Modeling kinetics of infused $^{13}$NN-saline in acute lung injury


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O'Neill, K., J. G. Venegas, T. Richter, R. S. Harris, J. D. H. Layfield, G. Musch, T. Winkler, and M. F. Vidal Melo. Modeling kinetics of infused $^{13}$NN-saline in acute lung injury. J Appl Physiol 95: 2471–2484, 2003. First published August 1, 2003; 10.1152/japplphysiol.00401.2003.—A mathematical model was developed to estimate right-to-left shunt ($F_s$) and the volume of distribution of $^{13}$NN in alveolar gas ($V_a$) and shunt tissue ($V_s$). The data obtained from this model are complementary to, and obtained simultaneously with, pulmonary functional positron emission tomography (PET). The model describes $^{13}$NN kinetics in four compartments: central mixing volume, gas-exchanging lung, shunting compartment, and systemic recirculation. To validate the model, five normal prone (NP) and six surfactant-depleted sheep in the supine (LS) and prone (LP) positions were studied under systemic recirculation. To validate the model, the model accurately describes measured arterial $^{13}$NN kinetics in acute lung injury.

QUANTIFICATION OF GLOBAL right-to-left shunt and the volumes of shunting tissue and alveolar gas is essential to the detailed study of acute lung injury (ALI). Recently, Galletti and Venegas (9) used positron emission tomography (PET) to estimate regional intrapulmonary right-to-left shunt from the lung kinetics of intravenously injected molecular $[^{13}N]$nitrogen ($^{13}$NN). Because of the low solubility of $^{13}$NN in blood, after an intravenous bolus injection at the onset of a period of apnea, most $^{13}$NN diffuses into alveolar gas spaces at first pass through the lung. In the study of Galletti and Venegas, the fast washout of tracer from lung fields during apnea was assumed to be indicative of, and was used to estimate, intrapulmonary shunt. In this study, we seek to provide validation of the theoretical assumptions associated with that method by comparing it with an independent measurement of overall right-to-left shunt obtained simultaneously with the PET imaging data. The independent method is based on the measurement and modeling of arterial $^{13}$NN kinetics after an intravenous bolus injection. $^{13}$NN is well suited for this measurement, given its large elimination into aerated units at first pass and its applicability in PET lung imaging.

Assessment of shunt from intravenously injected low-solubility tracers is not without complication. Reabsorption of tracer from alveolar gas spaces and recirculation have been long recognized as sources of significant inaccuracy in these methods (6, 8, 21, 22, 25). This is particularly critical in conditions of lung injury, because imaging techniques report reduced alveolar volumes and areas of reduced volume-to-perfusion ratios (10, 18, 19), both of which cause increased tracer reabsorption. Thus we expect that, during ALI, the tracer volume of distribution into aerated lung regions is important for accurate estimation of right-to-left shunt. In addition, this volume is physiologically significant, because it represents the effective volume available for distribution of gas eliminated by the pulmonary capillaries. To our knowledge, no estimates of this volume have been made. Although a reduction in alveolar volume during ALI has been demonstrated, the fraction of the remaining alveolar volume that is available for gas exchange has not been established.

The main objective of this study was to develop a method to estimate overall right-to-left shunt and the...
volumes of distribution of $^{13}$ NN in alveolar gas and shunt tissue on the basis of the arterial kinetics of $^{13}$ NN. The method is conceived to be complementary to, and performed simultaneously with, functional imaging of the lung with PET. In addition, we tested the following hypotheses: 1) estimates of total shunt on the basis of the arterial kinetics of $^{13}$ NN correlate with estimates derived from $O_2$ blood concentrations and from PET images, and 2) the alveolar gas volume of $^{13}$ NN distribution estimated from the peripheral kinetics of $^{13}$ NN is equivalent to the alveolar gas volume estimated with PET imaging techniques.

METHODS

Animal Preparation

The study was approved by the Massachusetts General Hospital Subcommittee on Research Animal Care. Eleven sheep were anesthetized, intubated, and mechanically ventilated. General anesthesia was induced with an intravenous bolus of thiopental sodium (30–35 mg/kg) and fentanyl (12.5–25 μg/kg) and maintained with a continuous infusion of thiopental sodium (15–25 mg·kg$^{-1}$·h$^{-1}$) and fentanyl (10–30 μg·kg$^{-1}$·h$^{-1}$). Pancuronium (0.2 mg·kg$^{-1}$·h$^{-1}$) was used for muscle paralysis. Five normal (22 ± 3 kg) and six lung-injured sheep (22 ± 3 kg) were studied. Lung injury was produced with bilateral warmed isotonic saline lung lavage (30 ml/kg) to remove lung surfactant. The solution was produced with bilateral warmed isotonic saline lung lavage (13NN. The method is conceived to be complementary to, and performed simultaneously with, functional imaging of the lung with PET. In addition, we tested the following hypotheses: 1) estimates of total shunt on the basis of the arterial kinetics of $^{13}$ NN correlate with estimates derived from $O_2$ blood concentrations and from PET images, and 2) the alveolar gas volume of $^{13}$ NN distribution estimated from the peripheral kinetics of $^{13}$ NN is equivalent to the alveolar gas volume estimated with PET imaging techniques.

Arterial Tracer Kinetics Model

Overview. The arterial kinetics model consisted of four compartments describing the central blood volume, right-to-left shunt, gas-exchanging, and systemic recirculation (Fig. 1). $^{13}$ NN dissolved in saline was injected into the superior vena cava at an infusion flow rate $Q_i$. The injectant was diluted in the central volume compartment, assumed to be well mixed, with a volume $V_{cv}$, and to be perfused by a continuous and uniform blood flow $Q_T$. This compartment represented tracer mixing between the injection site and the lungs (i.e., superior vena cava, right heart, and major pulmonary arteries) and between the lungs and the sampling site (i.e., major pulmonary veins, left heart, and aorta). Vasculature on both sides of the lung was lumped into a single compartment, because their time constants (volume/blood flow) are similar and, thus, indistinguishable on the basis of the effluent arterial tracer kinetics. The uniform concentration inside this compartment $c_{cv}(t)$ was used as the input for two independent, well-mixed compartments. One compartment corresponded to right-to-left shunt, including completely nonaerated atelectatic and flooded alveolar units and extrapulmonary shunt. This compartment had a volume $V_s$ and a uniform concentration $c_s(t)$ and was perfused by the shunting blood flow $Q_s = F_s'Q_T$, where $F_s$ is the shunt fraction. The other compartment represented gas-exchanging regions, consisting of perfused and aerated alveolar units with a volume $V_A$, uniform concentration $c_A(t)$, and blood flow $Q_A = (1 - F_s)Q_T$. The tracer concentrations in blood leaving the shunting and gas-exchanging compartments were $c_d(t)$ and $λc_A(t)$, respectively, where $λ = 0.0145$ is the $^{13}$ NN blood-gas partition coefficient at $37^\circ$C (20). The perfusion-weighted average of these concentrations represented the tracer concentration in arterial blood $c_{av}(t)$ after a time delay $\Delta t_s$. This time delay accounted for all convective delays between the injection site and the measurement site. The concentration $c_d(t)$, after a time delay $\Delta t_s$, was also used as an input to a recirculation compartment with a volume $V_t$, uniform concentration $c_{tot}(t)$, and blood flow $Q_T$. The time
Fig. 1. Basic features of the model to describe peripheral arterial tracer kinetics. A volume \( V_I \) of \(^{13}\)NN dissolved in saline with tracer concentration \( C_I \) is injected into a central vein at a flow rate \( Q_I \). It is diluted in a central volume compartment with a volume \( V_c \) and concentration \( c_{cv} \). This is the input to the lung region composed of a gas-exchanging compartment with perfusion \( Q_A \), volume \( V_A \) and concentration \( c_A \) and a shunt compartment with perfusion \( Q_s \), volume \( V_s \) and concentration \( c_s \). Perfusion-weighted average of these compartments delayed by \( \Delta t_s \) provides the arterial \(^{13}\)NN kinetics curve \( c_a \). This concentration, delayed by \( \Delta t_r \), is also input to the recirculation compartment with volume \( V_I \) and concentration \( c_{r,I} \). A fraction \( F_s \) of \( c_{r,I} \) is then input into the central volume compartment. \( Q_T \), total blood flow; \( \lambda \), \(^{13}\)NN blood-gas partition coefficient; \( c_{a,s} \), arterial concentration before \( \Delta t_a \) delay; \( c_{a,r} \), arterial concentration after \( \Delta t_a \) delay; \( c_{r,c} \), recirculated activity concentration.

delay \( \Delta t_r \) represented the recirculation time relative to \( \Delta t_a \). A fraction \( F_s \) of \( c_{r,I}(t) \) was used to represent the recirculated concentration \( c_{r,c}(t) \), which was input into the central volume compartment.

**Injection and central volume compartment.** The simulated injected \(^{13}\)NN \((Q_I, C_I)\) was normalized by \( C_I \) and modeled as a step function with an amplitude of 1 and a width of \( V_I/Q_I \). Thus all described concentrations are normalized by \( C_I \). The step function \( (Q_I) \) was input into the central volume compartment. With the use of the law of mass conservation and the assumption of a well-mixed uniform concentration \( c_{cv}(t) \) and constant \( Q_T \), this compartment is described by the first-order differential equation

\[
\frac{d c_{cv}(t)}{dt} = \frac{Q_I}{V_c} + \frac{Q_T}{V_c} [c_I(t) - c_{cv}(t)]
\]

where \( V_c \) is the only unknown, because \( Q_T \) is independently measured.

**Gas-exchanging lung and shunt compartments.** The tracer concentration \( c_{s}(t) \) was input to a shunting tissue and gas-exchanging lung compartment. The shunt compartment is described by

\[
\frac{d c_s(t)}{dt} = \frac{Q_s}{V_s} c_s(t) - \frac{Q_A}{V_s} [c_s(t) - c_A(t)]
\]

where \( \lambda_s \) is the partition coefficient between the blood and shunting units. If we divide by \( V_s \) and assume \( \lambda_s = 1 \), this becomes

\[
\frac{d c_s(t)}{dt} = \frac{1}{\tau_s} [c_{cv}(t) - c_s(t)]
\]

where the shunt compartment time constant \( \tau_s = V_s/Q_s \), and implicitly, \( F_s \) are unknowns. The gas-exchanging compartment is described by

\[
\frac{d c_A(t)}{dt} = \frac{Q_I}{V_I} c_I(t) - \frac{Q_A}{V_A} [c_A(t) - \lambda c_A(t)]
\]

where \( c_A(t) \) represents the \(^{13}\)NN concentration in the gas volume, \(^{13}\)NN alveolar-capillary equilibration is assumed, and \(^{13}\)NN dissolved in the alveolar tissue of the compartment is considered negligible. The tracer concentration in blood leaving the compartment is \( \lambda \cdot c_A(t) \). When solved for the normalized activity leaving the compartment, this equation becomes

\[
\frac{d [\lambda c_A(t)]}{dt} = \frac{1}{\tau_A} [c_{cv}(t) - [\lambda c_A(t)]]
\]

where the time constant of the gas-exchanging compartment \( \tau_A = V_A/(\lambda \cdot Q_A) \) and, implicitly, \( F_s \) are unknowns.

**Arterial sample.** The arterial tracer concentration \( c_{a,t}(t) \) is calculated as the perfusion-weighted average of \( c_s(t) \) and \( \lambda \cdot c_A(t) \) according to

\[
c_{a,t}(t) = \frac{Q_s}{Q_T} c_s(t) + \frac{Q_A}{Q_T} \lambda \cdot c_A(t) = F_s \cdot c_s(t) + (1 - F_s) \cdot \lambda \cdot c_A(t).
\]

This concentration is shifted in time by a delay \( \Delta t_a \) according to

\[
c_{a,t}(t) = c_{a,t}(t - \Delta t_a)
\]

which is then used to simulate the measured arterial kinetics.

**Recirculation.** The arterial concentration entering the recirculation compartment \( c_{a,r}(t) \) is calculated by shifting \( c_{a,t}(t) \) in time by a delay \( \Delta t_r \) according to

\[
c_{a,r}(t) = c_{a,t}(t - \Delta t_r)
\]
This recirculation compartment is described by

\[ V_r \frac{dc_{tot}(t)}{dt} = Q_r c_{a}(t) - \dot{Q}_r c_{tot}(t) \]  

(10)

where \( c_{tot}(t) \) is the total uniform concentration within the compartment. Normalizing by \( V_r \) and rearranging, this becomes

\[ \frac{dc_{tot}(t)}{dt} = \frac{1}{\tau_r} \left[ c_{a}(t) - c_{tot}(t) \right] \]  

(11)

where the time constant of the recirculation compartment \( \tau_r = V_r/Q_r \) is unknown. This compartment describes tracer interactions in the systemic circulation with time constants short enough to significantly influence the measured arterial kinetics. The remainder of the activity is assumed to be absorbed by tissues throughout the circulation or to have delay times greater than the time of measurement. A fraction \( F_r \) of the activity behaved with such short time constants. Thus the recirculated concentration that reached the pulmonary circulation is calculated according to

\[ c_i(t) = F_r \cdot c_{tot}(t) \]  

(12)

This concentration was then used as an input to the central volume compartment described by Eq. 2.

Simulations

The effect of \( F_r, \tau_a, \) and \( \tau_A \) on the arterial tracer kinetics was evaluated by using the developed mathematical model. The corresponding effect on the lung tracer kinetics was studied by using the model developed by Galletti and Vengas (9). Curves from both models were generated by using starting values of \( F_r = 0.25, \tau_a = 10 \text{s}, \) and \( \tau_A = 1,000 \text{s} \). Changes in the curves were studied by using ranges of \( 0 < F_r < 0.75, 5 \text{s} < \tau_a < 20 \text{s}, \) and \( 250 \text{s} < \tau_A < 2,000 \text{s} \). Each parameter was varied in that range, while the remaining two parameters were fixed at the starting values.

Experimental Apparatus

The experimental setup consisted of an automated \(^{13} \text{N} \)N tracer preparation system, PET camera, gamma counter, and in-line blood pump (Fig. 2). \(^{13} \text{N} \)N gas (half-life = 9.97 min) was dissolved in normal saline and injected as a rapid bolus (\( V_i = 23–34 \text{ ml} \) and \( C_i = 0.16–0.49 \text{ mCi/ml} \)) into a central vein at a rate \( Q_i \) of 10 ml/s. The PET camera was a multi-ring full-body camera that imaged a 10-cm cross section of the lung (Scanditronix PC4096, General Electric, Milwaukee, WI). Arterial \(^{13} \text{N} \)N concentration was measured with a peripheral dual-channel gamma counter (Scanditronix, General Electric). Arterial blood was drawn from the right femoral artery at a rate of 10 ml/min (Harvard Apparatus), passed through the gamma counter, and collected in two 60-ml syringes. Flexible polymer tubing (Tygon R-3603) was used throughout the system, except for an 8-inch section of glass tubing for the path through the counter.

Model Parameter Identification

Equations 2, 4, 6–9, 11, and 12 define a system of eight unknowns: \( V_v, F_r, \tau, \tau_A, \Delta t_r, \tau_r, F_r, \) and \( \Delta t_r \). To minimize the number of parameters estimated simultaneously by the optimization routine for each experimental set of arterial kinetics data, a stepwise identification strategy was used and simplifying assumptions were made, as described below. This reduced the number of parameters identified to three (\( F_r, \tau_a, \) and \( \tau_A \)).

Fixed parameters. \( V_v \) was assumed to be 200 ml on the basis of preliminary optimizations. Because of the low shunt in the lavage prone and normal prone conditions, the amount of recirculated tracer activity was considered negligible and \( c_i(t) \) was set to zero. Surfactant-depleted supine sheep exhibited much greater shunt fractions, so the kinetics of recirculated activity were approximated by setting \( \Delta t_r = -4 \text{s}, F_r = 0.493, \) and \( \tau_r = 38 \text{s} \) on the basis of the measurements and calculations described in Appendix A.

Optimization algorithm. The arterial kinetics defined by Eqs. 4, 6, 7, and 8 were simulated using Simulink and Matlab (MathWorks, Natick, MA). \( F_r, \tau_a, \) and \( \tau_A \) were identified by minimizing a weighted square difference (WSD) between the normalized kinetics simulated by the model (\( c_a \)) and the kinetics measured by the gamma counter (\( c_m \)). The WSD was defined by

\[ \text{WSD} = \sum_{i=1}^{N} \left[ (c_a(i) - c_m(i))^2 c_m(i) \right] \]  

(13)

where \( N \) is the total number of measured data points and each squared difference was weighted by \( c_m \). This provided more weight to the peak of the kinetics curve, which is the portion of the curve most closely related to the shunt fraction. Because of the nonlinear nature of the model, a global optimization routine was used to find the parameter set that minimized the WSD. The specific routine utilized was the multilevel coordinate search, developed by Huyer and Neu maier (15). The routine is an intermediate between a heuristic method (i.e., stochastic methods) and a deterministic method (i.e., branch and bound methods) and was chosen.
because it was written in Matlab, was easily amendable, and was shown to accurately identify global minima in a variety of conditions. The optimization was performed five times by using a range of sampling delays (\(\Delta t\)), including a value visually estimated from the arterial curve and four values defined as 1 and 2 s shorter and longer than the visual estimate. The parameter set that resulted in the lowest WSD was chosen as the final solution.

**Initial conditions and parameter bounds.** Parameter bounds of 0 \(\leq F_s \leq 1\), 1 s \(\leq \tau_s \leq 20\) s, and 20 s \(\leq \tau_A \leq 2,000\) s were used. Initial values of \(\tau_s\) and \(\tau_A\) were set to 10 and 500 s, respectively. To estimate an initial value for \(F_s\), linear regression was used to find the empirical relation between the shunt measured by the \(O_2\) method (\(F_o_{2,\text{O}_{2}}\) see Shunt Calculations) and the maximum normalized measured arterial concentration (\(C_{m,\text{max}}\)) from the experiments. The relation (\(F_o_{2,\text{O}_{2}} = 29.6 - C_{m,\text{max}} + 0.01\)) was then used along with \(C_{m,\text{max}}\) to make the initial \(F_s\) estimate.

**Optimization Accuracy**

Accuracy of parameter identification was evaluated with a Monte Carlo analysis. The mean identified \(F_s\), \(\tau_s\), and \(\tau_A\) in the lavage supine, lavage prone, and normal prone conditions were used to simulate noise-free kinetics curves. Noise was assumed to be normally distributed with a zero mean and a standard deviation that, for each experimental group, was estimated by the standard deviation (\(\sigma_{\text{noise}}\)) of the point-by-point difference \(c_m - c_a\) from all experiments within the group. Noise was added to each simulated data point by selecting a random number first from this distribution and then from a distribution with a standard deviation equal to 3\(\sigma_{\text{noise}}\). The mean and standard deviation of identified parameters, correlation coefficients between the original noise-free and simulated data, and residuals were calculated for 100 simulations at both noise levels. Recirculation parameter values were fixed to the values identified in APPENDIX A for the analysis with the mean parameters from the lavage supine condition, whereas recirculation was excluded for the analysis with the mean parameters from the lavage prone and normal prone conditions. Initial values were set as described in Initial conditions and parameter bounds.

Sensitivity to the fixed values of \(V_{\text{cv}}\), \(\tau_s\), and \(F_s\) was evaluated by performing the parameter identification when each of the values was changed by \(\pm 12.5\%\). Because recirculation was not considered in the analysis of the lavage prone and normal prone conditions, only the experiments from the lavage supine condition were used to evaluate \(\tau_s\) and \(F_s\). Mean identified values of \(F_s\), \(\tau_s\), and \(\tau_A\) were then compared with those found using the assumed values of \(V_{\text{cv}} = 200\) ml, \(\tau_s = 38\) s, and \(F_s = 0.493\).

**Shunt Calculations**

Arterial and mixed venous blood gases taken before each emission imaging sequence were used to calculate the \(O_2\) shunt fraction for the surfactant-depleted sheep and the venous admixture for the normal sheep, both of which will be noted as \(F_o_{2,\text{O}_{2}}\). Samples were taken from the pulmonary artery and right femoral artery. \(P_{O_2}\), \(P_{CO_2}\), and \(pH\) were measured with a rapid blood-gas analyzer (model ABL5/BPH5, Radiometer Medical, Copenhagen, Denmark). These values were used to calculate the arterial and venous \(O_2\) saturation fractions on the basis of an \(O_2\) dissociation curve for sheep (33). Total hemoglobin content was measured with a hemoximeter (model OSM3, Radiometer Medical). The lung model developed by Galletti and Venegas (9) was used to estimate the shunt fraction (\(F_s,\text{PET}\)) on the basis of the \(^{13}\text{NN}\) pulmonary kinetics.

**Aerated Lung Volume of Distribution**

Fractional gas content (\(F_{\text{gas}}\)), representing the fraction of the volume of a voxel (\(V_{\text{vox}}\)) occupied by gas, was calculated from the transmission scan, as previously described (5, 12, 35). The total imaged gas volume of the lung was then calculated as \(V_{\text{gas}} = V_{\text{vox}} \cdot \sum n (F_{\text{gas}})\), where \(n\) is the number of voxels within the imaged lung field. The volume of gas participating in exchange with pulmonary blood was estimated from the modeling results as \(V_A = \tau_A \cdot \lambda \cdot Q_A\). This volume was scaled by the estimated fraction of imaged lung gas volume (\(F_A\)) to compare it with \(V_{\text{gas}}\). To estimate \(F_A\), it was assumed that the volume-to-perfusion ratio (\(V_{\text{cv}}/Q_{\text{cv}}\)) was the same in the imaged and nonimaged lung. \(F_A\) was then calculated as the ratio of the peak activity in the lung kinetics measured by the PET camera, assumed to be proportional to the blood flow to the imaged region, to the total injected activity, assumed to be proportional to \(Q_{\text{FT}}\).

**Shunt Volume of Distribution**

The volume of distribution of \(^{13}\text{NN}\) in shunting blood and tissue was calculated from the modeling results as \(V_s = \tau_s \cdot Q_s\). This volume was scaled by \(F_s\) for comparison with the total imaged tissue volume, calculated as \(V_{\text{tis}} = V_{\text{vox}} \cdot \sum n (1 - F_{\text{gas}})\).

**Statistical Analysis**

Least-squares linear regression was used to estimate all regression relations. Student’s \(t\)-test for paired data was used to assess differences between the lavage supine and lavage prone conditions, and an unpaired Student’s \(t\)-test was used to assess differences between the surfactant-depleted (lavage supine and lavage prone conditions) and normal sheep. Values are means \(\pm SD\).

**RESULTS**

**Simulations**

In the absence of shunt, simulated arterial and lung tracer kinetics during apnea showed increasing activity converging to a plateau (Fig. 3, A and D). The presence of shunt produced marked changes in tracer kinetics. As shunt increased, a prominent early peak was followed by a monotonic decrease toward a plateau. In the lung kinetics, this peak was primarily caused by decreasing plateau activities with increasing shunt; in the arterial kinetics, the peak was caused by rising peak activities with increasing shunt. Changes in \(\tau_s\) affected the arterial kinetics more markedly than the lung kinetics (Fig. 3, B and E). Increases in \(\tau_s\) slightly raised the peak of the lung kinetics and caused a slower decrease from the peak toward the plateau. In contrast, increasing \(\tau_s\) caused a marked decrease in the height and an increase in the width of the arterial kinetics peak. Changes in \(\tau_s\) had the least effect on the lung and arterial kinetics (Fig. 3, C and F), inasmuch as decreases in \(\tau_s\) caused a slightly greater decline in the lung kinetics plateau and a small rise in the arterial kinetics curve.
Experimental Studies

Saline lung lavage caused deterioration of gas exchange, particularly in the supine position (Table 1). F_{so2} was markedly higher for this condition than for normal and surfactant-depleted prone sheep ($P < 0.01$). Consequently, PaO_2 was significantly lower in the surfactant-depleted supine than in the surfactant-depleted prone sheep ($P < 0.01$). Furthermore, although venous admixture, rather than shunt, was measured in the normal prone sheep, F_{so2} values for this group were clearly lower than those in the surfactant-depleted groups. No change in cardiac output was observed for the different conditions. Consistent with these physiological observations, the transmission scans showed less aeration in the surfactant-depleted supine sheep than in the normal and surfactant-depleted prone sheep ($P < 0.01$).

Table 1. Physiological measurement for normal prone, lavage supine, and lavage prone sheep

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Prone ($n = 5$)</th>
<th>Lavage Supine ($n = 6$)</th>
<th>Lavage Prone ($n = 6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F_{so2}</td>
<td>0.02 ± 0.03</td>
<td>0.46 ± 0.17*</td>
<td>0.08 ± 0.07‡</td>
</tr>
<tr>
<td>F_{Io2}</td>
<td>0.26 ± 0.04</td>
<td>1.00 ± 0.00</td>
<td>1.00 ± 0.00</td>
</tr>
<tr>
<td>P_{aO2}, Torr</td>
<td>140 ± 37</td>
<td>92 ± 37*</td>
<td>584 ± 86</td>
</tr>
<tr>
<td>P_{aCO2}, Torr</td>
<td>35 ± 3</td>
<td>50 ± 6</td>
<td>40 ± 4</td>
</tr>
<tr>
<td>pH</td>
<td>7.49 ± 0.04</td>
<td>7.26 ± 0.07</td>
<td>7.34 ± 0.06</td>
</tr>
<tr>
<td>Qt, ml/s</td>
<td>49 ± 13</td>
<td>51 ± 17</td>
<td>48 ± 11</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$, number of sheep. F_{so2}, calculated O_2 shunt; F_{Io2}, inspired O_2 fraction; P_{aO2} and P_{aCO2}, arterial P_{O2} and P_{CO2}; Qt, cardiac output. *$P < 0.01$ vs. lavage prone; †$P < 0.01$ vs. normal prone and lavage prone; ‡$P < 0.1$ vs. normal prone.
peaks were more prominent in the lavage supine than lavage prone condition and in the arterial than lung kinetics. The peak for the arterial tracer kinetics was 10 times larger in the lavage supine condition (Fig. 5F) than in the lavage prone condition (Fig. 5E).

In all cases, the model of arterial kinetics was able to accurately describe the measured data, as evidenced by high correlation coefficients ($r^2$) and low residuals ($R$; Table 2). Identified $F_s$ values were significantly higher for the lavage supine than lavage prone and normal prone conditions ($P < 0.01$). Also, $F_s$ was higher for the surfactant-depleted prone than normal prone sheep ($P < 0.05$). Identified $\tau_A$ values were significantly lower for the lavage supine than lavage prone and normal prone conditions ($P < 0.01$).

The Monte Carlo analysis demonstrated that the identification algorithm was able to accurately estimate $F_s$, $\tau_s$, and $\tau_A$. The mean values of these parameters from the 100 simulations were within 3% of the true values at the observed noise level ($\sigma_{\text{noise}}$) for the experimental data (Table 3). Furthermore, the parameters were identified within 17% of the true values at the exaggerated noise level ($3 \cdot \sigma_{\text{noise}}$).

Sensitivity analyses using data from the lavage supine condition revealed that $\tau_A$ was the most sensitive parameter to changes in the assumed values for $V_{cv}$, $F_r$, and $\tau_r$ (Fig. 6). Estimates of $F_s$, $\tau_A$, and $\tau_r$ for normal and surfactant-depleted prone sheep were less sensitive to changes in $V_{cv}$, with the mean $F_s$ remaining unchanged, the mean $\tau_s$ being identified within 14%, and the mean $\tau_A$ being identified within 4% of the true value for changes in $V_{cv}$ of $\pm 12.5\%$.

Estimates of $F_s$ were correlated with $F_{sO_2}$ ($r^2 = 0.85$, $n = 11$, $P < 0.01$) and with $F_{s,PET}$ ($r^2 = 0.82$, $n = 11$, $P < 0.01$; Fig. 7). The bias in $F_s$ was $0.01 \pm 0.11$ relative to $F_{sO_2}$ and $0.01 \pm 0.12$ relative to $F_{s,PET}$. The relations between these parameters were described by $F_s = 1.11 \cdot F_{sO_2} - 0.01$ and $F_s = 0.69 \cdot F_{s,PET} + 0.06$.

(V_A \cdot F_L)/V_{gas}$, representing the fraction of the available gas volume participating in gas exchange, was significantly lower in the lavage supine condition (0.18 $\pm 0.09$) than in the lavage prone (0.96 $\pm 0.28$) and normal prone (1.28 $\pm 0.30$) conditions ($P < 0.01$). In addition, $(V_s \cdot F_L)/V_{tis}$, representing the volume of $^{13}$NN distribution as a fraction of blood and tissue in the lung, was significantly higher in the lavage supine condition (0.46 $\pm 0.26$) than in the lavage prone (0.05 $\pm 0.08$) and normal prone (0.02 $\pm 0.03$) conditions ($P < 0.01$).

DISCUSSION
In this study, we developed a mathematical model to estimate overall right-to-left shunt and volume of dis-
tributions of $^{13}$NN in alveolar gas and shunt tissue on the basis of the arterial kinetics of $^{13}$NN after an intravenous bolus injection. The measurement is complementary to, and performed simultaneously with, PET imaging, thus allowing concurrent estimates of intrapulmonary shunt and lung gas volume. The main findings of this study were as follows: 1) the developed mathematical model provided accurate descriptions of experimental arterial $^{13}$NN kinetics measurements; 2) estimates of shunt derived from the model correlated well with estimates derived from O$_2$ blood concentrations and from PET imaging; and 3) the volume of distribution for $^{13}$NN in alveolar gas was equivalent to the total lung gas volume assessed from PET transmission scans in normal lungs and surfactant-depleted prone lungs. However, the volume of distribution was significantly smaller than the available gas volume in surfactant-depleted supine lungs.

**Simulations**

In the presence of shunt, lung and arterial kinetics curves during apnea were characterized by two distinct portions (Fig. 3): an early peak and a subsequent plateau. A peak in lung kinetics is a manifestation of intrapulmonary shunt, whereas a peak in arterial ki-
netics is a manifestation of overall right-to-left shunt, including extrapulmonary shunt. The lung kinetics plateau corresponds to tracer that diffuses into and remains in alveolar gas spaces. The plateau in arterial kinetics corresponds to tracer that is reabsorbed by the pulmonary circulation.

Our numerical simulations showed that the model parameters ($F_s$, $\tau_s$, and $\tau_A$) had markedly different effects on lung and arterial tracer kinetics. Increased $F_s$ leads to decreased plateau values in the lung kinetics and increased peak values in the arterial kinetics. The peak in relation to the plateau was larger in the arterial kinetics because of the low blood-gas partition coefficient of $^{13}$NN, which reduced the relative influence of the gas-exchanging compartment on the arterial kinetics. Thus arterial kinetics were more sensitive than lung kinetics to changes in $F_s$.

The shunt time constant $\tau_s$ reflects the amount of blood and tissue in the shunting compartment per unit of shunting blood flow. Consequently, as $\tau_s$ increased, the arterial kinetics showed lower peaks with prolonged time to reach a plateau, and the lung kinetics showed a slower decrease in activity from peak to plateau. Because of the greater relative influence of shunted activity on the arterial kinetics, $\tau_s$ affected the arterial kinetics more than the lung kinetics.

$\tau_A$ had the least effect on lung and arterial kinetics. Decreases in $\tau_A$ reflect decreases in $V_G/Q$ of aerated lung units. As $V_G/Q$ decreases, more tracer will be reabsorbed from alveolar gas spaces and measured arterially (6, 21). The relative decrease in activity near the end of apnea in the lung kinetics due to such reabsorption was small. Changes in $\tau_A$ were less marked on the arterial kinetics because of the relatively smaller influence of the aerated regions.

**Method and Model Critique**

Because of the large number of parameters and the nonlinear nature of the model, a global search for an...
optimum solution using all eight unknowns leads to multiple local solutions and consequent nonuniqueness in parameter identification. For this reason, we used a stepwise identification strategy and made the following simplifying assumptions to minimize the number of parameters and allow for a single, robust solution. 1) We used a compartmental approach with lumped parameters to model arterial $^{13}$NN kinetics and to estimate the model parameters. Compartmental models, despite their limitations (40), have been traditionally used to describe arterial tracer kinetics and to estimate right-to-left shunt and cardiac output (9, 11, 31, 37). The small residuals of the parameter estimation obtained in all cases with our model and the results of the Monte Carlo simulation showing robustness of identification corroborate the use of the compartmental model. Models with distributed parameters could be conceptually applied to this study. However, the complexity of the pulmonary and systemic circulation and the impracticality of describing their geometry and other physical properties in individual animals would increase the number of variables and involve additional assumptions, thus limiting the application of the model for parameter identification, an essential component of this study. 2) The mean convective transit time delays through shunting and gas-exchanging regions were assumed to be equal ($\Delta t_e$). This is a reasonable assumption, provided that large fistulas between major pulmonary vessels or direct right-to-left shunts in the heart were not present (8). 3) Transit time heterogeneity due to distributions in capillary geometry and flow (1, 2) and axial diffusion were not included in the model. The overall effect on the identified parameters would correspond to an increase in the volumes of distribution. 4) A single mixing compartment with a fixed volume ($V_{cv}$) was used to represent tracer dispersion between the injection site and the lungs and between the lungs and the gamma counter. Although a more anatomically realistic representation would include separate compartments to account for mixing before and after passage through the lungs, the time constants of each portion would be of the same order of magnitude and, thus, difficult to discriminate on the basis of the arterial kinetics. 5) For the surfactant-depleted supine sheep, recirculated tracer was modeled by using a single mixing compartment and convective delay to represent the systemic circulation (see Appendix A). The single compartment and delay were shown to accurately describe the measured venous kinetics. In cases with substantial right-to-left shunt, modeling recirculation is necessary for accurate description of arterial tracer kinetics and parameter identification. In the study of a general case, the significance of shunt can be determined from a variety of sources, such as visual inspection of the arterial or pulmonary tracer kinetics, pulse oximetry, and arterial and mixed venous blood gas measurements.

The Monte Carlo analysis indicated that all parameters were identified exactly for the noise-free simulation. Parameter identification remained accurate at the observed levels of experimental noise. Even in the presence of exaggerated noise, parameters were identified within $\sim$20% of their true values. The largest residuals corresponded to the portion of the curve immediately before the peak region (Fig. 5), where the simulated kinetics rose sharply while the measured kinetics initially rose slowly. This slow rise was due to dispersion mechanisms not accounted for in the model, such as transit time heterogeneity, axial mixing, and multicompartment behavior.

The model was able to accurately describe measured arterial $^{13}$NN kinetics by including the effects of tracer reabsorption and, in surfactant-depleted supine sheep, recirculation. Previous attempts to estimate physiological parameters on the basis of arterial tracer sampling presented significant variability in humans (16, 25) and animals (6, 16, 25) in conditions with less lung injury than in our study. As discussed below, variability in shunt estimates is expected to be highest for measurements made in an ALI model because of the greater contribution of factors such as tracer reabsorption and recirculation. Nevertheless, the variability in $F_s$ derived from the arterial tracer kinetics model was of the same order of magnitude as that reported in the literature. This suggests that accounting for tracer
reabsorption and recirculation in our modeling allowed for the recovery of reasonable estimates of physiological parameters under the most unfavorable conditions.

Estimation of Physiological Parameters

**Shunt fraction.** Previous measurements of shunt using arterial samples of low-solubility tracers (krypton, tritium, xenon, and nitrogen) reported significant limitations because of tracer reabsorption (“backpressure”) and recirculation (8, 16, 21, 22, 25). ALI is a condition associated with low \( V_G/Q \), which causes greater reabsorption, and increased shunt, which causes greater recirculation. Various methods, such as tracer rebreathing to estimate the amount of reabsorption (25) or diversion of recirculated blood (6), proved to be inaccurate or impractical. For the steady-state situation, the use of SF6, a gas with one-third the solubility of nitrogen, has been shown to yield the best estimates of shunt (13, 14). However, use of SF6 as a tracer does not allow for simultaneous PET imaging, and because SF6 is so insoluble, the time necessary to reach steady-state conditions (>20 min) (39) is much longer than the 60 s of apnea during which the PET and arterial \(^{13}\)NN kinetics measurements were made. Measurement of \( O_2 \) shunt is not affected by backpressure or recirculation, but breathing 100% \( O_2 \) may alter the physiological state by changing ventilation and perfusion distributions and causing \( O_2 \) absorption atelectasis (6, 13, 16). Our method of measuring shunt by modeling arterial \(^{13}\)NN kinetics has the advantages that recirculation and reabsorption are accounted for, that \(^{13}\)NN does not affect pulmonary physiology in the concentrations used here, and that it can be performed simultaneously with PET imaging of the lung.

Differences are expected between \( F_s \) and \( F_sO_2 \), because they assess different anatomic pathways and are based on different physiological maneuvers (13). \( F_sO_2 \) assesses the contribution of unsaturated blood to the arterial blood. It is affected by extra- and postpulmonary shunts through bronchial veins, thebesian veins, anterior cardiac veins, and portal-pulmonary venous anastomoses. In contrast, \( F_s \) measures the fraction of the pulmonary blood flow that does not encounter aerated alveoli. Another important potential source of differences is the recently described oscillation in \( PaO_2 \) throughout the respiratory cycle (3). Baumgardner et al. (3) presented evidence of cyclic recruitment of atelectasis in a rabbit model of ALI. With prolonged sampling of blood gases, such oscillations should not affect \( F_sO_2 \), because blood is sampled over several breathing cycles. In contrast, the described \( F_s \) measurement is performed during apnea at mean airway pressure and, thus, could be biased, particularly if apneic airway pressure does not result in a shunt equivalent to the mean shunt during the breathing cycle. Variations in the lung volume during apnea could add further bias to \( F_s \). There are no data at this time on the dynamic relation between airway pressures and right-to-left shunt. A possible source of overestimation of \( F_s \) is that regions of very low \( V_G/Q \) were identified as shunt. The amount of measured arterial tracer concentration is inversely related to \( V_G/Q \) (6, 21). In this study, shunting and gas-exchanging regions were arbitrarily defined on the basis of their time constants. The lower limit for \( \tau_A \) and upper limit for \( \tau_s \) were set at 20 s, corresponding to \( V_G/Q = 0.3 \) s (e.g., a unit with \( V_G = 3 \) ml and \( Q = 10 \) ml/s = 600 ml/min). Regions with \( V_G/Q < 0.3 \) s were identified as shunt. Other potential sources of error are the relative instability of physiological condition for severe lung injury and \( PO_2 \) electrode-based errors (13, 32). Despite these differences, our estimates of \( F_s \) were significantly correlated with \( F_{sO_2} \) with a mean bias of 1%. This confirms that \( F_s \) provides an estimate of right-to-left shunt.

\( F_s \) an estimate of the overall right-to-left shunt, approximated \( F_s^{PET} \), the intrapulmonary shunt assessed from PET, in most cases (Fig. 7). This supports the previous theoretical assumption that the initial fast drop in tracer activity during the apneic phase measured by PET corresponded to intrapulmonary shunt (9). Differences between \( F_s \) and \( F_s^{PET} \) may be attributed to extrapulmonary shunt or intrapulmonary shunt in regions outside the limited imaging field of our camera, in addition to experimental error and/or noise. Given that the imaging field does not include the entire lung, intrapulmonary shunt is only partially quantified with \( F_s^{PET} \). The fact that \( F_s \) and \( F_s^{PET} \) were well correlated and did not show any bias indicates that the imaged lung was a reasonable representation of the total lung. Future studies using full-body cameras, which are currently available, will provide a complete assessment of intrapulmonary shunt and, thus, allow, in theory, for estimates of extrapulmonary shunt. Availability of these cameras will also permit the development of more robust mathematical models describing the lung and arterial kinetics simultaneously.

**Shunt volume of distribution.** In the absence of extrapulmonary shunt, \( V_s \) corresponds to the volume of tissue, intra- and perialveolar fluids, and capillary blood into which \(^{13}\)NN carried by shunting blood distributes during the pulmonary transit. Although this study was not designed to assess the factors contributing to changes in the magnitude of \( V_s \), we can speculate that the parameter should increase, not only with the number of shunting alveolar units, as in “dry” reabsorption atelectasis, but also with the degree of alveolar flooding and/or lung edema of those units. If one assumes that the volume of tissue per unit of lung in the imaged region is representative of the whole lung, then \( V_s \) multiplied by the imaged lung fraction \( (F_L) \) should scale with the imaged intrapulmonary tissue volume \( (V_{Is}) \). In an attempt to account for the variability of \( V_s \) due to the extent of the lung injury, we calculated \( (V_s\cdot F_L) / V_{Is} \). \( (V_s\cdot F_L) / V_{Is} \) was significantly higher in our surfactant-depleted supine sheep than in surfactant-depleted prone sheep or normal sheep. This means that, in the supine position, a greater fraction of the intrapulmonary tissue was involved in shunt. We take this speculation with caution, because the sensitivity of the model to \( \tau_s \) and, thus \( V_s \), varies proportion-
ally to $F_s$. Thus, in situations where $F_s$ is high and the estimation of tissue shunting volume is relevant, the model has its highest sensitivity to $\tau_a$. On the other hand, in the limiting case of $F_s$ approaching zero, the simulated kinetics become totally insensitive to $\tau_a$. This probably explains the much greater variability of $(V_A \cdot F_L)/V_{gas}$ in the normal and surfactant-depleted sheep in the prone position that had substantially less shunt. 

Aerated lung volume of distribution. $V_A$ corresponds to the volume of alveolar gas in which the $^{13}$NN distributes during its transit through the lung. The volume of gas in unperfused units (alveolar dead space) or in conducting airways should not contribute to $V_A$. If alveolar gas volume and blood flow were homogeneously distributed within the lung, ignoring the small contribution of the conducting airways, $V_A \cdot F_L$ would scale with the imaged intrapulmonary gas volume ($V_{gas}$). Consistent with this theory, the average $(V_A \cdot F_L)/V_{gas}$ was around unity in normal and surfactant-depleted prone sheep. In contrast, in surfactant-depleted supine sheep, this ratio was $<$0.2. This means that, in the supine position, only 20% of the available intrapulmonary gas participated in gas exchange. Thus our findings suggest that, in addition to the reported reduction in total gas volume and functional residual capacity during lung injury (10, 18, 19), there is also a reduction in the fraction of that volume effective in gas exchange. A corollary to this observation is that the volume of intrapulmonary gas, assessed with imaging techniques, may overestimate the true volume of gas participating in gas exchange during ALI.

Although $\tau_a$ was sensitive to measurement error, the Monte Carlo simulations indicated that experimental error would not explain the fivefold discrepancy between $V_A \cdot F_L$ and $V_{gas}$ in the supine position compared with the prone position. One possible explanation for this discrepancy could be that because of the use of 100% O$_2$ inspired gas, mean alveolar volume was reduced as a result of rapid formation of reabsorption atelectasis during apnea. In APPENDIX B, evidence is presented that this is not the case. Another explanation could be that the mean alveolar volume could have been higher during breathing than during apnea because of the nonlinear shape of the pulmonary system pressure-volume curve. However, this is unlikely, because apnea occurred at a pressure equal to the mean airway pressure during breathing, resulting in a reduced number of collapsed units compared with the number of units that collapsed at the end of exhalation. Alternatively, fluid menisci could have formed intermittently, reducing the gas volume available for diffusion of $^{13}$NN. Further study of the dynamic relation between airway pressure and lung volume is necessary to substantiate these proposed explanations. Another potential explanation for the discrepancy could be the presence of substantial heterogeneity in local $V_C/Q$. Mismatch of local $V_C/Q$ would result in a lower global $V_C/Q$ than that computed from the ratio of imaged gas to pulmonary perfusion. However, estimates of blood flow-weighted $V_{gas}$ from our images minimally reduced the discrepancy between $V_A \cdot F_L$ and $V_{gas}$ for the supine position. This suggests that, if responsible for the discrepancy, the heterogeneity in local $V_C/Q$ must have occurred at a finer length scale than the imaging resolution of PET.

Other experimental and methodological considerations are expected to be less likely: 1) $F_s$ was overestimated; because $V_A = \tau_a \cdot (1 - F_s) \cdot \lambda \cdot Q_T$, an overestimation of $F_s$ results in an underestimate of $V_A$. 2) $V_{CV}$ was overestimated; overestimation of $V_{CV}$ causes an underestimate in $\tau_a$ (Fig. 6) and, consequently, $V_A$. 3) The larger percentage of conducting airways contributed to the total estimated aerated volume in the supine compared with the prone position. 4) $F_L$ was underestimated; calculation of $F_L$ was based on the assumption that $V_C/Q$ of the imaged lung represented that of the whole lung. If the imaged perfusion fraction were less than the imaged aerated volume, $F_L$ would be underestimated.

Summary

A method was developed to estimate the overall right-to-left shunt and the volume of distribution of $^{13}$NN tracer in alveolar gas and shunt tissue on the basis of measured arterial kinetics of $^{13}$NN after an intravenous bolus injection. A mathematical model describing arterial tracer kinetics was developed that accounted for tracer reabsorption and recirculation. The model accurately fit experimental data from normal and surfactant-depleted sheep studied in prone and supine positions. The main conclusions of this study are as follows: 1) estimates of shunt derived from the model correlated well with estimates obtained from blood gas sampling and with estimates obtained by PET imaging, and 2) the volume of distribution of $^{13}$NN in perfused and aerated alveolar units was equivalent to PET-measured total lung gas volume in normal and surfactant-depleted prone sheep. However, in surfactant-depleted supine sheep, that volume of distribution was substantially smaller than the available intrapulmonary gas volume.

APPENDIX A

To describe recirculation, 1-ml venous blood samples were collected every 30 s from the left femoral vein during the course of four emission-imaging sequences of surfactant-depleted sheep (2 each in the supine and prone positions). The concentration of these samples was determined with a well counter and standard gamma counting techniques. The arterial tracer kinetics were measured simultaneously with the peripheral gamma counter of the PET camera. The arterial kinetics were then used as an input to a model consisting of a single mixing volume described by Eqs. 9, 11, and 12. The recirculation parameters $\Delta t$, $F_r$, and $\tau_a$ were identified by finding the set of values that minimized the squared difference between the simulated and measured venous tracer kinetics. This was done by first incrementally setting $\Delta t$ (relative to $\tau_a$) from $-5$ and $+5$ s and then using the multilevel coordinate search optimization program (15) to find the best $F_r$ and $\tau_a$ for each value of $\Delta t$. The parameter set that yielded the least overall squared difference among the four sets of data was then used to describe the venous
kinetics of all surfactant-depleted sheep in the supine position. That parameter set of $t_r,F_r,$ and $\tau_r$ was 4 s, 0.493, and 38 s, respectively. With the use of these values, the model was able to simulate the measured venous kinetics (Fig. 8). The parameters $t_r,F_r,$ and $\tau_r$ are descriptive of the animal’s peripheral circulation and tissues. Thus they are expected to change in different species, sizes, and disease conditions.

**APPENDIX B**

The volume of distribution of $^{13}$NN in lung gas spaces was assessed by modeling the arterial $^{13}$NN kinetics during 60 s of apnea after a bolus intravenous injection. This volume was substantially smaller than that assessed from PET transmission scans. To rule out the possibility of rapid lung volume changes during the apneic period due to dynamic processes such as absorption atelectasis, we analyzed an additional series of PET images that were also acquired during the experiment. For these images, a mechanical ventilator coupled with two breathing circuits was utilized as previously described (36). The breathing system was designed to allow volume-controlled ventilation with fresh gas or with gas from a closed rebreathing circuit. The closed rebreathing circuit included a CO$_2$ absorber and a servo-controlled supplemental O$_2$ source to replace metabolic O$_2$ consumption and maintain a constant circuit volume. Remotely controlled solenoid valves allowed switching between the two breathing circuits. This system maintained a constant breathing pattern irrespective of the circuit being used. The PET scans consisted of ventilating the lungs with the closed rebreathing circuit containing $^{13}$NN-labeled gas. PET images were first acquired during a wash-in equilibration phase. Then ventilation was stopped during exhalation, and the airway was maintained at a pressure equal to mean airway pressure, previously measured during tidal breathing. After a series of scans during apnea, the inhaled gas was switched to tracer-free gas, and ventilation was resumed while imaging continued. The imaging and lung volume history during this protocol were therefore identical to those followed during intravenous tracer infusion scans. Because of the low solubility of nitrogen in body fluids and tissues, at the end of the wash-in equilibration period and throughout the apneic period, $^{13}$NN was mostly confined to air spaces within the lungs. Thus, after equilibration, the tracer concentration in the lungs was proportional to the regional gas content. These scans have been shown to correlate well with estimates made from transmission scans (34). The nearly constant relative gas content estimates in three regions of interest of equal height (Fig. 9) suggest that lung volume remained constant or may have even been slightly recruited in some regions during apnea. This finding is evidence against the argument that reabsorption atelectasis was responsible for the discrepancy between $V_A$ and $V_{gas}$. This is consistent with evidence that atelectasis is minimized by the use of PEEP (27) and with theoretical (17) and experimental (30) evidence estimating the time course of absorption atelectasis in preoxygenated lungs to be on the order of several minutes. We conclude that dynamic processes such as absorption atelectasis during

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**Fig. 8.** Set of measured arterial (solid line), measured venous (■), and simulated venous (dashed line) kinetics data for a surfactant-depleted supine sheep in which recirculation fraction ($F_r$) = 0.493, time constant ($\tau_r$) = 38 s, and delay ($t_r$) = -4 s.

**Fig. 9.** Representative $^{13}$NN kinetics from equilibration wash in, 60 s of apnea, and subsequent washout for nondependent (■), middle (▼), and dependent (●) regions normalized by mean activity in nondependent region during apnea. After equilibration and during apnea, tracer concentration in lungs is proportional to regional gas content. Gas content remains constant in nondependent and dependent regions and rises slightly in middle region during apneic period. Dashed lines, mean gas contents for each region estimated from transmission scans. Note similarity between gas contents estimated by the 2 methods.
the 60 s of apnea cannot explain differences between the aerated volumes estimated using the arterial kinetics and transmission scans.

DISCLOSURES

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