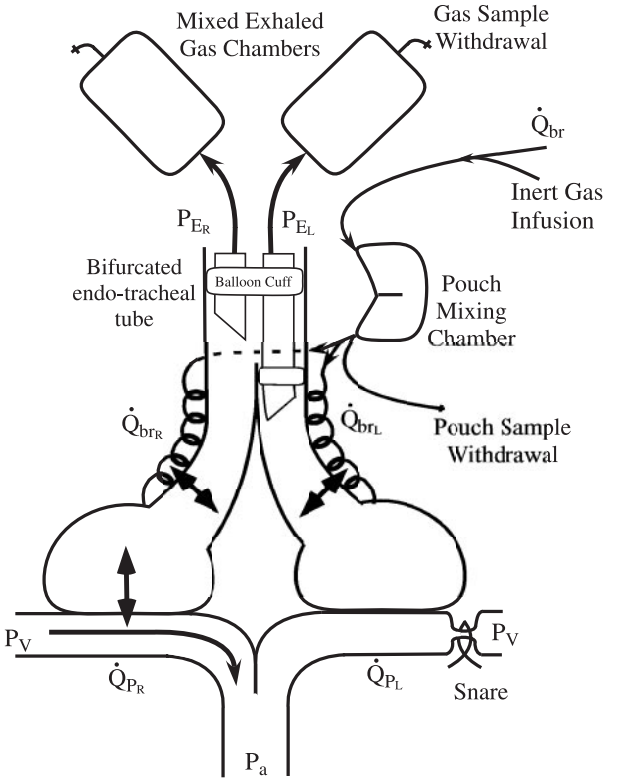

Fig. 2. Model for perfusion and gas exchange of the airways and alveoli for the left and right lungs (subscripts L and R, respectively) after occlusion of the left pulmonary artery. The left lung exchanges gas with the bronchial circulation only. The right lung exchanges with both pulmonary and bronchial circulation. $\dot{Q}_{br}$, bronchial blood flow; P_E, partial pressure of inert gas in mixed expired gas; $\dot{Q}_P$, pulmonary blood flow; P_a, arterial partial pressure, P_V, venous partial pressure.

Inert-gas excretion. Five inert gases[2] of different blood solubilities (SF_6, ethane, cyclopropane, halothane, and diethyl ether) were mixed in a 0.9% saline solution, according to method used for MIGET (16), and infused at 2 ml/min into the bronchial circulation via the mixing chamber (Fig. 2). Mixed expired gases for the left and right lungs were collected in separate 1.5-liter heated mixing chambers (Fig. 2). Tubing and connectors were heated to avoid condensation and loss of exhaled inert gases. Blood samples were drawn simultaneously from the aortic pouch, arterial line, and venous line. Average collected blood volume was 6 ml and was drawn over 1–2 min so that blood volume in the aortic pouch was reduced by no greater than 10%. Mixed expired gas samples were drawn from one or both mixing chambers after a delay time that was determined by the volume of the mixing chamber divided by minute ventilation for a given lung. All blood and gas samples were drawn in duplicate.

[2] Acetone was infused and measured. However, reequilibration time after left pulmonary artery occlusion was too long to be practical for measurement of changes in excretion for highly soluble gases.

Inert-gas concentrations for each sample were measured by gas chromatography (Hewlett-Packard Series II 5890 GC, Santa Clara, CA). Inert-gas concentrations in the mixed expired gas samples were measured directly. Inert-gas concentrations in blood samples were determined by the single-extraction method and calculated by using measured solubilities. Solubilities were measured with the double-extraction method (16) in triplicate from pooled blood samples for each study. Inert-gas solubilities in blood and all analysis of blood and gas samples were performed at the mean body temperature for each experiment. For all studies, body temperature varied by <1°C during a given experiment.

Data analysis. Bronchial excretion ($E_B = P_E/P_B$, where P_E and P_B designate the partial pressure of inert gas in the mixed expired gas and bronchial blood, respectively) was calculated for each inert gas for each bronchial blood flow condition by using the measured inert-gas concentrations in blood and expired gas. For each animal, best-fit lines were calculated by linear regression to describe the relationship between E_B for each inert gas and bronchial blood flow. For a particular inert gas, the slope of the best-fit line was averaged across all animals. This slope, $\Delta E_B/\Delta\dot{Q}_{br}$, where Δ is change and $\dot{Q}_{br}$ is bronchial blood flow, describes the sensitivity of bronchial excretion to bronchial blood flow. A one-tailed *t*-test was used to determine whether this average slope for a given gas was significantly different from zero. The average slope for each gas was plotted against the blood solubility of the gas. Regression analysis was done to determine how well blood solubility predicted the sensitivity of bronchial excretion to bronchial blood flow.

The slope for each gas and each animal was calculated by least squares for $\ln[E_B/(1 - E_B)]$ vs. $\ln(\dot{Q}_{br}/\dot{Q}_O)$, where $\dot{Q}_O$ is the native bronchial flow for a given animal. $\ln[E_B/(1 - E_B)]$ is called logit E_B and was used because E_B varies over several orders of magnitude for the gases studied. The logit transformation allows these data to be analyzed in one framework and gives all gases equal statistical weight. Previous studies of tracheal excretion have used the logit transformation to analyze their data. The logit transformation was used on these data so that the results from each study can be compared.

RESULTS

Mean values for systemic and pulmonary arterial blood pressures, cardiac output, right lung minute ventilation, left lung minute ventilation, arterial blood gases, and body temperature for six sheep are listed in Table 1. The animals were hemodynamically stable and maintained normal arterial P_{O_2}, P_{CO_2}, and pH.

Table 1. *Physiological variables for experimental animals during gas-exchange measurement*

Variable	Units	Mean ± SD
SAP	mmHg	80±6.1
PAP	mmHg	32±4.4
CO	l/min	1.6±0.2
$\dot{V}_{E_{LL}}$	l/min	3.8±0.3
$\dot{V}_{E_{RL}}$	l/min	5.4±0.5
Native $\dot{Q}_{br}$	ml/min	42.0±17.1
Experimental $\dot{Q}_{br}$	ml/min	38.5±6.9
pH_a		7.4±0.05
Pa_{O_2}	Torr	277.7±35.4
Pa_{CO_2}	Torr	36.7±3.9
T	°C	38.1±0.7

Values are means ± SE; $n = 6$ sheep. SAP, systemic arterial pressure; PAP, pulmonary arterial pressure; CO, cardiac output; $\dot{V}_{E_{LL}}$, left lung minute ventilation; $\dot{V}_{E_{RL}}$, right lung minute ventilation; $\dot{Q}_{br}$, bronchial blood flow; pH_a, arterial pH; Pa_{O_2}, arterial P_{O_2} for animals breathing 50% O_2; Pa_{CO_2}, arterial P_{CO_2}; T, body temperature.

Each panel in Fig. 3 shows the excretions of a particular inert gas at different bronchial blood flow rates for each study animal. The physical properties of each gas are shown in Table 2. Inert-gas excretions increased with increasing bronchial blood flow for all animals and all gases. Excretion values for each inert gas had some variability when compared between animals at a given blood flow rate. However, the intra-animal trends of excretion vs. blood flow were very consistent.

To better account for this interanimal variability, the change in excretion relative to the change in bronchial blood flow, $\Delta E_B/\Delta\dot{Q}_{br}$, for each gas and animal was calculated and presented in Table 3. All $\Delta E_B/\Delta\dot{Q}_{br}$ values for each gas in each sheep were statistically different from zero ($P < 0.05$) as determined by a *t*-test. The mean $\Delta E_B/\Delta\dot{Q}_{br}$ value for each gas across all sheep was statistically different from zero ($P < 0.05$) as determined by a *t*-test. A regression analysis was used to determine the best-fit line between $\Delta E_B/\Delta\dot{Q}_{br}$ vs. λ_b within each sheep and the best-fit line between the mean $\Delta E_B/\Delta\dot{Q}_{br}$ and λ_b values across all sheep. The slopes and coefficient of determination of these best-fit lines are presented in Table 3. Figure 4 shows the mean $\Delta E_B/\Delta\dot{Q}_{br}$ value of each gas plotted against λ_b and the best-fit line to these data. Notice that the mean $\Delta E_B/\Delta\dot{Q}_{br}$ values for SF_6 and halothane lie below the best-fit line.

Similarly, the slope of logit E_B vs. $\ln\dot{Q}_{br}/\dot{Q}_O$ was determined for each gas and each animal. Results are listed in Table 4. The mean slopes for each gas, for all animals, were not significantly different. The mean value for all gases, for all experiments, was 0.51 ± 0.025. The mean values shown on the right of Table 4 reflect the mean excretion for all five gases within a specific animal.

For each sheep, $\Delta E_B/\Delta\dot{Q}_{br}$ was regressed against λ_b to determine a best-fit line. The results of this analysis are summarized in Table 3. For each sheep and inert gas, a residual $\Delta E_B/\Delta\dot{Q}_{br}$ was calculated between the $\Delta E_B/\Delta\dot{Q}_{br}$ data and the best-fit line. For each inert gas, a mean (±SE) $\Delta E_B/\Delta\dot{Q}_{br}$ was calculated by using the data from all six animals. This mean residual (±SE) was plotted against the square root of molecular weight (MW) for each gas and is presented in Fig. 5. We then asked the following question: Could the MW of the inert gases explain the variation of the $\Delta E_B/\Delta\dot{Q}_{br}$ values about the best-fit line? To find an answer, a best-fit line between the residual $\Delta E_B/\Delta\dot{Q}_{br}$ values and the MW of each gas was calculated. Using a *t*-test, the slope of this line was found to be significantly different from zero ($P < 0.05$).

DISCUSSION

Summary of findings. For this study, we developed a novel method (the aortic pouch preparation) to isolate and control the bronchial circulation. This technique enabled investigation of the effect of bronchial blood flow on intraparenchymal airway gas exchange. We infused inert gases with different blood solubilities into the bronchial circulation of a ventilated sheep lung that was perfused only by the bronchial circulation. We measured the partial pressure of these inert gases in the mixed expired gas and bronchial blood to calculate their excretion from the airways for different bronchial blood flow conditions. We found that excretion of a given gas from the airways is dependent on solubility of the gas in blood, bronchial blood flow rate, and MW (i.e., molecular diffusivity) of the gas.

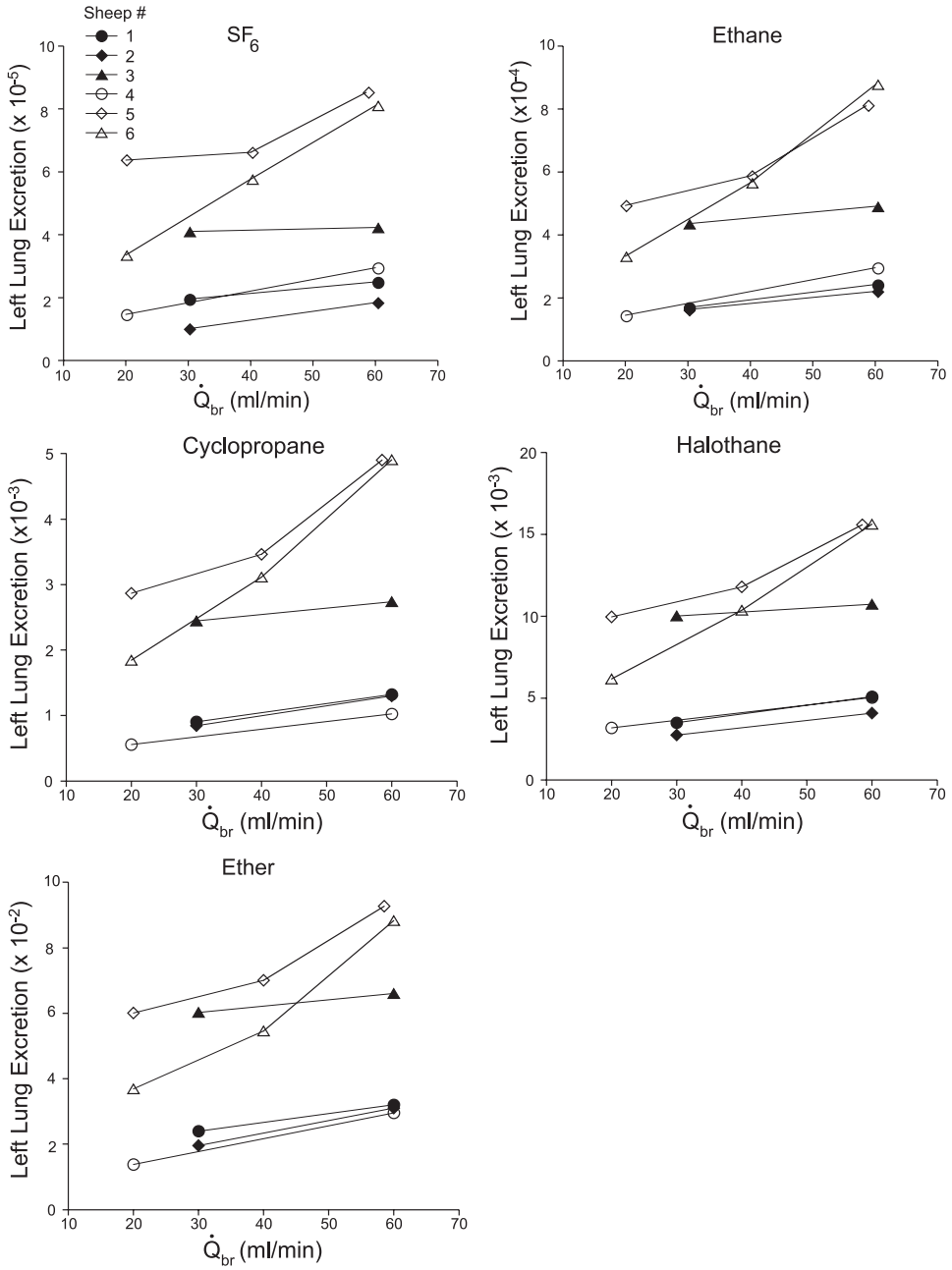

Fig. 3. Excretion plotted against bronchial flow for individual sheep. The slope, $\Delta E_B/\Delta \dot{Q}_{br}$ (where Δ is change and E_B is bronchial excretion), for gas data sets from individual animals is shown in Table 3.

Table 2. *Inert gas properties and mean excretion and solubility data for all experiments*

Inert Gas	Molecular Weight	$E_B \times 10^{-5}$	λ_b
SF_6	146	4.2±0.87	0.0075±0.0003
Ethane	30	41±7.7	0.077±0.0038
Cyclopropane	42	230±49	0.47±0.019
Halothane	197	800±150	1.9±0.086
Ether	74	4,800±890	11.3±0.26

Values are means ± SE; $n = 6$ sheep. E_B are excretion values and are the ratio of inert gas in the left lung mixed expired gas to bronchial blood. λ_b, solubility for each gas expressed as Ostwald partition coefficient ($\lambda_b = \beta_b/\beta_g$; ml gas/ml liquid at 1 atmosphere) at body temperature.

In our early studies of airway gas exchange, we infused inert gases with different blood solubilities and MWs into the venous circulation and measured their excretion (inert-gas partial pressure in mixed exhaled gases normalized by inert-gas partial pressure of venous blood) in an isolated segment of an in situ trachea. Excretion was directly related to solubility and inversely related to MW, indicating a diffusion limitation across the mucosal tissue (14). In a similar study using pharmacological methods to modify airway perfusion, excretion was found to be proportional to solubility and to perfusion (12). The results of the present study, which measured excretions for the pulmonary airways distal to the trachea, are remarkably consistent with studies of the isolated in situ tracheal segment.

Table 3. *Change in excretion relative to change in bronchial flow*

	$\Delta E_B/\Delta \dot{Q}_{br}$					Regression	
Sheep no.	SF_6	Ethane	Cyclopropane	Halothane	Ether	Slope	R^2
1	0.018	0.24	1.4	5.3	27	0.00166	1.00
2	0.028	0.19	1.5	4.5	38	0.00239	0.98
3	0.004	0.18	1.0	2.4	19	0.00012	0.98
4	0.037	0.38	1.2	4.7	39	0.00025	0.98
5	0.054	0.79	5.1	14.1	82	0.00051	0.99
6	0.119	1.36	7.7	23.6	129	0.00080	0.99
Mean ± SE	0.043 ± 0.0017	0.53 ± 0.19	3.0 ± 1.1	9.1 ± 3.4	56 ± 17	0.00096 ± 0.00036	0.990 ± 0.007
P value	0.038	0.024	0.031	0.017	0.013		

A regression analysis was used to determine the best-fit line between change in excretion relative to change in bronchial flow ($\Delta E_B/\Delta \dot{Q}_{br}$) and λ_b within each sheep and the mean $\Delta E_B/\Delta \dot{Q}_{br}$ values across all sheep (see Fig. 4). The value of the mean is statistically different from zero ($P < 0.05$).

Solubility and perfusion dependence. Inert-gas excretion increased with increasing bronchial blood flow (Fig. 3). Because of the significant interanimal variability between excretion values for a given gas at a given blood flow, the change in inert-gas excretion relative to bronchial blood flow rate was examined as a function of λ_b. We found that the sensitivity of inert-gas excretion to bronchial blood flow was directly related to λ_b (Fig. 4). To linearize the relationship between excretion and bronchial blood flow and facilitate comparison to previous results, we analyzed the logit $\ln[E_B/(1 - E_B)]$ vs. $\ln(\dot{Q}_{br}/\dot{Q}_{br})$ as described in Souders et al. (12) and Swenson et al. (14). The logit transform was originally applied to the equation for $R = E = \lambda/(\lambda + \dot{V}/\dot{Q})$ to become $\ln[(1 - R)/R] = \ln[(1 - E/E)] = \ln(\dot{V}/\dot{Q}) - \ln\lambda$, where R is retention and E is excretion. This enabled analysis to determine the independent effects of $\dot{V}/\dot{Q}$ and λ. This transformation has been used in subsequent studies by this group (12, 14) and enables comparison of results across studies. The values from the logit transform for each gas and each animal are listed in Table 4. At the bottom of each column is the average slope for all the animals for each of the five gases. The slopes are compared with those obtained by Souders et al. using the isolated trachea. The average values obtained in the isolated trachea were not statistically different from those obtained in this study using the bronchial circulation and airways distal to the trachea (mean slope = 0.61 ± 0.18 and 0.51 ± 0.10, respectively). This similarity in excretion data between these two studies is remarkable considering the differences in preparation (bronchial circulation pouch vs. isolated trachea), species (sheep vs. dog), and airflow (reciprocating vs. unidirectional).

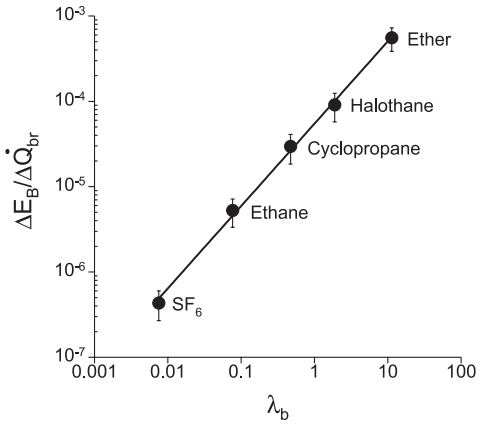

Fig. 4. Mean $\Delta E_B/\Delta \dot{Q}_{br}$ for individual gases for all animals ($n = 6$) vs. blood-air partition coefficient (λ_b). Slopes and R^2 for the data sets from each animal are shown in Table 3.

Diffusion dependence. Gas exchange in the trachea has been shown to be dependent on the MW of the gas. Using a dog trachea and three gases with similar solubilities but disparate MWs (acetylene, MW = 26; Freon-22, MW = 86.5; and isoflurane, MW = 184.5), Swenson et al. (14) showed these gases to have different excretions that could be primarily explained by accounting for their differences in MW. This MW dependence implies a diffusion limitation, assumed to occur within the tissue between the bronchial vessels and the tracheal lumen. Similarly, our data demonstrate a diffusion dependence to gas exchange between the bronchial circulation and the airways distal to the trachea. As shown in Fig. 5, residuals between the $\Delta E_B/\Delta \dot{Q}_{br}$ value and the best-fit line are positive for low MW gases (ethane, MW = 30; cyclopropane, MW = 42; and ether, MW = 74) and negative for high MW gases (SF_6, MW = 146 and halothane, MW = 197). This effect is statistically significant, $P < 0.05$. Thus the heavy gases are retarded in their excretion relative to the other gases studied because their molecular diffusion coefficient within tissue is smaller.

Study limitations. A potential problem with interpretation of our data is the presence of a reflux flow from the pulmonary venous circulation (4). This reflux flow may contribute a small amount of inert gas to the alveolar vessels in an amount dependent on ventilation (8, 9). We studied two additional animals to determine the contribution of alveolar exchange in the left lung both before and after left pulmonary artery occlusion, using MIGET. Venous infusion of inert gases was performed before and after occlusion, for bronchial flows of 0 and 20 ml/min. The partial pressure of inert gases in the left lung gas with no bronchial flow and after pulmonary arterial occlusion averaged <1% of the right lung which had intact pulmonary exchange. These left lung values were typically three orders of magnitude below left lung partial pressures measured during infusion of MIGET gas into the bronchial circulation via the aortic pouch. The partial pressure of inert gases in the left lung with bronchial flow of 20 ml/min and after arterial occlusion ranged from <1% (for SF_6, ethane, and cyclopropane) to 6% (for ether) relative to the right lung values. Excretions (inert-gas partial pressure in the mixed expired gas normalized by inert-gas partial pressure in the venous blood) were measured, which enables estimates of

Table 4. *Slope of $ln[E_B/(1 - E_B)]$ vs. $ln\dot{Q}_{br}/\dot{Q}_O$*

Sheep No.	SF_6	Ethane	Cyclopropane	Halothane	Ether	Mean	SE
1	0.356	0.514	0.550	0.544	0.425	0.48	0.085
2	0.869	0.442	0.621	0.578	0.678	0.64	0.156
3	0.045	0.172	0.164	0.100	0.141	0.12	0.052
4	0.639	0.653	0.559	0.422	0.704	0.60	0.110
5	0.244	0.437	0.473	0.401	0.413	0.39	0.088
6	0.806	0.870	0.876	0.838	0.804	0.84	0.034
Means ± SE	0.49 ± 0.13	0.52 ± 0.10	0.54 ± 0.094	0.48 ± 0.10	0.53 ± 0.10		

Change in ln of excretion vs. change in ln of bronchial blood flow. $\dot{Q}_O$, native bronchial flow for a given animal.

cardiac output using individual gas data (16). Cardiac output estimates calculated from left lung excretions for each inert gas, after pulmonary arterial occlusion, ranged from 0.9 to 2.5% of right lung estimates. Thus reflux flow for the left lung after arterial occlusion was estimated to be <3% of total cardiac output, and inert gases would contribute <0.03% of the gas exchange from the bronchial circulation.

An additional confounding factor is the diffuse nature of the bronchial venous circulation. Most bronchial blood flow empties into the pulmonary venous return. However, some bronchial blood flow, particularly to the large airways, empties into the azygous vein, whereas flow to the smaller airways empties into the pulmonary capillaries and may therefore contribute to gas exchange from the alveolar vessels (5, 15). It is unlikely that gas exchange from anastomotic blood flow is significant because of the diffusion limitation seen in this study with the bronchial circulation (see Fig. 5) and by Swenson et al. (14) in the isolated trachea. MW dependence of gas exchange would not be expected if gas exchange occurred only within the alveoli.

Anatomy of bronchial vs. tracheal circulation. The properties of bronchial circulation gas exchange are remarkably similar to the properties of tracheal gas exchange despite the differing anatomical features. The trachea is a relatively uniform tissue with similar diffusion distances from the bronchial vessels to the airway mucosa. On the other hand, the bronchial circulation, which is similar to the bifurcating bronchial tree, varies in capillary density and diffusion distance from the bronchial vessels to the lumen. Our recent study quantifies the anatomical details of the bronchial circulation distribution in the sheep (1).

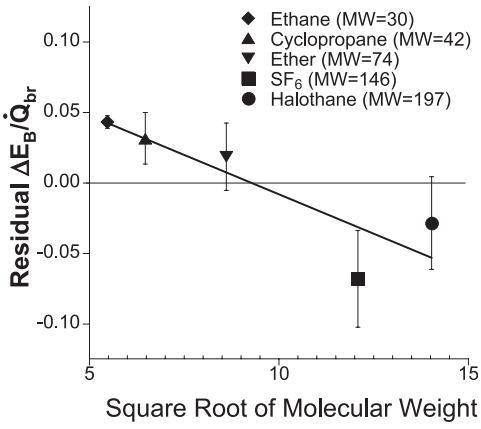

Fig. 5. Mean (SE) $\Delta E_B/\Delta\dot{Q}_{br}$ residual (difference between $\Delta E_B/\Delta\dot{Q}_{br}$ and the best-fit line for each sheep) of each inert gas was plotted against the square root of molecular weight (MW). The heavier gases (SF_6 and halothane) are retarded in their excretion relative to the other gases, thereby implying a diffusion dependence to airway gas exchange.

We speculate that the differences we observed in excretion among animals may reflect differences in the anatomy of the bronchial circulation or drainage pathways (15). Animals with a smaller mean excretion may have larger mean diffusion distances between the bronchial vessels and the lumen of the airways. The difference in excretion of any gas among animals likely reflects differences in the bronchial circulation (such as bronchial vessel density, diffusion distances from the bronchial vessels to the lumen, etc.) among the sheep.

Clinical relevance. This study demonstrates that inert gases of all blood solubilities exchange in the airways and that exchange increases with increasing solubility. This effect complicates the interpretation of techniques that use highly soluble gases to evaluate lung function, such as MIGET. MIGET uses six inert gases with blood solubilities that span six orders of magnitude to evaluate the efficiency of alveolar gas exchange. On the basis of early models of pulmonary gas exchange, MIGET assumes that all gases exchange completely in the alveoli, thereby ignoring the effects of airway gas exchange. This study demonstrates that airway exchange may affect MIGET-derived ventilation and perfusion distributions but does not provide sufficient information to quantify this effect. Because bronchial blood flow is normally only 1% of pulmonary blood flow, an effect would likely be restricted to only the very high-solubility gases, acetone and diethyl ether. We were not able to measure acetone exchange reliably, because it is so soluble in blood and tissue. Additionally, $\dot{V}_A/\dot{Q}$ (where $\dot{V}_A$ is alveolar ventilation) distributions determined by MIGET largely discount information from ether and acetone because MIGET uses a weighting procedure that assigns little weight to these high-solubility gases. However, our recent model of airway-alveolar exchange (2) predicts the relative contribution between exchange in airways and alveoli for gases of differing solubility. These predictions are consistent with the results of this study and provide additional insight into the potential impact of airway exchange on whole lung exchange as measured by MIGET.

The airway-alveolar gas exchange model (2) predicts that 96% of acetone ($\lambda \approx 330$) exchange occurs in the airways over a single breath. During inspiration, the respired air absorbs acetone from the airway surface and enters the alveoli essentially equilibrated with acetone. A small amount (~2%) of acetone is added to the respired air in the alveoli. On expiration, ~42% of the acetone absorbed by the gas stream during inspiration is deposited onto the airway surface. Ether has the second greatest blood solubility ($\lambda \approx 15$) of the MIGET gases. The airway-alveolar gas exchange model (2) predicts that 42%

of ether exchange occurs in the airways over a single breath. During inspiration, the majority of ether exchange (73%) occurs in the airways, with the remainder in the alveoli. Almost 36% of the ether absorbed during inspiration is deposited to the airway wall during expiration. This absorption-desorption mechanism is present for all soluble gas exchange. However, a progressively smaller proportion of exchange takes place in the airways compared with total lung exchange as gas solubility in blood decreases through halothane, cyclopropane, ethane, and SF_6.

On the basis of the above data and a mathematical model of airway and alveolar gas exchange (2), we can speculate on how the MIGET-calculated values of pulmonary gas exchange are affected by airway gas exchange. We suspect that the impact of airway exchange on the MIGET-predicted dead space should be minimal (5–10%) because acetone nearly completely exchanges within the airways and the mixed exhaled value for acetone is only slightly affected (10–15%) by large (e.g., 5-fold) changes in bronchial blood flow. More importantly, we feel that the influence of airway gas exchange has its greatest effect on the assessment of intermediate and high $\dot{V}_A/\dot{Q}$ regions because the airways act as a high V/Q unit ($V/Q > 100$) that permits high blood soluble gases like acetone and ether to exchange substantial quantities of gas but limits the quantity of low blood-soluble gas exchange. Therefore there will be an increase in the ventilation heterogeneity and little change in the perfusion distribution. A more complete discrimination of the influence of airway gas exchange awaits further research.

Recognizing soluble gas exchange between the airway lumen and the bronchial circulation may be important for understanding the exchange of very highly soluble gases. The alcohol breath test, developed in 1950s, assumes that alcohol exchanges completely in the alveoli. More recently, ethyl alcohol ($\lambda_b = 1{,}756$ at 37°C) has been shown to exchange entirely within the airways and not in the alveoli (7). Thus the accuracy of the alcohol breath test (i.e., estimation of alveolar, or blood, alcohol concentration) may be dependent on physiological events occurring within the airways such as heating and cooling of the respired air, inflammation of airway wall tissue, and changes in bronchial blood flow. In a similar fashion, the monitoring of body burden resulting from occupational exposure to particular solvents needs reassessment. Anderson et al. (2), using a theoretical model of gas exchange in the lung, have calculated that airway gas exchange exceeds alveolar gas exchange for gases with $\lambda_b \geq 15$. Many important industrial gases have $\lambda_b \geq 15$ such as *n*-butanol, acetone, methyl ethyl ketone, and toluene. According to the findings of this study, the excretion (or uptake) of these gases will be enhanced with increased bronchial blood flow, which can occur in inflammatory diseases of the airways such as asthma (3, 17), cystic fibrosis (6), and smoke-inhalation injury (13).

In summary, we developed a novel method of controlling bronchial blood flow in the sheep by using an aortic pouch preparation. Using this aortic pouch to adjust bronchial blood flow and infuse inert gases, we observed soluble gas exchange from bronchial blood to the respired air within the airways. We found this exchange to be dependent on solubility of blood, bronchial blood flow, and molecular diffusion of gas through the tissue. The effect of bronchial blood flow on inert-gas excretion is more important as inert-gas blood solubility increases. Further studies are needed to completely quantify the role that airway gas exchange has on the exchange of high-solubility gases.

ACKNOWLEDGMENTS

We thank Dowon An and Shen-Sheng Wang for technical assistance.

GRANTS

This work was supported in part by National Heart, Lung, and Blood Institute Grant HL-24163.

REFERENCES

1. **Anderson J, Bernard S, and Hlastala M.** Axial and radial distribution of the bronchial vasculature in sheep. *Respir Physiol Neurobiol* 132: 329–339, 2002.
2. **Anderson J, Bernard S, Luchtel D, Babb A, and Hlastala M.** Modeling soluble gas exchange in the airways and alveoli. *Ann Biomed Eng* 31: 1–21, 2003.
3. **Butler J.** The bronchial circulation. *News Physiol Sci* 6: 21–25, 1991.
4. **Butler J, Obermiller T, Willoughby S, and Lakshminarayan S.** Reflux pulmonary vein flow prevents pulmonary infarction after pulmonary artery obstruction. *Cor Vasa* 32: 183–190, 1990.
5. **Charan N, Turk G, and Dhand R.** Gross and subgross anatomy of bronchial circulation in sheep. *J Appl Physiol* 57: 658–664, 1984.
6. **Henig N, Glenny R, and Aitken M.** A hypertrophied bronchial circulatory system may participate in gas exchange. *Lancet* 351: 113, 1998.
7. **Hlastala M.** The alcohol breath test: a brief review. *J Appl Physiol* 84: 401–408, 1998.
8. **Obermiller T, Lakshminarayan S, Willoughby S, Mendenhall J, and Butler J.** Influence of lung volume and alveolar pressure on reverse pulmonary venous blood flow. *J Appl Physiol* 73: 195–199, 1992.
9. **Obermiller T, Lakshminarayan S, Willoughby S, Mendenhall J, and Butler J.** Influence of lung volume and left atrial pressure on reverse pulmonary venous blood flow. *J Appl Physiol* 70: 447–453, 1991.
10. **Onerato D, Demirozu M, Breitenbucher A, Atkins N, and Chediak A.** Airway mucosal blood flow in humans. Response to adrenegic agonists. *Am J Respir Crit Care Med* 149: 1132–1137, 1994.
11. **Peterson B, Petrini M, Hyde R, and Schreiner B.** Pulmonary tissue volume in dogs during pulmonary edema. *J Appl Physiol* 44: 782–795, 1978.
12. **Souders JE, George SC, Polissar NL, Swenson ER, and Hlastala MP.** Tracheal gas exchange: perfusion-related differences in inert gas elimination. *J Appl Physiol* 79: 918–928, 1995.
13. **Stothert JJ, Ashley K, Kramer G, Herndon D, Traber L, Deubel-Ashley, and Traber D.** Intrapulmonary distribution of bronchial blood flow after moderate smoke inhalation. *J Appl Physiol* 69: 1734–1739, 1990.
14. **Swenson ER, Robertson HT, Polissar NL, Middaugh ME, and Hlastala MP.** Conducting airway gas exchange: diffusion related differences in inert gas elimination. *J Appl Physiol* 72: 1581–1588, 1992.
15. **Wagner EM, Mitzner W, and Brown R.** Site of functional bronchopulmonary anastomoses in sheep. *Anat Rec* 254: 360–366, 1999.
16. **Wagner PD, Laravuso RB, Uhl RR, and West JB.** Continuous distributions of ventilation-perfusion ratios in normal subjects. *J Clin Invest* 54: 54–68, 1974.
17. **Wanner A.** Circulation of the airway mucosa. *J Appl Physiol*: 917–925, 1989.