Quantitative Spectral Contrast in Hyperpolarized $^{129}$Xe Pulmonary MRI

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Medical Physics Graduate Program in the Graduate School of Duke University

2016
ABSTRACT

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Abstract

Hyperpolarized (HP) $^{129}$Xe MRI has emerged as a viable tool for evaluating lung function without ionizing radiation. HP $^{129}$Xe has already been used to image ventilation and quantify ventilation defects. However, this thesis aims to further develop imaging techniques that are capable of imaging, not just ventilation, but also gas transfer within the lung. This ability to image gas transfer directly is enabled by the solubility and chemical shifts of $^{129}$Xe that provide separate MR signatures in the airspaces, barrier tissue, and red blood cells (RBCs).

While $^{129}$Xe in the airspace (referred to as gas-phase $^{129}$Xe) can be readily imaged with standard vendor-provided imaging sequences, $^{129}$Xe in the barrier and RBC compartments (collectively referred to as dissolved-phase $^{129}$Xe) has such a rapid T2* ($<$2 msec at 2T) that even simple gradient recalled echo (GRE) sequences are ineffective at imaging the limited signal before it decays. To minimize these losses from T2* decay, the 3D radial sequence offers much shorter TEs that can image the dissolved-phase $^{129}$Xe. Despite their ability to image dissolved-phase signal, however, 3D radial sequences have not yet been widely adopted within the hyperpolarized gas community. In order to demonstrate the potential of the 3D radial pulse sequence, chapter 3 uses standard $^{129}$Xe ventilation imaging to compare 3D radial image quality and defect conspicuity with that of the conventional GRE. Since the 3D radial sequence offered comparable performance in ventilation imaging, and also provided the ability to image dissolved-phase $^{129}$Xe,
Chapter 3 establishes that the 3D radial sequence is well-suited for imaging $^{129}$Xe in humans.

Though 3D radial acquisition offers clear advantages for functional $^{129}$Xe lung imaging, its non-Cartesian sampling of k-space complicates image reconstruction. Chapter 4 carefully explains the process of gridding-based reconstruction, and describes how problems arising from non-selective RF pulses and undersampling, both of which are commonly employed in hyperpolarized $^{129}$Xe imaging, can be avoided by using appropriate reconstruction techniques. Furthermore, we detail a generalized procedure to optimize reconstruction parameters, then demonstrate the benefits of our improved reconstruction methods across both $^1$H anatomical imaging as well as functional imaging of $^{129}$Xe in the gas- and dissolved-phases.

These dissolved-phase images are particularly interesting because they consist of separate contributions from $^{129}$Xe in the RBCs and barrier tissue. Once these two resonances are disentangled from one another, they provide a noninvasive means to measure gas exchange regionally. However, such decomposition of these two resonances is predicated on prior knowledge of their spectroscopic properties. To that end, chapter 5 describes a non-linear spectroscopic curve fitting toolbox that we developed to more accurately characterize the $^{129}$Xe spectrum in vivo. Though previously, only two dissolved-phase resonances have ever been described within the lung, our fitting tools were able to identify a third dissolved-phase resonance in both
healthy volunteers and healthy controls. Furthermore, we describe several spectroscopic features that differ statistically between our healthy volunteers and IPF subjects to demonstrate that this technique is sensitive to even subtle functional changes within the lung. These spectroscopic measurements provide the basis for imaging gas transfer.

Describing lung function regionally requires phase-sensitive imaging techniques that can decompose the dissolved-phase signal into images that represent the contribution from the RBC and barrier resonances. To date, only two implementations have been demonstrated, and both suffered from poor SNR and challenges in quantifying gas transfer. Chapter 6 adds quantitative processing techniques that improve phase sensitive imaging of $^{129}$Xe gas transfer. These methods 1) normalize both the RBC and barrier uptake images by gas-phase magnetization so that intensities can be compared across subjects, 2) compress the dynamic range of these functional images to enhance their perceived SNR, and 3) derive colormap thresholds from a healthy reference population to give intensities meaningful context.

To show the value of our quantitative gas transfer imaging, chapter 7 applies these techniques to a cohort of healthy volunteers and another of IPF patients. Since patients with IPF exhibit a progressive thickening and hardening of the pulmonary interstitium that severely restricts the transport of gases between the lungs and blood, they represent an ideal population to prove out our methods. This analysis identifies several patterns to the RBC and barrier distributions which could potentially represent
different stages of disease. Furthermore, we demonstrate that our MRI-based findings correlate well with DLco and FVC, and to a lesser extent with the structural cues seen in CT. This suggests that $^{129}$Xe imaging offers complimentary functional information that can’t be derived from CT, while also describing its spatial distribution unlike PFTs.

The work in this thesis has transitioned our HP $^{129}$Xe gas transfer studies from a proof of concept to an optimized and quantitative imaging protocol with robust processing pipelines. Using these MRI methods, we have shown that we can directly and quantitatively probe pulmonary ventilation and gas transfer within a single breath hold. In IPF, such noninvasive imaging methods are desperately needed to monitor the efficacy of these new treatments to ensure that the associated medical expense is justified with positive changes in outcomes. Finally, these new functional contrasts will be useful in studying other cardiopulmonary diseases such as asthma, chronic obstructive pulmonary disease, and pulmonary arterial hypertension.
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1 Significance and Motivation

Lung disease can be attributed to 1 in 6 deaths in the US, making it the 3rd leading cause of mortality (Murphy, 2013). It is also associated with substantial expense (~$106 billion/year in the US). However, diagnosis of many lung diseases remains non-definitive and treatments are often only effective among patient subpopulations (National Heart Lung and Blood Institute, 2005). Thus, the long-term goal of this work is to provide tools that help classify the underlying disease phenotypes based on their response to therapies. To do so, we first need non-invasive metrics that measure therapy response. However, today it remains difficult to objectively assess the extent of disease let alone to monitor progression or detect therapeutic response. Thus better diagnosis, phenotyping, and monitoring are needed along with novel therapies that can turn the tide on lung disease.

While this work has broader application to many lung diseases, much of this work was conducted on patients with idiopathic pulmonary fibrosis (IPF). The pathogenesis of IPF is thought to involve excess collagen deposition and interstitial inflammation that collectively limit the capacity of alveoli to participate in gas exchange (King, 2011, Wolters, 2014). IPF is the most common and severe form of interstitial lung disease (ILD), affecting ~89,000 people in the US (Nalysnyk, 2012). The disease is incurable, and its mortality (~40,000/year) is comparable to that of breast cancer. Furthermore, the severity and rate of progression of IPF are unpredictable and
vary greatly with age and sex (Nalysnyk, 2012). The increasing prevalence of IPF and poor survival suggest that there is a large unmet need in IPF for better diagnosis and monitoring of therapy (Raghu, 2014).

At present, lung transplantation is the only therapeutic option shown to increase survival, but due to the typical age and poor health of IPF patients, only a 1% minority are eligible for transplant. And of those that receive a transplant, less than half survive 5 years post-transplant (Thabut, 2003). Corticosteroids and immunosuppressants are used to decrease inflammation, but do not improve outcomes. In 2011, an official statement on IPF from the American Thoracic Society declared that there were no effective therapeutic agents for curing or treating IPF (Raghu, 2011). Since then, however, new therapies have shown great promise for IPF, including two which have been FDA approved (Richeldi, 2014a, King, 2014). These new therapies, which have only been shown to slow progression, are associated with significant cost and side effects that together create a pressing need for reliable metrics that predict therapeutic response and assess disease progression in patients with IPF. Furthermore, the search for more effective pharmaceuticals remains slow because current abilities to detect and monitor drug efficacy are either insensitive, unrepeatable, invasive, or time and cost intensive. Therefore, there is a strong need for a more comprehensive, noninvasive lung examination that offers both structural and functional information at a regional level to expedite the development of viable therapies. Without improved methods to determine
treatment efficacy, therapies for IPF will continue to advance slowly, and the prognosis of IPF will remain hopeless. Furthermore, without improved methods of identifying early stage disease with reversible damage, palliative treatments will remain the only option for these patients.

To date, PFT tests have been the primary end point for clinical trials (Raghu, 2011). Changes in PFTs such as the Forced Vital Capacity (FVC) or Diffusing Capacity of the Lung for CO₂ (DL₅CO) have been shown to weakly correlate with mortality. Moreover, PFTs are imprecise and effort dependent, leading clinicians to require a large and sustained change (10% FVC change 15% DL₅CO change) to be considered clinically significant (Collard, 2003). Given the high rates of progression (average survival of ~3.8 years), this requirement likely leads to delays in therapeutic management that allow significant disease progression to go unchecked. Furthermore, IPF is known to be heterogeneously distributed throughout the lung and PFTs only offer whole lung measurements. Because of the large reserve capacity of the lung, such global metrics are particularly insensitive to early stage disease and subtle changes in disease.

Imaging techniques such as high-resolution computed tomography (HRCT) better quantify the heterogeneity of how IPF manifests itself. Structural changes in fibrosis seen in HRCT have been shown to correlate with prognosis (Lynch, 2005). HRCT is used to detect the presence of usual interstitial pneumonia, which enables IPF to be diagnosed without a surgical biopsy. Recent studies have explored the use of
quantitative CT to measure longitudinal change, assess disease severity and predict mortality (Kim, 2015, Best, 2008, Maldonado, 2014, Salisbury, 2016). However, these repeat CT scans carry increasing risks of cumulative radiation exposure (Sodickson, 2009). And despite its exquisite resolution (~0.5 mm), CT cannot discern the alveoli or terminal bronchioles where gas exchange takes place. Thus, CT cannot assess lung function directly. Such functional information can only be inferred by assuming structure-function relationships (Jahani, 2015) or by using dual-energy techniques (Lu, 2012). Furthermore, the fibrotic regions that are detectable by CT predominantly represent late-stage, largely irreversible disease. Therefore, we suggest that using structural cues from CT as a biomarker to assess therapy response will be less sensitive than direct functional measurements.

Since efficient gas exchange requires both ventilation and perfusion, the ratio of these two quantities, termed the V/Q ratio, has been also studied by dual-energy CT (Lu, 2012), SPECT (Petersson, 2009), and PET (Rhodes, 1989). In a healthy lung, ventilation and perfusion are well-balanced, so the V/Q ratio falls near unity (Levin, 2016). Where the V/Q ratio is mismatched, pulmonologists look for associated abnormalities in gas exchange. It is important to note, however, that even healthy lungs exhibit significant heterogeneity in their regional V/Q ratios. Characterizing this heterogeneous distribution accurately, especially given the low SNR, spatial resolution, and temporal resolution, is challenging. Finally, the non-negligible radiation dose associated with
these modalities makes the longitudinal studies required for therapy development infeasible. To better stratify and manage IPF, we need a noninvasive probe of lung function that sensitively and robustly detects early changes in gas exchange on a regional basis.

To that end, MRI offers a noninvasive means to image soft tissues with exquisite contrast. Historically, MRI of the lung has been challenging because pulmonary tissue consists of small blood vessels, thin alveolar membranes, and is otherwise full of airspaces. Together, the low $^1$H density of the tissue affords little magnetization for imaging, and the abundant air-tissue interfaces create a harsh susceptibility environment that works to rapidly decay the limited signal and limit spatial resolution. The inherently short $T2^*$ of lung parenchymal tissue can be mitigated, in part, by using imaging at ultrashort echo times (Bergin, 1991). Such techniques have enabled imaging at sufficient resolution to identify the key textural features seen in HRCT (Johnson, 2013). Certain features, such as traction bronchiectasis, honeycombing, and opacities, are thought to represent late stage disease that will not respond to therapy. However, other textures, namely ground glass or consolidation, could indicate earlier stage disease that could be reversible with therapy. Thus while UTE MRI can only report on the structural cues of disease, this complimentary information provides useful context when interpreting functional MRI images.
\(^1\)H MRI can also be used to derive functional metrics within the lung. By monitoring the dynamics of a gadolinium contrast bolus as it travels through the cardiopulmonary system, \(^1\)H MRI can quantify regional perfusion (Wang, 2013) similarly to dual energy CT, SPECT, and PET, but without the ionizing radiation. An alternative to using injected contrast is to employ arterial spin labeling, where blood is magnetically labeled, then tracked as it flows through the pulmonary system (Arai, 2011). While such exogenous contrast is desirable, this ASL approach typically only measures perfusion in a few slices. However, measuring perfusion alone is insufficient to assess impaired gas exchange. At least ventilation must also be measured to provide information regarding gas transfer.

Ventilation imaging is relatively straightforward using HP \(^{129}\)Xe MRI. Since hyperpolarized \(^{129}\)Xe acts as a surrogate for oxygen, it can be readily imaged as it fills the airspaces. This gas-phase imaging has been used to quantify ventilation defects in other lung diseases such as COPD and asthma (Kirby, 2012, Svenningsen, 2013). While ventilation defects are not a hallmark of IPF, these defects could indicate impending exacerbations or accelerated progression in IPF patients. Also, when combined with \(^1\)H perfusion images, the derived V/Q maps can be used to correlate with other modalities. Furthermore, the gas-phase ventilation images are used to normalize the intensities of our functional gas transfer volumes. In chapter 3, we assess both the conventional GRE and 3D radial acquisition by quantifying their image quality tradeoffs and assessing
their ability to identify ventilation defects. We hypothesize that while the conventional GRE would offer higher SNR and in-plane spatial resolution, the isotropic resolution afforded by the 3D radial sequence would give comparable ability to detect ventilation defects. Furthermore, we expect the 3D radial sequence to be more robust to motion and better preserve the native gravitational intensity gradients that are physiologically expected in the lung. Finally, since a conventional GRE cannot achieve a short enough TE to image the short T2* signal associated with 129Xe dissolved in the blood and tissue, we need to migrate to a 3D radial sequence. Thus, chapter 3 characterizes the performance of our 3D radial acquisition in the context of the more familiar GRE sequence.

Despite these apparent advantages of 3D radial acquisition, reconstructing radial acquisitions is non-trivial. It requires gridding radial k-space data onto an evenly spaced Cartesian grid such that the Fast Fourier Transform (FFT) can be applied to reconstruct the image volume (Osullivan, 1985). The process of gridding, while a necessary step, can lead to reconstruction errors and therefore must be carried out judiciously. While this process has been extensively optimized for proton MRI applications (Fessler, 2003), minimal attention has been paid to radial image reconstruction issues specifically pertaining to HP gas MRI. Chapter 4 details the methods we have used to optimize how we reconstruct our 3D radial HP 129Xe lung images. These improved reconstruction methods have enhanced the image quality of our ventilation images, but perhaps their
most significant contribution has been to enable us to image $^{129}\text{Xe}$ that has dissolved into the blood and barrier tissues.

This dissolved-phase signal is particularly relevant in IPF because $^{129}\text{Xe}$ signal only arises in the red blood cells where there is efficient gas transfer, making it an excellent biomarker for gas exchange impairment. This ability to detecting dissolved-phase signal separately from the gas-phase signal is possible, not only because $^{129}\text{Xe}$ is soluble in the blood and tissue, but also because the $^{129}\text{Xe}$ atom experiences separate chemical shifts as it travels the same pathway as oxygen, from the airspaces through the interstitial tissue and into the blood. These chemical shifts are depicted in the image (top) and magnitude spectrum of $^{129}\text{Xe}$ (bottom) shown in Figure 1, which shows three obvious resonances in the human lung that are commonly reported as xenon in the airspaces (blue), barrier tissue (green), and red blood cells (red).
Figure 1: $^{129}$Xe atom is soluble in the pulmonary barrier tissue and blood (top). $^{129}$Xe also experiences separate chemical shifts (bottom) in the airspaces (blue), barrier tissue (green), and blood (red), which are reflected in the magnitude spectrum of $^{129}$Xe. Each of these resonances reports on a separate chemical environment of $^{129}$Xe, thus by characterizing these spectral properties, we can probe lung function on a global scale.

Chapter 5 develops quantitative methods to accurately decompose the $^{129}$Xe spectrum in vivo, investigates how the $^{129}$Xe spectrum changes in IPF patients compared to healthy controls, then correlates our spectroscopic findings with PFT results. Since these spectral measurements are sensitive to micron scale changes in the lung, we hypothesized that they could offer insights into the long-debated pulmonary question of whether the gas exchange impairment seen in IPF is driven primarily by restricted diffusion or perfusion.
(Agusti, 1991). In the case of diffusive restriction, we would expect two spectroscopic features to develop. First, the intensity of the RBC peak would decrease because it represents the amount of $^{129}$Xe that diffused through the blood-gas membrane into the RBCs (Kaushik, 2014). Second, the RBC peak would shift negatively because local hypoxemia causes nonlinear chemical shifts in the RBC peak (Wolber, 2002). In contrast, restricted perfusion would only exhibit changes to the RBC peak intensity, because even poorly perfused regions would still be well-oxygenated if diffusion takes place. Thus our spectroscopic techniques can not only more accurately characterize the spectrum of $^{129}$Xe in vivo, but they can also report on physiological changes seen in the lung.

Since spectroscopic measurements only consider the lung as a whole and IPF is known to manifest heterogeneously, there is a clear need for imaging the dissolved-phase compartments of $^{129}$Xe. While such phase-sensitive imaging has already been demonstrated, deriving quantitative measurements from these images has remained challenging given the low SNR of dissolved phase signal (Qing, 2014a, Kaushik, 2016a). However, using our 3D radial acquisition from chapter 3 and optimized reconstruction from chapter 4, we can now achieve higher SNR dissolved-phase images and therefore more reliably decompose the RBC and barrier resonances. This decomposition is accomplished by exploiting the differences in chemical shift between these two resonances. Dixon et al. first proposed this method to separate water and fat signals by imaging at a TE where the two resonances are exactly 90 degrees out of phase (Dixon,
1984). Imaging at this condition allows us to apply a simple phase shift to isolate these resonances to the real and imaginary channels of the receiver.

Chapter 6 develops a quantitative processing pipeline for these Dixon images that enables us to regionally measure how efficiently $^{129}$Xe transfers into the barrier tissue and RBCs. Furthermore, this imaging approach normalizes the RBC and barrier signal amplitudes by their source magnetization from $^{129}$Xe gas in the alveoli without being corrupted by bulk $^{129}$Xe signal in the airways. This normalization allows the RBC and barrier values to be compared across subjects in a way that is not possible spectroscopically. By quantifying these RBC and barrier images individually, we sought to investigate whether the spectroscopically-derived RBC:barrier ratio was found to be lower in IPF patients than healthy controls because of changes in the RBC amplitude, the barrier amplitude, or a combination of both (Kaushik, 2014). Interestingly, this work found three distinct patterns of the relative RBC and barrier signals. These patterns could potentially correspond to different stages of disease in IPF or might benefit from different methods of therapy.

Chapter 7 analyzes these quantitative functional images to establish the spatial patterns of disease, relates functional patterns to the structural patterns of disease seen in CT and correlates functional imaging metrics with PFTs. Through this initial validation work, we expected to find that regions of low $^{129}$Xe gas transfer tended to be predominantly found in the basal and sub-pleural lung where fibrosis is commonly
found histologically (Katzenstein, 1998). Similarly, we anticipated that regions of honeycombing in CT, which represent severe fibrosis, would correspond to regions of reduced RBC uptake in $^{129}$Xe MRI (Nishimura, 1992). Furthermore, we predicted that our MRI-based metrics would correlate reasonably well with PFT results. While we expected overall agreement between our $^{129}$Xe exam and other existing functional metrics, we also expected $^{129}$Xe to offer additional insights that could not be detected by global PFT metrics or structural CT imaging.

Collectively, this thesis aims to enhance the theoretical basis and mature the implementation of functional spectroscopic and imaging techniques using HP $^{129}$Xe so that they can be reliably deployed across multiple sites for clinical IPF trials.
2 Relevant Theory

This chapter briefly covers only the pulmonary anatomy and physiology that is pertinent to this research. ‘Respiratory Physiology: The Essentials’ by John West is an excellent additional reference.

2.1 Cardiopulmonary Anatomy and Physiology

The primary aims of the lung are to transport oxygen into the blood and excrete \( \text{CO}_2 \) from the body. These critical functions are accomplished efficiently due to the structure of the lungs, with airways branch in a fractal pattern to achieve a very high surface area (50-100 m\(^2\)) within a limited volume (4-6 L). This branching begins where the trachea divides into the right and left mainstem bronchi, which deliver the gases to the right and left lungs, respectively. From each mainstem bronchus, the airways continue branching and narrowing into a total of 23 generations. The first 16 generations, which are referred to as the conducting zone of the lung, only act to transport gases, and do not directly exchange gases with the blood. It is in these upper airways where obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) take place. In contrast, the later 7 generations of the lung, referred to as the respiratory zone, are where gases exchange between the airspaces and blood. While gases transfer throughout the respiratory zone, the majority of gas transfer occurs within the smallest functional units of the lung – the alveoli. These alveoli contain
nearly spherical alveolar sacs, which have a high surface area and thin membranes (<1 µm), so that gases readily diffuse between their airspaces and the neighboring pulmonary capillary beds. Consequently, changes to these alveoli or their membranes can affect pulmonary gas exchange. In emphysema, for example, the alveolar membrane degrades which decreases the alveolar surface area to volume ratio and makes gas exchange less efficient. In idiopathic pulmonary fibrosis, the disease of primary focus for this thesis, the interstitial tissue between these alveoli and blood becomes inflamed and eventually fibrotic, which presents a barrier that impedes gases from diffusing into the blood.

The pulmonary vasculature follows a similar branching pattern to that of the airways, and is closely integrated with the airway network. The diameter of each subsequent branch reduces, eventually reaching ~10 µm in the mesh-like capillary networks that surround the alveoli. These tiny capillaries are fed deoxygenated blood from the right atrium of the heart. As blood is pumped through the capillary beds, the flow slows to provide a sufficiently long transit time through the gas exchange regions (~750 ms at rest) to fully oxygenate the blood. This oxygenated blood then gradually collects in larger veins that combine until they enter the left atrium, where they are pumped through the heart to supply the body with oxygen.
2.1.1 Pulmonary Gas Exchange

In order for the lungs to efficiently exchange gases with the blood, three processes need to occur. First, the lung must be ventilated to supply an influx of oxygen and remove CO$_2$ from the lungs. Second, gases must readily diffuse from the alveolar airspaces into the pulmonary capillary blood. Third, the capillary network must be well-perfused to direct deoxygenated blood across the blood-gas barrier so that the red blood cells become oxygenated and are then pumped into the systemic circulation. The following sections will discuss each of these processes as well as metrics associated with these processes that are common in pulmonary medicine.

2.1.2 Ventilation

The flow of gases into the lung during inhalation is driven by negative pressures that are generated from the diaphragm pulling downward and the intercostal muscles pulling outward on the chest cavity. Thus the lung itself just passively expands and contracts to draw air in and out of the air spaces. This ability to expand is afforded by the thin, sponge-like network of very compliant alveolar membrane. However, this compliance also makes the lung sensitive to gravity and posture. Because of the weight of the lung and its vascular network, the lung compresses in the direction of gravity, which is termed the gravitationally dependent lung. Conversely, the lung is stretched in the direction opposing gravity. This stretching makes further expansion during
inhalation less efficient. Since the lung expands less in these stretched regions, the lung is also less ventilated than in the compressed gravity dependent regions (Glenny, 2009).

2.1.3 Perfusion

The effects of gravity and posture on perfusion parallel that of ventilation. That is because gravity causes the blood to pool in the gravitationally dependent lung. This larger volume of blood provides a greater capacity for diffused gases. Thus, like ventilation, perfusion is typically highest in the dependent lung (West, 1969).

2.1.4 Diffusion

Regional diffusion has not been investigated as thoroughly as ventilation and perfusion. This is likely because such it is extremely challenging to measure and spatially resolve this passive process in vivo. Instead, diffusion is commonly inferred from ventilation (V) and perfusion (Q) information. This method assumes that, in a healthy lung, ventilation and perfusion should be matched, giving a V/Q values of one. However, ventilation and perfusion are both known to be heterogeneously distributed, so regions of near-zero or near-infinite V/Q values can exist even in healthy lungs (Levin, 2016).

Fortunately, $^{129}$Xe provides an alternative means to measure diffusion noninvasively. In the lung, $^{129}$Xe diffuses according to Fick’s first law. This means that
the volume of diffused $^{129}$Xe is proportional to the surface area and partial pressure difference, and inversely proportional to the thickness of the barrier tissue. Therefore the structure of the lung, consisting of high surface area and exceedingly thin membranes, is clearly an efficient mechanism for diffusing gases. However, when the blood-gas membranes become fibrotic or inflamed, or the alveolar surface area decreases, diffusion can become impaired.

2.1.5 Hyperpolarized $^{129}$Xe Detects Diffusive Restriction

In the ventilated lung, the transport of oxygen across the blood-gas barrier is governed by both diffusion and perfusion. Historically, the degree to which these two processes restrict oxygen transfer has been measured by tracking the uptake of surrogate gases in the lung. For example, carbon monoxide (CO) is used to measure DL$_{CO}$, a PFT that is used to measure diffusion in lung. CO is used because its uptake is independent of perfusion, and therefore only limited by the rate at which diffusion can occur. Changes in perfusion do not affect CO uptake because CO has such a strong affinity for hemoglobin that it maintains a constant partial pressure gradient regardless of perfusion rate. For this reason, CO is considered a diffusion-limited gas.

Other non-reactive gases, such as CO$_2$, N$_2$O, and xenon, are used to measure changes in perfusion. These gases, which do not bind to hemoglobin or other molecules, quickly saturate to equilibrium values in the blood such that their uptake is not
governed by diffusion. As a result, additional CO₂ and N₂O can only be transferred to
the blood by increasing the perfused blood supply, which makes these gases perfusion-
limited.

This concept of gases being diffusion- or perfusion-limited is somewhat
confusing when we speak of HP ¹²⁹Xe MRI. That is because xenon is classically
considered to be a perfusion-limited gas. It is true that, being a noble gas, ¹²⁹Xe quickly
saturates in the blood and thus the net transfer of ¹²⁹Xe into the blood is governed, not by
diffusion, but by perfusion. However, the nature of our MRI detection inherently
destroy the HP ¹²⁹Xe from the RBC and barrier tissues, while largely preserving HP
¹²⁹Xe in the airspaces. This RF energy that excites ¹²⁹Xe also maintains a gradient of
hyperpolarized magnetization across the blood-gas membrane. This gradient causes the
amount of RBC signal that we detect in our MRI experiments to be limited by the
diffusion of HP ¹²⁹Xe across the barrier tissue. Thus, while ¹²⁹Xe itself is a perfusion-
limited gas, the gradient of hyperpolarized magnetization across the blood-gas
membrane allows us to probe diffusion with MRI-based ¹²⁹Xe experiments (Cleveland,
2014).
2.2 Physics of Hyperpolarization

2.2.1 NMR Signal

The basis of both nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI) lies in the existence of a magnetic moment within many nuclei. Nuclei that contain an even number of protons and an even number of neutrons have a net-zero magnetic moment; thus only a subset of nuclides are available for NMR techniques. Here we consider NMR of \(^1\)H and \(^{129}\)Xe, which are both NMR active. For these nuclides, the nonzero magnetic moment can be linearly related to its nuclear angular momentum:

\[
\mu = \gamma J
\]

where \(\mu\) is the magnetic moment, \(J\) is the angular momentum, and \(\gamma\) is the gyromagnetic ratio.

In the absence of a magnetic field, thermal fluctuations cause these magnetic moments to align in random orientations. This incoherence results in a net zero ensemble magnetic moment. However, when nuclei with non-zero spin are placed in a static magnetic field, the nuclei are split by the Zeeman Effect into one of its quantum-mechanical states. Both \(^1\)H and \(^{129}\)Xe are spin \(\frac{1}{2}\) systems, and consequently can exist in exactly two spin states. Each spin state has an associated energy, \(E\), which is defined as

\[
E = \frac{\gamma \hbar m B}{2\pi}
\]
Where \( h \) is Planck’s constant, \( B \) is the magnetic field, and \( m \) is the spin number. For spin \( \frac{1}{2} \) systems, the lower energy state (termed spin-up) represents when the \( z \) component of the magnetic moment vector is parallel to the applied magnetic field. Conversely, the higher energy state (termed spin-down) represents when the magnetic moment and magnetic field lie anti-parallel.

At absolute zero temperature, where no thermal interactions exist, all of the nuclei exist in the lower energy spin-up state. However, at body-temperature, these thermal interactions bring the two populations closer to equilibrium, albeit with a slight preference toward the low energy spin-up state remains. The relative number of spin-up and spin-down nuclei can be described by Boltzmann statistics:

\[
\frac{N^+}{N^-} = e^{\frac{\hbar B_0}{2kT}} \tag{1.3}
\]

where \( N^+ \) is the number of spin-up nuclei, \( N^- \) is the number of spin-down nuclei, \( B_0 \) is the magnetic field, and \( T \) is the temperature. We can alternatively describe the distribution of spins by quoting the polarization, which is percentage of total spins that are in the high energy state:

\[
p = \frac{N^+}{N^+ + N^-} \approx \frac{2kT - \hbar y B_0}{2kT + \hbar y B_0} \tag{1.4}
\]

Thus, at body temperature, our clinical 1.5T magnet only polarizes \(^1\text{H} \) nuclei to \( 4.9 \times 10^{-6} \) (4.9 ppm) and \(^{129}\text{Xe} \) nuclei to \( 1.4 \times 10^{-6} \) (1.4 ppm).

Most \(^1\text{H} \) MRI techniques exploit the fact that the human body is \( \sim70\% \) water and water contains \( \sim110 \) moles of \(^1\text{H} \) per L. Thus, \(^1\text{H} \) nuclei are naturally abundant
throughout most of the body. For these applications, it is the sheer density of $^1$H nuclei, and not their degree of nuclear polarization, that creates significant bulk magnetization. This bulk magnetization can be described by:

$$M_0 = \frac{\gamma^2 \hbar^2 B_0 \rho_0}{4kT} \quad (1.5)$$

Where $\rho_0$ represents the density of nuclei. The lungs, however, contain many airspaces, which lowers the $^1$H density and bulk magnetization by >75%. Furthermore, the interfaces between airspaces and the pulmonary interstitium introduce susceptibility gradients that shorten the transverse relaxation time dramatically ($T_2^* \sim 2$ ms). A third and equally significant problem is that $^1$H signal has a long T1 in the lung (1.3 sec at 1.5T), making it difficult to image quickly under breath hold (Wild, 2012). Finally, heart and lung motion are a common and mostly unavoidable source of blurring in vivo. Nevertheless, MRI of the lung microstructure, while challenging, has been demonstrated using an ultrashort echo time (UTE) pulse sequences that minimize T2* decay (Johnson, 2013). However, lung function can only be inferred from these structural images.

An alternative to using $^1$H signal is to employ hyperpolarized gases as a signal source. Using thermal $^{129}$Xe signal is impractical primarily because the density of xenon gas is ~2600 times lower than $^1$H (0.042 moles/L). Additionally, the lower gyromagnetic ratio of $^{129}$Xe and lower polarization as compared to $^1$H act to reduce the thermal signal. Fortunately, $^{129}$Xe can be hyperpolarized to enhance its signal by 5 orders of magnitude. Without such hyperpolarization, $^{129}$Xe would not be practical for use in vivo.
2.2.2 Spin Exchange Optical Pumping

Here we employ spin exchange optical pumping to hyperpolarize $^{129}$Xe gas, which is a two-part process (Drieuys, 1996). The first step, called optical pumping, aims to polarize rubidium (Rb) (Kastler, 1950). This is accomplished by using a high powered, circularly polarized laser that is tuned to the D1 resonances of the Rb valence electron (795 nm) within a 20 G magnetic field. The resonance of these photons allows them to be absorbed by the Rb electron and exchange a quanta of angular momentum, to put the electron into an excited state. This excited Rb valence electron is then nearly instantaneously quenched by N$_2$ buffer gas back into one of two ground states, spin-up or spin-down. However, to conserve angular momentum, the circularly polarized 795 nm light can only re-excite the spin-down electron. Over time, this spin-down state becomes depopulated, leaving the majority of Rb valence electrons polarized in the spin-up state. The timescale of this optical pumping is very short, as we can achieve 100% Rb polarization within a few microseconds.

The polarized Rb then participates the second step in the polarization process – spin exchange (Bouchiat, 1960). Spin exchange occurs when the polarized rubidium interacts with the $^{129}$Xe nucleus to undergo Fermi hyperfine interactions whereby angular momentum is transferred from the Rb electron to the $^{129}$Xe nucleus. This transfer switches the spin-up Rb to spin-down and the spin-down $^{129}$Xe nucleus to spin-up, thereby polarizing the $^{129}$Xe. In contrast to optical pumping, spin-exchange occurs on a
longer timescale, taking multiple seconds to polarize $^{129}$Xe to ~30%. This difference is primarily driven by the fact that rubidium atoms are 10000 times more dilute than $^{129}$Xe within the cell, so their interaction cross section is small.

2.2.3 Polarization Methods

This section briefly reviews the procedure we use to polarize $^{129}$Xe for clinical scans. Throughout this dissertation, these same methods were used to polarize $^{129}$Xe, so they are described here once to avoid redundancy.

Spin exchange optical pumping occurs in a glass cell that is housed in an oven. This glass cell has an inlet, where $^{129}$Xe, Rb, and buffer gases ($N_2$ and $^4$He) are supplied into the cell, and an outlet where the polarized $^{129}$Xe, Rb, and buffer gases exit the cell. Prior to entering the cell, Rb is vaporized by heating it to ~150° C so that it will absorb ~90% of the 100 W laser light. As the Rb and $^{129}$Xe pass through the cell, they undergo spin exchange optical pumping. The $^{129}$Xe leaving the cell is polarized to roughly ~30%.

After exiting the cell, the gases pass through a cold finger that is submerged in liquid nitrogen. The temperature of the liquid nitrogen (~77 K) is below the freezing point of $^{129}$Xe (165 K) but above that of $N_2$ (63 K) or ($^4$He, so this acts to cryogenically separate the $^{129}$Xe from the other gases. Furthermore, the frozen $^{129}$Xe is kept under a 2000 G magnetic field to extend the T1 (~2 hours) so that $^{129}$Xe can be accumulated for an hour (Limes, 2016). After $^{129}$Xe accumulation finishes, the liquid nitrogen is replaced.
with water to thaw $^{129}$Xe back into a gaseous state, which is then dispensed into a Tedlar bag (Jensen Inert Products, Coral Springs, FL). Until the dose is delivered to the patient, it is kept in a 20 G magnetic field to preserve the magnetization.

This thesis relies on the pulmonary physiology and polarization theory outlined in this chapter in order to develop robust quantitative techniques of evaluating lung function using hyperpolarized $^{129}$Xe in humans. This background theory provides the foundation for us to optimize our acquisition, tune our custom reconstruction software, and carefully establish quantitative processing techniques for their specific use in hyperpolarized $^{129}$Xe MRI. The following chapters further detail the tools and methods that have enabled us to realize this new approach to acquiring regional and direct measurements of diffusive gas transfer in vivo.
3 Optimizing Acquisition Techniques for Hyperpolarized $^{129}$Xe Imaging

Ventilation is the first requirement of healthy lung function and since hyperpolarized $^{129}$Xe acts as a surrogate for oxygen, it can be directly imaged as it fills the airspaces. This chapter evaluates $^{129}$Xe acquisition strategies from the perspective of image quality and defect conspicuity. The methods and results presented in this chapter have been adapted from the following peer-reviewed journal article:


3.1 Motivation

Hyperpolarized (HP) gas MRI has shown great promise for pulmonary applications. Having virtually no background signal, HP gases provide exquisite contrast of regional lung ventilation in a variety of pulmonary disorders such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and radiation-induced lung injury (RILI) (Virgincar, 2013, Shukla, 2012, Kirby, 2012a, Kirby, 2012b). These techniques are becoming increasingly sophisticated in their ability to quantify regional variation (He, 2016, He, 2014), and have been shown to detect impairment with higher reproducibility than PFTs (Ebner, 2016). To date, the bulk of published HP gas MR studies have employed multi-slice fast gradient recalled echo (GRE) imaging. That is because this sequence has the advantage of being fast, robust, readily implemented, and reconstructed directly on the scanner platform. However, imaging HP gases
within a breath-hold also faces unique challenges that constrain the optimal method of acquiring imaging data.

To this end, 3D radial imaging is emerging as a viable alternative to GRE acquisition. Radial imaging is particularly useful in imaging dissolved-phase $^{129}$Xe, where the shorter echo time are used to overcome the short $T_2^*$ (~2 ms) of $^{129}$Xe in pulmonary tissues and blood (Kaushik, 2013, Mugler JP). We suggest that such a short TE may be advantageous even for gas-phase $^{129}$Xe MRI, where susceptibility effects from the ribs (highlighted with white arrows in Figure 2) can manifest as false ventilation defects in GRE images.

![Figure 2: Susceptibility effects from ribs lower regional intensity of ventilation image, which can be confused with defects.](image)

Moreover, radial imaging typically samples the center of k-space immediately after each RF pulse, thereby enabling the decay of $^{129}$Xe magnetization to be tracked throughout the acquisition (Johnson, 1997). This may permit for the inherent signal decay that is present in all hyperpolarized MRI to be corrected (Wild, 2003). Furthermore, although 3D radial acquisition in principle requires $\pi$ more views of k-space than Cartesian imaging, the sequence is remarkably robust to
undersampling (Block, 2007, Chan, 2012). In practice, fully isotropic 3D image data can be undersampled 10×, which can reduce breath-hold duration or enable retrospective reconstruction to eliminate lung motion or premature exhalation (Holmes, 2008). Additionally, such acquisitions are isotropic and have no artificial intensity weighting imposed by the order of slice acquisition. This may prove increasingly important for revealing the gravitational gradients inherently present in lung function (Kaushik, 2013).

In order to compare the image quality across these two pulse sequences, we also need to consider the effects of xenon polarization, xenon volume, and isotopic fraction on SNR. $^{129}$Xe ventilation images to date have used up to 1 liter of isotopically enriched (~80% $^{129}$Xe) gas (Virgincar, 2013, Shukla, 2012, Kirby, 2012b). However, because the cost of enriched gas is significant (~$250/liter) and larger volumes of xenon take longer to polarize, there are cost and throughput advantages to using smaller doses. To this end, we must quantify the degree to which $^{129}$Xe dose affects image SNR and its ability to consequently quantify regional ventilation distribution, which has not yet been well-studied.

This chapter evaluates the influence of both the acquisition strategy and $^{129}$Xe dose on SNR and the ability to quantify inhaled hyperpolarized $^{129}$Xe ventilation MRI. We hypothesized that image SNR should scale with the inhaled $^{129}$Xe dose (polarization, volume, enrichment) and voxel volume. We further expected that regardless of which pulse sequence was used for acquisition, that at fixed bandwidth, SNR normalized by dose and voxel volume would be a constant. To test this, we acquired $^{129}$Xe ventilation images using both a multi-slice gradient recalled echo (GRE) and 3D-radial sequence. Furthermore, we characterized the SNR differences between high and low $^{129}$Xe doses, differing by 3× in their $^{129}$Xe magnetization. As a secondary objective, we sought to evaluate the ability of each sequence and dose to detect subtle ventilation defects in healthy non-
smoking subjects over the age of 50. This population was expected to exhibit subtle ventilation defects, based on previous studies showing that ventilation defects increase with age (Virgincar, 2013, Parraga, 2008).

3.2 Methods

3.2.1 Subject Inclusion Criteria

Studies were conducted under a protocol approved by the Institutional Review Board, and subject to an FDA Investigational New Drug application. A total of 10 non-smoking (< 5 pack-yrs) older volunteers (6 males, 4 females; mean age = 60.8 ± 7.9 yrs) were enrolled. All subjects provided written informed consent.

3.2.2 129Xe Polarization and Delivery

1-L and 300-ml volumes of isotopically enriched xenon (86% 129Xe, Spectra Gases Inc., Alpha, NJ) were hyperpolarized by rubidium vapor spin-exchange optical pumping as described in Section 2.2.3, then thawed into 1-L ALTEF bags (Jensen Inert Products, Coral Springs, FL). The 300-ml volumes were diluted with 700-ml of commercial N2 to achieve a consistent 1-L volume. 129Xe polarization was determined using a calibrated polarization measurement station (Polarean Inc., Durham, NC). The mean (±SD) polarization for the two volumes of isotopically enriched 129Xe was 8.3±1.3% for the 1-liter studies, and 9.3±2.4% for the 300-ml studies. To establish a SNR-consistent method of describing 129Xe doses, we define the concept of dose equivalent volumes, which represent an equivalent volume of 100% polarized, 100% isotopically enriched 129Xe. This dose equivalent volume can be calculated as follows:
\[ DE = f_{129} \times P_{129} \times V_{Xe} \]  

where \( f_{129} \) is the isotopic fraction of \(^{129}\text{Xe}\), \( P_{129} \) is the \(^{129}\text{Xe}\) nuclear spin polarization and, \( V_{Xe} \) is the xenon volume. Calculated in this manner, subjects received dose-equivalent (DE) volumes of 71±11 ml representing the high dose, and 24±6 ml for low doses. Prior to imaging, subjects were instructed to inhale fully and exhale to functional residual capacity (FRC) twice, and then to inhale the gas from the bag through a 6-mm ID Tygon tube. Subjects held their breath for the duration of the MR acquisition, which ranged from 8−15 seconds. All subjects received 3 doses of HP \(^{129}\text{Xe}\) plus an additional 15 ml DE for transmitter gain calibration.

### 3.2.3 Image Acquisition

All MR scans were performed on a 1.5 T GE Healthcare EXCITE 15M4 MR system. Subjects were fitted with a flexible chest coil (Clinical MR Solutions, Brookfield, WI) that was tuned to the 17.66 MHz \(^{129}\text{Xe}\) frequency and proton-blocked to permit anatomical scans to be acquired with the \(^1\text{H}\) body coil. After the initial localizers and proton thoracic cavity scans (described below), subjects underwent \(^{129}\text{Xe}\) ventilation MRI in the following order: GRE with DE = 71 ml, 3D radial with DE = 71 ml, and 3D radial with DE = 24 ml. Scans were performed in the supine position and subjects were coached to inhale the gas doses from functional residual capacity (FRC).

GRE images were acquired with parameters: field of view (FOV) = 40, matrix = 128×(90-128), slice thickness = 12.5 mm, bandwidth (BW) = 8.3 kHz, flip angle = 7-10°, repetition time (TR)/echo time (TE) = 8.1/1.9 ms. The \(^{129}\text{Xe}\) GRE ventilation images were analyzed in the context of a thoracic cavity image acquired using a breath-hold \(^1\text{H}\) steady state free precession (SSFP)
imaging sequence using the scanner’s body coil. With subjects in the same position as for $^{129}$Xe MRI, $^1$H images were acquired with FOV = 40 cm, matrix = 192×192, slice thickness = 12.5 mm, flip angle = 45°, TR/TE = 2.8/1.2 ms, and BW = 125 kHz.

For 3D-radial imaging, parameters were (71 ml/24 ml DE): FOV = 36/48 cm, matrix = 64$^3$, radial views = 4601, flip angle = 1.2°, TR/TE = 3.3/0.376 ms, BW = 15.63 kHz. To facilitate analysis of the 3D radial $^{129}$Xe images, a thoracic cavity image was acquired using a 4-minute, free-breathing, un-gated 3D radial $^1$H scan, again using the body coil. The thoracic cavity images were acquired with parameters: FOV = 36 cm, matrix=128$^3$, TR/TE = 3/0.24 ms, radial views = 80,001, BW = 62.5 kHz, flip angle = 15°.

Ventilation images acquired using the GRE sequence were reconstructed directly on the scanner using the default Fermi filter and imported as 256x256 DICOM slices for analysis. The 3D radial acquisitions were reconstructed from the raw data using an in-house reconstruction algorithm implemented in MATLAB (The MathWorks Inc., Natick, MA) (Robertson, 2015). For these images, no Fermi filter was applied.

3.2.4 Image Analysis

3.2.4.1 SNR Assessment

The SNR of each image slice was calculated as: $(\bar{S}_{\text{lung}} - \bar{S}_{BG}) / \sigma_{BG}$ where $\bar{S}_{\text{lung}}$ was the mean signal in the ventilated lung parenchyma, $\bar{S}_{BG}$ the mean background signal and $\sigma_{BG}$ its standard deviation. The mean lung signal for each image slice was calculated from pixels constrained by applying a mask that included only the ventilated lung within the thoracic cavity (see below). Subsequently a 5 x 5 cm$^2$ voxel region of interest (ROI) containing only background
noise was manually selected for each slice and its mean signal and standard deviation were calculated. Raw SNR was plotted as a function of slice position for each acquisition and average values for the entire image were calculated. Finally, for each image its raw average SNR was divided by voxel volume $V_{\text{vox}}$ and $^{129}$Xe dose equivalent to calculate normalized SNR, according to

$$SNR_n = \frac{SNR}{DE \times V_{\text{vox}}}$$

(1.7)

Since both DE and $V_{\text{vox}}$ are expressed in ml, SNR$_n$ has units of ml$^{-2}$.

### 3.2.4.2 Ventilated Volume and Ventilation Defect Percentage Calculation

All images were analyzed for ventilation defect percentage (VDP) using a corrected linear-binning approach introduced by He et al. that is depicted in Figure 3 (He, 2014). To summarize this approach, $^{129}$Xe images were first corrected for B$_1$ inhomogeneity using a bias field correction (Tustison, 2010). Next, the $^1$H thoracic cavity images were registered to the GRE $^{129}$Xe images using a multi-resolution affine transform (Figure 3b). The free-breathing radial $^1$H images were registered to the radial $^{129}$Xe ventilation images first using a multi-resolution affine transform, followed by a non-rigid landmark-based registration step. Subsequently, the registered $^1$H thoracic cavity images were segmented to create thoracic cavity masks (Figure 3c). These were used to confine the $^{129}$Xe image analysis to regions where ventilation is expected. The 99th percentile of their cumulative intensity distribution (Figure 3d) was then used to rescale the $^{129}$Xe images (Figure 3e) such that the intensities ranged from 0-1 (He, 2014). This rescaling is similar to the normalization of attenuation values to that of water in CT, as our method effectively normalizes
the values to the “free-gas” signal intensity of $^{129}$Xe in the trachea. Following this rescaling, each voxel was classified into one of 4 intensity clusters (Figure 3f) to generate a linear binning map (<0.2 defect, 0.2-0.4 low intensity, 0.4-0.8 medium intensity, and >0.8 high intensity). The volume of the lowest-intensity cluster (<0.2) relative to that of the thoracic cavity was used to quantify ventilation impairment, otherwise known as ventilation defect percentage (VDP). The remaining clusters within the thoracic cavity were used to calculate SNR.

Figure 3: Corrected linear-binning map workflow from He et al. The bias-field corrected ventilation images (a) were used to register the $^1$H thoracic cavity images (b). These were then segmented to define constrain the analysis the thoracic cavity (c). Pixels from the bias-field corrected ventilation image lying within the thoracic cavity volume (d) were rescaled by their top percentile (e), then classified into 4 intensity clusters to create the linear-binning map (f).
3.2.5 Statistical Methods

All statistical analysis was performed using JMP 11 (SAS Institute Inc., Cary, NC). The dependence of SNR on acquisition sequence and $^{129}$Xe dose equivalent was determined using linear regression analysis and the Pearson’s correlation coefficient ($r$). The same approach was used to test the dependence of VDP on acquisition sequence and dose. Any systematic deviation between sequences or volumes was further evaluated using Bland-Altman analysis.

3.3 Results

Ventilation images were successfully acquired using both pulse sequences in all subjects and doses. A sample dataset from a 65-year-old volunteer with FEV$_1$% $= 124\%$ is shown in Figure 4. For this subject, numerous small ventilation defects are clearly visible in all scans as shown by the arrows. The GRE image exhibited an SNR of 22.5, high-DE radial had SNR $= 8.1$, and low-DE radial had SNR $= 7.0$. After dividing by voxel volume and DE, the GRE image exhibited a normalized SNR of $2.3 \text{ ml}^2$, high-DE radial had SNR$_n = 0.5 \text{ ml}^2$, and low-DE radial had SNR$_n = 0.7 \text{ ml}^2$. 
3.3.1 3.1. SNR Comparisons

The mean, uncorrected SNR for all subjects obtained at high and low dose for each sequence is plotted in Figure 5a. For high-DE GRE images, mean SNR was 14.7±5.6, versus 11.3±4.3 for low-DE GRE. For high-DE radial images, mean SNR was 6.9±1.9 versus 6.2±3.2 for...
the low-DE radial scans. Similarly, Figure 5b shows SNR\textsubscript{n} values that have been normalized by voxel volume and dose equivalent. As was the case for the individual subject shown previously, the high-DE GRE images exhibited the highest SNR\textsubscript{n} of 1.9±0.8 ml\textsuperscript{-2} compared to 0.8±0.2 ml\textsuperscript{-2} for low-DE GRE. Similarly, the high-DE radial images had SNR\textsubscript{n} = 0.5±0.1 ml\textsuperscript{-2} versus 0.5±0.2 ml\textsuperscript{-2} for low-DE radial MRI.

**Figure 5**: SNR for ventilation images acquired using GRE and radial sequences at high and low dose. b) SNR normalized by voxel volume and dose equivalent polarization.

### 3.3.2 Ventilation Defect Percentage Validation

Additionally, all ventilation images were segmented using linear binning to map each voxel into one of four distinct intensity clusters. Such maps are shown in Figure 6, which were generated using the $^{129}$Xe images of the same subject shown in Figure 4. The maps highlight several ventilation defects that are present in this older volunteer. These appear to be similar in extent and location across all binning maps.
Figure 6: Representative $^{129}$Xe ventilation images and associated linear-binning maps for GRE and 3D radial sequences. For the 3D radial sequence, images were acquired at both high- and low-dose equivalent volumes. Note, the 3D-radial acquisition is isotropic and can be reformatted in any view plane. Features that appear similar across different images and binning maps are indicated by arrows.

The VDP derived from all sequences and doses across groups are shown in Figure 7. The mean VDP was greatest for the high-DE GRE images (6.4±2.8%), and lowest for the low-DE radial acquisitions (4.6±3.2%). However, these differences in VDP were not statistically significant. There was a trend towards higher VDP being detected in high-DE compared to the low-DE images.
Figure 7: Comparison of ventilation defect percentage (VDP) derived from both sequences and at high and low $^{129}$Xe dose equivalents for the 3D radial acquisition. No statistically significant differences were observed across any acquisitions. The GRE images, however, tended to exhibit higher VDP than 3D-radial, and high-dose equivalent images tended to have higher VDP than low-dose equivalent. Error bars represent standard error about the mean.

Figure 8 shows the correlations and Bland-Altman plots for VDP derived from the different acquisition sequences and $^{129}$Xe DEs. For the 3D radial acquisition VDP was well-correlated across high and low DE scans ($r = 0.97$). The VDP derived via GRE vs. radial acquisition was somewhat less strongly correlated ($r = 0.80$). Testing this further with Bland-Altman analysis found that the 3D radial images did not exhibit any significant bias between high- and low-DE scans (0.60 higher defect percentage points). However, VDP derived from the GRE acquisition was 1.3 points higher than for the 3D-radial acquisition.
3.4 Implications of $^{129}$Xe Dose and Acquisition Strategy

This chapter sought to compare the effects of acquisition strategy on $^{129}$Xe ventilation image quality. To do so, we introduced the notion of a dose equivalent volume that incorporates $^{129}$Xe polarization, volume, and enrichment into a single, relatively intuitive metric. This dose equivalent volume can simply be considered as the volume of 100% polarized, isotopically pure $^{129}$Xe that would provide the same signal intensity. By compensating for differences in the equivalent dose and the acquired voxel volume, we were able to compare the expected image SNR between a multi-slice GRE and radial acquisition.
3.4.1 SNR Assessment

In our study, we found that the radially acquired images gave consistent normalized SNR (SNR$_n = 0.5\pm0.1$ ml$^{-2}$ and $0.5\pm0.2$ ml$^{-2}$ for high and low-dose acquisitions, respectively). Interestingly, however, this normalized SNR of radial scans was much lower than that of the conventional GRE (SNR$_n = 1.9\pm0.8$ ml$^{-2}$). This is partially attributable to having acquired these scans at twice the bandwidth of the GRE scans to allow more frames to be acquired in the breath-hold. However, even scaling these SNR values by $\sqrt{2}$ to remove bandwidth differences, they remain well below the GRE value. This partially reflects the challenge of defining SNR and resolution for radially acquired images, as will be explained in chapter 4. Briefly, when radial images are reconstructed, SNR and resolution are strongly impacted by the convolution kernel sharpness parameter (Robertson, 2015). For our reconstructions, all kernel parameters were manually tuned by a trained observer to optimize perceived image quality. However, if a sharper kernel had been used, image SNR would have increased, but structural detail would be lost. Conversely, a broader kernel could have enhanced the spatial resolution, but only at the expense of the image SNR. Thus by using a trained observer to tune reconstruction parameters, we are able to achieve relatively consistent SNR, despite the differences in $^{129}$Xe doses. We further note that the radial images employed no additional Fermi filter, whereas a Fermi filter with Fermi radius equal to half the matrix size and Fermi width equal to 10 voxels was applied to the standard GRE image reconstructed on our scanner. Thus, while the radially acquired images have a lower SNR, it is interesting to note that SNR value is near that of multi-slice GRE.

To provide further context for our notion of normalized SNR, we compared our findings to those that could be calculated from previous literature reports (see Table 1). For example, Xu et al. (Xu, 2012) reported mean SNR of 36, and 44 for $^{129}$Xe ventilation MRI at 1.5 T and 3.0 T. They
employed a voxel volume of 0.24 ml and an estimated DE ~0.36 ml. This suggests that they achieved an SNR of 4.2 ml\(^2\) at 1.5 T, and 5.0 ml\(^2\) at 3.0 T. Even after accounting for their use of a lower 4 kHz bandwidth, their normalized SNR values are 50-86% higher than those we report here. One possible difference may be that Xu et al. reconstructed their images off-line, and therefore may have employed a stronger Fermi filter, or suffered less interpolation noise. Similarly, Svenningsen et al. (Svenningsen, 2013) reported a mean SNR of 22 for \(^{129}\)Xe images scanned with a three-dimensional fast gradient echo sequence with centric phase-encoding ordering at 3.0 T. Their images were acquired with a voxel volume of 0.15 ml, and assuming a mean polarization of 35%, they employed an estimated DE = 150 ml. This suggests they achieved a voxel- and dose-normalized SNR\(_n\) = 1.0 ml\(^2\), or SNR\(_n\) = 1.3 ml\(^2\) after accounting for their higher bandwidth, which is reasonably close to our observed value. Thus, although these comparisons of voxel size and DE-normalized SNR were performed using only literature-reported values, it is reassuring that all values (scaled to 8kHz bandwidth) are within a factor of 2 of what we report, ranging from approximately 1.3 – 3.6 ml\(^2\). This suggests that normalized SNR represents a fairly fundamental value and in conjunction with the dose equivalent concept can be used to predict achievable SNR for a given target image resolution. Moreover, such a normalized SNR value may represent a useful benchmark for evaluating more efficient hardware or pulse sequences, such as interleaved spiral (Salerno, 2001) and steady-state free-precession methods (Dregely, 2013, Mugler, 2009) that may extract more SNR from a given dose.
Table 1: Parameters and SNR summary for hyperpolarized $^{129}$Xe MRI acquired using multi-slice GRE sequence at different sites.

<table>
<thead>
<tr>
<th>Literature Citation</th>
<th>(He, 2015)</th>
<th>(Xu, 2012)</th>
<th>(Xu, 2012)</th>
<th>(Svenningsen, 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner</td>
<td>GE</td>
<td>GE</td>
<td>GE</td>
<td>GE</td>
</tr>
<tr>
<td>Field strength (T)</td>
<td>1.5</td>
<td>1.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Coil</td>
<td>Chest coil</td>
<td>Twin Helmholtz quadrature transmit–receive coil</td>
<td>Quadrature asymmetric birdcage coil</td>
<td></td>
</tr>
<tr>
<td>Voxel volume (ml)</td>
<td>0.12</td>
<td>0.24</td>
<td>0.24</td>
<td>0.15</td>
</tr>
<tr>
<td>BW (kHz)</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>15.63</td>
</tr>
<tr>
<td>Phase encoding</td>
<td>Centric</td>
<td>Centric</td>
<td>Centric</td>
<td>Centric</td>
</tr>
<tr>
<td>Flip angle</td>
<td>7–10</td>
<td>9</td>
<td>9</td>
<td>Variable</td>
</tr>
<tr>
<td>Xenon volume (ml)</td>
<td>1000</td>
<td>300</td>
<td>300</td>
<td>500</td>
</tr>
<tr>
<td>Polarization (%)</td>
<td>8</td>
<td>14</td>
<td>14</td>
<td>10-60</td>
</tr>
<tr>
<td>Enrichment (%)</td>
<td>86</td>
<td>86</td>
<td>86</td>
<td>86</td>
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<tr>
<td>DE (ml)</td>
<td>71</td>
<td>36</td>
<td>36</td>
<td>150</td>
</tr>
<tr>
<td>SNR</td>
<td>14</td>
<td>36</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Offline Recon (Y/N)</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>SNR, (ml⁻²)</td>
<td>1.6</td>
<td>4.2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>SNR, (8 kHz) (ml⁻²)</td>
<td>1.6</td>
<td>2.9</td>
<td>3.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

To gauge the practicality of delivering the dose ranges we report here in actual imaging studies, it is further useful to consider the DE production rates for $^{129}$Xe hyperpolarizers that have been reported in the literature. These are shown in Table 2 and range from approximately 40 ml/h to 240 ml/h. It is clear that all systems are capable of producing one or more low dose volumes per hour, and many are capable of producing one or more high-dose volumes per hour. Furthermore, this suggests that as systems continue to exhibit an ever-increasing trend towards higher polarization levels, this will enable smaller volumes of xenon or even potentially naturally abundant xenon to be used (Nikolaou, 2013).
Table 2: Polarization, xenon flow rate and maximum DE production rate for polarizer designs as reported in the literature. Note that DE rate assumes 100% isotopically enriched $^{129}$Xe.

<table>
<thead>
<tr>
<th>Polarizer</th>
<th>Laser Power (W)</th>
<th>Polarization</th>
<th>Xe Flow Rate (ml/h)</th>
<th>DE Rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Driehuys, 1996)</td>
<td>140</td>
<td>5%</td>
<td>1000</td>
<td>50</td>
</tr>
<tr>
<td>(Rosen, 1999)</td>
<td>30</td>
<td>7.50%</td>
<td>1884</td>
<td>141</td>
</tr>
<tr>
<td>(Zook, 2002)</td>
<td>&gt;150</td>
<td>67%</td>
<td>150</td>
<td>111</td>
</tr>
<tr>
<td>(Zook, 2002)</td>
<td>210</td>
<td>12%</td>
<td>1000</td>
<td>40</td>
</tr>
<tr>
<td>(Ruset, 2006)</td>
<td>90</td>
<td>64%</td>
<td>300</td>
<td>192</td>
</tr>
<tr>
<td>(Hersman, 2008)</td>
<td>90</td>
<td>64%</td>
<td>300</td>
<td>192</td>
</tr>
<tr>
<td>(Schrank, 2009)</td>
<td>60</td>
<td>84%</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>(Schrank, 2009)</td>
<td>30</td>
<td>20%</td>
<td>600</td>
<td>120</td>
</tr>
<tr>
<td>(Stewart, 2015a)</td>
<td>50</td>
<td>25%</td>
<td>720</td>
<td>180</td>
</tr>
<tr>
<td>(Korchak, 2013)</td>
<td>75</td>
<td>40%</td>
<td>97</td>
<td>39</td>
</tr>
<tr>
<td>(Korchak, 2013)</td>
<td>75</td>
<td>25%</td>
<td>390</td>
<td>98</td>
</tr>
<tr>
<td>(Nikolaou, 2014)</td>
<td>170</td>
<td>83%</td>
<td>130</td>
<td>108</td>
</tr>
<tr>
<td>(Nikolaou, 2014)</td>
<td>170</td>
<td>64%</td>
<td>230</td>
<td>147</td>
</tr>
<tr>
<td>GE 9800</td>
<td>100</td>
<td>8%</td>
<td>1000</td>
<td>80</td>
</tr>
<tr>
<td>Polarean 9800</td>
<td>60</td>
<td>12%</td>
<td>1000</td>
<td>120</td>
</tr>
<tr>
<td>Polarean 9810</td>
<td>60</td>
<td>24%</td>
<td>1000</td>
<td>240</td>
</tr>
</tbody>
</table>

3.4.2 Effects on Ventilation Defect Percentage Calculations

In this study of older, healthy non-smoking volunteers, the ventilation distribution was similarly visualized using both GRE and isotropic 3D-radial acquisitions, and also at both high and low $^{129}$Xe dose equivalents using the 3D-radial acquisition. As illustrated in Figure 4, most of the subtle defects could be visualized on all 3 scans. Furthermore, all images in this study were successfully quantified using a linear-binning-derived VDP metric and no statistically significant differences were found between scans or DEs. Moreover, the VDP derived from low-DE vs. high-DE $^{129}$Xe
MRI was extremely well correlated (r=0.97). This suggests that it may be possible to adequately resolve ventilation defects in these older subjects using the lower $^{129}$Xe dose and commensurately larger voxel volumes.

3.4.3 Potential Advantages of Radial vs. GRE MRI

Although thus far, the SNR in radial imaging lags that achieved by the conventional GRE, there continue to be reasons to pursue this approach. The first is seen in the way the 3D-radial acquisition exhibits SNR that increases in the anterior to posterior directions. Such variation is attributable to physiological factors that drive greater ventilation in the gravitationally dependent lung (Kaushik, 2013, Mugler, 2010, Cleveland, 2010). In contrast, these gravitational effects appear to be reduced or even reversed in the GRE images (Figure 9). This is likely because the GRE images were acquired from the anterior-to-posterior slice order, which attenuates the true signal enhancement in the better-ventilated posterior slices because they experience greater T1 and RF decay before being encoded (Xu, 2012, Mugler, 2010). By contrast the 3D-radial acquisition is a truly 3D scan that preserves the physiologically dictated ventilation distribution. Thus, a truly 3D isotropic acquisition more faithfully represents slowly varying functional gradients versus multi-slice approaches that confer slice order-dependent artifacts due to RF and $T_1$ decay.
Figure 9: Comparison of the SNR variation from the anterior-to-posterior slice positions for both GRE and 3D-radial acquisitions.

Perhaps the most significant advantage of the 3D-radial over the Cartesian GRE acquisition is illustrated in Figure 10. In a high-DE 3D-radial acquisition of one subject, the reconstructed image appeared to show two diaphragm borders near the right basal lung. We hypothesized that the artifact was caused by partial exhalation during the scan. Because the radial image was acquired with randomized views, it was possible to retrospectively reconstruct images in arbitrary subsets of time and k-space increments. By reconstructing multiple subsets of data, it was revealed that the lung position changed at approximately 1400 frames (4.6 seconds) into the scan (Figure 10c). Thus, by discarding the first 1400 frames and reconstructing only the frames obtained when the diaphragm was static, the artifact was removed, and the resulting image quality was suitable for quantitative analysis. Had a GRE acquisition been used instead, this retrospective correction would not have been feasible and a repeat scan would have been needed.
Figure 10: Possible benefits of 3D-radial acquisition illustrated in subject with changing right-lung volume. (a) Multi-slice GRE reference image showing homogeneous distribution. (b) 3D-radial $^{133}$Xe ventilation image shows a false lung border caused by probable motion in the right basal lung during acquisition. (c) 3D-radial image reconstructed 700 frames (2.3 seconds) at a time showing that the right lung position changed around frame 1400 (4.6 seconds). (d) This artifact of diaphragm movement was corrected by reconstructing only frames 1401 to 4601 (4.6-15.2 seconds).

3.5 Study Limitations

In this study, we investigated the relationship of SNR and dose equivalent by calculating the normalized SNR. It would have been interesting to acquire images across a broad range of doses and voxel volumes then correlate SNR to the dose equivalent and voxel volume via linear regression. Any nonlinearities in the regression might indicate that there are missing variables in the SNR/DE relationship that need to be addressed.
To that end, our notion of normalized SNR presented here assumes that dose equivalent and voxel volume are the only determinants of SNR. Clearly, one might also expect some dependence on subject lung volume and inhalation maneuver. Subjects with a larger lung volume might be expected to dilute the available dose to a greater extent than those with smaller lung volumes. In this work, however, we did not uncover any systematic relationship between the subject’s lung capacity and SNR.

While our data seem to suggest that lower $^{129}$Xe dose equivalents may comparably detect subtle age-related defects, this claim is also subject to limitations. The most significant is the assumption that, for a given subject, the ventilation distribution was identical over all inhaled doses. This assumption was not entirely valid, as shown in the example of Figure 4 where one defect is visible on the initial high-DE GRE scan, but not on subsequent scans. This could have been the result of a small region of atelectasis that opened up after subsequent inhalations. We note that, this example was a rather subtle change, and our short-term reproducibility studies have indicated that this ventilation defects analysis is in fact less variable than PFTs within a given MRI session (Ebner, 2016). Second, while ventilation defect percentage (VDP) has become the most widely used metric of regional ventilation, it does not capture all elements of pulmonary ventilation. Hence, it is possible that if these scans were compared with different metrics, the results could differ slightly. Third, the thoracic cavity and ventilation images were obtained during different breath-holds, or in the case of radial images, during free breathing. This introduces the necessary step of image registration, which can introduce error into the analysis. In this work, we found it especially challenging to register the free-breathing UTE images to the breath-held $^{129}$Xe MR images. We have since transitioned to using a lower-resolution, breath-held radial image to delineate the thoracic cavity. We note that even breath-held images pose challenges in registration, as diaphragm
position can be significantly different during a self-directed breath-hold of room air vs. inhalation from a 1-liter bag. We have since found it beneficial to collect breath-hold anatomical images after subjects inhale air from a 1-liter bag rather than a self-directed breath-hold. Alternatively, there may be benefit to simultaneously acquiring the $^1$H thoracic cavity image and the HP gas ventilation image within a single breath-hold, as described by Wild et al. (Wild, 2011). Such an approach should largely obviate the need for registration, or at least greatly reduce the degree of image warping required.

### 3.6 Summary

In this chapter we have characterized the effects of acquisition strategy on image SNR and ventilation defect calculations. To do so, we introduced the concept of a $^{129}$Xe dose equivalent that incorporates xenon volume, polarization, and isotopic enrichment into a single metric. This technique found that 3D-radial scans exhibited slightly lower image quality compared to GRE scans. As 3D radial imaging becomes more widely adopted within the hyperpolarized community, we expect the technology to mature and the SNR performance to improve. Regardless, the 3D radial sequence affords many advantages over the conventional GRE. Namely, it provides isotropic resolution that allows any slice plane to be visualized, the ability to monitor magnetization dynamics, preserves the visualization of physiological ventilation gradients, and enables us to reconstruct different temporal windows within an acquisition to eliminate problematic subsets of data. Combined, the advantages of 3D radial imaging and its near-comparable SNR make 3D radial imaging promising candidate for ventilation analysis going forward.

Additionally, this work allowed us to estimate that for our scanner configuration and
similar ones from the literature, the SNR one can expect from a conventional spoiled gradient echo ventilation scan is on order ~2 ml$^2$. Thus, for example, to obtain an image SNR of 15 for a voxel volume of 0.25 ml, an equivalent $^{129}$Xe dose of approximately 30 ml is required. Such a dose can be produced, for example using 250 ml of 86% enriched $^{129}$Xe, polarized to 14%. Alternatively, one could employ 500 ml of xenon in natural abundance (26% $^{129}$Xe) polarized to 23%. Since conducting this study, we have transitioned to using 300 mL $^{129}$Xe doses that are polarized to ~25%. This 63 mL DE gives sufficient SNR for ventilation defect analysis while reducing polarization time by 70% (40-minute decrease per dose). Of course, as pulse sequences and transmit/receive coil technology improve, dose efficiency will increase, and smaller volumes of xenon can be used. It would not be unreasonable to expect that normalized SNR$_n$ could increase from 2 ml$^2$ today to values of 5 ml$^2$ with further development.

In short, the future looks promising for developing an efficient and integrated $^1$H and $^{129}$Xe radial imaging exam that can readily yield quantitative maps of regional ventilation using modest xenon volumes. When complemented with the images of $^{129}$Xe gas exchange that will be discussed in chapter 6, this moves us towards a fully isotropic and comprehensive exam of regional pulmonary function (Qing, 2014a, Kaushik, 2016a).
4 Optimizing Reconstruction for Radial Hyperpolarized $^{129}$Xe Imaging

Chapter 4 showed that 3D radial acquisition, albeit at slightly lower SNR, can detect ventilation defects comparably to the conventional GRE. Furthermore, it cited several advantages to using a 3D radial acquisition for the purpose of ventilation imaging in vivo. As we move into imaging $^{129}$Xe dissolved into the blood, these properties that are afforded by 3D radial acquisition become essential. Consequently, this chapter aims to characterize the tradeoffs involved in reconstructing 3D radial data so that we can optimize reconstruction parameters specifically for use in HP gas MRI. The methods and results presented in this chapter have been adapted from the following peer-reviewed journal article:


4.1 Motivation

While HP $^{129}$Xe offers an array of potential contrast mechanisms, the simple task of imaging HP $^{129}$Xe in the lung requires overcoming several well-known challenges. First, HP magnetization is transient and decays during image acquisition, partially from collisions with paramagnetic oxygen, but primarily through depletion by radio frequency (RF) pulses applied during image acquisition. Such decay can result in
significant view-to-view variation during the scan, causing blurring and image artifacts (Marshall, 2012). Second, imaging of the lung is particularly impacted by variations in magnetic susceptibility resulting from the many air/tissue interfaces. While this problem is somewhat mitigated by motional narrowing of the gases within the airspace (Chen, 1999), the problem is significant when imaging $^{129}$Xe dissolved in the blood and tissue compartments, ($T_2^* < 2$ms at 2T). Third, imaging gases at high resolution is challenging because their diffusion causes significant signal attenuation and resolution loss in the presence of read-out and slice-select gradients (Driehuys, 2007). Finally, the recent advancement of $^{129}$Xe, with its 2.75-fold lower gyromagnetic ratio and generally lower polarization than $^3$He, requires efficient use of the limited magnetization.

As pointed out by Johnson et al. in its early development (Johnson, 1997), the challenges of HP gas MRI align well with the strengths of radial acquisition. By sampling the DC spatial frequency with every view, radial sequences measure the net magnetization over the duration of the scan. Such information can be used to adjust variable flip angle schedules (Miller, 2010) or account for signal decay (Marshall, 2012). Furthermore, the periodic resampling of low spatial frequencies and near-uniform distribution of radial rays throughout k-space and time cause temporal anatomic changes to be incoherently patterned in k-space, thereby providing robustness to motion artifacts (Chan, 2009). Moreover, the inherently short echo time (TE<500 µs) and readout reduce $T_2^*$ decay, motion artifacts, and susceptibility artifacts (Holmes, 2008).
Additionally, 3D encoding enables volumetric imaging in the absence of slice selection or rephasing gradients, thus minimizing diffusion-induced attenuation (Driehuys, 2007). Lastly, despite theoretically requiring more samples to meet Nyquist limits, radial sequences can be remarkably insensitive to undersampling artifacts, allowing for SNR-efficient isotropic acquisition (Barger, 2002).

For the aforementioned reasons, our laboratory has employed radial acquisition for preclinical HP gas studies for over 15 years (Moller, 1999). The essential pulse sequence was introduced by Shattuck et al. in 1997 (Shattuck, 1997) and has been steadily expanded from its original use in UTE proton MRI to imaging $^3$He in the guinea pig (Black, 1996), rat, and mouse (Driehuys, 2009). Radial acquisition has been instrumental for enabling concurrent imaging of $^{129}$Xe in both the gas- and dissolved-phase in rats and mice (Cleveland, 2014, Freeman, 2013).

However, despite the apparent advantages of 3D radial acquisition, reconstructing these non-Cartesian acquisitions is non-trivial. It requires interpolating radial k-space data onto an evenly spaced Cartesian grid such that the computationally efficient Fast Fourier Transform (FFT) can be applied to reconstruct the image volume (Osullivan, 1985). Such k-space interpolation, while a necessary step, can lead to reconstruction errors since signal intensity does not typically vary slowly across k-space. Therefore, interpolation must be carried out judiciously. Such subtleties of non-Cartesian reconstruction have been extensively optimized for proton MRI applications.
(Johnson, 2013, Osullivan, 1985, Fessler, 2003, Jackson, 1991, Johnson, 2009, Rasche, 1999); however, minimal attention has yet been paid to develop radial image reconstruction strategies that are tailored for HP gas MRI.

In HP gas MRI, non-selective RF excitation and highly undersampled acquisition are common, but these design choices introduce challenges to non-Cartesian reconstruction. Because non-spatially-selective pulses excite all $^{129}$Xe within the coil, any signal that originates from outside the prescribed field of view (FOV) will alias back into the image. Similarly, accelerating data acquisition by undersampling k-space can result in improper weighting of various spatial frequencies during reconstruction, ultimately imposing undesirable filtration.

This chapter evaluates and optimizes non-Cartesian reconstruction as it specifically applies to HP gas MRI. Although the methods we discuss are applicable to both small-animal and human radial HP gas MRI, we first describe these methods using $^{129}$Xe MRI in the mouse lung. That is because these preclinical acquisitions can exploit mechanical ventilation to replenish HP magnetization, allowing for higher resolution and SNR, thereby permitting these reconstruction strategies to be more thoroughly analyzed. At the end of the chapter we apply these optimized reconstruction methods to image human lungs in order to illustrate how readily these findings translate into clinical imaging tasks.
4.2 Reconstruction Theory

Reconstruction of radially encoded MRI data can, in principle, be achieved by directly computing the Discrete Fourier Transform (DFT). Unfortunately, even with modern computing hardware, calculating the DFT for most 3D images is computationally prohibitive. As a result, the DFT is practically limited to serving as a gold standard against which to compare the more computationally efficient gridding-based reconstruction. This gridding approach relies on the Fast Fourier Transform (FFT), and therefore requires evenly spaced k-space data. Thus, radially acquired data must first be cast onto a Cartesian grid (Beatty, 2005).

4.2.1 Continuous Signal Representation of Reconstruction

The gridding process can be mathematically considered as a series of linear processes that transform radially acquired k-space data into evenly spaced Cartesian samples. As a convention, capital letters represent quantities in k-space, and lower-case letters indicate quantities in the spatial domain.

\[ M_{\text{cartesian}}(k_x, k_y, k_z) = \left( \left( M_{\text{actual}} \cdot S_{\text{radial}} \cdot D_{\text{comp}} \right) \otimes \mathbb{C} \right) \cdot S_{\text{cartesian}} \otimes^{-1} \mathbb{C} \]  

(1.8)

Here \( M_{\text{actual}} \) represents the object’s true continuous magnetization distribution in k-space, which is sampled by a discrete radial sampling function, \( S_{\text{radial}} \). Because \( S_{\text{radial}} \) contains more samples at low than high spatial frequencies, the data must be weighted by a density compensation function (DCF), \( D_{\text{comp}} \). Subsequently, the signal intensity
from each radial sample is cast onto nearby, regularly-spaced Cartesian grid points. This is accomplished by convolving each discrete sample with a continuous, but truncated kernel, \( C \) to generate a smoothed continuous signal that can be resampled at the spatial frequencies defined by a Cartesian matrix \( S_{\text{cartesian}} \). Finally, the effects of the kernel on this resampled Cartesian data must be deconvolved in order to reverse the k-space blurring it caused.

Once the k-space data has been cast onto a Cartesian grid, the inverse FFT efficiently reconstructs the discrete spatial domain image, \( m_{\text{cartesian}} \).

\[
m_{\text{cartesian}}(x, y, z) = \mathcal{F}\{M_{\text{cartesian}}(k_x, k_y, k_z)\} = \frac{\left( (m_{\text{actual}} \otimes s_{\text{radial}} \otimes d_{\text{comp}}) \cdot c \right) \otimes s_{\text{cartesian}}}{c}
\]  

(1.9)

This spatial domain representation of the reconstructed image is useful to highlight the potential non-idealities of gridding reconstruction. First, note that the ideal, continuous object \( m_{\text{actual}} \) is convolved with the spatial domain representations of both the discrete radial sampling function \( s_{\text{radial}} \) and DCF values \( d_{\text{comp}} \). Because \( s_{\text{radial}} \) has a truncated representation in k-space, convolving it with \( m_{\text{actual}} \) creates ringing in the reconstructed image that is particularly pronounced near high contrast edges. Similarly, the DCF applies differential weighting to the various spatial frequencies of the ideal object, and thereby indirectly filters the image domain object. This filtered image is then multiplied by the spatial domain representation of the convolution kernel, whose
amplitude falls off towards the edges of the FOV to cause image domain shading (apodization). Next, the apodized image is convolved with the spatial representation of the Cartesian gridding pattern $s_{\text{cartesian}}$. Because its k-space representation consists of regularly spaced samples, $s_{\text{cartesian}}$ is also periodic. This periodicity causes the apodized image to be repeated infinitely with a spacing that is determined by the Cartesian k-space sampling interval. This overlap of spatial replicates (aliasing) can be addressed by simply resampling the data onto a more finely sampled Cartesian grid. This overgridding increases the distance between replicates and reconstructs a larger FOV. As long as this extended FOV encompasses all excited signal, the reconstructed FOV will contain no aliased wrap-around artifacts. The extended FOV can then be cropped to the prescribed image FOV without losing resolution. Finally, the blurred and aliased image is divided by the spatial representation of the kernel (deapodization) to reverse the kernel-induced image intensity roll-off.

4.2.2 Discrete Matrix Representation of Reconstruction

Although the continuous signal representation provides an intuitive framework for understanding potential artifacts of gridding, it can also be formulated into an equivalent, but more compact matrix notation that better represents its computer implementation and emphasizes the bidirectional nature of the gridding operation. As shown in Eq. (1.10), the matrix framework transforms a vector of $n$ discrete radial k-
space samples, \( M_{radial} \), into a vector representing a \( V \times V \times V \) matrix of discrete Cartesian k-space samples, \( M_{cartesian} \), by using a system matrix operator, \( [A] \). This matrix notation assumes that radial samples have been precompensated to account for non-uniform sampling density; that is \( M_{radial} = [M_{actual}] [S_{radial}] [D_{comp}] \). Thus, gridding is efficiently represented as

\[
[M_{radial}]_{row} = [A]_{row} [M_{cartesian}]_{row,1}
\]  

(1.10)

The system matrix, \( [A] \), relates the two sampling schemes through a set of interpolation coefficients. Each row of \( [A] \) reflects the degree to which a single radial sample contributes to every Cartesian sample. Conversely, every column reflects the amount that each Cartesian sample contributes to every radial sample. The individual coefficients of \( [A] \) are calculated from the convolution kernel, \( C \), which weights a local region according to its proximity in k-space. Proximity, in turn, is calculated from the k-space distance between radial and Cartesian samples derived from \( [S_{radial}] \) and \( [S_{cartesian}] \).

Note that the matrix notation of Eq. (1.10) actually calculates non-Cartesian samples from Cartesian ones, which describes the reverse gridding process. This difference results from an inconsistency between the gridding and Non-Uniform Fast Fourier Transform literature and can be conceptually addressed by considering the inverse of \( [A] \). However, a unique inverse does not typically exist because \( [A] \) is
commonly underdetermined and \( M_{radial} \) can be noisy, making this an ill-posed problem. Instead, a reverse “ungridding” operation is often used in place of inversion. Since the interpolation coefficients of \( A \) are a function of proximity but not direction, we can use the complex conjugate transpose of the system matrix, \( A^\dagger \) to ungrid Cartesian data into radial samples (Gaskill, 1978).

This matrix notation can be related to the continuous signal representation by substituting \( A^\dagger \) for the convolution kernel and resampling function.

\[
M_{cartesian} = [A]^\dagger [M_{radial}]
= (M_{radial} \otimes C) \cdot S_{cartesian}
\]  

(1.11)

After gridding, the FFT is applied and the resulting image is deapodized, just as before.

\[
m_{cartesian} = \frac{\mathcal{F}^{-1}[A]^\dagger [M_{radial}]}{c}
\]  

(1.12)

The matrix notation of Eq. (1.12) illustrates the two major contributions to the algorithmic complexity of gridding: interpolating the data onto a Cartesian matrix via \( A^\dagger \), and computing the FFT. The complexity of the interpolation step scales with the number of nonzero elements of \( A \), which is \( O(n \cdot (\alpha \cdot W)^3) \), where \( n \) is the number of non-Cartesian k-space samples, \( \alpha \) is the degree of overgridding, and \( W \) is the kernel extent in units of non-overgridded k-space voxels. Because \( n \) is set by the acquisition,
algorithmic complexity can only be decreased by limiting kernel extent and reducing overgridding. Employing a small kernel extent ensures that many of the interpolation coefficients in $\mathbf{A}$ will be zero, thereby making the system matrix sparse and decreasing the number of interpolation operations. Similarly, employing a small overgridding factor creates a coarser Cartesian grid and reduces the number of interpolations. The remaining complexity is associated with the FFT operation, which increases with the number of Cartesian voxels $v$ according to $O(v^3 \cdot \log(v^3))$. Thus, because $v$ is determined by the degree of overgridding prescribed, overgridding is the primary driver of FFT complexity. For comparison, the complexity of the DFT scales with the product of the number of measured k-space samples and reconstructed image voxels, $O((\mu v^3) \cdot v^3)$, where $\mu$ represents the undersampling fraction. Therefore, calculating the DFT is computationally equivalent to gridding an entirely non-sparse system matrix. These factors highlight the need to identify parameters that minimize reconstruction error while delivering acceptable reconstruction speed.

4.3 Preclinical Methods for Optimizing Reconstruction

To demonstrate the effects of key image reconstruction parameters, we employ a single high-resolution radially acquired HP $^{129}$Xe MR ventilation image of a mouse. We chose a preclinical dataset because we can both replenish the hyperpolarized signal as
well as manage motion through mechanical ventilation, which improves data consistency and SNR relative to current human imaging techniques.

### 4.3.1 Image Acquisition

The image was acquired in an anesthetized and mechanically ventilated 10-week old BALB/c mouse (Jackson Laboratory, Bar Harbor, ME). Over the course of the ~6-minute scan, a 17 mL dose equivalent was delivered to the mouse (He, 2015). A 3D radial sequence was employed on our 2T preclinical magnet (Oxford Instruments, Oxford, UK) with Magnex model SGRAD 205/120/S gradients (400 mT/m maximum amplitude, 3636 T/m/s maximum slew rate) and GE EXCITE 12.0 console (GE Healthcare, Milwaukee, WI) to image the $^{129}$Xe distribution at full inspiration (2501 radial views, 5 views/breath, TE/TR = 384 μs/10 ms, 30° hard pulse, 64 samples/ray, 2 cm FOV, 8 kHz acquisition BW).

### 4.3.2 Gridding Reconstruction

To enable comparison of various reconstruction techniques, we developed a flexible, open source, non-Cartesian reconstruction toolbox in MATLAB that uses MEX functions to call underlying C code for rapid calculation. The source code is freely available at www.civm.duhs.duke.edu/nonCartesianRecon. The code is for research use only and is well-documented to encourage collaboration and extension. It accepts
arbitrary gridding kernels, overgridding factors, and DCF algorithms, which are used to calculate a sparse system matrix \( [A] \) that can be used to directly or iteratively reconstruct 2D or 3D non-Cartesian data.

### 4.3.3 Preclinical Results

Although optimizing reconstruction requires concurrent tuning of all its parameters, we first illustrate the effects of each parameter by varying them one at a time from their optimal value. The fully optimized reconstruction is then compared to our previous reconstruction method and the DFT gold standard. While it is common to enhance image quality by applying additional image filtration, we intentionally omitted these steps to better visualize noise and artifacts associated with reconstruction. Similarly, we should note that the window width/level of the displayed images have been chosen to emphasize noise and artifacts of reconstruction rather than for visual appeal.

#### 4.3.3.1 Overgridding Reduces Wrap-Around Aliasing

One well-known artifact in HP MRI, wrap-around aliasing, can be readily mitigated by overgridding k-space. The example maximum intensity projection (MIP) in Figure 11a shows \(^{129}\text{Xe}\) in the trachea and intubation tube, illustrating that \(^{129}\text{Xe}\) is commonly excited well outside of the prescribed FOV. Therefore, reconstructing this
data without overgridding causes signal from outside the FOV to alias back into the image, as seen in Figure 11b. By instead overgridding k-space 3-fold, an extended FOV is reconstructed that contains all of the excited signal, and the wrap-around artifact is eliminated from the prescribed FOV (Figure 11c). We have found 3x overgridding to be robust for our typical preclinical application, because it extends the FOV beyond the sensitive region of the coil.
Figure 11: The effects of overgridding. (a) Extended FOV reconstruction shows that signal is excited outside the FOV. (b) Without overgridding, signal in the trachea causes wrap-around artifact. (c) The wrap-around artifact is eliminated by overgridding k-space threefold.

However, 3x overgridding comes at a 27x penalty in gridding complexity and $3^3 \cdot \log(3^3) \approx 89x$ increase in FFT complexity. This additional complexity would make
reconstruction times unreasonable in many $^1$H applications where large matrix dimensions are common. As a result, $^1$H applications commonly use slice-selective pulses and only 1.125 – 2x overgridding (Block, 2007, Beatty, 2005) to manage reconstruction times. By contrast, HP gas MRI often uses small matrix sizes, and therefore even with 3x overgridding, reconstruction remains fast (12.5 seconds for this example on a HP Z620 Workstation with an Intel Xeon 6-core 3.2 GHz processor). Thus, for HP gas MRI, in contrast to $^1$H applications, reconstruction time is a less critical constraint and greater overgridding can be used to optimize image quality and minimize artifacts. Nevertheless, it must still be applied reasonably since it improves image quality with diminishing returns, while increasing computational cost exponentially.

4.3.3.2 Density Compensation Appropriately Weights Spatial Frequencies

A significant challenge in gridding lies in managing how the density compensation strategy determines the balance of low and high spatial frequency information in the reconstructed image. Because the DCF applies different weights to the measured k-space data prior to gridding, it indirectly controls how various spatial frequencies contribute to the reconstructed image, and thereby acts as an image-domain filter. The way in which several density compensation strategies affect $^{129}$Xe image reconstruction is illustrated in Figure 12. For reference, reconstruction without density
compensation is illustrated in Figure 12a, where the low spatial frequencies are over-emphasized to cause excessive image blurring.

![Figure 12: Four density compensation functions and their effect on reconstructed images. (a) Without density compensation, low frequencies are over-weighted and images are blurry. (b) Analytical DCF compensates for the nonuniformity of radial samples along rays, but not the angles between them, and generates sharp, but noisy images. (c) The Voronoi method accounts for radial and angular nonuniformities, but is sensitive to aliased high-frequency noise. (d) Iterative DCF best achieves image sharpness while minimizing high frequency aliasing. The gray shading in the DCF plots below each image represents the range of DCF variation across the angular distribution of radial rays.]

The simplest way to approximate the DCF, illustrated in Figure 12b, is to use the analytical method. This approach aims to counteract the natural inverse square divergence of radial sampling by employing a DCF proportional to $k_r^{-2}$. This method is rapidly calculated at arbitrarily high spatial resolution and reduces image blurring relative to the uncompensated image. However, it has three undesirable properties.
First, it evaluates to zero at the DC frequency, which is equivalent to throwing away signal at the origin of k-space. Since DC information represents the net signal across the entire FOV, its absence diminishes the ability to detect scan-to-scan differences in gas concentrations or polarization from the reconstructed images. Second, the analytical DCF heavily weights the high spatial frequencies, where signal is weakest, relative noise is highest, and radial sampling is most sparse; this results in reconstructed images that are noisy and aliased. Third, the analytical DCF weights all radial rays identically by assuming they are uniformly distributed throughout k-space. However, such uniformity is not geometrically possible in 3D imaging. Thus, an ideal DCF would preserve DC signal, reduce the influence of the noisier and potentially aliased high spatial frequencies, and properly account for the inherently non-uniform angular distribution of radial rays.

An alternative to the analytical DCF is the Voronoi method (Rasche, 1999), illustrated in Figure 13. This geometric approach assigns DCF values that are directly proportional to Voronoi cell volumes, which represent the fraction of k-space nearest to the given sample. Thus, the Voronoi-derived DCF values in Figure 12c are relatively low in densely sampled portions of k-space and increase towards more sparsely sampled regions. As shown by the gray shading in Figure 12c, this method naturally accounts for the non-uniform angular distribution of radial k-space rays by the way Voronoi cell sizes are constructed. Moreover, the Voronoi method, unlike the analytical method,
generates small, but nonzero weights for the DC samples. Despite these advantages over the analytical method, the calculation of Voronoi cell volumes is time-consuming and the reconstructed images contain a hazy texture. This texture is the result of angular undersampling that causes signal gaps between radial rays to become more pronounced at high spatial frequencies. When the gaps exceed the Nyquist spacing limits, the signal from these frequencies aliases back into the reconstructed image, manifesting as a noise-like texture (Figure 12c). Ideally, the DCF would penalize this high-frequency aliasing by lowering the weight of these undersampled spatial frequencies. However, this advantage of reducing aliasing must be balanced against the consequent loss of high frequency imaging content that blurs the reconstructed images.

Figure 13: Voronoi cells (outlined in black) of an example 2D k-space sampling (blue circles) bound the area that is closest to each sample. The inverse volume of each Voronoi cell is an estimate of the local sample density, so the DCF is directly proportional to the Voronoi cell area.
In our experience, the density compensation strategy that best mitigates high frequency aliasing is the iterative DCF algorithm (Pipe, 1999). This method solves for a DCF that optimally reconstructs an ideal point spread function (PSF). Such a PSF, when transformed into k-space would generate a modulation transfer function (MTF) that is perfectly uniform across all k-space frequencies. Thus, by simulating a signal that is constant in k-space, measuring it with our radial sampling function, and then adjusting the DCF until the gridded Cartesian k-space becomes uniform, we can in principle perfectly reconstruct the ideal PSF. The iterative DCF algorithm stably converges towards this objective. Like the Voronoi method, the iterative method provides nonzero weighting at the DC frequency and appropriately handles the angular non-uniformity of radial rays (Figure 12d). The key benefit to this algorithm, however, is that its solution inherently suppresses aliasing from undersampled spatial frequencies by lowering their DCF weights (Pipe, 2000). This occurs because the approximated sampling density becomes constant at the spatial frequency where adjacent radial rays diverge beyond the proximity of the kernel. Conveniently, this spatial frequency is approximately where the Nyquist limit is exceeded. A noted by Pipe, the shape of the iteratively-derived DCF closely matches the analytical and Voronoi methods at low frequencies, but plateaus at high spatial frequencies, thereby suppressing these aliased signals (Pipe, 2000). The resulting images (Figure 12d), even though undersampled, contain reduced high-frequency noise and minimal blurring.
The iterative DCF algorithm converges quickly towards its final solution, and incremental changes in image appearance are difficult to discern beyond 3 iterations. However, since DCF coefficients can be calculated quickly or precomputed and stored, we used 10 iterations to ensure sufficient convergence. The iterative DCF algorithm does not diverge (Pipe, 2000), so there is no harm in computing further iterations.

One caveat in using iterative density compensation is that it can obscure wrap-around artifact. Because wrap-around is caused by insufficient k-space sampling resolution, simply increasing the reconstructed FOV and reducing interpolation errors through overgridding k-space would mitigate the artifact. However, in non-Cartesian acquisitions that sample k-space incoherently, such as the 3D radial sequence employed here, the iterative DCF algorithm naturally converges towards weights that preserve the spatial incoherence of aliased signals (Pipe, 2000). This incoherence obscures wrap-around and consequently conceals the need for overgridding. As an example, Figure 14a shows the obviously wrapped trachea that results from reconstructing with one DCF iteration, using no overgridding. However, after just 10 DCF iterations, signal from the wrapped trachea becomes incoherently distributed throughout the image, and the wrapped signal appears as a hazy noise with no obvious source. Although wrap-around causes the artifacts in both Figure 14a and b, it is only obvious in Figure 14a that overgridding will resolve the artifact. Therefore, when optimizing reconstruction parameters, we recommend selecting an overgridding factor first using only a single
DCF iteration to preserve wrap-around artifact. Once this is done, additional density compensation iterations can be used to more accurately compensate for sampling density variations without obscuring wrapped features (Figure 14c).

Figure 14: Influence of overgridding and density compensation on wrap-around artifact. (a) Reconstruction with 1 DCF iteration and no overgridding highlights the presence of wrap-around signal. (b) Additional iterations of density compensation obscure the wrapped trachea and introduce a noise-like texture. (c) Such issues can be avoided by first removing wrap-around signal with overgridding, then applying further DCF iterations.
4.3.3.3 Convolution Kernel Controls DCF Induced Image Filtration

Although many convolution kernel functions have been proposed for gridding reconstruction, we considered only three of the most common ones. Of these, the Kaiser-Bessel function is used most often because its Fourier transform is reasonably bound in both the spatial and frequency domains. An alternative is the simple Gaussian function, which is particularly straight-forward and intuitive to optimize. A third option is the min-max tuned function, which Fessler et al. showed is numerically optimized to minimize the maximum gridding error for unit input signal (Fessler, 2003). We used Fessler’s implementation of this min-max gridding kernel rather than repeating the optimization separately. Note that because Fessler’s code offers min-max tuned kernels for a maximum of 2x overgridding (Fessler, 2003), we also restricted our analysis of the Kaiser-bessel and Gaussian functions to 2x overgridding. For the Gaussian and Kaiser-bessel functions, the sharpness and extent of each kernel were empirically tuned by an expert reader using the techniques described in later sections.

A comparison of images reconstructed with all three kernel functions is shown in Figure 15. The most notable observation is that after individual tuning, all kernels produced similar image quality. Given their similar performance, we proceeded with the kernel that was fastest to calculate and most intuitive to tune. These two objectives eliminated the Kaiser Bessel kernel (Beatty, 2005), which although widely used, is relatively slow to calculate and must be re-tuned for each change in its shape parameter,
kernel width, or overgridding factor. Similarly, while the min-max kernel is analytically determined, it requires additional image-domain “scaling factors” that need separate optimization. Therefore, we chose the simple Gaussian kernel to conveniently illustrate the kernel tuning process going forward because it is rapid to calculate, is well defined in both the spatial and frequency domains, and its broadness, extent, and overgridding can be controlled independently. We should note that the Kaiser-Bessel function and min-max kernels, with proper tuning and sampling resolution, can reduce the mathematical error of reconstruction relative to the Gaussian kernel. However, because of the low SNR of the measured k-space data and large degree of undersampling, these subtle mathematical advantages do not noticeably improve the diagnostic value of the images we present in Figure 15.

![Image of sagittal slice illustrating the lack of detectable differences in image quality between different kernels.]

**Figure 15:** Sagittal slice illustrates the lack of detectable differences in image quality between optimized reconstructions using (a) Kaiser-Bessel, (b) min-max, and (c) Gaussian gridding kernels.

We found that more critical than the mathematical form of the kernel function is selecting its sharpness and extent. These parameters dramatically affect the reconstructed images because they determine the location of the DCF roll-off. This is
because the iterative algorithm computes the sampling density using the same gridding process as reconstruction, hence the DCF that naturally emerges is specific to the chosen reconstruction parameters. Since the DCF plateaus where adjacent radial rays diverge beyond the range of the kernel, we can control the DCF roll-off with the kernel sharpness and extent. This dependence of DCF weights on the kernel shape is similar to the influence of undersampling on DCF values that Pipe described (Pipe, 2000). However unlike undersampling, the kernel sharpness and extent can be tuned post-acquisition. Therefore, the kernel sharpness and extent serve as useful mechanisms to retrospectively trade off signal to noise (SNR) and image resolution on a scan-by-scan basis.

If a sharper image is desired, for example, we must suppress the natural tendency of the iterative DCF to reduce weighting of the high spatial frequencies. This can be best accomplished by more aggressively interpolating the measured radial data between radial rays using a broader kernel. A broader kernel disseminates information further in k-space to combine information between more distal radial rays, resulting in a DCF that rolls off at a higher spatial frequency and generates correspondingly sharper images. Increasing the extent of the kernel has a similar, but reduced effect, because the kernel intensity falls off with increasing distance. We have found that so long as the extent is sufficient to minimally truncate the tails of the Gaussian kernel, it has little effect on DCF. And since gridding complexity scales with $W^3$, it is practically necessary
to limit kernel extent. We found that parameterizing the kernel extent to be six times the sharpness, $W = 6\sigma$, causes only 0.3% of the underlying Gaussian kernel information to be truncated, while also minimizing excess computational burden. In this manner we can control the DCF-induced filtration properties of reconstruction using only a single parameter.

For comparison, several Gaussian kernels of differing sharpness, defined as the Gaussian standard deviation $\sigma$ in units of k-space voxels prior to applying overgridding, are shown in Figure 16a. Choosing a sharp kernel causes each radial sample to contribute its information to only a limited number of nearby Cartesian grid points. As a result of the restricted information dispersion, the sampling density becomes constant at a relatively low spatial frequency and consequently the DCF rolls off at a low spatial frequency (Figure 16b). Because the reconstructed images contain little high-frequency information, the images have high SNR but appear blurry (Figure 16c). A broader kernel, shown in Figure 16d, interpolates information from more distal radial rays, which increases DCF weights at high frequencies to generate sharper images. However, once the kernel becomes overly broad (Figure 16e), it weights the high spatial frequencies too heavily. At high frequencies, noise is most prevalent and angular sampling is most sparse, so enhancing them results in very sharp images, but also introduces a noise-like artifact due to high-frequency aliasing. For our test scan, we found that a Gaussian kernel with a sharpness value of $\sigma = 0.33$ optimally preserved
low- and high-frequency image details, while minimizing the noise-like texture from high-frequency aliasing.

Figure 16: Effects of kernel sharpness on image filtration. (a) The effect of three kernel sharpness parameters on kernel shape. (b) The effect of kernel sharpness on DCF weights. (c–e) Reconstructed images using these three kernel sharpness values.
4.3.3.4 Optimized Parameters

For this preclinical acquisition, we found that overall image quality was optimized by using 3x overgridding, a Gaussian kernel with $\sigma = 0.33$ and $W = 6\sigma$, and 10 DCF iterations. These parameters allow reconstruction at 0.015% the algorithmic complexity of the DFT, resulting in a reconstruction time of just 12.5 seconds. Reconstruction can be further reduced to just 2.5 seconds if the system matrix and DCF values are precomputed and stored for the given k-space sampling pattern. As shown in Figure 17b, the optimized reconstruction noticeably improved image quality compared to our previous reconstruction methods (Figure 17a), and does not differ appreciably from a reconstruction achieved by the DFT (Figure 17c). For reference, the previous reconstruction method used a trilinear interpolation kernel with $W = 2$, 2x overgridding, and density compensation that is similar to 1 round of iterative density compensation (Glover, 1992).
Figure 17: Relative to (a) previous reconstruction, (b) optimized reconstruction shows improved image quality. Optimized reconstruction shows little discernable difference compared to (c) DFT.

As is evident from the foregoing discussion of how reconstruction factors can impact image quality, it is not straightforward to quantitatively assess differences among reconstructions. It is tempting to simply compare image SNR; however, SNR can be artificially enhanced by using a sharp convolution kernel to smooth images at the expense of spatial resolution. Instead, we adjusted our kernel sharpness in the optimized reconstruction such that we achieved the identical SNR of 33 in the trachea that was generated by our previous reconstruction. This was achieved with a sharpness of \( \sigma = 0.36 \). We then examined the smallest discernable structure in each reconstruction.
through a user-guided segmentation of the airway trees in Avizo 8.1 (FEI Visualization Sciences Group, Burlington, MA). In the constant-SNR comparison shown in Figure 18, the optimized reconstruction resolved one additional order of airways (from 5th to 6th order) (Wallau, 2000).

Figure 18: Comparison of airways resolved by previous and optimized reconstruction. (a) Constant SNR MIPs of the right mouse lung shows that relative to (a) previous reconstruction, (b) the optimized reconstruction resolved sixth order airways, highlighted by the arrow.

4.3.3.5 Robustness of Techniques

While the optimization process was intentionally presented using only a single dataset to control for physiological variations and differences between acquisitions, we have found our reconstruction methods to be robust across a range of preclinical applications. This is illustrated in (Figure 19), which depicts both gas- and dissolved-phase $^{129}$Xe MRI, as well as the corresponding $^1$H anatomical image. Note that the only
reconstruction parameter that was modified for these different cases was the kernel sharpness. This parameter was empirically adjusted by an expert reader according to the degree of angular undersampling and the SNR of the raw k-space data of each particular scan. Scans that were more undersampled required a broader kernel and conversely, fully sampled data such as the $^1$H scan could be reconstructed at high resolution with a narrow kernel. Similarly, lower SNR scans such as the dissolved-phase $^{129}$Xe acquisitions, benefited from sharper kernels that sacrificed resolution to achieve reasonable image SNR.
Figure 19: Optimized reconstructions of radially acquired mouse lung MRI for anatomical \(^1\)H, gas-phase \(^{129}\)Xe, and dissolved-phase \(^{129}\)Xe images, along with their respective MIPs. The \(^1\)H image was 25% sampled and was optimized with the sharpest kernel of \(\sigma=0.125\). The gas-phase image, being only 5% sampled, required a broader kernel sharpness of \(\sigma=0.33\). The dissolved-phase image, while also 5% sampled, required a sharper kernel of \(\sigma=0.30\) to compensate for its lower inherent SNR.

4.4 Translating Optimization Techniques to Clinical Imaging

Our preclinical setup, with its ability to mechanically ventilate animals and consequently provide high quality imaging data, was employed to help develop a procedure for optimizing our reconstruction techniques. However, these optimization methods are readily translatable to our clinical imaging in humans. That is because our
clinical data is acquired in the same radial manner as the preclinical data. Therefore, it requires the identical procedure of gridding described in Section 4.2.

It is important to note that in our clinical protocol for imaging humans, because we cannot mechanically ventilate our subjects, only a single inhaled dose of $^{129}$Xe can be administered for a given scan. As a consequence of this non-renewable signal, we must employ small flip angles to preserve the magnetization throughout the scan. These smaller flip angles reduce the SNR of the measured data. Fortunately, the flip-angle induced loss in SNR is partially compensated by the larger lung volumes in humans relative to mice and greater volume of delivered HP. However, despite this large $^{129}$Xe volume, we are still limited to only a 15 second breath hold, so we must image quickly to maximize our use of the limited time and signal.

### 4.4.1 Clinical Acquisition and Reconstruction Parameters

A human 3D radial image was acquired using a 1.5 T GE Healthcare EXCITE 15M4 MR system. A flexible chest coil (Clinical MR Solutions, Brookfield, WI), tuned to the 17.66 MHz $^{129}$Xe frequency, was fitted on the subject. From FRC, the subject inhaled a 1L volume that contained a 71 ml dose equivalent of $^{129}$Xe (He, 2015). The following imaging parameters were used: FOV = 36 cm, matrix = $64^3$, radial views = 4601, flip angle = 1.2°, TR/TE = 3.3/0.376 ms, BW = 15.63 kHz. In order to provide an anatomical reference for the $^{129}$Xe images, a thoracic cavity image was acquired under breath-hold using the body coil with the following parameters: FOV = 40 cm, matrix=128$^3$, TR/TE = 0.264/0.24 ms, radial views = 5650, BW = 31.25 kHz, flip angle = 15°.
4.4.2 Clinical Results

Similar to reconstructing preclinical mouse images, 3D radial images of the human lung benefited from 3x overgridding to eliminate aliased wrapped signal from the trachea and dose bag. This is illustrated in the MIP image shown in Figure 20a, where the dose bag, as well as $^{129}$Xe residing in the mouth, lie outside the prescribed FOV. Without overgridding to reconstruct the larger FOV, this strong signal aliases incoherently back into the image, artificially increasing the perceived background noise (Figure 20b). However, by overgridding 3x as shown in Figure 20c, the reconstructed FOV encompasses all of the excited signal and the reconstructed image improves.
Figure 20: MIP images show that when $^{129}$Xe in the mouth, trachea, or dose bag lies outside the FOV (a), insufficient overgridding results in aliased signal that manifests itself as incoherent noise (b). This artificial noise can be removed by overgridding k-space threefold.

These clinical scans, like the mouse datasets described in Section 4.3.3, are best reconstructed using iterative density compensation and appropriately selected reconstruction kernel parameters. Figure 21 compares the same dataset reconstructed with our previous reconstruction methods (Figure 21a) to our optimized reconstruction (Figure 21b). Overlaying the optimized reconstruction onto a registered $^1$H image illustrates that the optimized reconstruction provides improved contrast and resolution that can detect vasculature which the previous reconstruction missed (Figure 21c).
Figure 21: Previous reconstruction (left) suffered from insufficient overgridding and improperly tuned kernel, which lowered the resolution and the perceived SNR. By overgridding 3x and tuning the kernel appropriately, the resolution and perceived SNR improve dramatically (right). Optimized reconstruction can resolve vasculature in ventilation image (green) that is also shown in $^1$H volume (magenta).

While these reconstruction techniques have improved our radial ventilation images, their greatest impact has been in enabling robust imaging of $^{129}$Xe that has dissolved into the barrier tissue and blood. This dissolved-phase signal, poses significant challenges to imaging methods because only ~1-2% of the gas-phase xenon dissolves into these compartments, and the dissolved-phase T2* in the lung is rapid (1.5-2.4 ms at 1.5T). Therefore, imaging this limited and rapidly decaying signal requires a short-TE acquisition and SNR-efficient reconstruction (Kaushik, 2016a). Both of these requirements are met by our optimized 3D radial acquisition and reconstruction.

Figure 22 compares the previous reconstruction method (left) to our optimized methods (middle) in reconstructing dissolved-phase images, with a simultaneously acquired gas-phase image (right) included for anatomical context. The differences
between these two reconstruction methods is striking. The previous reconstruction (left) has such poor SNR that it is difficult to identify any structure in the image. However, our optimized reconstruction method markedly improves the dissolved-phase images by carefully balancing the tradeoff between SNR and spatial resolution. In dissolved-phase imaging, achieving sufficient SNR is particularly important because, as will be discussed in chapter 6, these dissolved-phase images must be further decomposed into barrier and RBC images so that regional gas transfer can be evaluated. And since the SNR of the reconstructed dissolved-phase image, to a large extent, determines the quality of these decomposed images, this process of optimizing reconstruction methods is essential.

Figure 22: Comparison of images from previous (left) and optimized (right) reconstruction methods across both gas-phase (top) and dissolved-phase (bottom) datasets.
4.5 **Summary**

This chapter has shown that radial imaging has enormous potential for producing high-quality images of pulmonary structure and function using HP $^{129}$Xe. However, this work also makes clear that there are special considerations for HP $^{129}$Xe lung MRI. Since HP $^{129}$Xe MRI employs non-selective RF pulses, has limited SNR, and is often significantly undersampled, careful tuning of parameters can yield dramatic gains in image quality and airway conspicuity. Because long structures such as the trachea are excited outside the desired field of view, our application requires a high degree of overgridding to avoid wrap-around artifact. Moreover, HP gas radial MR acquisitions are typically highly undersampled, and thus benefit greatly from using an iterative DCF to compensate for high-frequency aliasing. However, the filtration imparted by the DCF roll-off must be controlled by appropriately selecting the kernel sharpness and ensuring that kernel extent is sufficient. Although we considered many reconstruction parameters here, we found that the bulk of the adjustment is limited purely to matching appropriate kernel sharpness to the degree of undersampling and SNR of the acquisition. This single parameter optimization makes tuning reconstruction much faster and simpler than might be expected. These techniques enable high SNR dissolved-phase imaging, which as detailed in chapter 6, can be decomposed into RBC and barrier images to quantify regional gas transfer.
5 Quantifying Spectroscopic Biomarkers of Lung Function

Chapter 3 showed that HP $^{129}$Xe has become a useful noninvasive tool for quantitatively evaluating pulmonary ventilation. Furthermore, chapter 4 illustrated that HP $^{129}$Xe is useful beyond gas-phase imaging because it is soluble in the blood and experiences a ~200 ppm chemical shift when it diffuses into the blood and barrier tissue. Together, the solubility and chemical shifts enable HP $^{129}$Xe to detect gas transfer in the lung. This chapter investigates and quantifies the spectral properties of $^{129}$Xe within the lung. The methods and results presented in this chapter are adapted from the following peer-reviewed journal articles:


5.1 Motivation

The $^{129}$Xe atom constitutes a sensitive and noninvasive probe of lung function. That is because $^{129}$Xe dissolves from the airspaces through the interstitial tissues of the lung into the red blood cells (RBCs) of the pulmonary capillaries (Otswald Solubility in RBCs $\sim 14\%$), where it is pumped through the heart to the rest of the body (Weathersby, 1980). In addition to its solubility, the large electron cloud of $^{129}$Xe is easily distorted by its chemical environment, which changes the degree of magnetic shielding that the nucleus experiences and introduces various $^{129}$Xe chemical shifts (Miller, 1981). The magnetic field experienced by the $^{129}$Xe nucleus is not only affected by the local chemical environment, but also the structure of the lung, as geometric changes can alter the susceptibility. Consequently, the NMR spectrum directly reports on both structural and functional changes in the lung.

Properties of the $^{129}$Xe spectrum were first characterized in vitro by Albert et al. using thermal $^{129}$Xe, where two distinct dissolved-phase resonances were detected in human blood (Albert, 1995). By dissolving hyperpolarized $^{129}$Xe into centrifuged blood, the spectral properties of red blood cells (RBCs) and plasma were isolated. In plasma, $^{129}$Xe was identified to resonate at 198 ppm and in RBCs at 217 ppm (Bifone, 1996). The spectral properties of these two dissolved-phase peaks vary with oxygenation, hematocrit, and temperature. Specifically, the T1 of the dissolved-phase signal increases with both increasing oxygenation and increasing temperature (Wolber, 1999). As
oxygenation increases, the chemical shift plasma resonance remains unchanged, but the resonant frequency of the RBC peak is strongly and nonlinearly shifted in the positive direction (4). This oxygenation-dependent chemical shift or the RBC resonance was recently confirmed by Norquay et al. who measured a 5.5 ppm range of $^{129}$Xe RBC chemical shifts when in vitro blood $s_0$ values ranged from 0.1 to 1 (Norquay, 2016). Changes in oxygenation, at least within the physiological range, do not significantly alter the linewidth of either dissolved-phase peaks (Wolber, 2000a). However, the linewidth of the plasma peak increases linearly with hematocrit, while the RBC peak is largely unaffected.

Because of the richness of the $^{129}$Xe spectrum, there currently exists great interest in quantifying spectral changes in vivo. Despite significant spectral broadening imparted by the inhomogeneous susceptibility environment in the lung, two dissolved-phase $^{129}$Xe resonances have been readily observed in vivo. The RBC peak has been generally reported at 217 ppm in humans, while the 198 ppm peak has been assigned to $^{129}$Xe dissolved in both plasma and other pulmonary tissues. This latter resonance is therefore commonly referred to as the “tissue/plasma” or “barrier” peak. Additional spectral peaks arise when dissolved-phase magnetization is allowed to wash "downstream" of the capillary beds into muscle (188 ppm), fat (189-194 ppm), grey matter (194 ppm), white matter 192 ppm) (Kilian, 2004, Norquay, 2015, Rao, 2016). By monitoring how these dissolved-phase peaks vary in vivo, $^{129}$Xe has begun to show
promise as a biomarker for multiple diseases and physiological processes. These have included measures of blood oxygenation (Norquay, 2016, Wolber, 2000b), brain perfusion (Kilian, 2004, Zhou, 2011), and weight regulation through brown adipose tissue stimulation (Branca, 2014). However, the most widely investigated application has been the characterization of pulmonary gas transfer (Patz, 2008, Ruppert, 2004, Abdeen, 2006, Stewart, 2015b). These studies exploit the fact that individual $^{129}$Xe resonances directly reflect the dynamics of $^{129}$Xe diffusing between the airspaces, interstitial barrier tissues, and capillary blood. For example, Kaushik et al. investigated $^{129}$Xe spectra from subjects with idiopathic pulmonary fibrosis (IPF) and reported that the ratio of the RBC to barrier signal was reduced by more than 3-fold relative to that in healthy subjects (Kaushik, 2014). Moreover, this work demonstrated that the ratio of $^{129}$Xe uptake in RBC versus barrier correlated strongly with the diffusing capacity for carbon monoxide (DLCO), the most common clinical marker of gas transfer. Kaushik et al. also found that subjects with IPF exhibited a negative frequency shift in the RBC peak, which was interpreted as reflecting diminished blood oxygenation in the capillary beds.

Since our interest in hyperpolarized $^{129}$Xe is to measure pulmonary function, we exploit short repetition times and large flip angles in order to deplete all the dissolved-phase hyperpolarized magnetization before it leaves the pulmonary capillary bed and thus restrict the measured signal to the gas exchange regions. It is important to note that, because we use a frequency selective RF pulse to preferentially excite the dissolved-
phase frequencies, each RF pulse only minimally depletes the gas-phase magnetization. In this way, the gas-phase magnetization acts as a persistent reservoir of magnetization that continuously replenishes the dissolved-phase signal. The rate of this replenishment is governed by the thickness of the alveolar septa. With a typical alveolus having a thickness of ~10µm, the dissolved-phase signal is replenished within ~40ms (Patz, 2011). Thus while the large flip angle virtually eliminates all dissolved-phase magnetization within only a few RF pulses, this dissolved-phase signal is rapidly replenished from the gas-phase reservoir. In this way we are able to efficiently deploy nearly the entirety of the inhaled magnetization towards acquiring the dissolved-phase spectrum despite 98% of the signal residing in the airspaces (Cleveland, 2010). The large flip angle and continual replenishment collectively enhance the SNR of the dissolved-phase FID, which facilitates its spectral decomposition.

To date, the methods to decompose the dissolved-phase $^{129}$Xe spectral properties have been somewhat rudimentary relative to $^1$H and $^{13}$C spectroscopy, where sophisticated modeling techniques have been developed that incorporate knowledge of the coupling between protons and carbon atoms in various compounds (Drost, 2002, Provencher, 2001). However, these advanced tools have not been readily applied to $^{129}$Xe spectra. That is because $^{129}$Xe is an inert gas with no J-coupling, but it does exhibit significant exchange and susceptibility broadening. Therefore, its spectrum can be accurately modeled by just two phenomena—precession and exponential decay. The
challenge with $^{129}$Xe spectroscopy lies in accurately accounting for the broad and overlapping nature of these resonances, as well as the substantial phase variation between them.

This chapter introduces techniques that better analyze $^{129}$Xe spectra acquired in human lungs. Using non-linear curve fitting to decompose complex $^{129}$Xe free induction decays (FIDs) in the time domain, we demonstrate that the spectrum of $^{129}$Xe in human lungs is accurately characterized by not two, but three dissolved-phase resonances. We report the frequencies, linewidths, and phases of these three resonances in a cohort of healthy normal and IPF subjects. We then illustrate the key differences in spectral characteristics between the two populations. This chapter indicates that spectral characteristics of dissolved-phase spectra are useful biomarkers for diseases such as IPF and PAH. Furthermore, the existence of three dissolved-phase resonances suggests that phase-sensitive imaging techniques need to accommodate the additional resonance to properly decompose the dissolved-phase images. These spectral characteristics therefore form the cornerstone of our functional imaging exam.

### 5.2 Methods

#### 5.2.1 Subject Recruitment

This study was approved by the Duke Institutional Review Board. Prior to participating, all subjects provided written informed consent. The population consisted of 12 healthy
normal (8 males, 4 females, 32.1 ± 13.8 years old) and 12 volunteers with IPF (10 males, 2 females, 68.5 ± 7.2 years old) who underwent HP 129Xe spectroscopy as part of a broader imaging protocol. Prior to spectroscopy, all subjects completed pulmonary function testing, which included measuring the total lung capacity (TLC), functional residual capacity (FRC), forced vital capacity (FVC), and DLco.

### 5.2.2 129Xe Polarization and Delivery

All spectroscopic scans consisted of 300 mL of 129Xe and 700 mL of UHP N2, representing on average a 51 mL dose equivalent volume (He, 2015). Each dose was prepared as described in Section 2.2.3. Immediately preceding delivery to the subject, the polarization of each dose was measured by a polarimeter (Model 2881, Polarean, Inc.) and recorded. Each subject was instructed to twice inhale to TLC, then exhale to FRC before inhaling the 1-L gas mixture for the 13-second breath hold scan. For each subject, heart rate and oxygen saturation were monitored using an MR-compatible monitoring system (Expression Model 865214, Invivo Corporation, Orlando, FL).

### 5.2.3 129Xe Spectroscopy

Both gas- and dissolved-phase spectra were acquired on a 1.5 T GE Healthcare 15M4 EXCITE MRI scanner using a quadrature 129Xe vest coil (Clinical MR Solutions, Brookfield, WI). The spectroscopic parameters for the gas- and dissolved-phase 129Xe
FIDs were: 512 samples per FID, TE/TR = 0.875/50 ms, BW = 8.06 kHz, 1.2 ms 3-lobe sinc pulse, flip angle ≈ 0.5/22°. Since this scan also served as a calibration for subsequent imaging, we used a 22° dissolved-phase flip angle to maintain consistent scan parameters between both sequences. In lieu of using a 90° flip angle to eliminate magnetization that had accumulated downstream of the capillary beds, we instead discarded the first 48 dissolved-phase FIDS. We then averaged the 38 remaining steady-state frames in order to maximize FID SNR prior to curve fitting.

5.2.4 Spectroscopic processing

The complex FIDs from the single gas-phase and averaged dissolved-phase excitations were individually decomposed using a custom MATLAB® toolkit (The MathWorks, Inc., Natick, MA). This open-source code is available for research use from www.civm.duhs.duke.edu/NmrSpectroscopy. The toolkit models each FID as a summation of precessing and exponentially decaying components. Each component signal is described by four parameters: an amplitude ($a_n$), starting phase ($\phi_n$), resonant frequency ($f_n$), and linewidth ($w_n$). Using these parameters, the fitted signal, $s_{fit}$, can be calculated at any time, $t$, according to:

$$s_{fit}(t) = \sum_{n=0}^{n_{components}} a_n e^{i\phi_n} e^{2\pi i f_n t} e^{-\pi w_n t}$$
Using a trust-region-reflective algorithm, this code iteratively solves for the parameters that minimize the least squares error between the measured and fitted data in the time domain (Coleman, 1996). Unlike more common frequency-domain fitting methods, this approach does not require using linebroadening, zeropadding, or parameter constraints. Fit results were compared after allowing for either 2 or 3 dissolved-phase resonances. The starting phase of each resonance is reported relative to that of the RBC resonance in the 3-peak fit, which was set to zero.

### 5.2.5 Distinct Alveolar and Airway Gas-Phase Resonances Exist

Similar to recent preclinical work in mice by Virgincar et al., we found that in humans the gas-phase $^{129}$Xe spectrum consists of two distinct resonant frequencies (Virgincar, 2016). Figure 23 shows that at 1.5 T, these two peaks are separated by 55 Hz, which after correcting for differences in magnetic field strength, is consistent with the 70 Hz found in mice at 2T (Virgincar, 2016). We propose that, like in mice, the more negative peak represents $^{129}$Xe in the alveoli, and the more positive peak represents $^{129}$Xe in the conducting airways.
5.2.6 Identifying a Robust In Vivo Reference Frequency

In order to report chemical shifts in a reproducible manner, a stable and readily detectible reference frequency must first be identified. That is because the absolute frequencies of a given resonance (in Hz) vary from day to day due to B0 inhomogeneity and magnetic field drift. These variations in frequency thus confound measurements of physiologically relevant frequency variations. In order to remove these external sources of frequency variation, we can compare the frequencies of in vivo gas-phase spectra to those of two thermally polarized $^{129}$Xe phantoms. These thermally polarized phantoms
are stable sources of signal because they have a fixed volume and pressure, so they consistently resonate at a frequency that is directly proportional to the magnetic field strength. Thus, by looking at relative frequency changes between in vivo and thermal phantom spectra, we can eliminate the variability due to magnetic field drift. Figure 24 illustrates in vivo spectra from two separate days of the same subject where the (top) the raw frequencies of the individual peaks all appear shifted (arrows), but (bottom) after correcting for the frequency shift measured in the thermal phantom, the dissolved-phase peaks become consistent in frequency.
Figure 24: In vivo spectra from the same subject on two different days shows that magnetic field drift adds variable shifts to spectra (top), shown in arrows. After using a thermal phantom to identify the size of the shift, the in vivo spectra can be corrected to make them consistent in frequency (bottom).

While these thermal phantoms provide an accurate and useful reference frequency, acquiring this information requires scanning a phantom immediately before each subject. The additional time to setup and take down the phantoms, would be unacceptable for a clinical workflow. Preferably, a stable in vivo $^{129}$Xe reference frequency would be used instead, because it would not require additional phantom scanning. To that end, we evaluated the stability of these resonances in a subpopulation
of 7 subjects by comparing their relative gas-phase frequencies to those of both thermally polarized $^{129}$Xe in a phantom and hyperpolarized $^{129}$Xe in a dose bag. For these subjects, the standard deviation of the airway peak frequency was only 5 Hz (0.3 ppm), whereas the standard deviation of the alveolar peak was 18 Hz (1.0 ppm). Thus in humans, unlike in mice, the airway peak exhibits the most stable frequency (Virgincar, 2016). As a result, we report all chemical shifts relative to the airway peak of the dedicated gas-phase spectrum. The chemical shifts are also corrected for shifts arising from Xe-Xe collisions (0.03 ppm for 0.3 atm Xe partial pressure in the airways). With this reference, the alveolar peak appeared, on average, at −2.3 ppm. This is very similar to the -2.2 ppm found in mice, and reasonably close to the −2.9 ppm predicted from bulk magnetic susceptibility shifts (-3.02 ppm) for a spherical alveolus (Virgincar, 2016) corrected for Xe-O2 (0.09 ppm) and Xe-Xe (0.03 ppm) collisions. Using the airway gas-phase peak as a reference also improves the accuracy with which we can detect changes in the chemical shifts of the dissolved-phase peaks, making this a critical step to our analysis.

5.2.7 Statistical Analysis

All statistical analysis was performed in MATLAB. Differences between healthy normal and IPF cohorts were evaluated using a Mann–Whitney–Wilcoxon U-test, and determined to be statistically significant if $P < 0.05$. The coefficient of determination ($r^2$)
was used to assess correlations between spectroscopically-derived metrics and pulmonary function test (PFT) results.

5.3 Study Results

5.3.1 Three Dissolved-Phase $^{129}$Xe Resonances Exist in the Lung

For both subject groups, the only way to avoid leaving significant and patterned residual error was to fit the $^{129}$Xe spectrum using three dissolved-phase resonances. This is illustrated in Figure 25a, showing a representative dissolved-phase $^{129}$Xe FID (top) and spectrum (bottom) from a subject with IPF, in which a 2-peak fit was inadequate. Although the net-fitted signal from 2 peaks (blue line) appears to match the measured spectrum (large black circles at discrete spectral sampling points) reasonably well, the residual error (small red circles) shows distinct oscillation in the region of dissolved-phase signal. When a third peak was introduced into the fit (Figure 25b), these fluctuations were eliminated and the residual error dropped to the noise floor. Using the 3-peak fit, the RBC resonance maintained similar intensity and phase, but its linewidth became broader and its frequency shifted positively by ~3.5 ppm relative to the 2-peak fit results. This was related to a second observation that fitting to 3 peaks caused the barrier peak to split into two resonances that were ~5 ppm apart. These two peaks were individually had smaller amplitudes than the single barrier peak derived from the 2-peak fit; they were both broader, and their starting phases were strikingly different.
considering their proximal frequencies. Throughout this work, we refer to the higher-frequency peak as barrier 1, and to the lower-frequency as barrier 2.
Figure 25: Decomposing the dissolved-phase $^{129}$Xe spectrum of a representative IPF subject. (a) Using 2 peaks resulted in non-negligible and patterned error in both the time and spectral domains. (b) The error was largely eliminated when decomposed into 3 peaks consisting of one RBC and two barrier resonances.
Allowing for 3 dissolved-phase peaks also improved the fit quality in healthy subjects, although less dramatically than for subjects with IPF. This is illustrated in Figure 26, depicting a representative dissolved-phase $^{129}$Xe FID and spectrum decomposed into 2 versus 3 peaks. Fitting only 2 peaks resulted in residual error with a similar oscillating pattern, although of smaller magnitude than for the IPF subject. This was again eliminated by decomposing the FID into 3 resonances. As with the IPF subject, the 3-peak fitting also found the chemical shift of the RBC peak to be more positive than the 2-peak fitting. In the healthy subject, the linewidth and phase of the RBC peak were similar between the 2- and 3-peak fits. The 2-peak barrier resonance again split into two resonances that were individually less intense, broader, and ~4.7 ppm apart.
Figure 26: Decomposing the dissolved-phase $^{129}$Xe spectrum in a representative healthy subject. a) Using 2 peaks resulted in residual error that was small but patterned. b) The error was reduced to the noise floor by decomposing the spectrum into 3 peaks.
5.3.2 Quantifying Spectral Parameters from 2- and 3-Peak Fits

Figure 27 compares RBC:barrier ratios derived from 2- and 3-peak fits; in the latter case, termed RBC:barriers for clarity, this ratio is calculated by dividing the RBC amplitude by the sum of both barrier peak amplitudes. In the 2-peak fit, RBC:barrier was reduced by 65.1% in IPF vs healthy subjects ($P < 0.001$), whereas in the 3-peak fit the reduction was only 47.1% lower ($P < 0.001$). This difference is driven by the inclusion of the third dissolved-phase peak, which yielded lower RBC:barrier(s) in healthy subjects, but did not substantially affect the ratio in subjects with IPF.

![Figure 27: For both 2- and 3-peak fits, the RBC:barrier ratio is statistically reduced in IPF subjects relative to healthy subjects. * indicates a statistical difference between groups ($P < 0.05$).](image)

Figure 28 illustrates how the chemical shifts, linewidths, and starting phases varied when the FID was decomposed into 2 vs. 3 peaks in our healthy normal and IPF cohorts. Using a 2-peak fit (Figure 28a) found the RBC peak to be 3.15 ppm more negative ($P < 0.001$) and the barrier peak to be 0.45 ppm more negative relative to healthy subjects ($P = 0.003$). Similarly, 2-peak fitting reported linewidths that were 2.15
ppm narrower for the RBC peak \((P < 0.001)\) and 1.04 ppm narrower for the barrier peak \((P < 0.001)\) in subjects with IPF versus healthy subjects. Using only a 2-peak fit caused the starting phase of the RBC peak to be highly variable in subjects with IPF. Moreover, this starting phase was 54.9 degrees higher \((P < 0.001)\) in subjects with IPF relative to healthy subjects.

Using a 3-peak fit instead, the RBC resonance in subjects with IPF was only 0.70 ppm more negative than in healthy volunteers \((P = 0.005)\). The chemical shift of barrier 1 was not statistically different between the two cohorts \((P = 0.21)\), but barrier 2 was 0.6 ppm more negative \((P = 0.009)\). Using the 3-peak fit, the linewidth of the RBC peak was indistinguishable between groups \((P = 0.80)\). However, 3-peak fitting reported linewidths for barrier 1 and barrier 2 that were 3.2 ppm narrower \((P < 0.001)\) and 2.0 ppm narrower \((P < 0.001)\) in IPF versus healthy subjects. In patients with IPF, the phase of the barrier 1 peak was 20.2 degrees higher compared to healthy normal subjects \((P = 0.01)\). The phase of barrier 2 was consistent between subjects with IPF versus healthy subjects \((P = 0.19)\).
Figure 28: Comparing 2- vs 3-peak fits among healthy subjects (green) and subjects with IPF (red). * indicates a statistical difference between groups (P < 0.05).

5.3.3 Spectroscopic Measurements Illustrate Differences Between IPF and Healthy Subjects

Because decomposing the FIDs into 3 peaks eliminated residual error and patterns in both groups, only 3-peak fit parameters and spectral SNR are summarized in Table 3. Spectral SNR was defined as the magnitude of the fitted signal divided by the magnitude of the residual error. Pulmonary function test results are also included for each subject.
Table 3: Subject demographics, PFT results, and spectral parameters.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Sex</th>
<th>Age</th>
<th>DLCO (mL/min/mmHg)</th>
<th>FVC (%)</th>
<th>RBC:barriers</th>
<th>RBC Barrier 1 (ppm)</th>
<th>RBC Barrier 2 (ppm)</th>
<th>Linewidth (ppm)</th>
<th>Phase (degrees)</th>
<th>SNR</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>26</td>
<td>25.1 (79%)</td>
<td>4.4 (90%)</td>
<td>0.496</td>
<td>216.8 (202.2)</td>
<td>196.9</td>
<td>11.1</td>
<td>15.3</td>
<td>9.1</td>
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<td>3.7 (97%)</td>
<td>0.418</td>
<td>216.6 (201.2)</td>
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<td>2.8 (103%)</td>
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<td>3.2 (65%)</td>
<td>0.539</td>
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<td>4.1 (112%)</td>
<td>0.488</td>
<td>217.4 (201.0)</td>
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<td>4.2 (97%)</td>
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<td>215.8 (201.8)</td>
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<td>16.8 (55%)</td>
<td>3.3 (67%)</td>
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<td>12.9</td>
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<td>23.2 (83%)</td>
<td>5.1 (106%)</td>
<td>0.349</td>
<td>216.2 (199.0)</td>
<td>195.3</td>
<td>10.9</td>
<td>10.8</td>
<td>8.8</td>
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<td>11</td>
<td>M</td>
<td>29</td>
<td>36.2 (112%)</td>
<td>5.6 (103%)</td>
<td>0.494</td>
<td>215.5 (200.4)</td>
<td>196.3</td>
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<td>12</td>
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<td>30.5 (95%)</td>
<td>5.1 (103%)</td>
<td>0.495</td>
<td>217.4 (202.2)</td>
<td>197.1</td>
<td>10.8</td>
<td>18.8</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Mean: 32 (90.8%), 4 (92.3%)
Std Dev: 13.6 (16.1%), 0.9 (15.2%)

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Sex</th>
<th>Age</th>
<th>DLCO (mL/min/mmHg)</th>
<th>FVC (%)</th>
<th>RBC:barriers</th>
<th>RBC Barrier 1 (ppm)</th>
<th>RBC Barrier 2 (ppm)</th>
<th>Linewidth (ppm)</th>
<th>Phase (degrees)</th>
<th>SNR</th>
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<td>1.78 (42%)</td>
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<td>195.6</td>
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<td>10.2 (41%)</td>
<td>1.25 (29%)</td>
<td>0.143</td>
<td>215.4 (200.8)</td>
<td>195.4</td>
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<td>10.7</td>
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<td>215.8 (200.6)</td>
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<td>196.3</td>
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<td>17 (72%)</td>
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<td>215.7 (200.8)</td>
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<td>3.1 (62%)</td>
<td>0.344</td>
<td>215.8 (201.0)</td>
<td>195.6</td>
<td>10.8</td>
<td>10.3</td>
<td>6.9</td>
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<td>F</td>
<td>67</td>
<td>8.9 (54%)</td>
<td>1.68 (77%)</td>
<td>0.173</td>
<td>216.7 (201.2)</td>
<td>196.3</td>
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<td>M</td>
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<td>14.8 (59%)</td>
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<td>0.277</td>
<td>216.3 (201.8)</td>
<td>196.1</td>
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<td>22</td>
<td>M</td>
<td>69</td>
<td>13.6 (53%)</td>
<td>3.95 (70%)</td>
<td>0.344</td>
<td>216.2 (201.0)</td>
<td>195.9</td>
<td>11.3</td>
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<td>4.6 (61%)</td>
<td>0.221</td>
<td>213.3 (200.3)</td>
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<td>12.8</td>
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<td>2.31 (54%)</td>
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<td>216.1 (200.8)</td>
<td>195.8</td>
<td>10.5</td>
<td>11.4</td>
<td>7.4</td>
</tr>
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</table>

Mean: 69 (11.6%), 2.5 (62.8%)
Std Dev: 7.2 (13.8%), 0.9 (19.3%)

Mean: 32 (90.8%), 4 (92.3%)
Std Dev: 13.6 (16.1%), 0.9 (15.2%)

Figure 29 shows that the 3-peak RBC:barriers ratio strongly correlated with both DLco and FVC. The correlation was stronger with DLco ($r^2 = 0.84$, $P < 0.001$) than with FVC ($r^2 = 0.71$, $P < 0.001$). Both correlation plots separated the cohorts of IPF and healthy subjects, although they were further separated in the DLco correlation.
Figure 29: 3-peak RBC:barriers ratio correlated strongly with $DL_{CO}$ and FVC. Green crosses represent healthy volunteers, red circles represent subjects with IPF, and black line represents linear fit.

5.4 Inferences on Gas Exchange

5.4.1 Model-based Decomposition of Dissolved-Phase $^{129}$Xe Spectrum

To date, the in vivo $^{129}$Xe spectrum in human lungs has been reported to consist of only two dissolved-phase resonances. This is likely due, in part, because previous studies involved primarily healthy subjects, where the two barrier resonances are much broader. Thus, the presence of three dissolved-phase peaks is less evident than it is in IPF subjects where both barrier resonances become narrower, and barrier 2 shifts slightly away from barrier 1. An additional reason this third peak has likely eluded detection is because robust curve fitting methods have not generally been applied to $^{129}$Xe spectroscopy.

The most prevalent method for decomposing the dissolved-phase $^{129}$Xe spectrum has been to phase-correct the spectrum to first order and visually identify peaks. For
each resonance, its signal amplitude is estimated by integrating the peak area, its
frequency is determined by the location of the local peak maxima, and its linewidth is
approximated from the measured peak full width at half maximum. This approach,
while readily available, has several limitations. First, because the dissolved $^{129}$Xe
resonances are broad and close in frequency, it is difficult to accurately identify resonant
frequencies visually. The high degree of overlap and differences in starting phase can
obscure peaks entirely, or the tails of a nearby resonance can shift local maxima away
from their true positions. Second, when peaks overlap significantly, calculating
linewidths from FWHMs becomes impossible. Third, this overlap reduces the accuracy
of area under the curve measurements. Fourth, applying only zeroth- and first-order
phase corrections does not allow the multiple dissolved-phase peaks to be
simultaneously in-phase with the receiver, making measurements of peak integrals,
frequencies and linewidths impossible to quantify accurately.

Although recent years have seen increasingly more sophisticated approaches to
fitting $^{129}$Xe spectra (Kaushik, 2014, Norquay, 2016, Chang, 2014), the model used in this
work has three key advantages: 1) fitting is performed in the time domain; 2) it accounts
for differences in starting phase among individual peaks; and 3) it simultaneously
considers both the real and imaginary signals to minimize the complex error. By fitting
in the time domain, we minimize the error between the fitted model and the actual
acquired data. Furthermore, time domain fitting avoids artifacts that can be introduced
by additional processing steps such as zeropadding and linebroadening. Zeropadding in the time domain, particularly with long-lived signals that have not fully decayed by the end of the FID, can introduce spectral ringing as an artifact of truncating the FID. Therefore, spectral-domain fitting seeks to reduce such truncation artifacts by line broadening the signal, which apodizes the long-lived FID using an exponential decay function prior to Fourier transformation. By contrast, fitting in the time domain eliminates the need for Fourier transformation, rendering it immune to these truncation artifacts. In addition, the fitting method used here allows each peak to retain an individual starting phase. This is particularly important since acquiring dissolved-phase $^{129}$Xe spectra without contamination from the much more abundant gas-phase signal requires using long, frequency-selective pulses. This delays the start of FID acquisition, during which each peak accumulates significant additional phase. Therefore, it is essential that the fitting routine incorporate different starting phases for each resonance by fitting the absorptive and dispersive components in the real and imaginary channels simultaneously.

### 5.4.2 Fitting the $^{129}$Xe Spectrum Requires Three Dissolved-Phase Resonances

Including a third dissolved-phase peak into the spectral decomposition more accurately fit the measured signal for both subject groups. Although the magnitude of the net residual error could have been decreased further by introducing additional
spectral components, we found them to have areas on the order of the noise floor, while their other spectral characteristics varied widely across subjects. In Figure 30, the 4-peak fitted spectrum (left) illustrates that the fourth dissolved-phase peak (brown) is very small in amplitude and has linewidth that is very broad (~50 ppm). Similarly, the time domain FID (right) shows that the signal is near the amplitude of the noise floor and rapidly decays due to the broad linewidth. Though this peak does decrease the residual error, the change is very small, which suggests that this peak is actually a result of overfitting and does not represent a fourth dissolved-phase peak.

Figure 30: Decomposing four dissolved-phase peaks reveals that fourth dissolved-phase peak (brown line) can be attributed to overfitting. The fourth peak is typically small in amplitude, very broad, and varies greatly in frequency from subject to subject.
Thus, error reduction achieved by decomposing more than three dissolved-phase peaks is attributable to overfitting. In contrast, three dissolved-phase peaks were consistently necessary to eliminate the structure seen in the residual error, and all three peaks had reproducible frequencies and linewidths. This suggests that our findings are not merely a consequence of overfitting, and rather that the dissolved-phase $^{129}$Xe spectrum consists of three resonances. We can further conclude that this evidence of third dissolved-phase peak is not a consequence of averaging FIDs because we were able to decompose single FIDs into three dissolved-phase peaks with reasonable agreement between subsequent FIDs. However, we suggest averaging at least 5 FIDs to obtain sufficient SNR to reproducibly characterize all of the dissolved-phase peaks.

Decomposing the FIDs into three dissolved-phase resonances also made the spectral parameters of the RBC peak more consistent across subjects. As seen in Figure 28, without the third resonance, the RBC frequency and starting phase were highly variable among IPF subjects. Including the third peak caused both the RBC frequency and its starting phase to become stable across subjects. Moreover, it eliminated differences in RBC linewidth between IPF patients and healthy subjects. This suggests that when using only 2-peak fits, the RBC peak must absorb part of the signal from the missing barrier peak, causing its spectral parameters to become sensitive to changes in barrier signal. By introducing the third dissolved-phase resonance, the RBC peak becomes untangled from barrier 1, and its spectral parameters become stable across
subjects. While including a third peak improves the fit of the RBC peak, it also must split
the single barrier peak into two. Given that they are broad and close in frequency; this
makes them difficult to fit in healthy subjects. As a result, the spectral parameters of the
barrier peaks varied slightly more in healthy subjects using the 3-peak fit than the 2-
peak fit.

5.4.3 RBC:barriers is reduced in IPF

In aggregate, 3-peak fitting has identified six spectral parameters that exhibited
statistically significant changes between IPF and healthy subjects. This speaks to the rich
information contained in the dissolved-phase $^{129}$Xe spectrum. The most significant of
these changes was that RBC:barriers was 47.1% lower in IPF versus healthy subjects ($P <
0.001$). This reduction was less than the 65.1% difference obtained using only a 2-peak
fit. This difference is caused predominantly by 3-peak fits producing larger barrier
amplitudes in healthy subjects. Because barrier 1 and barrier 2 are nearly perfectly out of
phase, this causes the 2-peak fit to underestimate the overall barrier signal and
consequently overestimate RBC:barrier. Nonetheless, RBC:barriers strongly correlated
with DLCO ($r^2 = 0.84$, $P < 0.001$), which is similar to the correlation of 0.89 we previously
reported using 2-peak fits (Kaushik, 2014). Such strong correlations with the primary
marker of gas transfer suggests that this reduction in RBC:barriers reflects on a
combination of interstitial thickening, that restricts the diffusion of $^{129}$Xe into the RBCs, and diminished capillary blood volume, caused by regional perfusion deficits.

5.4.4 RBC frequency is decreased in IPF, while RBC linewidth remains unchanged

Further insights into the gas exchange dynamics can be gained by examining both the RBC linewidth and frequency. By using 3-peak fits, the RBC peak linewidth remained consistent between IPF and healthy subjects at ~11.5 ppm. This stands in contrast to the apparent narrowing that had previously been reported in IPF when using the 2-peak fit (Kaushik, 2014). This suggests that RBCs experience essentially the same physical environment in the capillary beds of healthy and IPF subjects. However, the in vivo RBC line width we measure here is still broader than the 8.6 ppm linewidth reported for $^{129}$Xe in RBCs in vitro (Wolber, 2000a). This broadening likely arises from the inhomogeneous lung environment.

Similarly, the 3-peak fits reduced the magnitude of the apparent RBC frequency shift in patients with IPF. We did observe a 0.7 ppm negative shift for the RBC peak in IPF, but this was much smaller than reported in our initial studies, which used 2-peak fits to report a shift of ~2.4 ppm in subjects with IPF (Kaushik, 2014). In fact, applying the same 2-peak fits to the present study, we measured a similar, albeit more pronounced ~3.15 ppm negative shift of the RBC peak in IPF subjects. Thus, it now appears that this larger apparent RBC shift in the 2-peak fits was primarily a
consequence of incompletely decomposing the spectrum. We now understand from our 3-peak fit that the barrier consists of 2 resonances, which in IPF, are both more intense and narrower. Therefore, when the dissolved-phase spectrum was fit to only 2-peaks, a portion of the missing barrier peak was allocated to the RBC resonance. This caused the least squares fitting solution to miscalculate both the frequency, linewidth, and phase of the RBC resonance.

The RBC frequency shift is of particular importance in light of in vitro work demonstrating that this resonance can shift by as much as 5.5 ppm, depending on blood oxygenation (Wolber, 2002). Thus, the relatively modest negative shift of 0.7 ppm for the RBC resonance we now report, suggests that capillary blood in IPF patients is not as poorly oxygenated as previously thought. While we must acknowledge that there may still be local regions where blood is poorly oxygenated, our whole-lung spectroscopic measure of blood oxygenation indicates that even in IPF, the RBCs are on average still well-oxygenated. Nonetheless, temporal changes in oxygenation should be observable in $^{129}$Xe spectra acquired during prolonged breath-hold. This was demonstrated in healthy volunteers by Norquay et al., where a decrease of up to 1 ppm in RBC frequency was detected over the course of a 35-second breath-hold (Norquay, 2016).
5.4.5 Possible Origins of the Two Barrier Peaks

While the physical origin of the two barrier peaks remains to be confirmed, this work provides important clues to their sources. The acquisition methods used here were designed to minimize downstream magnetization such that the measured signal, and its constituent resonances, must spatially originate near the lung’s gas exchange regions. We can also deduce how the barrier peaks interact physiologically by noting that, unlike the RBCs, the linewidths of the barrier resonances became significantly narrower in IPF. This narrowing could be caused by diminished chemical exchange between these compartments or decreased susceptibility-driven distortions of the local magnetic field. Diminished chemical exchange could be the result of the two barrier compartments becoming physically larger and more spatially separated in IPF. Alternatively, spectral narrowing could be caused by the reduced surface area and geometric changes of the air-tissue interfaces as barrier tissues occupy an increasingly larger fraction of the lungs in IPF subjects. This possibility is bolstered by changes in the starting phases of barrier 1 and barrier 2 during the sub-millisecond delay between excitation and readout. First, the two barrier resonances were ~100 degrees out of phase with one another. This phase dispersion cannot be explained by chemical shifts alone because the two peaks are separated by only 83 Hz (4.7 ppm). Instead, we hypothesize that the phase differences between these two components arise during the long duration of RF excitation in the presence of the inhomogeneous magnetic field environment of the lung. Second, the
starting phase of barrier 1 was 20.2 degrees higher in IPF subjects versus healthy subjects (P = 0.01). This leads us to suspect that barrier 1 may originate from areas closest to the lung’s air-tissue interfaces, where susceptibility differences are greatest. This premise is further reinforced by the linewidth of barrier 1 being broader than that of barrier 2. Therefore, we hypothesize that the barrier 1 peak represents tissue residing close to the alveolar wall and its associated large susceptibility gradient caused by neighboring airspaces. Barrier 2 is substantially narrower, with a linewidth in IPF patients that is nearly identical to the 7.2 ppm in vitro linewidth measured in plasma (Wolber, 2000a). Moreover, it also has a chemical shift near that of $^{129}$Xe in water (196 ppm) (Miller, 1981). For these reasons, we postulate that barrier 2 arises from both plasma and aqueous inflammatory processes residing in the interstitial space.

5.5 Study Limitations

In this work, we administered a fixed gas volume for all subjects, regardless of individual lung volumes. Ideally, each subject would have inhaled a gas volume equal to a known proportion of their TLC, in order to control for lung inflation effects. However, breath-coaching subjects to an exact lung inflation level is challenging without resorting to more invasive means such as mechanical ventilation. Moreover, recent work by Qing et al. found that the effects of lung inflation are most severe at residual volume, most strongly affect the dissolved:gas ratios, and do not affect measures of alveolar
septal thickness (Qing, 2014b). Because our interest here is in the dissolved-phase compartments, and since our spectra were acquired at ~60% of TLC for healthy volunteers and ~80% for subjects with IPF, we expect inflation effects to affect our results only modestly.

Given the difficulty of normalizing dissolved-phase spectra to the gas-phase signal, we instead chose to normalize our spectral intensities to the sum of both barrier signals. Our findings clearly indicate that RBC:barriers is reduced in IPF; however, they are not able to reliably inform on whether RBC signal is diminished or the barrier signals are increased. If gas-phase signal could be acquired such that it originates only from the gas exchange regions, this would serve as a better quantitative reference, since it represents the source magnetization for RBC and barrier peaks (Kaushik, 2014, Qing, 2014b). To this end, future studies should strive to spatially constrain the gas-phase signal either by selective excitation or perhaps by applying diffusion weighting to preserve $^{129}$Xe signal from the alveoli, while suppressing signal from large airways. Alternatively, we can exploit the spatial information afforded by imaging to only calculate these ratios within the gas exchange regions on a voxel-by-voxel basis.

And finally, our healthy and IPF populations had significant differences in mean age. Thus our findings must be attributed to a combination of age and disease effects. It would be useful in the future to acquire additional data from a cohort of healthy volunteers that are age-matched to the IPF subjects. This would enable us to compare
both the age effects between the two healthy cohorts, as well as the effects of disease between the IPF subjects and age-matched controls.

5.6 Summary

In this chapter, we illustrated the advantages of using complex time-domain fitting to decompose $^{129}$Xe FIDs acquired in the human lung. By employing these sensitive techniques, we uncovered a third dissolved-phase resonance, which aids in characterizing the spectral differences between healthy subjects and subjects with IPF. We confirm that the RBC:barriers ratio continues to be significantly reduced in subjects with IPF compared to healthy subjects. However, we reconsider the magnitude of our previously reported negative frequency shifts in the RBC resonance among subjects with IPF. We now suggest that the magnitude of these shifts was previously overestimated as a result of decomposing a 3-peak spectrum using only 2 peaks. This small change in global oxygenation, combined with no detectible change in RBC chemical exchange indicates that the diffusional limitation imposed by IPF at rest may not be as significant as previously thought, and perhaps many of the spectroscopic changes observed are rather a consequence of fibrotic and healthy tissues being heterogeneously distributed throughout the lung in IPF.
6 Quantitative Analysis Methods for Hyperpolarized $^{129}$Xe Gas Transfer MRI

As shown in chapter 5, the distinct dissolved-phase resonances in the pulmonary tissue and blood enable spectroscopic techniques to probe the transfer of xenon into these functional compartments. While spectroscopic measurements are exquisitely sensitive, they only consider the lung as a whole. This chapter moves beyond these global metrics of gas transfer and develops phase-sensitive imaging techniques that enhance sensitivity to regional disease. The methods and results presented in this chapter are adapted from the following peer-reviewed journal article:

1. Z. Wang, S. H. Robertson et al. ‘Quantitative Analysis of Hyperpolarized $^{129}$Xe Gas Transfer MRI’, Medical Physics, (submitted)


6.1 Motivation

While it has long been understood that the chemical shifts of $^{129}$Xe hold great potential for new functional imaging contrast in the lung, imaging dissolved-phase $^{129}$Xe signal has only recently become possible. That is because only ~2% of the $^{129}$Xe resides in the dissolved-phase at any given instant and dephases rapidly ($T_2^* \approx 2$ ms) (Qing, 2013).
This small and rapidly decaying signal was first imaged at low resolution by CSI techniques that encode a single k-space position at a time in order to minimize T2* decay (Swanson, 1999). Soon after, indirect techniques that probe the spatial distribution of dissolved-phase $^{129}$Xe were introduced to increase the spatial resolution (Ruppert, 2000). However, these indirect techniques were very sensitive to both RF and gas-phase T1 decay, and were unable to discriminate the RBC and barrier resonances. Conveniently, the dissolved-phase signal, while small in instantaneous intensity, is continually replenished from the alveolar airspaces. Thus, so long as the TR allows sufficient replenishment and a frequency RF selective pulse is used to preferentially excite the dissolved-phase magnetization and spare the gas-phase magnetization, large flip angles can be employed to image the dissolved-phase directly. When paired with the short TE and robustness to undersampling that radial imaging affords, this technique enabled isotropic dissolved-phase imaging in vivo (Cleveland, 2010).

These dissolved-phase images represent the collective signal from multiple compartments within the lung. Each of these compartments can, in principle, be decomposed using phase sensitive imaging techniques. Qing et al., first demonstrated such decomposition by employing the hierarchical iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) method (Reeder, 2005) to enable separate imaging of $^{129}$Xe transfer from airspaces to the barrier and RBC compartments in a single breath (Qing, 2014c). This approach showed that patterns of
gas transfer in smokers and patients with asthma differed from those in healthy volunteers (Qing, 2014a). Following this, our own group employed interleaved 3D radial imaging of gas and dissolved-phase $^{129}$Xe and the simple 1-point Dixon method to separate the gas-phase and dissolved-phase resonances to create single-breath isotropic images of $^{129}$Xe in the airspaces, barrier, and RBCs (Kaushik, 2016b). Relative to the IDEAL method, this approach uses a single, sub-millisecond TE, which helps to mitigate the effects of short $^{129}$Xe $T_2^*$ in the dissolved phase (1.5-2.4 ms at 1.5 T). This work revealed that patients with idiopathic pulmonary fibrosis (IPF) had severely diminished RBC uptake in regions of fibrosis seen on CT.

While these early images of gas transfer impairment represent an important technical advancement, methods to quantify and interpret such acquisitions are still in their infancy. To date, the most powerful marker of gas exchange impairment appears to be the RBC:barrier ratio (Kaushik, 2014, Kaushik, 2016b). However, while low RBC:barrier is indicative of decreased gas transfer, it cannot identify whether this is caused by decreased RBC uptake, increased barrier uptake, or a combination of both. The separate assessment of these effects requires first accounting for changes in regional ventilation, which provides the source magnetization for the dissolved compartments. Thus, using this airspace signal to divide the RBC and barrier images on a voxel-by-voxel basis enables the transfer efficiency to each compartment to be measured (Qing, 2014a). But, given the relatively low SNR of dissolved-phase images, and the insufficient
ventilation of some regions to permit analysis, careful masking is required prior to Dixon decomposition and division. Moreover, it is also desirable to quantify the ventilation distribution itself (He, 2014). Combining these strategies enables quantitative mapping of the $^{129}$Xe distribution in all three compartments from a single acquisition.

Once the RBC and barrier maps have been decomposed and then normalized by the gas-phase signal, the resulting maps, which suffer from low SNR, are generally not well represented by a simple continuous color map. Instead, we propose compressing the dynamic range of these maps to highlight both defects and hyper-intense regions, by classifying the data into a limited set of bins. Such binning is rooted in semi-automated segmentation methods that were initially developed to analyze $^3$He ventilation MRI. Kirby et al. introduced methods for semi-automatic segmentation using $^1$H MRI of the thoracic cavity (Kirby, 2012a). More recently, Zha et al. have used K-means clustering to quantify $^3$He MRI intensities into four or five bins (Zha, 2016). Alternatively, our group has introduced a relatively straight-forward linear binning algorithm using thresholds derived from a healthy reference population (He, 2016).

In this chapter we apply a similar linear binning approach to depict quantitative maps of $^{129}$Xe in airspaces and its uptake in barrier and RBC compartments. We carefully chose binning thresholds that appropriately characterize the airspace, barrier:gas, and RBC:gas distributions. These thresholds were derived from the distribution of a reference population of healthy volunteers. We then demonstrate the sensitivity of this
method for detecting both defects and enhancements of barrier and RBC transfer in a population of patients with IPF. Since this patient population exhibits known gas exchange impairment, it is particularly appropriate to evaluate the proposed image analysis method.

6.2 Materials and Methods

6.2.1 Subject Recruitment

This study was conducted under protocols approved by the Duke University Institutional Review Board. Prior to participating, all subjects provided written informed consent. A total of 13 healthy subjects (ages = 43 ± 22 years) and 12 IPF subjects (ages = 66 ± 15 years) were enrolled. All subjects were at least 18 years-old and had no cardiac arrhythmias. Healthy controls had no history of smoking and had never been diagnosed with any pulmonary disorders. IPF subjects were diagnosed and confirmed by CT or biopsy, according to American Thoracic Society guidelines (Raghu, 2011). Subjects were excluded if they had a respiratory illness within 30 days of MRI, or if they were pregnant or lactating.

6.2.2 \(^{129}\text{Xe}\) Polarization and Delivery

For this study, each subject inhaled two \(^{129}\text{Xe}\) doses: a 26 mL dose equivalent (DE) for spectroscopic calibration and a 103 mL DE to obtain an image of \(^{129}\text{Xe}\)
distribution in both the gas- and dissolved-phases (He, 2015). Each dose was prepared as described in Section 2.2.3. Immediately preceding delivery to the subject, the polarization of each dose was measured by a polarimeter (Model 2881, Polarean, Inc.) and recorded. Subjects were first instructed to inhale to total lung capacity (TLC) and exhale to functional residual capacity (FRC) twice. They then inhaled the full 1L-dose and held their breath for the 13–15-second scan. Throughout the study, an MR-compatible monitoring system (Expression Model 865214, Invivo Corporation, Orlando, FL) was used to monitor the heart rate and oxygen saturation.

6.2.3 Calibration Spectra and Image Acquisition

All spectroscopy and MRI scans were performed on a 1.5T GE Healthcare 15M4 EXCITE MRI scanner. Subjects were fitted with a quadrature $^{129}$Xe vest coil (Clinical MR Solutions, Brookfield, WI), which was proton-blocked to enable $^1$H MRI using the body coil without repositioning the subject. The first $^{129}$Xe dose was used as a spectroscopic calibration that determined the echo time (TE) at which the RBC and barrier resonances are 90° out of phase (TE$_{90}$). This calibration scan consisted of 50 FIDs, acquired using a 1.2 ms 3-lobe sinc pulse (~22° flip), 8-kHz bandwidth (BW), TE/TR = 0.875/50 ms, 512 samples. Subsequently, the second $^{129}$Xe dose was used to image the regional distribution of both the gas- and dissolved-phases. By alternating between $^{129}$Xe gas and dissolved views in an interleaved 3D radial sequence, the gas- and dissolved-phase
images were acquired nearly simultaneously. The imaging parameters were consistent between the gas and dissolved excitations: radial views: 1001/1001, 64 samples per radial ray, BW = 15.625-kHz, 1200-µsec 3-lobe sinc pulse, TE/TR = TE/7.5ms, and FOV = 40 cm. The only difference was that a large flip angle (~22°) was employed for the dissolved-phase views, whereas a smaller 0.5° flip angle was applied during the gas-phase views to preserve magnetization.

After the interleaved $^{129}$Xe scan, an additional $^1$H breath-hold 3D radial scan was acquired to delineate the thoracic cavity and provide structural context to the functional $^{129}$Xe images. This $^1$H image was volume-matched to the $^{129}$Xe scan by having subjects inhale 1L of room air from FRC. The $^1$H imaging parameters were: flip-angle = 5° (132µs hard pulse), TR/TE = 2.4/0.199ms, FOV = 40 cm, matrix = 64³, and BW = 15.625 kHz.

6.2.4 Quantitative Analysis Methods

Our entire quantitative analysis method is diagramed in Figure 31. Each step in this process is detailed in the following subsections.
Figure 31: Diagram of image reconstruction and quantitative analysis workflow.

6.2.4.1 Image Reconstruction Methods

All the radially acquired $^{129}$Xe datasets were reconstructed using non-Cartesian gridding methods described in chapter 4 (Robertson, 2015). For the gas transfer analysis, the $^{129}$Xe gas and dissolved imaging data were separately reconstructed with identical reconstruction parameters so that the intensity scaling from gridding was consistent in both images. Reconstruction parameters were selected that provided sufficient SNR in the dissolved-phase image to permit it to be further decomposed into RBC and barrier images. The following reconstruction parameters were used: 3x over-gridding, matrix size = 64$^3$, a Gaussian interpolation kernel with $\sigma = 0.14$ and a kernel extent of $9\sigma = 1.26$ pre-over-gridded k-space voxels, and 25 iterations of calculating sample densities for
density compensation (Pipe, 2000). Using this sharp kernel sacrificed minimal image resolution in order to preserve the SNR of the $^{129}$Xe dissolved-phase image (Robertson, 2015).

The $^{129}$Xe gas-phase images, which have inherently higher SNR than the dissolved-phase images, were additionally reconstructed with a broader gridding kernel ($\sigma = 0.32$ and a kernel extent of $9\sigma = 2.88$) to achieve higher resolution with only a minor loss in SNR. This higher resolution reconstruction was used for quantitative ventilation mapping, described below.

The $^1$H thoracic cavity data was reconstructed onto a 64$^3$ matrix with 3x over-gridding, a Gaussian kernel with $\sigma = 0.3$ and extent $= 9\sigma = 2.7$ pre-over-gridded k-space voxels, and 25 iterations of calculating sampling densities.

### 6.2.4.2 Methods to Delineate Regions for Analysis

To constrain the ventilation analysis to the lungs, the breath-hold $^1$H image was first segmented to generate a thoracic cavity mask. In healthy subjects, this was readily achieved by semi-automatic segmentation as done previously (Kaushik, 2016b). However, in IPF patients, such segmentation was confounded by the presence of fibrosis. Therefore, in these patients a $^1$H lung template was constructed from the $^1$H images of 10 IPF subjects using Advanced Normalization Tools (ANTS) (Avants, 2010). This template was then registered to the shape of each individual patient’s $^1$H scan and
then segmented to generate the individual’s lung mask. For both healthy and IPF cohorts, this lung mask was further refined to better delineate sharp edges near the diaphragm using an active contour model (Ray, 2003, Osareh, 2010, Middleton, 2004). The \(^1\)H MRI-derived thoracic cavity masks were then registered to the high-resolution \(^{129}\)Xe gas image by an affine transformation.

The gas transfer analysis required further spatial constrains, beyond just the thoracic cavity, because our methods that normalize the RBC and barrier volumes by the gas-phase signal only give meaningful results within the ventilated regions of the lung. To this end, pixels where the ventilation signal was two standard deviations lower than the mean were removed from the gas transfer mask (Pukelsheim, 1994). We note that gas transfer could still occur in these regions on a longer timescale, however we did not investigate such dynamics in this work.

### 6.2.4.3 Method to Decompose RBC and Barrier Images

The \(^{129}\)Xe dissolved-phase image was decomposed into separate RBC and barrier images by the Dixon method (Dixon, 1984). Employing this method requires acquiring the \(^{129}\)Xe dissolved image at an echo time such that the RBC and barrier signals are 90° out of phase. By imaging at this condition, termed the TE90, a simple phase shift can be applied to the image to isolate RBC and barrier signals to the real and imaginary image channels. However, this phase shift is randomly imparted by the scanner, and thus is
not known a priori. Instead, this phase shift was empirically found by solving for the phase shift that, when applied to the masked gas transfer region, gave an imaging-derived RBC:barrier ratio that matched the same ratio measured from global spectroscopy. Once the proper phase shift was found and applied, a phase map derived from the single-resonance $^{129}$Xe gas-phase image was used to further correct the complex image for $B_0$ inhomogeneity. These $B_0$-corrected images occasionally resulted in voxels that had small negative signals. Since negative RBC or negative barrier signals do not make any physical sense, a positivity constraint was applied to both the RBC and barrier images to correct the few voxels that exhibited residual negative signals.

6.2.4.4 Methods to Normalize Images for Quantitative Analysis

Since the RBC, barrier, and ventilation images were all collected at a TE of $90^\circ$ that was calculated for each individual subject, the images differ in the amount of time that $T_2^*$ decay can occur. Since the $T_2^*$ of these dissolved-phase compartments is rapid, we must correct these effects prior to comparing images across subjects. To this end, the RBC and barrier images were corrected to $t = 0$ using $T_2^* = 2$ ms (Qing, 2014c), while the gas-phase was corrected to $t = 0$ using $T_2^* = 50$ ms (Xu, 2012). Additionally, differences in the flip angles employed for dissolved and gas-phase imaging cause the $^{129}$Xe gas-phase image intensities to be artificially increased by $\sin (22^\circ) / \sin (0.5^\circ) = 43$. Therefore, we reduced the gas-phase image intensity by a factor of 43 to account for these flip angle
effects. Finally, the T2*-corrected RBC and barrier images were divided by the T2*- and flip angle-corrected $^{129}$Xe gas image to create RBC:gas and Barrier:gas maps to eliminate the effects of differences in polarization or inhaled $^{129}$Xe volume across subjects.

We need to similarly normalize the high resolution gas-phase image for differences in polarization and $^{129}$Xe volume. To do so, we adopted an approach that is akin to the Hounsfield units in CT, which uses the attenuation of water as a reference. Here we use the signal of bulk $^{129}$Xe in the large airways as our reference. This bulk gas signal is estimated as the top percentile of the $^{129}$Xe intensity histogram. This approach was used by our group previously to normalize GRE images for binning analysis, and was found to be effective at accounting for intensity differences across multiple scans and subjects (He, 2014).

6.2.4.5 Methods to Generate Binning Maps

To facilitate visualization and quantitative analysis, the normalized $^{129}$Xe gas, RBC:gas and barrier:gas images were displayed after undergoing linear binning. The normalized $^{129}$Xe gas image and RBC:gas images were mapped into 6 bins, and the barrier:gas image was mapped into 8 bins. Each bin had a width equal to the standard deviation of the collective distribution derived from the healthy young reference population. This consisted of 10 of the 13 healthy subjects who exhibited no visually
apparent ventilation defects. Each bin was assigned a color that provided noticeable contrast and transitioned smoothly between adjacent bins.

6.2.4.6 Quantitative Analysis Methods

For each subject, ventilation maps were quantified according to the fraction of voxels falling into three regions of the intensity histogram: the lowest bin or ventilation defect region (VDR); the second lowest bin, or low ventilation region (LVR); and the highest two bins, or high ventilation region (HVR) (He, 2014). For barrier:gas, we report the fraction in the lowest two bins (Barrier\text{Low}), as well as the fraction falling in the highest 3 bins (Barrier\text{High}). For RBC:gas maps, we also report the fraction of voxels falling in the lowest two bins (RBC\text{Low}) and the highest bin (RBC\text{High}). The percentage of voxels in each bin was compared between the IPF and healthy cohorts using a two-sided student’s t-test. A significance level of 5% (P<0.05) was used for all comparisons.

6.3 Results

6.3.1 Template Lung Enables the Thoracic Cavity to be Segmented in IPF Patients

Figure 32a shows that the thoracic cavity of a representative healthy volunteer was readily amenable to automatic segmentation, owing to the distinctive air/tissue contrast that is inherent to the lungs. However, the IPF patient shown in Figure 32b,
exhibits regions of high signal intensity fibrotic tissue that caused the segmentation to erroneously exclude regions in the peripheral and basal lung. However, employing the template IPF lung and registering it to this patient’s thoracic cavity (Figure 32c) effectively averaged out the fibrotic regions and thus restored the lung/tissue contrast that is required for robust segmentation. The IPF template maintains the individual’s lung shape, excludes major vasculature, and includes regions of fibrosis in the lung mask.

Figure 32: Thoracic cavity images of (a) a healthy subject could be natively segmented, but (b) an IPF subject failed to be accurately segmented until (c) an averaged template was registered to the subject and segmented instead.
6.3.2 Healthy Reference Population Provides Meaningful Context to Bin Thresholds

Figure 33 illustrates that the distributions of ventilation, RBC:gas and barrier:gas from the collective reference population of 10 healthy subjects (n=10, age 29 ± 8 years) were all nearly Gaussian. Consequently, their mean and standard deviations were used to define the thresholds of intensity bins used to display the binning maps. For consistency, we maintained the same color-coding for ventilation and RBC maps as previously introduced (He, 2014): red for defects, orange for low intensity, greens for the two bins nearest to the mean of the reference population, and blues for higher intensities. For the barrier maps, we maintained the first 4 colors bins from the ventilation and RBC bins. However, to allow for visualization of the high barrier signal anticipated in IPF patients, the highest bins were assigned pink and purple colors.
Figure 33: Aggregate gas, barrier:gas and RBC:gas reference distributions derived from the reference population of 10 healthy subjects are nearly Gaussian. The color bins and quantitative metrics area all defined according to the mean and standard deviation of each reference distribution.

6.3.3 Quantitative Mapping in Healthy Control

Figure 34 shows the ventilation, RBC:gas and barrier:gas maps, along with their associated histograms, for a representative healthy subject. The maps are displayed in
both the coronal and axial planes to emphasize that these image volumes are isotropic.

The ventilation map (top) exhibits a largely homogeneous distribution in both planes, with a few regions of low intensity at the lung periphery. Similarly, the barrier distribution (middle) is largely homogeneous, with a subtle anterior-posterior (AP) gradient, evident in the axial plane. The RBC:gas distribution (bottom), is also reasonably homogenous, again with a subtle AP gradient visible in the axial plane.

To the right of each map, are its corresponding intensity histogram. For comparison, we also include the Gaussian fit of the aggregate healthy reference distribution (dashed line). This healthy subject exhibits a ventilation distribution (top) that is similar to the reference distribution, with a low VDR (<1%) and modest LVR (17%). Similarly, both barrier and RBC maps appear Gaussian, with a mean near that of the healthy reference distribution. The barrier map exhibited few voxels in either the low (3%) or high (<1%) bins. For the RBC distribution, 13% of voxels fell into the low intensity region; however, these were found primarily in the anterior, gravitationally non-dependent lung. On the RBC map, 2% of voxels exhibited a high intensity, and were found in the gravitationally dependent lung.
6.3.4 Quantitative Mapping in IPF

Figure 35 shows ratio maps of a representative IPF patient using the same format to illustrate its striking contrast to the healthy control. Only the ventilation map is similar to that of the healthy subject – being relatively homogeneous, with minimal
defects (VDR = 3%), and modest LVR (21 %). This is also reflected in the ventilation histogram, which is similar to the reference distribution. However, the barrier:gas maps exhibit dramatically increased $^{129}$Xe uptake, with most voxels falling in the three highest intensity bins. Furthermore, this increased uptake is heterogeneously distributed, and is more predominant in the lung periphery. This is also reflected in the barrier:gas histogram, which is Gaussian in shape, but is greatly shifted towards higher ratios. Nearly all the voxels fell into the high intensity tail of the reference distribution (Barrier$_{\text{High}}$ = 98%). Similarly, the RBC:gas maps exhibited heterogeneous uptake, with defects that predominated in the peripheral and basal lung. Unlike the example healthy subject, this IPF subject’s RBC distribution did not exhibit a detectable A-P gradient. Moreover, the distribution of RBC:gas intensities was non-Gaussian and skewed toward lower ratios, with a large percentage of voxels falling in the low intensity tail (RBC$_{\text{Low}}$ = 52%).
Figure 35: Representative ventilation, barrier:gas, and RBC:gas binning maps and histograms derived from an example IPF patient.

6.3.5 Quantitative Histogram Analysis in IPF Versus Controls

Figure 36 compares the distribution of binned intensities for ventilation, barrier:gas, and RBC:gas volumes between the healthy and IPF cohorts. Ventilation in healthy subjects had a somewhat higher mean of $0.51 \pm 0.19$, versus $0.43 \pm 0.19$ in IPF.
Analyzing the distribution along the intensity bins shows that all but bin 3 contained significantly different fractions of pixels in IPF patients versus healthy subjects.

The difference between healthy and IPF subjects was most dramatic in the barrier:gas distribution. In healthy controls, the barrier:gas intensities were normally distributed such that the low and high intensity bins were fairly symmetrically populated, with the bulk of voxels falling into bins 3 and 4. However, in IPF subjects, the barrier uptake distribution was heavily skewed towards higher intensities, resulting in a broader range and a mean ($9.1 \times 10^{-3}$) that was nearly double that of normal subjects. In IPF patients, all but the lowest 8 bins were significantly different across these cohorts. In IPF subjects, less than 1% of voxels fell in $\text{Barrier}_{\text{low}}$, compared to 14% in healthy controls ($P = 0.006$). By contrast, the fraction of voxels in the three highest intensity bins ($\text{Barrier}_{\text{high}} = 69\%$) was nearly 9-times higher in IPF than in healthy subjects ($\text{Barrier}_{\text{high}} = 8\%$, $P < 0.001$).

The RBC:gas histogram also differs between healthy and IPF patients, but to a lesser extent than the barrier:gas distribution. In IPF patients, the RBC:gas histogram is skewed toward lower ratios, resulting in a mean value ($1.9 \pm 1.2 \times 10^{-3}$) that was roughly 70% that of healthy subjects. This was also evident in the two lowest bins, which had significantly higher percentages of voxels in IPF than healthy subjects. $\text{RBC}_{\text{low}}$ was 41% in IPF patients, representing a 2.7-fold greater fraction of the lung than the 15% seen in
healthy controls (P < 0.001). However, both cohorts exhibited small, but similar fractions of voxels in RBC\text{High}.

Figure 36: Quantitative comparison of binning populations for $^{129}$Xe ventilation barrier:gas, and RBC:gas distributions between healthy subjects and IPF patients.
6.3.6 Gas Transfer Maps in Emphysema and in Pulmonary Arterial Hypertension

Although the majority of the work presented here has shown enhanced barrier and decreased RBC transfer in IPF, it is helpful to also illustrate the ability of the method to detect gas transfer impairments caused by other conditions. One such example is shown in Figure 37, depicting a patient with CT-confirmed emphysema that was caused by alpha1-antitrypsin deficiency. In this case, the $^{129}$Xe gas-phase image reveals substantial ventilation defects (VDR = 23%), and low ventilation (LVR = 30%). In the VDR, $^{129}$Xe gas transfer cannot be further evaluated. However, in the remaining lung, gas transfer to barrier tissues is significantly reduced compared the healthy cohort (Barrier$_{Low}$ = 87%), while virtually no pixels exhibit high barrier uptake (Barrier$_{High}$ < 1%). Many of the regions of low barrier transfer also exhibit low RBC transfer (RBC$_{Low}$ = 34%). Transfer to RBCs is significantly decreased in the anterior and apical lung.
Figure 37: Representative ventilation, Barrier:gas, and RBC:gas binning maps and histograms derived from a patient with alpha1-antitrypsin deficient emphysema.

A second example (Figure 38) applies this same method to a patient with pulmonary arterial hypertension (PAH), on whom we had previously reported (Dahhan, 2016). This patient exhibits few defects (VDR = 2%), and slightly elevated LVR of 27%, as well as mildly enhanced barrier uptake (BarrierHigh = 33%). However, RBC transfer is
significantly diminished ($\text{RBC}_{\text{Low}} = 77\%$, $\text{RBC}_{\text{High}} < 1\%$), with significant defects evident in the right lung.

Figure 38: Representative ventilation, Barrier:gas, and RBC:gas binning maps and histograms derived from a patient with pulmonary arterial hypertension.
6.4 Inferences on Quantitative Gas Transfer Imaging

The methods outlined here provide an effective means to transform simultaneously acquired images of $^{129}$Xe in airspace, barrier, and RBC compartments into quantitative functional maps. However, generating such quantitative maps required careful attention to appropriately mask and correct the intensities of each dataset such that subjects could be compared meaningfully.

6.4.1 Template Robustly Segments IPF Lungs Despite Fibrosis

Both our quantitative binning analysis and Dixon decomposition rely on accurate masks to be generated from the $^1$H thoracic cavity image (He, 2016, He, 2014, Kaushik, 2016b). Such segmentation is uniquely challenging in patients with IPF, because fibrosis is heterogeneously distributed, so these patients often exhibit significant $^1$H signal throughout (Biederer, 2012). This problem was effectively overcome by generating a $^1$H MRI template from the images of 10 IPF patients. In this way, the heterogeneity of fibrosis was averaged out across the cohort to restore the necessary lung/tissue contrast required for segmentation. The template was constructed from IPF patients rather than healthy volunteers, given their significantly different lung morphology. For this study, 10 subjects were sufficient to adequately represent the heterogeneity of lung shape and fibrosis distributions encountered.
6.4.2 Quantitative Ventilation Mapping

In this study, the mean and standard deviation of the normalized ventilation histogram of our healthy reference population derived from 3D radial imaging (0.51 ± 0.19), was quite similar to what we recently reported with multi-slice GRE acquisitions (0.51 ± 0.18) (He, 2016). The reference distribution found here is slightly broader, which is likely attributable to using a fully 3-D sequence that more faithfully captures the gravitational ventilation gradient (He, 2015). Using this reference distribution to define binning thresholds permitted the ventilation distribution to be analyzed in patients with IPF. Although ventilation defects are a hallmark of obstructive lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (He, 2014, Mugler, 2010, Thomen, 2016, Samee, 2003, Altes, 2001), we find they are not a major feature in IPF. Nonetheless, the capability to generate such quantitative ventilation maps in the same breath as the gas exchange maps should provide complementary information across a range of diseases. This is illustrated in the subject with emphysema, who exhibited significant ventilation defects, as well as the patient with PAH, where ventilation was relatively normal. Thus, when used to evaluate the causes of dyspnea, this ability to quantify both ventilation and gas transfer from a single scan has clear value.
6.4.3 Gas-normalized Regional Maps Quantify RBC and Barrier Transfer

The gas normalization techniques used here enable the RBC and barrier transfer to not just be intuitively visualized, but to be placed on a quantitative footing. That is because dividing the RBC and barrier signals by the concurrently acquired $^{129}$Xe gas signal on a voxel-by-voxel basis provides a direct and normalized measure of gas transfer to each compartment. But doing so, requires first correcting the source images for differences in flip angles used for the gas- and dissolved-phase excitation, as well as for the effects of T2* at the TE used (Qing, 2014a). Given the short T2* of dissolved-phase $^{129}$Xe, this correction has a particularly large effect, and in our study eliminated intensity variations of order ~35%.

6.4.4 Healthy Reference Population Values for Barrier and RBC Transfer

Establishing appropriate thresholds for barrier and RBC maps requires first characterizing these distributions in a healthy reference population (He, 2016). From this reference group, this analysis returned mean values of barrier:gas = 0.49 ± 0.15% and RBC:gas = 0.26 ± 0.10%. Dividing these measures results in RBC:barrier = 0.53 ± 0.18, which agrees well with our previously published spectroscopically-derived ratio of 0.55 ± 0.13 (Kaushik, 2014). Interestingly, while RBC:gas is similar to that found by Qing (RBC:gas = 0.34 ± 0.05%) (Qing, 2014a), our value of barrier:gas is roughly a factor of 2.4
smaller than reported by Qing (barrier:gas = 1.19 ± 0.14%). While some of this discrepancy could be attributable to lung inflation differences (Qing, 2014b, Theilmann, 2009) and acquisition parameters, the difference in barrier values is perplexing, given that the TR and flip angle were relatively similar between the two studies. While future efforts are needed to reconcile such differences between sites, we were able to use our distributions as a robust reference framework for generating binning maps of barrier and RBC uptake.

6.4.5 Barrier Transfer is Enhanced in IPF

Arguably, the most striking feature found in these functional gas transfer maps is the enhancement of barrier uptake in patients with IPF. The mean barrier uptake was nearly 2× higher, and the number of voxels falling in the bins that contribute to \( \text{Barrier}_{\text{High}} \) was nearly 9-fold higher in the IPF cohort than healthy controls. Although the barrier signal was enhanced throughout the lung of IPF patients, many patients exhibited even higher uptake in the lung periphery. This observation is consistent with the histologic and radiographic evidence of fibrosis seen in IPF, which is also peripheral (Raghu, 2011). Given the large flip angle and short TR used in these acquisitions, \(^{129}\text{Xe} \) signal is largely confined to the gas exchange region of the lung. Thus, the enhancement in barrier signal can be interpreted as increased interstitial thickening at the level of the...
alveolar septa (Patz, 2011). Together, the observations speak to the potential of barrier uptake to serve as a marker of therapy response in IPF (Baroke, 2013).

6.4.6 RBC Transfer is Impaired in IPF

The mapping techniques described here suggest that in healthy volunteers, RBC transfer is largely homogeneous, as previously reported by Qing (Qing, 2014a). Healthy subjects tend to exhibit a modest anterior-posterior gradient, consistent with increased perfusion and capillary blood volume in the gravitationally dependent lung (West, 1972, Brudin, 1987, Hopkins, 2007). Similarly, when low RBC transfer is observed in healthy volunteers, it is typically confined to the anterior lung, and rarely if ever in the gravitationally dependent lung. By contrast, IPF patients, exhibit reduced RBC transfer and focal defects, primarily in the basal and peripheral lung. This is noteworthy given that it is in these regions where fibrosis is commonly detected on CT (Raghu, 2011). Given the spatial correspondence between RBC transfer defects and locations of fibrosis seen on structural imaging, these defects may serve as a marker of diminished perfusion (Kaushik, 2014) and may correspond to non-recoverable areas of disease.

6.4.7 Interpreting Combined RBC and Barrier Maps

The observation that barrier signal is often enhanced throughout the lung, while RBC transfer is diminished more focally, suggests that previous observations of globally
diminished RBC:barrier in IPF (Kaushik, 2016b) is primarily attributable to increased barrier thickness. Remarkably, in many other areas, significantly enhanced barrier signal co-exists with normal RBC transfer. This mismatch reveals that barrier thickening is not necessarily immediately accompanied by decreased transfer to RBCs. This may suggest that such regions correspond to earlier stages of the disease and could potentially be targets for therapeutic response. However, other regions exhibit high barrier uptake coupled with low RBC transfer. This may point to fibrosis that has advanced sufficiently to impair transfer to the RBCs (Kaushik, 2014, Kaushik, 2016b). Previous modelling has shown that only a ~5-μm increase in the thickness of the interstitial barrier can significantly delay the RBC transfer (Driehuys, 2006). And finally, in some patients with very advanced disease, we observe reduced RBC transfer in regions where barrier uptake appears to have returned to the normal range. However, those regions typically also exhibit severe fibrosis on CT and even structural proton MRI. This may be indicative of scarring that has progressed to the point that xenon is no longer soluble in, or diffuses much more slowly into the underlying structures.

6.4.8 Applying the Method to Diseases Beyond IPF

Although here, we have applied gas transfer mapping primarily to patients with IPF, our initial testing in other diseases strongly suggests the method is more broadly applicable. The patient with emphysema exhibits transfer patterns that are distinct from
both healthy subjects and IPF patients. This patient has significant ventilation defects, but more striking is the observation that transfer to the barrier tissues is unusually low. Furthermore, in many regions of low barrier transfer, RBC transfer was also diminished. This is consistent with the pathophysiology of emphysema, which impairs gas exchange by diminishing tissue surface area (Rabe, 2007, Vestbo, 2013).

Yet another example is illustrated by the patient with pulmonary arterial hypertension (PAH). Like in IPF, ventilation remains relatively normal, while transfer to RBCs is significantly impaired. This patient also exhibits a modest increase in barrier transfer, which may be caused by interstitial edema that results from higher pulmonary vascular pressures. Future work will be needed to discriminate the gas exchange patterns in IPF from those of PAH (Dahhan, 2016). However, this initial inspection suggests that the distribution of impaired RBC transfer and enhanced barrier uptake is very different between the two diseases.

6.5 Study Limitations

This study of quantitative $^{129}$Xe gas transfer mapping has several limitations. First, it is important to note that the healthy reference group was not age-matched to the relatively older IPF cohort. It is known that aging affects ventilation (He, 2015, Martinez, 2015), and can reasonably be expected to similarly impair gas transfer. Therefore, future studies must also characterize gas exchange in older healthy subjects to better
discriminate true disease from normal aging. Second, we did not control for lung inflation levels during imaging. It is likely that RBC:barrier was somewhat dependent on lung inflation, and this could affect differences between IPF and normal subjects. Particularly IPF subjects with their smaller forced vital capacity (FVC) than healthy subjects, after inhaling a 1-liter dose are likely imaged at a volume closer to their total lung capacity (TLC). We do note that we have conducted preliminary studies in two healthy volunteers who were imaged at both FRC + 1 liter and at FRC, and barrier and RBC transfer patterns were not significantly different between them. This observation is interesting in its own right and may support the proposal by Qing et al, that lung inflation involves primarily the recruitment of additional alveoli, not increasing their individual volume (Qing, 2014a). Also important to note is that our method currently cannot unambiguously determine whether decreased RBC transfer is caused by diffusion limitation or perfusion deficits. As noted by Agusti et al. (Agusti, 1991), the degree to which impaired gas exchange is dominated by ventilation-perfusion mismatching versus diffusion impairment changes depending on whether the subject is at rest or exercising.

6.6 Summary

This chapter demonstrates a straightforward means to transform single-breath interleaved acquisition of gas- and dissolved-phase $^{129}$Xe images into quantitative
binning maps depicting ventilation, and gas transfer to barrier and RBC compartments. These methods provide an intuitive means to visualize both enhanced barrier uptake and decreased RBC transfer in patients with IPF, while preliminary testing suggests it is also capable of visualizing reduced barrier uptake in emphysema, and diminished RBC transfer in pulmonary vascular disease. While further study is required to establish the robustness of gas transfer MRI, and its dependence on lung inflation, these results suggest that quantitative binning maps of $^{129}$Xe gas transfer could be potentially useful for comprehensively assessing of a wide array of pulmonary disorders.
7 Clinical Performance of Quantitative Hyperpolarized $^{129}$Xe Gas Transfer MRI

Chapter 6 developed quantitative methods to evaluate $^{129}$Xe gas transfer MRI. This chapter compares the $^{129}$Xe MRI findings in a cohort of IPF patients to the two clinical gold standards: PFTs and CT. The methods and results presented in this chapter are adapted from a journal article that is in preparation:


7.1 Motivation

The in vivo spectrum of $^{129}$Xe contains an abundance of functional information that can be probed to reveal details about oxygenation, inflammation, and gas transfer noninvasively within the lung. These spectral properties have been characterized using spectroscopic techniques under breath hold, and studies have also investigated the dynamics of the multiple dissolved-phase $^{129}$Xe resonances (Kaushik, 2014, Norquay, 2016). This dissolved-phase signal has also been imaged independently from the gas-phase signal in humans (Cleveland, 2010), and further decomposed $^{129}$Xe in the RBCs and barrier tissue (Qing, 2014a, Kaushik, 2016a). These early images of gas transfer impairment marked an important technical achievement for the field, but were not able to quantitatively compare images across subjects.
To this end, chapter 6 introduced methods that quantify gas transfer in a way that provides inherent context to a healthy reference population. While these quantitative analysis methods showed great promise for detecting regional differences associated with IPF disease and progression, we still need to confirm that these methods accurately detect real changes associated with disease. To that end, the objective of this work is to develop a framework by which to begin validating quantitative $^{129}$Xe gas transfer MRI. To do so, we first apply these methods to a cohort of healthy subjects as a control experiment in order to verify that individual subjects are indeed consistent with the distribution from the healthy reference population. To assess the validity of our findings among IPF patients, we correlate $^{129}$Xe imaging derived metrics of gas transfer to two gold standards for evaluating lung function in IPF: PFTs and CT. Finally, we characterize the spatial distribution of gas transfer metrics to test the hypothesis that impaired RBC transfer follows that of the radiographic and pathologic manifestations of IPF, which are known to present predominantly in the basal and sub-pleural lung (Raghu, 2011, Hunninghake, 2003, Carrington, 1978). Establishing the quantitative accuracy of these methods will ultimately strengthen the claims we can make about gas transfer. Given the current lack of reliable metrics to assess therapeutic response and disease progression in patients with IPF, novel and validated biomarkers of gas transfer such as $^{129}$Xe are desperately needed.
7.2 Materials and Methods

This study was conducted under protocols approved by the Duke University Institutional Review Board. Prior to participating, all subjects provided written informed consent. The same 13 healthy subjects (ages = 43 ± 22 years) and 12 IPF subjects (ages = 66 ± 15 years) that were described in chapter 6 were also used for the analysis in this chapter. Thus the subject recruitment, $^{129}$Xe polarization and delivery, spectroscopy and imaging, reconstruction, and quantitative binning analysis techniques are identical to what is described in Section 6.2. Prior to MRI studies, all subjects underwent baseline pulmonary function testing to obtain FVC by spirometry and DL$^co$ by the single-breath method. The diagnosis of IPF was determined using ATS criteria confirming a UIP pattern either on CT or from surgical lung biopsy (Raghu, 2011). All IPF subjects had prior CT scans, with an interval of 4.6 ± 4.3 months from their MRI scan. CT scans were evaluated by a chest radiologist using established criteria to produce a mean fibrosis score, which included the extent of reticulation and honeycombing, ranging from 0-100% in six distinct lung zones (Ley, 2014). These were used to classify IPF disease severity as (mild: <11% affected, moderate: 11-30% affected, and severe >30% affected) (Ley, 2014).
### 7.2.1 Functional Gradient Analysis

To quantify the spatial variation in functional gas transfer, the lungs were divided into two equal volumes and gradients were calculated in the apical/basal and anterior/posterior direction. Similarly, to evaluate central/peripheral gradients, the peripheral lung was defined as the outermost 2-3 cm of the sub-pleural lung perimeter, totaling roughly 60% of the total lung volume. Spatial gradients for both the RBC:gas and barrier:gas maps were then calculated using the difference between mean apical and basal regions, anterior and posterior regions, and central and peripheral regions. These differences were normalized by the mean value over the entire lung to yield the percentage difference in each of the 3 directions.

### 7.2.2 Statistical Methods

All statistical analyses were performed using JMP 12 (SAS Institute Inc., Cary, NC). The unpaired two-tailed Student’s t-test was used to evaluate differences in the spatial distribution of gas transfer between the anterior/posterior, apical/basal, and central/peripheral lung segments in the healthy and IPF groups. Linear regression analysis and the Pearson correlation coefficient (r) were used to assess correlation between functional MRI parameters (average RBC:gas, barrier:gas, and RBC:barrier) and PFT results (FVC and DLCO). For all comparisons, the level of significance was 5% ($P < 0.05$).
7.3 Results

Single breath, isotropic images of gas- and dissolved-phase $^{129}$Xe were successfully acquired in all subjects and reliably decomposed into separate ventilation, RBC:gas and barrier:gas maps. Subject demographics, PFT results, and functional imaging-derived ratios are summarized in Table 4. Subjects with repeat MR studies are listed using the same subject number followed by a letter. CT fibrosis scores are only listed for subjects where associated CT scans were available.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>FVC (% pred)</th>
<th>DLCO mL/min/mmHg (% pred)</th>
<th>Ventilation (% ref)</th>
<th>Barrier:Gas Ratio (x10^2) (% ref)</th>
<th>RBC:Gas Ratio (x10^2) (% ref)</th>
<th>RBC:Barrier Ratio (% ref)</th>
<th>CT Fibrosis Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>002-039B</td>
<td>26</td>
<td>M</td>
<td>4.39 (90)</td>
<td>25.1 (79)</td>
<td>0.425 (83)</td>
<td>0.453 (93)</td>
<td>0.276 (107)</td>
<td>0.639 (120)</td>
<td></td>
</tr>
<tr>
<td>002-040C</td>
<td>65</td>
<td>M</td>
<td>4.17 (108)</td>
<td>30.1 (122)</td>
<td>0.481 (94)</td>
<td>0.357 (73)</td>
<td>0.227 (88)</td>
<td>0.654 (123)</td>
<td></td>
</tr>
<tr>
<td>002-049D</td>
<td>65</td>
<td>M</td>
<td>3.74 (97)</td>
<td>27.9 (113)</td>
<td>0.475 (93)</td>
<td>0.585 (120)</td>
<td>0.315 (121)</td>
<td>0.540 (101)</td>
<td></td>
</tr>
<tr>
<td>002-055</td>
<td>29</td>
<td>F</td>
<td>2.77 (103)</td>
<td>14.9 (76)</td>
<td>0.438 (86)</td>
<td>0.476 (98)</td>
<td>0.218 (84)</td>
<td>0.481 (90)</td>
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</tr>
<tr>
<td>002-064</td>
<td>26</td>
<td>M</td>
<td>5.03 (98)</td>
<td>28.8 (89)</td>
<td>0.440 (86)</td>
<td>0.498 (102)</td>
<td>0.254 (98)</td>
<td>0.539 (101)</td>
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</tr>
<tr>
<td>002-065</td>
<td>27</td>
<td>M</td>
<td>3.18 (65)</td>
<td>26.5 (92)</td>
<td>0.490 (96)</td>
<td>0.416 (86)</td>
<td>0.272 (105)</td>
<td>0.677 (127)</td>
<td></td>
</tr>
<tr>
<td>002-083</td>
<td>21</td>
<td>F</td>
<td>2.77 (83)</td>
<td>20.7 (94)</td>
<td>0.469 (92)</td>
<td>0.478 (98)</td>
<td>0.260 (100)</td>
<td>0.543 (102)</td>
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<tr>
<td>002-084</td>
<td>21</td>
<td>F</td>
<td>3.96 (112)</td>
<td>20.4 (91)</td>
<td>0.561 (110)</td>
<td>0.452 (93)</td>
<td>0.236 (91)</td>
<td>0.547 (103)</td>
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<tr>
<td>002-085</td>
<td>22</td>
<td>F</td>
<td>4.15 (97)</td>
<td>24.7 (102)</td>
<td>0.575 (113)</td>
<td>0.762 (157)</td>
<td>0.279 (108)</td>
<td>0.376 (70)</td>
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<td>IPF Patients</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>002-046A</td>
<td>55</td>
<td>M</td>
<td>2.27 (53)</td>
<td>9.9 (37)</td>
<td>0.467 (92)</td>
<td>1.149 (236)</td>
<td>0.179 (69)</td>
<td>0.157 (29)</td>
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<td>002-046B</td>
<td>56</td>
<td>M</td>
<td>2.06 (49)</td>
<td>7.26 (29)</td>
<td>0.495 (97)</td>
<td>1.178 (242)</td>
<td>0.159 (61)</td>
<td>0.130 (24)</td>
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<tr>
<td>002-046C</td>
<td>56</td>
<td>M</td>
<td>1.78 (42)</td>
<td>6.1 (23)</td>
<td>0.422 (83)</td>
<td>0.972 (200)</td>
<td>0.128 (49)</td>
<td>0.124 (23)</td>
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</tr>
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<td>002-050</td>
<td>72</td>
<td>M</td>
<td>2.9 (72)</td>
<td>9.4 (39)</td>
<td>0.418 (82)</td>
<td>0.881 (181)</td>
<td>0.152 (59)</td>
<td>0.178 (33)</td>
<td></td>
</tr>
<tr>
<td>002-054</td>
<td>67</td>
<td>M</td>
<td>2.51 (60)</td>
<td>9.4 (38)</td>
<td>0.398 (78)</td>
<td>0.845 (174)</td>
<td>0.139 (54)</td>
<td>0.167 (31)</td>
<td></td>
</tr>
<tr>
<td>002-054A</td>
<td>68</td>
<td>M</td>
<td>1.25 (29)</td>
<td>10.2 (41)</td>
<td>0.296 (58)</td>
<td>0.733 (151)</td>
<td>0.091 (35)</td>
<td>0.131 (25)</td>
<td></td>
</tr>
<tr>
<td>002-056</td>
<td>79</td>
<td>M</td>
<td>2.27 (55)</td>
<td>7.2 (31)</td>
<td>0.464 (91)</td>
<td>1.002 (206)</td>
<td>0.148 (57)</td>
<td>0.150 (28)</td>
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</tr>
<tr>
<td>002-067</td>
<td>60</td>
<td>F</td>
<td>2.54 (81)</td>
<td>9.7 (51)</td>
<td>0.530 (104)</td>
<td>0.588 (121)</td>
<td>0.102 (39)</td>
<td>0.182 (34)</td>
<td></td>
</tr>
<tr>
<td>002-067A</td>
<td>61</td>
<td>F</td>
<td>2.51 (85)</td>
<td>11.9 (65)</td>
<td>0.438 (86)</td>
<td>0.634 (130)</td>
<td>0.114 (44)</td>
<td>0.188 (35)</td>
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</tr>
<tr>
<td>002-068</td>
<td>67</td>
<td>M</td>
<td>1.93 (45)</td>
<td>11.5 (46)</td>
<td>0.386 (76)</td>
<td>1.056 (217)</td>
<td>0.256 (99)</td>
<td>0.250 (47)</td>
<td></td>
</tr>
<tr>
<td>002-068A</td>
<td>68</td>
<td>M</td>
<td>1.86 (49)</td>
<td>11.6 (48)</td>
<td>0.422 (83)</td>
<td>1.093 (225)</td>
<td>0.319 (123)</td>
<td>0.298 (56)</td>
<td></td>
</tr>
<tr>
<td>002-069</td>
<td>69</td>
<td>M</td>
<td>4.43 (104)</td>
<td>18.73 (17)</td>
<td>0.453 (89)</td>
<td>0.712 (147)</td>
<td>0.171 (66)</td>
<td>0.271 (51)</td>
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<tr>
<td>002-069B</td>
<td>70</td>
<td>M</td>
<td>4.3 (99)</td>
<td>17.72 (17)</td>
<td>0.382 (75)</td>
<td>0.879 (181)</td>
<td>0.217 (84)</td>
<td>0.260 (49)</td>
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<tr>
<td>002-073</td>
<td>62</td>
<td>M</td>
<td>3.1 (62)</td>
<td>12.8 (47)</td>
<td>0.532 (104)</td>
<td>0.952 (196)</td>
<td>0.294 (114)</td>
<td>0.304 (57)</td>
<td></td>
</tr>
<tr>
<td>002-076</td>
<td>67</td>
<td>F</td>
<td>1.68 (77)</td>
<td>8.9 (54)</td>
<td>0.531 (104)</td>
<td>1.195 (246)</td>
<td>0.189 (73)</td>
<td>0.159 (30)</td>
<td></td>
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<tr>
<td>002-079</td>
<td>66</td>
<td>M</td>
<td>2.67 (64)</td>
<td>14.8 (59)</td>
<td>0.455 (89)</td>
<td>0.906 (187)</td>
<td>0.235 (90)</td>
<td>0.280 (53)</td>
<td></td>
</tr>
<tr>
<td>002-079A</td>
<td>67</td>
<td>M</td>
<td>3.04 (71)</td>
<td>14.6 (58)</td>
<td>0.484 (95)</td>
<td>0.840 (173)</td>
<td>0.239 (92)</td>
<td>0.293 (55)</td>
<td></td>
</tr>
<tr>
<td>002-080</td>
<td>69</td>
<td>M</td>
<td>3.55 (76)</td>
<td>13.6 (53)</td>
<td>0.447 (88)</td>
<td>0.816 (168)</td>
<td>0.215 (83)</td>
<td>0.285 (53)</td>
<td></td>
</tr>
<tr>
<td>003-007</td>
<td>75</td>
<td>M</td>
<td>2.31 (54)</td>
<td>11.4 (48)</td>
<td>0.461 (90)</td>
<td>0.933 (192)</td>
<td>0.219 (85)</td>
<td>0.252 (47)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.0</td>
<td></td>
<td>2.58 (64.6)</td>
<td>11.3 (47.8)</td>
<td>0.446 (88)</td>
<td>0.914 (188)</td>
<td>0.188 (72)</td>
<td>0.214 (40)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Subject Demographics, PFT Metrics, and Imaging-Derived Parameters.

7.3.1 Representative Healthy Subject

Representative ventilation and gas transfer maps and CT images are depicted in Figure 39 for a healthy control subject with FVC = 97% predicted, DLco = 113% predicted. The ventilation images show a majority of green and blue voxels contributing
to an overall signal that is 93% of the reference mean. The barrier map reveals a majority of voxels falling into the green bins that represent ratios within ±1 standard deviation of the average healthy mean. In the axial plane, the barrier intensity is seen to increase slightly in the gravitationally dependent regions of the lung. This subject exhibited a mean barrier signal that was 120% of the reference population, with only 4% of voxels falling into Barrier\textsuperscript{High} (pink). Similarly, the RBC maps in this subject reveal a majority of voxels falling into the green bins that again represent values within ±1 S.D. of the mean RBC transfer in healthy subjects. In the axial plane, the RBC signal was clearly enhanced in a gravitationally dependent manner, as indicated by the blue voxels in the posterior lung. The mean RBC intensity was 121% of reference, and only 10% of voxels fell into RBC\textsubscript{Low} (red and orange). These were found exclusively in the gravitationally non-dependent (anterior) portions of the lung.
Healthy Subject (FVC: 97%, DL\textsubscript{CO}: 113%)

Figure 39: Coronal and axial slices of RBC and barrier binning maps in a healthy subject with normal FVC (97%) and DL\textsubscript{CO} (113%). Barrier and RBC signal are 120% and 121%, respectively, of the reference population. 4% of barrier voxels fall into the highest 3 pink bins (B\textsubscript{Hi}=Barrier\textsubscript{High}) and 10% of RBC voxels fall in the lowest 2 red and orange bins (R\textsubscript{Lo}=RBC\textsubscript{Low}). The green barrier and blue-green RBC binning maps indicate barrier and RBC uptake are within the healthy range. The normal axial and coronal CT images show no parenchymal abnormalities.

7.3.2 Functional and Structural Imaging in IPF Subjects

Figure 40 depicts ventilation, barrier, and RBC maps in a subject with moderate IPF (FVC = 55% predicted, DL\textsubscript{CO} = 31% predicted, CT fibrosis score = 25.4%). Although the ventilation maps resemble the healthy ventilation images with a mean of 91%, the barrier signal was strikingly enhanced throughout the lung (206% of reference), with
98% of voxels falling in \text{Barrier}_{\text{High}}. Enhanced barrier uptake was most notable in the sub-pleural regions. This distribution of elevated barrier intensity was matched by reduced RBC signal in the same regions. In this subject, 52% of RBC voxels fell into \text{RBC}_{\text{Low}}, predominantly in the peripheral lung. Mean RBC transfer was 57% of the reference population. The corresponding CT images depict predominantly basal and peripheral reticulation and areas of ground glass attenuation. In the affected areas, mild traction bronchiectasis is equally represented.

**IPF Subject (FVC: 55\%, \text{DL}_{\text{CO}}: 31\%)**

![Figure 40: Coronal and axial slices of RBC and barrier binning maps in an IPF subject with decreased FVC (55\%) and \text{DL}_{\text{CO}} (31\%). The gas signal is 91\% of the mean ventilation from the reference population. Barrier and RBC signal are 206\% and 57\%, respectively, of the reference population. Nearly all barrier voxels fall into the highest]
3 bins (B\textsubscript{H}=98%) and almost half of the RBC voxels fall in the lowest 2 bins (R\textsubscript{L}=52%). The sub-pleural regions of elevated barrier intensity corresponded to a reduced RBC signal. CT images show peripheral and basal reticulations accompanied by areas of ground glass attenuation and mild traction bronchiectasis. The CT fibrosis score was 25.4%.

Figure 41 depicts ventilation and gas transfer maps in a patient with severe IPF (FVC = 42% predicted, DL\textsubscript{CO} = 23% predicted, CT fibrosis score = 34.2%). Ventilation maps reveal mildly reduced signal at 83% of the healthy mean, however the most striking feature is the highly elevated barrier signal intensity that is seen throughout most of the lung. The mean barrier uptake was 200% of reference, with 77% of voxels falling into the Barrier\textsubscript{High}. Similarly, this subject exhibited significant regions of low RBC uptake, with a whole-lung mean that was 49% of reference and 65% of voxels falling into RBC\textsubscript{Low}. Regions of low RBC transfer are most evident in the posterior coronal slice and the most basilar axial slice. In this patient, these regions of impaired RBC transfer match well with extensive distortion of the lung architecture and honeycombing seen on CT. Interestingly, these posterior slices exhibited a matching decrease of barrier uptake.
Figure 41: IPF subject with end-stage disease. DLCO and FVC are significantly reduced (42% and 23%, respectively). The gas signal is 83% of the mean ventilation from the reference population. Global barrier signal (200%) is enhanced and RBC signal (49%) is diminished. Both $B_H$ and $R_L$ are increased (77% and 65%, respectively). Gas transfer maps show locally decreased barrier matched with absent RBC transfer in regions of severe scarring. On CT, this subject shows extensive honeycombing and architectural distortion. The CT fibrosis score was 25.4%.

Figure 42 shows ventilation and gas transfer maps in an IPF subject with severe disease (FVC = 62% predicted, DL$_{CO}$ = 47% predicted, CT fibrosis score = 46.7%), and a CT scan notable for honeycombing and parenchymal changes consistent with a UIP pattern. Ventilation signal is preserved throughout the lung with a mean that is 104% of the reference population. Nonetheless, the barrier maps again exhibited significant enhancement throughout the lung with a mean that was 196% of reference and 84% of
voxels belonging to Barrier_{High}. However, $^{129}$Xe transfer to RBCs remained largely in the normal range through most of the lung, with a mean that was actually higher than reference (114%). Some regions of low RBC transfer were evident in the peripheral lung with a small patch of poor RBC transfer in the posterior slice. Overall, 18% of voxels were classified as RBC_{Low}. It is noteworthy that RBC transfer remained relatively normal, even in regions where CT exhibited significant abnormalities. Moreover, this subject exhibits normal RBC transfer, even in regions where barrier signal is significantly enhanced.

**IPF Subject (FVC: 62%, DL_{CO}: 47%)**

![Image of IPF subject with moderately reduced FVC and DLCO (62% and 47%, respectively). The gas signal is maintained at 104% of the mean ventilation from the](image)

Figure 42: IPF subject with moderately reduced FVC and DLCO (62% and 47%, respectively). The gas signal is maintained at 104% of the mean ventilation from the
reference population. Gas transfer metrics and binning maps show enhanced barrier signal (Mean barrier = 196%, BH = 84%), but preserved RBC transfer (Mean RBC = 114%, RL = 18%). The CT scan is notable for honeycombing and parenchymal changes consistent with a UIP pattern. Regions of structural lung injury on CT images are not well matched to regions of gas transfer impairment on MRI. The CT fibrosis score was 46.7%.

Figure 43 shows an IPF subject with mild disease (CT fibrosis score = 10.4%) and the highest FVC (77% predicted) and DLCO (54% predicted) in the cohort. Similar to previous IPF subjects, the ventilation signal resembles the healthy ventilation maps at 104% of the reference mean. This subject exhibited the highest barrier signal at 246% of reference, with 99% of voxels throughout the lung falling in BarrierHigh. In this subject, the RBC maps still exhibit significant regions of normal gas transfer in the mid-lung. However, areas of low RBC transfer are readily visible, predominantly in the basal lung. This led to a reduced mean RBC that was 73% of reference, with 36% of the voxels falling into RBCLow. In this patient with biopsy confirmed UIP, CT showed a possible UIP pattern with a peripheral reticular pattern and mild traction bronchiectasis, but no honeycombing. The spatial correlation between functional 129Xe transfer metrics and structural findings on CT is not immediately evident.
7.3.3 Correlation with Pulmonary Function Tests

As shown in Figure 44, each of the image-derived average gas transfer metrics, ventilation, RBC:gas, barrier:gas, and RBC:barrier, correlated significantly with FVC and DLco. Imaging-derived ventilation had a moderately positive correlation with FVC ($r =$
0.386, p = 0.026). Barrier:gas correlated negatively with FVC (r = -0.612, p < 0.001), while RBC:gas correlated positively with FVC (r = 0.628, p < 0.001). Similarly, RBC:barrier correlated well with FVC (r = 0.754, p < 0.001). Individually, ventilation had a moderately positive correlation with DLCO (r = 0.349, p = 0.047) while barrier:gas correlated well with DLCO (r = -0.752, p < 0.001), as did RBC:gas (r = 0.718, p < 0.001). However, the strongest correlation by far, was the direct ratio of RBC to barrier with DLCO (r = 0.936, p < 0.001).

Figure 44: RBC:barrier, RBC:gas, and barrier:gas ratios all correlate well with FVC and DLCO. Ventilation does not correlate well with either FVC or DLCO. The strongest correlation is between RBC:barrier and DLCO (r = 0.936, p < 0.001). Unlike DLCO, RBC:barrier can be further dissected to identify regional changes in RBC and barrier,
individually. Compared with DLCO, FVC does not correlate as well with functional metrics.

7.3.4 Correlation with CT

To better quantify the findings and patterns visualized on the preceding CT images, all IPF subjects had at least one CT scan from which the CT fibrosis score was calculated. This score was used to determine the correlation between anatomic and functional imaging metrics. Figure 45 reveals the CT fibrosis score had a weak, insignificant correlation with all functional metrics, including ventilation ($r = 0.089$, $p = 0.770$), barrier:gas ($r = 0.265$, $p = 0.384$), RBC:gas ($r = 0.214$, $p = 0.480$), and RBC:barrier ($r = -0.045$, $p = 0.875$).
Figure 45: The functional metrics, ventilation, Barrier:gas, RBC:gas and RBC:Barrier, are all poorly correlated with global CT fibrosis scores, a combination of reticulation and honeycombing seen on CT images which ranges from 0-100%. None of the correlations between functional metrics and CT fibrosis scores were determined to be significant.
7.3.5 Spatial Gas Transfer Analysis

Given that regional $^{129}$Xe gas transfer metrics do not readily correlate with structural CT findings, it is useful to test whether spatial gradients in $^{129}$Xe gas transfer are consistent with known physiology and patterns of disease. This is illustrated in Figure 46, which shows the ventilation, barrier, and RBC gradients in the central/peripheral, apical/basal, and anterior/posterior directions in the healthy and IPF groups.

![Figure 46: RBC and barrier gradients in 3 directions. Barrier transfer exhibits a spatial gradient only in the anterior-posterior direction of gravity, and only in healthy lungs. This gradient is also strong in RBC transfer for healthy subjects, but absent in IPF. In IPF, RBC transfer follows a large apical/basal gradient, and a moderate central/peripheral gradient, consistent with known patterns of disease.](image-url)
In the ventilation images, we found no significant differences in gradients of any direction between the healthy and IPF cohorts. In the anterior/posterior direction ventilation increased by 11% in the healthy cohort and 20% in the IPF patients (p = 0.078). A similar trend was seen in the apical/basal direction, where ventilation increased 10% in the healthy volunteers and 14% in the IPF subjects (p = 0.391). In the central/peripheral direction, ventilation decreased in both groups, 15% in healthy subjects and 19% in IPF subjects (p = 0.131).

The barrier images exhibited larger anterior/posterior gradients in healthy volunteers (22%) than in IPF patients (mean = 8%, p = 0.009). No significant differences in barrier intensity gradients were identified in the other directions. In the apical/basal direction, it changed by 5% in healthy subjects and 3% in IPF (p = 0.634). In the central/peripheral direction it varied by 5% in healthy subjects and 6% in IPF (p = 0.353).

Regional RBC uptake was characterized by a similarly large anterior/posterior gradient in healthy controls (mean = 32%). This gradient was significantly diminished and nearly eliminated in IPF subjects (mean = 2%, p < 0.001). RBC uptake also increased significantly in apical/basal direction in both populations. In healthy volunteers, the apical/basal gradient was -12%, while in IPF subjects it was significantly larger at -36% (p = 0.016). RBC transfer dropped off modestly in the central/peripheral direction for healthy subjects at -10%, but this gradient was significantly larger in the IPF cohort at -22% (p = 0.001).
7.3.6 Longitudinal Analysis

An initial example wherein these $^{129}$Xe MRI metrics are used to monitor disease progression and therapy response is seen in Figure 47, showing 2 IPF subjects followed longitudinally at 9 and 5 months. Both subjects had stable symptoms and no oxygen requirement at baseline or follow-up. Figure 47A and B depict scans of one IPF subject’s at baseline and at 9-month follow-up. In this subject who had started nintedanib 1 month prior to baseline evaluation, PFT metrics were stable, with FVC of 104% at baseline and 99% at follow-up, while DL$\text{co}$ was 73% and 72%. Nonetheless, gas transfer MRI still exhibits heterogeneously increased barrier signal at 9-month follow-up (Figure 47B). Quantitatively, the mean barrier increased from 147% to 181% with a corresponding increase in Barrier$\text{High}$ from 30% to 75%. However, in this subject RBC transfer did improve in the apical lung, while the basal lung showed regions of dramatic reduction. The net effect was that mean RBC increased from 66% to 84% at follow-up, while RBC$\text{Low}$ diminished from 41% at baseline to 37% at follow-up.
Figure 47: Follow-up of two IPF subjects without oxygen requirement and with stable symptoms. IPF subject (a) 1 month after starting nintedanib and (b) at 9-month follow-up. At follow-up, RBC transfer is increased in the apical lung, but reduced in the basal lung. However, barrier is increased throughout, suggesting progressive fibrosis. IPF subject (c) 2 months after starting pirfenidone and (d) at 5-month follow-up. PFTs and RBC transfer are stable or slightly improved. Notably, barrier transfer is decreased at follow-up.

Figure 47C and D shows longitudinal MRI changes in a second IPF subject at baseline and 5-month follow-up. In this subject who started pirfenidone 2 months prior to baseline, PFT metrics were stable or slightly improved at follow-up with FVC going from 64% to 71% and DLCO stable from 59% at baseline to 58% at follow-up. At 5-month follow-up (Figure 47D) barrier transfer was decreased throughout the lung, from 187%
at baseline to 173%. BH was similarly reduced from 78% at baseline to 63% at follow-up. RBC transfer remained stable, going from 90% at baseline to 92% at follow-up with RBC_{Low} essentially remaining unchanged from 24% at baseline to 23% at follow-up.

### 7.4 Inferences on Gas Transfer in IPF

This work demonstrates that $^{129}$Xe MRI provides unique functional information that gives additional insight into the gas transfer impairments seen in IPF. IPF subjects exhibited a globally enhanced barrier uptake, coupled with regionally diminished RBC transfer. This suggests that, at least in some regions, increased fibrosis impairs gas transfer to RBCs, which agrees with the current understanding of IPF pathophysiology (King, 2011). In some patients with advanced disease, we also observe regions of low barrier in the posterior lung, matched with regions of absent RBC transfer. One possible interpretation is that gas-phase $^{129}$Xe is unable to diffuse into these regions of end-stage, severely fibrotic lung to reach the RBCs, resulting in a low dissolved-phase signal. Alternatively, these regions could have not been perfused, which would also result in low dissolved-phase signal. Clinically, subjects exhibiting such a pattern had reduced PFT metrics, FVC and DL_{CO}, indicative of advanced lung disease.
7.4.1 PFT Correlations Support Functional Imaging Findings

The mainstays of diagnosis and monitoring progression in IPF continue to be PFTs. As DLco is a direct marker of global gas exchange, it is encouraging then that our functional markers well correlate with DLco. RBC:barrier had the highest correlation to both FVC and DLco, which is consistent with previous spectroscopic studies (Kaushik, 2014), and provides strong grounding for the functional information derived from $^{129}$Xe MRI. Unlike DLco, however, RBC:barrier can be further dissected to identify regional changes in barrier and RBC transfer, individually. In addition, one of the weaknesses of DLco is that measurements are only reproducible if subject can achieve a maximum inspiratory effort (MacIntyre, 2005). Our functional metrics are normalized to the gas-phase signal, which accounts for differences in the volume of inhaled xenon, and thus are not strongly effort dependent.

7.4.2 Functional $^{129}$Xe MRI Compliments Structural CT Findings

With a wealth of information from $^{129}$Xe MRI, the intuitive next step would be to compare functional imaging with conventional structural imaging, as CT imaging has long been a part of the work-up for patients with pulmonary fibrosis. In subjects with late-stage IPF, MR and CT images agree well visually. This is particularly true in regions of absent RBC and barrier transfer where $^{129}$Xe does not efficiently diffuse, which often exhibit extensive honeycombing on CT. In subjects with less severe IPF, however,
agreement between MR and CT is considerably less. Within this cohort, some patients exhibited definite UIP patterns on CT, but these significant structural abnormalities did not translate to impaired RBC transfer. Thus, there are cases where MR imaging paints a picture of preserved lung function while CT imaging tells a story of extensive structural injury. On the other end of the spectrum we found subjects whose MR images exhibited global barrier enhancement paired with regions of absent RBC transfer, indicating severe functional impairment. However, these observations did not manifest as detectable structural changes and the possible UIP pattern on CT. This discordance between CT and MR was further supported by the lack of correlation between our functional metrics and anatomic fibrosis scores. These preliminary findings suggest that perhaps considering both this structural and functional information is integral to understanding the entire spectrum of disease stages and phenotypes.

7.4.3 Functional Imaging Depicts Physiologically Relevant Features

\(^{129}\text{Xe MRI allows us to both visualize pulmonary physiology in healthy individuals and quantitatively evaluate the spatial patterns of gas transfer. In a healthy subject lying supine, the gravitational gradient leads to decreased gas transfer in the anterior lung where perfusion is diminished (West, 1964). These anterior regions, known as the physiologic dead space (Fowler, 1948), do not routinely participate in gas exchange in a healthy individual lying supine. The healthy RBC maps reflect this}
physiology with increased RBC transfer in the posterior lung. Barrier transfer is also
increased in the dependent lung and this may represent atelectasis. These observations
further validate that our functional imaging modality can elucidate key principles of
pulmonary physiology, allowing us to then delve further in examining changes seen in
disease.

7.4.4 Functional Imaging Explains IPF Disease Pathophysiology

The pathophysiology of IPF can be understood by closely examining how the
physiologic gradients seen in a healthy subject are altered in disease to differentiate
normal from functionally impaired lung. We first observed that the gravitational
dependence in barrier transfer was absent in IPF, leading us to hypothesize that the
widespread pattern of fibrosis and inflammation (King, 2011) results in patchy barrier
enhancement throughout the lung. In IPF patients, regions of relatively normal RBC
transfer were seen in close proximity to regions of functional impairment. This agrees
with histologic findings where such temporal heterogeneity of patchy fibrotic zones,
honeycomb changes, and fibroblastic foci coexisting with regions of normal lung has
long been appreciated in IPF (Katzenstein, 1998, Smith, 2013). Furthermore, the absence
of a gravitational gradient in RBC transfer suggests that anterior lung regions are
actively recruited in order to maintain stable lung function and reduce ventilation-
perfusion mismatch in disease (Hsia, 2016).
Such observations prompted further quantitative analysis by dividing the lung into well-defined regions. These results supported the qualitative imaging findings by showing nearly absent barrier gradients in IPF and increased barrier transfer in the healthy dependent lung. Furthermore, the fibrotic sub-pleural and basal regions of honeycombing on histology and CT (Raghu, 2011, Nishimura, 1992) corresponded to regions of reduced RBC transfer. Although this pattern of honeycombing and fibrosis is useful in detecting IPF, it is likely that early stage disease occurs in seemingly normal areas on CT. In fact, the extensive barrier enhancement indicates that perhaps larger portions of the lung may be damaged than CT reveals.

7.4.5 Proposed Models of Gas Transfer in IPF

Interestingly, the fibrotic changes in IPF did not lead to enhanced barrier signal and diminished RBC transfer in all IPF patients. Instead, three different patterns were evident, which could represent three distinct disease phenotypes that are depicted in cartoon form in Figure 48. In healthy individuals (Figure 48a), inhaled $^{129}$Xe freely diffuses from the alveoli through the thin alveolar-capillary membrane to reach circulating RBCs. In one subset of patients with IPF (Figure 48b), we see globally enhanced barrier signal with a concomitant decrease in RBC signal. This process can be readily explained by our initial hypothesis that increased interstitial fibrosis thickens this alveolar-capillary membrane, reducing gas transfer to capillary RBCs. In patients
with severe IPF (Figure 48c), we noted decreased RBC and largely normal barrier signal in regions of end stage fibrosis and honeycombing. In these regions, the fibrosis prevents $^{129}\text{Xe}$ from diffusing into the blood just as before. However, we hypothesize that the interstitial membrane reduces its inflammatory response as the membrane essentially becomes scar tissue, which results in the largely normal, or even slightly low barrier uptake. The most interesting pattern of disease was seen in subjects found to have increased barrier signal in regions with preserved RBC transfer (Figure 48d). On a microscopic level, we propose that the alveoli are surrounded by patchy fibrosis as well as regions of relatively healthy membrane that compensates to allow adequate gas transfer. If this model accurately depicts IPF pathophysiology, then it would be prudent that novel therapies and methods of monitoring disease progression target these at-risk regions where anatomic alterations could precede impending functional decline.
Figure 48: Proposed model of gas transfer in a healthy alveolus (a) compared with several alveoli at different stages of functional impairment (b) - (d). In (a), inhaled gaseous $^{129}$Xe freely diffuses from the alveolus through the thin blood-gas membrane and into the RBCs. In (b), increased interstitial fibrosis limits the ability of $^{129}$Xe to diffuse into the blood, therefore decreasing RBC signal. $^{129}$Xe is trapped in fibrotic tissues, causing an increased barrier signal. In (c), the alveolus is surrounded on the right by a fibrotic region, creating a high barrier signal. However, $^{129}$Xe maintains pathways to diffuse into the RBCs (left), thus preserving the RBC signal. In (d), the alveolus is completely surrounded by end stage fibrosis. Gas transfer is severely limited and $^{129}$Xe is unable to diffuse into either the RBCs or interstitial tissues, resulting in low RBC and barrier signals.

7.4.6 Tracking Disease Progression with $^{129}$Xe

These initial results are promising and indicate that $^{129}$Xe MRI aligns with many findings from PFTs and CT, but can also contribute to developing a deeper
understanding of regional gas transfer impairment. Notably, when we acquired repeat MR scans in several IPF subjects, we have seen subjects follow very different trajectories. This lends support to the theory that there are numerous clinical courses of disease in IPF patients that are often difficult to predict (42, 43).

In the first subject (Figure 47A and B), our functional imaging paints a picture of continual disease progression, with a persistent increase in barrier transfer that together implies active disease and progressive fibrosis despite therapy. The patient’s clinical stability may be explained by a redistribution of gas transfer patterns, where high functioning apical lung units maintain adequate gas transfer despite the presence of defects in the basal lung.

More encouraging, the second subject (Figure 47C and D) seems to show decreasing barrier signal at follow-up with no apparent progression of RBC impairment in the basal lung, possibly indicating positive therapeutic response that is in concordance with PFT metrics. While these changes have only been observed in a single subject, we hope that with more follow-up subjects, we can identify key patterns that allow us to use changes in barrier and RBC to guide treatment planning, predict outcomes, and better inform our patient care.
7.5 Study Limitations and Future Directions

Although $^{129}$Xe MRI clearly provides a wealth of information, it will be critical to apply these current methods in a larger cohort of subjects, and also assess the short term reproducibility of these methods. One of the limitations of this study is the use of younger subjects in our control group. Literature suggests the aging lung undergoes physiologic changes, including changes in chest wall compliance, respiratory muscle function and the lung parenchyma, leading to functional alterations involving gas exchange (Stam, 1994, Janssens, 1999). An older, age-matched population of healthy controls needs to be included in future studies. All of our subjects also inhaled the same volume of xenon gas without adjustments for differences in lung volumes between healthy lung and lung with restrictive disease. Additionally, PFT metrics have been incorporated into several methods of staging IPF and predicting outcomes, including the GAP index and du Bois score (Ley, 2012, du Bois, 2011). It would be helpful in the future to correlate such metrics against $^{129}$Xe MRI in larger studies. Although every IPF subject had an initial CT scan for comparison with MRI, several subjects had scans that were months apart, which may limit our ability to directly compare our findings with CT. Furthermore, we did not account for comorbidities in our study that may affect gas transfer, including cardiovascular diseases such as pulmonary hypertension and heart failure, as well as underlying ventilation defects and anemia. Such questions could be answered with additional testing and imaging. Finally, acquiring tissue pathology in
regions of functional impairment as the gold standard for additional validation of our methods would provide important insight in future work.

7.6 Summary

Our preliminary data suggests that $^{129}$Xe MRI can add unique insight throughout the clinical decision-making process. Furthermore, the considerable expenses of available IPF drugs (Loveman, 2014) and significant adverse effects that may limit therapy adherence (Richeldi, 2014, King, 2014) point to the pressing need for more sensitive markers that can aid clinicians in making treatment decisions earlier in the disease course with greater confidence. $^{129}$Xe MRI is well suited to provide the regional and functional information necessary to meet these challenges. In addition, current guidelines recommend that IPF patients with advanced disease be evaluated for lung transplantation (Raghu, 2011, He, He, 2014) longitudinally, $^{129}$Xe MRI could aid in determining the extent of functional lung injury and guide the decision to proceed with surgical intervention.

Hyperpolarized $^{129}$Xe imaging is a promising functional imaging modality that is safe and well tolerated and can be harnessed as a powerful tool for understanding pulmonary physiology and alterations seen in disease. It is well poised for studying IPF, from understanding disease pathophysiology to characterizing disease progression and ultimately to determining treatment response, as these are all critical yet elusive
questions that remain largely unanswered with current methods. With emerging therapies and an increasing focus on understand the mechanisms behind lung injury in IPF, novel methods of functional imaging are both necessary and now, feasible.
8 Summary and Future Directions

This thesis developed noninvasive MR techniques, both spectroscopic and imaging-based, that exploit the multiple chemical shifts of HP $^{129}$Xe in order to quantify xenon transfer from the alveolar airspaces, through the blood-gas barrier tissue, and into the blood. In IPF, we have established that 1) these methods well-quantify differences in the RBC and barrier distributions, 2) the locations where gas transfer is impaired often correspond to CT findings of IPF, and 3) MRI-derived metrics correlate with PFTs. This suggests that our MRI-based functional pulmonary exam provides a solid foundation for evaluating lung health comprehensively.

Future work should first aim to identify spatial and functional patterns that can differentiate areas of early stage IPF from more permanent disease. By detecting areas that are most likely to respond to treatment, $^{129}$Xe imaging could greatly accelerate the development of new therapies for IPF. Furthermore, tracking these areas longitudinally, would permit therapies to be adjusted before the disease progresses irreparably. The ultimate goal of $^{129}$Xe MRI is to stratify IPF patients into phenotypes based on their potential response for different therapies. This will require long term clinical studies that connect patient outcomes with imaging patterns seen at baseline.

Looking beyond IPF, it will be interesting to extend our $^{129}$Xe exam to study patients with pulmonary vasculature diseases (PVD) such as pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD). Both patients with
PAH and PVOD exhibit high blood pressures in the pulmonary arteries, but they differ in whether the cause is due to changes in the pulmonary arteries (PAH) or veins (PVOD). These two diseases present with similar symptoms, and as a result, PVOD is commonly misdiagnosed as PAH (Montani, 2009). Unfortunately, treatment options are limited for both of these diseases, and the prognosis is only 2-3 years post diagnosis (Shackelford, 1977). Furthermore, current methods of diagnosing and assessing therapy response require either cardiac catheterization (Barst, 2004) or surgical lung biopsy (Mandel, 2000). Therefore, $^{129}$Xe research should focus on identifying spatial, spectral, and functional signatures that differentiate these two diseases, so that we can provide earlier and more accurate diagnosis (Dahhan, 2016).

### 8.1 Decomposing Three Dissolved-Phase Peaks using IDEAL

While our phase-sensitive imaging techniques and associated image processing pipeline have greatly enhanced our image quality and improved our ability to quantify gas-transfer images, these methods do not yet incorporate the second barrier peak that we identified in chapter 5. Here we briefly consider the effect of additional resonances and potential ways to better account for this third dissolved-phase resonance.

One option is to directly decompose all three dissolved-phase resonances via the IDEAL method, which was introduced to separate water from fat resonances in $^1$H imaging (Reeder, 2004). While to date this technique has only been demonstrated to
decompose 2 dissolved-phase $^{129}$Xe peaks in the lung, this method is capable of decomposing additional resonances. However, decomposing more resonances also requires images to be acquired at additional echo times. Specifically, four echo times are needed to decompose three resonances and correct for B0 inhomogeneities. Here we briefly review the IDEAL algorithm so that we can discuss the specific considerations for imaging the three dissolved-phase resonances.

The IDEAL algorithm uses data from each echo time to fit the complex signal in each voxel according to Equation (1.13).

$$s(t_n) = \left( \sum_{j=1}^{M} a_j e^{i\phi_j} e^{i2\pi f_j t_n} e^{-\pi w_j t_n} \right) e^{i2\pi t_n}$$  \hspace{1cm} (1.13)

Where $s(t_n)$ is the image signal at the $n^{th}$ echo time, $t_n$, which is calculated as a sum of $M$ resonances that have spin densities, $a_j$, starting phases, $\phi_j$, resonant frequencies, $f_j$, linewidths, $w_j$, and B0 variation defined as $\Psi$. Equation (1.13) can be simplified if the B0 variation is assumed to be known and is first demodulated. This B0-corrected image can be described by:

$$\hat{s}(t_n) = s(t_n) e^{-i2\pi t_n} = \sum_{j=1}^{M} a_j e^{i\phi_j} e^{i2\pi f_j t_n} e^{-\pi w_j t_n}$$  \hspace{1cm} (1.14)

Equation (1.14) is exactly equivalent to the spectroscopic fitting descried in chapter 5, only the resonant frequencies and linewidths are assumed to be known a priori. This prior knowledge makes equation (1.14) linear, so we can alternatively use matrix notation to describe the problem.
Here $\hat{s}$ represents an image voxel at each of the $n$ TEs, and $[c]$ represents each of the $M$ component spin densities the image voxel (with their associated phases). Describing the B0-corrected signal in this matrix notation, the decomposition problem can be solved in a least-squares sense by the well-known pseudoinverse by Equation (1.16).

$$[c] = \left( [A]^T [A] \right)^{-1} [A]^T \hat{s}$$  (1.16)

Since the pseudoinverse efficiently calculates the contribution from each resonance, we can then employ iterative techniques, such as a gradient descent approach, to solve Equation (1.13) for the B0 inhomogeneity term as well as the spin densities of each resonance.

This IDEAL algorithm, as first described by Reeder et al., performs the decomposition in the spatial domain (Reeder, 2004). However, taking the Fourier transform of Equation (1.14), the IDEAL algorithm can also be analogously described in the frequency domain (Brodsky, 2008) by Equation (1.17).

$$\hat{S}(t_{n,k}) = \sum_{j=1}^{M} a_j(k) e^{i\phi_j(k)} e^{i2\pi f_j(t_{n,k}+\tau_{k,n})} e^{-\pi w_j(t_{n,k}+\tau_{k,n})}$$  (1.17)

This k-space version of IDEAL introduces an additional time variable, $\tau_{k,n}$, that varies with k-space position and represents the time that has accumulated since the center of k-
space was acquired. By solving this problem in k-space, there are two key advantages for our dissolved-phase imaging. First, these dissolved-phase images are significantly undersampled in k-space, therefore reconstructing these non-Cartesian images can potentially introduce errors that would corrupt our ability to decompose individual resonances accurately. By instead decomposing the resonances in k-space, this method fits the raw data, which is not contaminated by the imperfections of non-Cartesian reconstruction. Second, decomposing the resonances in k-space allows the phase accumulation that occurs during readout to be corrected. For the imaging methods used in this work, this phase accumulation is significant. That is because a lower bandwidth is required to achieve sufficient SNR for imaging, which also lengthens the readout to ~1 msec. During this long readout time, ~130 degrees of phase accumulation occurs between the RBC and barrier peaks. Thus during imaging, the dissolved-phase components alternate from the real to imaginary channel within a single readout, which effectively mixes the two components back together, albeit primarily at the higher spatial frequencies. Fortunately, the k-space IDEAL formulation offers the potential to undo this mixing.

To decompose these resonances in k-space, we can write Equation (1.17) in matrix notation:
\[
\begin{bmatrix}
\hat{S}(t_1, k) \\
\hat{S}(t_2, k) \\
\vdots \\
\hat{S}(t_n, k)
\end{bmatrix} =
\begin{bmatrix}
e^{i2\pi ft_1} e^{-\pi n t_1} & \cdots & e^{-\pi n t_1} \\
\vdots & \ddots & \vdots \\
e^{-\pi n t_n} & \cdots & e^{-\pi n t_n}
\end{bmatrix}
\begin{bmatrix}
e^{i2\pi f r(k)} e^{-\pi n r(k)} & 0 & 0 \\
\vdots & \ddots & \vdots \\
0 & 0 & e^{i2\pi f r(k)} e^{-\pi n r(k)}
\end{bmatrix}
\begin{bmatrix}
C_1(k) \\
\vdots \\
C_M(k)
\end{bmatrix}
\]

\[
\hat{S} = [A]_{m \times M} [D]_{M \times M} [C]_{M \times 1}
\]

(1.18)

Equation (1.18) can also be solved by a pseudoinverse calculation:

\[
[C] = [D]^T [(A^T A)]^{-1} A^T \hat{S}
\]

(1.19)

Solving for the B0 term in Equation (1.13) is not straightforward in this k-space approach, since the B0 term, rather than being multiplied by each sample like in its image-domain analog, is convolved with each k-space sample. Consequently, the B0 term is typically first solved for using the image-domain approach, then after demodulating the B0 inhomogeneities, the constituent resonances are decomposed using the k-space approach.

While in theory, the IDEAL decomposition offers the ability to decompose the three dissolved-phase resonances, there are practical challenges that first need to be overcome. First, the SNR of our dissolved-phase images is inherently low, and decreases with successive TEs. This low SNR makes the decomposition prone to errors. Furthermore, the two broad and overlapping barrier resonances, just like in the spectroscopic decomposition, are difficult to separate accurately. Since the IDEAL
method only acquires data from a few time samples, in contrast to the many time samples of a FID that are acquired for spectroscopy, the least squares fitting is sensitive to noise. To this end, it is likely that in order to reproducibly decompose these low SNR dissolved-phase images into 3 distinct resonances, we will need to acquire images at more than four echo times. However, acquiring images at additional echo times within the 15 second breath hold would require additional undersampling that would further constrain imaging.

To initially investigate these challenges of decomposing resonances using the IDEAL algorithm, a preclinical model could be employed, where mechanical ventilation would allow for essentially unlimited scan time. Such an approach could accurately approximate the number of echo times that are needed to reliably separate these resonances. Also, the high resolution images that are achievable in preclinical imaging could help confirm that these decomposed images truly represent $^{129}$Xe in the blood and barrier tissues. For example, imaging at a longer TR would allow $^{129}$Xe magnetization to travel downstream of the pulmonary capillary beds into the heart and beyond. Thus we would expect to see RBC signal in these regions, while the barrier signal would still be largely confined to the pulmonary region.
8.2 Adapting the 1 Point Dixon Technique for a Third Dissolved-Phase Resonance

Given the challenges associated with robustly decomposing the three dissolved-phase resonances in human lungs, a second option is to adapt the Dixon technique to better account for the third dissolved-phase resonance. Directly decomposing more than two resonances using the original 1 point Dixon technique is not possible. However, perhaps rather than attempting to directly decompose the third dissolved-phase resonance, which we know is prone to errors due to the low SNR, we should instead focus on properly isolating the RBC from the two barrier resonances in a simpler two-peak decomposition. To that end, one could acquire Dixon images at a modified $\text{TE}_{90}$ condition that maximally isolates the true RBC signal to one channel of the receiver, while leaving the other two resonances to combine into the other channel. This can be accomplished by first fitting the dissolved phase spectrum to three resonances to identify the proper RBC frequency, then constraining the RBC frequency in a subsequent two-peak fit to calculate the modified $\text{TE}_{90}$ condition for imaging. Interestingly, we have found that this modified $\text{TE}_{90}$ condition occurs at an echo time that is very close to the original Dixon $\text{TE}_{90}$. The similarity of these echo times, likely due to the fact that the two barrier resonances are not far from 180 degrees out of phase with one another, suggests that even imaging at the original Dixon condition separates the RBC from barrier signals reasonably well. Furthermore, the combination of the two barrier peaks could potentially be better approximated by a non-Lorentzian lineshape such as a Gaussian or
Voight lineshape, as these lineshapes are meant to encompass a distribution of resonant frequencies (Marshall, 1997).

### 8.3 Characterizing Dissolved-Phase Imaging at Other Field Strengths

One important question that remains is how sensitive our hyperpolarized techniques are to the magnetic field strength. All of the work discussed here has been performed at 1.5T, but the field of multinuclear applications is moving towards higher magnetic field strengths, and soon few vendors will offer 1.5T scanners with multinuclear capabilities. Therefore, it will be important to characterize any differences that arise at higher field strengths.

When considering hyperpolarized gases, it is important to remember that, unlike in $^1$H applications, the equilibrium magnetization does not increase with the magnetic field strength. That is because the polarization of nuclei is achieved, not by the main magnetic field, but by external means (spin exchange optical pumping in this case). While the magnetization is not increased significantly by a larger magnetic field, the precession of nuclei increases linearly with the magnetic field. This faster precession, because of Faraday’s law, induces a larger current in the receive coil. Therefore, in hyperpolarized gas MRI, the detected signal increases proportional to the main magnetic field strength. In contrast, the noise in hyperpolarized MRI is typically a combination of body-noise and coil-noise. Body noise increases proportional to the main magnetic field
strength, but coil noise is fixed for a given coil. Combined, the increase in signal and noise partially cancel out so that, unlike in \(^1\)H imaging, the SNR for hyperpolarized MRI will only improve marginally at higher magnetic field strength.

While SNR improves slightly with magnetic field strength, there are other effects that are important to consider for phase sensitive imaging. First, the frequency separation of the multiple dissolved-phase resonances increases as the magnetic field strength increases. This increased frequency difference causes the relative phase between resonances to also accumulate faster, which ultimately makes the TE\(_{90}\) occur earlier. Imaging at an earlier TE\(_{90}\) should result in higher SNR because there is less time for T2* decay to occur before imaging. However, the T2* decreases as the magnetic field strength increases, so the dissolved-phase signal decays even more rapidly at higher field strength (Parra-Robles, 2008). This not only eliminates the SNR benefit of the earlier TE\(_{90}\), but it also limits spatial resolution.

Overall, we expect little benefit in SNR from higher magnetic field strength, and potentially worse spatial resolution from the more rapid T2*, which suggests that lower magnetic field strengths may be preferable for \(^{129}\)Xe imaging applications. Therefore, we need to anticipate the push towards higher field strengths, and adapt how we image and decompose these gas transfer volumes to be robust to the shorter T2* that comes at higher field strength. To this end, center out k-space trajectories, such as spiral and 3D radial sequences, offer short TE imaging that minimizes T2* losses.
8.4 Disseminate Quantitative $^{129}$Xe Gas Transfer MRI

There exists great interest in the multiple dissolved-phase resonances of $^{129}$Xe. To date, however, only two sites have demonstrated the ability to separately image $^{129}$Xe in the RBC and barrier tissues (Qing, 2014a, Kaushik, 2016a). This is likely, in part, due to the expense of the additional hardware that is required to polarize $^{129}$Xe and perform multinuclear studies. Also, additional noise sources are commonly detected in multinuclear systems since filters were designed to primarily filter resonances that are pertinent to $^1$H imaging. Perhaps the most significant hurdle, however is in developing robust pulse sequences, reconstruction techniques, and phase-sensitive decomposition methods. That is because vendors do not currently offer out-of-the-box solutions for imaging these dissolved-phase resonances. To convince the MRI industry to invest in this much needed infrastructure will require clinical trials that conclusively demonstrate the value of $^{129}$Xe gas exchange imaging. To that end, the xenon clinical trials consortium, headed by Jason Woods, aims to begin this process by first demonstrating the clinical value of $^{129}$Xe ventilation imaging. This thesis provides a further stepping stone that encourages other sites to adopt non-Cartesian pulse sequences, non-Cartesian reconstruction, and phase sensitive imaging methods that enable gas transfer to be imaged and quantified. By more broadly disseminating this technology, we will over time establish the important role for $^{129}$Xe MRI in the clinic.
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10 Biography

Scott Haile Robertson was born on July 25, 1984 in Asheville, NC. He spent his entire childhood enjoying the mountains of Western North Carolina, eventually graduating from the Carolina Day School in 2003. After high school, Scott studied at the University of Virginia, where he studied Biomedical Engineering. During the summer between his third and fourth year of college, Scott was an intern in the Early Identification Program where he spent the summer working on the CT detectors team. Before heading back for his final year in college, Scott accepted a job in the Edison Engineering Development Program at GE Healthcare post-graduation. Later that year, Scott earned a B. S. in Biomedical Engineering with a minor in Electrical Engineering from the University of Virginia, then moved to Wisconsin to work for GE Healthcare. While in the Edison program, Scott took night classes to complete his Masters in Engineering at the University of Wisconsin, Milwaukee. Upon graduating from the Edison program, Scott worked on the CT Advanced Applications Team to develop a cutting edge dual-energy CT application. After a total of 5 years at GE Healthcare, Scott pursued a Ph. D. from the Duke Medical Physics Graduate Program. At Duke, Scott was advised by Bastiaan Driehuys within the Center for In Vivo Microscopy, where he researched pulmonary applications of hyperpolarized $^{129}$Xe. After graduating from Duke, Scott has accepted a Radiologic Physicist position in the Clinical Imaging Physics Group within the Duke Medical Center.