Modeling diffusion limitation of gas exchange in lungs containing perfluorocarbon

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VanLöbensels, Elisabeth Mates, Joseph C. Anderson, Jacob Hildebrandt, and Michael P. Hlastala. Modeling diffusion limitation of gas exchange in lungs containing perfluorocarbon. J. Appl. Physiol. 86(1): 273–284, 1999.—We reported changes in alveolar-arterial $P_{O_2}$ gradient, ventilation-perfusion heterogeneity, and arterial-alveolar $P_{CO_2}$ gradient during partial liquid ventilation (PLV) in healthy piglets (E. A. Mates, P. Tarczy-Hornoch, J. Hildebrandt, J. C. Jackson, and M. P. Hlastala. In: Oxygen Transport to Tissue XVII, edited by C. Ince. New York: Plenum, 1996, vol. 388, p. 585–597). Here we develop two mathematical models to predict transient and steady-state (SS) gas exchange conditions during PLV and to estimate the contribution of diffusion limitation to SS arterial-alveolar differences. In the simplest model, perfluorocarbon is represented as a uniform flat stirred layer and, in a more complex model, as an unstirred spherical layer in a ventilated terminal alveolar sac. Time-dependent solutions of both models show that SS is established for various inert and respiratory gases within 5–150 s. In fluid-filled unventilated terminal units, all times to SS increased sometimes by hours, e.g., $SF_6$ exceeded 4 h. SS solutions for the ventilated spherical model predicted minor end-capillary disequilibrium of inert gases and significant disequilibrium of respiratory gases, which could explain a large portion of the arterial-alveolar $P_{CO_2}$ gradient measured during PLV (14). We conclude that, during PLV, diffusion gradients for gases are generally small, except for $CO_2$.

liquid breathing; perfluorocarbon liquids; mathematical model; gas exchange

PARTIAL LIQUID VENTILATION (PLV) is a technique of ventilatory support in which the air spaces of the lung are partially replaced with liquid perfluorocarbon (PFC) and then periodically insufflated with $O_2$-enriched gas with use of a conventional mechanical ventilator. PLV was first described by Fuhrman et al. (3) and has been shown to improve oxygenation and lung mechanics in animal models and in humans with acute respiratory distress syndrome (2, 4, 8, 10, 11). We previously showed that PLV in healthy piglets causes mild increases in arterial-alveolar $P_{O_2}$ and $P_{CO_2}$ gradients [(A-a)DO$_2$ and (a-A)DCO$_2$] (12–14). Compared with conventional gas ventilation with 100% $O_2$, there was a 50% increase in ventilation-perfusion (VA/Q) heterogeneity and a 50% increase in $O_2$ shunt, both of which can contribute to the alveolar-arterial difference. We hypothesized, but were unable to verify experimentally, that a diffusion barrier exists across the PFC in the lung periphery and that it is responsible for a significant portion of measured increases in alveolar-arterial differences in healthy animals during PLV. To test the feasibility of this hypothesis, we developed two mathematical models of gaseous diffusion in partially PFC-filled lung subunits.

In our experimental studies we used the multiple inert gas elimination technique (MIGET) to measure VA/Q heterogeneity in healthy piglets during PLV (13, 14, 20). The use of this method raised the question of whether inert and respiratory gas exchange reaches steady state during PLV within a time frame similar to conventional gas ventilation. Steady state refers to the condition in which, given a constant source of a gas infused into mixed venous blood, the ratio of input to output partial pressures across the lung (i.e., $P_{in}/P_{f}$ and $P_o/P_{f}$, where $P_{in}$, $P_{f}$, and $P_o$ are arterial, mixed venous, and expired pressures, respectively) does not change with time and there is no further storage or net loss of mass within the lung over time. Using a very simple model, we showed previously that the time to steady state for $SF_6$ (a gas used in MIGET to estimate shunt) was prohibitively long because of its high solubility in PFC vs. blood (13). This required us to modify MIGET by eliminating $SF_6$ from the analysis, inasmuch as it did not satisfy the underlying assumption that steady-state conditions exist (13). With the more sophisticated models described here, we were able to refine and verify these original predictions and further explore the effects of PFC on attainment of steady-state gas exchange for the remaining five inert gases as well as $O_2$ and $CO_2$. We are also able to explore the effect of PFC dose on diffusion-limited gas transport in the alveolus.

In recent publications, PLV has been shown to improve gas exchange in humans with acute lung injury (4, 8, 11). We have focused our efforts on studying the effects of PLV in healthy animals to shed light on the fundamental differences in gas exchange between gas- and liquid-filled lungs. Many of the equations in traditional gas exchange theory are based on the assumptions that steady-state mass flux exists and that there is a negligible diffusion barrier in the alveolus (e.g., Berggren shunt and Bohr dead space). These assumptions need to be critically evaluated in the novel situation of a fluid-filled lung. Despite mild increases in (A-a)DO$_2$ and (a-A)DCO$_2$ during PLV in healthy animals, oxygenation and ventilation can be achieved surprisingly well through a liquid-filled lung. The success of PLV in a clinical setting may depend on altering our thinking about shunt and dead space when we add a high-solubility fluid with diffusion resistance to the air.
space of the lung. The models described here have been helpful in exploring these ideas.

MATHEMATICAL MODELS

In prior publications we presented two different models of gas exchange during PLV: 1) a two-compartment well-mixed model used to estimate times to steady state (13) and 2) a spherical gas exchange model used to estimate steady state arterial-alveolar differences across a PFC diffusion barrier (14). Here we expand on both models, adding a gas compartment to the one-dimensional well-mixed model, providing time- and space-dependent numerical solutions to the spherical model, and providing a full discussion of the underlying assumptions and model behavior. We explore solutions to the time rate of change of partial pressures of $O_2$, $CO_2$, and six MIGET gases in PFC after a step change in input partial pressures.

A comparison of two separate model configurations is particularly enlightening, since the in vivo PFC-filled alveolus probably includes some features of both. The well-stirred compartment model reflects a PFC layer with complete convective mixing and no diffusion limitation within the gas exchange unit, whereas the spherical shell model imitates a perfectly still diffusion barrier interposed between gas and blood. The true nature of gas exchange in PFC lies somewhere between these models. With each breath, PFC probably moves in and out of some alveoli and small airways and exists as small stagnant puddles in others.

Glossary

- $\beta$: Solubility of a tracer gas in a solvent (ml gas/100 ml solvent·Torr$^{-1}$)
- $C$: Concentration of a tracer gas in a solvent (ml gas/ml solvent)
- $D$: Molecular diffusion coefficient (cm$^2$/s)
- $M$: Mass of tracer gas in a solvent (ml gas)
- MIGET: Multiple inert gas elimination technique
- $n$: Number of gas exchange units in a piglet lung
- $P$: Partial pressure of a tracer gas (Torr)
- PFC: Perfluorochemical
- PLV: Partial liquid ventilation
- $Q$: Blood flow (ml/s)
- $RR$: Respiratory rate (min$^{-1}$)
- $r$: Radial distance from center of gas compartment (cm)
- $r_c$: Radius of gas exchange unit at the capillary boundary (cm)
- $r_g$: Radius of gas compartment (cm)
- $t$: Time (s)
- $\tau$: Time constant (s)
- $T$: Temperature (°C or K)
- $T_{98}$: Time to 98% of steady state (s)
- $V_D$: Dead space (ml/breath)
- $V_T$: Tidal volume (ml/breath)
- $a$: Arterial
- $A$: Alveolar
- $b$: Blood
- $c$: Capillary
- $g$: Alveolar gas
- $gi$: Inspired gas
- $pfc$: Perfluorocarbon
- $v$: Mixed venous
- $P_{A}$: Arterial pressure
- $P_{C}$: Capillary pressure
- $P_{C}$: Mixed venous pressure
- $P_{PFC}$: Partial pressure of the PFC gas
- $P_{G}$: Partial pressure of the gas
- $P_{C}$: Partial pressure of the capillary
- $Q$: Blood flow
- $Q_{A}$: Alveolar gas
- $Q_{PFC}$: PFC gas
- $Q_{R}$: Recirculated component
- $Q_{V}$: Ventilation
- $Q_{W}$: Water vapor
- $r$: Radius of the gas compartment
- $t$: Time
- $T$: Temperature
- $T_{98}$: Time to 98% of steady state
- $V_D$: Dead space
- $V_T$: Tidal volume
- $C_{A}$: Arterial concentration
- $C_{G}$: Gas concentration
- $C_{P}$: Perfluorochemical concentration
- $C_{V}$: Mixed venous concentration
- $P_{P FC}$: Partial pressure of the PFC gas
- $P_{A}$: Arterial pressure
- $P_{C}$: Capillary pressure
- $P_{C}$: Mixed venous pressure
- $P_{G}$: Partial pressure of the gas
- $P_{C}$: Partial pressure of the capillary
- $Q$: Blood flow
- $Q_{A}$: Alveolar gas
- $Q_{P FC}$: PFC gas
- $Q_{R}$: Recirculated component
- $Q_{V}$: Ventilation
- $Q_{W}$: Water vapor
- $r$: Radius of the gas compartment
- $t$: Time
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- $T_{98}$: Time to 98% of steady state
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- $P_{C}$: Capillary pressure
- $P_{C}$: Mixed venous pressure
- $P_{G}$: Partial pressure of the gas
- $P_{C}$: Partial pressure of the capillary

Model assumptions. In both models we assumed that the blood and gas compartments on either side of the PFC are well mixed. The models also assume that diffusion barriers at the capillary membrane and the PFC-gas interface are negligible. Because the presence of the PFC in the alveolar space does not affect gas exchange properties of the alveolar-capillary membrane, the assumption of complete equilibrium across the membrane is as valid as in the gas-filled lung. Blood flow and ventilation are assumed continuous and non-pulsatile (i.e., $Q$ and $V_T$ are constant).

$P_T$ of tracer gases was assumed to be constant, and variation in body tissue partial pressures was assumed to be negligible. In the experimental situation, $P_T$ of the inert gases will vary slightly with time as the body comes to a new steady state after a perturbation in gas exchange. We believed that this variation was small, inasmuch as the body tissues were previously equilibrated with inert gas and the recirculated component is a small fraction of the total $P_T$. The error introduced by this assumption will lead to a slight underestimation of the true time to reach steady state.

Time-dependent gas exchange in a well-stirred three-compartment model. Figure 1 schematically describes this model, in which blood is delivered to the capillary compartment at a flow rate $Q$ (ml/s) and ventilation through the gas compartment occurs at a rate $V_A$ (ml/s). A tracer gas may enter the gas exchange unit dissolved in blood at partial pressure $P_b$ or via ventilation at partial pressure $P_g$. Mass balance for the tracer in three compartments is given by Eq. 1 with the assumption that the PFC layer is well mixed. Thus the gas partial pressures in all compartments are equal (i.e., $P_c = P_{pfc} = P_g$) at time $t$

$$\frac{d(M_c + M_{pfc} + M_g)}{dt} = Q \cdot (C_T - C_c) - V_A \cdot (C_g - C_g) \quad (1)$$
Converting mass (M = C · V) and concentration (C = β · P) to partial pressures (P), applying the assumption \( P_c = P_{pfc} = P_g \) (i.e., well-mixed with no diffusion gradients), and rearranging into the standard form for a first-order differential equation \( \tau \cdot P + P = K \) (where \( \tau \) is the time constant and \( K \) is the steady-state asymptotic value of \( P \))

\[
\frac{dP_{pfc}}{dt} = \frac{V_A \cdot \beta_g + Q \cdot \beta_b}{V_A \cdot \beta_g + Q \cdot \beta_b} \cdot P_{pfc}
\]

\[
+ \frac{V_c \cdot \beta_{pfc} + V_g \cdot \beta_g}{V_A \cdot \beta_g + Q \cdot \beta_b} \cdot \frac{P_{pfc}}{V_A \cdot \beta_g + Q \cdot \beta_b}
\]

\[
\tau = \frac{V_c + V_{pfc} \cdot \frac{\beta_{pfc}}{\beta_b} + V_g \cdot \frac{\beta_g}{\beta_b}}{V_A \cdot \frac{\beta_g}{\beta_b} + Q}
\]

The standard solution to Eq. 2 takes the form

\[
P = K \cdot (1 - e^{-t/\tau})
\]

where \( K = \left[ V_A \cdot P_{gl} \cdot \frac{(\beta_g/\beta_b) + Q \cdot P_g}{V_A \cdot (\beta_g/\beta_b) + Q} \right] \).

The rate at which \( P_{pfc} \) approaches steady-state equilibrium is determined by \( \tau \), the time for the exponential term to decrease by 63%. At \( 4\tau \), steady-state equilibrium is \( >98\% \) complete. The standard MIGET theory assumes that \( P_c = P_g = \) constant; i.e., after a change in the ventilate, the rate at which gas exchange measurements are taken is much longer than \( \tau \), so the exponential term in Eq. 3 becomes negligible.

Equation 3 shows that when PFC is present in the alveolus and \( \beta_{pfc} > \beta_b \), \( \tau \) is prolonged, especially if \( \beta_{pfc} \) is greater than both \( \beta_b \) and \( \beta_g \). For gases in which this holds true, larger volumes of PFC result in longer times to equilibrium. For \( O_2 \), \( \tau \) is actually prolonged in the absence of PFC, because \( \beta_g > \beta_{pfc} \). It is also prolonged as \( V_A \) approaches zero (i.e., shunt), because PFC must equilibrate to a higher final value, i.e., input partial pressures \( P_g \) or \( P_g \). When \( V_A \) is nonzero, the steady-state partial pressure (K) is less than input partial pressure and \( \tau \) is accordingly shorter. Increasing \( V_A \) or \( Q \) shortens \( \tau \) for all gases.

Time-dependent gas exchange in a spherical shell with radial diffusion. To simulate gas exchange in a functional subunit of lung (Fig. 2), we chose a spherically shaped structure with an outer layer of capillary blood surrounding a layer of PFC that, in turn, surrounds a gas-filled center. The branching, space-filling nature of lung architecture is too complex for small-scale mathematical modeling. We chose to model gas exchange at the level of the terminal alveolar duct and represented them as smooth spheres. If the anatomic subunit is larger than this, the surface area of a smooth sphere would greatly underestimate the surface-to-volume ratio. On the other hand, representing a structure as small as an alveolus by a closed sphere would overestimate the ratio, since alveoli are roughly hexagonal cups. We therefore compromised on a structure the size of a single terminal alveolar sac to be portrayed by a sphere with dimensions derived accordingly.

We assumed that the capillary and alveolar gas compartments were individually well mixed and that uniform radial diffusion occurred in the PFC. Mass exchange between the compartments is dependent on the interfacial area bounding two adjacent regions. The area of the capillary-PFC interface is fixed at \( 4\pi r_c^2 \). The area of the inner gas space (\( 4\pi r_g^2 \)) depends on the volume of PFC administered and on total lung volume. PFC is assumed to distribute uniformly as a spherical layer with the ventilated gas "hole" in the center. As the hole radius approaches zero, the unit becomes "flooded" with PFC. As \( r_g \) approaches \( r_c \) the model represents a gas-filled lung with no diffusion gradient (see parameter estimates for description of actual dimensions used).

We use three coupled differential equations to describe mass flux between blood, PFC, and gas. Equation 4 represents the rate of change of mass \( (\beta \cdot V \cdot P) \) of a dissolved gas in the capillary blood compartment. It is equal to the rate of gas delivery to the capillary space via blood flow, the rate of gas removal via blood flowing out of the capillary, and the rate of diffusive gas flux
across the alveolar capillary membrane into the PFC. Equation 5 describes radial diffusion in the PFC shell, which has spherical symmetry (1). Equation 6 represents the rate of change of mass in the central air space determined by addition of gas via inspiration, subtraction of gas removed by expiration, and subtraction of gas diffusing across the air-liquid interface from the PFC layer adjacent to the compartment.

\[
\beta_b \cdot V_c \frac{dP_c}{dt} = Q \cdot \beta_b \cdot (P_T - P_c) - \left( D_{pfc} \cdot \beta_{pfc} \cdot 4 \cdot \pi \cdot r_c^2 \right) \frac{\partial P_{pfc}}{\partial r} \bigg|_{r = r_c}
\]

\[
\beta_{pfc} \cdot V_{pfc} \frac{dP_{pfc}}{dt} = D_{pfc} \cdot \beta_{pfc} \cdot V_{pfc} \cdot \left( \frac{\partial^2 P_{pfc}}{\partial r^2} + \frac{2}{r} \frac{\partial P_{pfc}}{\partial r} \right)
\]

\[
\beta_g \cdot V_g \frac{dP_g}{dt} = \dot{V}A \cdot \beta_g \cdot (P_g - P_c) + \left( D_{pfc} \cdot \beta_{pfc} \cdot 4 \cdot \pi \cdot r_g^2 \right) \frac{\partial P_{pfc}}{\partial r} \bigg|_{r = r_g}
\]

The system of three partial differential equations was solved numerically to determine the partial pressure profiles in the PFC layer from the capillary-PFC interface to the PFC-gas interface. Spatial derivatives were determined by finite difference, and time derivatives were solved using LSODE, a time-integrating algorithm developed by Hindmarsh (7). The executable program was submitted as a batch job in which each simulation was solved numerically using an IBM model RS6000 computer running Unix version 4.2. \( P_c \) and \( P_g \) are equal to \( P_{pfc}(r) \) at the \( r_c \) and \( r_g \) boundaries. The time to steady-state equilibrium (\( T_{eq} \)) was defined as the time for the numerical solutions to converge to 98% of the analytically determined \( P_c \) and \( P_g \) for a steady-state gas diffusion in a spherical shell, as defined by Crank (1) (see Eqs. 7–11). The two calculated mass flow rates across the capillary-PFC and PFC-gas boundaries were nearly equal at “steady state” by use of these criteria.

Steady-state gas exchange in a spherical shell with radial diffusion. Under steady-state conditions, the time rate of change of compartmental partial pressures is zero and mass flow is equal across all boundaries. We used Crank’s (1) steady-state solution to Eq. 5 describing the concentration profile as a function of radial position \( C(r) \) in a spherical shell to simplify the above system of equations and to analytically calculate blood-gas partial pressure differences.

\[
C(r) = \frac{r_g \cdot \beta_{pfc} \cdot P_g \cdot (r_c - r) + r_c \cdot \beta_{pfc} \cdot P_c \cdot (r - r_g)}{r \cdot (r_c - r_g)} = \beta_{pfc} \cdot P_{pfc}(r)
\]

Differentiating Eq. 7 with respect to \( r \), evaluating \( \beta_{pfc} \cdot dP_{pfc}/dr \) at \( r = r_c \) and also at \( r = r_g \), and then substituting into Eqs. 4 and 6 gives

\[
Q \cdot \beta_b \cdot P_T = \left( \frac{Q \cdot \beta_b + D_{pfc} \cdot \beta_{pfc} \cdot 4 \pi \cdot r_c \cdot r_g}{r_c - r_g} \cdot P_c - \frac{D_{pfc} \cdot \beta_{pfc} \cdot 4 \pi \cdot r_c \cdot r_g}{r_c - r_g} \cdot P_g \right)
\]

\[
P_g \cdot \beta_g \cdot \dot{V}A = \left( D_{pfc} \cdot \beta_{pfc} \cdot 4 \pi \cdot r_c \cdot r_g \right) \frac{r_c \cdot r_g}{r_c - r_g} \cdot P_c + \left( \dot{V}A \cdot \beta_g + D_{pfc} \cdot \beta_{pfc} \cdot 4 \pi \cdot r_c \cdot r_g \right) \frac{r_c \cdot r_g}{r_c - r_g} \cdot P_g
\]

Equations 8 and 9 constitute simultaneous equations in two unknowns \( P_c \) and \( P_g \). Substituting \( K_1 = D_{pfc} \cdot 4 \pi \cdot (r_c \cdot r_g)/(r_c - r_g) \) and solving for \( P_c \) and \( P_g \)

\[
P_c = \frac{P_T \left( 1 + \frac{\dot{V}A \cdot \beta_g \cdot P_g}{K_1 \cdot Q \cdot \beta_b} \right)}{1 + \dot{V}A \left( \frac{1}{K_1} \right) + \frac{\beta_g}{Q \cdot \beta_b}}
\]

\[
P_g = \frac{P_T \left( 1 + \frac{\dot{V}A \cdot P_g}{K_1 \cdot \beta_g} + \frac{\dot{V}A \cdot \beta_g \cdot P_g}{Q \cdot \beta_b} \right)}{1 + \dot{V}A \left( \frac{1}{K_1} \right) + \frac{\beta_g}{Q \cdot \beta_b}}
\]

and

\[
P_c - P_g = \frac{P_T - P_{gl}}{1 + \frac{K_1 \cdot \beta_g}{\dot{V}A \cdot Q \cdot \beta_b}}
\]

At the extremes of no PFC \( (r_c = r_g) \) and \( P_g = 0 \), Eqs. 10 and 11 reduce to the MIGET equations for retention \( R \) and excretion \( E \): \( R = E = \lambda \cdot \dot{V}A / (\lambda_b + \dot{V}A / Q) \), where \( \lambda_b = \beta_b / \beta_g \). Notice that the capillary-to-gas partial pressure \( (P_c - P_g) \) difference is dependent on the absolute values of \( \dot{V}A \) and \( Q \).

PARAMETER ESTIMATES

Parameter values were chosen to correspond to the dimensions of lung structure and function of healthy piglets weighing 2–4 kg. Piglets this size typically have a functional residual capacity of 30 ml/kg and respiratory rate (RR) of 20 breaths/min. For calculation purposes, an average weight of 2.5 kg was used. As discussed above, our gas exchange unit represents a terminal sac in the lung of a piglet. Haefeli-Bleuer and Weibel (5) measured the outer diameter of human terminal sacs (an alveolar duct plus 2 alveoli in total width) to be 656 ± 127 μm. Tenney and Remmers (18) showed that species variation in alveolar diameter was correlated to metabolic rate per unit body weight, with adult pig alveolar diameter ~91% of the diameter of
human alveoli (656 × 0.91 = 597 μm). On the basis of these data we chose an end-inspiratory \( r_c \) of 300 μm. Surface area and volume of a single spherical unit are therefore 0.0113 cm\(^2\) and 0.000113 cm\(^3\), respectively. The number \( n \) of terminal sacs or gas exchange units in a piglet lung was then determined by the ratio of end-inspiratory lung volume \([48\, ml/kg] \times (2.5 \, kg) = 120 \, ml \) at \( r_c = 300 \, μm \) to gas exchange unit volume \((1.13 \times 10^{-5} \, ml)\), 1,062,000 units/lung, which we rounded to \( 1 \times 10^6 \). End-inspiratory lung volume was determined as the sum of functional residual capacity lung volume \((30\, ml/kg)\), tidal volume \((V_t, 15\, ml/kg)\), and 3 ml/kg associated with positive end-expiratory pressure of 5 cmH\(_2\)O used in all our experimental work (12). If there are 20 alveoli per terminal gas exchange unit, there would be \( 20 \times 10^6 \) alveoli/piglet. Lung volume is obviously not constant throughout the respiratory cycle. We evaluated the steady-state model (Eqs. 10 and 11) for several lung volumes in the range of tidal breathing, i.e., \( r_c \) of 270 and 300 μm, to illustrate the impact of lung volume on \((A-a)\text{DO}_2\). 

### Table 1. Normal model parameters for \( V_{A}/\dot{Q} = 1 \) and \( V_{pfc} = 30\, ml/kg\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r_g )</td>
<td>Gas volume radius</td>
<td>210 μm</td>
</tr>
<tr>
<td>( r_c )</td>
<td>Gas exchange unit radius</td>
<td>300 μm</td>
</tr>
<tr>
<td>( V_c )</td>
<td>Capillary volume</td>
<td>4.24 × 10(^{-6}) ml</td>
</tr>
<tr>
<td>( D_{pfc} )</td>
<td>Diffusion coeff in PFC</td>
<td>4.36 × 10(^{-5}) cm(^2)/s</td>
</tr>
<tr>
<td>( V_A )</td>
<td>Exchange unit ventilation</td>
<td>8.74 × 10(^{-6}) ml/s</td>
</tr>
<tr>
<td>( Q )</td>
<td>Exchange unit blood flow</td>
<td>8.33 × 10(^{-6}) ml/s</td>
</tr>
<tr>
<td>( n )</td>
<td>No. of exchange units</td>
<td>1 × 10(^6)</td>
</tr>
</tbody>
</table>

PFC, perfluorocarbon.

### Table 2. Solubilities of 6 inert gases, \( O_2 \), and \( CO_2 \) in blood and PFC

<table>
<thead>
<tr>
<th>Gas</th>
<th>( b_p )</th>
<th>( b_{pfc} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF(_6)</td>
<td>0.000974</td>
<td>0.000049</td>
</tr>
<tr>
<td>Ethane</td>
<td>0.0116</td>
<td>0.0047</td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>0.0749</td>
<td>0.0078</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.396</td>
<td>0.047</td>
</tr>
<tr>
<td>Ether</td>
<td>1.34</td>
<td>0.036</td>
</tr>
<tr>
<td>Acetone</td>
<td>38.4</td>
<td>0.42</td>
</tr>
<tr>
<td>( O_2 )</td>
<td>0.003</td>
<td>0.0658</td>
</tr>
<tr>
<td>( CO_2 )</td>
<td>0.779</td>
<td>0.256</td>
</tr>
</tbody>
</table>

Values are expressed in ml gas:100 ml solvent \(^{-1}\)-100 Torr \(^{-1}\). Inert gas solubilities in pig blood \((b_p, n = 9, \text{ means } \pm \text{ SE})\) and in PFC \((b_{pfc}, n = 6, \text{ means } \pm \text{ SE})\) were measured by gas chromatography with flame ionization detector and electron capture. \( O_2 \) and \( CO_2 \) solubilities in blood are described in PARAMETER ESTIMATES. “Solubility” in gas (\( b_p \)) is 0.132 for all gases.

### Vent, Alliance Pharmaceutical, San Diego, CA (12).

The “solubility” of a tracer gas in the phase \((b_p)\) is defined in the classic paper by Piiper et al. (16) as 0.00132 Torr \(^{-1}\) (1/760 at sea level).

The solubility of \( O_2 \) and \( CO_2 \) in blood was determined by the slope of the curve of gas content vs. partial pressure. This relationship is nonlinear over the physiological range of partial pressures of these gases because of chemical binding in the blood. \( O_2 \) combines with Hb, resulting in an S-shaped concentration vs. pressure curve in the partial pressure range 0–150 Torr. For \( PO_2 > 150 \) Torr, the concentration vs. partial pressure curve is linear, because Hb is saturated, and for \( O_2 \), \( b_p \) is the same as in plasma: 0.003 ml·100 ml solvent\(^{-1}\)-1·Torr\(^{-1}\). For \( PO_2 < 150 \) Torr, \( b_p \) for \( O_2 \) is much higher; e.g., at \( PO_2 \) of 40 Torr it is 0.06 ml·100 ml solvent\(^{-1}\)-1·Torr\(^{-1}\) as determined by the slope of the \( O_2 \) content (\( CO_2 \) ml·100 ml blood) vs. \( PO_2 \) (Torr) curve generated by the subroutines of Olszowka and Farhi (15). For the steady-state partial pressure differences calculated using Eqs. 10 and 11, we used only \( b_p \) of 0.003, because for all the experimental data against which we are comparing model results arterial \( PO_2 \) (\( PaO_2 \)) was >150 Torr (12). The solubility of \( CO_2 \) in blood is a function of dissolved \( CO_2 \) as well as \( CO_2 \) converted to \( HCO_3^- \). The content (\( CC_{CO_2} \)) vs. \( P_{CO_2} \) curve is approximately linear within 40–80 Torr \( P_{CO_2} \). With use of the blood-gas routes of Olszowka and Farhi, \( b_p \) for \( CO_2 \) was determined from the slope of \( CC_{CO_2} \) vs. \( P_{CO_2} \) over this range and was found to be 0.779 ml·100 ml blood\(^{-1}\)-1·Torr\(^{-1}\). \( O_2 \) and \( CO_2 \) solubilities in PFC were provided by Alliance Pharmaceutical (Table 2).

Few molecular diffusion coefficients \((D_{pfc})\) of dissolved gases in PFC are precisely known. Tham et al. (19) measured \( D_{pfc} \) of \( O_2 \) and \( CO_2 \) in three perfluorochemicals (Caroxin-D, Caroxin-F, and FC-80), finding the average diffusion coefficient for \( O_2 \) in PFC to be 5.61 × 10\(^{-3}\) cm/s at 37°C with a range of 5.57–5.65 × 10\(^{-5}\) cm/s and for \( CO_2 \) in PFC at 37°C to be 4.36 × 10\(^{-5}\) cm/s with a range of 4.21–4.48 × 10\(^{-5}\) cm/s. The diffusion coefficients of \( O_2 \) and \( CO_2 \) in H\(_2\)O at 37°C are 3.3 × 10\(^{-5}\) and 2.6 × 10\(^{-5}\) cm/s, respectively (6).

We used the average value of the \( CO_2 \) diffusion coefficient as measured by Tham et al. (19) to estimate
D_pfc of each respiratory gas in perflubron, the PFC used in our experiments. There are no experimental data available measuring diffusivity in PFC of the six inert gases used in MIGET (9, 20). Their diffusivities in H_2O at 37°C are 1.63 x 10^-5 cm^2/s for SF_6, 1.96 x 10^-5 cm^2/s for ethane, 1.84 x 10^-5 cm^2/s for cyclopropane, 1.28 x 10^-5 cm^2/s for halothane, 0.85 x 10^-5 cm^2/s for ether, and 1.62 x 10^-5 cm^2/s for acetone (17, 21). Because their diffusivities in H_2O are only slightly less than those of CO_2 in H_2O, we chose the value of D_pfc for CO_2 in PFC to represent the diffusivity of the six inert gases in the absence of experimental data.

RESULTS

Solutions for both of the models were well behaved with no instances of negative results or mass imbalance. Partial pressures at the boundaries between compartments were continuous. The numerically integrated time- and space-dependent solutions for the spherical model converged on the analytic steady-state solutions. For each of the eight gases simulated, the time to steady-state equilibrium was estimated by two independent models, and the times generated by both models were within 30% of each other and usually within 10%.

Time to reach steady-state equilibrium. Figure 3 illustrates the time rate of change of partial pressure of the eight gases in the simpler well-mixed three-compartment model with V_pfc of 30 ml/kg after a step change in the input partial pressure of each gas. For O_2 this involved setting P_g at 650 Torr and P_g at 40 Torr and for the remaining 7 gases P_g at 0 Torr and P_g at 1 Torr at time 0. Figure 3A illustrates the application of Eq. 3 for normal conditions of matched V_A and Q (V_A/Q = 1). Figure 3B illustrates the same for near-zero ventilation (shunt conditions). Because O_2 is delivered by ventilation, P_O2 was not simulated for shunt conditions. Whenever V_A is negligible, Eq. 3 shows that the final value is always P_g, and the time constants are lengthened. Both features are apparent in Fig. 3B. Gases with the lowest θ_pfc ratio (i.e., SF_6) take the longest to equilibrate, because PFC acts as a large capacitor that fills slowly when there is great disparity in solubilities.

Figure 4 demonstrates the time and space rate of change in the spherical gas exchange unit with 30 ml/kg PFC and matched V_A and Q (as described in PARAMETER ESTIMATES). Figure 4A shows successive time traces of P_CO2 vs. radial distance from the capillary through PFC to the central gas region. After a step change in P_g from 0 to 40 Torr, P_CO2 increases in the gas exchange unit until it converges on the steady-state value. Figure 4B shows similar successive time traces of P_O2 vs. radial distance through the PFC after a step change in P_g from 0 to 650 Torr.

Table 3 reports the T_98 for eight gases in each of the two models with V_pfc of 30 ml/kg. T_98 values were defined slightly differently for the two models. In the well-mixed model T_98 was defined as 4τ in Eq. 3; for the spherical model it was the time at which the time-dependent solutions (Eqs. 4–6) converged to 98% of the analytic steady-state solutions (Eqs. 10 and 11). We evaluated the model for three conditions to illustrate the range of T_98 likely to be encountered in the lung partially filled with PFC: matched V_A and Q, V_A approximately zero with Q normal (shunt), and Q near zero with V_A normal (dead space).

For V_A and Q well-matched (V_A/Q = 1), all times to steady state were <3 min. The gas with the longest time to steady state was cyclopropane followed by ether, SF_6, halothane, O_2, CO_2, and acetone. Under shunt conditions all times to steady state were prolonged (except for acetone, which is insensitive to shunt), with SF_6 having the longest times at ~5 h. The time to steady state for O_2 was also markedly prolonged at ~27 min, whereas that for CO_2 remained short at 15–20 s. Under dead space conditions the times were intermediate, with the longest being for acetone at ~26 min. CO_2 equilibration times were mildly prolonged under these conditions, ~95 s.
Steady-state gas exchange in a PFC-filled spherical shell. Steady-state partial pressure differences of inert and respiratory gases were calculated from Eqs. 10 and 11. SF₆ was left out of the following discussion, since it was not included in our experimental MIGET analysis (12, 13) because of its prohibitively long time to reach steady state under shunt conditions. Figure 5 shows Pₑ–Pᵢ differences of seven gases normalized by input partial pressure (Pₑ) for the 5 inert gases and CO₂ and Pᵢ for O₂ vs. r₀ for V˙A of 8.74 × 10⁻⁶ ml/s and Q of 8.33 × 10⁻⁶ ml/s. An r₀ of 0 corresponds to a flooded terminal sac with no gas compartment, and r₀ of 300 µm corresponds to a gas exchange unit with no PFC. Values of r₀ equal to 210, 250, and 280 µm correspond to the three doses of PFC used in our experimental work: 30, 20, and 10 ml/kg, respectively (12). CO₂ shows the largest difference at all values of r₀ with the Pₑ–Pᵢ difference nearly 10% of the input pressure at r₀ of 210 µm. The partial pressure gradient of O₂ is very low at the same dose (<1% of Pᵢ), rising only when r₀ becomes very small as the gas exchange unit becomes flooded with PFC. The inert gases also show a negligible Pₑ–Pᵢ difference for r₀ of 210 µm, with halothane having the largest Pₑ–Pᵢ difference at 3% of Pₑ followed by cyclopropane, ethane, acetone, and ether. As the PFC layer increases in thickness, the Pₑ–Pᵢ difference rises exponentially, approaching Pₑ values for CO₂ and the inert gases and Pᵢ for O₂. For these simulations, Pₑ for O₂ was set to zero and Pᵢ for O₂ to 1 for the sake of comparison.

Figure 6 illustrates the effect of gas exchange unit volume (“lung volume”) on partial pressure difference of O₂ and CO₂. Although our model does not incorporate features of tidal breathing, we explored the effect of varying the gas exchange unit volume between the extremes of end inspiration (rₑ = 300 µm) and end

**Table 3. T⁹⁸ after a step change in input partial pressure (Pₑ or Pᵢ) with V_pfc = 30 ml/kg and rₑ = 300 µm**

<table>
<thead>
<tr>
<th>Gas</th>
<th>Normal (V˙A = 8.74 × 10⁻⁶, Q = 8.33 × 10⁻⁶)</th>
<th>Quasi-shunt (V˙A = 8.74 × 10⁻⁶, Q = 8.33 × 10⁻⁶)</th>
<th>Quasi-dead space (V˙A = 8.74 × 10⁻⁶, Q = 8.33 × 10⁻⁶)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF₆</td>
<td>122.87</td>
<td>173,578.07</td>
<td>15,025.79</td>
</tr>
<tr>
<td>Ethane</td>
<td>72.33</td>
<td>933.10</td>
<td>78.40</td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>144.76</td>
<td>441.57</td>
<td>223.29</td>
</tr>
<tr>
<td>Halothane</td>
<td>61.28</td>
<td>82.65</td>
<td>237.08</td>
</tr>
<tr>
<td>Ether</td>
<td>126.14</td>
<td>139.13</td>
<td>1,350.45</td>
</tr>
<tr>
<td>Acetone</td>
<td>5.67</td>
<td>5.69</td>
<td>1,581.69</td>
</tr>
<tr>
<td>CO₂</td>
<td>34.06</td>
<td>1,601.64</td>
<td>1,505.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>47.85</td>
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</tr>
</tbody>
</table>
expiration \((r_c = 270 \mu m)\). This might be equivalent to breath-holding maneuvers at the extremes of cyclic breathing. For both gases, the \(P_c-P_g\) difference increased at the lower lung volume for all PFC doses. The percent increase in the \(P_c-P_g\) difference was greater with larger doses of PFC. The \(P_c-P_g\) difference for \(CO_2\) with a \(P_g\) of 40 Torr and 30 ml/kg PFC in the lung varied from 3.7 Torr at the large lung volume to 9.6 Torr at the lower lung volume. At the small PFC dose of 10 ml/kg, the \(P_c-P_g\) difference for \(CO_2\) varied from 0.8 to 1.2 with the change in lung volume. We previously showed \((a-A)CO_2\) in healthy animals with 30 ml/kg PFC in the lungs to be 12 Torr \((12)\). The difference for \(P_c-P_g\) difference for \(O_2\) varied in a similar manner with an increase from 6 to 18 Torr as the gas exchange unit volume decreased with 30 ml/kg PFC in the lung and \(P_g\) of 650 Torr.

We examined the impact of varying \(V_A\) and \(Q\) independently on the \(P_c-P_g\) difference for inert gases, \(O_2\), and \(CO_2\). At PFC thicknesses up to 100 \(\mu m\) (PFC dose \(-30 ml/kg\)), varying \(V_A\) and \(Q\) had a small impact on MIGET gas \(P_c-P_g\) differences. At PFC thicknesses \(>100 \mu m\), the gradients increased exponentially, as in the case of matched \(V_A\) and \(Q\) (Fig. 5). The \(P_c-P_g\) difference for the inert gases never exceeded 10\% of \(P_g\) over this range of \(V_A\) and \(Q\). Each gas was affected to a different degree depending on their relative solubilities. Figure 7 illustrates the effect of varying \(V_A\) and \(Q\) on \(O_2\) and \(CO_2\). Figure 7A shows minimal effect on the \(P_c-P_g\) difference for \(O_2\) with varying \(V_A\) over a range from 0.1 to 10 times the average ventilation of a terminal alveolar sac \((8.74 \times 10^{-6} ml/s)\) with \(Q\) fixed \((8.33 \times 10^{-6} ml/s)\). Figure 7B shows an 8-fold increase in the \(P_c-P_g\) difference for \(O_2\) with a 10-fold increase in \(Q\). The gradient drops to near zero as \(Q\) decreases to 0.1 its average value. Changes in partial pressure differences of \(CO_2\) with varying \(V_A\) and \(Q\) are shown in Fig. 7, C and D. There is a 3-fold increase in the \(P_c-P_g\) difference for \(V_A\) 10 times its average value, and the gradient drops to near zero with \(V_A\) at 0.1 its average value. The \(P_c-P_g\) difference for \(CO_2\) drops in half with a decrease in \(Q\) but is essentially unchanged with a 10-fold increase in \(Q\). Comparison of the solutions \(10 \times V_A\) and \(0.1 \times Q\) in Fig. 7, A and B, as well as 7, C and D, illustrates that the \(P_c-P_g\) gradient is different for each condition, despite equivalent \(V_A/Q\) ratios.

**DISCUSSION**

Evaluation of model assumptions. We had two specific questions in mind when developing these models of gas exchange in a terminal sac filled with PFC: 1) Do gases that are exchanged in a PFC-containing alveolus reach steady state at usual respiratory rates? 2) How large are the alveolar-arterial differences as a result of diffusion across PFC barriers? Two different models were developed in an attempt to answer these questions. The well-mixed three-compartment model provided a simple approach to estimating time to steady state. Its major assumptions are that neither diffusion times in the PFC nor the geometry of a gas-exchanging subunit significantly affect the solutions. By contrast, our spherically model explicitly incorporated the diffusion gradients and more realistic geometry but, despite major mathematical differences, the results showed very close agreement with the well-mixed compartment model predictions of time to steady state (Table 3).

Both models depict gas exchange in a single terminal alveolar sac. Parameters such as \(Q\), \(V_A\), and \(V_{plc}\) were arrived at by partitioning an equal amount of \(Q\), \(V_A\), and \(V_{plc}\) to all terminal sacs in the lung. The lung is not homogeneous in its distribution of any of these parameters, and application of model results to interpretation of experimental data must be done with this in mind. In reality, there will be a heterogeneous distribution of gas exchange units ranging from completely PFC filled to partially PFC filled to completely gas filled that are ventilated and perfused in some heterogeneous distribution. Measured arterial and expired gas partial pressures are weighted averages of gas exchange subunits. Model predictions of gas exchange in a single terminal sac help us explore the range of possible alveolar \(P_c-P_g\) differences due to diffusion limitation and provide a gross approximation to overall lung arterial-alveolar differences.
Additionally, the choice of a spherical shape of our gas exchange unit to approximate the terminal alveolar sac likely overestimates the diffusion barrier somewhat. A terminal sac is not a smooth sphere but, rather, a cluster of cup-shaped alveoli opening up to a common duct. There are sheets of perfused alveolar-capillary membrane extending inward toward the duct that increase the surface area for exchange and bring those parts of the membrane close to the PFC-gas interface. This would be equivalent to "thinning" the PFC spherical shell in our model and decreasing the $P_c-P_g$ gradient for ventilated units. On the other hand, regions of shunt where $V_A$ is zero probably behave similarly to the model as the PFC pool equilibrates with mixed venous blood and geometry becomes irrelevant.

We feel justified in our choice of inert gas diffusion coefficients on the basis of the fact that the inert gases and CO$_2$ had similar diffusion coefficients in H$_2$O and that all should have increased diffusivity in perfluorocarbon because it is a nonpolar solvent. The rate of diffusion of a molecule through a fluid medium depends on the "effective radius" of the molecule, a function of molecular size and van der Waals interactions with neighboring molecules. Increased $D_{pfc}$ for O$_2$ and CO$_2$ in PFC compared with H$_2$O suggests that the molecules have smaller effective volumes in PFC because of reduced van der Waals interactions. Although there are certain to be discrepancies between the true diffusion coefficients of these gases in PFC and our approximated $D_{pfc}$ model results show little dependence of our time- or space-dependent solutions on diffusive resistance. As we demonstrate, the disparity in $P_c-P_g$ gradients for different gases with the same $D_{pfc}$ (i.e., CO$_2$ vs. ether) supports the conclusion that minor variations in $D_{pfc}$ will not significantly affect our model results.

Time to reach steady state. Of particular interest to us was whether the inert gases used in MIGET would reach steady state during PLV within the time period of our experimental measurements (12, 13). In using MIGET to assess $V_A/Q$ heterogeneity in healthy piglets during PLV, we modified the standard protocol (9, 20) to incorporate a 60-min equilibration period between experimental conditions (15 min is more common). Results from our two models suggest that all gases come to equilibrium well within this time period with the exception of SF$_6$ under shunt conditions (>4 h). We showed this previously and eliminated SF$_6$ from MIGET analyses during PLV (12, 13). The remaining five inert gases reach steady state within the 1-h time frame. The next longest equilibration time was for acetone, which
took ~26 min to come to steady state under “dead space” conditions (Q = 0). Except for one case, O₂ and CO₂ reached steady state in <2 min for the range of possible Vₐ and Q that might exist during PLV. O₂ took 26.6 min to reach steady state under shunt conditions because of the slow delivery rate.

We did not incorporate the periodic nature of Vₐ and Q in our model, but this would be a useful extension. It would be interesting to see if O₂ and CO₂ reach steady state, despite breath-to-breath variations in Pₐ and pulsatile changes in Pₐ that occur over a 2- to 4-s time period. Intuition leads us to think that a gas exchange unit would reach steady state about an average value of Pₐ and Pₚ, filtering out second-to-second fluctuations.

Partial pressure differences at steady state. PFC acts as a mild diffusion barrier for all gases in the steady state, creating a Pₐ-Pₚ difference that increases with volume of liquid in the alveolar space (Fig. 5). Less intuitive is the fact that the partial pressure gradient for each gas is different on the basis of the relative solubility of the gas in blood, PFC, and the gas phase. The presence of a partial pressure gradient in alveoli during steady-state gas exchange has several important consequences. Gas exchange efficiency is reduced with overall arterial-alveolar partial pressure gradients increased compared with healthy gas-filled lung. This impacts gas exchange calculations using formulas derived for the gas-filled lung such as the Berggren shunt, Bohr dead space, and the model underlying MIGET. Each will be in error by an amount proportional to the partial pressure gradient in the alveolus.

The alveolar gas exchange model underlying MIGET (9, 20) assumes no diffusion gradient in the alveolus,

\[ \frac{P_c}{P_{PLV}} = \frac{P_g}{P_{PLV}} = \lambda_1(\lambda_b + V_{A/Q}) \]

This equation compares with our Eqs. 10 and 11, which reduce to this simpler case when P₉ is zero and r₉ equals r (no fluid in the alveolus). There is a variable effect of PFC on the Pₐ-Pₚ difference of each of the five inert gases, with halothane and cyclopropane showing the largest gradients (Fig. 5). However, we have shown through model solution for a wide range of PFC thickness, Vₐ, and Q that Pₐ-Pₚ is very small compared with the driving pressure, Pₑ, for the inert gases, except when alveoli are flooded with PFC. This would lead us to conclude that the more complicated model in this paper is insignificantly different from that underlying the MIGET model, except in the case of flooded alveoli. In this extreme case, MIGET should detect shunt as Pₐ and Pₑ diverge in the same way retention and excretion curves separate at low Vₐ/Q (9, 20). In addition, the smoothing algorithm employed by MIGET to fit an S-shaped curve to measured data points will smooth out the nonsystematic differences in retention and excretion that result from interaction with the PFC.

Further inspection of Eqs. 10 and 11 shows that when PFC is present, differences between Pₐ and Pₑ are a function of solubility in each of the three media: D, Vₐ/Q, and Vₐ independent of Q. This last point is a significant departure from the theoretical framework of MIGET as well as our understanding of Vₐ/Q heterogeneity as it affects gas exchange physiology. Our model shows that Pₐ and Pₑ are dependent on the absolute values of Vₐ and Q during PLV. Figure 7B shows that the Pₐ-Pₑ difference for O₂ is very sensitive to Q (at fixed Vₐ), with the gradient widening when Q is high and becoming negligible when Q is very small. Variation of Vₐ produces little change in the O₂ gradient for given Q (Fig. 7B). Partial pressure differences for CO₂ show the opposite: increasing with high Vₐ, becoming negligible with low Vₐ, and changing little with Q (Fig. 7, C and D). This is similar to gas exchange in gas-filled lungs where Pₐ₂ is sensitive to shunt and arterial PCO₂ (Paco₂) is sensitive to dead space. The difference is that during PLV the absolute value of Vₐ and Q independent of Vₐ/Q will affect overall gas exchange. This may be the most significant pitfall in the use of MIGET during PLV, inasmuch as it does not incorporate this feature in the basic model. The implications are that regions of higher-than-average blood flow will have greater (a-a)DO₂ and those with higher than average ventilation result in larger (a-a)CO₂. Pooling of PFC in dependent regions of lung that receive a greater proportion of blood flow may exacerbate this effect.

Partial pressure gradients of O₂ in the partially PFC-filled gas exchange unit with an inspiratory O₂ fraction of 650 Torr ranges from 1.2 Torr for a 10 ml/kg dose at high lung volumes to 18 Torr for a 30 ml/kg dose at low lung volumes (Fig. 6A). The Pₐ-Pₑ gradient for O₂ is maximal for an unventilated pool of PFC approaching a Pₕ-Pₑ difference of ~600 Torr. The partial pressure differences in ventilated gas exchange units with 10, 20, and 30 ml/kg doses (Fig. 6A) are negligible compared with measured (a-a)DO₂ in piglets during PLV, which ranged from 150 to 320 Torr (14). We concluded that diffusion limitation does not significantly contribute to measured (a-a)DO₂ (or Berggren shunt) in partly PFC-filled, ventilated gas exchange units. It does contribute to the alveolar-arterial gradient in cases where the unit is nearly filled with PFC (Fig. 5, gas radius <50 μm). In this situation, Berggren shunt would reflect true shunt (blood flow to unventilated regions of lung) as well as blood flow to PFC-filled regions of lung. Changes in PFC dosing, ventilator strategies, and patient positioning designed to decrease the population of flooded gas exchange units may help decrease shunt during PLV.

CO₂ shows the greatest degree of disequilibrium at the level of the terminal sac due, in part, to its relative insolubility in PFC compared with blood (Table 2). CO₂ retention has not been a problem during PLV, primarily because of ease of adjustment of ventilation to optimize CO₂ elimination. In our experimental studies we found an increase in PaCO₂ during PLV when holding minute ventilation constant (12–14). Figures 5, 6B, and 7, C and D, illustrate the degree of Pco₂ disequilibrium in the terminal alveolar sac over a range of PFC volumes, lung volumes, and Vₐ and Q. In an “average” gas exchange unit during PLV, the Pₐ-Pₑ gradient for CO₂ was as much as 10 Torr for a 30 ml/kg dose at low lung volumes and <1 Torr for a 10 ml/kg dose at high lung volumes.
volumes (Fig. 6B). Introduction of ventilation heterogeneity broadens the range of partial pressure differences even further with a Pc-Po gradient for CO₂ of 13.2 Torr for a 30 ml/kg dose and Va 10 times larger than average (Fig. 7C). Large airway mixing and heterogeneity of PFC and ventilation distribution will likely produce a global (a-A)DCO₂ somewhere between these extremes. We measured an (a-A)DCO₂ of 12 Torr during PLV with 30 ml/kg PFC in healthy piglets (14). This suggests that diffusion limitation could be responsible for a significant portion of (a-A)DCO₂ in this animal model during PLV.

Dead space ventilation (V₀, ml/min) is classically determined using mass balance and substitution to arrive at the following equation: V₀/VT = (PACO₂ - PECO₂)/PACO₂, where PE CO₂ is expired CO₂. The final form of this equation is arrived at by making the assumption that alveolar P CO₂ (PACO₂) equals PaCO₂, so that each of the terms on the right-hand side of the equation are measurable. This assumption leads to significant overestimation of V₀ when a diffusion gradient exists in the alveolus. For example, in a lung with true V₀ of 10% and (a-A)DCO₂ of 10 Torr (e.g., PACO₂ = 40 Torr and PACO₂ = 30 Torr), substitution of PaCO₂ for PACO₂ results in an estimated V₀/Vₜ of 32% One could argue that the effect of diffusion limitation on (a-A)DCO₂ is equivalent to that of V₀, and we should call this “effective dead space” just as we could call flooded alveoli “shunt” in place of diffusion-limited O₂ exchange. The advantage of thinking about PFC as a diffusion barrier is that maneuvers can be performed to alter its effects, such as decreasing the total volume of PFC given or rotating the subject to redistribute pooled fluid. This may be preferable to increasing VT or RR to decrease “dead space” that predisposes to barotrauma.

Summary. Increased shunt during PLV in healthy animals (12) is due to flooded gas exchange units in which the PFC-gas interface is located in small airways throughout the respiratory cycle. Alveoli that are partly filled with PFC (the air-liquid interface resides inside the terminal sac) do not contribute significantly to measured (a-A)DCO₂. In contrast, any amount of PFC in alveoli causes a significant increase in (a-A)DCO₂ by virtue of the gas’s low solubility in PFC relative to blood. Thus diffusion-limited gas exchange during PLV is an important mechanism of impaired CO₂ elimination and less important for oxygenation.

A very interesting result of our modeling effort was the realization that gas exchange during PLV is dependent on the absolute value of Va and Q, and not simply their ratio Va/Q. This increases the complexity of gas exchange analysis and may be the most important reason why MIGET is not applicable in the analysis of gas exchange during PLV. Further work needs to be done to fully investigate this novel situation.

The results of this modeling effort reflect gas exchange in healthy, uncompromised lungs. In diffuse lung injury, gas exchange is improved during PLV (2, 4, 8, 10, 11) because of the combined effects of reduced surface tension and improved delivery of O₂ to edematous areas of lung. We hope that this study may be used to help optimize the treatment of acute respiratory distress syndrome with PLV by illustrating some of the basic principles and limitations of gas exchange through a fluorocarbon medium. PLV is an exciting new methodology in the treatment of diffuse lung injury, and we hope this modeling effort stimulates further refinement of the technique.

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