Quantification of Intrapulmonary Blood Shunt and Ventilation / Perfusion Distributions in Injured Lungs by Positron Emission Tomography

by

Desmond Seow

Submitted to the Department of Mechanical Engineering in partial fulfillment of the requirements for the degree of

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at the

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Chapter 1

Introduction

1.1 Importance

The importance of adequate ventilation-perfusion (\(\dot{V}_A/\dot{Q}\)) matching for the lung to function as an effective gas-exchanging unit has prompted many researchers to examine the \(\dot{V}_A/\dot{Q}\) relationship more closely [7]. In fact, the most common cause of impaired gas exchange in the lung is caused by uneven matching of alveolar ventilation \(\dot{V}_A\) and pulmonary blood flow \(\dot{Q}\) at the alveolar level [3]. In pulmonary diseases, the \(\dot{V}_A/\dot{Q}\) mismatches are caused by structural changes of the lung parenchyma and/or pulmonary vasculature, resulting in an impairment of both \(O_2\) and \(CO_2\) transfer in the lungs [13].

Unlike the cyclic nature of ventilation, where a portion of air spaces known as dead space do not participate in gas exchange, perfusion in healthy lungs is a pulsatile quasi-continuous process, resulting in a quasi-continuous gas exchanging process. However, in some pulmonary diseases, it is possible that gas exchange to certain regions of the lung is stopped, resulting in intrapulmonary shunt. In adult respiratory distress syndrome, for example, 50 percent of the cardiac output can be shunted [3]. In the presence of true shunt, administration of large doses of oxygen has little effect in overcoming the desaturation resulting from the abnormality. This observation is in contrast to arterial desaturation due to \(\dot{V}_A/\dot{Q}\) mismatches where even a small increase
in inspired oxygen concentration leads to significant improvement [3]. Hence, it is important to be able to differentiate the two causes of desaturation.

Traditionally, $\dot{V}_{A}/\dot{Q}$ mismatches could be assessed in terms of venous admixture, physiological dead space, arterial and expired $pO_2$ and $pCO_2$. However, these methods provided little information that is helpful to the physicians about the $\dot{V}_{A}/\dot{Q}$ distribution within the lung [14]. 20 years ago, a technique known as the multiple inert gas elimination technique (MIGET) was developed by Wagner and coworkers [12]. This technique is based on a model that subdivides the lung into many (50) compartments and assesses the global gas exchange resulting from them. Although the technique has yielded crucial information about the physiology of gas exchange, the results obtained in some cases can be ambiguous. For example, if ventilation is altered by a change in airway properties, it is not clear whether the change in $\dot{V}_{A}/\dot{Q}$ distribution is due to the changes in ventilation or whether it is due to the change in perfusion in response to the ventilation change [8].

For the past 10 years, clinical use of radionuclides to study regional lung function has become commonplace. Ventilation studies involve the use of Xe-133, and Kr-81m, however, the use of these radionuclides for $\dot{V}_{A}/\dot{Q}$ studies provide only planar projections of the distribution and have no spatial resolution in the depth direction. Methodologies of determining regional perfusion involve the intravenous injections of $^{99m}$Tc-macroaggregates or microspheres of albumin that are well mixed with blood in their passage through the heart [2][3][4][9], and Positron Emission Tomography (PET) imaging techniques using radioactive tracers labeled with Oxygen-15 gas [9]. However, due to the short half life of $^{15}$O ($T_{1/2} = 123$ s), using this tracer generally results in images with low signal to noise ratio. In addition, although perfusion scans have a reputation for great safety, a few patients with severe pulmonary hypertension have died as a direct result of the injection of these particles [1][11]. More importantly, the above methods of perfusion scans are unable to distinguish between intraregional blood flow to collapsed shunting units from flow to gas exchanging units.

Studies have recently shown the feasibility of using PET with radioactive nitrogen-13 ($^{13}$NN) as tracer to obtain sectional images of $\dot{V}_{A}$ and $\dot{V}_{A}/\dot{Q}$ distributions in the normal lung [7A][7B][10]. With its intrinsic high resolution and relatively easy attenuation correction procedures, PET is ideal for high-quality tomographic imaging of pulmonary gas exchange in both normal and diseased lungs. The main advantage of
PET imaging in diseased lungs is its ability to non-invasively obtain the variables (\(\dot{V}_A\), \(\dot{Q}\), and \(\dot{V}_A/\dot{Q}\)) within the same patient as opposed to the various different methods presented above. Furthermore, due to its relatively short imaging time, the patient's radiation exposure time will be minimal.

1.2 Project Goals

The long term goal of the project is to develop a reliable technology that can be used as a clinical diagnostic tool to help physicians assess the gas exchanging properties of diseased lungs. The current goal of this project is to demonstrate the feasibility of this technology to obtain the necessary variables need for assessing lung function and to verify our findings with current methods.

1.3 Scope of Thesis

The main goals of this thesis will be to:

1. Present methods of determining the signal to noise ratio in single and ratio PET images.
2. Assess, using pig and canine models, perfusion (\(\dot{Q}\)), Ventilation (\(\dot{V}_A\)) and ventilation-perfusion (\(\dot{V}_A/\dot{Q}\)) ratio in injured lungs.

The thesis will cover methods of examining and quantifying noise in single and ratio PET images at various spatial resolutions (Chapter 2). The latter three chapters will examine the use of PET to quantify the perfusion (\(\dot{Q}\)), ventilation (\(\dot{V}_A\)), and ventilation/perfusion (\(\dot{V}_A/\dot{Q}\)) ratio of the lungs under various injured conditions. Chapter 3 will look at the use of PET to non-invasively verify the condition of post operative transplanted lungs. Chapter 4 will quantify the above mentioned variables in a lung with bronchial stenosis under high frequency jet ventilation (HFJV) and examine the effects using heliox, a gaseous mixture of helium and oxygen instead of air on the distribution of ventilation. Finally, in chapter 5 we will be developing models, on a regional as well as on a voxel-by-voxel basis, to quantify regional \(\dot{Q}\) and estimating the shunt fraction in a unilaterally surfactant depleted lung.
1.4 References


Chapter 2

Determination of Noise in Single and Ratio Positron Emission Tomography Images

2.1 Introduction

In order to quantify regional heterogeneity in lung function from images created using Positron Emission Tomography (PET), it is important to assess the contributions of noise to the total heterogeneity of the images. Under experimental conditions, several causes contribute to image noise and deterioration of image fidelity:

1. Noise in the correction for tissue attenuation propagated from the transmission scan.
2. Error in corrections for detector non-uniformity and/or non-linearity.
3. Random coincidences detected by the camera.
5. Statistical noise due to limited counts and radioactive decay during measurements with short-lived radionuclides (in our case, $^{13}$NN) [1].
6. Smoothing of the image caused by the reconstruction filter resulting in artifactal smearing of the edges.
This chapter describes an experimental method to estimate the contributions of statistical noise and imaging artifacts to the heterogeneity of PET images using specially designed gas phantoms.

2.2 Theoretical Considerations

2.2.1 Use of a Lung Phantom to Determine the Coefficient of Variation (COV) in Ratio Images

The spatial heterogeneity of a physiological variable object can be characterized by a regional coefficient of variation (COV) defined as the standard deviation ($\sigma_x$) of the local data normalized by its mean ($\bar{x}$). The square of the COV, ($\sigma_x / \bar{x}$)$^2$, corresponds to the mean-normalized-variance of the data and, as a first order approximation, can be expressed as a sum of all uncorrelated sources of heterogeneity. The total normalized variance of a PET image can be separated into different components:

$$\left( \frac{\sigma_x}{\bar{x}} \right)^2_{\text{Image}} = \left( \frac{\sigma_x}{\bar{x}} \right)^2_{\text{Variable}} + \left( \frac{\sigma_x}{\bar{x}} \right)^2_{\text{TM, Edge}} + \left( \frac{\sigma_x}{\bar{x}} \right)^2_{\text{Noise}}$$

(2-1)

where:

- ($\sigma_x / \bar{x}$)$^2_{\text{Image}}$ = Total heterogeneity of the PET Image
- ($\sigma_x / \bar{x}$)$^2_{\text{Variable}}$ = True spatial heterogeneity of the imaged variable
- ($\sigma_x / \bar{x}$)$^2_{\text{TM, Edge}}$ = Heterogeneity introduced by the PET camera and by reconstruction filtering and/or partial volume artifacts
- ($\sigma_x / \bar{x}$)$^2_{\text{Noise}}$ = Contribution of statistical noise to the heterogeneity of the image

With the use of a lung phantom (figure 2-2, page 27), one can estimate and correct for the fraction of the variance due to statistical noise, ($\sigma_x / \bar{x}$)$^2_{\text{Noise}}$ in the following manner. For a given camera, the normalized variance created by random noise is, to a first order approximation, proportional to the square of the pixel size ($l$) and inversely proportional to the average number of counts per pixel ($n$) and the effective resolution length ($L$) of the reconstruction filter raised to the 3rd power. It can be shown that if an image is created from the ratio of two
different images, i and j, of the same object and reconstructed at the same resolution length, the contribution of \((\sigma_x \div \overline{x})^2_{TM,Edge}\) to each image must be perfectly correlated and thus will cancel out in an image created by taking their ratio. Hence, the normalized variance of the ratio image, \(((\sigma_x \div \overline{x})^2_{\eta})\), should be caused exclusively by noise and should be proportional to the sum of the sum of variances caused by noise on the respective images:

\[
\left(\left(\frac{\sigma_x}{\overline{x}}\right)^2\right)_{(i \div j)} = K \cdot \hat{I}^2 \cdot \left(\frac{1}{n_i} + \frac{1}{n_j}\right) \times \frac{1}{L}
\]

where i and j are two different images and K is a proportionality constant.

Hence, knowing \(n_i\), \(n_j\), and L for a series of ratio images of the same object, the slope, m, of a plot of \(((\sigma_x \div \overline{x})^2_{\eta})\) vs. \((1/n_i+1/n_j) \cdot 1/L^3\) can be estimated as the product of K, the proportionality factor, and \(I^2\). Knowledge of the slope m allows the calculation of \((\sigma_x \div \overline{x})^2_{Noise}\) for any ratio of two images and thus, its true heterogeneity:

\[
\left(\frac{\sigma_x}{\overline{x}}\right)^2_{Ratio\ Variable} = \left(\frac{\sigma_x}{\overline{x}}\right)^2_{Ratio\ Image} - \left(\frac{\sigma_x}{\overline{x}}\right)^2_{Noise}
\]

(2-3)

2.2.2 Use of a Disk Phantom to Determine Errors from the Attenuating of Positrons at the Edges

To estimate the contribution to variance stemming from the smoothing of the filtering edge and from the transmission correction scan, we assessed the heterogeneity of a central region of interest (ROI) in a very high count rate disk phantom image reconstructed before transmission correction, \((\sigma_x \div \overline{x})^2_{Central}\) and the heterogeneity of a chest wall surrounded lung phantom image reconstructed after transmission correction, \((\sigma_x \div \overline{x})^2_{CW}\) masked by thresholding at 50% of the peak number of counts.

Assuming that the inherent heterogeneities of the two phantoms are the same (they were built from the same material), then the contributions of transmission correction and edge effects, \((\sigma_x \div \overline{x})^2_{TM,Edge}\) can be estimated as:
\[
\left( \frac{\sigma_x}{\bar{x}} \right)_{\text{TM, Edge}}^2 = \left( \frac{\sigma_x}{\bar{x}} \right)_{\text{CW}}^2 - \left( \frac{\sigma_x}{\bar{x}} \right)_{\text{Central}}^2
\]  
(2-4)

With the empirical knowledge of the slope, \( m \) between \( (\sigma_x / \bar{x})^2 \), \( \text{Noise} \) and \( (1/n_i+1/n_j) \cdot 1/L^3 \), and of \( (\sigma_x / \bar{x})^2 \), \( \text{TM, Edge} \), equation (2-1) can be written as:

\[
\left( \frac{\sigma_x}{\bar{x}} \right)_{\text{Variable}}^2 = \left( \frac{\sigma_x}{\bar{x}} \right)_{\text{Image}}^2 - \left( \frac{\sigma_x}{\bar{x}} \right)_{\text{TM, Edge}}^2 - \left( \frac{\sigma_x}{\bar{x}} \right)_{\text{Noise}}^2
\]  
(2-5)

### 2.2.3 Theoretical Estimation of Noise

A theoretical estimation of noise including a correction for the effect of photon attenuation has been previous derived by Alpert et. al. [1]. This estimate is obtained by reconstructing original sinograms with the square, instead of the first power, of the reconstruction filter yielding an image of local variance per voxel, \( \sigma_E^2 \), or the expected local variance due to counts fluctuations in the projection data with a noiseless attenuation correction. By dividing, voxel-by-voxel, the \( \sigma_E^2 \) image by the square of the original image \( (\bar{x}^2) \), an image of theoretical estimate of expected normalized variance, \( (\hat{\sigma}_E / \bar{x})^2 \) can be obtained. The mean value of such an image is an estimator of the global normalized variance of the image. Contribution to the variance caused by a noisy attenuation correction was neglected in our analysis.

### 2.3 Methods

#### 2.3.1 Phantom Models

To simulate the low density of lung tissue structures, 2 different phantom models were built. The phantoms were cut from open-cell synthetic rubber foam with a void to total volume ratio of approximately 15%. The surfaces were first covered with two layers of helium balloon Mylar material, and two plastic nipples were then glued to the surface. Finally, the phantoms were coated with approximately 1 mm of latex rubber.

One of the phantom was a 5 cm thick disk with a diameter of 12 cm. This diameter was chosen to be comparable in size to the cross sectional area of the dog lungs imaged (figure 2-1, page 26). The other phantom was cut to mimic the...
shape of the imaged lung cross sections including a space to accommodate a simulated heart (figure 2-2). The outside diameter of the phantom had the same diameter as that of the disk phantom.

2.3.2 Experimental Set-up

$^{11}$C labeled CO gas ($T_{1/2} = 20.4$ min.) was generated by a cyclotron and used to load the phantoms. We used this gas because its half life was short enough to allow for sequential imaging of the same object at decreasing levels of activity but long enough to provide reasonable imaging count rates before decay. The tracer gas was received and stored in a two-liter rubber bag initially collapsed and connected to the phantom nipples were a series of connected tubings and stop-cock valves (figure 2-3, page 28). The phantom was initially collapsed using a high vacuum pump and then allowed to passively re-expand with the tracer gas from the rubber bag. To minimize areas within the phantoms with non-uniform low tracer concentration, the phantoms were loaded and collapsed 2 to 3 times prior to imaging. The phantom was then positioned in the camera field inside a 12 cm diameter, 1 mm thin plexi-glass ring and a series of 16 three minute images were collected. A sample for camera calibration collected from the gas remaining in the bag was cross calibrated with a scintillation counter (model System 5000, Nucleus Inc., Oak Ridge, TN).

To stimulate the effects of the chest wall and heart tissues in the lung phantom, the plexi-glass ring was also surrounded with an approximately 2 cm layer of play-dough and a lump of play-dough was placed at the appropriate position to mimic the heart. The plexi-glass ring allowed the phantoms to fully collapse and fully re-expand without deforming the dough. This material and geometry created a degree of gamma-ray attenuation equal to that created by the chest wall in our experimental animals.

2.3.3 Analysis

2.3.3.1 Processing of Collected Sinograms

Sinograms were corrected for non-uniform camera sensitivity and were reconstructed both before and after a transmission correction. A Hanning filter
was used in reconstruction with resolution lengths set at 1.0 cm, 0.71 cm, and 0.5 cm.

Masks were made to analyze the disk and lung phantom data. A central mask was defined from the disk phantom images without chest wall nor transmission correction by thresholding to only include voxels with counts ≥ 70% of the peak number of counts. This mask was 9.48 cm in diameter and virtually excluded the contribution to variance caused by edge effects. A lung phantom mask was defined, from the chest wall surrounded lung phantom images reconstructed with transmission correction, by thresholding to 50% of the peak number of counts (figure 2-7, page 32). For analysis, single images of disk or lung phantoms were added together in various combinations to obtain a final set of 22 images with total number of counts per image spreading over a decade. Image combinations of these sets of images were divided in pairs to obtain 16 ratio images.

2.3.3.2 Processing of Single and Ratio Images

From the set of 22 single images, \((\sigma_x / \bar{x})^2\) was determined from each image of lung or disk phantom made with and without chest wall, and plotted against \(1/n\) for resolution lengths of 0.5, 0.71 and 1.0 cm. Since the disk phantoms without chest wall produced negligible attenuation, the y-axis intercept from the plot of \((\sigma_x / \bar{x})^2\) versus \(1/n\) of non-transmission corrected images with a central mask should correspond to the inherent heterogeneity of the disk foam and uncorrected camera sensitivity, \((\sigma_x / \bar{x})^2_{Central}\). The y-axis intercept of similar plots of \((\sigma_x / \bar{x})^2\) against \(1/n\) for transmission corrected images of the lung phantom with chest wall yielded a value for \((\sigma_x / \bar{x})^2_{CW}\) that included the heterogeneity of the foam, uncorrected camera sensitivity, transmission correction and edge effects. Thus, the variance due to edge effects and transmission correction, \((\sigma_x / \bar{x})^2_{TM,Edge}\), was obtained as the difference between \((\sigma_x / \bar{x})^2_{CW}\) and \((\sigma_x / \bar{x})^2_{Central}\).

For ratios of images reconstructed at spatial resolutions (L) of 1, 0.71, and 0.5 cm, \((\sigma_x / \bar{x})^2\) was determined and plotted against \((1/n_i + 1/n_j)^{-1}/L^3\) (figure 2-6, page 31). The slope \((m)\) between \((\sigma_x / \bar{x})^2_{Noise}\) and \((1/n_i + 1/n_j)^{-1}/L^3\) was estimated by fitting a linear regression line to the data.
2.3.3.3 Theory Confirmation

A reconstruction program was modified to create an image of expected variance described in section 2.2.3. Sinograms for lung phantoms and actual dog lung images were reconstructed using this program keeping the resolution lengths equal to that used in normal image reconstruction (1 cm). This produced images of $\sigma^2$ that were divided by the original images to generate images of local $\left(\frac{\sigma_E}{x}\right)^2$. Mean values of such images were obtained and compared with estimated values using the empirically derived method.

Empirical data from $\left(\frac{\sigma_x}{\bar{x}}\right)^2_{\text{Noise}}$ was plotted against theoretical data of $\left(\frac{\sigma_E}{x}\right)^2$ from single and ratio lung phantom, as well as, from dog lungs images. A correlation between empirical and theoretical data was obtained by a linear regression fit to the data.

2.4 Results/Discussion

2.4.1 Experimental Findings

The intercepts of the plots of $\left(\frac{\sigma_x}{\bar{x}}\right)^2$ versus $1/n$ for the central ROI of a disk phantom image without a transmission correction at resolution lengths of 1.0, 0.71 and 0.5 cm were all very close to a value of 0.0033 (figure 2-4, page 29). This value provides an estimate of $\left(\frac{\sigma_x}{x}\right)^2_{\text{Central}}$. The equal intercept means that the intrinsic heterogeneity of the phantom has a length scale larger than or equal to 1 cm. The increasing slope as the resolution length decreases shows the increase of heterogeneity of the images at higher resolutions.

A similar plot of $\left(\frac{\sigma_x}{\bar{x}}\right)^2$ against $1/n$ for a transmission corrected lung phantom image with chest wall, masked with a threshold of 50% shows much higher intercepts which increases as resolution lengths (L) decreases. For the resolution used in our studies (L=1 cm), the intercept was 0.0185 providing an estimate of $\left(\frac{\sigma_x}{x}\right)^2_{\text{CW}}$ (figure 2-5, page 30). Accordingly, the expected variance created by attenuation correction and edge effects $\left(\frac{\sigma_x}{\bar{x}}\right)^2_{\text{TM,Edge}}$ is the difference of 0.0185 and 0.0033 (0.0152). Intercepts increasing with lower resolution lengths means that noise magnitude by chest wall attenuation is propagated at all length scales and is not eliminated by increasing image counts.
Also, the increasing slope at lower resolution lengths shows that the heterogeneity increases with decreasing L.

The slope (m) of the plot of \((\sigma_x / \bar{x})^2\) versus \((1/n_i + 1/n_j)*1/L^3\) for the 50% thresholded transmission corrected image of a lung phantom with chest wall (figure 2-6) was determined by linear regression to be 0.624 (\(R^2 = 0.97\)). Knowledge of m allows for the estimation of \((\sigma_x / \bar{x})^2_{\text{Noise}}\) of any image reconstructed at a resolution length of 1 cm and n counts per voxel as \([(0.624)/n]\). Note that the intercept of this plot is very close to zero, confirming the hypothesis that \((\sigma_x / \bar{x})^2_{\text{TM,Edge}}\) cancel out in ratio images.

With knowledge of \((\sigma_x / \bar{x})^2_{\text{Noise}}\) and \((\sigma_x / \bar{x})^2_{\text{TM,Edge}}\), true spatial heterogeneity of the imaged object in a single or a ratio of images could be estimated using equations (2-5) and (2-3) respectively.

### 2.4.2 Theory Confirmation

A plot of empirical \((\sigma_x / \bar{x})^2_{\text{Noise}}\) versus theoretical \((\sigma_x / \bar{x})^2\) was made for data obtained from single and ratio lung phantom, as well as, dog lungs images (figure 2-8, page 33). From the ratio lung phantom data, slope of 1.272 ± 0.070, y-intercept of -0.0025 ± 0.0019 and correlation coefficient (R) of 0.992 were obtained. With the single lung phantom data slope of 1.151 ± 0.003, y-intercept of 0.000 ± 0.000, and R of 0.9999 were obtained. From dog lungs data, slope of 0.975 ± 0.092, y-intercept of 0.0047 ± 0.0063 and R of 0.987 were calculated. Finally, by combining the 3 data sets, we obtained a slope of 1.007 ± 0.029, y-intercept of 0.0034 ± 0.0012 and R of 0.993. With the above results, we could conclude that the empirical estimate of global image noise showed good correlation with the theoretical estimate of noise. Furthermore, because the variance caused by noisy attenuation correction was neglected in our theoretical estimations, the empirical data were more conservative in most cases.

### 2.5 Conclusion

With the use of novel open-cell foam collapsible phantoms for PET imaging, we are able to experimentally determine the contributions of noise to the heterogeneity of a PET image. This method of noise estimation is in good
agreement with the theoretical estimation of noise developed by Alpert et. al [1].
for both phantoms and images obtained from dog lungs.
2.6 Figures

Figure 2-1  Schematic of the Collapsible Disk Phantom
Figure 2-2  Schematic of the Collapsible Lung Phantom
Figure 2-3  Experimental setup of phantom studies
Figure 2-4 Normal variance $\left(\frac{\sigma_x}{\bar{X}}\right)^2_{\text{Central}}$ of individual phantom images plotted against the inverse of the average counts per pixel for images reconstructed at 0.5 [square], 0.71 [circle] and 1.0 [triangle] cm. The images were not corrected with the transmission matrix, hence the intercepts are approximately identical and correspond to the heterogeneity of the phantom. The images are masked to exclude edges by only including voxels with counts that are > 70% of the peak number of counts.
Figure 2-5  Plot of \( (\sigma_x / \bar{x})^2 \) for the lung phantom with chest wall against the inverse of the average counts per pixel for the images reconstructed at 0.5 [square], 0.71 [circle] and 1.0 [triangle] cm. The images are transmission corrected and hence have different intercepts due to the noise contribution from a transmission image.
Figure 2-6  Plot \((\sigma_x / \bar{X})^2_{\text{Noise}}\) against \((\gamma_i + \gamma_j) L^3\) for lung phantom images with chest wall after transmission correction reconstructed at 0.5 [square], 0.71 [circle] and 1.0 [triangle] cm. Note that the intercept of the plot is approximately zero which confirms the theory that taking the ratio of images, inaccuracies due to reconstruction, attenuation correction and edge effects are canceled out.
Figure 2-7  Illuminated surface plots where the z coordinate represents the normalized counts per pixel from the phantoms. (a) corresponds to the central ROI of the disk phantom illustrating the inherent heterogeneity of the phantom material. (b) represents a single lung phantom image where inherent heterogeneity, edge effects and transmission noise contribute to the overall variance of the image.
Figure 2-8  Plot of empirical $(\frac{\sigma_x}{\bar{x}})^2_{\text{Noise}}$ versus theoretical $(\frac{\sigma_e}{x})^2$ for representative single lung phantom [circle], ratio lung phantom [triangle] and dog lungs [square]. Note that the empirical estimate of noise is more conservative than the theoretical estimator.
2.7 References


Chapter 3

Determination of Transplanted Lung Condition with the use of Positron Emission Tomography (PET)

3.1 Introduction

Unilateral lung transplant is becoming an increasingly common procedure in hospitals today. Hence, the ability to follow up on the condition of gas exchange of the transplanted lung has become increasingly important. Currently, the post operative condition of a transplanted lung is assessed with Trans-Bronchial Biopsy, where small samples of the transplanted lung are removed from the patient to determine morphological and cellular changes, or, with ventilation and perfusion scans using a gamma scintillation camera. These scans, although non-invasive, only provide a qualitative description of local gas exchange [3]. Trans-Bronchial Biopsy is a reliable method of determining the condition of a small fraction of the lung; but, it is both invasive and prone to sampling error, since only small amounts of the transplanted lung can be removed.

In this chapter, non-invasive PET imaging methods for determining local gas exchange are applied to assess lung function after unilateral lung transplantation.
3.2 Methods

3.2.1 Subject Preparation

Unilateral left lung transplants were performed on six pigs under various conditions of donor-host tissue matching. Two of the six subjects (pig #1 and pig #2) had auto transplant, where the subject's own lung was removed and transplanted back into the subject. This procedure was done to eliminated the process of rejection by the animal. The remaining four animals received allo transplants from litter mate donors and the following matching conditions:

- Pig #3: Mismatched for airway (class 1) and vasculature (class 2).
- Pig #4: Matched for class 2 and mismatched for class 1.
- Pig #5: Matched for class 1 and mismatched for class 2.
- Pig #6: Matched for class 1 and class 2.

3.2.2 Imaging Protocols

3.2.2.1 Experimental Setup

Mechanically ventilation was administered to the animal using a Harvard Pump (VT = 25 ml/kg, frequency = 10 bpm, and inspiratory time fraction = 30%). The imaging system used included a single slice PET camera, a mechanical respirator in a closed loop rebreathing circuit, an infusion system for the administration of $^{13}$NN-saline solution, and an apparatus for the preparation of the $^{13}$NN-saline solution (figure 3-1, page 45).

The PET camera, described in detail elsewhere [1], is a high sensitivity stationary camera imaging a 1 cm thick slice. A closed loop rebreathing circuit, including CO$_2$ absorber and supplemental oxygen, allowed for ventilation with $^{13}$NN-labeled gas, or with tracer free gas. A solenoid valve system allowed rapid switching between respiratory gas sources. $^{13}$NN gas, produced by a cyclotron, was introduced into the rebreathing circuit for inhaled tracer studies, or forced into previously degassed saline solution and temporarily stored in a chamber for perfused studies. $^{13}$NN-saline solution was infused into the animal via a 15 gauge catheter using a peristaltic pump. A remotely controlled solenoid valving system was used to allow flushing of the tubing with $^{13}$NN-labeled saline between the storing chamber and the catheter.
All pigs were imaged in the prone position for the study and monitored with a pulse oxymeter around the tail.

3.2.2.2 Positioning and Regional Gas Volume Content (\(V_A\)) Scans

After equilibration with inhaled radioactive \(^{13}\)NN gas between the lungs and the breathing circuit (= 5 minutes), the animal was advanced into the field of view of the camera until the highest count rate was recorded by the camera. This position corresponded to the section of the lungs with maximal cross-sectional area.

Once proper position was achieved, an imaging sequence was collected for a total of 240 seconds. Because of the low solubility of nitrogen in body fluids and tissues, \(^{13}\)NN remains mostly confined to the air-spaces within the lungs. This equilibration image was therefore proportional to the local gas volume content. During imaging, a 1 ml gas sample was obtained from the rebreathing circuit and its specific activity was assessed with a radiation analyzer (model System 5000, Nucleus Inc., Oak Ridge, TN), previous cross calibrated with the PET camera. At the end of collection of the equilibration image, the inspiratory gas was switched to room air and an imaging sequence of 7 frames, 3 minutes 54 seconds in duration (4 6-seconds, 1 30-seconds, 1 60-seconds, 1 120-seconds images), was collected as the tracer was washed out from the lungs.

3.2.2.3 Perfusion (\(\dot{Q}\)) and \(\dot{V}_A / \dot{Q}\) scans

During steady state breathing with tracer free 100% oxygen, the ventilator was stopped at end exhalation and a bolus of \(^{13}\)NN-saline solution (specific activity: 0.1 - 0.2 mCi/ml) was infused into the right atrium at a constant flow rate of 1.87 ml/sec (Infusion time, \(T_{\text{inf}} = 3-4\) s). A sequence of 4 images, the first 2 of five-seconds and the last 2 of fifteen-seconds in duration were collected while the animal remained in apnea.

At the end of the perfusion sequence, the ventilator was restarted and an infusion of \(^{13}\)NN-saline solution was initiated into the right atrium using the peristaltic pump at a constant flow rate of 0.47 ml/sec. Simultaneous with the start of infusion a collection of 5 images (2 60-seconds, 3 120-seconds in
duration) was made. Once a steady state activity had been reached (usually before the first 3 minutes, see figure 3-2, page 46), samples of infusate solution, pulmonary artery and systemic blood were obtained to assess their respective specific activity.

At the conclusion of the 8 minutes constant infusion sequence, the tracer was washed out with an image sequence similar to that used in the regional lung volume washout.

3.2.3 Data Analysis

The collected sinograms were corrected for tissue attenuation using the data from a 30 minute transmission scan and reconstructed at a resolution length of 1 cm. A mask was created by thresholding the gas volume image to 50% of the peak number of counts. The mask was then separated into two regions of interests (ROI), the left (transplanted) and right (control) lung. The ROIs were further refined to exclude regions of tracer trappings in the lungs, as determined from regions that were not washed out during the constant infusion washout sequence. Graphs of average counts per voxel per second for each ROI were plotted against time (figure 3-2), and analyzed as described below. Results from that analysis were presented as the ratio of transplanted to native (T/N) for the obtained parameters.

3.2.3.1 Determination of Regional Gas Volume, \( V_A \), and Specific Ventilation from Regional Gas Volume Washout, \( (sV_A)_l \)

From the equilibration image of inhaled \( ^{13} \text{NN} \), voxel data is directly proportional to regional gas volume content per voxel, \( V_A \).

Specific ventilation, \( (sV_A) \), or ventilation per unit volume of aerated alveoli was estimated from the PET images collected during the washout of \( ^{13} \text{NN} \) tracer following a regional gas volume sequence. Given the heterogeneous nature of the washout in the transplanted lung, it was modeled as a 2 compartment process. The model assumed a single exponential washout for slow regions, estimates their fraction volume, and subtracts their contribution from the overall washout curve. A modified Stewart-Hamilton method was then applied to the
remaining washout curve to calculate a regional mean residence time (MRT) that is inversely proportional to the region's ventilation per unit volume [specific ventilation (\(sV_A\))] \([4]\). A full description and derivation of the model described above was done by Simon et. al. [2]. The overall \(sV_A\) of the region is calculated as the volume-weighted average of the \(sV_A\) of two compartments:

\[
sV_A = V_1(sV_A)_1 + V_2(sV_A)_2
\]

This approach corrects for washout truncation, estimates of the relative size of the trapped or slow region while eliminating its bias on the estimate of global regional ventilation, and retaining the unrestricted and robust nature of the Stewart-Hamilton method in the analysis of well-ventilated regions [2].

The final two images points of the washout sequence were used to assess the specific ventilation from slowest regions, \((sV_A)_2\), calculated from the slope of the line in the semilog plot of local counts per second over time. The total counts of the regional gas volume image were decay corrected to the start of the washout and taken as the initial tracer content \((C_0)\). Using \(C_0\) and time constant, \(\tau_2\), the relative volume of the region \(V_2\) over a specified imaging interval \(\Delta t\) can be expressed as:

\[
V_2 = \frac{\Delta t \cdot C_N \cdot e^{\frac{t_f}{\tau_2}}}{\tau_2 \cdot C_0 \left[ e^{\left(\frac{\Delta t}{\tau_2}\right)} - 1 \right]}
\]

where \(C_N\) represents the final image counts and \(t_f\) represents the time at which the washout was truncated. Derivation of equation (3-2) could be found in [2]. Since the sum of the two fractional compartment volumes must equal 1, \(V_1\) must equal to \((1 - V_2)\).

To calculate \((sV_A)_1\), the area \(A_1\), from figure (3-3) on page 47, is obtained by subtracting area \(A_2\) from the total area under the washout curve. \(A_2\) was obtained by integrating under the region 2 curve:
\[ A_2 = \frac{V_C}{\Delta t} \frac{C_0 x_2}{x_2} \left( 1 - e^{-t/f_2} \right) \]  

(3-3)

and subsequently, the area \( A_1 \) could be calculated using:

\[ A_1 = \left( \sum_i C_i \right) - A_2 \]  

(3-4)

where \( C_i \) is the sum of the acquired counts. Knowing the values of \( A_1 \), \( V_1 \), and \( C_0 \), \( (sV_A)_1 \) could be expressed as:

\[ \left( sV_A \right)_1 = \frac{V_1 \cdot C_0}{A_1 \cdot \Delta t} \]  

(3-5)

### 3.2.3.2 Determination of \( \dot{Q} \) and \( s\dot{Q} \)

From the four images collected during the perfusion scan sequence as described in section 3.2.2.3, the last 2 fifteen-seconds images were added to form a more robust image with higher signal to noise ratio, which was taken as proportional to local perfusion (\( \dot{Q} \)).

An image of specific perfusion (\( s\dot{Q} \)), was obtained by dividing, pixel-by-pixel, the perfusion image by the regional gas content image (\( V_A \)). The ratio of transplanted to native lung mean \( s\dot{Q} \) for the defined ROI was calculated.

### 3.2.3.3 Determination of \( \dot{V}_A / \dot{Q} \) ratio

A steady state constant infusion (CI) image, which is approximately proportional to the ratio, \( \dot{Q} / s\dot{V}_A \), was created by adding, on a pixel-by-pixel basis, the last three steady state images of the CI imaging sequence. To obtain an image of \( \dot{V}_A / \dot{Q} \), the regional gas content image, \( V_A \), was divided on a pixel-by-pixel basis, with the image of \( \dot{Q} / s\dot{V}_A \). The resulting \( \dot{V}_A / \dot{Q} \) image was then analyzed in terms of transplant to native of mean \( \dot{V}_A / \dot{Q} \) using the previously defined ROIs.
3.2.3.4 Determination of $sV_A$ from Washout after Constant Infusion, $(sV_A)_{Cl}$

Specific ventilation or ventilation per unit volume for perfused alveoli was estimated from the PET images collected during the washout of $^{13}$NN tracer following constant infusion sequence. A method similar to that used to determine $(sV_A)_I$ was used to determine $(sV_A)_{Cl}$. The initial tracer content, $C_0$, in this case was the steady state constant infusion image, decay corrected to the start of the washout; and the specific ventilation was determined using data from the washout images collected during the constant infusion sequence.

3.3 General Results

The results obtained are summarized in tables 3-1 and 3-2 (pages 52 and 53 respectively). In general, regional perfusion and ventilation to the transplanted lungs were always lower than that of the control lungs $(Q_{(T/N)}, (sV_A)_{Cl} < 1)$. Also, $sQ_{(T/N)}$ was less than or close to unity for all the animals, and was always closer to unity than $Q_{(T/N)}$ suggesting that a fraction of the drop in $Q$ to the transplanted lung was caused in part by a decrease in the number of functioning alveolar units. Despite the lower $Q_{(T/N)}$, $V_A / Q_{(T/N)}$ was also lower than unity in some studies. The lower $V_A / Q_{(T/N)}$ suggests that the change in $Q$ was of a lesser magnitude than the change in $(sV_A)_{Cl}$. $(sV_A)_I$ and $(sV_A)_{Cl}$ were highly correlated ($R = 0.91$) (figure 3-5, page 49). However, there was no correlation between $sQ_{(T/N)}$ and either $(sV_A)_I$ ($R = -0.25$) or $(sV_A)_{Cl}$ ($R = -0.11$).

3.4 Discussion

3.4.1 Left Lung Auto-transplant

In pigs #1 and 2, auto-transplants were performed on the left lung. During the first week of operation, pig #1 showed the following T/N ratios: $V_A / Q$ ratio of $V_A = 0.99$, $Q = 0.81$, $sQ = 0.82$, $(sV_A)_I = 0.96$, $(sV_A)_{Cl} = 0.95$, and $V_A / Q = 1.35$. By the second experiment, starting at POD# 16, $V_A(T/N)$ had decreased slightly ($V_A(T/N) = 0.91$), and $Q(T/N)$ further decreased from 0.81 to 0.71. As a result of the small decrease in $V_A(T/N)$ as compared to the decrease in $Q(T/N)$, there was a lesser decrease in the specific perfusion from 0.82 to 0.77. In this animal, both $(sV_A)_I$ and $(sV_A)_{Cl}$ showed little change over time, and there was a small change in the $V_A / Q$ ratio.
In pig #2, the following T/N ratios for \( V_A \), (s\( V_A \))_I, and (s\( V_A \))_CI are approximately equal to unity (\( V_A(T/N) = 0.88 \), (s\( V_A \))_I(T/N) = 0.96, (s\( V_A \))_CI(T/N) = 0.89) with \( \dot{Q}_{(T/N)} = 0.24 \). Due to the much lower perfusion as compared to \( V_A(T/N) \), the resulting s\( Q_{(T/N)} \) was equal to 0.28 and it's \( \dot{V}_A / \dot{Q}_{(T/N)} \) was much greater than unity (\( \dot{V}_A / \dot{Q}_{(T/N)} = 2.21 \)). The low perfusion ratio measured was correlated with the presence of a severe left atrium stenosis found postmortem.

### 3.4.2 Left Lung Allo-transplant

#### 3.4.2.1 Unmatched Transplant

An unmatched allo-transplant was performed on pig #3, and the animal was imaged on three separate occasions. On POD #3, the animal exhibited the following (T/N) ratios: \( V_A(T/N) = 0.82 \), (s\( V_A \))_I(T/N) = 1.01 and (s\( V_A \))_CI(T/N) = 0.69. However, its perfusion ratio was well below unity (\( \dot{Q}_{(T/N)} = 0.23 \)), resulting in a \( \dot{V}_A / \dot{Q} \) ratio that was much greater than unity (\( \dot{V}_A / \dot{Q}_{(T/N)} = 2.03 \)) (figure 3-4, page 48). These results help illustrate the importance of using PET imaging to determine the gas exchange of an injured lung. With the \( V_A(T/N) \) of 0.82, a X-ray scan would reflect no abnormalities. Furthermore, the high \( \dot{V}_A / \dot{Q}_{(T/N)} \) in the injured lung would show a normal \( pO_2 \).

At POD #10, the regional gas volume ratio increased towards unity (\( V_A(T/N) = 0.98 \)) and its perfusion ratio remained constant (\( \dot{Q}_{(T/N)} = 0.23 \)). We also observed a decrease in (s\( V_A \))_I, while (s\( V_A \))_CI remained the same [(s\( V_A \))_I(T/N) = 0.84, (s\( V_A \))_CI(T/N) = 0.69] as compared to values taken on POD #3. It was later found that the animal developed acute rejection between POD #10 and POD #17, verifying that the image data taken at POD #10 may have indicated an initial onset of rejection.

The last image sequences was taken at POD #17. By this time, it was observed that the animal was not in a good condition; showing no aerated regions in the transplanted lung, little perfusion to those regions and poor gas exchange in that lung (\( V_A(T/N) = 0.059 \), (s\( V_A \))_I(T/N) = 0.081, (s\( V_A \))_CI(T/N) = 0.097, \( \dot{Q}_{(T/N)} = 0.060 \), \( \dot{V}_A / \dot{Q}_{(T/N)} = 0.077 \)). It was later determined that the animal developed vascular rejection and died on POD #20.
3.4.2.2 Class 2 Matching, Class 1 Mismatch Allo-Transplant

A class 2 vascular matching with a class 1 airway mismatch allo-transplant was performed on pig #4. The first imaging scans done on POD #34 showed $V_{A(T/N)}$, $\dot{Q}_{(T/N)}$, and $(s\dot{V}_A)_{(T/N)}$ values of 0.764, 0.707, 0.863 respectively. Due to technical difficulties, images acquired during the constant infusion sequence had very low signal to noise ratios and hence not included in our analysis.

On POD #147, the animal showed an increment of gas volume ratio towards unity, but a slight decrease of transplant-native perfusion ratio ($V_{A(T/N)} = 0.96$, $\dot{Q}_{(T/N)} = 0.63$). We were also able to obtain $\dot{V}_A / \dot{Q}_{(T/N)}$, $(s\dot{V}_A)_{I(T/N)}$ and $(s\dot{V}_A)_{CI(T/N)}$ of 1.50, 1.19, and 0.87 respectively. The $\dot{V}_A / \dot{Q}_{(T/N)}$ ratio was greater than unity because of the low specific perfusion $(s\dot{Q}_{(T/N)} = 0.66)$ and specific ventilations of approximately one.

Class 1 mismatch in this animal did not result in airway rejection for up to 147 days post operative.

3.4.2.3 Class 1 Matching, Class 2 Mismatch Allo-Transplant

In pig #5, a class 1 (airway) matching with a class 2 (vascular) mismatch allo-transplant was performed. Imaging scans were done on POD #7, and the following results obtained: $V_{A(T/N)} = 1.02$, $(s\dot{V}_A)_{I(T/N)} = 0.80$, $(s\dot{V}_A)_{CI(T/N)} = 0.77$, $\dot{Q}_{(T/N)} = 0.85$, and $\dot{V}_A / \dot{Q}_{(T/N)} = 1.09$.

On POD #35, a smaller tracer content in the alveoli was recorded, $V_{A(T/N)} = 0.79$, as compared to POD #7. In addition, $\dot{Q}_{(T/N)}$ worsen as compared to POD #7 ($\dot{Q}_{(T/N)} = 0.62$). It was later concluded, postmortem, that the animal had developed bronchiectasis, as well as, vascular rejection.

3.4.2.4 Class 1 and Class 2 Matching Allo-Transplant

In pig #6, a matched class 1 and class 2 allo-transplant was performed with immunosuppressions. At POD #5, the animal was scanned and found to have $V_{A(T/N)}$ of 1.12 and low $(s\dot{V}_A)_{I(T/N)}$, $(s\dot{V}_A)_{CI(T/N)}$ of 0.13 and 0.06 respectively. $\dot{Q}_{(T/N)}$ was also low, 0.47, resulting in a $s\dot{Q}_{(T/N)}$ of 0.42 and a $\dot{V}_A / \dot{Q}_{(T/N)}$ of 0.43.
With the pig having recovered and taken off the immunosuppressions, a second sequence of imaging was performed at POD #28. $(sV_A)_{(T/N)}$ and $(sV_A)_{C_{(T/N)}}$ improved to 0.62 and 0.67 respectively. $\dot{Q}_{(T/N)}$ was still below unity at 0.58. However, $V_{A(T/N)}$ was observed to have decreased from the ratio found in POD #5 of 1.12 ($V_{A(T/N)} = 0.60$). The lower value of $V_A$ in the transplanted lung could be correlated with Pneumonia developed by the animal at POD #33.

### 3.5 Conclusion

In summary, we performed a series of scans with PET on six unilateral transplanted pigs under various conditions. In 4 cases, one or more scans were performed within the first 2 weeks of the operation. In all animals, one or more scans were also performed after two weeks of post operative. In most cases, the PET images correlate well with pathological or postmortem findings. Hence, we could conclude that this non-invasive PET technique using could be promising clinically in the post operative follow-up to a unilateral lung transplant patient.
3.6 Figures

Figure 3-1  The experimental set-up of the PET imaging system which includes the PET camera, gas rebreathing and ventilation system, and $^{13}$NN labeled-saline infusion system.
Figure 3-2 Representative data collected during a perfusion, constant infusion, and washout series. The first 40 seconds of imaging corresponds to the perfusion sequence, the constant infusion sequence is shown from time, t = 40 to t = 520 seconds, with the washout sequence shown in the final 200 seconds. Note that a steady state is reached after the first 3 minutes (t = 220) of the constant infusion series.
Figure 3-3  Idealized $^{13}$NN regional lung washout curve for 2 compartment model in which majority of lung region consists of normal tissue, with fractional volume $V_1$ and exponential time constant $\tau_1$. Remainder of the lung region "traps" gas, with fractional volume $V_2$ and time constant $\tau_2$. $A_1$ and $A_2$ are areas of respective shaded sections and $t_1$ is the total washout collection time [2].
Figure 3-4  Illuminated surface plots of pig #3 at POD #5 where the z coordinate (height) represents the local counts per pixel from the lung region normalized by the mean of the image. (a) Tracer concentration in the lungs after the inhalation of $^{13}$NN gas representing the local gas content per voxel, $V_A$. (b) Image of tracer concentration ($\propto \dot{Q}$) collected after the bolus infusion of $^{13}$NN tracer. (c) Image of $\dot{V}_A / \dot{Q}$.  

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Plot of \((s\dot{V}_A)_I\) versus \((s\dot{V}_A)_\text{Cl}\) showing a correlation, \(R\), of 0.911.
### Table 3-1: Time Progression Table of Transplanted/Native for Regional Gas Volume, Perfusion, and Specific Perfusion

<table>
<thead>
<tr>
<th>Mismatch</th>
<th>Pig #</th>
<th>POD*</th>
<th>(V_A)</th>
<th>(\dot{Q})</th>
<th>(s\dot{Q})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auto</strong></td>
<td>1</td>
<td>7</td>
<td>0.988</td>
<td>0.809</td>
<td>0.818</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>0.910</td>
<td>0.713</td>
<td>0.773</td>
</tr>
<tr>
<td><strong>Auto</strong></td>
<td>2</td>
<td>23</td>
<td>0.877</td>
<td>0.242</td>
<td>0.281</td>
</tr>
<tr>
<td><strong>CL 1, CL 2</strong></td>
<td>3</td>
<td>3</td>
<td>0.823</td>
<td>0.229</td>
<td>0.315</td>
</tr>
<tr>
<td></td>
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<td>0.850</td>
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<td>28</td>
<td>0.603</td>
<td>0.577</td>
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</table>

* POD - Post Operative Date
Table 3-2: Time Progression Table of Transplanted/Native for Specific Ventilation (Inhaled), Specific Ventilation (CI), and $\dot{V}_A / Q$

<table>
<thead>
<tr>
<th>Mismatch Conditions</th>
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<th>POD*</th>
<th>$s\dot{V}_A$ (Inhaled)</th>
<th>$s\dot{V}_A$ (CI)</th>
<th>$\dot{V}_A / Q$</th>
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<td>17</td>
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<td>0.077</td>
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<td>Noise</td>
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<td>0.867</td>
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</tr>
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<td>1.101</td>
<td>0.776</td>
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<td>0.058</td>
<td>0.427</td>
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<td>28</td>
<td>0.623</td>
<td>0.667</td>
<td>0.774</td>
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</tbody>
</table>

* POD - Post Operative Date
3.8 References


Chapter 4

Effects of Helium on Regional Transport in Stenosed Lung During High Frequency Jet Ventilation (HFJV)

4.1 Introduction

Previous PET imaging studies have assessed the distribution of alveolar ventilation during high frequency oscillatory ventilation (HFOV) in normal animals [6][7] and after unilateral airway obstruction or surfactant depletion [5]. This chapter presents an imaging study of gas transport distribution during High Frequency Jet Ventilation (HFJV), a different mode of high frequency ventilation which provides gas exchange by introduction of a high velocity jet at frequency equal or less than 5 Hz.

HFJV is primary used during tracheal thoracic and laryngeal surgery to provide ventilation while minimizing interference with the surgical field. HFJV, however, has been found to be ineffective in maintaining adequate ventilation in patients with increased airway resistance such as in COPD. Recent studies by Cros, A.M., have suggested that such a limitation can be partially corrected by using a mixture of helium and oxygen as a ventilatory gas. It was then postulated that the increase in ventilation with heliox was not only related to the increase
tial volumes delivered by the jet with the lower density gas, but also to a potential improvement in the distribution of ventilation/perfusion ratios.

Based on the findings in previous studies done by Simon et al.[3], it was theorized that as in HFOV, the distribution of ventilation during HFJV should be more dependent on discipative and inertial forces and less dependent on elastic forces. It was thus expected that in the case of severe bronchial stenosis, decreasing the density of the breathing gas by ventilation with a helium-oxygen mixture (heliox) should have resulted in a more uniform distribution of gas transport than ventilation with nitrox, a nitrogen-oxygen mixture. To test this hypothesis, animals were studied with PET in the presence of a severe left main stem stenosis during ventilation with nitox and with heliox.

4.2 Methods
4.2.1 Subject Preparation

Five mongrel dogs (Mean weight = 21.4 ± 1.7 kg) were anesthetized intravenously with sodium pentobarbital (25 ml/kg) with additional 5 ml/kg hourly to maintain anesthesia for the duration of the study. Femoral arterial and venous catheters were cannulated and used during the course of the experiment for blood sampling, periodic administration of anesthetic, and arterial pressure monitoring. A tracheotomy was performed and a cuffed HI-LO jet endotracheal (ET) tube was inserted.

The ET tube consisted of three separate lumens. The main lumen was used for conventional ventilation and for expiration when the animals were being ventilated under HFJ. An auxiliary lumen, ending 6 cm before the tracheal end of the tube was used for jet injection. A second auxiliary lumen ended 4 cm beyond the injection port was used for monitoring airway pressure from the jet ventilator. A Swan Ganz catheter (model 93A-131H-7F, Edwards Laboratory, Santa Ana, CA), was inserted in the right jugular vein and advanced into the pulmonary artery, leaving its proximal port to drain into the superior vena cava. This catheter was used to monitor the pulmonary artery (PA) pressure, the cardiac output by thermo-dilution, injection of \(^{13}\)NN-saline solution and for sampling of mixed PA blood. The animals were positioned supine and held in place with gentle traction.
To create a bronchial stenosis, a 1 cm long cylindrical piece of plexi-glass with an diameter orifice calculated at 85% of the bronchial cross-sectional area was used. A soft foam ring was glued around it and soaked with KY-jelly to serve as a seal between the stenosis and the bronchus. A 1.5 mm diameter metal guide wire was fixed on the obstruction to facilitate its placement and to secure its location during ventilation. Stenosis of different diameters were made to approximately fit the diameter of the left main stem bronchus. The stenosis were introduced under fiber optic bronchoscoposcopic guidance. The metal guide wire position was secured by inflation of the ET tube. A blind end catheter of diameter 1 mm provided with side holes was placed at the level of the carina for measurement of airway pressure. The ET tube was finally secured by a tie around the trachea.

4.2.2 Ventilation Preparation

HFJV was delivered by an Acutronic jet ventilator AMS 1000 (Acutronic Medical Systems, Jona, Switzerland). The jet was electronically controlled by a solenoid valve, and pulsed via a non-compliant tubing (120 cm in length and 7 mm in diameter). This tubing was connected to the special lumen of the HI-LO jet tube. Heliox (80% helium in oxygen) and Nitrox (80% nitrogen in oxygen) were provided in tanks, with the FiO₂ being checked with a mass spectrometer and supplied to the jet ventilator at a pressure of 4 bars. In order to accurately control the tidal volume and FiO₂, the entrainment was blocked by a one way unidirectional valve positioned at the top of the ET tube allowing flow in the expiratory direction only. The inspiratory time was short (30% of the total breathing cycle) so as to prevent inspiratory back flows. The occurrence of a back flow was monitored by recording in an oscilloscope, the pressure at the proximal end of the tracheal tube above the site of injection and noting that the signal was negative during jet injection.

Gas flow rate delivered to the injector was determined by the ventilator from the differential pressure across an orifice. Flow rate and pulse volume delivered were displayed in the front panel. The accuracy of the tidal volume calculation for nitrox was validated with a bell spirometer. A similar measurement was performed for heliox and a correction factor derived. The frequency was set at 5 Hz, and the driving pressure was adjusted to obtain a desired tidal volume.
4.2.3 Imaging Protocols

4.2.3.1 Positioning of Animal and Determination of Gas Content Image, $V_A$

To avoid changes in mean lung volume resulting from the change in respiratory gas, we monitored the change in chest wall expansion using an inductance plethysmograph (Respitrace) following a sudden stop of the ventilator. After switching from nitrox to heliox, we adjusted an expiratory resistance until the change in chest wall expansion after a sudden stop was equivalent to that recorded with nitrox.

After equilibration of the lungs with inhaled radioactive $^{13}$NN gas (≈ 5 minutes) under conventional ventilation, the animal was advanced into the field of view of the camera until the highest count rate was record by the camera. This position corresponded to the cross section of the lungs with maximal cross-sectional area.

Since equilibration of the lungs with inhaled $^{13}$NN gas was not possible under HFJV, transmission scans of duration 20 minutes were used to obtain $V_A$ images prior to the start of each constant infusion sequence.

4.2.3.2 Constant Infusion (CI)

During steady state breathing, an infusion of prepared $^{13}$NN gas in saline solution was initiated into the superior vena cava using the peristaltic pump at a constant flow rate of 0.88 ml/sec. Simultaneous with the start of infusion, a collection of 6 images (4 60-seconds, 2 120-seconds in duration) was made. Samples of the infusate solution, pulmonary artery and systemic venous blood were obtained during the imaging sequence to assess their respective specific activities.

At the conclusion of the 8 minutes constant infusion sequence, tracer infusion was halted and the tracer remaining in the lung was washed out while a collection washout sequence consisting of 10 images (5 2-seconds, 1 10-seconds, 1 20-seconds, 2 60-seconds, and 1 120-seconds in duration) took place.
Data sets were obtained in HFJV with nitrox before and after stenosis and with heliox after stenosis.

4.2.4 Data Analysis

Collected sinograms were attenuation corrected with the corresponding transmission images and reconstructed at a resolution length of 1.0 cm. Masks for two regions of interest (ROI) were defined to divide the lung field into left and right lungs. ROI data was analyzed as the ratio of left to right lung under HFJV with normal lungs ventilated with nitrox and after left main stem bronchial stenosis. Comparisons between the left (obstructed) and right (control) lung were done for ventilation with nitrox and with heliox.

4.2.4.1 Determination of \( V_A / Q \) and \( V_A / \dot{Q} \) ratio

Measurements of \( V_A / \dot{Q} \) with PET using constant infusion of \( ^{13}\text{NN} \) labeled saline has been previously reported by Rhodes et al. [2] and Treppo et al. [4]. A similar technique was used in these studies to determine the \( V_A / \dot{Q} \) in the control lung where a steady tracer concentration was reached within the first three minutes of constant infusion. However, in the presence of severe airway obstruction, tracer concentration in the stenosed lung did not reach a steady state during the 8 minutes of infusion time available for imaging. To estimate such steady value, we fitted the experimental data to a single exponential model:

\[
\dot{S} \propto C_\infty \left(1 - e^{-\frac{t}{\tau_{CI}}}\right)
\]

(4-1)

where

- \( \dot{S} \) represents the count rate in the image.
- \( \tau_{CI} \) represents the exponential time constant of the tracer during constant infusion.
- \( C_\infty \) represents the extrapolated steady tracer concentration.

The value of \( C_\infty \) was then normalized by the tracer concentration measured at the pulmonary artery and corrected for an estimated contribution of activity from the pulmonary artery. This correction was assumed to be 12.8% of the average \( (C_\infty/C_{pa}) \) per voxel in the normal lung, a value obtained from a previous study in normal eucapnic dogs by labeling the blood with \( ^{11}\text{CO} \) [1]. Values of \( (C_\infty/C_{pa}) \^* \) for
each lung during obstructed conditions were corrected for blood activity by subtracting a value, assuming that the activity contributed by pulmonary arterial blood was the same to that before bronchial obstruction. Thus:

\[
\left( \frac{C_n}{C_{pa}} \right)^* = \left[ \frac{C_n}{C_{pa}} - f_{\text{blood}} \left( \frac{C_n}{C_{pa}} \right)_{\text{control}} \right] \tag{4-2}
\]

where

- \( C_{pa} \) represents the specific tracer activity measured from the pulmonary artery during CI after left bronchial obstruction (LBO).
- \( (C_n/C_{pa})_{\text{control}} \) represents the normalized steady state tracer concentration measured in the lungs before LBO.
- \( f_{\text{blood}} \) represents the fractional contribution of local activity in the arterial blood, which was taken to be 0.128.

To obtain an estimate of the ventilation/perfusion ratio \((\dot{V}_A/\dot{Q})\) from \((C_n/C_{pa})^*\), regional gas volume content \((V_A)\) was required so that:

\[
\frac{\dot{V}_A}{\dot{Q}} = \frac{V_A}{\left( \frac{C_n}{C_{pa}} \right)^*} - \lambda \tag{4-3}
\]

where

- \( V_A \) represents the local gas content per voxel in the region and \( \lambda \), the partition coefficient of \(^{13}\)NN tracer between air and water.

Images of \( \dot{V}_A/\dot{Q} \) were analyzed using the ROI defined above and taking the left (obstructed) to right (control) \( \dot{V}_A/\dot{Q} \) ratio \([ (\dot{V}_A/\dot{Q})_{(L/R)} ] \).

### 4.2.4.2 Determination of gas volume, \( V_A \)

As described by Rhodes et al. [2], we utilized the transmission scan to obtain an estimate of the local gas content per ml of voxel. By assuming that a region defined over the heart had a tissue/blood content of 100%, the local air content could be estimated on a pixel by pixel basis from a reconstructed attenuation matrix \((\phi)\) as:

\[
V_A = 1 - \frac{\phi_{\text{lung}}}{\phi_{\text{heart}}} \tag{4-4}
\]
where

\[ \phi_{\text{lung}} \] is the local attenuation by the lung (tissue/blood) and \[ \phi_{\text{heart}} \] represents the average attenuation per voxel by the heart.

Due to imaging artifacts, data collected from the transmission scan in 2 dogs could not be used. In dog #3, the transmission scan before LBO with nitrox was not utilized. Instead, the transmission image from the LBO in nitrox was used as a substitute. Similarly, in dog #5, transmission scans under HFJV after LBO in nitrox and heliox could not be utilized, and the transmission scan obtained during nitrox inhalation before LBO was used as a substitute.

### 4.2.4.3 Determination of \( V_A \) and \( \dot{Q} \)

Specific ventilation or ventilation per unit volume was estimated from the PET images collected during the washout of \(^{13}\)NN tracer following constant infusion sequence. Given the heterogeneous nature of the washout, it was modeled as a 2 compartmental system. For each region, overall \( sV_A \) was defined as the volume weighted sum of the compartment \( sV_A \)’s:

\[
sV_A = \frac{V_1 (sV_A)_1 + V_2 (sV_A)_2}{V_1 + V_2} \quad (4-5)
\]

Tracer washout from such a model obeys the equation:

\[
S(t) = V_1 e^{-t(sV_A)_1} + V_2 e^{-t(sV_A)_2} \quad (4-6)
\]

Average concentration per voxel for each image of the washout and for each lung was plotted against time. Equation 4-6 was fitted to the data (figure 4-3, page 66) yielding parameters \( V_1 \), \( V_2 \), \((sV_A)_1\), and \((sV_A)_2\); from which \( sV_A \) could be estimated using equation (4-5). From the values of \( sV_A \), \( V_A \) could be obtained by multiplying \( sV_A \) by \( V_A \).

A \( \dot{Q} \) ratio between left and right lung could then be calculated using values of \( \dot{Q} / sV_A \) and \( sV_A \). Comparisons were made using the two tail Student’s \( t \)-test and results are deemed significant if \( p < 0.05 \).
4.3 Results/Discussion

4.3.1 Effects of Heliox on $\tau$, $V_A$ and $\dot{V}_A$

Before LBO, regional tracer concentration during the constant rate infusion of $^{13}$NN-saline was similar for both lungs and reached a plateau before 300 seconds. As expected, left to right ratios of $V_A$, $\dot{V}_A$, and $\dot{V}_A / \dot{Q}$ were around unity (figure 4-1, page 64). LBO resulted in higher tracer concentration in the corresponding lung, and in most cases the tracer had not reached a plateau at the end of the 8 minutes of imaging (figure 4-2, page 65).

In nitrox-HFJV before LBO, the time constant of the exponential rise in tracer concentration during constant infusion ($\tau$) was not significantly different between left (Mean = 53.79 seconds) and right (Mean = 57.39 seconds) lung and varied between 15.7 seconds and 85.47 seconds (Mean 55.59 ± 6.87). After LBO, $\tau$ increased to a mean of 142.56 ± 18.41 seconds in the obstructed lung and decreased to a mean of 56.93 ± 4.58 seconds in the control (right) lung (table 4-1, page 66). During heliox-HFJV after LBO, $\tau$ did not change significantly in either lung as compared to nitrox-HFJV.

Mean left/right ratio (L/R) of $V_A$ before LBO was not significantly different from unity (Mean 0.991 ± 0.010). After LBO, $V_A$ increased to a mean of 1.056 ± 0.017 (p > 0.05) and after heliox, to a mean of 1.124 ± 0.054 (p > 0.05) (Table 4-2, page 67). Thus, the severe LBO created a small degree of hyperinflation of the obstructed lung that increased with the use of heliox.

$\dot{V}_A$ was also close to unity (Mean 1.036 ± 0.072) during HFJV before LBO. As expected, LBO under HFJV resulted in a significant drop in $\dot{V}_A$ caused by a shift in ventilation away from the obstructed left lung (Mean 0.370 ± 0.071). Under heliox-HFJV, $\dot{V}_A$ moved towards unity in 4 out of the 5 dogs as compared to with nitrox-HFJV, and in one animal, $\dot{V}_A$ decreased by 0.018 (Table 4-2).
4.3.2 Effects of heliox on $\dot{V}_A / \dot{Q}$ and perfusion ($\dot{Q}$)

Mean $(\dot{V}_A / \dot{Q})_{(LR)}$ was $0.907 \pm 0.021$ under nitrox-HFJV before LBO. LBO significantly decreased $(\dot{V}_A / \dot{Q})_{(LR)}$ in nitrox-HFJV to $0.395 \pm 0.041$ ($p < 0.05$). Ventilation with heliox-HFJV made the $\dot{V}_A / \dot{Q}$ distribution more uniform in all dogs as compared with nitrox-HFJV. While the improvement in dog #3 was substantial (0.117), improvements in the other 4 animals were only minimal (ranging from 0.016 to 0.086, Mean 0.045 ± 0.016) (Table 4-3, page 68).

Nitrox-HFJV before LBO produced a $\dot{Q}_{(LR)}$ that was greater than unity in 3 dogs (values ranged from 1.15 to 1.34). In the other 2, $\dot{Q}_{(LR)}$ had values close to unity (0.97 and 0.98). After LBO, $\dot{Q}_{(LR)}$ under nitrox-HFJV decreased in dogs 3, 4 and 5, and increased in dogs 1 and 2 (Table 4-3). The 3 dogs that showed a decrease in $\dot{Q}_{(LR)}$ after LBO were also the animals with the greatest changes in $\dot{V}_{A(L/R)}$ ranging from 0.18 to 0.32 suggesting an effect of hypoxic vasoconstriction (HPV). In contrast, in the 2 animals that showed an increase in $\dot{Q}_{(LR)}$, $\dot{V}_{A(L/R)}$ were only 0.50 and 0.57. With heliox-HFJV, the trend in $\dot{Q}_{(LR)}$ shift was similar, with the 3 dogs showing a decrease relative to before LBO and 2 dogs showing an increase.

Therefore, we could conclude that the effect of HPV correlates with the degree of ventilation heterogeneity created by LBO; whereby a shift in $\dot{Q}$ away from the obstructed lung was present only in dogs with $\dot{V}_{A(L/R)} < 0.5$ and absent in dogs with $\dot{V}_{A(L/R)} \geq 0.5$.

4.4 Conclusion

In summary, we studied the effects of nitrox versus heliox on the distribution of ventilation and perfusion during high-frequency jet ventilation after a left main bronchial obstruction. After LBO, $\dot{V}_A / \dot{Q}_{(LR)}$ dropped due to the decrease in $\dot{V}_{A(L/R)}$ although compensatory changes in $\dot{Q}$ decreased the impact in $\dot{V}_A / \dot{Q}$ changes when $\dot{V}_{A(L/R)} < 0.5$. The use of heliox as a breathing gas made $\dot{V}_A / \dot{Q}$ and $\dot{V}_A$ slightly more uniform, but the magnitude of the effect was highly variable between animals.

We conclude that the clinical effects in ventilation and oxygenation observed in patients using heliox with HFJV must have been primarily the result
of increased delivered tidal volume ($V_T$) by the jet with the lower density gas. Since the changes in $\dot{V}_A$ and $\dot{V}_A/\dot{Q}$ distributions in severe unilateral obstruction found in this study, when the delivered $V_T$ is kept unchanged, were very small.
4.5 Figures

Figure 4-1  Representative plot of average counts per pixel per second against time showing the data obtained during the constant infusion of $^{13}\text{NN}$ tracer with the single exponential numerical best fit. The 'o' and 'x' represents the experimental data obtained from the left and right regions of a lung before stenosis respectively. The solid line represents the numerical best fit using the Levenberg-Marquardt method.
Figure 4-2  Representative plot of average counts per pixel per second against time showing the data obtained during the constant infusion of $^{13}$NN tracer with the single exponential numerical best fit. The 'o' and 'x' represents the experimental data obtained from the obstructed (left) and control (right) regions of a lung respectively. The solid line represents the numerical best fit using the Levenberg-Marquardt method.
Figure 4-3 Representative plot of average counts per pixel per second against time showing the data obtained during the washout of $^{13}$NN tracer with a double exponential decay fit. The 'o' represents the washout data from the obstructed (left) region and the 'x' represents the washout data from the control (right) region of the lungs.
4.6 Tables

Table 4-1: Table of Time Constant, \( \tau \), during Constant Infusion of 13NN tracer under HFJV

<table>
<thead>
<tr>
<th>Representative Region</th>
<th>Condition</th>
<th>Control</th>
<th>LBO</th>
<th>LBO (Heliox)</th>
</tr>
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<tr>
<td>Dog #</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>Left</td>
<td>84.03</td>
<td>131.58</td>
<td>87.72</td>
</tr>
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<td></td>
<td>Right</td>
<td>85.47</td>
<td>63.69</td>
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<td>Left</td>
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<td>Right</td>
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</tr>
<tr>
<td>Mean</td>
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<td>142.56</td>
<td>139.36</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>57.39</td>
<td>56.93</td>
<td>52.34</td>
</tr>
<tr>
<td>Std Error</td>
<td>Left</td>
<td>11.72</td>
<td>18.41</td>
<td>28.07</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>8.55</td>
<td>4.58</td>
<td>4.14</td>
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</tbody>
</table>
Table 4-2: Table of Gas Volume Content and Ventilation Left to Right Ratio (L/R) of Lung Regions under HFJV

<table>
<thead>
<tr>
<th>Dog #</th>
<th>Condition</th>
<th>Control (Nitrox)</th>
<th>LBO (Nitrox)</th>
<th>Change in L/R before and after LBO (Nitrox)</th>
<th>Change in L/R between Heliox and Nitrox (LBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$V_A$</td>
<td>0.977</td>
<td>1.056</td>
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<td>$V_A$</td>
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<td>0.570</td>
<td>-0.461</td>
<td>0.027</td>
</tr>
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<td>2</td>
<td>$V_A$</td>
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<td>1.009</td>
<td>0.004</td>
<td>0.029</td>
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<tr>
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<td>$V_A$</td>
<td>0.837</td>
<td>0.496</td>
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<td>0.130</td>
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<td>$V_A$</td>
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<td>-</td>
<td>0.194</td>
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<td>-</td>
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<td>0.071</td>
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Table 4-3: Table of Ventilation/Perfusion and Perfusion Left to Right ratio (L/R) of Lung Regions under HFJV

<table>
<thead>
<tr>
<th>Dog #</th>
<th>( \dot{V}_A / \dot{Q} )</th>
<th>Control (Nitrox)</th>
<th>LBO (Nitrox)</th>
<th>Change in L/R from before to after LBO (Nitrox)</th>
<th>Change in L/R from Nitrox to LBO (Heliox)</th>
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<td>0.395</td>
<td>0.453</td>
<td>-0.513</td>
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<td>0.380</td>
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<tr>
<td>Mean</td>
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<td>0.395</td>
<td>0.453</td>
<td>-0.513</td>
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</tr>
<tr>
<td>Std Error</td>
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4.7 References


Chapter 5

Assessment of Intrapulmonary Perfusion ($Q_{\text{tot}}$) and Shunt ($Q_s$) With Positron Emission Tomography (PET)

5.1 Introduction

The current available methodologies of determining regional pulmonary perfusion include: PET imaging techniques using radioactive tracers labeled with Oxygen-15 gas [5], Single photon emission computed tomography (SPECT) with the use of $^{99m}$Tc-marcoaggregated albumin [3], and Infusion of microspheres into the pulmonary circulation [2].

Due to the short half life of $^{15}$O ($T_{1/2} = 123$ s), using this tracer generally results in images with low signal to noise ratio. SPECT, where attenuation of gamma rays by thoracic tissues is difficult to assess, has been found to be quantitative inferior to tomographic imaging using PET. In addition, PET gives better spatial resolution ($\approx 1$ cm) than SPECT ($\approx 3$ cm). The method of injected microspheres requires postmortem division of the excised lung, which needs to be dried and inflated to total lung capacity (TLC). Furthermore, the number of studies on the same experiment subject with microspheres are
limited; while the artifacts of sphere clustering and streaming artifacts cannot be ruled out.

More importantly, the above three methods are unable to distinguish between intraregional blood flow to shunting units ($\dot{Q}_s$) from flow to aerated gas exchanging units ($\dot{Q}_A$). In this chapter we will present methodologies to quantify both $\dot{Q}_A$ and $\dot{Q}_s$ on a regional and pixel-by-pixel basis using PET. We will also present a method of estimating local tracer arrival times from injection site to the capillaries. The method for assessing $Q$ using PET presented here is non-invasive, repeatable after a short period of tracer decay and washout, and not affected by the potential artifacts as mentioned above.

5.2 Model

Due to the low solubility of Nitrogen-13 gas ($^{13}$NN) in blood and tissues, (partition coefficient of $^{13}$NN, $\lambda$, is 0.015), after an apneic intravenous (IV) bolus injection of $^{13}$NN-labeled saline solution, virtually all the tracer in the blood is transferred to gas-filled alveoli in the first pass and the regional tracer content remaining in the alveolar gas is nearly constant and proportional to the fraction of blood flow reaching that region (figure 5-1, page 82). In atelectactic regions of the lungs, however, observations showed that local tracer content reached a peak within the first 10 seconds after bolus infusion, and subsequently decreased monotonically to an asymptote level. It was theorized that such a decrease in tracer content could be attributed to a removal of the tracer from tissues and fluid in non-aerated alveoli by the continuing local blood flow, and therefore, providing direct evidence of regional shunt ($\dot{Q}_s$) (figure 5-2, page 83). We present below methods to assess regional $\dot{Q}$ and $\dot{Q}_s$ in both region of interests and voxel by voxel basis.

5.2.1 Determination of Regional Perfusion ($\dot{Q}$)

A model to calculate intrapulmonary shunt in user defined regions of interest was developed (figures 5-1 and 5-2). The following assumptions were made with the model:
1. Following an IV bolus injection of $^{13}$NN-saline, the tracer injected distributes in proportion to the regional perfusion.
2. Tracer content of end-capillary blood and tissues after equilibrium is negligible in normally aerated alveoli.
3. The tracer is removed from poorly or non-aerated alveoli with a single exponential process at a time constant of $\tau_E$.
4. Tracer kinetics from aerated and non-aerated alveoli are mutually independent, and the effects of tracer intra regional diffusion are neglected.
5. The effects of tracer recirculation are negligible.

From a tracer mass balance, the rate of change in mass within a voxel is equal to the rate of tracer influx by arterial perfusion ($Q_{Cpa}$) minus the rate of tracer removal ($\lambda QC_A$):

$$V \frac{dC_A}{dt} = \dot{Q} C_{pa} - \lambda \dot{Q} C_A$$ \hspace{1cm} (5-1)

where $C_{pa}$ represents the tracer concentration in the pulmonary arterial blood, $C_A$ represents the tracer concentration in the alveoli and $V$ represents the volume of tracer distribution per unit of voxel volume. Equation (5-1) under different conditions can be applied to both aerated and non-aerated regions. In the case of aerated regions, at steady state, with $\lambda$ taken to be approximately zero, the differential equation becomes:

$$V_A \frac{dC_A}{dt} = 0$$ \hspace{1cm} (5-2)

where $V_A$ is the alveolar gas volume content per ml of voxel.

In the case of non-aerated alveoli, assuming that $\lambda$ for tissues is approximately one, the differential equation then becomes:

$$V_s \frac{dC_s}{dt} = \dot{Q}_s C_s$$ \hspace{1cm} (5-3)

where $V_s$ is the volume of tracer distribution per unit of voxel volume and $C_s$ is the tracer concentration in that volume.
Since a region of interest could contain both aerated and non-aerated alveoli, the model was developed by combining equations (5-2) and (5-3), and solving for local perfusion to aerated (\( \dot{Q}_a \)) and non-aerated regions (\( \dot{Q}_n \)), giving:

\[
C_{\text{local}} = \left[ C_\infty + \left( C_0 - C_\infty \right) e^{-\frac{t}{\tau}} \right]
\]  
(5-4)

where

- \( C_{\text{local}} \) represents the global tracer activity in a voxel (\( \mu \text{Ci/ml of voxel} \)).
- \( C_\infty \) represents the tracer in the aerated alveoli (\( \mu \text{Ci/ml of voxel} \)).
- \( C_0 \) represents the average local tracer content extrapolated from the model to time = 0 (\( \mu \text{Ci/ml of voxel} \)).

5.3 Methods

5.3.1 Subject Preparation

Five mongrel dogs (mean weight = 14 kg) were anesthetized with Pentobarbital IV (25 mg/kg), and paralyzed with Pancuronium (0.1 mg/kg). With additional 5 mg/kg of Pentobarbital and 0.1 mg/kg of Pancuronium given every hour to maintain anesthesia. Femoral arterial and venous catheters were cannulated and used during the course of the experiment for blood sampling, periodic administration of anesthetic, and arterial pressure monitoring. A Swan-Ganz catheter (model 93A-131H-7F, Edwards Laboratory, Santa Ana, CA) was inserted in the right jugular vein and advanced into the pulmonary artery, leaving its proximal port to drain into the superior vena cava. Monitoring and recording of the airway, systemic and pulmonary arterial pressures signals were done using Hewlett-Packard (Palo Alto, CA) 1280D pressure transducers and chart (model 7754B). Mechanically ventilation was administered using a Harvard Pump (VT = 25 ml/kg, frequency = 10 bpm, and inspiratory time fraction = 30%). Following a tracheotomy the dogs were intubated with a double lumen endotracheal (ET) tube and the left lung was unilaterally lavaged after 5 or 6 repeated inflations with an emulsion of Tween80 (20 cc) in 1 liter of warm saline.

The PET camera, described in detail elsewhere [1], is a single ring high sensitivity stationary camera that was triggered to begin imaging in synchrony with a signal from a mechanical ventilator (figure 3-1, page 46). A closed loop rebreathing circuit, including CO\(_2\) absorber and supplemental oxygen, allowed
for ventilation with $^{13}$NN-labeled gas, or with tracer free oxygen. A solenoid valve system allowed rapid switching between respiratory gas sources.

$^{13}$NN gas, produced by a cyclotron, was introduced into the rebreathing circuit for inhaled tracer studies, or forced into previously degassed saline solution and temporarily stored in a chamber for perfusion studies. $^{13}$NN-saline solution was infused into the animal via the proximal port of the Swan Ganz catheter. A remotely controlled solenoid valving system allowed flushing of the tubing with $^{13}$NN-labeled saline between the storing chamber and proximal end of the Swan Ganz catheter.

5.3.2 Imaging Protocols
To ensure that the position and degree of inflation of the lungs was equivalent in images taken at apnea and during breathing, image collection during breathing was gated in synchrony with breathing. An electrical signal produced by the mechanical ventilator triggered image collection at the start of inspiration. Collection of two consecutive images each of duration 2.5 seconds that were signal averaged over multiple breaths were made. The inspiratory time of the ventilation was set at 30% and the breathing period to 6 seconds. Thus, the first image included all inspiration and the initial part of expiration. The second image included the latter part of expiration, in which expiratory flow is small and the lungs remain almost stationary at a lung volume close to resting functional residual capacity (FRC). The animals were imaged in the supine position at a tomographic section corresponding to the base of the lung.

5.3.2.1 Positioning and Determination of Regional Gas Volume Content ($V_A$)
After equilibration with inhaled radioactive $^{13}$NN gas between the lungs and the breathing circuit ($\approx 5$ minutes), the animal was advanced into the field of view of the camera until the highest count rate was record by the camera. This position corresponded to the cross section of the lungs with maximal cross-sectional area.
Once proper position was achieved, a gated imaging sequence was collected for a total of 240 seconds. Because of the low solubility of nitrogen in body fluids and tissues, $^{13}$NN remained mostly confined to the air-spaces within the lungs. This equilibration image was therefore proportional to the local gas volume content ($V_A$). During imaging, a 1 ml gas sample was obtained from the rebreathing circuit and its specific activity was assessed with a radiation analyzer (model System 5000, Nucleus Inc., Oak Ridge, TN) that was previously cross calibrated with the camera.

5.3.2.2 Regional Perfusion ($q_{tot}$)

During steady state breathing, the ventilator was stopped at end exhalation and a bolus of $^{13}$NN-saline solution (specific activity: 0.1 - 0.2 mCi/ml) was infused into the right atrium at a constant flow rate of 3 ml/sec (Infusion time, $T_{inf} = 3-4$ s). A sequence of 7 images, the first 4 of five-seconds and the last 3 of ten-seconds in duration were collected while the animal remained in apnea.

5.3.3 Image Analysis

The collected sinograms were corrected with transmission and uniformity scans and reconstructed with a resolution length of 1 cm$^3$. With the reconstructed images, the lung field was divided into two regions of interest (ROI) defining the normal control lung and the lavaged lung. A regional mask of the control side was created by thresholding the $V_A$ image to exclude extrapulmonary regions (50% of maximum number of counts). A regional mask of the lavaged lung was defined by thresholding the sum of all $\dot{Q}$ images to 50% and subtracting from this mask, the control mask. The collected data was then corrected for tracer decay and plotted (figure 5-5, page 86).

5.3.3.1 Determination of Regional Perfusion ($\dot{Q}_r$)

$^{13}$NN tracer content per unit volume in a given region ($C_r$) is proportional to the regional perfusion fraction ($\dot{Q}_r$), and the concentration ($C_i$) and volume ($V_i$) of the infused tracer:
\[ C_r = \frac{\dot{Q}_r}{C_{\text{TOT}}} (\frac{V_r}{V_A}) \] (5-5)

where

\[ \dot{Q}_{\text{TOT}} \] represents the cardiac output of the subject.

To quantify \( Q_r \) from PET images, one needs to relate the local tracer content to the coincidence rate in the region as detected by the camera. The average coincidence count rate collected from a region can be expressed as the integral product of \( C_r \), normalized by the collection time (\( \Delta t \)):

\[ S_r = K_{\text{cam}} \frac{1}{\Delta t} \int_{T_1}^{T_2} C_r \, dt \] (5-6)

where

\( S_r \) represents count rate in the region.

\( K_{\text{cam}} \) represents the calibration factor of the camera correlating tracer specific activity per voxel with the rate of coincidence counts registered by the PET camera (counts/s)/(\( \mu \text{Ci-ml} \)).

By substituting the variables \( V_A C_A \) in equation (5-6) with equation (5-4), the following integral was obtained:

\[ \hat{S}_i = K_{\text{cam}} \left( \frac{1}{T_2 - T_1} \right) \left[ C_{\text{av}} + (C_0 - C_{\text{av}}) e^{\frac{-\Delta T_{ij}}{\tau_s}} \right] \] (5-7)

where

\( \hat{S}_i \) represents the average count rate of the image collected after the time of peak tracer concentration, \( T_{\text{peak}} \), and between times \( T_i \) and \( T_j \) respectively (counts/s).

After integration, the following solution represents the theoretical counts for images after \( T_{\text{peak}} \):

\[ \hat{S}_i = K_{\text{cam}} C_{\text{av}} \left[ 1 + \frac{T_{\text{peak}}}{\Delta T_{ij}} \left( \frac{C_0}{\tau_s} - 1 \right) \left( 1 - e^{\frac{-\Delta T_{ij}}{\tau_s}} \right) \right] \] (5-8)

where

\( \Delta T_{ij} \) represents the time interval of each image (sec).

and

\[ \frac{1}{\tau_s} = \frac{1}{\tau_s} + \frac{1}{\tau_{\text{BSS}}} \] (5-9)
where
\[ \tau_E \]
represents the equivalent decay constant.
\[ \tau_s \]
represents physical decay constant.
\[ \tau_{13NN} \]
represents tracer decay constant.

Equation 5-8 was fitted to the experimental data (figure 5-4, page 85) yielding the following parameters, \( C_\infty, C_0, \) and \( \tau_E \). From these, it is clear that \( C_\infty \propto \dot{Q}_{tot} \).

5.3.3.2 Determination of Mean Tracer Arrival Time (\( T_{arr} \)) and Shunt

Mean arrival time of the \( ^{13}\text{NN} \) tracer, was estimated for both lavaged and controlled ROI's of lung (figures 5-2 and 5-3, pages 83 and 84, respectively) with the following assumptions:

1. Mean arrival time of the tracer to the alveolus (\( T_{arr} \)) occurs some time between the infusion time of the bolus (\( T_{inf} \)) and \( T_{peak} \).
2. The area, \( A_1 \), under the tracer content curve between \( T_{inf} \) and \( T_{max} \) is equal to the area under the theoretical model from \( T_{arr} \) to end of the imaging sequence, \( T_{max} \) (figure 5-2 for lavage model and figure 5-3 for control model).
3. The \( ^{13}\text{NN} \) bolus arrives instantly to the capillary bed.

In the lavaged lung, using the equation (5-7), and knowing \( C_\infty, C_0, \) and \( \tau_E \), the arrival time of the tracer bolus (\( T_{arr} \)) to the regional could be solved numerically with the integral:

\[
\sum_{i=T_0}^{T_{max}} \hat{S}_i \propto \int_{T_{arr}}^{T_{max}} \left[ C_\infty + \left( C_0 - C_\infty e^{-\frac{t}{\tau_E}} \right) \right] dt
\]

(5-10)

where
\[
\sum_{i=T_0}^{T_{max}} \hat{S}_i
\]
represents the sum of images from the start of image, \( T_0 \) to \( T_{max} \) (counts/s).
Knowing \( T_{\text{arr}}, C_{\infty}, C_0, \) and \( \tau_E \), equation (5-4) can be used to obtain \( C_{\text{arr}} \).
Using the constants, \( C_{\text{arr}} \) and \( C_{\infty} \), the fraction \( \left( \frac{\dot{Q}_s}{\dot{Q}_{\text{tot}}} \right) \) of blood flow to shunt units can be determined:

\[
\left( \frac{\dot{Q}_s}{\dot{Q}_{\text{tot}}} \right) = \left( 1 - \frac{C_{\infty}}{C_{\text{arr}}} \right)
\] (5-11)

where
- \( \dot{Q}_{\text{tot}} \) represents the total perfusion to the region.
- \( \dot{Q}_s \) represents the perfusion to the shunting regions.

In the control lung (figure 5-3), the arrival time could be estimated as:

\[
T_{\text{arr}} = T_2 - \left( \frac{\sum_{i=T_0}^{T_{\text{max}}} \bar{T}_i}{\sum_{i=T_0}^{T_{\text{max}}} \bar{S}_i} \right) \sum_{i=T_0}^{T_{\text{max}}} \bar{S}_i
\] (5-12)

where
- \( T_{\text{arr}} \) represents the starting time of an image after \( T_{\text{peak}} \) (s).
- \( \sum_{i=T_0}^{T_{\text{max}}} \bar{S}_i \) represents the sum of images as the tracer arrives from time \( t = 0 \) to time \( t = T_2 \) (counts/s).
- \( \sum_{i=T_0}^{T_{\text{max}}} \bar{T}_i \) represents the sum of images as the tracer arrives from time \( t = T_2 \) to the end of the imaging sequence, \( T_{\text{max}} \) (counts/s).
- \( \sum_{i=T_0}^{T_{\text{max}}} T_i \) represents the total imaging time from \( t = T_2 \) to \( t = T_{\text{max}} \) (s).

### 5.3.3.3 Determination of Shunt \( \left( \frac{\dot{Q}_s}{\dot{Q}_{\text{tot}}} \right) \) (Pixel Basis)

The model developed for the regional analysis was not usable in a voxel-by-voxel analysis. The limitation arising from low signal to noise ratio of the data. Hence, a second model to estimate intrapulmonary shunt fraction on a voxel basis was developed. In our analysis, a resolution length of 1.0 cm was used when reconstructing the images, and the following assumptions were made:

1. the peak local tracer concentration, \( C_{\text{peak}} \), occurring shortly after the bolus injection is proportional to the total local blood flow, \( \dot{q}_{\text{tot}} \).
2. the tracer concentration remaining in the lung field 40 seconds after the bolus injection, \( C_{40} \), is proportional to the fraction of local blood flow in the aerated units, \( q_A \).

3. voxels in \( q_A \) images with expected noise-to-signal ratio \( [(\sigma_x/\bar{x})_{\text{Noise}}] > 0.10 \) were not included in the analysis. The number of counts \( n \) corresponding to a \( (\sigma_x/\bar{x})_{\text{Noise}} \) of 0.10 was determined using the estimation of noise \( (0.624/n) \) developed in chapter 2; voxels with counts less than 250 were not included in the analysis.

Given that \( \dot{q}_s = \dot{q}_{\text{tot}} - \dot{q}_A \), then the shunt fraction, \( \dot{q}_s/\dot{q}_{\text{tot}} \), could be estimated as:

\[
\frac{\dot{q}_s}{\dot{q}_{\text{tot}}} = \frac{\dot{q}_{\text{tot}} - \dot{q}_A}{\dot{q}_{\text{tot}}} = 1 - \frac{C_{40}}{C_{\text{peak}}}
\]  

(5-13)

5.4 Results

5.4.1 Experimental Findings (Regional)

The tracer content (counts/s) in the lavaged region reached a maximum within the first 10 seconds of imaging and subsequently decreased monotonically to an asymptote. In contrast, the tracer in the controlled lung rose to a plateau and remained relatively constant or increased slightly during imaging (figure 5-5).

The lavaged to control perfusion ratio, \( \dot{Q}_{\text{tot(L/C)}} \), varied from 0.71 to 1.63 (Mean 1.07 ± 0.16). Shunt fraction calculated from ROI data varied between 77.5% and 96.5% in the lavaged lung (Mean 85.0 ± 3.68%). Arrival times of the tracer varied from 4.35 to 8.78 seconds (Mean 6.60 ± 0.68) for the lavaged lung and 4.43 to 6.82 seconds (Mean 5.88 ± 0.40) for the control lung. Table 5-1, on page 89, summarizes the regional results obtained for the five dogs with unilateral lavaged lungs.
5.4.2 Experimental Findings (Voxel-by-Voxel)

Most of the lavaged lung had little or no air content, whereas the control lung showed normal aeration (figure 5-6 (a), page 87). The average perfusion per voxel to the lavaged lung, $\dot{q}_{\text{tot}}$, was about the same as that in the control lung (figure 5-6 (b)). In contrast, the amount of tracer remaining in the lavaged lung was only a fraction of that remaining in the aerated lung (figure 5-6 (c)). Also, the lavaged lung showed local values of $\dot{q}_s/\dot{q}_{\text{tot}}$ ranging from 80-100% (figure 5-6 (d)), while the control lung presented shunt fractions of only $4.16\% \pm 0.1\%$ within the 10% noise limits of our method. The amount of shunt in the control lung was calculated by taking the average number of counts on the right lung (control) in figure 5-6 (d).

5.5 Discussion

Although the model presented in this chapter yielded reasonable values of $\dot{q}_{\text{tot}}$ and $\dot{q}_s/\dot{q}_{\text{tot}}$ for an atelectatic lung, it may have overestimated $\dot{q}_{\text{tot}}$ to aerated regions and underestimated $\dot{q}_s/\dot{q}_{\text{tot}}$. The reason for this is tracer recirculation from atelectatic regions back to the lung that was ignored in the analysis. As a result of tracer recirculation, a continued tracer accumulation in the aerated regions would result in an apparently higher $C_{\infty}$ value and thus, a lower shunt fraction.

Perfusion to the lavaged lung was, in some cases, equal or higher than that of the control lung ($\dot{q}_{\text{lavage}}/\dot{q}_{\text{control}} > 1$). Since a hypoxic vasoconstrictive stimulus should be present in the atelectatic lung, vasodilation is an unlikely cause for a higher perfusion. A more likely explanation would be that the collapse of lung increased the number of alveoli per voxel resulting in an increase in alveolar units per voxel and thus, $\dot{q}_{\text{tot}}$.

Due to the low counts left in the perfusion images of the lavaged lung, tracer kinetics models previously developed by Mijailovich et. al. [4] for normal lungs were not accurate enough to determine model parameters in a voxel-by-voxel analysis; hence, a more robust but less accurate simplified approach had to be used. The $\dot{q}_A$ image, acquired after 40 seconds of apnea, showed a substantial reduction in tracer concentration relative to the image collected soon
after bolus infusion; a decrease caused by removal of tracer by the pulmonary circulation. From the values recovered for the time constant \(\tau_s\) of tracer removal in the ROI analysis, it is clear that in 3 out of the 5 animals studied, the assumption that \(C_{40}\) represents \(q_A\) is reasonable since \(\tau_s < (40 - T_{arr})/3\). In the other two animals, however, \(\tau_s\) was too long and \(q_A\) was clearly overestimated.

5.6 Conclusion

We implemented new imaging methods for assessing regional and local blood flow, as well as, shunt fraction with PET.

Although still crude, with future refinements, these methodologies could be applicable to the clinical assessment of pulmonary perfusion and shunt fraction.
Figure 5-1  A model of regional pulmonary circulation including collapsed and aerated alveoli.
Figure 5-2  Theoretical regional tracer activity vs time after a rapid IV bolus injection of $^{13}$NN-saline solution at time = 0 for the lavaged lung.
Figure 5-3  Model to determine arrival time of tracer bolus in the control lung.
Figure 5-4  Levenberg-Marquardt numerical best fit method of the developed model to experimental data. Solid line represents the numerical best fit with the open circles representing the data points.
Figure 5-5  Representative experimental data showing tracer concentration in the lavaged and normal regions. The average counts per pixel per second of the data is plotted against time.
Figure 5-6  Illuminated surface plots where the z coordinate (height) represents the local counts per pixel from the lung region normalized by the mean of the image. (a) Tracer concentration in the lungs after the inhalation of $^{13}$NN gas representing the local gas content per voxel. (b) Image at peak tracer concentration ($\propto q_{bol}$) collected 5 seconds after the bolus infusion of $^{13}$NN tracer. (c) Representative image of tracer ($\propto q_{A}$) remaining in the lungs 30 seconds after the bolus infusion of $^{13}$NN tracer. (d) Image of shunt fraction calculated using images (a) and (b).


### 5.8 Tables

**Table 5-1: Summary Table for Regional Perfusion and Regional Shunt Fraction**

<table>
<thead>
<tr>
<th>Representative</th>
<th>( \tau_s ) (s(^{-1}))</th>
<th>( \frac{\dot{q}<em>{\text{lavage}}}{\dot{q}</em>{\text{control}}} )</th>
<th>( \frac{\dot{q}<em>s}{\dot{q}</em>{\text{tot}}}_{\text{lavage}} )</th>
<th>( (T_{arr})_{\text{lavage}} ) (s)</th>
<th>( (T_{arr})_{\text{control}} ) (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog # 1</td>
<td>11.23</td>
<td>0.786</td>
<td>0.799</td>
<td>7.258</td>
<td>5.871</td>
</tr>
<tr>
<td>Dog # 2</td>
<td>6.59</td>
<td>1.104</td>
<td>0.802</td>
<td>7.775</td>
<td>4.426</td>
</tr>
<tr>
<td>Dog # 3</td>
<td>110.56</td>
<td>1.633</td>
<td>0.965</td>
<td>4.347</td>
<td>6.816</td>
</tr>
<tr>
<td>Dog # 4</td>
<td>8.02</td>
<td>1.093</td>
<td>0.908</td>
<td>8.777</td>
<td>6.196</td>
</tr>
<tr>
<td>Dog # 5</td>
<td>29.99</td>
<td>0.707</td>
<td>0.775</td>
<td>8.445</td>
<td>6.105</td>
</tr>
<tr>
<td>Mean</td>
<td>33.28</td>
<td>1.065</td>
<td>0.860</td>
<td>6.601</td>
<td>5.882</td>
</tr>
<tr>
<td>Std Error</td>
<td>19.77</td>
<td>0.163</td>
<td>0.0368</td>
<td>0.679</td>
<td>0.396</td>
</tr>
</tbody>
</table>
5.9 References


