Pulmonary Imaging of Chronic Obstructive Pulmonary Disease using Multi-Parametric Response Maps

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Graduate Program in Biomedical Engineering
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Engineering Science
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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction caused by airway remodelling and parenchymal destruction. Clinically, observation of COPD is performed using spirometry, but this technique only provides a global measure of lung health. To supplement these clinical measurements, thoracic computed tomography (CT) and hyperpolarized gas magnetic resonance imaging (MRI) have been used to measure regional structure and function abnormalities. Although CT and MRI have been used to research COPD, combination of both modalities into an interrelated image has never been performed. Therefore, we developed an image processing pipeline to combine MRI-CT information into a multi-parametric response map. In a COPD cohort, multi-parametric measurements became more abnormal as disease severity increased, were related to pulmonary function and quality of life, and revealed novel disease labels. This technique has potential to visualize and quantify the transition phases of COPD allowing for the possible identification of new treatment targets.

Keywords
Chronic Obstructive Pulmonary Disease, Magnetic Resonance Imaging, X-ray Computed Tomography, Hyperpolarized Noble Gas MRI, Multi-parametric Response Mapping, Pulmonary Imaging, Imaging Biomarkers
Summary for Lay Audience

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Presently, there is no cure for COPD so treatment focuses on alleviating symptoms, reducing exacerbations and hospitalizations, and improving quality of life. COPD is diagnosed and monitored using spirometry, a method for measuring airflow at the mouth. While spirometry is widely available and easy to use, it provides only a global measurement of lung function and cannot provide any regional information about the underlying abnormalities present within patients’ lungs.

To supplement spirometry, medical imaging has been used to provide regional measurements as well as information about the underlying abnormalities present within the lungs. Two imaging techniques used in studying COPD are x-ray computed tomography (CT) and hyperpolarized gas magnetic resonance imaging (MRI). Chest CT is used to measure structural changes within the lungs such as tissue destruction and airway abnormalities; whereas hyperpolarized gas MRI measures lung function by using an inhaled gas to identify unventilated regions of the lung known as ventilation defects. Typically, research in COPD uses either CT or MRI, but never a combination of the two in a single complementary image.

In this study, we developed a technique to combine information from both CT and MRI into a single lung map and used this map to categorize patient with COPD. We observed that combined CT-MRI labels became more abnormal with increasing disease severity, were associated with measurements of pulmonary function, quality of life, and exercise capacity, and visualized possible transitory phases of COPD. This study is the first to use a combined CT-MRI label map approach in the investigation of COPD, and the visualization ability of this combined CT-MRI label map may allow for the identification of new treatment targets and endpoints.
Co-Authorship Statement

The following thesis contains one manuscript that has been accepted and is in press. As first author of this manuscript, I was a significant contributor to all aspects of the studies as well as manuscript preparation and submission. I was responsible for pipeline and software development, conception of the study, experimental design, image processing, statistical analysis and interpretation, as well as manuscript preparation and submission. Grace Parraga, as the Principle Investigator and thesis Supervisor, provided continued guidance and was responsible for the conception of the study, experimental design, data interpretation and drafting and approval of the manuscript. She was also the guarantor of data integrity and responsible for Good Clinical Practice. Study visits and acquisition of pulmonary function data were performed under the supervision of Lyndsey Reid-Jones, Rachel L Eddy, and Danielle Knipping. Polarization of hyperpolarized gas was performed by Andrew Wheatley, Dante PI Capaldi, Heather Young, and Andrew Westcott. MRI acquisition was performed by Trevor Szekeres and David Reese. Below outlines the specific contributions for all co-authors for the manuscript contained in this thesis.

Chapter 2 is an original research article entitled “Pulmonary Imaging Phenotypes of Chronic Obstructive Pulmonary Disease using Multi-parametric Response Maps” and it was submitted to the journal Radiology on December 16, 2019. The manuscript was co-authored by Jonathan L MacNeil, Dante PI Capaldi, Andrew Westcott, Rachel L Eddy, Andrea L Barker, David McCormack, Miranda Kirby and Grace Parraga. As first author, I was responsible for analysis and interpretation, pipeline and software development, concept development, experimental design, image processing as well as manuscript preparation and submission. Dante PI Capaldi assisted in concept development, pipeline and software development, and manuscript revisions. Andrew Westcott assisted in pipeline and software development, concept development, image processing, and manuscript revisions. Rachel L Eddy assisted in concept development, data interpretation and manuscript revisions. Andrea L Barker assisted in concept development, image processing, and manuscript revisions. David McCormack and Miranda Kirby assisted in data interpretation and manuscript revisions.
The appendix contains a peer-reviewed conference proceeding entitled “Development and evaluation of pulmonary imaging multi-parametric response maps for deep phenotyping of chronic obstructive pulmonary disease” and it was accepted and published in the *SPIE Medical Imaging* conference proceedings. The proceeding was co-authored by Jonathan L MacNeil, Dante PI Capaldi, Rachel L Eddy, Andrew Westcott, Alexander M Matheson, Andrea L Barker, Cathy Ong-Ly, David McCormack, and Grace Parraga. I was responsible for analysis and interpretation, pipeline and software development, concept development, experimental design, image processing, as well as manuscript preparation and submission. Dante PI Capaldi assisted in data collection, image processing, concept development, and pipeline and software development. Andrew Westcott assisted in pipeline and software development, concept development, and manuscript revisions. Rachel L Eddy assisted in concept development and manuscript revisions. Alexander Matheson, Andrea L Barker, and Cathy Ong-Ly assisted in concept development. David McCormack assisted in study subject recruitment.
Acknowledgments

I would first like to thank my supervisor, Dr. Grace Parraga for continually pushing me to overcome my limits. Thanks to your constant drive and support, I was able to accomplish things I did not think I could possibly do. I am very grateful for the opportunities you have provided to me to grow both personally and professionally. And thank you for teaching me how to seize opportunities, plan for life and focus on the future.

I would also like to thank the members of my advisory committee: Dr. Aaron Fenster, Dr. Narinder Paul, Dr. Alia Kashgari, and Dr. Alexei Ouriadov for your support and guidance. In every meeting, your comments and feedback not only helped me improve my research but also myself.

To everyone in the Parraga lab, I would like to thank all of you for your support, and I do not think I would have made it through this degree without all of you. To Lyndsey Reid-Jones, thank you for being so kind and always open to talk with. You always brought some laughter and smiles to help brighten any day. To Tamas Lindenmaier, thank you for your advice on getting through graduate school. To Danielle Knipping, thank you for being so kind and cheerful. To Sarah Svenningsen and Miranda Kirby, thank you for your support and advice on how to survive in the Parraga lab. To Dave Reese, thank you for all you help with our MR acquisitions and for bringing some laughter to all of our scans.

To Rachel Eddy, thank you for being my sounding board for all my ideas and worries. Thank you for all the evenings spent segmenting airway trees and listening to me vent about my project as well as constantly telling me to stop over thinking things. You are an amazing senior student and mentor; the lab would be lost without you. To Andrew Westcott, thank you for being a great mentor and always being open to talk to about my project and life. Your wit and laughter made all our lunchtime discussions enjoyable, and your willingness to help and explain made starting my masters less difficult. To Andrea Barker, thank you for your positivity and encouragement which has helped me throughout my degree. I am a little sad that I still cannot top my “beets by Dre” pun, but I will keep trying. To Alexander Matheson, thank you for being an amazing colleague and helping me out with all my questions and ideas.
humor, puns, poems, and knowledge (both ancient and modern) make talking with you so very enjoyable. May you continue to find increasingly creative ways of describing the transition from archeology to biophysics. To Cathy Ong-Ly, thank you for your positivity and interesting factoids and making each day a little brighter. To Maksym Sharma and Marrissa McIntosh, thank you for your dedication and hard work. Seeing you overcome the hectic start that all of us went through, I know that you will do amazing things during your time here. Thank you to all the other members of the lab who make our research possible: Dr. Fabio Salerno, Dr. Hana Sarejeddini, Dr. Bingyu Hou, and Hannah Yaremko.

To my family and friends, thank you for the love and support you have provided me over the past few years. Your encouragement has helped me make it through all of this and without you, none of this would have been possible.
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List of Abbreviations

\(^1\)H=proton
\(^{129}\)Xe=Xenon-129
\(^3\)He=Helium-3
4DCT=four-dimensional computed tomography
6MWD=six-minute walk distance
ADC=apparent diffusion coefficient
ANOVA=one-way analysis of variance
BMI=body mass index
COPD=chronic obstructive pulmonary disease
CT=computed tomography
\(D_{LCO}\)=diffusing capacity of the lung for carbon monoxide
FD=Fourier Decomposition
FEV\(_1\)=forced expiratory volume in 1 second
FGRE=fast-spoiled gradient recalled echo
FRC=functional residual capacity
FVC=forced vital capacity
GOLD=Global initiative for chronic Obstructive Lung Disease
HIPAA=health insurance portability and accountability act
HU=Hounsfield units
IC=inspiratory capacity
MIND=modality independent neighborhood descriptor
mPRM= multi-parametric response map
MRI=magnetic resonance imaging
PRM=parametric response map
RA\(_{950}\)=relative area of the lung \(<950\) Hounsfield units
Rb=Rubidium
RV=residual volume
SGRQ=St. George’s Respiratory Questionnaire
SPECT=single-photon emission computed tomography
TE=echo time
TINCan=Thoracic Imaging Network of Canada
TLC=total lung capacity
TR=repetition time
TV=tidal volume
UTE=ultra-short echo time
VDP=ventilation defect percent
ZTE=zero echo time
CHAPTER 1

1 INTRODUCTION

Irreversible airflow obstruction due to parenchymal destruction, airway remodelling and luminal obstruction is the defining characteristic of chronic obstructive pulmonary disease (COPD). Imaging of COPD has focused on x-ray computed tomography (CT) or hyperpolarized gas magnetic resonance imaging (MRI) to measure the underlying pathophysiology and phenotype the disease, but no studies have investigated measurements obtained by combining information from both modalities. In this thesis, MRI and CT imaging measurements were combined to generate multi-parametric response maps (mPRM) and these maps were used to reveal phenotypes of COPD undetected using CT or MRI alone.

1.1 Motivation and Rationale

Chronic obstructive pulmonary disease (COPD) is a debilitating disease affecting 252 million people globally\(^1\) and constitutes the third leading cause of death worldwide.\(^2\) Figure 1-1 highlights COPD as the most prominent cause of death compared to other chronic lung diseases. In addition to being a major contributor to worldwide mortality, this disease also constitutes a large healthcare burden. COPD exacerbations are the largest cause of prolonged hospital stays in Canada aside from giving birth,\(^3\) and these patients are more likely to be re-admitted to hospital than any other chronic disease.\(^4\) In 2008, the direct cost of hospitalization in Canada from a COPD exacerbation was estimated at $10,000 per patient with combined costs of the disease totaling $1.5 billion every year.\(^5\) By 2011, this total severely underestimated the cost of COPD as the combined healthcare cost of this disease contributed about $3.9 billion in Ontario alone.\(^6\)
Figure 1.1: Chronic Respiratory Disease Global Deaths.
Amongst chronic respiratory diseases, COPD is the leading cause of death (n=3.2 million). Number of deaths are displayed using a logarithmic scale. This figure was adapted from GBD 2017 Causes of Death Collaborators, Lancet (2018).

COPD is clinically diagnosed and monitored using pulmonary function tests due to their ease of use and extensive validation. Although these tests are the gold standard, they only provide a global measure of lung health and cannot determine the specific underlying pathophysiology in patients with similar outputs. To compensate for these limitations, x-ray computed tomography (CT) and hyperpolarized gas magnetic resonance imaging (MRI) have been used to collect regional structure and function information in the lungs. Pulmonary CT has been used to quantify lung structure abnormalities such as parenchymal destruction and airway remodelling, while hyperpolarized gas MRI has been used to provide lung function and structure measurements such as ventilation heterogeneity and airspace enlargement. This thesis focuses on the development and application of a multi-modality imaging method to combine pulmonary CT structure and MRI structure/function to phenotype COPD.

This chapter provides the relevant background knowledge to understand the motivation for the original research provided in Chapter 2. In section (1.2), an overview of the respiratory system’s structure and function is presented, followed by the pathophysiology of COPD (1.3). Next, the current clinical measurements and diagnostic criteria of COPD (1.4) as well as...
pulmonary imaging techniques (1.5) will be discussed. Finally, the hypotheses and objectives of this thesis will be stated (1.6).

1.2 Structure and Function of the Lung

The lung’s primary function is the transportation of oxygen to the bloodstream, and the removal of carbon dioxide from the body. To accomplish this task, the lung conducts air into the trachea, down the bronchi, through the bronchioles, into the alveolar ducts and ends in the alveoli where gas exchange occurs.

1.2.1 Airways

The airways are the main conduits of the respiratory system. As we move down the airway tree, the airways begin to bifurcate and increase in number. These smaller airways gradually decrease in diameter but increase in total cross-sectional area. Furthermore, the composition of the airway walls begins to change from cartilaginous to smooth muscle to epithelium as you progress more distally. The entire airway tree can be divided into the conducting zone and the respiratory zone (Figure 1-2). The conducting airways comprise the trachea, the bronchi and the terminal bronchioles, and contain only a small portion of the lung volume (approximately 150 mL). The conducting zone is also known as “anatomic dead space” since it does not participate in gas exchange. Alternatively, the lung region that participates in gas exchange is called the respiratory zone. This area comprises the respiratory bronchioles, the alveolar ducts and the alveolar sacs. Since total cross-sectional area of all the airways increases further down the airway tree, this zone constitutes the majority of the lung volume (2.5 – 3.0 L).11
1.2.2 Parenchyma

The primary function of the lung, gas exchange, occurs in tiny (0.3 mm in diameter) air sacs called alveoli. Within the respiratory zone, approximately 500 million alveoli\textsuperscript{11,12} are clustered together to create a very large surface area (approximately 85 m\textsuperscript{2}) for gas exchange. The efficient architecture of the extremely thin alveolar walls (approximately 0.2-0.3 μm thick),
and the dense network of capillaries encompassing these alveoli allows for the near instantaneous exchange of oxygen and carbon dioxide with the bloodstream.

### 1.3 Pathophysiology of Chronic Obstructive Pulmonary Disease

COPD is defined by irreversible airflow obstruction caused by parenchymal destruction, airway remodelling, and luminal occlusion. These physiologic abnormalities are heterogeneously distributed throughout the lungs, and the extent of these abnormalities varies between people. The most common risk factor for developing COPD is the inhalation of noxious particles such as cigarette smoke, chemicals or inorganic dust, but other risk factors of the disease include a history of severe respiratory infection or genetic disorders such as alpha-1 antitrypsin deficiency.

![Diagram of Pathologic Changes in COPD](image)

**Figure 1-3:** Diagram of Pathologic Changes in COPD. Panels from left to right: normal small airway, normal lung parenchyma, emphysematous destruction of parenchyma, and remodelled airway with inflammatory exudates and thickened airway wall. Airway panels were adapted from Hogg (2004) and parenchyma panels were adapted from Woods et al. (2006). Permission to reproduce provided in Appendix C.
1.3.1 Emphysema

Emphysema is characterized by parenchymal tissue destruction resulting in the permanent enlargement of the airspaces\textsuperscript{17,18} (Figure 1-3). The location and extent of parenchymal destruction varies between patients, but can be sub-classified into centrilobular, panlobular, paraseptal, and bullous emphysema.\textsuperscript{19} Centrilobular emphysema predominately affects the central part of the respiratory bronchioles leaving the alveoli unaffected and is associated with cigarette smoking. Conversely, panlobular emphysema affects both the respiratory bronchioles and the alveoli and is commonly observed in alpha-1 antitrypsin deficiency patients. Finally, paraseptal emphysema affects the lung tissue near the pleural septa. As emphysema progresses, the increased tissue destruction forms large airspaces known as bulla (bullous emphysema). In COPD, this destruction of parenchymal tissue reduces the surface area of the lungs needed for gas exchange as well as causes narrowing of the airways through loss of radial traction.\textsuperscript{20}

1.3.2 Airway Remodeling

Airway remodeling is caused by chronic inflammation and mucus plugging commonly associated with chronic bronchitis (Figure 1-3). Excessive mucus secretion in the airways combined with inflammatory exudates form semi-solid plugs that occlude smaller bronchioles. Additionally, the repeated inflammation of the airways leads to a narrowing of the small airways due to cellular infiltration thickening the airway wall, increases in smooth muscle, and fibrotic restriction of airway enlargement.\textsuperscript{15,20,21} This remodeling process either occludes the airways thereby reducing the number of alveoli able to participate in gas exchange, or narrows the airways substantially that closure occurs during exhalation trapping air in the lungs (gas-trapping).

The majority of airway obstruction occurs in the small airways (< 2 mm diameter).\textsuperscript{22-24} Since these small airways have a large total cross-sectional area and only account for a small portion of total airway resistance, obstructions in these airways have little impact on total airway resistance making them relatively invisible on spirometry and allowing them to accumulate undetected in these airways over a long time.\textsuperscript{22} More recently, the obstruction of the small airways termed small airways disease has been observed to precede emphysematous destruction of the lung.\textsuperscript{25,26}
1.4 Clinical Measures of Global Lung Function

The gold standard for diagnosing and assessing COPD is pulmonary function testing. These tests provide an overall measure of lung health and function and are used to quantify disease progression and treatment efficacy. Pulmonary function tests include spirometry, plethysmography, and the diffusing capacity of the lung for carbon monoxide (DL\textsubscript{CO}). The assessments provided by these tests are commonly presented as a percent of the predicted value calculated from the patient’s age, sex, height, and ethnicity.\textsuperscript{27}

1.4.1 Spirometry

Spirometry is the simplest of the pulmonary function tests to perform and can be administered using a handheld device as shown in Figure 1-4. This test is performed by having the patient make a tight seal around the mouthpiece and begin breathing normally through the device. After a couple of normal breaths, the patient inhales to total lung capacity (TLC) then forcefully exhales until no more air can be expelled.\textsuperscript{28} The volume of air the patient can expel from TLC in 1 second is known as the forced expiratory volume in 1 second (FEV\textsubscript{1}), and the volume expelled from TLC to full exhalation is known as the forced vital capacity (FVC).

![Handheld Spirometer and Volume-time Curve Used to Measure FEV\textsubscript{1} and FVC. FEV\textsubscript{1}: forced expiratory volume in 1 second; FVC: forced vital capacity](image)

These two measures, FEV\textsubscript{1} and FVC, are used to clinically diagnose COPD. In COPD, there is a reduction in both FEV\textsubscript{1} and FVC due to increased airway resistance and early airway
closure respectively. A ratio of FEV$_1$/FVC < 0.70 post-bronchodilator is the clinical definition of COPD according to the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria. Once the presence of COPD has been established, FEV$_1$ percent predicted is used to determine severity as seen in Table 1-1.

**Table 1-1: COPD Severity Based on GOLD Criteria**

<table>
<thead>
<tr>
<th>GOLD I</th>
<th>Mild</th>
<th>FEV$<em>1$ %$</em>{pred}$ $\geq$ 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD II</td>
<td>Moderate</td>
<td>50% $\leq$ FEV$<em>1$ %$</em>{pred}$ $&lt;$ 80%</td>
</tr>
<tr>
<td>GOLD III</td>
<td>Severe</td>
<td>30% $\leq$ FEV$<em>1$ %$</em>{pred}$ $&lt;$ 50%</td>
</tr>
<tr>
<td>GOLD IV</td>
<td>Very Severe</td>
<td>FEV$<em>1$ %$</em>{pred}$ $&lt;$ 30%</td>
</tr>
</tbody>
</table>

1.4.2 Plethysmography

Plethysmography calculates different lung volumes using Boyle’s Law. The lung volumes measured include functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV). FRC is the lung volume present after exhalation during normal breathing, TLC is the maximum lung volume attainable through inhalation, and RV is the minimum lung volume remaining after exhalation. From these three volumes, the inspiratory capacity (IC) and vital capacity (VC) can be calculated. The IC measures the maximum volume inspired from FRC and the VC is the maximum volume inspired from RV. Tidal volume (TV) is the volume inspired during normal breathing (figure 1-5).

This measurement is performed in a sealed chamber known as a body plethysmograph. The patient sits upright inside the sealed chamber and performs a set of breathing maneuvers. The test starts with the patient breathing normally, and when the patient reaches near FRC, a shutter closes in the mouthpiece. The patient lightly pants into the shuttered mouthpiece for a few seconds then the shutter opens and the patient inhales to TLC and exhales to RV. From these breathing maneuvers, changes in pressure at the mouthpiece and inside the chamber can be used to calculate FRC from Boyle’s law since the volume of the sealed chamber is known. In COPD, these lung volumes are elevated due to gas-trapping in the lungs.
1.4.3 Diffusing Capacity of the Lung for Carbon Monoxide

Diffusing capacity of the lung for carbon monoxide (D_{LCO}) can be used to probe alveolar tissue integrity in patients with emphysema. This test is performed by having the patient first exhale to RV, then inhale a specific gas mixture containing a small amount of carbon monoxide (0.3%) to TLC. At TLC, the patient holds their breath for 10 seconds allowing for the carbon monoxide to diffuse into the blood stream and then exhales. The difference in the concentration of carbon monoxide between the inhaled and exhaled gas mixtures is used to calculate the amount of gas that diffused into the blood stream.\(^{30}\) D_{LCO} is reduced in COPD due to emphysema decreasing the surface area for gas exchange as well as airway occlusions blocking the gas mixture from reaching the alveoli.

1.5 Imaging Pulmonary Structure and Function

Although widespread, validated, and clinically diagnostic, pulmonary function tests provide only information about the global health of the lung and are not sensitive to regional changes.\(^{31}\) To supplement these measurement, pulmonary imaging provides regional information about the lungs and assists in quantifying underlying pathophysiology. Pulmonary imaging can be broadly divided into structural and functional components. Lung structure has been imaged using CT, and ultra-short echo time (UTE) MRI, and provides measurements of
emphysema,\textsuperscript{7,32} gas-trapping,\textsuperscript{33,34} and airway architecture.\textsuperscript{8,35} Lung function can be assessed through multiple imaging modalities such as single-photon emission computed tomography (SPECT), CT, and MRI, and these modalities focus on ventilation within the lungs.\textsuperscript{36-38} As mentioned in Section 1.1, this thesis focuses on the development of a multi-modality structure-function map in COPD. In this section, I highlight the diverse pulmonary imaging techniques used in studying COPD and provide some of their applications in COPD for possible use in expansion of the method presented in this thesis.

1.5.1 Structural Imaging

Advances in medical imaging has allowed for the non-invasive monitoring of changes in lung tissue and identification of anatomical abnormalities. The changes in lung tissue include airway remodelling through airway wall thickening or bronchiole destruction and parenchymal changes through emphysema or fibrosis.

Computed Tomography

CT was developed in the 1970s and has become the imaging modality of choice when assessing pulmonary diseases. Three-dimensional volumes are generated by acquiring multiple x-ray images at various angles as the x-ray source and detector are rotated around the patient, and these 2-D x-ray images are reconstructed into a 3D volume. Tissue density in these images is measured in Hounsfield Units (HU), a measurement of an object’s density relative to water,\textsuperscript{39} and is calculated using the equation below:

$$ HU = \left( \frac{\mu_{\text{Tissue}} - \mu_{\text{Water}}}{\mu_{\text{Water}}} \right) \times 1000 $$

where the linear attenuation coefficients for the tissue of interest is $\mu_{\text{Tissue}}$ and water is $\mu_{\text{Water}}$. The dynamic range of this measurement transitions from bone (1000 HU) to water (0 HU) to air (-1000 HU) with all other tissue falling in between. From these density measurements, tissue abnormalities in the lung such as emphysema and gas-trapping can be measured. With emphysema, the destruction of the surrounding tissue creates large pockets of air in the lungs thereby reducing the tissue density in those regions. This reduction in tissue density creates low attenuating regions on CT with HU values similar to air. In COPD, these low attenuating
areas can be quantified on inspiratory CT as a measure of the extent of emphysema in the lungs. Figure 1-6 visualizes these low attenuating regions as dark patches on CT and highlights the extent of emphysema within the lungs in yellow. Commonly set thresholds for emphysema include -910 HU,$^{40}$ -950 HU,$^{7}$ and -960 HU.$^{41}$ Additionally, gas-trapping is similarly measured as low attenuating areas on full expiratory CT due to airway closures trapping air within the lungs. A commonly used threshold of gas-trapping is -856 HU.$^{42,43}$

In addition to measuring tissue integrity, the airway tree can be segmented using CT analysis packages such as VidaVision (Vida Diagnostics, Coralville, IA, USA), Pulmo3D (Fraunhofer MEVIS, Bremen, Germany) or thoracic VCAR (General Electric Healthcare, Milwaukee, WI, USA). The number of airway generations visible is limited by the resolution of the CT images, but typically it can be segmented down to the beginning of the small airways (<2 mm diameter). From these trees, airway measurements such as wall area percent, wall thickness, and lumen area can be used to assess the narrowing of the small airways. The thickening of the airway walls and reduction of the lumen area have been associated with a decline in pulmonary function,$^{8,44}$ increased prevalence of symptoms,$^{45}$ and progression of COPD.$^{25}$ Additionally, the loss of peripheral airways$^{21,22}$ and reduction in total airway count$^{46}$ have also been associated with disease progression.$^{25,26}$
Figure 1-6: Computed Tomography Images of COPD. Top: coronal centre slices for healthy, mild and severe COPD. Low attenuating areas (RA_{950}) indicative of emphysema are highlighted in yellow. Bottom: 3D models of CT airway trees.

Ultra-short Echo Time MRI

While CT provides many structural measurements of the lung, the main disadvantage of this technique is the radiation dose to the patient which limits its uses. MRI on the other hand has no dose concerns but suffers from low signal in the lungs. The low signal stems from a low proton density present within the lung tissue and local magnetic field susceptibility at the air-tissue interfaces leading to fast signal decay.\textsuperscript{47,48} By shortening the echo time required, improved k-space acquisition techniques such as ultra-short echo time (UTE) and more recently zero echo time (ZTE)\textsuperscript{49} are able to minimize the signal lost through decay. These
techniques have provided measures of tissue density that correlate well with CT measures of emphysema, CT functional lung volume and pulmonary function in COPD as well as provided similar structural measurements as low-dose CT without the radiation dose.

### 1.5.2 Functional Imaging

In contrast to measuring structural changes, functional imaging identifies defects in the lungs by mimicking respiration. These techniques can be broadly divided into two groups depending on whether or not inhaled gas contrast agents are used.

#### Xenon Enhanced Dual Energy CT

Xenon enhanced dual energy CT leverages the different attenuation properties of xenon at high and low photon energies to separate it from the surrounding air and soft tissue. Using this difference, xenon can work as an inhaled contrast agent to measure ventilation in the lungs. This is performed by having the patient wear a secured positive-pressure ventilation facemask and breathing a 30%/70% xenon/oxygen mixture until the lungs are filled with 30% xenon. Once this point is reached, simultaneous acquisitions from two x-ray sources occur allowing for three-material decomposition to separate the xenon signal from the surrounding air and tissue. This technique has been applied to COPD and other pulmonary diseases. In COPD, low attenuating regions on CT retained xenon during dynamic washout and xenon ventilation correlated with pulmonary function. Although research into this imaging technique has provided measures of lung ventilation in COPD, a few limitations, such as xenon inhalation side effects, radiation exposure, and cost, still need to be addressed.

#### Four-Dimensional X-ray Computed Tomography (4DCT)

In addition to using inhaled xenon to assess lung ventilation, regional volume changes during the respiratory cycle can be used as a surrogate for lung ventilation. This surrogate measurement follows the assumption that healthy lung will have a large change in volume while gas-trapping and restricted areas will have a small change in volume with the respiratory cycle. To measure this volume change, an imaging technique known as four-dimensional CT (4DCT) acquires multiple CT images throughout the respiratory cycle. These images are binned into specific respiratory phases, and expiratory and inspiratory images are co-registered together. After co-registration, the voxel deformations are used to calculate this surrogate
measure of ventilation. This technique has shown reasonable correlation with xenon enhanced CT\textsuperscript{60} and SPECT ventilation\textsuperscript{62,63}. Current implementation of this technique has been focused in lung cancer. CT ventilation in these patients has correlated with pulmonary function\textsuperscript{64,65} and is reduced in areas of emphysema\textsuperscript{66}. Since lung cancer is commonly co-morbid in COPD, similar results with pulmonary function and emphysema are expected. Although 4DCT provides reasonable measures of ventilation, artifacts stemming from the binning process or registration have a major effect on lung ventilation\textsuperscript{62,63}.

**Parametric Response Mapping**

Another surrogate functional imaging technique, parametric response mapping (PRM), uses co-registered inspiratory and expiratory CT images to classify lung tissue based on the presence of air. This voxel-wise mapping technique was first introduced using MRI measures of water diffusion and relative blood volume and flow to detect treatment efficacy in glioblastomas\textsuperscript{67,68} and later applied to thoracic CT for phenotyping disease severity in COPD\textsuperscript{69}. This technique labels spatially co-registered voxels using tissue density thresholds of emphysema (<-950 HU on inspiratory)\textsuperscript{7} and gas-trapping (<-856 HU on expiratory).\textsuperscript{42} The lung tissue is divided into three groups based on these thresholds: normal, functional small airways disease, and emphysema. As seen in Figure 1-7, normal (green) tissue is defined as any co-registered voxel with a value that is greater than both the inspiratory and expiratory thresholds. Functional small airways disease (yellow) tissue is defined as any voxel that is greater than the inspiratory threshold but less than the expiratory threshold. This classification indicates early closure of the airways during exhalation leading to gas-trapping in the lungs. Finally, emphysema (red) tissue is defined as any voxel that is less than both the inspiratory and expiratory thresholds. Voxels that are less than the inspiratory threshold and greater than the expiratory threshold indicate noise within the images. In studies of participants with COPD, PRM measurements were correlated with pulmonary function\textsuperscript{69,70}, determined presence of COPD in current and former smokers\textsuperscript{71}, and were associated with decline in FEV\textsubscript{1}\textsuperscript{72}. Additionally, PRM measures of functional small airways disease predicted patient survivability after lung transplant\textsuperscript{73} and more recently have been histologically validated as an imaging measure of small airways disease in severe COPD\textsuperscript{74}. This technique has also provided imaging evidence to the idea that small airways disease precedes emphysema in the progression of COPD\textsuperscript{25,26,69,75}. 

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Figure 1-7: Diagram for Paired Inspiratory/Expiratory CT Parametric Response Mapping. Spatially registered voxels (left) are labeled based on CT densities (centre) to generate a functional map of the tissue (right).

Single-Photon Emission Computed Tomography (SPECT)

SPECT uses inhaled radioactive tracers that emit high energy photons (gamma rays) when they decay. After the inhalation of the tracer, multiple images are acquired from a single or multiple gamma cameras rotating around the patient to collect the gamma rays. These images are then reconstructed to generate a three dimensional volume of the radioactivity. The commonly inhaled radioactive tracers to generate ventilation images are gaseous $^{81}\text{Kr}$, $^{133}\text{Xe}$, or an ultrafine aerosol $^{99}\text{mTc}$-labeled carbon (“Technegas”). In COPD, SPECT ventilation has a longer washout time in areas of emphysema,\textsuperscript{76} and correlates with pulmonary function.\textsuperscript{77} It has also shown ventilation and gas-trapping in emphysematous bullae\textsuperscript{78} and correlation with disease severity.\textsuperscript{77,79}

Oxygen Enhanced MRI

In order to reduce radiation exposure during functional imaging, new MRI techniques have been developed. These techniques use non-radioactive inhaled gas contrast to mimic inhaled air and highlight functioning tissue. Oxygen enhanced MRI as a functional imaging technique was first developed in 1996.\textsuperscript{80} This technique leveraged the weakly paramagnetic properties of oxygen and the large surface area of the lungs to increase MRI signal in the parenchyma.
Ventilation of the lungs is calculated by acquiring T1-weighted proton images at baseline (21% oxygen saturation) and oxygen enhanced (100% oxygen saturation) and finding the relative change in signal intensity for each voxel between the oxygen enhanced image and the baseline room air image. In COPD, this oxygen enhancement ratio has shown correlation with diffusing capacity, CT measures of emphysema, post-treatment clinical outcomes, and pulmonary function loss and disease severity.

Hyperpolarized Gas MRI

Hyperpolarized gas MRI uses noble gases such as 3He and 129Xe as an inhaled contrast agent to visualize the regional ventilation of the lungs. Due to the low density of atoms in gases, these gases must be hyperpolarized to increase their MR signal. To polarize these gases, spin-exchange from a laser-based optical pumping technique is used. Briefly, alkali metal vapor (typically Rubidium) absorbs circularly polarized laser light. Collisions between the vaporized metal and the noble gas transfers the stored angular momentum from the vaporized metal to the noble gas nucleus. This transfer of angular momentum flips the spin of the unpaired proton in the noble gas. This optical pumping technique allows for an increase in the signal of the gas by 5 orders of magnitude compared to its thermal equilibrium value. Hyperpolarized gas imaging of the lungs started in 1994 using 129Xe. The field transitioned to 3He for its larger gyromagnetic ratio allowing for better signal-to-noise and improved polarization, but factors such as limited availability and increased cost of 3He as well as technological improvements in 129Xe polarization have led the field back to 129Xe again.

Hyperpolarized gas MRI allows for the visualization of functional lung regions through mimicking the movement of air into the lungs by inhaling the polarized gas. As seen in Figure 1-8, the teal areas highlight functioning regions of the lung that the gas can travel to while the dark areas are unventilated regions of the lung known as ventilation defects. Quantification of non-functioning lung has been performed using the ratio of unventilated lung volume to total lung volume, known as ventilation defect percent (VDP). In COPD, this measure of ventilation is correlated with SPECT ventilation, related to disease severity, highly repeatable, related to pulmonary function, diffusing capacity, and CT measures of emphysema and gas-trapping, as well as improves with application of a bronchodilator.
This imaging technique has also been used to predict exacerbations, longitudinal changes in quality of life, and visualize collateral ventilation in COPD.

Another imaging technique using hyperpolarized gas is diffusion weighted imaging. Diffusion weighted imaging takes advantage of the restricted Brownian motion of the gas within the lungs to provide a measure of tissue integrity known as the apparent diffusion coefficient (ADC). These ADC values are highly reproducible and are sensitive to regions of emphysema. This sensitivity comes from changes in alveolar dimensions caused by emphysema. In healthy tissue, the movement of the gas molecules is restricted by the airways and alveolar walls; while in emphysematous regions, destruction of these tissue structures allows the gas molecules to move around more freely. ADC measurements are also related to CT measures of emphysema, pulmonary function, diffusing capacity, quality of life, and are a sensitive measure of reduced exercise capacity in mild COPD.

While an important measure of emphysema, there are other factors that can influence ADC values such as gravity induced tissue compression, alveolar distension due to gas-trapping, and age.

While $^3$He and $^{129}$Xe MRI provide important measures of lung function, there are some safety and imaging factors that need to be considered as the field transitions back to xenon. The use of xenon is well tolerated in patients, but there are some side effects such as dizziness, light-headedness and euphoria due to the analgesic nature xenon. Although present, these side effects subside within a few minutes. With respect to imaging measures, $^{129}$Xe ventilation has greater defect volumes compared to $^3$He, which has been attributed to the lower diffusivity of xenon in air thereby preventing the gas from traveling through partially occluded airways within the timeframe of the breath hold scan. Additionally, these regions of unventilated lung on $^{129}$Xe are related to increased emphysema in those areas. Although hyperpolarized gas provides important measures, this modality is limited by high costs, specialized equipment and hardware, and clinical approval.
Figure 1-8: Hyperpolarized Gas MRI for Healthy and COPD Subjects.
Top: $^3$He static ventilation for healthy and COPD subjects. The healthy subject has uniform ventilation throughout the lungs, while the COPD subjects have a more heterogeneous ventilation. 
Bottom: $^3$He ADC images for healthy and COPD subjects. The healthy subject has uniformly low ADC values indicating normal tissue integrity while the COPD subjects have higher ADC values indicating tissue destruction.

Free-Breathing Fourier Decomposition Magnetic Resonance Imaging (FDMRI)
Another proton-based functional imaging technique is Fourier decomposition MRI (FDMRI). Similar to 4DCT, FDMRI uses the deformation of lung tissue as a surrogate of ventilation. As air fills the lungs, tissue density decreases thereby reducing MR signal and voxel intensity. This technique uses multiple images of a single slice acquired over a time series during tidal breathing. These images are then non-rigidly registered together, and the changing voxel intensities from the tissue expansion and compression are used to create an oscillating signal for each voxel. A fast Fourier transform is applied to these oscillating signals to create a frequency spectrum. The peak amplitude at the respiratory frequency for each voxel is determined, and from these amplitudes, a ventilation weighted image is generated.\textsuperscript{113} FDMRI ventilation is consistent with hyperpolarized $^3$He\textsuperscript{114-116} and SPECT\textsuperscript{117} measures of ventilation,
and in COPD, FDMRI ventilation is correlated with pulmonary function\textsuperscript{118} while ventilation defects are correlated with airways resistance and CT measures of emphysema.\textsuperscript{114}

1.6 Thesis Hypotheses and Objectives

COPD is diagnosed and monitored using spirometry. While this measurement is widely available and easy to use, it provides only a global assessment of lung health. Recently, CT and hyperpolarized gas MRI have been used to measure regional information about the lungs. Generally, imaging measurements of COPD have only focused on one of these imaging modalities and have not used both in combination. Therefore, the overarching objective of this thesis was to develop a multi-modality image processing pipeline to generate combined CT and MRI measurements in the form of a multi-parametric response map. To do this, hyperpolarized gas MRI and CT images were segmented and registered together. CT and MRI thresholds of normality were used to generate voxel-wise labels, and these labels were combined to create multi-parametric response maps. We hypothesized that combining MRI and CT measurements would reveal phenotypes of COPD that are undetected using MRI or CT alone. The objective of Chapter 2 was to develop a multi-modality image processing pipeline to combine CT and MRI measurements and to apply it to a cohort of COPD patients.

In Chapter 3, I provide a summary of the important findings and conclusions from Chapter 2 and discuss the limitations of this work. Finally, I conclude with some future directions to build upon the work presented in this thesis.
1.7 References


4 Canadian Insitute for Health Information. Health Indicators 2008. (Ottawa: CIHI, Ottawa, 2008).


20 West, J. B. *Pulmonary Pathophysiology: The Essentials*. (Lippincott Williams & Wilkins, 2008).


CHAPTER 2

2 PULMONARY IMAGING PHENOTYPES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING MULTI-PARAMETRIC RESPONSE MAPS

2.1 INTRODUCTION

In patients with chronic obstructive pulmonary disease (COPD), irreversible airflow obstruction related to parenchymal destruction, airway remodeling and luminal obstruction drives debilitating symptoms, poor quality of life and premature death. While the forced expiratory volume in 1 second (FEV₁) remains a key clinical and diagnostic measurement of COPD, it cannot provide regional information nor adequately discriminate between patients with different underlying pathologies such as airspace enlargement and small airways disease that present differently in individual patients.

To address some of the limitations of spirometry measurements, thoracic x-ray CT has been used to provide quantitative airway and parenchyma information as well as indirect information related to small airways disease generated using parametric response maps (PRM). Pulmonary CT has been used widely in studies such as COPDGene, SPIROMICS, MESA, CanCOLD and ECLIPSE. CT PRM quantifies COPD severity, monitors COPD progression and predicts post-transplant survival.

Hyperpolarized noble gas MRI has also been used to measure regional lung ventilation and airspace enlargement in patients with COPD. MRI ventilation heterogeneity is quantified using ventilation defect percent, which is related to COPD severity and exacerbations. Hyperpolarized ³He MRI apparent diffusion coefficients (ADC) may also be used in patients with COPD to estimate terminal airspace enlargement and such measurements have been histologically validated.

The Thoracic Imaging Network of Canada (TINCan) study acquired volume-matched CT and MRI in ex-smokers with and without COPD in whom spatial correlations between MRI
ventilation defects and non-contrast low-dose CT measurements of emphysema and airways disease were reported.\textsuperscript{18} CT PRM in TINCan participants also revealed spatial correlations between PRM measures of emphysema and gas-trapping with MRI values.\textsuperscript{21} In addition, in a small group of at-risk TINCan ex-smokers without CT evidence of emphysema and modestly abnormal diffusing capacity, there was abnormal MRI ADC, profound exercise limitation and diminished quality of life.\textsuperscript{22} Given the complementary nature of pulmonary CT and hyperpolarized gas MRI, we postulated that combining the information of these two modalities would provide new measures of lung abnormality not seen using CT or MRI alone. Based on these previous findings, we hypothesized that by combining MRI and CT measurements using a multi-parametric voxel approach, phenotypes would be observed that are undetected using CT or MRI alone. The purpose of this study was to generate multi-parametric response map (mPRM) measurements in ex-smokers with and without COPD using volume-matched CT and hyperpolarized \textsuperscript{3}He MRI measurements acquired within a few minutes of one another.

\section*{2.2 MATERIALS AND METHODS}

\subsection*{2.2.1 Study Participants and Design}

We evaluated ex-smokers with and without COPD who provided written informed-consent to a research ethics board approved (Institutional Ethics Board # 00000984) and HIPAA-compliant, registered study (NCT02279329 clinicaltrials.gov). Participants were recruited from local tertiary care clinics and through advertisements as a convenience sample. Inclusion criteria for the study were men and women between 45-90 years of age, clinical diagnosis of COPD or >10 pack year smoking history, in stable health and ambulatory. Exclusion criteria included MRI contraindications, complete CT and MRI datasets missing or participants with bronchiectasis only (Figure 2-1). The study was prospectively planned and performed from December 2010 to January 2019; participants underwent a single two-hour visit and performed spirometry, plethysmography, quality of life questionnaires, exercise capacity tests, MRI and CT as previously described.\textsuperscript{20} Evaluations were performed 20 minutes after administering Novo-Salbutamol HFA using a metered-dose inhaler (four doses of 100 ug, Teva Novopharm Ltd., Toronto, ON, Canada) through a spacer (\textit{AeroChamber Plus} spacer, Trudell Medical International, London, ON, Canada). Participants in the TINCan study have been previously described.\textsuperscript{18,22-26} These prior articles dealt with a cross-sectional and longitudinal analysis of
the CT and MRI data and their relationships with quality of life, exacerbations and exercise capacity, whereas in this manuscript we report on the development of an mPRM approach and apply this to 175 TINCan participants who had complete image datasets required for the analysis. Data generated during the study are available from the corresponding author and the mPRM method we developed is also available online (www.imaging.robarts.ca/parraga/).

![Flowchart](image)

**Figure 2-1.** Participant Flowchart
Flowchart showing the participants enrolled in the study. COPD=chronic obstructive pulmonary disease; mPRM=multi-parametric response maps.
2.2.2 Pulmonary Function and Quality of Life Tests

Spirometry, plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO) were performed according to American Thoracic Society/European Respiratory Society guidelines\textsuperscript{27-29} using a body plethysmograph (MedGraphics Elite Series, MGC Diagnostic Corporation, St. Paul, MN) with an attached gas analyzer. The St. George’s Respiratory Questionnaire was administered,\textsuperscript{30} and a six-minute walk test was performed.\textsuperscript{31}

2.2.3 MRI

All MRI acquisitions were performed using methods that were previously described.\textsuperscript{20} Briefly, anatomical proton ($^1$H), hyperpolarized $^3$He static ventilation, and diffusion weighted MRI were performed supine on a 3.0-T Discovery MR750 system (GE Healthcare, Milwaukee, WI) with broadband imaging capabilities. $^1$H MRI was acquired using a fast-spoiled gradient recalled echo sequence (FGRE) (TR/TE/flip angle = 4.7ms/1.2ms/30°) with a whole-body radio-frequency coil during a breath-hold after inhalation of 1.0-L of N$_2$.

$^3$He polarization was performed to 30%-40% polarization and all $^3$He MRI was performed using a single-channel rigid elliptical transmit-receive chest coil (RAPID Biomedical, Wuerzburg, Germany) during a 1.0-L breath-hold of diluted hyperpolarized gas. $^3$He static ventilation was acquired using an FGRE sequence (TR/TE/flip angle = 4.3ms/1.4ms/7°) while diffusion-weighted $^3$He was acquired using an FGRE sequence (TR/TE/flip angle = 7.6ms/3.7ms/8°) with and without diffusion sensitzation with b = 1.6 s/cm$^2$. A detailed description of the MRI acquisition parameters is provided in the Supplement.

2.2.4 CT Imaging

Within 30 minutes of the MRI, CT was acquired supine on a 64-slice Lightspeed VCT scanner (GE Healthcare) under breath-hold after inhalation of 1.0-L N$_2$ from functional residual capacity using the following parameters: 64 x 0.625 mm, 120 kVp, 100 mA effective current, rotation time = 500 ms, and pitch = 1.0.\textsuperscript{22} Specific CT acquisition parameters are provided in the Supplement. Total effective dose was estimated as 1.8 mSv using the ImPACT CT patient dosimetry calculator (based on Health Protection Agency [UK] NRBP-SR250).
2.2.5 Image Analysis

MR and CT image segmentations were performed by a single observer (J.L.M with 1.5 years of experience). $^3$He and $^1$H MRI were semi-automatically segmented and co-registered using in-house software. Diffusion-weighted images were automatically processed to generate lung ADC images. CT images were segmented using Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, IA). Image registration of $^3$He ventilation, ADC, and CT images was performed using a custom algorithm in MATLAB R2018a (Mathworks, Natick, MA). CT and $^1$H MRI were non-rigidly registered using the modality-independent neighborhood-descriptor method; $^3$He ventilation and ADC images were co-registered using intensity-based rigid registration. Image analysis specifics are provided in the Supplement.

2.2.6 Development of Multi-Parametric Response Maps

Once all the images were co-registered, voxels within the proton thoracic cavity were labelled to generate mPRM. These labels were generated based on ventilation, ADC values and CT density histogram threshold values as shown in Figure 2-2. The CT threshold of -950 Hounsfield units (HU) was used as a well-established and validated measure of emphysema in the lungs; whereas the ADC threshold of 0.3 cm$^2$/s was based upon experimentally acquired ADC values reported in a group of elderly never-smokers. The threshold we used was equal to one standard deviation of the mean of this group, as a conservative estimate. ADC values for this group of never-smokers were previously reported. Although CT imaging was performed at functional residual capacity+1L, this lung volume is roughly 80-90% of total lung capacity in COPD patients, especially when supine in the scanner; moreover, Madani and colleagues also previously reported that such differences related to lung volume are within a few percent for RA950 values and that these are unlikely to be clinically relevant. Multi-parametric response maps were evaluated by a single observer (J.L.M). Figure 2-3 shows in schematic, for a representative Global initiative for chronic Obstructive Lung Disease (GOLD) III-IV ex-smoker, the generation of mPRM values and the five resultant mPRM voxel classifications: 1) Normal in green, 2) Ventilated, CT $\geq$ -950 HU, Abnormal ADC in yellow, 3) Ventilated, CT Emphysema, Abnormal ADC in orange, 4) Not Ventilated, CT $\geq$ -950 HU, No ADC in red and 5) Not Ventilated, CT Emphysema, No ADC in burgundy. ADC values reflect gas displacement but only in ventilated regions of the lung. Because CT and MR images were
acquired at the same lung volume, the potential for co-registration errors is low but not impossible. Hence, voxels labelled Ventilated, CT Emphysema, Normal ADC were classified as registration errors because of the high sensitivity of MRI to emphysema which suggests that normal ADC and CT emphysema are unlikely in the same voxel, although this finding may also stem from partial volume averaging.
**Figure 2-2.** Multi-parametric Response Map Thresholds and Decision Tree

HU=Hounsfield unit; ADC=apparent diffusion coefficient

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<th>Image Thresholds</th>
<th>Normal</th>
<th>Abnormal</th>
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<td>&lt; -950 HU</td>
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**Figure 2-3.** Schematic for Multi-parametric (MRI and CT) Response Maps in COPD

Top: Co-registration of three contemporaneously acquired images of a GOLD III/IV ex-smoker (CT, MRI ventilation, MRI ADC) into a single map.

Bottom: Three-dimensional mPRM voxel classification. Green=ventilated voxels, CT ≥ -950 HU and normal ADC; Yellow=ventilated voxels, CT ≥ -950 HU and abnormal (>0.30cm²/s) ADC; Orange=ventilated voxels, CT emphysema and abnormal ADC; Red voxels=not ventilated, CT ≥ -950 HU, no ADC values measurable; Burgundy voxels=not ventilated, CT emphysema, no ADC values measurable. Clear=registration error.
2.2.7 Statistical Analysis

Statistical tests were performed using SPSS Statistics V25.0 (SPSS Inc., Armonk, NY). A Shapiro-Wilk test was used to determine the normality of the data. Kruskal-Wallis tests with post hoc Dunn-Bonferroni were used to determine differences between groups for mPRM voxel distributions. Spearman correlation coefficients with a Bonferroni correction were determined for mPRM voxel distributions, pulmonary function, and quality of life test measurements. Since each clinical measurement was correlated multiple times with every mPRM classification measurement, a Bonferroni correction of six was multiplied to the original p-values, and the adjusted p-values were compared for significance. All results were considered statistically significant when the probability of making a Type I error was less than 5% (p<.05).

2.3 RESULTS

2.3.1 Study Participants

All participants were 48-87 years old (mean age: 69±9 years; mean age in men: 70±10 years; age range in men: 48-87 years; mean age in women: 68±8 years; age range in women: 52-83 years). We generated mPRM measurements as shown in Figure 2-2 and 2-3 in 175 ex-smokers without (n=67, 68±10 years, 39 men) and with GOLD grade I (n=24, 74±7 years, 20 men), II (n=49, 69±8 years, 29 men), and III/IV (n=35, 68±9 years, 20 men) COPD. The mean and standard deviation of ADC values within the never-smoker group was 0.26 ± 0.04 cm²/s, which was consistent with previous work,³⁵ and was used to determine the abnormal ADC threshold. The flowchart in Figure 2-1 shows that for 263 total participants enrolled, 53 withdrew prior to the first visit, 10 participants had bronchiectasis, not COPD and 25 participants did not complete imaging (either MRI or CT), resulting in 175 participants who were evaluated.

Table 2-1 provides demographic, pulmonary function test, imaging and quality of life measurements for all participants and by subgroup classified according to GOLD criteria which were different across subgroups (all p<.05). Figure 2-4 shows representative ³He ventilation MRI as well as ADC and CT relative area of the lung <-950 HU (RA₀₉₅₀) maps. Figure 2-4 also shows there was qualitatively worse or increased MRI ventilation heterogeneity, ADC, and RA₀₉₅₀ voxels (in yellow) with increasing COPD severity.
<table>
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<td>98 (19)</td>
<td>95 (11)</td>
<td>64 (9)</td>
<td>35 (7)</td>
</tr>
<tr>
<td>FVC %pred</td>
<td>91 (19)</td>
<td>92 (17)</td>
<td>109 (12)</td>
<td>92 (15)</td>
<td>71 (15)</td>
</tr>
<tr>
<td>FEV₁/FVC %</td>
<td>62 (18)</td>
<td>80 (6)</td>
<td>63 (5)</td>
<td>53 (9)</td>
<td>38 (8)</td>
</tr>
<tr>
<td>TLC %pred</td>
<td>111 (18)</td>
<td>101 (14)</td>
<td>112 (12)</td>
<td>115 (18)</td>
<td>125 (17)</td>
</tr>
<tr>
<td>RV/TLC %pred</td>
<td>121 (27)</td>
<td>107 (18)</td>
<td>107 (17)</td>
<td>125 (18)</td>
<td>161 (23)</td>
</tr>
<tr>
<td>RₘAW %pred</td>
<td>170 (140)*</td>
<td>115 (66)</td>
<td>122 (44)</td>
<td>175 (112)</td>
<td>314 (218)**</td>
</tr>
<tr>
<td>DLₜCO %pred</td>
<td>65 (23)*</td>
<td>79 (21)</td>
<td>69 (19)</td>
<td>57 (18)***</td>
<td>42 (18)****</td>
</tr>
<tr>
<td>RA₉₅₀ %</td>
<td>6 (9)</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>8 (9)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>VDP %</td>
<td>12 (10)</td>
<td>6 (4)</td>
<td>8 (5)</td>
<td>14 (8)</td>
<td>25 (9)</td>
</tr>
<tr>
<td>ADC cm²/s</td>
<td>0.35 (.11)</td>
<td>0.26 (.03)</td>
<td>0.34 (.08)</td>
<td>0.39 (.10)</td>
<td>0.46 (.09)</td>
</tr>
<tr>
<td>SGRQ Total</td>
<td>35 (22)‡</td>
<td>25 (22)†</td>
<td>23 (16)‡‡</td>
<td>38 (15)***</td>
<td>58 (13)****</td>
</tr>
<tr>
<td>6MWD m</td>
<td>393 (87)¶</td>
<td>405 (91)£</td>
<td>420 (49)</td>
<td>399 (88)§</td>
<td>340 (83)¶</td>
</tr>
</tbody>
</table>

%pred, percent predicted; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; RₘAW, airways resistance; DLₜCO, diffusing capacity of the lung for carbon monoxide; RA₉₅₀, relative area of the lung < -950 Hounsfield units; VDP, ventilation defect percent; ADC, apparent diffusion coefficient; SGRQ, St. George’s Respiratory Questionnaire; 6MWD, six-minute walk distance; SD, standard deviation; GOLD, Global initiative for chronic Obstructive Lung Disease grade; COPD, chronic obstructive pulmonary disease.

* n=173 ** n=33 *** n=48 **** n=34 ‡n=165 † n=61 * * n=22 †† n=163 £ n=65 § n=46 ¶ n=28
Figure 2-4. Representative Coronal MRI and CT by COPD Severity
Ventilation is shown in aqua. Yellow highlights areas of the lung with CT attenuation < -950 Hounsfield units on inspiratory CT
Ex-smoker without COPD: 56-year-old man with a 41-pack-years smoking history and normal pulmonary function including FEV$_1$=101%, FEV$_1$/FVC=0.89; RV/TLC=106%, DL$_{CO}$=79% (all % predicted)
GOLD I: 87-year-old man with a 15-pack-years smoking history and modestly abnormal pulmonary function including FEV$_1$=88%, FEV$_1$/FVC=0.60; RV/TLC=95%; DL$_{CO}$=59% (all %predicted)
GOLD II: 77-year-old woman with a 112-pack-years smoking history and abnormal airflow, hyperinflation and diffusing capacity FEV$_1$=66%, FEV$_1$/FVC=0.51, RV/TLC=145%, DL$_{CO}$=49% (all %predicted)
GOLD III/IV: 76-year-old woman with a 30-pack-years smoking history and highly abnormal airflow, hyperinflation and highly abnormal diffusing capacity (FEV$_1$=37%, FEV$_1$/FVC=0.52, RV/TLC=139%, DL$_{CO}$=19% (all %predicted))

FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DL$_{CO}$, diffusing capacity of the lung for carbon monoxide; COPD, chronic obstructive pulmonary disease; RA$_{950}$, relative area of the lung < -950 Hounsfield units; ADC, apparent diffusion coefficient.
2.3.2 mPRM Lung Fraction Measurements

Figure 2-5 shows the resultant mPRM findings for all participants by lung fraction and representative centre-slice coronal mPRM maps for a representative ex-smoker and representative COPD participants. Figure 2-5A shows there was a larger fraction of normal (green) mPRM voxels in ex-smokers (all p≤.001) and a smaller fraction of abnormal (yellow, orange, red and burgundy) mPRM voxels compared with all subgroups of COPD participants. Ex-smokers without COPD also reported a smaller fraction of unventilated, normal CT voxels compared to ex-smokers with GOLD II and III/IV COPD (all p<.001). mPRM revealed two novel mPRM voxel types (yellow and red) that were both present in “normal” ex-smokers and which reflect mild emphysema or hyperinflation and airways disease respectively. Figure 2-5B also shows there was a greater fraction of abnormal mPRM voxels as COPD severity increased.
Figure 2-5. mPRM Lung Fraction Measurements and Increasing COPD Severity

A. mPRM voxel category by lung fraction for all ex-smokers without COPD (n=67), GOLD grade I (n=24), II (n=49) and III/IV (n=35). In ex-smokers with no spirometric evidence of COPD there was a greater fraction of normal voxels and smaller fraction of abnormal voxels than in subgroups of COPD. As COPD grade increases, there is a decrease in normal voxels, and an increase in abnormal voxels.

B. Representative mPRM voxel maps for an ex-smoker without COPD (79-year-old, 32 pack years) (mainly green (normal) and yellow (ventilated, CT ≥ -950 HU, abnormal ADC) voxels) and participants with GOLD grade I (71-year-old, 66 pack years) (mainly yellow, orange (ventilated, CT emphysema, abnormal ADC) and red (not ventilated, CT ≥ -950 HU) voxels), GOLD grade II (86-year-old, 50 pack years) (similar to GOLD I except with a greater amount of orange and red voxels) and GOLD grade III/IV (68-year-old, 93 pack years) (similar to GOLD II except with greater amounts of burgundy (not ventilated, CT emphysema) voxels).

* indicates p≤.001 compared to ex-smokers without COPD
** indicates p<.01 compared to GOLD I
2.3.3 mPRM Relationships with Pulmonary Measurements

Table 2-2 shows Spearman correlation coefficients for mPRM lung fraction measurements with FEV\textsubscript{1} %pred, the ratio of FEV\textsubscript{1} to forced vital capacity (FVC), DL\textsubscript{CO}, the St. George’s Respiratory Questionnaire (SGRQ) total score, and six-minute walk distance in ex-smokers with and without COPD. In all participants, normal mPRM lung fraction measurements (green voxels in Figure 2-3 and 2-5) were correlated with FEV\textsubscript{1} %pred ($r = 0.65$, $p<.001$), FEV\textsubscript{1}/FVC ($r = 0.81$, $p<.001$), DL\textsubscript{CO} ($r = 0.75$, $p<.001$), and SGRQ ($r = -0.48$, $p<.001$). mPRM ventilated, normal CT and abnormal ADC (yellow) lung fraction measurements were correlated with FEV\textsubscript{1} %pred ($r = -0.42$, $p<.001$), FEV\textsubscript{1}/FVC ($r = -0.60$, $p<.001$), DL\textsubscript{CO} ($r = -0.60$, $p<.001$), and SGRQ ($r = 0.33$, $p<.001$). Table 2-2 also shows that mPRM ventilated, CT emphysema and abnormal ADC (orange) lung fraction measurements were correlated with FEV\textsubscript{1} %pred ($r = -0.64$, $p<.001$), FEV\textsubscript{1}/FVC ($r = -0.83$, $p<.001$), DL\textsubscript{CO} ($r = -0.66$, $p<.001$), and SGRQ ($r = 0.45$, $p<.001$). Unventilated with normal CT (red in Figure 2-3 and 2-5) mPRM lung fraction measurements were correlated with FEV\textsubscript{1} %pred ($r = -0.65$, $p<.001$), FEV\textsubscript{1}/FVC ($r = -0.70$, $p<.001$), DL\textsubscript{CO} ($r = -0.53$, $p<.001$), and SGRQ ($r = 0.45$, $p<.001$) whereas unventilated, CT emphysema (dark burgundy) lung fraction measurements were correlated with FEV\textsubscript{1} %pred ($r = -0.72$, $p<.001$), FEV\textsubscript{1}/FVC ($r = -0.86$, $p<.001$), DL\textsubscript{CO} ($r = -0.63$, $p<.001$), and SGRQ ($r = 0.46$, $p<.001$). Table 2-2 also shows that all mPRM lung fraction measurements except for ventilated, CT ≥ -950 HU, abnormal ADC voxels were correlated with six-minute walk distance. Figure 2-6 to 2-10 show univariate regressions for mPRM lung fraction measurements and clinical measures while Table 2-3 provides Spearman correlation coefficients for all disease severity subgroups.
Table 2-2: Spearman Correlation Coefficients for mPRM Voxel Classes as a Fraction of Total Lung

<table>
<thead>
<tr>
<th>Spearman correlation coefficient R (p)</th>
<th>Normal (%) of lung</th>
<th>Ventilated+ CT ≥ -950 HU+ Abnormal ADC (%) of lung</th>
<th>Ventilated+ CT Emphysema+ Abnormal ADC (%) of lung</th>
<th>Not Ventilated+ CT ≥ -950 HU+ No ADC (%) of lung</th>
<th>Not Ventilated+ CT Emphysema+ No ADC (%) of lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1%pred</td>
<td>.65 (&lt;.001)</td>
<td>-.42 (&lt;.001)</td>
<td>-.64 (&lt;.001)</td>
<td>-.65 (&lt;.001)</td>
<td>-.72 (&lt;.001)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>.81 (&lt;.001)</td>
<td>-.60 (&lt;.001)</td>
<td>-.83 (&lt;.001)</td>
<td>-.70 (&lt;.001)</td>
<td>-.86 (&lt;.001)</td>
</tr>
<tr>
<td>DLCO%pred</td>
<td>.75 (&lt;.001)</td>
<td>-.60 (&lt;.001)</td>
<td>-.66 (&lt;.001)</td>
<td>-.53 (&lt;.001)</td>
<td>-.63 (&lt;.001)</td>
</tr>
<tr>
<td>SGRQ**</td>
<td>-.48 (&lt;.001)</td>
<td>.33 (&lt;.001)</td>
<td>.45 (&lt;.001)</td>
<td>.45 (&lt;.001)</td>
<td>.46 (&lt;.001)</td>
</tr>
<tr>
<td>6MWD***</td>
<td>.28 (.002)</td>
<td>-.19 (.08)</td>
<td>-.27 (.003)</td>
<td>-.29 (.001)</td>
<td>-.29 (.001)</td>
</tr>
</tbody>
</table>

All study participants (n=175)

P values adjusted using Bonferroni correction of six to account for multiple comparisons for multi-parametric response map voxel classes. Significant correlations are bold. ADC, apparent diffusion coefficient; HU, Hounsfield unit; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; SGRQ, St. George’s Respiratory Questionnaire total score; 6MWD, six-minute walk distance; mPRM, multi-parametric response map.

*n=173 **n=165 ***n=163
Figure 2-6: Spearman Correlations for Normal mPRM Voxel Class and Clinical Measures.

%pred, percent predicted; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; SGRQ, St. George’s Respiratory Questionnaire; mPRM, multi-parametric response map.
Figure 2-7: Spearman Correlations for Ventilated, CT Normal with Abnormal ADC mPRM Voxel Class and Clinical Measures

%pred, percent predicted; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; DL$_{CO}$, diffusing capacity of the lung for carbon monoxide, SGRQ, St. George’s Respiratory Questionnaire; mPRM, multi-parametric response map; ADC, apparent diffusion coefficient.
Figure 2-8: Spearman Correlations for Ventilated, CT Emphysema and Abnormal ADC mPRM Voxel Class and Clinical Measures

%pred, percent predicted; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; DL$_{CO}$, diffusing capacity of the lung for carbon monoxide, SGRQ, St. George’s Respiratory Questionnaire; mPRM, multi-parametric response map; ADC, apparent diffusion coefficient.
Figure 2-9: Spearman Correlations for Unventilated, CT Normal mPRM Voxel Class and Clinical Measures
%pred, percent predicted; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide, SGRQ, St. George’s Respiratory Questionnaire; mPRM, multi-parametric response map; ADC, apparent diffusion coefficient.
Figure 2-10: Spearman Correlations for Unventilated, CT Emphysema mPRM Voxel Class and Clinical Measures

%pred, percent predicted; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide, SGRQ, St. George’s Respiratory Questionnaire; mPRM, multi-parametric response map; ADC, apparent diffusion coefficient.
Table 2-3: Spearman Correlation Coefficients for mPRM Voxel Classes as a Fraction of Total Lung

<table>
<thead>
<tr>
<th>Spearman R (p)</th>
<th>Normal (% of lung)</th>
<th>Ventilated+ CT ≥ -950 HU+ CT Emphysema+ Abnormal ADC (% of lung)</th>
<th>Ventilated+ CT ≥ -950 HU+ Abnormal ADC (% of lung)</th>
<th>Not Ventilated+ CT ≥ -950 HU+ No ADC (% of lung)</th>
<th>Not Ventilated+ CT Emphysema+ No ADC (% of lung)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=175)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%pred</td>
<td>.65 (&lt;.001)</td>
<td>-.42 (&lt;.001)</td>
<td>-.64 (&lt;.001)</td>
<td>-.65 (&lt;.001)</td>
<td>-.72 (&lt;.001)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>.81 (&lt;.001)</td>
<td>-.60 (&lt;.001)</td>
<td>-.83 (&lt;.001)</td>
<td>-.70 (&lt;.001)</td>
<td>-.86 (&lt;.001)</td>
</tr>
<tr>
<td>DL-CO%pred</td>
<td>.75 (&lt;.001)</td>
<td>-.60 (&lt;.001)</td>
<td>-.66 (&lt;.001)</td>
<td>-.53 (&lt;.001)</td>
<td>-.63 (&lt;.001)</td>
</tr>
<tr>
<td>SGRQ***</td>
<td>-.48 (&lt;.001)</td>
<td>.33 (&lt;.001)</td>
<td>.45 (&lt;.001)</td>
<td>.45 (&lt;.001)</td>
<td>.46 (&lt;.001)</td>
</tr>
<tr>
<td>6MWD***</td>
<td>.28 (.002)</td>
<td>-.19 (.08)</td>
<td>.27 (.003)</td>
<td>-.29 (.001)</td>
<td>-.29 (.001)</td>
</tr>
<tr>
<td>Ex-smokers (n=67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%pred</td>
<td>-.14 (&gt;.99)</td>
<td>.10 (&gt;.99)</td>
<td>.12 (&gt;.99)</td>
<td>.06 (&gt;.99)</td>
<td>-.05 (&gt;.99)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>.22 (.08)</td>
<td>-.20 (.65)</td>
<td>-.27 (.18)</td>
<td>-.16 (&gt;.99)</td>
<td>-.33 (.04)</td>
</tr>
<tr>
<td>DL-CO%pred</td>
<td>.40 (.01)</td>
<td>-.41 (.01)</td>
<td>-.06 (&gt;.99)</td>
<td>-.27 (.18)</td>
<td>-.09 (&gt;.99)</td>
</tr>
<tr>
<td>SGRQ‡</td>
<td>-.30 (.12)</td>
<td>.32 (.08)</td>
<td>.24 (.40)</td>
<td>.06 (&gt;.99)</td>
<td>.18 (&gt;.99)</td>
</tr>
<tr>
<td>6MWD‡</td>
<td>.33 (.04)</td>
<td>-.35 (.02)</td>
<td>-.30 (.09)</td>
<td>-.20 (.64)</td>
<td>-.31 (.08)</td>
</tr>
<tr>
<td>GOLD I (n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%pred</td>
<td>.15 (&gt;.99)</td>
<td>-.15 (&gt;.99)</td>
<td>-.14 (&gt;.99)</td>
<td>-.14 (&gt;.99)</td>
<td>-.15 (&gt;.99)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>.40 (.31)</td>
<td>-.38 (.40)</td>
<td>-.46 (.13)</td>
<td>-.03 (&gt;.99)</td>
<td>-.27 (&gt;.99)</td>
</tr>
<tr>
<td>DL-CO%pred</td>
<td>.70 (.001)</td>
<td>-.62 (.01)</td>
<td>-.68 (.001)</td>
<td>-.39 (.37)</td>
<td>-.46 (.14)</td>
</tr>
<tr>
<td>SGRQ §</td>
<td>-.25 (&gt;.99)</td>
<td>.25 (&gt;.99)</td>
<td>.17 (&gt;.99)</td>
<td>.33 (.82)</td>
<td>.33 (.84)</td>
</tr>
<tr>
<td>6MWD §</td>
<td>-.01 (&gt;.99)</td>
<td>.09 (&gt;.99)</td>
<td>-.09 (&gt;.99)</td>
<td>-.40 (.31)</td>
<td>-.36 (.52)</td>
</tr>
<tr>
<td>GOLD II (n=49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%pred</td>
<td>.18 (&gt;.99)</td>
<td>-.02 (&gt;.99)</td>
<td>-.18 (&gt;.99)</td>
<td>-.24 (.57)</td>
<td>-.37 (.05)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>.47 (.01)</td>
<td>-.15 (&gt;.99)</td>
<td>-.55 (&lt;.001)</td>
<td>-.36 (.07)</td>
<td>-.65 (&lt;.001)</td>
</tr>
<tr>
<td>DL-CO%pred§</td>
<td>.67 (&lt;.001)</td>
<td>-.54 (&lt;.001)</td>
<td>-.63 (&lt;.001)</td>
<td>.03 (&gt;.99)</td>
<td>-.44 (.01)</td>
</tr>
<tr>
<td>SGRQ $</td>
<td>-.11 (&gt;.99)</td>
<td>.22 (.80)</td>
<td>0 (&gt;.99)</td>
<td>.03 (&gt;.99)</td>
<td>-.08 (&gt;.99)</td>
</tr>
<tr>
<td>6MWD$</td>
<td>.05 (&gt;.99)</td>
<td>-.12 (&gt;.99)</td>
<td>-.02 (&gt;.99)</td>
<td>-.03 (&gt;.99)</td>
<td>0 (&gt;.99)</td>
</tr>
<tr>
<td>GOLD III/IV (n=35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%pred</td>
<td>-.08 (&gt;.99)</td>
<td>.41 (.08)</td>
<td>-.31 (.41)</td>
<td>.04 (&gt;.99)</td>
<td>-.34 (.28)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>.51 (.01)</td>
<td>.34 (.27)</td>
<td>-.62 (&lt;.001)</td>
<td>-.12 (&gt;.99)</td>
<td>-.63 (&lt;.001)</td>
</tr>
<tr>
<td>DL-CO%pred‡</td>
<td>.73 (&lt;.001)</td>
<td>.14 (&gt;.99)</td>
<td>-.71 (&lt;.001)</td>
<td>.03 (&gt;.99)</td>
<td>-.58 (.002)</td>
</tr>
<tr>
<td>SGRQ‡</td>
<td>-.17 (&gt;.99)</td>
<td>-.14 (&gt;.99)</td>
<td>.07 (&gt;.99)</td>
<td>.14 (&gt;.99)</td>
<td>.22 (&gt;.99)</td>
</tr>
<tr>
<td>6MWDδ</td>
<td>.09 (&gt;.99)</td>
<td>.28 (94)</td>
<td>-.14 (&gt;.99)</td>
<td>-.20 (&gt;.99)</td>
<td>-.23 (&gt;.99)</td>
</tr>
</tbody>
</table>

P values adjusted using Bonferroni correction of six to account for multiple comparisons for multi-parametric response map voxel classes. Significant correlations are bold. ADC, apparent diffusion coefficient; HU, Hounsfield unit; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; SGRQ, St. George’s Respiratory Questionnaire total score; 6MWD, six-minute walk distance; mPRM, multi-parametric response map.

* n=173 ** n=165 *** n=163 **** n=61 † n=65 ‡ n=22 § n=48 ¶ n=46 †† n=34 ‡‡ n=28
2.3.4 mPRM Phenotypes in Ex-smokers without COPD

Figure 2-11 shows mPRM maps for four representative ex-smokers with normal spirometry and CT. These maps highlight the heterogeneity observed in ex-smokers and the regional distribution of mPRM voxels including green (normal ventilation, CT and ADC), yellow (normal ventilation and CT, abnormal ADC) and red (not ventilated, normal CT) voxels. For example, Figure 2-11A shows the resultant green (or normal) mPRM map for a 51-year-old man with 32-pack-year history, normal spirometry (FEV₁=75%pred, FEV₁/FVC=0.77) and normal DLCO (95%pred). In contrast, in Figure 2-11B, there is a mixture of green (normal) and yellow (ventilated, CT ≥ -950 HU, abnormal ADC) mPRM voxels in a 76-year-old man with 24-pack-years smoking history, normal spirometry (FEV₁=115%pred, FEV₁/FVC=0.72) and abnormal DLCO (59%pred). Figure 2-11C provides another mPRM map for a participant with similar pulmonary function measurements (80-year-old woman, 27-pack-year history, normal spirometry (FEV₁=124%pred, FEV₁/FVC=0.71), abnormal DLCO (49%pred)) which is comprised of mainly yellow (ventilated, CT ≥ -950 HU, abnormal ADC) mPRM voxels. Finally, Figure 2-11D shows the mPRM map for a 72-year-old man, with 20-pack-years smoking history, normal spirometry (FEV₁=122%pred, FEV₁/FVC=0.80) and DLCO (73%pred) which consists of a mixture of green (normal) mPRM voxels throughout and red (not ventilated, CT ≥ -950 HU) voxels in wedge-shaped peripheral (subsegmental) lung regions.
Figure 2-11. mPRM Maps in Representative Ex-smokers without COPD
A. Mainly green (normal) voxels in a 51-year-old man, 32-pack-years, FEV₁=75%, FEV₁/FVC=0.77, DLCO=95%
B. Mixture of green (normal) and yellow (ventilated, CT ≥ -950 HU, abnormal ADC) voxels in a 76-year-old man, 24-pack-years, FEV₁=115%, FEV₁/FVC=0.72, DLCO=59%
C. Mainly yellow (ventilated, CT ≥ -950 HU, abnormal ADC) voxels in a 80-year-old woman, 27-pack-years, FEV₁=124%, FEV₁/FVC=0.71, DLCO=49%
D. Mixture of green (normal), yellow (ventilated, CT ≥ -950 HU, abnormal ADC) and red (not ventilated, CT ≥ -950 HU) voxels in a 72-year-old man, 20-pack-years, FEV₁=122%, FEV₁/FVC=0.80, DLCO=73%
(all %predicted)

2.4 DISCUSSION

Previous work has shown that hyperpolarized gas MRI and CT provide complementary disease information in COPD, but this information has not been combined into a single image. In this study, we generated mPRM measurements, combining CT and MRI, in 175 ex-smokers including 108 participants with and 67 participants without COPD. We observed: 1) significantly different mPRM lung fraction measurements with increasing disease severity, 2) significant associations for mPRM lung fraction measurements with pulmonary function and quality of life (all p<.001), and 3) two mPRM voxel types that were suggestive of disease transition/progression in ex-smokers with normal spirometry and CT, neither of which were detected using CT or MRI alone.

Lung fraction measurements using mPRM were significantly different with increasing COPD severity which is not surprising in light of previous single modality CT and MRI studies in COPD. These previous studies also showed that as COPD severity increases, there is a
decrease in total airway count and terminal bronchioles.\textsuperscript{24,36} With increasing COPD severity, mPRM measurements also transition from mainly normal voxels to hyper-inflated or mild emphysema voxels, to ventilation abnormalities and then advanced emphysema with ventilation abnormalities.

These mPRM lung fraction measurements were also correlated with pulmonary function, quality of life and exercise capacity measurements. The relationship of mPRM phenotypes with DL\textsubscript{CO} measurements appears to transition from potential sub-clinical emphysema in ex-smokers with normal spirometry and CT to progressively more severe emphysema in COPD. These results are consistent with previous findings of the strong relationship between DL\textsubscript{CO} and measures of emphysema.\textsuperscript{2,3,22}

By identifying abnormal lung regions using mPRM maps, there is the potential to provide insight into the transition from normal to diseased COPD states and this hypothesis requires testing in a prospective longitudinal study. The heterogeneity of mPRM maps in at-risk ex-smokers shows the presence of abnormal lung regions that are not obvious on CT or MRI alone. Voxels with normal CT and ventilation but abnormal ADC can be interpreted in the context of previous work that revealed MRI evidence of subclinical airspace enlargement (due to emphysema or alveolar distension) in a small group of ex-smokers without CT RA\textsubscript{950} measurements consistent with emphysema.\textsuperscript{22} Regions of elevated ADC may indicate regions of subclinical emphysema, possible alveolar distension or gas-trapping and are consistent with previous findings.\textsuperscript{21,22} While not visible on CT or reflected using spirometry, these microstructural changes may also be an indicator of early terminal airspace destruction.

Another key finding, in an apparently normal ex-smoker, is regions of the lung that have normal CT voxels but no gas distribution. These regions are consistent with subsegmental small airways disease. In COPD, the narrowing or destruction of the small airways is thought to precede the development of emphysema,\textsuperscript{36} but these affected small airways cannot be detected with spirometry and are CT invisible.\textsuperscript{14,37} CT PRM has also provided a way to regionally identify gas-trapping based on voxels that are normal on inspiration CT but abnormal (<856HU) on expiration CT,\textsuperscript{4,14} and has been validated as an imaging measurement of small airways disease in very severe COPD.\textsuperscript{38} Multi-modality mPRM maps unite structural
and functional abnormalities in a way that resembles CT PRM measurements of emphysema and small airways disease, and may provide another way to highlight the transition phases in COPD. Further evaluation of unventilated, normal CT voxels is required with CT airway and PRM measurements to clarify the pathophysiology responsible for these findings.

We expected to observe overlap of structure-function imaging findings in participants with COPD. In other words, the mPRM findings in GOLD grade I through IV are in keeping with our understanding of COPD pathophysiology and the finding of increasingly abnormal tissue and airway structure-function in participants with more advanced or severe COPD. However, we did not expect, based on previous findings to observe mPRM evidence of airways disease (not ventilated, normal CT) and mild emphysema (ventilated, normal CT, abnormal ADC) in ex-smokers with otherwise normal CT and spirometry values. These two novel findings in a highly heterogeneous convenience sample of ex-smokers without airflow obstruction challenge our understanding of normal pulmonary function test results in ex-smokers who currently are not considered to have, nor are treated for COPD.

We acknowledge several study limitations including the fact that MRI-CT co-registration errors will influence voxel classification. Importantly, CT and MRI were acquired at the same lung volume, assisting with image registration accuracy (Supplement). ADC images have twice the slice thickness compared to the ventilation images, which often makes resampling complex. We also used a fixed threshold for CT emphysema and an experimentally derived fixed ADC threshold based on assumptions about age-matched never-smoker ADC values. Other factors may influence ADC values in participants with relatively healthy lungs and therefore the ADC threshold we used may not represent terminal airspace enlargement or emphysema but perhaps airspace distention. We acquired CT images at functional residual capacity+1L instead of full inspiration, validated for CT emphysema measurements (950HU). For the participants in our study, and based on plethysmographic data, functional residual capacity+1L = 80-90% of total lung capacity, especially when lying supine in the scanner. This means that the estimates of CT emphysema here should be considered as fractionally lower than estimates for patients at full inflation, but this difference is unlikely to be clinically relevant. Nevertheless, the emphysema estimates in our participants are similar to those in other published studies such as MESA, CanCOLD, SPIROMICS and
COPDGene. Another limitation of this study was the lack of a control group of age-matched never-smokers which would help provide a better understanding of the physiological relevance of the mPRM values. Longitudinal data on the lack of progression (or the progression of) these two new imaging phenotypes of COPD remains to be investigated.

In conclusion, we developed a multi-modality image processing pipeline to generate pulmonary mPRM measurements that were related to pulmonary function tests and quality of life and revealed phenotypes in at-risk ex-smokers not detected using CT or MRI alone. To our knowledge, this is the first multi-parametric analysis of thoracic CT and MRI in patients with COPD and at-risk ex-smokers.
2.5 REFERENCES


2.6 SUPPLEMENT

2.6.1 Materials and Methods

2.6.1.1 Pulmonary Function and Quality of Life Tests

Participants were seated in a body plethysmograph (MedGraphics Elite Series, MGCDiagnostic Corporation, St. Paul, MN) and coached through the breathing maneuvers for spirometry, plethysmography, and diffusing capacity according to the American Thoracic Society and European Respiratory Society guidelines. Afterwards, the participants filled out the St. George’s Respiratory Questionnaire with staff nearby to answer any questions they may have about the questionnaire. Finally, the participants performed a six-minute walk test at a brisk walking pace that was comfortable to them. Before and after the test, participant’s heart rate and SaO2 were recorded.

2.6.1.2 MRI Acquisition

All MR acquisition parameters have been described elsewhere; but briefly, anatomical proton (^1H) was acquired using a fast-spoiled gradient-recalled echo (FGRE) sequence with a partial echo: total acquisition time = 16 seconds, repetition time [TR] = 4.7 ms, echo time [TE] = 1.2 ms, flip angle = 30°, field of view [FOV] = 40x40 cm; matrix =128x80 (zero padded to 128x128), bandwidth = 24.4 kHz, one excitation, 15-17 slices, slice thickness = 15 mm, 0 gap. Hyperpolarized ^3He static ventilation was acquired using an FGRE sequence with a partial echo: total acquisition time = 14 seconds, TR = 4.3 ms, TE = 1.4 ms, flip angle = 7°, FOV = 40x40 cm, bandwidth = 48.8 kHz, matrix = 128x80 (zero padded to 128x128), 15-17 slices, slice thickness = 15 mm, 0 gap. Diffusion-weighted ^3He MRI was performed using an FGRE sequence with total acquisition time = 14 seconds, TR = 7.6 ms, TE = 3.7 ms, flip angle = 8°, FOV = 40x40 cm, matrix = 128x128, 7-9 slices, slice thickness = 30 mm, 0 gap, with and without additional diffusion sensitization with b = 1.6 s/cm^2 (gradient amplitude (G) = 1.94 G/cm, rise and fall time = 0.5 ms, gradient duration = 0.46 ms, diffusion time = 1.46 ms).

2.6.1.3 CT Imaging

CT acquisition parameters have been described elsewhere. Briefly, a non-contrast low-dose single spiral acquisition during a breath-hold was used: detector configuration = 64x0.625 mm, peak voltage = 120 kVp, effective current = 100 mA, rotation time = 500 ms, pitch = 1.0, slice
thickness = 1.25 mm, number of slices = 200-250, matrix = 512x512. The CT was acquired axially, and reconstructed to a slice interval of 1.25 mm using a standard convolution kernel. Total effective dose was estimated as 1.8 mSv using the ImPACT CT patient dosimetry calculator (based on Health Protection Agency [UK] NRBP-SR250).

2.6.1.4 MR Image Analysis

$^3$He static ventilation images were segmented using a k-means clustering algorithm to divide the image into five clusters with the first cluster being ventilation defect, and the fifth cluster being regions of hyper-intense signal. The thoracic cavity volume was segmented for the $^1$H images using a seeded region growing algorithm as previously described$^2$. Diffusion-weighted images were segmented by applying a 2-D Hanning window to the k-space data of the non-diffusion-weighted image to improve the signal-to-noise ratio between the lungs and the background. An intensity-based threshold was applied to the non-diffusion-weighted image to generate a mask of ventilated lung and this mask was then applied to both the diffusion-weighted and non-diffusion-weighted images to isolate the ventilated lung. These segmented images were processed to generate lung apparent diffusion coefficient (ADC) maps on a voxel-wise basis using equation 1:

$$ADC = \frac{1}{b} \ln \left( \frac{S_0}{S} \right) \quad (1)$$

where $S_0$ is the signal intensity of the non-diffusion-weighted image, $S$ is the signal intensity of the diffusion-weighted image, and $b$ is the diffusion gradient ($b = 1.6 \text{ s/cm}^2$).

2.6.1.5 Image Registration

The image registration pipeline has been described elsewhere.$^3$ Briefly, the volume matched CT and ADC images were resized to match the proton image voxel dimensions using nearest neighbor interpolation to preserve the original image information. Volume matched $^3$He and $^1$H images were registered using a landmark-based affine registration approach as previously described$^2$. The CT and $^1$H MRI were non-rigidly registered using a symmetric modality independent neighborhood descriptor (MIND) method.$^4$ Since the $^3$He static ventilation and ADC images are both determined by lung ventilation, a rigid registration method was used to co-register these images. The Dice Similarity Coefficients for the 175 participants were $95\pm1\%$ for the CT to $^1$H registration and $84\pm5\%$ for $^3$He ADC to $^3$He ventilation registration.
2.6.2 References


3 MacNeil, J. L. et al. in *Medical Imaging 2019: Biomedical Applications in Molecular, Structural, and Functional Imaging*. 109530J (International Society for Optics and Photonics).

CHAPTER 3

3 CONCLUSIONS AND FUTURE DIRECTIONS

In this final chapter, a summary and overview is provided for the important findings and conclusions presented in Chapter 2. Limitations specific to this study are provided along with possible solutions. Finally, the chapter concludes by discussing future directions for the methods developed and discussed here.

3.1 Overview and Research Objectives

Hyperpolarized gas MRI and CT have been used to provide regional information about the lung and to supplement spirometry in the phenotyping of COPD. Typically, only one imaging modality is used, looking at either CT structure or MRI structure/function. The overarching objective of this thesis was to develop and apply a multi-modality image processing pipeline to generate combined CT and MRI measurements. We postulated that combined CT and MRI measurements would reveal phenotypes of COPD that were undetected using MRI or CT alone. The specific objectives were first to develop a multi-modality image processing pipeline to generate multi-parametric response maps from CT and MRI measurements, and second to apply this pipeline to a large cohort of COPD patients.

3.2 Summary and Conclusions

In Chapter 2, we developed an image processing pipeline to generate multi-parametric response maps from co-registered CT, $^3$He MRI ventilation and ADC images. We applied this pipeline to a large cohort of ex-smokers with and without COPD and investigated the relationship between our multi-parametric measures and disease severity, pulmonary function, quality of life, and exercise capacity. 175 ex-smokers (108 with and 67 without COPD) were evaluated. Multi-parametric measurements became increasingly more abnormal with disease severity, and correlated with pulmonary function, exercise capacity, and quality of life measurements. These results indicate the potential of this multi-parametric approach to detect new phenotypes of COPD as well as clarify the relationship of these measures with disease severity.
3.3 Limitations

Although Chapter 2 presented positive results for the first MRI-CT multi-parametric analysis of COPD, there are a number of limitations that need to be addressed. The first major limitation is the fact that MRI-CT co-registration errors will influence voxel classification. To assist with image registration accuracy, CT and MRI were acquired at the same lung volume. Additionally, the larger slice thickness of the ADC images compared to the ventilation images made resampling complex due to signal averaging and partial volume effects. Next, the fixed thresholds we used were based on an established cut-off for CT emphysema\(^1\) as well as an experimentally derived fixed ADC threshold based on assumptions about age-matched never-smoker ADC values.\(^2\) Other factors such as gravity induced tissue compression,\(^3\)-\(^6\) age\(^7\) and airspace distention due to gas-trapping\(^8\),\(^9\) may influence ADC values in participants with relatively healthy lungs; therefore, the ADC threshold we used may not represent terminal airspace enlargement or emphysema. As mentioned above, we acquired CT images at functional residual capacity+1L instead of full inspiration to help with image registration, but this volume may influence the CT emphysema measurements calculated from the validated threshold (-950HU)\(^1\) used. For the participants in our study, and based on plethysmographic data, functional residual capacity+1L = 80-90% of total lung capacity, especially when lying supine in the scanner. This means that the estimates of CT emphysema here should be considered as fractionally lower than estimates for patients at full inflation, but this difference is unlikely to be clinically relevant.\(^10\) To further address any differences, emphysema measurements from other published studies such as MESA,\(^11\) CanCOLD,\(^12\) SPIROMICS\(^13\) and COPDGene\(^14\) were similar to those measured in our cohort. The last limitation was the lack of a control group of age-matched never-smokers which would help provide a better understanding of the physiological relevance of the mPRM values, and any longitudinal data on the lack of progression (or the progression of) these new imaging phenotypes of COPD.

A general limitation to the method presented in this thesis is the availability of the specific imaging data necessary to generate the multi-parametric response maps. The limited availability of hyperpolarized gas MRI due to cost and specialized hardware, the differences in diffusivity between \(^{129}\)Xe and \(^3\)He as well as the need for same-day CT acquisitions reduces
the generalizability of this method to other sites. Application of the multi-parametric method to other imaging modalities may be possible to overcome this limitation.

3.4 Future Directions

3.4.1 mPRM in Normal versus Abnormal DL\textsubscript{CO}

As seen from the results of our study, multi-parametric measures related to possible microstructure abnormalities are present in ex-smokers without COPD and are related to diffusing capacity. Previous work\textsuperscript{3,15} observed that impairment in diffusing capacity was related to reduced exercise capacity and worse quality of life independent of CT evidence of emphysema, and suggested that diffusing capacity may be sensitive to sub-clinical emphysema within COPD. Using the ability of this mPRM analysis to visualize possible transition phases of COPD, we hypothesize that multi-parametric measures related to sub-clinical emphysema will be related to exercise capacity and quality of life in ex-smokers with abnormal diffusing capacity. This investigation may elucidate early transitions of the disease and possibly identify new targets for treatment.

3.4.2 Longitudinal Study of mPRM in TINCan Cohort

As mentioned in the limitations, future work must be done to apply the method developed in Chapter 2 to longitudinal data. From our cross-sectional analysis, we can infer a progression of mPRM measurements with increasing disease severity. By investigating these measurements over time, information would be provided about the progression of COPD in individuals and its corresponding visualization on mPRM. Previous work has observed significant changes in CT and MR imaging measurements over time in COPD.\textsuperscript{16,17} Therefore, it is hypothesized that the method presented in this thesis will also provide similar results.

3.4.3 Multi-parametric Measures in Other Modalities

Finally, our method relies on the uniqueness of the TINCan imaging data to generate our multi-parametric measures. Application to other imaging modalities may provide a more clinically feasible implementation of our methodology. Advances in xenon enhanced dual energy CT, UTE and FDMRI allow for the unique application of the multi-parametric methodology to be
investigated in COPD. First, the simultaneous acquisitions in xenon enhanced dual energy CT allows for inherent co-registration between the structure and ventilation images and reduces the effects of registration errors on the multi-parametric response maps. By using this imaging technique, additional information from airway measurements can be integrated into the analysis and underestimation of emphysema can be reduced by acquiring at total lung capacity. Next, UTE MRI would provide a radiation free implementation of this method in sites setup for hyperpolarized gas MRI. Current UTE acquisitions provide similar structural information to low-dose CT,\textsuperscript{18} and since our method used low-dose CT to provide the structural measurements, UTE may provide a suitable replacement. Additionally, using UTE would provide similar spatial resolution as hyperpolarized gas MRI thereby reducing any errors generated during the resampling process. Finally, FDMRI’s capability to generate ventilation images combined with UTE MRI’s structural images allows for an entire $^1$H based multi-parametric response map. Such an application would take advantage of more widely available $^1$H MRI and possibly provide a clinical implementation of the multi-parametric response map method.

### 3.5 Significance and Impact

Many studies\textsuperscript{17,19-21} have used CT and hyperpolarized gas MRI to provided measure of lung structure and function for phenotyping the underlying pathophysiology of COPD. These studies have focused on using only one modality but not a combination of the two. By combining information from both imaging modalities, the method outlined in this thesis provided an imaging technique to visualize progression/transition phases in COPD and may be used to possibly identify new targets for treatment and disease monitoring.
3.6 References


APPENDICES

Appendix A - Development and Evaluation of Pulmonary Imaging Multi-Parametric Response Maps for Deep Phenotyping of Chronic Obstructive Pulmonary Disease

In Appendix A we developed a novel image processing pipeline to generate combined CT and MRI Multi-Parametric Response Maps and evaluated these maps in a small cohort of ex-smokers with and without COPD.

The contents of this chapter have been previously published in SPIE Proceedings Volume 10953, Medical Imaging 2019: Biomedical Applications in Molecular, Structural, and Functional Imaging; 109530J (2019) and permission to reproduce the article was granted by SPIE and is provided in Appendix C.


INTRODUCTION

Thoracic x-ray computed tomography (CT) has provided invaluable information about lung structure and function including patients with chronic obstructive pulmonary disease (COPD). A number of key cohort studies including ECLIPSE,1 COPDgene,2 SPIROMICS3 and CanCOLD4 have identified unique phenotypes related to airways disease and emphysema as well as bronchiectasis and gas-trapping. In addition to CT biomarkers of lung disease, hyperpolarized gas magnetic resonance imaging (MRI) has provided insight into asthma, COPD, and cystic fibrosis via ventilation5-8 and lung tissue microstructure9-11 measurements.

Using lung CT and MRI measurements, COPD disease severity and risk of poor outcomes can be predicted. A recent approach12 used CT parametric response map (PRM) of voxel-wise CT inspiration and expiration images to monitor COPD progression in patients. Previous studies have used PRM to quantify changes in lung structure with increasing COPD severity,13
survival post-lung transplant,\textsuperscript{14} and survival/therapy efficacy in brain, neck, bone, and breast cancer treatment.\textsuperscript{15-18} Recently, PRM approaches have been extended to include a multi-modality imaging methods towards the generation of multi-parametric response maps (mPRM).\textsuperscript{19} This mPRM approach was applied to MRI measurements of glioblastoma in patients which significantly predicted patient survival when PRM methods did not.

In the TINCan cohort study,\textsuperscript{20} spatial correlations between hyperpolarized gas MRI static ventilation and CT measurements of healthy tissue, emphysema, and gas-trapping were shown.\textsuperscript{21} In addition, hyperpolarized gas MRI apparent diffusion coefficients (ADC) have also been validated histologically as biomarkers of emphysema.\textsuperscript{22,23} Unfortunately, multi-parametric response maps with thoracic CT and MRI information have not been generated or tested in COPD patients, in whom it is difficult to predict disease worsening. Therefore, the purpose of this work was to create a pipeline to generate multi-parametric response maps, and to evaluate these maps to provide unique phenotypes of chronic obstructive pulmonary disease (COPD).

**MATERIALS AND METHODS**

**Image Segmentation**

Figure 1 outlines the segmentation pipeline. Briefly, $^1$H/$^3$He MR images were segmented by a single observer (D.P.I.C. with 3 years of experience) as previously described.\textsuperscript{24} The thoracic cavity was segmented from the $^1$H images using a seeded region-growing algorithm, and the $^3$He ventilation was segmented using k-means clustering to classify the voxels into five categories (signal void to hyper-intense signal) to create a ventilation cluster map. The CT images were segmented by a single observer (D.P.I.C. with 2 years of experience) using Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, IA, USA) to generate a lung mask to be applied to the CT images.
K-means Clustering

$^{3}$He MR images were segmented using k-means clustering.$^{24}$ Four clusters were chosen to define signal void, hypointense signal, normal signal, and hyperintense signal. The initial cluster centroids were chosen by equally dividing the full pixel range (0-255) into four groups and choosing the interval center of each cluster as the centroid. The voxels were initially labelled by the nearest centroid (1).

$$C^i := \arg \min_j \|x^i - \mu_j\|^2$$  \hspace{1cm} (1)

$C^i$ is the cluster label, $x^i$ is the pixel intensity, and $\mu_j$ is the mean pixel intensity of the cluster. Once the labelling step was completed, a new centroid (2) was calculated as the mean pixel intensity of all the pixels within that cluster.

$$\mu_j = \frac{\sum_{i=1}^{m} [c^i = j] x^i}{\sum_{i=1}^{m} [c^i = j]}, \text{ for } 1 \leq j \leq k$$  \hspace{1cm} (2)

where $k$ is the total number of clusters wanted, $j$ is the index of the current cluster, and $m$ is total number of voxels within that cluster. This assignment step and centroid updating step were repeated until the algorithm converged. After the clustering algorithm converged, k-means clustering was performed again with four clusters on the first cluster because it contained voxels of both the background and hypointense signal. After the algorithm converged again, the first two clusters were merged to represent the background and ventilation defects, and the last two clusters were merged to represent the hypointense signal. Combining
these two new clusters with the three previous clusters provided a $^3$He cluster map with five distinct clusters.

**Seeded Region Growing**

The proton images were segmented using seeded region growing. Before the algorithm was applied, the proton images were preprocessed using a two-dimensional radially symmetric low-pass Gaussian filter of size 15 X 15 and $\sigma = 2.0$ in order to prevent algorithm leakage. After filtering, the images were binarized using a threshold to create a mask of the lungs; the threshold was set to half the maximum intensity of the first K-means cluster (background/ventilation defect) obtained from the $^3$He image clustering. The initial seeds were automatically selected by finding 20 vertically adjacent pixels within each of the lungs of the binary mask. Using these seeds as the starting point, the algorithm checks the boundary conditions of the labelled voxels and their neighboring voxels. When a labelled voxel touches an unlabeled voxel, the algorithm determines the difference $\delta(x)$ between that voxel and the labelled voxels.

$$T = \{ x \in \bigcup_{i=1}^{n} A_i \ | \ N(x) \cap \bigcup_{i=1}^{n} A_i \neq \emptyset \}$$  \hspace{1cm} (3)

where $T$ is all the voxels that are not labelled, $N(x)$ are the neighboring voxels to voxel $x$, and $A_i$ is the set of labelled voxels.

$$\delta(x) = \left| g(x) - \text{mean}_{y \in A_{i(x)}} [g(y)] \right|$$  \hspace{1cm} (4)

where $g(x)$ is the signal intensity of voxel $x$, $g(y)$ is the signal intensities of all labelled voxels within the region. Once the difference between the labelled voxels ($A_i$) and the target voxel ($x \in T$) has been calculated, the algorithm weighs the difference to determine if that voxel should be labelled. If the voxel’s intensity is not different from the mean voxel intensity of the labelled voxels, the target voxel is added to the labelled voxels ($x \in A_i$). These steps are then continuously iterated until all of the available voxels are labelled. Finally, a morphological closing algorithm is used to fill in any gaps within each lung.

**ADC Segmentation**

The ADC images were segmented by applying masks to the raw images. These masks were generated by applying a 2-D Hanning window to the original k-space images to improve the
signal-to-noise ratio between the lungs and the background. Once filtered, the masks were generated by applying an intensity threshold to the image to separate the lungs from the background. Clean up of the masks was performed manually using MATLAB.

**CT Segmentation**

The inspiration and expiration CT images were segmented using an automatic algorithm within Pulmonary Workstation 2.0 (VIDA Diagnostics, Coralville, IA). This algorithm produces masks for each lung using an optimal thresholding technique. These masks were then applied to the original CT images to segment the lungs.

**Image Registration**

Figure 2 outlines the registration pipeline. Briefly, the $^3$He and $^1$H MR images were registered using a landmark based algorithm. The inspiration CT was registered to the expiration CT using an affine registration algorithm with a deformable step provided by the NiftyReg package. Before registration to the $^3$He and $^1$H MR images, the CT images and the ADC maps were resized and resampled to the $^1$H MR image dimensions using a built-in MATLAB function with nearest-neighbor interpolation. CT to $^1$H MR co-registration was performed using modality-independent neighborhood descriptor (MIND) deformable registration. The registration of the ADC maps to the $^3$He cluster maps was performed using a built-in MATLAB intensity based rigid registration algorithm.

**Figure 2:** Graphical representation of the registration pipeline used to co-register all of the MR and CT images.
Landmark based Registration

$^3$He to $^1$H co-registration followed geometric operations to transform the images given N landmarks $L_n$’ \{n=1,2,…..,N\} in the $^3$He image that corresponded to the same number of landmarks $L_n$ in the proton image. $L_n$’ $\{i'_n\}$ and $L_n$ $\{i_n\}$ denote the location of each landmark in the $^3$He and $^1$H images respectively. The ideal transformation was determined using a simple mean-squared distance cost function (5).

$$ C = \frac{1}{N} \sum_{i=1}^{N} ||L_n' - T(L_n)||^2 \quad (5) $$

Where T($L_n$) is the geometric transform of the proton image landmarks (6)

$$ T(L_n) = s \begin{bmatrix} \cos \theta & -\sin \theta \\ \sin \theta & \cos \theta \end{bmatrix} \begin{bmatrix} i_n \\ j_n \end{bmatrix} + \begin{bmatrix} \Delta j \\ \Delta i \end{bmatrix} \quad (6) $$

Where s is the scaling factor, $\Delta i$ and $\Delta j$ are the translation (i is the x-direction and j is the y-direction), $\theta$ is the clockwise rotation angle. By substituting the transformation function (6) into the cost function (5), we can compute the transform by solving this cost function (7).

$$ C = \frac{1}{N} \sum_{i=1}^{N} [(j_n' - s j_n \cos \theta + s i_n \sin \theta - \Delta j)^2 + (i_n' - s j_n \sin \theta - s i_n \cos \theta - \Delta i)^2] \quad (7) $$

Intensity based rigid registration

ADC to $^3$He co-registration was accomplished by minimizing the mean square error metric between the two images (8).

$$ \min \frac{1}{N} \sum_1^N E_{ij} \quad (8) $$

The error metric is calculated as the square of the difference between each pixel of the two images (9).

$$ E_{ij} = (I_1(i,j) - I_2(i,j))^2 \quad (9) $$

Where $E_{ij}$ is the error metric, $I_1$ (i, j) is the intensity of the pixel at the location ij in the first image, and $I_2$ (i, j) is the intensity of the pixel at the location ij in the second image.

Nifty Registration

To register the CT images, the affine registration algorithm starts by dividing both the reference and warped images into sets of blocks of equal size. A symmetric block matching approach is used to find blocks of voxels in the warped image that correspond to blocks of voxels in the
reference image. When the normalized cross correlation (NCC) (10) is maximized for a set of blocks, those blocks are considered matching.

\[
NCC = \frac{1}{N} \sum_{\vec{x} \in b_r} \frac{[b_r(\vec{x}) - \mu_{b_r}][b_f(\vec{x}) - \mu_{b_f}]}{\sigma_{b_r} \times \sigma_{b_f}}
\]  

(10)

Where N is the number of voxels in the block, \( \mu \) and \( \sigma \) are the mean and standard deviation of the block, and \( b_r \) and \( b_f \) are the blocks from the reference and warped image respectively. This block matching approach creates two sets of registered points \( \{ \tilde{C}_{i\rightarrow j} \} \) and \( \{ \tilde{C}_{j\rightarrow i} \} \) to account for both transformation directions. Once all the corresponding points are defined, the transformation parameters for these points are calculated using a least trimmed squares (LTS) regression method. The block matching and LTS regression are repeated in a coarse-to-fine fashion by starting with large blocks and moving toward smaller blocks.

**MIND Registration**

This algorithm first creates a descriptor for each voxel which defines the similarity between that voxel and its surrounding neighborhood (11)

\[
MIND(I, x, r) = \frac{1}{n} \exp \left( -\frac{D_p(I, x, x+r)}{V(I, x)} \right) \quad r \in R
\]

(11)

where \( D_p(I, x, x+r) \) is the distance between the voxel of interest and each of its neighboring voxels, \( V(I, x) \) is the noise variance of the neighborhood surrounding the voxel, and \( r \) is the search region. Once these descriptors are generated, it measures the similarity of each descriptor for the stationary \( I_H \) and the moving image \( I_CT \) (12).

\[
S(x) = \frac{1}{|R|} \sum_{r \in R} |MIND(I_H, x, r) - MIND(I_CT, x, r)|
\]

(12)

Using the similarity between these descriptors, the algorithm performs a deformable registration of the two images by trying to minimize the cost function (13)

\[
\arg \min_u \sum_x S(I_H(x), I_CT(x + u))^2 + \alpha \text{tr} (\nabla u(x)^T \nabla u(x))^2
\]

(13)

where the first section is the similarity term for the two images, the second section is the deformation field regularization term, and the deformation field \( u = (u, v, w)^T \) is defined by (14).

\[
\begin{align*}
    u &= x' - x = q_1 x + q_2 y + q_3 z + q_{10} - x \\
    v &= y' - y = q_4 x + q_5 y + q_6 z + q_{11} - y \\
    w &= z' - z = q_7 x + q_8 y + q_9 z + q_{12} - z
\end{align*}
\]

(14)
where the transformed location of voxel \( \mathbf{x} = (x, y, z)^T \) is \( \mathbf{x}' = (x', y', z')^T \), and \( \{q_1, q_2, \ldots, q_{12}\} \) are the transformation parameters. The deformation is optimized using a Gauss-Newton optimization method, and the optimization is solved using successive over-relaxation. Registration accuracy was determined using a Dice Similarity Coefficient (DSC).

**Multi-Parametric Response Maps**

We used MATLAB (Mathworks, Natick, MA, USA) to generate multi-parametric response maps from the co-registered voxels by assigning each voxel on mPRM to a group based on the values of the co-registered voxels. Table 1 describes the criteria for each voxel label. An expiration CT threshold of -856HU was used to determine gas-trapping, and an inspiration CT threshold of -950HU was used to determine emphysema. An ADC threshold of 0.3 cm\(^2\)/s was used based on previously determined values from healthy and mild to severe COPD subjects. An ADC value of 0.0 cm\(^2\)/s represented unventilated regions in the ADC map.

<table>
<thead>
<tr>
<th>Group</th>
<th>He MRI SV</th>
<th>Expiration CT</th>
<th>Inspiration CT</th>
<th>He MRI ADC</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ventilated</td>
<td>≥ -856 HU</td>
<td>≥ -950 HU</td>
<td>&lt;0.3 cm(^2)/s and &gt;0.0 cm(^2)/s</td>
<td>Green</td>
</tr>
<tr>
<td>2</td>
<td>Ventilated</td>
<td>≥ -856 HU</td>
<td>≥ -950 HU</td>
<td>≥0.3 cm(^2)/s or =0.0 cm(^2)/s</td>
<td>Yellow</td>
</tr>
<tr>
<td>3</td>
<td>Ventilated</td>
<td>&lt; -856 HU</td>
<td>&lt; -950 HU</td>
<td>&lt;0.3 cm(^2)/s and &gt;0.0 cm(^2)/s</td>
<td>Dark Yellow</td>
</tr>
<tr>
<td>4</td>
<td>Ventilated</td>
<td>&lt; -856 HU</td>
<td>&lt; -950 HU</td>
<td>≥0.3 cm(^2)/s or =0.0 cm(^2)/s</td>
<td>Orange</td>
</tr>
<tr>
<td>5</td>
<td>Unventilated</td>
<td>≥ -856 HU</td>
<td>≥ -950 HU</td>
<td>NA</td>
<td>Bright Red</td>
</tr>
<tr>
<td>6</td>
<td>Unventilated</td>
<td>&lt; -856 HU</td>
<td>&lt; -950 HU</td>
<td>NA</td>
<td>Dark Red</td>
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ADC: apparent diffusion coefficient; HU: Hounsfield units

**Study Subjects, Spirometry and Other Tests**

Five ex-smokers without COPD and 15 ex-smokers with COPD provided written informed consent to a study protocol (registered at clinicaltrials.gov as NCT02279329) approved by a local research ethics board and underwent pulmonary function tests, MRI and CT. Hyperpolarized \(^3\)He static ventilation (SV) and diffusion-weighted MRI were performed, as well as CT at full inspiration and full expiration breath hold scans as previously described.
RESULTS

**Subject Demographics**

Subject demographics for five ex-smokers, five subjects with GOLD I COPD, five with GOLD II COPD, and five with GOLD III COPD (Table 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ex-smokers</th>
<th>GOLD 1</th>
<th>GOLD 2</th>
<th>GOLD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>67 (12)</td>
<td>74 (5)</td>
<td>73 (9)</td>
<td>74 (7)</td>
</tr>
<tr>
<td>Male, n</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>30 (4)</td>
<td>28 (3)</td>
<td>27 (2)</td>
<td>27 (2)</td>
</tr>
<tr>
<td>Pack Years</td>
<td>28 (9)</td>
<td>28 (18)</td>
<td>44 (33)</td>
<td>39 (37)</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>99 (15)</td>
<td>97 (9)</td>
<td>62 (13)</td>
<td>39 (7)</td>
</tr>
<tr>
<td>FVC %pred</td>
<td>93 (15)</td>
<td>111 (14)</td>
<td>87 (8)</td>
<td>73 (14)</td>
</tr>
<tr>
<td>FEV₁/FVC %</td>
<td>80 (4)</td>
<td>64 (4)</td>
<td>52 (11)</td>
<td>40 (6)</td>
</tr>
<tr>
<td>TLC %pred</td>
<td>95 (9)</td>
<td>111 (10)</td>
<td>116 (14)</td>
<td>114 (20)</td>
</tr>
<tr>
<td>RV/TLC %</td>
<td>42 (7)</td>
<td>42 (5)</td>
<td>49 (9)</td>
<td>58 (13)</td>
</tr>
<tr>
<td>DL_{CO} %pred</td>
<td>84 (13)</td>
<td>86 (24)</td>
<td>70 (21)</td>
<td>53 (13)</td>
</tr>
</tbody>
</table>

BMI: Body mass index; FEV₁: Forced expiratory volume in one second; FVC: Forced vital capacity; TLC: Total lung capacity; RV: Residual volume; DL_{CO}: Diffusing capacity for carbon monoxide; %pred: Percent predicted.

**Image Co-registration**

Figure 3 displays a representative set of registered images for a subject with GOLD grade 1 COPD. In the 20 subjects presented, we achieved a DSC of 83 ± 4 % for the ADC map to ¹H image registration and 92± 3% for the CT image to ¹H image registration.

**Figure 3:** Comparison of MRI and CT images in a GOLD Grade 1 subject
A) ³He ventilation cluster map, B) ADC map, C) Expiration CT, D) Inspiration CT
**Multi-Parametric Response Maps**

Figure 4 shows multi-parametric response maps for a representative ex-smoker, GOLD 1, GOLD 2, and GOLD 3 subject. As COPD severity increases, the volume of normal voxels (group 1) decreases, the volume of normal voxels with abnormal ADC (group 2) increases, and the volume of abnormal voxels (groups 5 & 6) increases. mPRM generated from expiration CT show increases in ventilated, gas-trapping voxels (groups 3 & 4) with increasing COPD severity; while mPRM generated from inspiration CT show limited change in ventilated, emphysematous voxels (groups 3 & 4) with increasing COPD severity. These results are summarized in Table 3.

![Multi-Parametric Response Maps](image)

**Figure 4:** Multi-parametric Response Maps (mPRM) from co-registered $^3$He ventilation map, $^3$He ADC map, and inspiration/expiration CT images for representative subjects. Ex-smoker without COPD (A, E), GOLD 1 (B, F), GOLD 2 (C, G), GOLD 3 (D, H).
Table 3: Voxel Group Distributions

<table>
<thead>
<tr>
<th>Group</th>
<th>EXP (%)</th>
<th>INSP (%)</th>
<th>Group</th>
<th>EXP (%)</th>
<th>INSP (%)</th>
<th>Group</th>
<th>EXP (%)</th>
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<th>Group</th>
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<th>Group</th>
<th>EXP (%)</th>
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<tr>
<td>1</td>
<td>62 ± 7.9</td>
<td>32 ± 13</td>
<td>2</td>
<td>31 ± 7.9</td>
<td>46 ± 8.2</td>
<td>3</td>
<td>32 ± 7.8</td>
<td>54 ± 11</td>
<td>4</td>
<td>.75 ± 1.1</td>
<td>4.8 ± 3.3</td>
<td>5</td>
<td>0 ± 0</td>
<td>1.4 ± 0.9</td>
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<tr>
<td>2</td>
<td>63 ± 7.6</td>
<td>37 ± 11</td>
<td>3</td>
<td>32 ± 7.8</td>
<td>54 ± 11</td>
<td>5</td>
<td>3.8 ± 3.0</td>
<td>.14 ± 0.9</td>
<td>6</td>
<td>0 ± 0</td>
<td>1.4 ± 0.9</td>
<td>6</td>
<td>.06 ± .12</td>
<td>0.53 ± .63</td>
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<tr>
<td>3</td>
<td>30 ± 24</td>
<td>12 ± 8.3</td>
<td>4</td>
<td>46 ± 8.2</td>
<td>33 ± 8.2</td>
<td>6</td>
<td>3.8 ± 3.0</td>
<td>.14 ± 0.9</td>
<td>7</td>
<td>0 ± 0</td>
<td>1.4 ± 0.9</td>
<td>7</td>
<td>5.6 ± 2.9</td>
<td>8.9 ± 5.0</td>
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<tr>
<td>4</td>
<td>34 ± 25</td>
<td>15 ± 8.8</td>
<td>5</td>
<td>33 ± 8.2</td>
<td>33 ± 6.5</td>
<td>8</td>
<td>5.0 ± 7.3</td>
<td>34 ± 9.7</td>
<td>8</td>
<td>5.6 ± 2.9</td>
<td>8.9 ± 5.0</td>
<td>8</td>
<td>1.1 ± 2.3</td>
<td>1.9 ± 3.3</td>
</tr>
<tr>
<td>5</td>
<td>12 ± 8.3</td>
<td>15 ± 8.8</td>
<td>6</td>
<td>47 ± 9.0</td>
<td>40 ± 2.5</td>
<td>9</td>
<td>13 ± 9.7</td>
<td>34 ± 9.7</td>
<td>9</td>
<td>1.9 ± 3.3</td>
<td>1.9 ± 3.3</td>
<td>9</td>
<td>13 ± 9.7</td>
<td>34 ± 9.7</td>
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NEW OR BREAKTHROUGH WORK TO BE PRESENTED
We developed a segmentation and registration pipeline for the generation of multi-parametric response maps using hyperpolarized gas MRI and CT. The proposed approach provides promising results as a new metric for phenotyping COPD.

DISCUSSION AND CONCLUSION
mPRM provides a way to combine the functional and structural information of multiple imaging modalities. However, a robust image processing pipeline is required to generate these maps. Segmentation and registration errors may result in voxel mislabeling thereby reducing the mPRM differentiation ability. Therefore, we developed and evaluated an image processing pipeline to generate mPRM. The proposed pipeline provides moderate registration accuracy between the imaging modalities, but a large amount of user interaction hinders efficient implementation of the pipeline. Future work will focus on improving the registration to increase the overall accuracy of mPRM, and on automating the image segmentations to reduce mPRM generation time and increase efficiency.
REFERENCES


Ma, B. et al. in *Information Processing in Medical Imaging. IPMI 2009*. 276-287 (Springer Berlin Heidelberg).


Appendix B – Health Science Research Ethics Board Approval Notices

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Grace Parraga
Department & Institution: Schulich School of Medicine and Dentistry Imaging, Robarts Research Institute

Review Type: Full Board
HSREB File Number: 6014
Study Title: Longitudinal Study of Helium-3 Magnetic Resonance Imaging of COPD (REB #15930)
Sponsor: UWO Internal Research Fund

HSREB Amendment Approval Date: June 07, 2017
HSREB Expiry Date: February 10, 2018

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The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

EO: Erika Basile, Grace Kelly, Katelyn Harris, Nicola Morphet, Karen Copeland, Patricia Sargeant

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1L6  t: 519-850-5000  f: 519-850-2464  www.uwo.ca/research/ethics

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Appendix D - Curriculum Vitae

Jonathan MacNeil BSc

February 2020

Education

2018-Present  Masters of Engineering Science, Biomedical Engineering  
*The University of Western Ontario, London Ontario*

2012-2017  Bachelors of Science, Honours Medical Biophysics  
*The University of Western Ontario, London Ontario*

Honours and Awards

2019  CIHR Institute of Circulatory and Respiratory Health  
*Institute Community Support Travel Award ($1000)*

2019  Western University, School of Biomedical Engineering  
*Conference Travel Bursary ($500)*

2019  American Thoracic Society Annual Meeting  
*Respiratory Structure and Function Abstract Scholarship ($300 USD)*

2019  International Society of Magnetic Resonance in Medicine  
*Trainee Stipend ($535 USD) Declined*

2019  American Thoracic Society Annual Meeting  
*Canadian Thoracic Society Poster Competition Finalist  
Top 30 abstracts from Canadian Researchers submitted to ATS*

2018  Western University, School of Biomedical Engineering  
*Ontario Graduate Scholarship ($15,000)*

2018  Western University, School of Biomedical Engineering  
*Western Graduate Research Scholarship ($2022.34 per term)*

2014-2015  Western University, Department of Medical Biophysics  
*Dean’s Honour List*

2012-2013  Western University, Department of Medical Biophysics  
*Dean’s Honour List*
Manuscripts

A Peer Reviewed Journal Manuscripts

Under Review (n=1)


B Peer Reviewed Published Conference Proceedings

Accepted (n=1)


Abstracts and Presentations

Peer-Reviewed Oral Presentations

Accepted (n=3)


Peer-Reviewed Poster Presentations

Accepted (n=5)


**Submitted and under review (n=5)**


**Professional Societies**

2018-  **American Thoracic Society**  
*Trainee Member*

2018-  **International Society for Magnetic Resonance in Medicine**  
*Trainee Member*

**Research Experience**

2015-2016  **Undergraduate Honors Thesis Project**  
*The Application of a Custom Multispectral Camera for Remote Heart Rate Detection*  
Supervisors: Dr. Jeff Carson and Dr. Najimainini  
Lawson Health Research Institute, London ON

2015  **Six-week Research Project**  
*The Use of Image Segmentation to Automate the Identification of Regions of Interest in Histological Slides for Further Study of Arteriosclerotic Plaque Biology*