Quantification of Pulmonary Physiological Parameters for use with Positron Emission Tomography

by

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Abstract

Knowledge of the dead space breathing volume is important in order to insure that mechanical ventilation is sufficient and to standardize experimental conditions. Measurement of the dead space at various time points within an experimental protocol provides useful information in elucidating the meaning and possibly the cause of other physiologic changes. Therefore, a system has been developed to measure the dead space volume in real-time for mechanically ventilated subjects. Calculations were made using an algebraic implementation of Fowler's method on identified exhalations of measured capnographic curves. The system was successfully utilized on two intubated, mechanically ventilated sheep, and advantages and limitations were discussed.

Regional pulmonary parameters have been analyzed using positron emission tomography (PET) studies in which an IV bolus injection of $^{13}$NN in saline is given at the onset of a period of apnea. However, low alveolar gas-volume to perfusion ratios complicate the analysis because such regions cause a greater amount of $^{13}$NN to be reabsorbed from alveolar spaces by the bloodstream following the passage of the initial bolus. Because of these complications in analyzing the PET images directly, two mathematical models of the tracer kinetics measured in the lungs by the PET camera and in the systemic arteries by a peripheral gamma-counter were developed. The models were based on first-order differential equations describing the behavior of a shunting lung unit representing all atelectatic, edematous, or fluid-filled alveoli and an aerated lung unit representing well-aerated alveoli. Physiologic parameters in the models were identified by minimizing the error between the simulated and measured data. The model was used to simulate data collected from normal sheep in the prone position, and from sheep experimentally injured with surfactant depletion in both the prone and supine position. Advantages and limitations of the models and identification routines were discussed.

In the final chapter, calculations of the shunt fraction, imaged lung fraction, and alveolar gas-volume of tracer distribution were made directly from the PET images and kinetics curves. Assumptions of the calculations were described, and the developed PET and arterial models were used to quantify the associated errors.

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Chapter 1
Real Time Measurement of Anatomical Dead Space

1 Introduction

Determination of the dead space volume is a physiological problem of continuing interest that has been applied to gauge the effectiveness and efficiency of ventilation. The anatomic dead space \( V_D \) is defined as the volume of air in the conducting airways that does not participate in gas exchange during breathing. Part of the utility of this value is in determining alveolar ventilation \( VA \), which is the rate at which alveoli receive inspired gas. This is calculated by multiplying the volume that reaches the alveoli \( VA \) during each breath of a given tidal volume \( VT \) by the breathing frequency \( f \), or

\[
VA \cdot f = (VT - V_D) \cdot f.
\]

Estimating \( VA \) is important in order to evaluate if the lungs are being satisfactorily ventilated and, in cases of existing hypoxemia, to eliminate hypoventilation as a possible cause. Furthermore, in addition to their inherent value, knowledge of \( V_D \) and \( VA \) at different times during experimental protocols provides valuable information in elucidating the meaning and possibly the cause of other physiologic changes. Therefore, a system to measure \( V_D \), \( VT \), and \( f \) in real-time has been developed for mechanically ventilated subjects. While the subject breathed carbon-dioxide (CO\(_2\)) free gas, the system acquired continuous flow rate and CO\(_2\) partial pressure signals, divided them into inhalation and exhalation regions, and calculated \( VT \) and \( f \) based on the divisions. \( V_D \) was calculated for each identified exhalation from a capnograph curve using an algebraic implementation of Fowler’s graphical method [2]. The system was used successfully on two intubated, mechanically ventilated sheep: one with acute lung injury induced by broncho-alveolar lavage with normal saline and another with autologous blood clot pulmonary embolism. In this chapter, the system and developed methodologies are described and advantages and disadvantages are discussed.
2 Methods

The system utilized a rapid inline infra-red CO$_2$ analyzer (Hewlett Packard Inc, Palo Alto, CA, USA), a flow rate monitor based on a pneumotachograph connected to a differential pressure transducer with an orifice restricted by a rotatable flap (BiCore), and a laptop computer. The transducers were connected in the breathing circuit directly to the endotracheal tube. The computer ran custom-made LabView (National Instruments) software to acquire and process the data. The beginning and end of sampling were user-controlled, and the average dead space over the sampling period was calculated.

2.1 Overview

The program developed to calculate $V_D$ was based on an adaptation of Fowler's graphical method for capnographic traces. CO$_2$ partial pressure ($P_{CO_2}(t)$) and expired flow ($V_E(t)$) were recorded over the duration of the exhalation after inhalation of CO$_2$-free gas. Expired volume was calculated by $V_E(t) = \int V_E(t) \, dt$. $P_{CO_2}(t)$ was then plotted versus $V_E(t)$, as illustrated schematically in Figure 1.1.

![Figure 1.1](image)

Figure 1.1 – Method for anatomical dead space ($V_D$) calculation. CO$_2$ partial pressure is plotted versus expired volume over the course of an exhalation. The curve presents three phases (I, II, III; see text for details), and the volume ($V_f$) and CO$_2$ partial pressure ($P_{CO_2, f}$) of the point separating Phase II and III is shown. The dead space is calculated as the volume that equalizes area A (under the curve) and area B (area between extrapolated Phase III line with slope $m$ and the curve).
Three traditional exhalation phases are identified:

- **Phase I** – The dead space, containing inspired CO₂-free gas, is exhaled.
- **Phase II** – A mixture of inspired gas within the dead space and alveolar gas containing CO₂ is detected.
- **Phase III** – The CO₂ concentration reaches a “plateau” as alveolar gas continues to be exhaled.

The plateau may rise slowly as higher CO₂ concentrations in distal alveolar regions are washed out. The expired volume \( (V_f) \) and CO₂ concentration \( (P_{CO_2,f}) \) at the point separating Phase II and III were determined. The slope \( (m) \) of Phase III was then calculated and used to extrapolate a line through Phase II. \( V_D \) was determined as the volume during Phase II that equalized areas A and B (Figure 1.1). This volume represents the midpoint of dilution between the alveolar and dead space gases.

### 2.2 Calibration

The flow rate monitor calibration was done using a steady-state flow \( (V_{cal}, mL/s) \). After subtracting the initial offset, the average voltage \( (\bar{v}) \) was recorded over a period of 5-10 s during which the flow remained at a constant value, as measured using a standard rotometer. Calibration points were obtained three times on different days over a range of 0-1000 mL/s for both the inspiratory and expiratory flow directions. Separate second-order polynomials were fit to the inspiratory and expiratory calibration points using minimization of least-squares, resulting in the calibration curve shown in Figure 1.2. Expiratory flows were taken as positive, and inspiratory flows were taken as negative.
Figure 1.2 – Calibration curve for flow rate monitor. Separate second-order polynomials were fit through the inspiratory and expiratory calibration points, determined by averaging the voltage signal over 5-10 s during which the flow remained at a known constant value.

The resulting calibration equations are given in Equation 1.1 below.

\[ V_{\text{cal, expiratory}} = 75 \cdot \bar{v}^2 + 416 \cdot \bar{v} \]

\[ V_{\text{cal, inspiratory}} = -134 \cdot \bar{v}^2 + 371 \cdot \bar{v} \]  

(1.1)

The CO₂ monitor calibration was done using a steady-state calibration with a known fraction of CO₂ (5%, \( P_{\text{CO₂}} = 38 \) torr) in nitrogen. Assuming the calibration curve to be linear, the calibration constant was simply calculated as the ratio of \( P_{\text{CO₂}} \) to the average voltage of the monitor over a 5-10 s sampling period \( \bar{w} \). The calibration equation thus found is given in Equation 1.2 below.

\[ P_{\text{CO₂}} = 22 \cdot \bar{w} \]  

(1.2)

2.3 CO₂ Delay and Response Time Corrections

The dead space calculation was based on the \( P_{\text{CO₂}} \) versus \( V_E \) curve. Because \( V_E \) was determined by integrating \( \dot{V}_E \), it was essential that the \( P_{\text{CO₂}} \) and \( \dot{V}_E \) data were synchronized. Therefore, the delay time \( (\Delta t_d) \) between the CO₂ and flow rate monitor and response time constant \( (\tau) \) of the CO₂ monitor’s step response were determined. A
A test system was built to create a step input to the CO₂ analyzer while simultaneously initiating flow through the flow transducer. A schematic of this system is shown in Figure 1.3.

![Schematic of the system](image)

**Figure 1.3 – Schematic illustrating the system used to determine the CO₂ analyzer delay time and response time so that its output could be synchronized with that of the flow rate monitor.**

The test system consisted of a bag filled with a uniform concentration of CO₂ and closed with a thin latex seal between the CO₂ and flow rate transducers. Pressure was applied to the bag such that when the thin seal was punctured, the gas inside the bag burst through the transducers, approximately creating an impulse of flow and a step of CO₂ from zero to the uniform concentration initially filling the bag. The difference between the start of the CO₂ and flow signals, each determined by when a value first exceeded the mean plus three standard deviations of the baseline signal, was taken as $\Delta t_d$. The absolute value of the slope of the logarithm of the normalized step response between 10-70% of the maximum partial pressure was used to compute $\tau$. Using these methods, $\Delta t_d$ was found to be $0.12 \pm 0.01 \text{s (mean± std)}$ based on 14 measurements on three different days, and $\tau$ was found to be $0.067 \pm 0.009 \text{s (mean± std)}$ based on 8 measurements on two different days. Correction for the time delay between instruments was implemented by using a
simple time shift. Correction for the capnograph time response ($\tau$) was implemented using a first-order approximation [5], as given in Equation 1.3.

$$C_i' = C_i + \tau \frac{C_{i+1} - C_i}{T}$$

(1.3)

In this equation, $C_i'$ is the i-th corrected CO₂ data point, $C_i$ is the i-th measured CO₂ data point, and $T = 0.01\,s$ is the sampling period.

2.4 Filtering Routines

Two separate filtering routines, a low-pass Butterworth and a moving average filter, were applied to the CO₂ and flow rate data simultaneously in order to remove high-frequency noise. Using raw signals from a representative experimental trial, 99% of the power in the CO₂ signal was found to be below 1.2 Hz and 99% of the power in the flow rate signal was found to be below 5.2 Hz. The Butterworth filter was thus set with a cutoff frequency of 5 Hz and order of 5, while the moving average filter used 15 data points before and after each point (corresponding to a 50% cutoff frequency of 5.5 Hz). However, due to the implementation of the CO₂ monitor response time correction (Equation 1.3), high frequency noise was amplified in the CO₂ signal such that the effective system frequency response for the two signals differed. This is illustrated in Figure 1.4, where the frequency response for the CO₂ signal and flow signal using the sampling frequency of 100 Hz are shown along with each respective power distribution (normalized by the dc power).
Figure 1.4 – Magnitude of frequency response and normalized power spectrum are shown for the CO\textsubscript{2} (left) and flow rate (right) signals.

As shown, the system leaves the low frequency regions of each signal, which are of primary interest, largely unchanged. After filtering and the CO\textsubscript{2} correction, 99\% of the power was found below 1.4 Hz for the CO\textsubscript{2} signal and below 3.5 Hz for the flow signal for the same experimental trial as above. Note that two filtering routines were utilized in order to gain an extra degree of freedom in choosing how to filter the signals, the Butterworth filter providing continuous filtering and the moving average providing recursive, dependent filtering. This allows greater flexibility for the software to be used with other monitors that may require alternate filtering operations in the future.

2.5 Program Specifics

After calibrating and synchronizing acquired data, a custom-made LabView program was used to make estimates of $V_D$, $V_T$, and $f$.

2.5.1 Breath Divisions and Volume Estimates

Assuming the voltage offset of the flow meter to be zero, the beginning of exhalation was detected by a zero crossing (from negative to positive flow using the current convention) along with conditions on following data points that insured a rapid rise in flow (and prevented noise interference). The end of the exhalation was simply detected by the first zero crossing (from positive to negative flow) following detection of the beginning of the exhalation. The average frequency of ventilation (breaths per
minute) was calculated by dividing 60 s by the time difference between consecutive beginning or end data points. Each inhaled or exhaled volume was calculated by numerically integrating the flow in its respective region, and the mean tidal volume was taken as the average both sets of volumes. All of these calculations were iteratively repeated while incrementally changing the voltage offset until the mean inhaled and exhaled volumes agreed within 10 mL, which was typically less than 5% of the tidal volume.

2.5.2 Phase III Detection and Dead Space Estimate

\( V_E \) was numerically integrated to give \( V_E \). For each exhalation, \( V_E \) and \( P_{CO_2} \) were zeroed by subtracting the first respective data point. This was necessary so that volumes were measured relative to the beginning of each exhalation and so that there was no offset in the CO2 signal. Such an offset would cause \( V_D \) to be underestimated, as can be seen in Figure 1.1. Area A would increase proportionally with the initial offset such that a lower \( V_D \) would be needed to equalize area B.

In order to calculate the beginning of Phase III, two slopes were calculated for each data point. The first, called the tangent slope (\( m_{tan} \)), was calculated as the average of four slopes (\( \frac{\Delta P_{CO_2}}{\Delta V_E} \)), each calculated using the data point and one of the four points located \( \pm 0.01 \) s and \( \pm 0.05 \) s before and after it. The second, called the fit slope (\( m_{fit} \)), was computed using a linear regression on the points between the data point and the end of exhalation. By beginning with data points in which \( P_{CO_2} > 15 \) mm Hg (generally during Phase II), \( m_{tan} \) was guaranteed to initially be greater than \( m_{fit} \). Progressing towards points at higher exhaled volumes, the two slope calculations converged and, due to noise in the slope calculations, eventually began to repeatedly cross. The beginning of Phase III was thus taken as the point where \( m_{tan} \) first crossed \( m_{fit} \). This point was then used to define \( V_f \) and \( P_{CO_2,f} \), and the Phase III slope \( m \) was taken as \( m_{fit} \) representing the point.
An algebraic implementation of Fowler's method [2] was then used to find $V_D$. It was calculated by setting the area under the curve between zero and $V_f$ to the trapezoid area enclosed by $V_D$, $V_f$, and the extrapolated plateau, which is theoretically the same as equating areas A and B (see Figure 1.1). This was expressed as

\[
\int_0^{V_f} P_{CO_2} dV = \frac{1}{2} (P_{CO_2,f} + P_{CO_2,d}) \Delta V = \frac{1}{2} (P_{CO_2,f} + (P_{CO_2,f} - m\Delta V)) \Delta V = P_{CO_2,f} \Delta V - \frac{1}{2} m\Delta V^2 \tag{1.4}
\]

where $\Delta V = V_f - V_D$ and $P_{CO_2,d}$ is the CO$_2$ partial pressure of the extrapolated Phase III line at $V_D$. Solving this equation for $V_D$,

\[
V_D = V_f - \frac{P_{CO_2,f}}{m} + \sqrt{\left(\frac{P_{CO_2,f}}{m}\right)^2 - 2m \int_0^{V_f} P_{CO_2} dV} \tag{1.5}
\]

for $m < 0$. If $m = 0$, the dead space was simply calculated as

\[
V_D = V_f - \int_0^{V_f} P_{CO_2} dV \tag{1.6}
\]

Combining Equations 1.5 and 1.6 gives

\[
V_D = V_f - \frac{\int_0^{V_f} P_{CO_2} dV}{P_{CO_2,f}} \cdot \frac{2}{1 + \sqrt{1 - \frac{2m \int_0^{V_f} P_{CO_2} dV}{P_{CO_2,f}^2}}} \tag{1.7}
\]

This calculation was repeated for each exhalation identified over the sampling period. The final $V_D$ estimate was taken as the average of all individual estimates.

2.6 System Characteristics

2.6.1 Accuracy Test

Accuracy was tested using the system shown schematically in Figure 1.5.
An inflatable bag filled with a uniform concentration of CO₂ was used to simulate the lungs. When the valve is opened the dead space volume is forced out ahead of the CO₂, as in the lungs when beginning an exhalation.

A bag was filled with a uniform concentration of CO₂ and sealed by a valve connected to a plastic tube with a known volume. The plastic tube was in turn connected to the flow and CO₂ transducers. Pressure was applied to the bag such that when the valve was opened the CO₂ emptied through the tube, forcing the air-filled dead space volume out ahead of it. This is similar to the anatomic dead space being forced out at the beginning of an exhalation. By varying the pressure applied to the bag, the flow rate of the simulated exhalation was varied.

### 2.6.2 Sensitivity Tests

In order to quantify the sensitivity of the $V_D$ measurement to where $V_f$ is taken, a trial taken from a lavaged supine animal was analyzed. The analysis consisted of incrementally taking $V_f$ at lower volumes and calculating the average change in $V_D$ and $m$ over the 8 recorded exhalations with $V_T = 229 \pm 22 \text{ mL}$ (mean ± std).

Sensitivity to changes in $\Delta t_d$, $\tau$, and the voltage offset determined by the process described in Section 2.2 were also analyzed. A representative trial was used to calculate $V_D$ for a range of each respective parameter around its estimated value. The percent
change in \( V_D \) was then plotted versus the percent change in each parameter, and a dimensionless sensitivity constant \( (\delta) \) was computed for each parameter as the absolute value of the slope of a linear regression done on each respective set of data points.

3 Results

Results from the lavage and embolism studies are summarized in Table 1.1. Maximum flow rates for all trials were between 338 and 658 m/s.

<table>
<thead>
<tr>
<th>Params</th>
<th>Lavage Study</th>
<th>Embolism Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prone</td>
<td>Supine</td>
</tr>
<tr>
<td>( V_T ) (mL)</td>
<td>Mean</td>
<td>STD</td>
</tr>
<tr>
<td>223</td>
<td>18</td>
<td>239</td>
</tr>
<tr>
<td>( V_D ) (mL)</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>( V_A ) (mL)</td>
<td>163</td>
<td>19</td>
</tr>
<tr>
<td>( f ) (bpm)</td>
<td>19.2</td>
<td>0.9</td>
</tr>
<tr>
<td>( V_A ) (mL/s)</td>
<td>52</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 1.1 – Summary of parameters identified with the developed system during two separate sets of measurements. The mean and standard deviation (STD) are given for the tidal volume \( (V_T) \), dead space volume \( (V_D) \), alveolar volume \( (V_A) \), and ventilation frequency \( (f) \) for each condition.

The accuracy test was performed 9 times, first using a 75 mL tube and then a 100 mL tube. The system estimated dead space volumes of 72 ± 7 mL (mean ± std) for the 75 mL tube and 92 ± 11 mL (mean ± std) for the 100 mL tube. Maximum flow rates varied between 137 and 873 mL/s.

Results from analyzing the sensitivity to \( V_f \) are summarized in Table 1.2.

<table>
<thead>
<tr>
<th>( V_D ) (mL)</th>
<th>( V_f ) (mL)</th>
<th>( m ) (torr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>207</td>
<td>0.0023</td>
</tr>
<tr>
<td>86</td>
<td>193</td>
<td>0.0030</td>
</tr>
<tr>
<td>83</td>
<td>171</td>
<td>0.0112</td>
</tr>
<tr>
<td>80</td>
<td>149</td>
<td>0.0202</td>
</tr>
</tbody>
</table>

Table 1.2 – Results of sensitivity test of the dead space calculation to the choice of the Phase III beginning. Large changes in the volume of the beginning of Phase III \( (V_f) \) resulted in large changes in the calculated Phase III slope \( (m) \) but only small changes in the estimated dead space \( (V_D) \).
The results of the $\Delta t_d$, $\tau$, and the voltage offset sensitivity tests are illustrated in Figure 1.6.

![Plot illustrating the sensitivity of the dead space calculation to error in the baseline voltage offset, delay time between monitors, and response time of the CO$_2$ monitor.](image)

Figure 1.6 – Plot illustrating the sensitivity of the dead space calculation to error in the baseline voltage offset, delay time between monitors, and response time of the CO$_2$ monitor.

The dimensionless sensitivity constant was found to be $\delta_{\text{delay}} = 0.6$ for $\Delta t_d$, $\delta_{\text{response}} = 0.3$ for $\tau$, and $\delta_{\text{offset}} = 0.2$ for the voltage offset.

4 Discussion

The most significant conclusions of this project are:

1. A system was successfully developed that measures the dead space, tidal volume, and ventilation frequency in real-time.

2. The system utilizes only basic equipment (flow rate monitor, CO$_2$ monitor, laptop computer) so that it can be easily implemented into study protocols and adapted to future changes in function or equipment.
4.1 Methodology Evaluation

4.1.1 Flow Calibration

The flow transducer used is a type of restriction flow meter in which an orifice with reduced cross-sectional area is used to create a measurable pressure difference between two taps located on either side of the orifice. The measured pressure difference is then output as a voltage. A schematic of the transducer is shown in Figure 1.7.

![Schematic of flow transducer](image)

Figure 1.7 – Schematic of flow transducer, showing rotating orifice flap and two pressure taps on either side of the orifice.

For an orifice with a fixed cross-sectional area, Bernoulli’s equation can be used to relate the volume flow rate \( Q \) to the pressure difference \( \Delta P = P_1 - P_2 \) according to

\[
Q = A \sqrt{\frac{2 \cdot \Delta P}{\rho}},
\]

where \( A \) is the cross-sectional area of the transducer and \( \rho \) is the air density. However, the transducer in this experiment used a flap that rotated in the direction of flow, thus reducing the measured pressure difference for high flows. In fact, the calibration curve (see Figure 1.2) showed an inverse relation to that predicted by Equation 1.8. Due to the rotatable flap, flow fluctuations and inertial forces have a significant influence on the transducer response. These factors, inherent in typical breathing patterns, were not considered when doing the steady-state flow calibration. One alternative calibration method that would better account for these factors would be using a known volume to create a step input through the transducer at varying constant flow rates. Dividing the known volume by the integral of acquired monitor voltages of the step function would provide a calibration constant characteristic of the voltage height of the step (representing...
the various flow rates). Fitting a curve through the calibration constants plotted versus the representative voltages would then provide another calibration curve. Though such a volume calibration would account for the mentioned qualities, it would be significantly more difficult and make repeated calibrations a time consuming procedure. Furthermore, a device would be needed to generate the step function of a known volume at various constant flow rates. The steady-state flow calibration, though it did not account for flow fluctuations and inertia, did allow the simple determination of the monitors response through a wide range of flows. Another alternative would be to use a transducer that is less sensitive to fluctuations and inertial forces, such as a Fleisch flow transducer. This would then require the recalculation of the monitor response characteristics and calibration curve.

Finally, due to the flow rate measurement dependence on \( \rho \), additional errors may result from doing the calibrations using dry air at room temperature rather than actual expired gases at body temperature that contain saturated water vapor. Assuming a water vapor partial pressure of 47 torr, standard atmospheric pressure of 760 torr, and body temperature of 37°C, the air density of expired gases will be approximately 10% greater than that of air at 20°C. Assuming the flow rate measurement to be inversely proportional to the square root of density as in Equation 1.8, such an error in density would result in flow errors on the order of 5%.

### 4.1.2 CO2 Response Time Correction

Incorporating the response time correction \( \tau \) for the CO2 analyzer had two effects. First, it more accurately reflected the CO2 concentrations near the beginning of the signal where there was a rapid increase in concentration. Because this is the most significant portion of the signal insofar as it is used to make the \( V_0 \) measurement, the increased accuracy was important. Second, it amplified high frequency noise in the CO2 signal and caused the system frequency response between the two signals to differ, as described in Section 2.4. The additional noise is mostly removed by the combined filtering operations.
4.1.3 Program Calculations

A critical function of the software program was to divide each signal into inhalation and exhalation regions over the course of several breaths based on the flow rate data. This is difficult because of the many different flow profiles that can be generated. For instance, simply using zero crossings to detect the beginning of each region does not work if there are low flow portions of the profile (such as at the end of exhalation or during an inspiratory pause) where a small amount of noise can cause numerous crossings. Therefore, rather than attempting to account for all such possibilities, the system was programmed to expect a profile in which there is a rapid exhalation following the end of inhalation (i.e. no inspiratory pause), and in which the expiratory flow decays to zero before the start of the following inhalation. Such a profile is common to the mechanically ventilated subjects of interest in this study.

The algebraic implementation of Fowler’s graphical method exploited the theoretical equivalence of equating area A with area B and equating the area under the curve up to Phase III with the trapezoidal area enclosed by $V_D$, the extrapolated Phase III slope, and the beginning of Phase III (see Figure 1.1). This is also analogous to equating the area between the curve and extrapolated Phase III slope up to the beginning of Phase III with the trapezoidal area enclosed by the extrapolated Phase III slope and $V_D$, which has been shown to be equivalent to Fowler’s method [3]. In addition, as noted by the authors, combining the sloping (Equation 1.5) and non-sloping (Equation 1.6) dead space equations as in Equation 1.7 eliminates instabilities resulting from using the sloping equation with $m$ close to zero.

4.2 System Characteristics

4.2.1 Accuracy Test

The accuracy test revealed a bias towards underestimating the dead space. It is unclear whether this is a characteristic of the system or a systemic error of the test apparatus, possibly due to turbulent mixing between the CO$_2$ and air when the valve was opened. Nevertheless, the test showed that the system was able to predict both the 75 and 100 mL tube dead space volumes within a single standard deviation. An alternative accuracy test could be performed as done by Mitchell [4], where a tube with a known
volume was used to provide additional dead space during mechanical ventilation of a subject. The difference between dead space predictions with and without the inserted tube was then compared to the known tube volume. This method has the additional advantage of gauging the accuracy of the system as it would be used experimentally.

4.2.2 Sensitivity Tests

The most often cited problem with using Fowler's method to determine the dead space is the inability to accurately determine the beginning of and range of data to define Phase III [3,4]. In the methodology developed here, the beginning is taken as where the tangent slope first approximately matches the slope fit through the remainder of Phase III, taken to the end of the exhalation. Using this method yields conservative estimates of $V_D$ in diseased cases where $V_f$ is difficult to discern. In such cases, the normally linear (sloping or non-sloping) plateau takes on a curvilinear form, and the two slopes do not match until higher volumes are reached. This results in overestimations of $V_D$, the degree of which depends on the concavity of Phase III. However, the results of the sensitivity test (Table 1.2), which were done using such a curvilinear plateau from a diseased lung, indicate that the $V_D$ estimate is relatively insensitive to where $V_f$ is chosen, as $V_D$ showed only a 7% change from choosing $V_f$ 58% lower. This robustness is due in part to using the slope fit through Phase III through the end of exhalation rather than the tangent slope or a slope fit through a portion of the data between the Phase III beginning and the end of exhalation. Though this choice is not traditional [2,3,4], the reliability and ability to automate the calculation were thought to more than offset any resultant inaccuracies.

The $\Delta t_d$, $\tau$, and the voltage offset sensitivity tests (Figure 1.6) showed that the dead space determination had the greatest sensitivity to errors in the delay time between the monitors ($\delta_{\text{delay}} = 0.6$), with underestimates in the time resulting in overestimates of the dead space. The response time has the same relation, but the calculation is less sensitive to errors ($\delta_{\text{response}} = 0.3$). The reason for the relation is that increases in either time parameter shift the CO$_2$ response to lower exhaled volumes. The determination was
least sensitive to errors in the offset ($\delta_{\text{offset}} = 0.2$). Underestimates in the offset resulted in underestimates in the dead space. Changing the offset simply redistributes volume between the inhaled and exhaled portions, such an increase in the offset increases all exhaled volumes, including that where the dead space is found.

5 Summary

A system was created that gives accurate estimates of the respiratory dead space, tidal volume, and frequency in real-time. Capnographic traces over the user-defined sampling period were divided into inhalation and exhalation regions, and identified exhalations were used to provide dead space estimates based on an algebraic implementation of Fowler’s graphical method. Use of the system in two studies of intubated, mechanically ventilated sheep demonstrated the utility of the system. Advantages, limitations, and characteristics of the system were discussed in detail.
6 References


Chapter 2
Lung and Arterial Kinetics Analysis

1 Introduction

Regional pulmonary perfusion and ventilation are often measured non-invasively by means of nuclear imaging techniques and analyzed using models of tracer kinetics. Spatial distribution of pulmonary perfusion has been measured with positron emission tomography (PET) following deposition in the lung during the first transit of intravenously (IV) injected tracer-labeled particles ($^{68}$Ga), water ($H_2^{15}$O), and molecular nitrogen ($^{13}$NN) dissolved in saline [7,8,9]. Of these three isotopes, only the $^{13}$NN tracer allows the differentiation of perfusion to aerated alveolar gas spaces versus that to shunting alveolar regions. The validity of the measurement following an IV injection of $^{13}$NN gas dissolved in saline rests on the assumption that at first pass all of the tracer that encounters aerated alveoli diffuses into the gas space. Because of the low solubility of nitrogen in water and tissues ($\lambda = 0.0145$ at $37 \, ^\circ C$ [5]), in normal aerated lungs, the $^{13}$NN tracer remains in the alveoli during a breath hold and its intrapulmonary distribution measured by PET is directly proportional to local perfusion [7]. The process is complicated in lungs with pulmonary pathology involving atelectatic or edematous lung units or with aerated units of low gas volume to perfusion ratios since the injected $^{13}$NN tracer is not retained in these units during breath hold. Instead, it either remains in the blood altogether or is quickly reabsorbed by the bloodstream following passage of the initial bolus. Therefore, in the presence of intrapulmonary shunt, raw PET images of $^{13}$NN content collected during apnea cannot be directly used to quantify perfusion, but instead must be used with a mathematical model of the tracer kinetics to derive physiological parameters. Such a model has been previously described [2], and in this study, a modified version of the model was created along with a model of the systemic arterial tracer kinetics. Both models were developed with the goal of describing the tracer kinetics by quantifying the perfusion to shunting and aerated units and characterizing their behavior in terms of time constants and volume of tracer distribution. Physiological parameters included in the models were identified by finding the set of
parameters that minimized the error between the simulated and measured data. Furthermore, by optionally including recirculation in each model, its effects on the models and parameter identification were investigated. The models were applied to PET data from the lung fields and arterial samples obtained from normal sheep, and from sheep experimentally injured with surfactant depletion in both supine and prone positions. The models, their relevant assumptions, and methods of parameter identification are described, and advantages and limitations of the methods are discussed.

2 Methods
2.1 Experimental and Imaging Protocols
2.1.1 Animal Preparation

Twelve sheep were anesthetized, intubated, and mechanically ventilated. General anesthesia was induced with an intravenous bolus of sodium thiopental (35 mg/kg) and fentanyl, and maintained with a continuous infusion of sodium thiopental (15 mg·kg⁻¹·h⁻¹) and fentanyl. Pancuronium (0.2 mg/kg) was used for muscle paralysis. Five of the sheep were maintained in a normal condition, while seven were injured with a saline lung lavage. The ventilator (Harvard Apparatus, Millis, MA, USA) was set at an inspired oxygen fraction (F₁₀₂) of 0.26 ± 0.04 for normal sheep and 1.0 for injured sheep, a positive end-expiratory pressure (PEEP) of 5 cm H₂O, a tidal volume (V₉) of 11 ± 2 mL/kg (262 ± 61 mL) for normal sheep and 8 mL/kg (176 ± 25 mL) for injured sheep, and an inspiratory time of 30% of the breathing period. Respiratory rate (RR = 17 ± 4 bpm) was set to maintain normocapnic arterial blood gases at the beginning of the experiment and fixed at that value for the rest of the experiment. The right femoral artery was cannulated for systemic arterial pressure monitoring and blood sampling and the right femoral vein for administration of drugs. A Swan-Ganz catheter (model 93A-131H-7F, Edwards Laboratory, Santa Ana, CA, USA) was inserted in the left femoral vein and advanced into the pulmonary artery. Its distal port was used for monitoring of pulmonary arterial pressure (PAP) and sampling of pulmonary arterial blood. A central line was introduced in a jugular vein and positioned into the superior vena cava for delivery of the ¹³NN-labeled saline solution. Heparin was infused in order to prevent blood clotting within the sampling tubes and catheters. Airway, arterial, and pulmonary artery pressures
were continuously monitored using a strip chart recorder (Hewlett Packard Inc, Palo Alto, CA, USA). Total cardiac output \((Q_T)\) was measured using thermodilution (Model COM-1, Edwards Laboratory, Santa Ana, CA, USA).

2.1.2 Experimental Apparatus

The PET camera was a multi-ring full body camera (Scanditronix PC4096, General Electric, Milwaukee, WI, USA) with detectors positioned around circular rings. The camera collected 15 transverse cross sectional slices of 6.5 mm thickness providing 3-dimensional information over a 9.7 cm long cylinder. \(^{13}NN\) gas, created by bombarding CO\(_2\) in a cyclotron, was used as the radioactive tracer (9.97 min half-life). The \(^{13}NN\) was dissolved in degassed physiologic saline, yielding a specific activity \((C_t)\) that ranged from 0.16 to 0.49 mCi/ml, and a rapid bolus \((V_t = 23-34 ml)\) was injected into a central vein at a rate of 10 ml/s. The infusion system consisted of a computer controlled device for production and injection of the \(^{13}NN\) -saline solution. Arterial blood was drawn from the right femoral artery. The sampling system consisted of an inline pump (Harvard Apparatus, Millis, MA, USA) that drew blood continuously through the peripheral gamma-counter of the PET camera (calibrated to give activity concentration) at a rate of 10 ml/min and collected it in two 60 mL syringes. Flexible polymer tubing was used throughout the system, except for an 8-inch section of glass inserted through the counter. This was used in place of the polymer in order to prevent tracer gas from being absorbed in the tube, which preliminary experiments revealed had caused significant additional activity to be measured. Collected blood was returned to the animal following each emission imaging sequence. A schematic overview of this experimental set-up is shown in Figure 2.1.
2.1.3 Imaging Protocol

Sheep were initially placed supine or prone in the PET camera (5 normal animals prone, 4 lavaged animals prone, 3 lavaged animals supine). A 5 min. transmission scan was collected prior to each set of emission scans to correct for absorption of annihilation photons in the animal’s body. For this, a radioactive source was rotated around the imaging field and the resulting signal used for reconstruction of an image that can be compared to a low resolution computed tomography (CT) scan. Regional density was inferred from this image as the amount of the initial radioactive beam absorbed by the tissues at each point in the animal’s body. An emission scan consisted of the following: after steady state breathing, the ventilator was stopped at mean lung volume. Simultaneously, a bolus of $^{13}$NN in saline solution was injected into the jugular venous catheter, and the camera began collecting a series of images. Ten consecutive 2.5 s images followed by four 10 s images were collected during 60 s of apnea. Emission scans of local tracer activity were reconstructed with appropriate correction for detector sensitivity and for tissue attenuation using a convolution back-projection algorithm with a Hanning filter yielding an effective in-plane resolution of 6 mm (determined from the width at one-half height of a point source image). Resulting images consisted of an interpolated matrix of $128 \times 128 \times 15$ volume elements (voxels) of $2 \times 2 \times 6.5$ mm. Arterial blood sampling was started prior to the initiation of the emission scans to remove the volume initially in the tubing. The concentration was then measured for the duration of
the imaging sequence at a sampling frequency of 1 Hz. For the lavage studies, the animal was rotated to the opposite position following this imaging sequence and an identical sequence was repeated. In total, 5 normal prone (NP), 7 lavaged prone (LP), and 7 lavaged supine (LS) sheep were imaged.

2.1.4 Lung Kinetics

A unity mask was first created to isolate the lung field of the images and exclude voxels corresponding to extrapulmonary regions, heart tissue, or major blood vessels. The single-frame mask (with 15 slices) was manually delineated, slice-by-slice, using a combination of two single-frame images to distinguish lung tissue: (1) the corresponding transmission scan, and (2) the sum of activities from apneic emission frames following passage of the tracer through the imaged heart region. The transmission scan was used to identify aerated lung regions, while the sum of emission frame activities was used to identify non-aerated regions being perfused. The mask was then multiplied voxel-by-voxel with each frame of the emission image and with the single-frame transmission image. Average total activity (nCi) within the masked region was then calculated for each emission frame, resulting in a tracer kinetics curve for the lungs over the imaging period such as that illustrated in Figure 2.2.

Figure 2.2 – A representative PET kinetics curve derived from apneic emission image frames, showing the peak \( A_{\text{peak}} \) and quasi-steady-state plateau \( A_{\text{plateau}} \) data points.
2.2 Oxygen Shunt Calculation

Collected arterial and mixed venous blood samples were used to calculate the global shunt fraction ($F_{O_2}$), which includes both intrapulmonary and extrapulmonary shunt. Samples were taken from the pulmonary artery and right femoral artery prior to each imaging sequence. Oxygen ($P_{O_2}$) and carbon-dioxide ($P_{CO_2}$) partial pressures and pH were measured using a rapid blood gas analyzer (Model ABL5/BPH5, Radiometer Medical, Copenhagen, Denmark). These values were used to calculate the arterial and venous oxygen saturation fractions (SAT) based on a dissociation curve for sheep blood [10]. Total hemoglobin content ($Hb$) was measured using a hemoximeter (Model OSM3, Radiometer Medical, Copenhagen, Denmark). Arterial ($C_{a,O_2}$) and venous ($C_{v,O_2}$) oxygen contents were calculated according to

$$C_{O_2} = 0.003 \times P_{O_2} + 1.39 \times SAT \times Hb.$$  \hspace{1cm} (2.1)

The theoretical end-capillary oxygen content ($C_{ec}$) was calculated according to Equation 3.1 with $SAT = 1$ and

$$P_{O_2} = P_{O_2,\text{inspired}} - 47 \times \frac{P_{CO_2}}{0.8},$$  \hspace{1cm} (2.2)

where $P_{O_2,\text{inspired}}$ is the inspired oxygen pressure, 47 torr is the water vapor pressure at 37°C, and 0.8 is the respiratory quotient. $F_{O_2}$ was then calculated as

$$F_{O_2} = \frac{C_{ec} - C_{a,O_2}}{C_{ec} - C_{v,O_2}}.$$  \hspace{1cm} (2.3)

2.3 Kinetics Models

Arterial and PET kinetics models are described. Each optionally includes the effect of tracer recirculated through the systemic cardiovascular system. Both are described including this recirculated activity, and the small model modifications necessary to neglect this activity are later explained.
2.3.1 Arterial Model

Overview. A schematic of the basic features of the arterial tracer kinetics model is shown in Figure 2.3.

![Diagram of Arterial Model]

Figure 2.3 – Schematic showing the basic features of the arterial model. Variables are as follows: (V) volume, (C) time-dependent tracer concentration, (Q) blood flow, (Δt) time delay, and (λ) $^{13}$NN blood:gas partition coefficient. Indices are as follows: (I) injection, (h) heart, (T) total, (s) shunting alveolar unit, (A) aerated alveolar unit, (s) sampling, (a) arterial, and (r) recirculation.

$^{13}$NN-labeled saline (volume $V_I$, specific activity $C_I$) was injected into the superior vena cava at an infusion flow rate of $Q_I$. The injectant was diluted in a well-mixed compartment with blood volume $V_h$ through which the total cardiac output $Q_T$ flowed (assumed to be continuous and uniform). The uniform concentration inside this compartment $C_h(t)$ was used as the input for two independent, well-mixed, alveolar compartments. One shunting compartment lumped all atelectatic, edematous, or fluid-filled alveolar units with no gas content. This compartment had a tracer volume of distribution $V_s$, uniform concentration $C_s(t)$, and was perfused by the shunting blood flow $Q_s = F_s \cdot Q_T$ where $F_s$ is the shunt fraction. The second compartment represented aerated alveolar units with a tracer volume of distribution $V_A$, uniform concentration
\( C_A(t) \), and aerated blood flow \( Q_A = (1 - F_s) \cdot Q_T \). The tracer concentration in the pulmonary vein was taken as the perfusion weighted average of the capillary blood concentrations leaving the shunting and aerated compartments, assumed to be equal to \( C_s(t) \) and \( \lambda C_A(t) \), respectively. This pulmonary vein concentration was used for two purposes: (1) an input to the modeled systemic circulation consisting of a convective time delay \( \Delta t_r \), a volume of distribution \( V_r \), and uniform concentration \( C_r(t) \) that was used to model recirculated activity and was input into the heart compartment along with the original injectant, and (2) the simulated arterial concentration \( C_a(t) \), after a time delay \( \Delta t_s \) that represented all convective delays between consecutive chambers.

**Injection and Heart Compartment.** The simulated injected \( ^{13}\text{NN} \) was normalized by \( C_I \) and thus modeled as a step function with a height of one and a width of \( \frac{V_L}{Q_I} \). This function was input into a lumped mixing volume representing the right heart, major vasculature between the injection site and lungs, the left heart, and major vasculature between the left heart and the sampling site. Note that a single compartment was used to represent both sides of the heart in order to reduce the number of variable parameters. Using the law of mass conservation and assuming a well-mixed uniform concentration \( C_h(t) \) within the volume, with activity entering both from the injectant and from any recirculated activity, this volume was described by the first-order differential equation

\[
V_h \frac{dC_h(t)}{dt} = Q_I C_I + Q_T C_r(t) - Q_T C_h(t),
\]

where it was assumed that \( Q_T \gg Q_I \) such that only the blood flow \( Q_I \) was modeled leaving the compartment. Normalizing by \( C_I \) and dividing by \( V_h \), the equation becomes
\[
\frac{dC_h(t)}{dt} = \frac{Q_T}{V_h} C_h(t) - \frac{Q_T}{V_h} (C'_h(t) - C'_h(t)) \\
= \frac{Q_I}{V_h} + \frac{1}{\tau_h} (C'_r(t) - C'_h(t))
\]

(2.5)

where the convention \( C'_x = \frac{C_x}{C_I} \) is utilized. In this form, the time constant of the heart, \( \tau_h = \frac{V_h}{Q_T} \), was the variable parameter to be identified.

**Alveolar Compartments.** \( C_h(t) \) was input to both a shunting and aerated compartment. The shunt compartment was described by

\[
V_s \frac{dC_s(t)}{dt} = Q_s C_h(t) - Q_s (\lambda_s C_s(t))
\]

(2.6)

Upon normalization and rearrangement, and assuming that the partition coefficient between the blood and atelectatic, edematous, or fluid-filled alveolar units (\( \lambda_s \)) was one, this becomes

\[
\frac{dC'_s(t)}{dt} = \frac{Q_s}{V_s} (C'_h(t) - C'_s(t)) \\
= \frac{1}{\tau_s} (C'_h(t) - C'_s(t))
\]

(2.7)

where the shunt compartment time constant \( \tau_s = \frac{V_s}{Q_s} \) and implicitly \( F_s \) were the variable parameters. Similarly, the aerated compartment was described by

\[
V_A \frac{dC_A(t)}{dt} = Q_A C_h(t) - Q_A (\lambda C_A(t))
\]

(2.8)

The tracer concentration leaving the compartment in capillary blood is proportional to the concentration within the volume of tracer distribution by the partition coefficient (\( \lambda = 0.0145 \) at 37°C). It was thus assumed that the volume of blood within aerated units was negligible compared with the gas volume, such that the tracer concentration in the gas volume was approximately \( C_A(t) \). When solved for the normalized activity leaving the compartment, this equation becomes
\[
\frac{d(\lambda C_A'(t))}{dt} = \frac{\lambda Q_A}{V_A} \left( C_A'(t) - (\lambda C_A'(t)) \right)
\]

\[
= \frac{1}{\tau_A} \left( C_A'(t) - (\lambda C_A'(t)) \right)
\]

where the time constant of the aerated compartment, \( \tau_A = \frac{V_A}{\lambda Q_A} \) and implicitly \( F \), were the variable parameters.

*Arterial Sample and Recirculation.* The tracer concentration in the pulmonary vein, and subsequently in the systemic arteries, was taken as the perfusion weighted average of capillary blood concentrations in the shunting and aerated compartments. Thus, upon normalization by \( C_I \),

\[
C_A'(t) = \frac{Q_r}{Q_T} C'(t) + \frac{Q_A}{\lambda Q_A} \lambda C_A'(t).
\]

(2.10)

This concentration, time-shifted by \( \Delta t_s \), was taken as the simulated arterial activity. It was also used as the input for a recirculation compartment described by

\[
V_r \frac{dC_r(t)}{dt} = Q_r C_r(t) - Q_T C_r(t).
\]

(2.11)

Normalizing and rearranging, this becomes

\[
\frac{dC_r(t)}{dt} = \frac{Q_T}{V_r} \left( C'_a(t) - C_r(t) \right)
\]

\[
= \frac{1}{\tau_r} \left( C'_a(t) - C_r(t) \right)
\]

(2.12)

where the time constant \( \tau_r = \frac{V_r}{Q_T} \) was the variable parameter. If recirculation was modeled, the concentration leaving this compartment was then used as an input to the heart compartment described by Equations 2.1 and 2.2. If it was not modeled, the input into the heart compartment was not made and \( C_r(t) = 0 \).
2.3.2 **PET Model**

*Overview.* A schematic overview of the lung model used to simulate the PET tracer kinetics is shown in Figure 2.4.

![Schematic showing the basic features of the P.E.T. model.](image)

Figure 2.4 - Schematic showing the basic features of the P.E.T. model. Variables are as follows: (V) volume, (C) time-dependent tracer concentration, (Q) blood flow rate, and (Δt) time delay. Indices are as follows: (I) injection, (rh) right heart, (T) total, (s) shunting alveolar unit, (A) aerated alveolar unit, and (r) recirculation.

The $^{13}NN$ tracer (volume $V_I$, specific activity $C_I$) was injected at an infusion flow rate $Q_I$. The injectant, along with any recirculated activity delayed by $Δt_r$, was input into a well-mixed compartment with blood volume $V_{rh}$ and uniform concentration $C_{rh}(t)$ through which the total cardiac output $Q_T$ flowed. A time delay $Δt_{rh}$ accounted for the brief convective delay between the injection site and lungs. The time-shifted concentration $C_{rh}(t)$ was then used as the input for a shunting and an aerated alveolar compartment, through which $Q_s$ and $Q_A$ flowed, respectively. Because the PET camera images correspond to the average activity during each imaging period, the sum of the total activity in these compartments ($V_sC_s$ and $V_A C_A$) was used as the simulated input to the PET camera, where an averaging routine was used to produce data points ($PET_i$) corresponding to those measured.
Injection, Recirculation, and Heart Chamber. The injected $^{13}	ext{NN}$ was normalized by $C_I V_I$ and modeled as a step function with a height of $\frac{1}{V_I}$ and a width of $\frac{V_I}{Q_I}$. A step function was also used to model the recirculated concentration $C_r$, which upon normalization had a height of $\frac{F_r}{V_I}$, where the recirculation fraction $F_r = \frac{C_r}{C_I}$. When recirculation was included, $F_r$ was estimated using $F_r O_2$ according to the method described in Appendix A. When it was not included, $F_r$ was set to zero. The recirculated input lasted from time $\Delta t_r$ throughout the apneic period. The right heart and major vasculature between the injection site and lungs were modeled using Equation 2.4, substituting $C_{rh}(t)$ and $V_{rh}$ for $C_h(t)$ and $V_h$ since only the right heart is modeled here.

Alveolar Compartments and PET Camera. Total activity was used because the camera measured the total activity in each voxel, without distinguishing where the radioactive tracer was located (i.e. gas, blood, or tissue). The shunt compartment was again modeled by Equation 2.6, but was solved for the total activity $V_s C_s(t)$ rather than the concentration $C_s(t)$, leading to

$$\frac{d(V_s C_s(t))}{dt} = Q_s C_{rh}(t) - \frac{Q_s}{V_s} (V_s C_s(t))$$

(2.13)

Similarly for the aerated compartment described by Equation 2.8, solving for $V_A C_A(t)$ results in

$$\frac{d(V_A C_A(t))}{dt} = Q_A C_{rh}(t) - \frac{\lambda Q_A}{V_A} (V_A C_A(t))$$

(2.14)

Having estimated the total activity from shunting and aerated compartments, the PET camera data was simulated using
\[ \text{PET}_i = F_L \left( \int_{t_i}^{t_{i+T(i)}} \frac{(V_i C_i + V_a C_A)}{T(i)} \right), \]  

(2.15)

where averaging of activity over the PET camera sampling time \((T(i))\) and imaging of a fraction of the lung \((F_L)\) were accounted for.

### 2.4 Optimization Routines

In each experiment, lung kinetics data was collected from the PET camera and arterial kinetics data was collected from the peripheral gamma-counter. An optimization was then performed to find the set of physiological parameters that minimized a weighted mean-square-error (MSE) between the measured data and simulated data from each respective model. Due to the non-linear nature of the models, a global optimization routine was used to find this optimum parameter set. The constrained global optimization problem can be written

\[
\min \{ \text{MSE} \} \quad \text{s.t. } u_i \leq x_i \leq v_i, \ i = 1, \ldots, n
\]

(2.16)

where \(x_i\) is a physiologic parameter to be estimated, \(u_i\) and \(v_i\) are the lower and upper bounds on \(x_i\), respectively, and \(n\) is the number of parameters to be estimated. The specific routine utilized, called Multilevel Coordinate Search (MCS), was developed by W. Huyer and A. Neumaier of the University of Vienna, Austria [3]. This routine was chosen because it was written in Matlab, freely available, and easily amendable.

Though this optimization program was used with both models, its implementation differed between them and is described in the following sections. The variable parameters identified in each model along with their respective bounds are summarized in Table 2.1.
Table 2.1 – Variable parameters of both the lung and arterial models. Parameters marked with (x) were identified by the optimization routine using the lower and upper bounds shown.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Arterial Model</th>
<th>P.E.T. Model</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_s$</td>
<td>Shunt Fraction</td>
<td>x</td>
<td>x</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>$\tau_s$</td>
<td>Shunt Time Constant (s)</td>
<td>x</td>
<td>x</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>$\tau_A$</td>
<td>Aerated Time Constant (s)</td>
<td>x</td>
<td>x</td>
<td>30</td>
<td>3000</td>
</tr>
<tr>
<td>$\tau_r$</td>
<td>Recirculation Time Constant (s)</td>
<td>x</td>
<td></td>
<td>25</td>
<td>225</td>
</tr>
<tr>
<td>$\Delta t_r$</td>
<td>Recirculation Delay (s)</td>
<td>x</td>
<td></td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>$\tau_h$</td>
<td>Heart Time Constant (s)</td>
<td></td>
<td>x</td>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>$\Delta t_m$</td>
<td>Right Heart Delay (s)</td>
<td>x</td>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>$F_L$</td>
<td>Lung Fraction Imaged</td>
<td>x</td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

To distinguish variables identified by the arterial model optimization and by the PET model optimization, subscripts “ART” and “PET” were added to each variable throughout the remainder of this report. Variables without the added subscripts were used to represent the quantities generically.

2.4.1 Arterial Model

The recirculation delay was set to a constant value of 20 s based on preliminary measurements. The remaining five variables were identified from the optimization routine using the following initial conditions: $F_{s,\text{ART}} = F_s O_2$, $\tau_{s,\text{ART}} = 10$ s, $\tau_{A,\text{ART}} = 500$ s, $\tau_{r,\text{ART}} = 60$ s, and $\tau_{h,\text{ART}} = 5$ s. The optimization routine was run five times using five different sampling delays: a value visually estimated from the arterial curve and four values $\pm 1$ s and $\pm 2$ s from that value. The parameter set with the lowest MSE between the simulated and measured curves was then chosen, where

$$MSE = \frac{\sum_{i=1}^{N} \left[ (C_{\text{simulated}}(i) - C_{\text{measured}}(i))^2 \times C_{\text{measured}}(i) \right]}{\sum_{i=1}^{N} C_{\text{measured}}(i)}.$$  \hspace{1cm} (2.17)

In this equation, each squared error between the simulated ($C_{\text{simulated}}$) and measured ($C_{\text{measured}}$) data points is weighted by $C_{\text{measured}}$ and the sum is normalized by the sum of
Using this optimization scheme, one parameter set was recorded when the model included recirculation and another was recorded when it did not.

### 2.4.2 PET Model

Initial estimates were made of each variable parameter as follows: $F_{s,PET}$ was set to a shunt fraction calculated from the apneic PET kinetics data according to $1 - \frac{A_{\text{plateau}}}{A_{\text{peak}}}$, where $A_{\text{plateau}}$ and $A_{\text{peak}}$ are shown in Figure 2.2 (see Chapter 3, Section 2.1). $\tau_{s,PET}$, $\Delta t_{rh,PET}$, and $\Delta t_{r,PET}$ were set to 5 s, 2 s, and 30 s, respectively. $\tau_{A,PET}$ was set to a value calculated by fitting an exponential to the final two apneic data points. (If the estimated $\tau_{A,PET}$ was not between the chosen bounds of 30 and 3000 s, the nearest bound was taken as the initial estimate.) $F_{L,PET}$ was then set by taking the ratio of the peak simulated activity from the model using $F_{L,PET} = 1$ and the other initial estimates to the measured peak activity $A_{\text{peak}}$. The optimization was then done by iteratively repeating three steps:

1. $\Delta t_{rh,PET}$ was identified by fitting the first two PET data points. These points were primarily affected by $\Delta t_{rh,PET}$ and $V_{rh,PET}$, the latter of which was set to 50 mL.

2. An estimate of $F_{L,PET}$ was made by taking the ratio of the peak simulated activity using $F_{L,PET} = 1$ and other previously identified parameters to $A_{\text{peak}}$.

3. $F_{s,PET}$, $\tau_{s,PET}$, $\tau_{A,PET}$, and $\Delta t_{r,PET}$ were identified by fitting the remaining apneic data points.

These steps were repeated three times, each time beginning with the previously identified parameter set as initial conditions. The parameter set with the lowest MSE between the simulated and measured curves was then chosen, where
\[
MSE = \frac{\sum_{i=1}^{N} [C_{\text{simulated}}(i) - C_{\text{measured}}(i))^2 \times T(i)]}{\sum_{i=1}^{N} T(i)}.
\] (2.18)

Here the error is weighted by the PET camera imaging period \(T(i)\) and normalized by the total apneic imaging time. As in the previous model, two parameter sets, one including and another excluding recirculation, were recorded for each experimental trial using this optimization scheme.

### 2.5 Post-Processing

\(\tau_{s,\text{ART}}\) and \(\tau_{s,\text{PET}}\) were converted to volume of distributions \(V_{s,\text{ART}}\) and \(V_{s,\text{PET}}\) by multiplying by \(Q_{s,\text{ART}}\) and \(Q_{s,\text{PET}}\), respectively. \(\tau_{A,\text{ART}}\) and \(\tau_{A,\text{PET}}\) were converted to volume of distributions \(V_{A,\text{ART}}\) and \(V_{A,\text{PET}}\), assumed to be equal to alveolar gas volumes of distribution, by multiplying by \(\lambda Q_{A,\text{ART}}\) and \(\lambda Q_{A,\text{PET}}\), respectively. \(V_{s,\text{ART}}\) and \(V_{A,\text{ART}}\) were further converted to imaged volumes by multiplying by the imaged lung fraction calculated by \(\frac{A_{\text{peak}}}{C_I A_I}\) (see Chapter 3, Section 2.2).

### 2.6 Optimization Accuracy

Accuracy of the identified parameters was tested by using the models to simulate measured PET and arterial data (\(C_{\text{measured}}\) in Equations 2.17 and 2.18) using known parameters. The optimization was then run on these simulated kinetics curves in order to test how closely the identified parameter set matched the known input parameter set. For each model (including recirculation), this test was performed three times using the mean identified parameters from the LS, LP, and NP animals to define the simulated kinetics curves.
3 Results

3.1 Subject Characteristics

The mean and standard deviation (STD) of the $F_1O_2$, blood gas measurements, $Q_T$, and $F_1O_2$ from each experimental group are given in Table 2.2.

Table 2.2 – Mean and standard deviation (STD) of the inspired O₂ fraction ($F_1O_2$), measured blood gas data ($P_{O_2}, P_{CO_2}, pH$), measured cardiac output ($Q_T$), and calculated O₂ shunt ($F_sO_2$) from 7 lavaged supine (LS), 7 lavaged prone (LP), and 5 normal prone (NP) sheep.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LS</th>
<th>LP</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_1O_2$</td>
<td>1.00 0.00</td>
<td>1.00 0.00</td>
<td>0.26 0.04</td>
</tr>
<tr>
<td>$P_{O_2}$ (torr)</td>
<td>79 39</td>
<td>519 172</td>
<td>120 28</td>
</tr>
<tr>
<td>$P_{CO_2}$ (torr)</td>
<td>49 5</td>
<td>41 4</td>
<td>36 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 0.06</td>
<td>7.33 0.06</td>
<td>7.48 0.04</td>
</tr>
<tr>
<td>$Q_T$ (mL/s)</td>
<td>55 20</td>
<td>48 10</td>
<td>55 14</td>
</tr>
<tr>
<td>$F_sO_2$</td>
<td>0.52 0.22</td>
<td>0.11 0.12</td>
<td>0.04 0.04</td>
</tr>
</tbody>
</table>

3.2 Modeling and Optimization Data

The identified $F_r$, $\tau_s$, and $\tau_A$ values and resulting correlation coefficients ($R^2$) from the optimizations (Data Fit) and accuracy tests (Test) of both models (including recirculation) are summarized in Table 2.3 for each of the three studied conditions.
Table 2.3 – Identified shunt fraction \( (F_s) \), shunt time constant \( (\tau_s) \), and aerated time constant \( (\tau_A) \) and the resulting correlation coefficient \( (R^2) \) between the measured and simulated data from the optimizations (Data Fit) and accuracy tests (Test Fit) of both models (including recirculation) for 7 lavaged supine (LS), 7 lavaged prone (LP), and 5 normal prone (NP) sheep.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>LS</th>
<th>LP</th>
<th>NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>( F_s )</td>
<td>0.41</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Model</td>
<td>( T_s (s) )</td>
<td>8</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Data Fit</td>
<td>( T_A (s) )</td>
<td>106</td>
<td>59</td>
<td>996</td>
</tr>
<tr>
<td></td>
<td>( R^2 )</td>
<td>0.982</td>
<td>0.932</td>
<td>0.885</td>
</tr>
</tbody>
</table>

| Arterial  | \( F_s \) | 0.4   | -      | 0.01   |
| Model     | \( T_s (s) \) | 8     | 11     | 30     |
| Test Fit  | \( T_A (s) \) | 98    | 704    | 1035   |
|           | \( R^2 \)   | 1.000 | 0.996  | 0.993  |

| PET Model | \( F_s \) | 0.49  | 0.10   | 0.00   |
| Data Fit  | \( T_s (s) \) | 11    | 8      | 14     |
|           | \( T_A (s) \) | 1223  | 639    | 1557   |
|           | \( R^2 \)   | 0.988 | 0.997  | 0.998  |

Representative plots showing the acquired data and fits from both models are shown in Figure 2.5 for the LS, LP, and NP animals. These fits were made including recirculation. Comparisons between \( F_s \), \( \tau_s \), and \( \tau_A \) including and excluding recirculation are shown in Figure 2.6 where the difference between estimates is plotted versus the mean estimate.
Figure 2.5 – Plots showing fits from the PET (left side) and arterial (right side) models for the lavaged supine (LS, top), lavaged prone (LP, middle), and normal prone (NP, bottom) sheep. Correlation coefficients ($R^2$) for each fit are: (a) 0.999, (b) 0.991, (c) 1.000, (d) 0.939, (e) 1.000, and (f) 0.945.
Figure 2.6 – Comparison of shunt fraction ($F_s$, top), shunt volume of distribution ($V_s$, middle), and aerated gas volume of distribution ($V_A$, bottom) from PET (left side) and arterial (right side) model showing difference between estimations including recirculation and excluding recirculation versus the mean estimate.
4 Discussion

The most important findings of this study were:

1. Two mathematical models were developed that fit the measured PET data and arterial tracer concentration well.

2. Recirculated activity was found to influence both model simulations. In the arterial model, the inclusion of recirculation resulted in better fits for the LS animals while having little effect on other identified parameters. In the PET model, the fits were similar with and without recirculation but the identified parameters, most notably \( \tau_{A,\text{PET}} \), varied greatly.

4.1 PET Model Evaluation

This model simulated the PET kinetics curve of the lungs by dividing the single acquired curve representing the total activity in the imaged region into curves representing activity in aerated alveoli and activity in atelectatic, edematous, or fluid-filled alveoli. The model was based on the previous work of G. Galletti [2]. Fundamental changes were the identification of \( \tau_A \) (previously assumed infinite), a more accurate determination of \( F_r \), the identification of \( \Delta t_r \) (previously set to 30 s), and the inclusion of \( F_L \). The most notable of these alterations was the inclusion of finite values of \( \tau_A \) that result from finite aerated alveolar gas-volume to perfusion (\( V_A / Q_A \)) ratios. The inverse relation between the ratio and the amount of tracer reabsorbed by the bloodstream has been documented [1,6]. In normal healthy lungs, it is acceptable to assume this ratio to be nearly infinite such that only a negligible amount of tracer is reabsorbed by arterial blood. In such well-aerated lungs, the methods described by Mijailovich et. al. [7] can be directly applied to quantify regional pulmonary perfusion from the PET images with little error. However, in lungs with acute injuries such as those with surfactant depletion in this study, the finite nature of the ratio must be accounted for and the methods described by Mijailovich et. al. are compromised. If it is erroneously assumed that the ratio remains infinite in such cases, regional blood flow to aerated units will be underestimated and the amount of shunting blood flow will be
overestimated because tracer removal from low $V_A/Q_A$ regions is falsely attributed to shunting blood flow. Secondly, the effects of recirculated activity entering the imaged region after passage through the systemic circulation were modeled using $F$, determined according to the method described in Appendix A and $\Delta t_r$ determined from the optimization routine. Again, though neglecting recirculation in normal healthy lungs may be acceptable, it is increasingly important to model recirculation in acutely injured lungs due to the existence of significant low $V_A/Q_A$, edematous, or atelectatic lung regions that result in greater amounts of tracer being retained in the arterial blood. Unfortunately, modeling low $V_A/Q_A$ regions that remove additional activity simultaneously with recirculation that introduces additional activity is problematic due to the non-unique solutions that can arise from these counteracting influences. The modeling is further complicated by long $\tau_s$ values that result in shunting activity remaining in the imaged lung field throughout the 60 s apneic period. To understand the cause of such non-unique solutions, it is useful to illustrate how $\tau_s$ and $\tau_A$ affect the PET kinetics. These effects are shown in Figure 2.7, where the model was used to produce a series of curves using a range of each time constant while $F_s = 0.5$, $\tau_A = 3000$ s while $\tau_s$ was varied (left), and $\tau_s = 5$ s while $\tau_A$ was varied (right).

![Figure 2.7](image.png)

**Figure 2.7** – Plots showing effects of varying the shunt time constant ($\tau_s$, left) and aerated time constant ($\tau_A$, right) on the kinetics simulated by the lung model.
As shown, $\tau_s$ had a large effect on the height of the peak during the first 30 s and influenced the final 30 s of apneic data points for values greater than approximately 10 s. $\tau_A$ had little effect on the peak portion of the kinetics but a large effect on the latter 40 s. The relative influence of $\tau_s$ and $\tau_A$ on the overall kinetics curve depends on the perfusion to each respective compartment, $Q_s$ and $Q_A$, which depends on the shunt fraction $F_s$. In addition, $\Delta t_r$ was found to be $21 \pm 8$ s, meaning that recirculated activity affected roughly the same portion of the curve as $\tau_A$. For robust parameter identification from the kinetics curves, it is desirable that each parameter have a unique influence on independent portions of the curve. However, as indicated, significant interdependence between $F_r$, $F_s$, $\tau_s$, and $\tau_A$ allows identification of non-unique solutions. The dependence on $F_s$ is clearly seen in the wide variations in identified $F_s$, $\tau_s$, and $\tau_A$ values shown in Figure 2.6, where the difference between estimates is plotted versus the mean estimate. The identification of non-unique solutions is evident in the fact that, despite these variations, the mean correlation coefficient $R^2$ between the measured and simulated data did not change by more than 0.001 when recirculation was excluded for the three conditions studied. Therefore, an independent estimate of $F_r$ was obtained using $F_sO_2$ by the method described in Appendix A, and the parameter was fixed in subsequent modeling. $F_sO_2$ was used for this purpose because it provides a global shunt estimate, which is necessary in describing the recirculated activity because that activity comes from the entire lung, not just the imaged portion of the lung. This was also the reason that $F_{s,PET}$, which describes the shunt fraction of the imaged region, was not set to $F_sO_2$.

However, even with a reasonable estimate for $F_r$, the interdependence between $F_s$, $\tau_s$, and $\tau_A$ still allowed non-unique solutions. For instance, $\tau_A$ could still vary somewhat as $F_s$ varied, and vice versa, while maintaining an equally good fit to the measured data. This is illustrated by comparing the two optimized fits shown in Figure 2.8 made when $\tau_A$ was set to 300 s (left) and 3000 s (right).
Figure 2.8 – Two optimized fits made with the aerated time constant ($\tau_A$) set at 300 s (left) and 3000 s (right). The identified shunt fractions were 0.45 and 0.53 and the correlation coefficients ($R^2$) were 0.997 and 0.999 for the left and right fits, respectively.

The identified shunt fractions were 0.45 and 0.53 and the $R^2$ values were 0.997 and 0.999 for the left and right fits, respectively. Thus, a high $\tau_A$ and high $F_s$ had a similar effect as a low $\tau_A$ and low $F_s$.

The identification of non-unique solutions was also evident in the large amount of error found in the identified $\tau_A$ values from the accuracy test. In these tests, where $F_r$ was fixed, overestimates in $\Delta t_r$ resulted in overestimates of $\tau_A$. Qualitatively, longer $\Delta t_r$ values delay the arrival of recirculated activity, such that $\tau_A$ must be larger in order to maintain a level of activity that could have otherwise been achieved with shorter $\Delta t_r$ and lower $\tau_A$ values. Resulting errors from this non-unique situation were substantial, as a mean error of 25% in identified $\Delta t_r$ values resulted in a mean error of 179% in identified $\tau_A$ values. Because of the interdependence between parameters, these errors also induced errors in $F_s$ and $\tau_s$. Despite these errors, the $R^2$ value from the test fits for all three conditions was 1.000. This difficulty was also evident in the parameters identified by fitting the measured data, as evidenced by the large STD’s for $\tau_A$ values.

In conclusion, physiologic parameters, especially $\tau_A$, determined using this model were highly unreliable due to the existence of non-unique solutions. The non-
unique solutions were evidenced by: (1) the model fitting the measured data well whether recirculation was included or not (yielding average $R^2$ values between 0.987 and 0.998 for the three conditions studied) despite large variations in other parameters, (2) similar fits being obtained for high $\tau_A$ and high $F_s$ values as low $\tau_A$ and low $F_s$ values, and (3) large errors in the identified parameters from the accuracy test despite $R^2$ values of 1.000 for all three conditions. Therefore, although good fits to the measured data were obtained, the validity of the physiologic parameters used to create the good fits was questionable due to the identification of potentially non-unique solutions.

4.2 Arterial Model Evaluation

This model simulated the arterial tracer concentration kinetics acquired during the apneic period of emission imaging sequences. As in the PET model, finite $\tau_A$ values were allowed in order to describe regions with low $V_A/Q_A$ ratios. Recirculation was included in the model using a mixing volume with time constant $\tau_r$ and a convective delay $\Delta t_r = 20\text{ s}$. However, though similar in the compartments that were modeled, the arterial model showed less parameter interdependence than the PET model. The reason for this can be understood by examining the influence of each parameter on the arterial kinetics curve.

Recirculation again affected the second half of the apnea data ($\Delta t_r$ was set to 20 s), but to a much lesser extent than in the PET model. The reason for this is two-fold. First, all of the recirculated activity influences the PET data, regardless of whether it goes to shunting or aerated regions, whereas only 1.45% of the activity in the aerated regions influences the arterial data. Second, due to the additional blood volume in which the recirculated activity is mixed prior to sampling (in the pulmonary veins, left heart, and systemic arteries) along with the range of tracer transit times through the lung, the influence was less pronounced until the final 20 s of apneic data. This is shown in the representative plots in Figure 2.5. As a result, the inclusion or exclusion of recirculation from the model had little influence on the identified parameters, as shown in Figure 2.6 for $F_s$, $\tau_s$, and $\tau_A$.
The effect of $\tau_s$ and $\tau_A$ on the arterial kinetics are shown in Figure 2.9, where the model was used to produce a series of curves using a range of each time constant. The profiles were made using $F_s = 0.5$, $\tau_h = 5\, s$, $\tau_A = 3000\, s$ while $\tau_s$ was varied (left), and $\tau_s = 5\, s$ while $\tau_A$ was varied (right). Note that $\Delta t_s$ was set to zero such that only the 60 s of apneic data are shown.

Figure 2.9 – Plots showing effects of varying the shunt time constant ($\tau_s$, left) and aerated time constant ($\tau_A$, right) on the kinetics simulated by the arterial model.

The shunt time constant is seen to primarily influence the height and width of the peak during the first 30 s of apneic data. $\tau_A$, in contrast to the PET model where it primarily affected the latter 40 s of data, here is seen to affect nearly the entire curve equally.

Therefore, since the parameters in this model affected the kinetics curve uniquely, the identified parameters exhibited less interdependence than the PET model. This is evident in the increased accuracy of the identified parameters using test data (Table 2.3) for all three conditions. Due to the small influence of recirculation, there was some difficulty in identifying $\tau_s$. This again caused error in $\tau_A$, with overestimates in $\tau_s$ resulting in underestimates of $\tau_A$, and vice versa. However, the magnitude of the induced error was much less than in the PET model, as a mean error of 67% in $\tau_s$ values resulted in a mean error of only 4% in $\tau_A$ values. These errors resulted in small errors in $F_s$ and $\tau_s$ due to remaining interdependence between the parameters.
In conclusion, this model was able to provide more robust estimates of $F_s$, $\tau_s$, and $\tau_A$ than the PET model. Recirculation had little influence on the identified parameters, and each parameter had a more unique influence on the kinetics: $\tau_s$ primarily affected the height and width of the peak, $\tau_A$ affected nearly the entire curve, and $F_s$ affected the relative influence of the shunting and aerated compartment by controlling the amount of perfusion to each.

### 4.3 Optimization Evaluation

For an unknown function such as the optimization problem defined by Equation 2.16, it is impossible to guarantee that the identified minimum value was an absolute global minimum rather than a local minimum. There are a wide variety of global optimization routines that attempt to find global minima either with a high probability (heuristic methods) or within a required accuracy (stochastic methods). The chosen optimization routine, called the Multilevel Coordinate Search (MCS), is described as having qualities of both of these methods, combining the robust minimum identification of stochastic methods with local enhancements typical of heuristic methods [3].

Assuming that the routine is able to find the global minimum, it also must be remembered that the set of parameters defining the minimum is a characteristic of the defined mathematical system rather than a characteristic of the physiological system. Thus, changes in the system result in changes in the optimal set of parameters. For instance, if the MSE in Equation 2.17 were weighted by $C_{measured}^{1.1}$ rather than by $C_{measured}$, a new set of parameters would be identified. Furthermore, changes in the initial conditions often resulted in different identified parameters. (This proves that the global minimum was not guaranteed, since the same set was not determined in all cases.)

The results of the optimization accuracy test (Table 2.3) show that for all three parameters and all three conditions, the arterial model was able to more accurately identify the input test parameters. Both models had difficulty identifying the recirculation parameters ($\Delta t_r$ for the PET model, $\tau_r$ for the arterial model). These identification problems were expected due to the simultaneous and counteracting effects of $\tau_A$ on the PET kinetics and due to the small portion of the arterial kinetics affected by
recirculation (~ final 10-20 s). In both cases, these difficulties resulted in induced errors in \( \tau_A \). However, the amount of error in \( \tau_A \) introduced from the arterial model (4\%) is significantly less than that from the PET model (179\%), illustrating the more robust identification resulting from fitting the arterial kinetics.

Finally, note the large mean identified \( \tau_s \) values for the NP animals. For this condition, there was very little shunting activity, and as a result, there was little signal available to identify the time constant. Therefore the error in these values was significant. This also explains the poor identification of the test \( \tau_s \) parameter from both models.

5 Summary

Two mathematical models were developed to describe the tracer kinetics of experimental PET data from lung fields and arterial sampling. Both models described the data with high correlation coefficients. However, due to non-unique solutions, the physiological parameters identified from the model based on lung field kinetics were highly variable. Parameters identified from the model based on arterial kinetics were more robust. Recirculated activity was found to have complicating effects on both model simulations.
Appendix A: Estimating the Recirculation Fraction

The recirculation fraction, $F_r$, for individual cases was estimated from a linear regression between $F_r$ and $F_{\text{r}O_2}$ established in four experiments. In each such experiment, a series of venous samples were taken at approximately 30 s intervals during an imaging sequence with $F_{\text{r}O_2}$ between 0 and 32%. The concentration of these samples was determined using a well-counter and standard gamma-counting techniques. A linear regression of the maximum venous activity normalized by the injected activity versus $F_{\text{r}O_2}$ was performed, as shown in Figure 2.10. The recirculation fraction for each trial was then estimated using measured $F_{\text{r}O_2}$ values and the equation of the fitted line.

![Graphs showing venous and arterial activities and recirculation fraction vs. shunt fraction.]

Figure 2.10 – Representative venous sample activities are shown on the left along with the associated arterial kinetics curve. The maximum venous activity was normalized by the injected activity and plotted versus the shunt fraction for this and three other similar trials. A linear regression was then done such that the recirculation fraction could be estimated for any given shunt fraction.
References


Chapter 3
PET Derived Parameters

1 Introduction

It is desirable to be able to make accurate estimates of pulmonary physiological parameters and imaging characteristics directly from the kinetics of measured PET data from lung fields and arterial sampling, as such straightforward calculations avoid the complexity and time-consuming analyses that may otherwise be necessary to obtain the estimates. Four parameters that have been calculated with such direct calculations are the shunt fraction \( F_s \) and imaged lung fraction \( F_l \) from the apneic PET kinetics data, the aerated alveolar volume from the PET transmission and emission images \( V_{A,\text{transmission}} \), and the aerated alveolar volume from the lung and arterial kinetics of emission images \( V_{A,\text{emission}} \). In this chapter, these calculations were applied to the five normal sheep in the prone position (NP) and seven sheep experimentally injured with a saline lung lavage in the supine (LS) and prone (LP) position that were described in Chapter 2. In addition, the developed lung and arterial models were used to analyze the dependencies of the calculations by simulating the kinetics curves under various conditions and using them to calculate the parameters. Underlying assumptions of each calculation are discussed, and sources of error are identified and quantified.

2 Methods

2.1 Intrapulmonary Shunt Fraction

The intrapulmonary shunt fraction of the imaged lung \( F_{s,\text{img}} \) was estimated from the apneic data points. Relevant parameters are illustrated in Figure 3.1.
Figure 3.1 – A representative PET kinetics curve derived from apneic emission image frames, along with parameters used in calculating the intrapulmonary shunt fraction of the imaged lung ($F_{s,\text{img}}$). $A_{\text{peak}}$ was assumed to be proportional to the total imaged pulmonary perfusion $Q_{T,\text{img}}$, and $A_{\text{plateau}}$ was assumed to be proportional to imaged perfusion to aerated alveolar units $Q_{A,\text{img}}$, such that $F_{s,\text{img}} = 1 - A_{\text{plateau}} / A_{\text{peak}}$.

The quasi-steady-state activity ($A_{\text{plateau}}$) that was reached following removal of tracer from shunting regions, taken as the final apneic data point, was assumed to be proportional to perfusion to imaged aerated lung units ($Q_{A,\text{img}}$). The peak activity ($A_{\text{peak}}$) was assumed to be proportional to the perfusion to the imaged region ($Q_{T,\text{img}}$), including perfusion to both aerated and shunting ($Q_{s,\text{img}}$) units. $F_{s,\text{img}}$ was then calculated by
The influence of the following four factors on this calculation were investigated: (1) time constants of the shunting ($\tau_s$) and aerated ($\tau_A$) compartments, (2) sampling intervals of the PET camera, (3) recirculation, and (4) blood mixing volume of the right heart ($V_{rh}$).

2.1.1 Shunt and Aerated Alveolar Time Constants

To understand the influence of the time constants on $A_{peak}$ and $A_{plateau}$, the PET model was first used to characterize the response of the shunting and aerated compartments to their respective time constant. Because the two compartments are only distinguishable by their time constants, the effect of $\tau_s$ on the shunting compartment and of $\tau_A$ on the aerated compartment can be analyzed by considering the effect of a single generic time constant. This was done by isolating the effect of $\tau_A$ by using the model (without recirculation) to simulate a series of curves using a range of values for $\tau_A$, $F_s = 0$, $V_{rh} = 50$ mL, $\Delta t_{rh} = 0$ s, and $F_L = 1$, where ($\Delta t_{rh}$) is the delay between the injection site and imaged lung region. (Note that an analogous set of curves could have been created using a range of $\tau_s$ values and $F_s = 1$.) $A_{peak}$ and $A_{plateau}$ were calculated for each curve and plotted versus the time constant between 1 and 3000 s. Then, as in the PET model, $\tau_s$ was assumed to be between 1 and 30 s, while $\tau_A$ was assumed to be between 30 and 3000 s, such that the effect of each time constant on $A_{peak}$ and $A_{plateau}$ could be analyzed by examining the curves within their respective ranges.

Next, the PET model (without recirculation) was used to illustrate the dependence of the $F_{s, img}$ calculation on $F_s$, $\tau_s$, and $\tau_A$. The model was used to simulate PET kinetics curves using a range of $F_s$ values (0, 0.2, 0.4, 0.6, 0.8 and 1), a range of $\tau_s$ values between 1 and 30, and a range of $\tau_A$ values (30 s, 100 s, 500 s, and infinity). For each curve, $F_{s, img}$ was calculated according to Equation 3.1, resulting in a $6 \times 30 \times 4$
matrix of estimates along the \( F, \tau_s, \) and \( \tau_A \) dimensions, respectively. Six plots were then made for each known input shunt fraction \( F_s \), where \( F_{s, \text{img}} \) was plotted versus \( \tau_s \) for the four values of \( \tau_A \). Knowing \( F_{s, \text{img}}, \tau_s, \) and \( \tau_A \), it was then possible to estimate the actual shunt fraction and thus the amount of error in \( F_{s, \text{img}} \). This was done for the mean values \( F_{s, \text{img}}, \tau_s, \text{PET}, \) and \( \tau_A, \text{PET} \) for the three studied conditions, where \( \tau_s, \text{PET} \) and \( \tau_A, \text{PET} \) are the time constants identified using the PET model of the lungs (Table 2.3).

2.1.2 PET Camera Sampling Period

To illustrate the effect of the finite sampling period of the PET camera, the PET model (without recirculation) was used to create three pairs of simulated kinetics curves using \( F_s = 0.50, \tau_s = 5 \text{ s}, \tau_A = 3000 \text{ s}, V_r = 50 \text{ mL}, F_L = 1, \) and \( \Delta t_r \) values of 0, 0.5, and 1 s. The first curve of each pair represented the actual lung kinetics and was created using uniform 0.1 s sampling periods, while the second curve was created by converting this data to simulated PET data points using Equation 2.15 with the experimental sampling periods (2.5 s during the first 20 s of imaging, 10 s during the final 40 s). Errors in \( A_{\text{peak}} \) and \( A_{\text{plateau}} \) from the simulated PET data were then recorded and used to estimate the maximum expected error in \( F_{s, \text{img}} \) as a result of the PET sampling periods.

2.1.3 Recirculation

The effect of recirculation on \( A_{\text{plateau}} \) was investigated by using the PET model to create two series of curves using a range of \( F_s \) values between 0 and 0.5, \( \tau_s = 5 \text{ s}, \tau_A = 3000 \text{ s}, V_r = 50 \text{ mL}, \Delta t_r = 0, \) and \( F_L = 1 \). In the first series, recirculation was not included, while in the second series recirculation was included with \( \Delta t_r = 30 \text{ s} \) and \( F_r \) calculated according to Appendix A using each \( F_s \) value. The difference in \( A_{\text{plateau}} \) values with and without the additional recirculated activity was recorded throughout the \( F_s \) range, and was then used to calculate the percentage error in \( F_{s, \text{img}} \) by dividing the difference between the two shunt estimates by the true \( A_{\text{peak}} \) values (that when used in
Equation 3.1 with the $A_{\text{plateau}}$ values found without recirculation resulted in the simulated $F_s$ values). Note that recirculation did not influence $A_{\text{peak}}$ because the peak occurred prior to the arrival of recirculated activity. The curve was then used to estimate the error for each condition using the mean $O_2$ shunt values ($F_s O_2$, Chapter 2, Section 2.2) for each condition.

2.1.4 Heart Blood Volume

Finally, the influence of blood volume in the right heart and major vasculature between the injection site and imaged region was investigated. A series of curves was created using a range of $V_{rh}$ values (25, 50, 75, and 100 mL), $F_s = 0.50$, $\tau_s = 5$ s, $\tau_A = 3000$ s, $\Delta t_{rh} = 0$ s, and $F_L = 1$. Changes in $A_{\text{peak}}$ were recorded for these curves and used to calculate the maximum expected error in $F_{s, \text{img}}$ as a result of different blood volumes.

2.2 Imaged Lung Fraction

The imaged lung fraction ($F_{L, \text{img}}$) was also estimated from the apneic lung kinetics (Figure 3.1). $A_{\text{peak}}$ was again assumed to be proportional to $Q_{T, \text{img}}$, and the total activity injected $V_t C_t$ was assumed to be proportional to $Q_T$. Also, completely uniform perfusion was assumed. $F_{L, \text{img}}$ was then calculated as

$$F_{L, \text{img}} = \frac{A_{\text{peak}}}{C_t V_t}.$$  

(3.2)

If the perfusion was not uniform to all parts of the lung (while other assumptions remained valid), this value corresponded to the fraction of the pulmonary blood flow that was imaged rather than the fraction of lung that was imaged. Because this calculation partly depends on determining $A_{\text{peak}}$, it was subject to the same influences on $A_{\text{peak}}$ as discussed in the $F_{s, \text{img}}$ calculation: changes in $V_{rh}$, the PET cameral sampling interval, and an interdependence between $F_s$, $\tau_s$, and $\tau_A$.  

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2.2.1 Heart Blood Volume

The analysis of the effect of \( V_{rh} \) on the \( F_{s,\text{img}} \) calculation was used here to estimate the error in \( F_{L,\text{img}} \).

2.2.2 PET Camera Sampling Interval

The analysis of the effect of the PET camera sampling interval on the \( F_{s,\text{img}} \) calculation was used here to estimate the error in \( F_{L,\text{img}} \).

2.2.3 Shunting and Aerated Alveolar Time Constants

An analysis analogous to that done for \( F_{s,\text{img}} \) was done to determine the effects of \( F_s \), \( \tau_s \), and \( \tau_A \). Using the same ranges of the three parameters along with \( V_{rh} = 50 \text{ mL} \), \( \Delta t_{rh} = 0 \), and \( F_L = 1 \) but calculating \( F_{L,\text{img}} \) instead of \( F_{s,\text{img}} \), six plots were made for each known input shunt fraction \( F_s \), where \( F_{L,\text{img}} \) was plotted versus \( \tau_s \) for the four values of \( \tau_A \). Knowing \( F_{L,\text{img}} \), \( \tau_s \), and \( \tau_A \), it was then possible to estimate the amount of error in \( F_{L,\text{img}} \). This was done for the mean values of \( F_{L,\text{img}} \), \( \tau_s,\text{PET} \), and \( \tau_A,\text{PET} \) for all three standard conditions. A plot was also made of \( F_{L,\text{PET}} - F_{L,\text{img}} \) versus the mean of the two lung fraction estimates, where \( F_{L,\text{PET}} \) is the lung fraction identified by the PET model.

2.3 Alveolar Gas Volume of Tracer Distribution: Transmission Estimate

The transmission scan was used to calculate the gas fraction of each voxel by placing the activity within each voxel on a linear scale between 0 and 1, where 0 corresponds to the attenuation in an area of known dense tissue and 1 corresponds to the attenuation of the surrounding air. The resulting gas content image was then corrected such that values less than 0 were set to 0 and values greater than 1 were set to 1. A single-frame image of activity assumed to be in alveolar gas spaces was created by taking the sum of voxel activities from emission frames where a plateau had approximately been reached. Activities in this image were assumed to be proportional to the perfusion to
aerated alveoli. A perfusion weighted average gas fraction \( F_{gas} \) was then calculated according to

\[
F_{gas} = \frac{\sum_{i=1}^{N} (Q_i \cdot F_i)}{\sum_{i=1}^{N} Q_i},
\]

where \( Q_i \) is the activity within the \( i \)-th voxel, \( F_i \) is the \( i \)-th voxel gas fraction, and \( N \) is the number of voxels within the masked lung region. This is the effective gas fraction that the arterial blood "sees", meaning that the arterial activity will behave as though it were coming from a single-compartment lung with that gas fraction. For example, if all of the blood flow was going to shunting units with no gas content \( (F_i \cdot Q_i = 0) \), the effective gas content would be zero, despite the fact that there may actually have been alveolar gas spaces that were just not perfused, and the resulting arterial activity would behave as though it came from a completely collapsed or edematous lung. Finally, the effective imaged aerated volume \( V_{A,\text{transmission}} \) was calculated by multiplying \( F_{gas} \) by the total imaged lung volume, equal to \( N \) times the voxel volume.

2.3.1 Gas Fraction

To estimate the magnitude of the error in the gas fraction calculation used in estimating \( V_{A,\text{transmission}} \), two different methods were used to create gas fraction images for all three conditions studied. The first assumed an attenuation value for air (1-point), while the second made an estimate of the value based on the image (2-point). The average gas fraction was calculated for each method, and the difference between these averages and the mean of the two averages was taken as the amount of error to expect in the gas fraction images.

2.4 Alveolar Gas Volume of Tracer Distribution: Emission Estimate

Another estimate of the alveolar gas volume of distribution was made using the lung and arterial tracer kinetics curves from the emission scans. \( F_i O_2 \) was calculated from measured blood gases (Chapter 2, Section 2.2). \( A_{\text{plateau}} \) was calculated as described.
in Section 2.1, and an analogous arterial plateau concentration \( C_{a,\text{plateau}} \) was calculated by taking the average of the final 10 s of arterial apneic data points. Assuming that by the time the plateau had been reached there was no longer a shunt contribution \( (C_s = 0) \), the arterial plateau concentration was calculated as the perfusion weighted average of activities from the shunting and aerated compartments (Chapter 2, Equation 2.10) according to

\[
C_{a,\text{plateau}} = \frac{Q_A}{Q_T}(\lambda C_A) + \frac{Q_s}{Q_T}(0) \\
= (1 - F_{O_2})\frac{A_{\text{plateau}}}{V_{A,\text{emission}}} 
\]

where it was assumed that the total alveolar concentration \( C_A \) of the lung was equal to that of the imaged lung, which in turn was assumed to be the result of the alveolar activity \( A_{\text{plateau}} \) being distributed throughout the imaged gas the volume of distribution \( V_{A,\text{emission}} \). Solving for this volume,

\[
V_{A,\text{emission}} = (1 - F_{O_2})\frac{A_{\text{plateau}}}{C_{a,\text{plateau}}} 
\]

The influence of recirculation, shunting and aerated alveolar time constants, and gas-volume to aerated perfusion \( (V_A/Q_A) \) heterogeneity on the \( V_{A,\text{emission}} \) calculation were examined.

### 2.4.1 Recirculation

The effect of recirculation was analyzed by using the lung model to create two sets of kinetics curves, one including and another excluding recirculation, and using the arterial model to create analogous sets of arterial kinetics curves, again with one including and another excluding recirculation. All four sets were created using a range of \( F_s \) values between 0 and 0.5. In the arterial model, the curves were made using \( \tau_s = 5 \ s \), \( \tau_h = 3000 \ s \), \( \Delta \tau_s = 5 \ s \), \( \Delta \tau_h = 20 \ s \), and \( \Delta \tau_s = 0 \ s \), and when recirculation was included \( \tau_s = 50 \ s \). In the PET model, the curves were made using \( \tau_s = 5 \ s \), \( \tau_A = 3000 \ s \),
$V_{rh} = 50 \text{ mL, } \Delta t_{rh} = 0 \text{ s, } F_{L} = 1$, and when recirculation was included $\Delta t_{r} = 30 \text{ s}$ and $F_{r}$ was set equal to the maximum normalized activity being recirculated in the arterial model. For each value of $F_{s}$, two $V_{A,\text{emission}}$ calculations were made using Equation 3.5 with $F_{s}O_{2} = F_{s}$. The first was made from the lung and arterial curves including recirculation, and the second was made from the curves excluding recirculation. The error for each $F_{s}$ value caused by the presence of the recirculated activity was then taken as the difference between the $V_{A,\text{emission}}$ calculations. This error was plotted versus the input $F_{s}$ value, and the error expected from $V_{A,\text{emission}}$ calculations for the three studied conditions was estimated using mean $F_{s}O_{2}$ values.

### 2.4.2 Shunting and Aerated Alveolar Time Constants

To quantify the dependence of the $V_{A,\text{emission}}$ calculation on $F_{s}$, $\tau_{s}$, and $\tau_{A}$, the lung and arterial models (without recirculation) were used to simulate kinetics curves for a range of $F_{s}$ values (0.2, 0.4, 0.6, and 0.8), a range of $\tau_{s}$ values between 1 and 30, and a range of $\tau_{A}$ values (30, 100, 500, and 3000 s) using the same parameters for each model. Other lung model parameters were set with $V_{rh} = 50 \text{ mL, } \Delta t_{rh} = 0 \text{ s, and } F_{L} = 1$, while other arterial model parameters were set with $\tau_{h} = 5 \text{ s, } \Delta t_{r} = 20 \text{ s, and } \Delta t_{s} = 0 \text{ s}$. $V_{A,\text{emission}}$ was then calculated for each set of curves, and errors were calculated relative to the value calculated using $\tau_{s} = 1 \text{ s}$, which was low enough that shunting activity did not contribute to either plateau calculation. For each of the four $F_{s}$ values, the percentage error was plotted versus the range of $\tau_{s}$ for the four $\tau_{A}$ values. These plots were then used to estimate the error in $V_{A,\text{emission}}$ due to these three parameters using the mean $F_{s}O_{2}$, the mean of $\tau_{s, PET}$ and $\tau_{s, ART}$, and the mean of $\tau_{A, PET}$ and $\tau_{A, ART}$ for the three studied conditions, where $\tau_{s, ART}$ and $\tau_{A, ART}$ are the time constants identified by the arterial model (Table 2.2).
2.4.3 Aerated Gas-Volume to Perfusion Heterogeneity

Finally, the effect of heterogeneity in which the $V_A/Q_A$ ratio of the un-imaged lung differed from that of the imaged lung was examined. This was done by considering a hypothetical two-compartment lung model with no shunt ($F_s = 0$), as shown in Figure 3.2.

![Schematic showing hypothetical two-compartment lung model with no shunt.](image)

Figure 3.2 – Schematic showing hypothetical two-compartment lung model with no shunt. The top compartment was within the imaged region (IR) of the PET camera, and had an activity $A_{IR}$ distributed throughout its gas volume $V_{IR}$ while receiving a blood flow $Q_{IR}$. The bottom compartment was not imaged (NI), and analogously had an activity $A_{NI}$ distributed throughout its gas volume $V_{NI}$ while receiving a blood flow $Q_{NI}$. The concentration of activity in the capillary blood leaving these compartments ($C_{IR}$ and $C_{NI}$, respectively) was used to calculate the systemic arterial concentration $C_a$.

The top compartment was within the imaged region (IR), received blood flow $Q_{IR}$, and contained activity $A_{IR}$ distributed throughout a gas volume $V_{IR}$. The bottom compartment was not imaged (NI) and had analogous characteristics $Q_{NI}$, $A_{NI}$, and $V_{NI}$.

The theoretical end-capillary concentrations ($C_{IR}$, $C_{NI}$) were calculated by $C = \frac{A}{V}$, and
the systemic arterial concentration ($C_a$) was calculated by the perfusion weighted average of these concentrations according to

$$C_a = \lambda \left( \frac{Q_{IR} A_{IR}}{Q_T V_{IR}} + \frac{Q_{NI} A_{NI}}{Q_T V_{NI}} \right).$$  \hspace{1cm} (3.6)

Using Equation 3.5 to estimate $V_{A,\text{emission}}$, which in this case was known to be equal to $V_{IR}$, results in

$$V_{A,\text{emission}} = \frac{\lambda A_{IR}}{\lambda \left( \frac{Q_{IR} A_{IR}}{Q_T V_{IR}} + \frac{Q_{NI} A_{NI}}{Q_T V_{NI}} \right)}. \hspace{1cm} (3.7)$$

Assuming that $A$ was proportional to $Q$ in each compartment, and after canceling and rearranging terms, this becomes

$$V_{A,\text{emission}} = V_{IR} \left( \frac{Q_{IR}}{Q_T} + \frac{V_{IR} Q_{NI} V_{NI}}{Q_T} \right)^{-1}. \hspace{1cm} (3.8)$$

This equation was used to plot the error in $V_{A,\text{emission}}$ versus a range of $\frac{Q_{IR}}{Q_{NI}}$ ratios (0.75-1.25) for a range of imaged lung fractions (0.5-0.9). Errors for each condition were then estimated for each condition using mean $F_{L,\text{img}}$ values and assuming that the $\frac{V_{IR}}{Q_{IR}} : \frac{V_{NI}}{Q_{NI}}$ ratio was between 0.9 and 1.1.

3 Results

3.1 Intrapulmonary Shunt Fraction

A comparison between $F_{s,\text{img}}$ and $F_s O_2$ from the LS and LP animals is shown in Figure 3.3. NP animals were omitted from the plot because the shunt fractions from both calculations were low. Average $F_{s,\text{img}}$ values were 0.38±.12 for LS, 0.09±.09 for LP, and 0.02±.02 for NP, compared with average $F_s O_2$ values of 0.52±.22 for LS, 0.11±.12 for LP, and 0.04±.04 for NP.
Figure 3.3 – Comparison between the shunt fraction calculated from the lung kinetics ($F_{s,\text{img}}$) and the O$_2$ shunt ($F_sO_2$) for lavaged supine (diamonds) and lavaged prone (circles) animals, with $F_{s,\text{img}} - F_sO_2$ plotted versus $F_sO_2$.

3.1.1 **Shunting and Aerated Alveolar Time Constants**

The response of the shunting or aerated compartment to their respective time constant is shown in Figure 3.4, where $A_{\text{peak}}$ and $A_{\text{plateau}}$ are plotted versus the generic time constant.
Figure 3.4 – Plot showing dependence of $A_{\text{peak}}$ and $A_{\text{plateau}}$ on the time constant of the shunting alveolar unit (between 1 and 30 s) and aerated alveolar unit (between 30 and 3000 s).

For time constants between 1 and 30 s, $A_{\text{peak}}$ varied between 0.22 and 0.87 of the total activity reaching the compartment, while $A_{\text{plateau}}$ varied between 0.00 and 0.18. For a time constant of 3000 s, $A_{\text{peak}}$ equaled 1.00, while $A_{\text{plateau}}$ equaled 0.98. $A_{\text{plateau}}$ remained below 0.01 for time constants below 12 s, and remained below 0.05 for time constants below 18 s. Plots showing the dependence of $F_{s, \text{img}}$ on $F_s$, $\tau_s$, and $\tau_A$ are shown in Figure 3.5.
Figure 3.5 – Plots showing the dependence of $F_{s,\text{img}}$ on $F_s$, $\tau_s$, and $\tau_A$. $F_{s,\text{img}}$ is plotted versus $\tau_s$ between 0 and 30 s using $\tau_A$ values of 30 s, 100 s, 500 s, and infinity in each of the six plots made using $F_s$ values of 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0.
The \( F_{s,\text{img}} \) calculation is independent of \( \tau_s \) when \( F_s = 0 \) and independent of \( \tau_A \) when \( F_s = 1 \). For \( F_s < 1 \), greater \( \tau_A \) values consistently result in lower \( F_{s,\text{img}} \) estimates, while for \( 0 < F_s < 1 \) greater \( \tau_s \) values result in an initial increase followed by a decrease in the estimate. Using the mean \( F_{s,\text{img}} \) (0.38 for LS, 0.09 for LP, 0.02 for NP), \( \tau_{s,PET} \) (11 s for LS, 6 s for LP, and 14 s for NP), and \( \tau_{A,PET} \) (1223 s for LS, 639 s for LP, and 1557 s for NP) values, the true shunt fractions were estimated to be 0.45 for LS, 0.06 for LP, and 0.00 for NP, which is equivalent to errors of -0.07, +0.03, and +0.02 in \( F_{s,\text{img}} \), respectively.

### 3.1.2 PET Camera Sampling Interval

Results from analyzing the effect of the PET camera sampling interval on \( A_{\text{peak}} \) are shown in Figure 3.6.

![Figure 3.6 - Plot showing the effect of PET sampling intervals on \( A_{\text{peak}} \) for heart delays of 0.0 s, 0.5 s, and 1.0 s. The difference between the peak of the actual lung kinetics curves (solid lines) and that of the acquired PET kinetics curve (data points) depends in part on the delay, which alters the portion of the actual kinetics curve within each sampling interval.](image-url)
The actual lung kinetics curve peak was 0.78 for $\Delta t_{rh}$ values of 0.0 s, 0.5 s, and 1.0 s, while $A_{peak}$ measured from the acquired PET kinetics curve was 0.74, 0.75, and 0.76, respectively. $A_{plateau}$ was found to be 0.49 for all cases, such that $F_{s,\text{img}}$ was calculated as 0.33, 0.35, and 0.36, respectively. Using the actual peak, $F_{s,\text{img}}$ was calculated as 0.37. Therefore, a maximum error of 0.04 is expected for the PET sampling intervals used in these experiments, which is 8% of the actual shunt fraction (0.5) used to generate the curves.

### 3.1.3 Recirculation

Results from analyzing the effect of recirculation on the $F_{s,\text{img}}$ calculation are shown in Figure 3.7.

![Plot showing error in the shunt fraction calculated from the lung kinetics ($F_{s,\text{img}}$) caused by increasing amounts of recirculated activity for shunt fractions between 0 and 0.5.](image)

**Figure 3.7** – Plot showing error in the shunt fraction calculated from the lung kinetics ($F_{s,\text{img}}$) caused by increasing amounts of recirculated activity for shunt fractions between 0 and 0.5.

The plot shows an increasing error at higher shunt fractions. An error of 1.6% is expected at a shunt fraction of 0, while an error of 11.8% is expected at a shunt fraction of 0.5. For the mean $F_iO_2$ values of each condition (0.52 for LS, 0.11 for LP, and 0.04 for NP), the error due to recirculation was estimated as 12%, 5%, and 3%, respectively.
3.1.4 Heart Volume

Results from analyzing the effects of $V_{rh}$ on $A_{peak}$ are shown in Figure 3.8, where the first 20 s of each PET kinetics curve created using $V_{rh}$ values of 25, 50, 75 and 100 mL are plotted.

![Figure 3.8](image)

**Figure 3.8 – Plot showing the effect of the right heart volume ($V_{rh}$) on the first 20 s of the PET kinetics curve.** $A_{peak}$ varied between each volume, while $A_{plateau}$ was unaffected.

$A_{plateau}$ was found to be 0.49 for all cases, while $A_{peak}$ varied between 0.70 and 0.76, resulting in $F_{s,\text{img}}$ calculations between 0.30 and 0.36. Therefore, a maximum error of 0.06 is expected from varying $V_{rh}$ values, which is 12% of the actual shunt fraction (0.5) used to generate the curves.

3.2 Imaged Lung Fraction

A comparison between $F_{L,\text{img}}$ and $F_{L,\text{PET}}$ is shown in Figure 3.9.
Figure 3.9 – Comparison between the lung fraction calculated from the lung kinetics ($F_{L, img}$) and identified using the lung model ($F_{L, PET}$) for lavaged supine (LS), lavaged prone (LP), and normal prone (NP) animals, with $F_{L, PET} - F_{L, img}$ plotted versus average of the two estimates.

Average $F_{L, img}$ values were 0.64±.10 for LS, 0.56±.10 for LP, and 0.75±.08 for NP, while average $F_{L, PET}$ values were 0.79±.12 for LS, 0.62±.15 for LP, and 0.76±.07 for NP.

3.2.1 Heart Volume

An maximum error of 12% was expected from changes in $V_{rh}$, as described in Section 3.1.4.

3.2.2 Shunting and Aerated Alveolar Time Constants

The six plots showing the dependence of $F_{L, img}$ on $F_s$, $\tau_s$, and $\tau_A$ are shown in Figure 3.10.
Figure 3.10 – Plots showing the dependence $F_{Limg}$ on $F_s$, $\tau_s$, and $\tau_A$. $F_{Limg}$ is plotted versus $\tau_s$ between 0 and 30 s using $\tau_A$ values of 30 s, 100 s, 500 s, and infinity in each of the six plots made using $F_s$ values of 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0.
$F_{L,\text{img}}$ underestimates the actual lung fraction for all cases except when $F_s = 0$ with $\tau_A$ equal to infinity. The calculation is independent of $\tau_s$ for $F_s = 0$ and independent of $\tau_A$ for $F_s = 1$. For $F_s < 1$, the error decreases for all $F_s$ and $\tau_A$ values as $\tau_s$ increases. Using mean $F_{L,\text{img}}$ (0.64 for LS, 0.56 for LP, and 0.75 for NP), $\tau_{s,\text{PET}}$ (11 s for LS, 6 s for LP, and 14 s for NP), and $\tau_{A,\text{PET}}$ (1223 s for LS, 639 s for LP, and 1557 s for NP) values from each condition, the $F_{L,\text{img}}$ estimates were underestimated by approximately 16% for LS, 7% for LP, and 2% for NP.

3.3 Alveolar Gas Volume of Tracer Distribution

Two plots showing aerated volume ratios versus $F_sO_2$ are shown in Figure 3.11, where $V_{A,\text{emission}}$ is normalized by $V_{A,\text{transmission}}$. The $V_{A,\text{emission}} : V_{A,\text{transmission}}$ ratio was 0.09±.06 for LS, 0.72±.31 for LP, and 0.92±.20 for NP (mean±std).

![Figure 3.11](image)

Figure 3.11 – Comparison of aerated volume estimates from emission ($V_{A,\text{emission}}$) and transmission ($V_{A,\text{transmission}}$) images, with the ratio $V_{A,\text{emission}} : V_{A,\text{transmission}}$ plotted versus the $O_2$ shunt fraction ($F_sO_2$).
### 3.3.1 Gas Fraction

The average gas fraction for all animals found from the 1-point method was $0.36 \pm 0.13$ (mean ± std), while that found from the 2-point method was $0.42 \pm 0.13$ (mean ± std). Assuming the average of the means (0.39) to be the true mean, the difference of 0.03 between the true mean and estimated mean is equivalent to an 8% error in the gas fraction. Therefore, an equivalent error is expected in $V_{A,\text{transmission}}$.

### 3.3.2 Recirculation

Results from analyzing the effect of recirculation on the $V_{A,\text{emission}}$ calculation are shown in Figure 3.12, where the error percentage in $V_{A,\text{emission}}$ is plotted for shunt fractions between 0 and 0.5.

![Figure 3.12](image)

Figure 3.12 - Plot of error percentage in the aerated volume estimate from emission images ($V_{A,\text{emission}}$) caused by recirculation as a function of the shunt fraction between 0 and 0.5 s.

$V_{A,\text{emission}}$ is shown to be increasingly underestimated for higher shunt fractions, with an underestimate of 92% at $F_s = 0.5$. Using the mean $F_sO_2$ values of 0.52 for LS, 0.11 for LP, and 0.04 for NP, the expected error due to recirculation was estimated as -93%, -26%, and -8%, respectively.
3.3.3 Shunting Alveolar Time Constant

Results from analyzing the effect of $F_s$, $\tau_s$, and $\tau_A$ on the $V_{A,\text{emission}}$ calculation are shown in the four plots of Figure 3.13, where the error percent in $V_{A,\text{emission}}$ for each $F_s$ value is plotted versus $\tau_s$ for a range of $\tau_A$ values.

Figure 3.13 – Error in the aerated volume estimate from emission images ($V_{A,\text{emission}}$) plotted versus the shunt time constant ($\tau_s$) for shunt fractions ($F_s$) of 0.2, 0.4, 0.6, and 0.8 and aerated time constants ($\tau_A$) of 30, 100, 500, and 3000 s.

Using the mean $F_sO_2$ (0.52 for LS, 0.11 for LP, and 0.04 for NP), identified $\tau_s$ (10 s for LS, 7 s for LP, and 19 s for NP), and identified $\tau_A$ (665 s for LS, 678 s for LP, and 1277 s for NP).
s for NP) values, errors of -41%, -2%, and -20% were expected in $V_{A,\text{emission}}$ for the three conditions, respectively.

3.3.4 Alveolar Gas-Volume to Perfusion Heterogeneity

Results from analyzing the effect of heterogeneity on $V_{A,\text{emission}}$ are presented in Figure 3.14.

Figure 3.14 - Plot showing error in the aerated volume estimate from emission images ($V_{A,\text{emission}}$) resulting from unequal gas-volume to aerated perfusion ratios ($V_A/Q_A$) between the imaged and un-imaged lung regions for a range of imaged lung fractions ($F_L$).

As the imaged lung fraction increases, the $V_{A,\text{emission}}$ calculation becomes less sensitive to heterogeneity in which the $V_A/Q_A$ ratio of the imaged lung differs from that of the un-imaged lung. As described in Section 3.2, average $F_{L,\text{img}}$ values were $0.64 \pm 0.10$ for LS, $0.56 \pm 0.10$ for LP, and $0.75 \pm 0.08$ for NP. Assuming the $V_A/Q_A$ ratio of the un-imaged lung was within 10% of the imaged lung, errors of 4%, 5%, and 3% were expected for each respective condition.
4 Discussion

4.1 Intrapulmonary Shunt Fraction

Evaluation of the intrapulmonary shunt fraction $F_{s,\text{img}}$ from the PET images according to the method described in Section 2.1.4 is fundamentally flawed by the fact that $A_{\text{peak}}$ and $Q_{T,\text{img}}$ are related by a different proportionality constant than $A_{\text{plateau}}$ and $Q_{A,\text{img}}$. To understand the cause of this difference and its effect on the $F_{s,\text{img}}$ calculation, it is first useful to discuss the primary basis of this calculation: that peak activities within a given unit are proportional to the perfusion to those units. Because the correlation of $A_{\text{plateau}}$ with $Q_{A,\text{img}}$ is based on the assumption that $A_{\text{plateau}}$ is the result of all of the activity perfusing aerated alveolar units diffusing into and accumulating in the gas spaces, it is equivalent to the peak activity of the aerated compartment (i.e. $A_{\text{peak},A} = A_{\text{plateau}}$). Therefore, because of the assumption that $A_{\text{peak}}$ is the sum of $A_{\text{peak},A}$ and the peak activity in the shunting compartment ($A_{\text{peak},s}$), the $F_{s,\text{img}}$ calculation is effectively based on $A_{\text{peak},A}$ being proportional to $Q_{A,\text{img}}$, $A_{\text{peak},s}$ being proportional to $Q_{s,\text{img}}$, and both being proportional by the same constant. However, the proportionality constant between peak activity and blood flow depends on the time constant of the compartment, and because $\tau_s$ and $\tau_A$ are inherently different, that assumption is invalid. This is clearly seen when Equation 3.1 is rewritten in its fundamental form

$$F_{s,\text{img}} = \frac{Q_{s,\text{img}}}{Q_{s,\text{img}} + Q_{A,\text{img}}} = 1 - \frac{K(\tau_A) \cdot A_{\text{peak},A}}{K(\tau_s) \cdot A_{\text{peak},s} + K(\tau_A) \cdot A_{\text{peak},A}}, \quad (3.9)$$

where the proportionality constant $K(\tau)$ is explicitly shown. Therefore, only when $\tau_A = \tau_s$ such that $K(\tau_A) = K(\tau_s)$ do the proportionality constants cancel. Furthermore, because $A_{\text{peak}} = A_{\text{peak},A} + A_{\text{peak},s}$ only when $\tau_A = \tau_s$, Equation 3.9 may alternatively be written
where the proportionality constant again only cancels when $\tau_A = \tau_s$.

### 4.1.1 Shunting and Aerated Time Constants

As long as $\tau_A = \tau_s$ the calculations in Equations 3.9 and 3.10 are valid. However, by using $A_{plateau}$ to approximate $A_{peak,A}$ as in Equation 3.1, it was assumed that $\tau_A$ was infinite (no activity was reabsorbed by the blood from the gas spaces) such that finite values for either $\tau_A$ or $\tau_s$ result in errors. First, consider the effect of decreased $\tau_A$ values that result from low $V_A/Q_A$ ratios. Activity is reabsorbed by the blood over the 60 s of apnea (the amount of which increases with decreased $V_A/Q_A$ ratios [1,2]) and a plateau value is not reached. Nevertheless, in Equation 3.1 the final apneic data point is used to calculate $A_{plateau}$ regardless of $\tau_A$. This results in $F_{s,\text{img}}$ being overestimated for one of two equivalent reasons: (1) $A_{plateau}$ does not represent a steady-state plateau value, or (2) $A_{plateau}$ does not represent $A_{peak,A}$. As shown in Figure 3.5, $F_{s,\text{img}}$ is increasingly overestimated for lower $\tau_A$ values resulting from low $V_A/Q_A$ ratios. This can be interpreted as the result of one of two equivalent things: (1) assuming a lower, non-existent steady-state plateau value and attributing higher prior activities to shunt, or (2) underestimating $A_{peak,A}$ and as a result effectively creating a non-existent $A_{peak,s}$.

Finite $\tau_s$ values caused additional error in $F_{s,\text{img}}$. (Note that the error is truly caused by the difference between $\tau_s$ and $\tau_A$, but since Equation 3.1 implicitly assumes that $\tau_A$ is infinite such that $A_{peak,A} = A_{plateau}$, it is more useful to consider errors relative to infinite $\tau_s$ values.) As shown in Figure 3.4, $A_{peak}$ increased as $\tau_s$ increased, indicating that the proportionality constant in Equations 3.9 and 3.10 decreases as $\tau_s$ increases. However, the figure also shows that $A_{plateau}$ increased for time constants.
greater than 12 s. This is the result of activity from shunting units remaining within the imaged region while \( A_{\text{plateau}} \) is calculated, which in this case is the final 10 s of apneic imaging. Therefore, \( \tau_s \) has two counteracting effects for increasing values: (1) \( A_{\text{peak}} \) increases resulting in greater \( F_{s,\text{img}} \) estimates, and (2) \( A_{\text{plateau}} \) increases resulting in lower \( F_{s,\text{img}} \) estimates. These counteracting influences are clearly seen in Figure 3.5, where \( F_{s,\text{img}} \) estimates initially increase with \( \tau_s \) as \( A_{\text{peak}} \) increases and then begin to decrease as \( A_{\text{plateau}} \) rises.

### 4.1.2 PET Camera Sampling Interval

The finite sampling period of the camera caused \( A_{\text{peak}} \) to be lower than the actual, instantaneous peak activity in the imaged region. This error increases with larger sampling periods that increase the averaging interval of Equation 2.15 and with lower \( \tau_s \) values, and depends in part on the convective delay between the injection site and imaged region (\( \Delta t_{rh} \)). As shown in Figure 3.6, a maximum error of approximately 8% is expected due to these factors. It is noted that \( \tau_s \) values less than 5 s values would cause the peak to narrow more and could result in even greater errors. However, because average \( \tau_{s,\text{PET}} \) values were greater than 5 s (Table 2.3: 11±8 s for LS, 6±11 s for LP, 14±15 s for NP), this was not thought to be a significant concern.

### 4.1.3 Recirculation

Recirculation introduces additional activity during the period when \( A_{\text{plateau}} \) is calculated, and similarly to the effect of large \( \tau_s \) values, causes \( A_{\text{plateau}} \) to be overestimated and \( F_{s,\text{img}} \) to be underestimated. As shown in Figure 3.7, the amount of overestimation increases with increased shunt fractions that result in greater amounts of activity being recirculated, with errors of 12%, 5%, and 3% expected for the LS, LP, and NP conditions.
4.1.4 **Heart Blood Volume**

Changes in the heart blood volume are not thought to be significant for repeated measurements in a single subject. However, inter-subject comparisons must account for this additional error, as neglecting it could lead to erroneous conclusions about the level of shunt present.

4.1.5 **Conclusions**

The total estimated error in each $F_{s,\text{img}}$ calculation was estimated as 19% for LS, 15% for LP, and 15% for NP, assuming the errors to be independent and neglecting errors resulting from the combined effect of various $F_s$, $\tau_s$, and $\tau_A$ values. However, though these errors may seem reasonable, it must be remembered that they are the result of larger counteracting errors rather than errors of the measurement itself. Due to these limitations in the computation of $F_{s,\text{img}}$, it is recommended that the estimates be used only for qualitative assessments of the amount of shunt and not be used as quantitative calculations. Furthermore, since only a fraction of the lungs are imaged, the estimates are not indicative of the global shunt, but rather of the shunt of the imaged lung. Only when the entire lung is imaged, or more accurately when all of the pulmonary blood flow is imaged, can $F_{s,\text{img}}$ be used to make a direct assessment of the global shunt.

4.2 **Imaged Lung Fraction**

Similarly to the $F_{s,\text{img}}$ calculation, the $F_{L,\text{img}}$ estimate is based on $A_{\text{peak}}$ being proportional to $Q_{T,\text{img}}$, the injected activity ($C IV_t$) being proportional to $Q_T$, and both of them being proportional by the same constant value. By simply taking the ratio of activities to represent the ratio of imaged lung (or imaged pulmonary blood), it is assumed that these proportionality constants are equal and cancel, resulting in Equation 3.2.

4.2.1 **Heart Blood Volume**

However, because the tracer reaching the imaged lung region was additionally diluted by blood in the right heart and major vasculature between the injection site and
imaged lung region, the two proportionality constants necessarily differ. As shown in Figure 3.8, $A_{\text{peak}}$ varied between 0.70 and 0.76, resulting in an error of 12% in the $F_{s,\text{img}}$ calculation.

### 4.2.2 PET Camera Sampling Interval

The sampling interval of the PET camera has the same effect of causing $A_{\text{peak}}$ to be underestimated as discussed in Section 4.1, and analogously may cause an underestimation of $F_{L,\text{img}}$ by up to approximately 8%.

### 4.2.3 Shunting and Aerated Time Constants

As shown in Figure 3.10, this calculation depends only weakly on $\tau_A$. This is due to the relatively small influence of $\tau_A$ on $A_{\text{peak}}$, as shown in Figure 2.7 of Chapter 2. The calculation does depend on $\tau_s$, which causes the peak to decrease for smaller values (Figure 3.4), and on $F_s$, which amplifies the effect of $\tau_s$ at higher values.

### 4.2.4 Conclusions

There are three additional limitations to this calculation: (1) heterogeneous perfusion, (2) extrapulmonary shunt, and (3) determination of the $C_1$. If the assumption of uniform perfusion to all lung regions fails, the fraction represents the imaged pulmonary blood rather than imaged lung. For example, if only half of the lung was imaged but all of the pulmonary blood flowed through the imaged region, the fraction would be one. Extrapulmonary shunt allows tracer to bypass the lung such that $C_1V_t$ no longer corresponds to $Q_T$, and $F_{L,\text{img}}$ is underestimated by an amount proportional to the extrapulmonary shunt. It was assumed that extrapulmonary shunt was negligible. Finally, errors in $C_1$ result in proportional errors in $F_{L,\text{img}}$. Previous experiments have estimated the error in $C_1$ to be approximately 15%. Therefore, in total, errors of 26%, 22%, and 21% are expected for LS, LP, and NP conditions, assuming the errors to be independent. Because the effect of $V_m$, $F_s$, $\tau_s$, and $\tau_A$ all cause underestimates in
this estimate is consistently below that of $F_{L,PET}$ where these factors are accounted for, as shown in Figure 3.9.

4.3 Alveolar Gas Volume of Tracer Distribution

4.3.1 Transmission $V_A$ Estimate

This calculation relies on the accuracy of the gas fraction and aerated perfusion images derived from the transmission and emission images, respectively. In creating the gas fraction image, there was approximately an 8% error introduced from the attenuation values chosen to represent tissue and air. Furthermore, in creating the perfusion image using the final 2-4 apneic frames, it was assumed that the activity in each voxel represented that within aerated alveoli, such that the sum was proportional to $Q_{A,\text{img}}$. This being similar to the correlation of $A_{\text{plateau}}$ with $Q_{A,\text{img}}$ discussed in Section 4.1, it is also subject to the same sources of error: recirculation and $\tau_v$ values greater than 12 s. Both result in voxels with shunting areas receiving additional activity during the plateau frames. Thus, non-aerated regions would receive additional weighting such that $F_{\text{gas}}$, and hence $V_{A,\text{transmission}}$, would be underestimated. Approximate estimates of the amount of error introduced from these factors can be inferred from Figure 3.5 and Figure 3.7.

Finally, since the calculation given in Equation 3.3 depends on a voxel-by-voxel multiplication between the two images, it is assumed that the two images correspond exactly. Certainly some error is introduced from this assumption, as the transmission scan is taken during normal breathing and the apneic portion of the emission scan is taken at mean lung volume. This, in addition to any slight positional movements between the two imaging sequences, clouds the correlation between the voxels of the two images. It is unclear how much error was introduced due to such un-correlated voxels.

4.3.2 Emission $V_A$ Estimate

This calculation relied on three primary assumptions: (1) that the final emission PET data point was representative of only aerated alveolar activity reached after all shunting activity has passed through the imaged region, (2) that the final 10 s of apneic
data points from the arterial curve was solely the result of tracer re-absorption from those aerated alveoli, and (3) that un-imaged lung behaved as imaged lung. The validity of the first assumption was discussed in Section 4.1 regarding $A_{\text{plateau}}$ in the $F_{r,\text{img}}$ calculation. Similarly to that calculation, recirculated activity and large $\tau_s$ values will cause activity in shunting units to be included in estimating $A_{\text{plateau}}$ and $C_{a,\text{plateau}}$. However, because it is the ratio of these values that is used in Equation 3.5, it is more important to consider the relative effects between the PET and arterial plateaus than the absolute effect on one. At higher shunt fractions, there is less relative increase in $A_{\text{plateau}}$ than in $C_{a,\text{plateau}}$ because most of the recirculated activity transiently passes through the lungs, and thus contributes less to the kinetics curve than in the arteries where the recirculation leads to nearly proportional increases in activities. This is evident in Figure 3.12, which shows that $V_{A,\text{emission}}$ is increasingly underestimated for higher shunt fractions.

As discussed in Section 4.1, $\tau_s$ values greater than 12 $s$ prevent the elimination of shunt activity from the imaged region such that $A_{\text{plateau}}$ is overestimated. Similarly, large $\tau_s$ values cause an overestimation in $C_{a,\text{plateau}}$. However, unlike the lung model, here $\tau_s$ must be considered along with $\tau_h$ because the effects of the shunting and heart compartments on the arterial activity are indistinguishable (see Chapter 2, Figure 2.4). Therefore, in order to insure that the shunted activity does not influence $C_{a,\text{plateau}}$, the sum of the two time constants must be less than approximately 12 $s$. Since estimated $\tau_h$ values for all three conditions were $9 \pm 5$ $s$, $\tau_s$ values greater than approximately 3 $s$ result in $C_{a,\text{plateau}}$ being overestimated. Because this threshold is lower than that of $A_{\text{plateau}}$, $C_{a,\text{plateau}}$ will be overestimated more than $A_{\text{plateau}}$ for all $\tau_s > 3$ $s$, and $V_{A,\text{emission}}$ will be underestimated. As shown in Figure 3.13, $V_{A,\text{emission}}$ can be dramatically underestimated when large $\tau_s$ values are present.

Finally, the third assumption fails when significant heterogeneity exists such that the aerated volume to perfusion ratio in the un-imaged lung differs from that imaged. As an example, if 75% of the lungs (or pulmonary perfusion) were imaged and the imaged ratio were 20% greater than the non-imaged ration, an underestimate of 5% would result.
This overestimate increases as the imaged lung fraction decreases, such that if only 50% of the lungs were imaged and the ratio remained 20% greater than the un-imaged ratio, an underestimation of 9% would result.

4.3.3 Conclusions

In looking at the $V_{A,\text{emission}}:V_{A,\text{transmission}}$ results in Figure 3.11, three striking features are noted. First, $V_{A,\text{emission}}$ is much less than $V_{A,\text{transmission}}$ for LS animals, averaging a ratio of $0.09 \pm 0.06$. Systemic errors that may explain this discrepancy include those that cause an overestimation in $V_{A,\text{transmission}}$ or an underestimation in $V_{A,\text{emission}}$, as discussed in Sections 4.3.1 and 4.3.2, respectively. These errors include those from: (1) determining attenuation values to represent air and tissue in creating the gas fraction image, (2) uncorrelated voxels between the transmission and perfusion images, (3) gas volume heterogeneity in which the gas volume to perfusion ratio of the imaged region was greater than that of the un-imaged region, (4) recirculated activity, and (5) $\tau_s$ values greater than 3 s. Errors in the gas fraction calculation were estimated to be approximately 8% in Section 4.3.1, while un-correlated voxels added an unknown amount or error. The existence of un-imaged lung heterogeneity cannot be confirmed, but based on the magnitude of the errors of the hypothetical cases discussed in Section 4.3.2, experimental errors were estimate to be less than 5%. The average $F,O_2$ for LS was $0.52 \pm 0.22$ for LS (mean± std), which means that $V_{A,\text{emission}}$ was underestimated by approximately 94% due to recirculation. Finally, the average $\tau_s$ according to the arterial simulation was $8 \pm 2$ s (mean± std), which means $V_{A,\text{emission}}$ was approximately underestimated by an additional 49%. Therefore, considering the worst case, $V_{A,\text{transmission}}$ may have been overestimated by 8% and $V_{A,\text{emission}}$ may have been underestimated up to 106%. Clearly these errors are more than enough to explain the low alveolar volume ratios in Figure 3.11 for LS animals.

The second striking feature of the plot is that at lower shunt fractions, there are five cases (2 LP and 3 NP animals) in which $V_{A,\text{emission}}$ is greater than $V_{A,\text{transmission}}$. The alveolar volume ratios for these trials were between 1.04 and 1.07. Systemic errors that
may explain this discrepancy include those that cause an underestimation in $V_{A,\text{transmission}}$ or an overestimation in $V_{A,\text{emission}}$, as discussed in Sections 4.3.1 and 4.3.2, respectively. There are three such sources of error: (1) determining attenuation values to represent air and tissue in creating the gas fraction image, (2) un-correlated voxels between the transmission and perfusion image, and (3) gas volume heterogeneity exists such that the gas volume to perfusion ratio of the imaged region is greater than that of the un-imaged region. These three factors have been discussed, such that a worst case error of 9% was expected in the alveolar volume ratio. Again, this amount of error is able to explain the fractions that are greater than one.

Finally, the third notable feature in Figure 3.11 is the wide range of fractional volumes exhibited by the 6 LP and 5 NP animals with $F_O_2$ values less than 0.2. For these groups, the fractional alveolar volumes were $0.80 \pm 0.25$ and $0.92 \pm 0.20$, respectively.

5 Summary

The assumptions and limitations of four calculations made directly from the images and kinetics curves acquired during functional pulmonary PET imaging were described. The benefit of these calculations is that they provide fast estimations of important parameters (shunt fraction, imaged lung fraction, alveolar gas volume of distribution). However, the cost of these straightforward calculations is accuracy. Significant errors were found in all four calculations. These errors were greater for injured lungs, where the assumptions of the calculations break down. In conclusion, though these calculations provide an efficient means of qualitatively assessing the parameters, they should not be used as quantitative calculations.
6 References
