



Early View

Series

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COPD Biomarkers and Phenotypes: Opportunities for Better Outcomes with Precision Imaging

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Review article

Take Home Message

COPD imaging has not improved outcomes in patients with advanced lung disease. For patients to benefit, imaging phenotypes must be developed that reflect early, reversible disease or be used in a more pragmatic fashion to improve clinical outcomes.

ABSTRACT

A number of chronic diseases have benefited from both imaging and personalized medicine, but unfortunately, for patients with COPD, there has been little clinical uptake or recognition of the key advances in thoracic imaging that might help detect disease early or perhaps, more importantly, help develop and phenotype patients for novel or personalized therapies that may halt disease progression. We outline our vision for how CT and MRI may be used to better inform COPD patient care, and perhaps more importantly, how these may be used to help develop new therapies directed at early disease. We think that imaging and precision medicine should be considered and used together as “precision imaging” at specific stages of COPD when the major pathologies may be more responsive to therapy. Whilst “precision medicine” is the tailoring of medical treatment to individual patients, we define “precision imaging” as the tailoring of specific therapies and interventions to individual patients with a detailed quantitative understanding of their specific imaging phenotypes and measurements. Finally, we stress the importance of “seeing” the pathology, because without this understanding, you cannot treat, nor cure patients with COPD.

INTRODUCTION

Precision medicine offers the hope for therapy that is tailored to individual patients and results in minimized therapeutic risk and improved clinical outcomes. This is particularly relevant for patients with chronic obstructive pulmonary disease (COPD) where there is marked heterogeneity in both the structural and clinical manifestations of disease as well as therapeutic outcomes. For example, it is well-understood that individual COPD patients with similar degrees of spirometric impairment can be very different in terms of symptoms, exercise capacity and exacerbation risk. Moreover, these same patients may also have marked differences in the extent of parenchymal damage (or emphysema) and airway abnormalities including airway wall remodeling, mucous plugging and airway obliteration. Finally, the pathological determinants of COPD often reside in the silent zones of the peripheral lung where, because of its redundant design in peak health, they can progress undetected or are incorrectly ascribed to advancing age, until disease is quite advanced. Thoracic imaging provides tools that enable the *in vivo* detection of these processes and we believe that the inclusion of such data in therapeutic decision-making, i.e. “Precision Imaging”, will improve patient care. *While precision medicine refers to the tailoring of treatment to the physiology of individual patients, precision imaging is a way to tailor specific therapies and interventions to patients based on their imaging phenotypes and measurements.* This goal is not new, but we believe that past efforts have been incomplete, and in many cases, not sufficiently bold.

There have been innumerable reports on the application of imaging in COPD patients but aside from efforts to mechanically deflate emphysematous lung, they have had little impact on patient care, leaving many clinicians thinking that it is unnecessary (at best) and resource-wasteful (as worst) to requisition more than a chest X-ray for clinical decision making. Some of the reasons for this include a limited ability to deploy advanced imaging methodologies at the site of clinical care, an absence of emphasis on the detection of “early” disease and,

finally, a failure to recognize that while not every patient with advanced disease may benefit from imaging, there are subgroups in which such efforts may afford a marked clinical benefit. Our intention is to provide guidance on how imaging can be used to enhance patient care. To do this we will begin by outlining a broad set of unmet needs in clinical care followed by a brief review of advances in CT and MRI (Table 1). Finally, we provide some forward-looking suggestions on the application of imaging in the detection of early disease and the management of more advanced COPD (Table 2). This is not meant to be a comprehensive review of imaging or clinical care but rather an opinion piece that stimulates dialogue and constructive critique.

THE GOALS OF IMAGING FOR COPD PATIENTS AND AT-RISK EX-SMOKERS

Smoking cessation is one of the most impactful interventions in clinical care. It slows the decline in lung function and improves survival [1, 2]. Additional treatments such as oxygen therapy and lung volume reduction surgery have also been shown to improve survival in select patients [3-5], but the additional benefits afforded by pharmacologic therapy have been more modest. These latter treatments may improve lung function, reduce COPD symptoms [6], exacerbations and hospitalizations [7, 8] but their effect is not large and generally not discernable on a per patient basis. Furthermore, COPD hospitalization and mortality rates continue to rise, especially in women [9]. In light of this, how can imaging methods and measurements be strategically used in COPD patients?

Based on our collective experience in cohort and small patient studies, we think efforts must be based upon an understanding of disease pathobiology and how these processes change with disease progression. For example, imaging measurements of therapy response offered at a certain stage of disease may be unhelpful, yet, if therapy had been offered at an earlier time, the disease trajectory may have been directly measured and altered. **Figure 1** shows histological evidence (panels B-D taken from Leopold and Gough, 1957) [10] of different disease stages starting in the acinus with inflammation (B), remodeling (C) and destruction of the distal airway and parenchyma (D). This evidence supports the concept that while an anti-inflammatory therapy may be highly effective in patients in stage B, this is unlikely to be the case in C and certainly not in stage D when the benefits likely do not outweigh the risks and cost. These histological findings, described over 6 decades ago, clearly

show that without “seeing” the pathology responsible for symptoms and disease worsening, you cannot treat it and you certainly cannot cure it.

Precision imaging in COPD patients should also go beyond efforts to measure and arrest disease progression and should focus on optimizing therapies that reduce hospitalization and prevent rehospitalization. This further emphasizes the time dependence of our model of precision imaging and how this needs to incorporate susceptibility to events such as acute respiratory exacerbations and their response to treatment. Imaging can be a foundation for such a holistic vision but it is clear that such efforts will have to incorporate additional biomarkers as well as clinical data and be constantly in flux based upon the patient experience. To guide these efforts, precision imaging should focus on the three general compartments of the lung: 1) the parenchyma, including the terminal bronchioles, alveoli and the alveolar gas-blood tissue barrier, 2) the airway tree including the large and small airways, and, 3) the large pulmonary vessels and the small vessel tree.

For the purposes of this perspective we focus on advances pertinent to thoracic CT where the bulk of research experience lies and then we review emerging functional MRI biomarkers of COPD developed over the past few years. The main contributions of CT thus far include high resolution emphysema, vessel and airway measurements to the 5th and 7th generation, close to the small airways, while the main contributions of MRI relate to functional and serial measurements of ventilation abnormalities and parenchyma microstructure in early subclinical disease.

X-RAY COMPUTED TOMOGRAPHY

Emphysema

Regional tissue destruction or emphysema is very common in COPD patients and in full-inspiration CT images, this appears as regions of low attenuation because of the loss of tissue and increased presence of air. CT densitometry threshold values and percentile points have been extensively used to quantify emphysema including -950HU [11-13] and the 15th percentile on the frequency distribution curve [14]. **Figure 2** shows a CT image with all lung voxels less than the -950HU threshold highlighted. The three-dimensional reconstruction of the CT airway tree and the low attenuation clusters (colour-coded for the different lung lobes) are also shown. Although it is clear for the patient with moderate and severe COPD that emphysema is predominantly in the upper and middle lobes, the low attenuating cluster

analysis also shows a visual representation of size of emphysematous bullae and their location as well as quantitative measurements. Notably, CT emphysema measurements can be used to identify patients that may have greater responses to lung-volume-reduction surgery and endobronchial valve implantation [15, 16].

Airways

Airways disease, chronic bronchitis and chronic sputum production are also hallmark pathological features of COPD. The proximal airways can be directly visualized and quantified using CT methods and numerous approaches have been used to segment the airway tree and then quantify the airway wall dimensions with the belief that mural thickening in the central airways represents a distinct pathologic process. The results of these efforts have repeatedly demonstrated that objective assessments of central airway morphology provide data that are statistically complementary to parenchymal density measurements in the prediction of lung function. Other work has also demonstrated that airway morphology can predict respiratory exacerbations [17], the risk of future lung disease [18] and are abnormal in symptomatic smokers with normal spirometry [19]. The critical challenge that remains however, is the clinical translation of CT airway measurements. The relatively large inter-subject variability in these measures and their narrow dynamic range means that while they may provide some insight into trends in large cohorts, they are still of limited clinical utility in individual patients. Another critical limitation stems from the fact that early findings in relation to airway abnormalities are nearly never identified because CT is not used to phenotype ex-smokers without spirometry evidence of disease.

There are also approaches that attempt to quantify small airway disease using expiratory CT imaging. These include simple densitometric thresholding of the expiratory CT scan as well calculation of the inspiratory-to-expiratory volume change of voxels with attenuation values from -860 to -950 HU (RVC_{-860 to -950}) [20] and the expiratory-to-inspiratory ratio of mean

lung density in HU (E/I ratio) [21, 22] and Jacobian analyses [23]. Another approach uses voxel-by-voxel comparison of CT attenuation after co-registration of inspiration and expiration CT, otherwise known as Parametric Response maps [24, 25]. Such PRM measurements have been shown to be reproducible over short periods of time [26], correlated with pulmonary function, showed spatial agreement with MRI functional abnormalities [27], and were associated with longitudinal changes in FEV₁ [28]. There is ongoing work to determine the histopathologic basis of these measures and with those efforts, their clinical utilization may become better understood.

Perfusion and the Pulmonary Vasculature

There are several techniques under investigation for the static assessment of the pulmonary vascular tree and heart. These generally provide measurements of blood vessel volume and vascular tortuosity for the intraparenchymal vessels as well as epicardial measures of the right and left ventricular volumes [29-31]. Such techniques have been used for disease stratification and in smaller studies of arterial and venous segmented vasculature, discrimination of disease subtypes. Further preliminary work focused on the heart suggests that such techniques may be used to identify patients who may benefit most from therapies to reduce the risk for acute respiratory exacerbations [32].

A limitation to these approaches is that they cannot provide direct assessments of lung ventilation or perfusion – *functional* information. Therefore, other approaches such as dual-energy CT (DECT) [33-35] have been developed and evaluated. A recent study investigating DECT with combined xenon-enhanced ventilation and iodine contrast enhanced perfusion imaging demonstrated the feasibility of obtaining regional and quantitative ventilation and perfusion measurements and, importantly, the measurements of the ventilation-perfusion relationship on a voxel-by-voxel basis [36]. In patients with COPD, these DECT ventilation-

perfusion measurements were shown to be significantly associated with measures of pulmonary function [36].

MAGNETIC RESONANCE IMAGING

Functional and Microstructural MRI

Pulmonary MRI has been developed as a research tool in part due to its speed, excellent safety and tolerability profile [37, 38], and because of the unique combination of morphological and functional phenotypes MRI provides. Morpho-functional pulmonary measurements can be achieved using conventional ^1H MRI using the inherent signal of the parenchyma. In addition, functional information may also be derived using physiologic signal alterations such as pulsatile blood flow or ventilation stemming from the ^1H MRI signal itself or using intravenous or inhaled contrast agents.

Ventilation and Diffusion-weighted inhaled noble gas MRI

MRI with inhaled hyperpolarized ^3He or ^{129}Xe gas provides a unique and direct way to measure pulmonary ventilation and the destruction of the terminal bronchi and alveoli [39]. Parenchyma microstructural information can be obtained using a variety of diffusion-weighted MR pulse sequences. During inspiration breath-hold, the gas diffuses within the lung micro-structure and the “apparent” diffusion coefficient (ADC) is derived such that it reflects the level of restriction of the gas to diffusion thereby providing *in vivo* measurements of the distal airspaces [40, 41]. In addition to lung microstructural information, ventilation images may be acquired that show the regional distribution of inhaled gas [42-47]. ^3He and ^{129}Xe static ventilation images and diffusion-weighted images are shown in **Figure 3** for a single healthy volunteer and three COPD patients in whom ^3He and ^{129}Xe ventilation defects are readily visualized. The ^3He and ^{129}Xe ADC maps are also brighter reflecting larger ADC numbers for subjects with COPD which are indicative of pathologic enlargement of the distal airspaces.

Perfusion

First-pass perfusion contrast-enhanced MRI involves an intravenous bolus injection of a gadolinium chelate contrast agent during continuous time-resolved T1-weighted ultrashort TR and TE gradient-echo (GRE) imaging. The resulting images can be assessed visually or objectively to detect and quantify relative differences in immediate and delayed regional enhancement which represent perfusion defects [48]. Absolute quantification, however, remains difficult due to the non-linear relationship of contrast material concentration and T1-shortening effects [49, 50].

Additional assessments of regional lung perfusion can be obtained with the administration of inhaled agents such as hyperpolarized ^{129}Xe . Hyperpolarized ^{129}Xe gas is soluble in blood and tissues making it possible to simultaneously measure regional perfusion [51] and alveolar transport kinetics [52]. While there is still limited clinical experience using this approach in COPD patients, measurements have been shown to be strongly associated with the diffusing capacity of the lung for carbon monoxide (DL_{CO}) in patients with idiopathic pulmonary fibrosis [53].

The *sine qua non* for all such is their validation against other outcomes so these may be considered in EMA and FDA COPD drug and device therapy regulatory approval processes. Moreover, for reimbursement through national formularies, cost-effectiveness and health care cost savings need to be considered, which is especially important if we consider novel complex technologies that are more commonly based in hospital radiology departments. In this regard, advanced MRI methods are poised for implementation at a number of sites in the US and Canada as well as in the EU. For example, ^{129}Xe MRI is already approved for clinical use in the UK (National Health Service) and clinical approval in the US is currently under development.

WHAT'S NEXT?

Given the recent research investments in pulmonary imaging for COPD, and the myriad of approaches available, thoracic CT and MRI, either independently or in combination, can provide detailed *in vivo* measurements of the parenchyma, airways and vasculature as well as more holistic assessments of the comorbid conditions present in COPD patients. Why then, have they not revolutionized therapy and led to a cure? We believe that the answer to this question can be found in both the features being examined and how they are utilized (technology costs and complexity as well as choice of patients) in clinical investigations.

Pulmonary imaging in clinical, epidemiologic and genetic investigation has been most heavily utilized for correlative analyses. How does the degree of parenchymal remodeling on CT relate to symptomatic or functional limitations found in a cohort of smokers? Do patients with more severe expiratory airflow obstruction have greater defects in the perfusion of the peripheral parenchyma?

Such studies of people with a shared exposure to tobacco smoke who represent a spectrum of disease severity have told us what we already suspect, sicker people tend to look worse by any measure. An airway wall may be fractionally thicker or a perfusion defect relatively more striking, but we do not have absolutes because we have not defined what is normal. Further, for some of these features, the knowledge of what is normal may not enhance their utility in clinical care.

The expectations placed on imaging in clinical care are higher than those in biomedical research. What then is a potential path forward? We think two key approaches may help: 1) development of imaging biomarkers of lung injury in those at risk for future disease and 2) utilization of novel imaging phenotypes in patients with advanced disease to optimize care and to stratify patients in clinical trials of new therapies. We summarize our proposed approach in Table 3 and provide a more detailed description below.

Biomarkers of Early COPD

As shown in **Figure 4**, MRI can provide exquisite *in vivo* assessments of alveolar microstructure and regional defects in ventilation even in ex-smokers at the very earliest stages of disease when they present without airflow limitation or CT evidence of airways disease or emphysema [54]. With very little additional effort, we think it is possible and quite necessary to define normal age- and sex-based distributions of ADC and regional lung ventilation. Such measurements could then be applied in focused assessments of those at greatest risk of future lung disease, not the 60-year-old 40 pack-year smoker with normal lung function who may never develop COPD, but the 25-year-old, 5 pack-year smoker reporting cough, wheeze or shortness of breath. Multiple birth cohort and long term observational studies suggest that these latter symptomatic young adults may be at greatest risk for future airflow obstruction and parenchymal disease such as emphysema [55]. The first step to treating early and potentially reversible disease is to more dependently detect early disease. Further work is obviously needed to achieve this goal, but we need to be pragmatic in these efforts and not have the implementation of imaging based upon such things as the rate of decline in lung function. Longitudinal measures of function and physiology may be available in well controlled investigations but are not part of routine

clinical care in young otherwise healthy individuals who may not even go for annual checkups.

Phenotyping established disease

COPD is more than a spirometric abnormality and to understand how imaging may be impactful for patient care we must first establish a definition of disease. The true scope of such an effort is beyond this opinion piece but there are practical criteria that can be immediately employed to enhance image utilization. All patients with GOLD grade 3 and 4 COPD should undergo CT imaging at least once to determine eligibility for resectional and non-resectional lung volume reduction. Additional disease criteria that can be used to guide the implementation of imaging include clinical impairment (symptoms and functional status) beyond what would be expected for disease stage, disease refractory to standard therapy, and recurrent episodes of respiratory insufficiency/failure.

Imaging may reveal bronchiectatic dilation of the airways, right ventricular enlargement, coronary calcification or sarcopenia. Each represents a unique condition not discernable by measures of lung function and the knowledge of their presence could significantly impact further clinical evaluation and therapeutic intervention. Even in the absence of such co-morbid conditions, imaging may prove to be a useful predictor of health care utilization. Examples of this include a recent investigation where ^3He MRI measurements but not lung function were significant predictors of hospitalization in patients with mild-to-moderate COPD [56].

We acknowledge that some of our criteria for imaging utilization such as disproportionate symptoms and the presence of refractory disease are difficult to objectify but imaging is meant to augment and not replace clinical acumen. These “softer” indications force a necessary engagement between clinicians and the imaging community, whereas up to now efforts have been largely siloed and often lacked guidance from experts in bedside medicine. Finally, we must also contend with the increasing utilization of CT scanning as a screening tool for the early detection of lung cancer. COPD is largely undiagnosed in the community and treatment is predicated on awareness of a condition. The presence of emphysema or other co-morbid conditions provides a point of entry for these patients into the health care system where additional diagnostics can be performed and management plans can be instituted.

Looking forward – The potential for Deep Learning and Artificial Intelligence

The field of medical image analysis is undergoing rapid changes that mirror the improvements made in computational speed and capacity. The potential provided by artificial intelligence methods to analyse images have, to some extent, outstripped our ability to clinically leverage the information they provide. New

approaches to data extraction are now possible and the research community is now also changing how images are quantified and processed. No longer are we constrained to measuring anatomical or physiological features of interest to predict clinical outcomes. We can now use techniques such as convolutional neural networks to mine the information content in medical images and predict outcomes without measuring the visible and sometimes less visible features responsible. We may similarly wish to predict future acute respiratory exacerbations, hospitalizations or other forms of health care utilization in COPD patients undergoing a clinically indicated CT scan or otherwise “normal undiagnosed” former smoker undergoing lung cancer screening. Now that deep learning methods provide a way to reveal novel predictive information based on patient images, it is important to safeguard and not discard clinically actionable data and features that were previously hidden within COPD images.

CONCLUSION

We are in the early stages of understanding of how MRI and CT may be used to personalize and optimize therapy in patients with COPD. Until now, we have not exploited the pathologic information provided by these imaging tools to stratify patients in clinical trials nor used imaging phenotypes to drive the development of new therapies or guide treatment decisions in complex COPD patients. We suggest that our current one-size fits all approach based on spirometry information needs to change and we must embrace higher risk research and development strategies in COPD. Bold ideas and proposals need to be explored about all the different pathologies that reside within the COPD umbrella term and reclassifying COPD patient severity based on imaging measurements of the pathologies directly responsible for symptoms and progression. Renaming these different phenotypes in COPD, especially in early stages of the disease, may comprise a first step towards developing and using precision imaging to generate a deeper understanding of disease overlap/co-occurrence and the initiation of personalized or at least optimized therapies.

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Table 1. State-of-the-art CT and MRI measurements for COPD phenotyping

Phenotypes	CT	MRI
Airway wall thickness	Wall area thickness, Pi10	x
Airway Lumen calibre	Lumen area	x
Ventilation abnormalities	Ventilation	Ventilation defect percent
Small Vessels	√	x
Perfusion	√	√
Large arteries	√	√
Gas Trapping	< -856 HU; PRM functional small airways	√
Emphysema	< -950 HU; PRM emphysema	Apparent Diffusion coefficients
Bronchiectasis	√	Airway filling
Fibrosis	√	√
Pulm artery abnormalities	Ratio aorta/PA	x
Inflammation and edema	√	√

Table 2. Recommendations on optimal use of thoracic imaging to improve COPD outcomes

<i>Imaging for</i>	<i>CT (structure)</i>			<i>MRI (structure-function)</i>		
	<i>Airways</i>	<i>Parenchyma</i>	<i>Vessels</i>	<i>Airways</i>	<i>Parenchyma</i>	<i>Vessels</i>
Disease Detection	√	√	√	√	√	x
Early Disease Phenotyping	x	√	x	√	√	x
Image-guided therapy	x	√	x	√	x	x
Measure/Monitor Treatment Response	x	x	x	√	x	x
Predict Exacerbation	x	x	x	√	√	x

X= not yet observed or studied

Table 3. What's Next for COPD Precision Imaging

PRECISION IMAGING OUTCOMES	TIME FRAME			
	NOW <1 year	Soon 1 Year	Later 2-5 years	Long-Term 10 years
Early subclinical COPD phenotypes	x			
Stratifying established COPD	x			
Machine and Deep Learning understandings		x	x	x
Image-guided Interventions	x	x		
Predict Exacerbation risk	x			
Explain symptoms/exercise capacity	x			
FDA/EMA approval functional MRI		x	x	
Use to Change COPD Outcomes			x	x

Figure 1. Histological Evidence of Airway and Alveolar Abnormalities across the Spectrum of COPD severity. A) normal alveolar pathology, B) airway inflammatory abnormalities, C) Airway wall remodeling, D) severe emphysematous destruction. Original from Leopold and Gough 1957: 20x image scale: Blue arrow is 50 μm

Figure 2. Centre coronal thoracic CT Emphysema measurements: Relative area of the CT density-histogram voxels < -950 Hounsfield units (RA_{950}) in red and Low attenuation (<-950 HU) clusters (LAC)
Mild/Early COPD: 74-year-old male, $\text{FEV}_1=86\%_{\text{pred}}$, $\text{FEV}_1/\text{FVC}=59\%$, $\text{RV}/\text{TLC}=88\%_{\text{pred}}$, $\text{DL}_{\text{CO}}=45\%_{\text{pred}}$, $6\text{MWD}=486\text{m}$, pack years=40, $\text{RA}_{950}=6\%$, $\text{LAC}=-2.0$
Severe/Advanced COPD: 71-year-old female, $\text{FEV}_1=47\%_{\text{pred}}$, $\text{FEV}_1/\text{FVC}=41\%$, $\text{RV}/\text{TLC}=144\%_{\text{pred}}$, $\text{DL}_{\text{CO}}=31\%_{\text{pred}}$, $6\text{MWD}=441$, pack years=52, $\text{RA}_{950}=22\%$, $\text{LAC}=-1.61$

Figure 3. Pulmonary MRI and CT in older never-smoker and ex-smokers

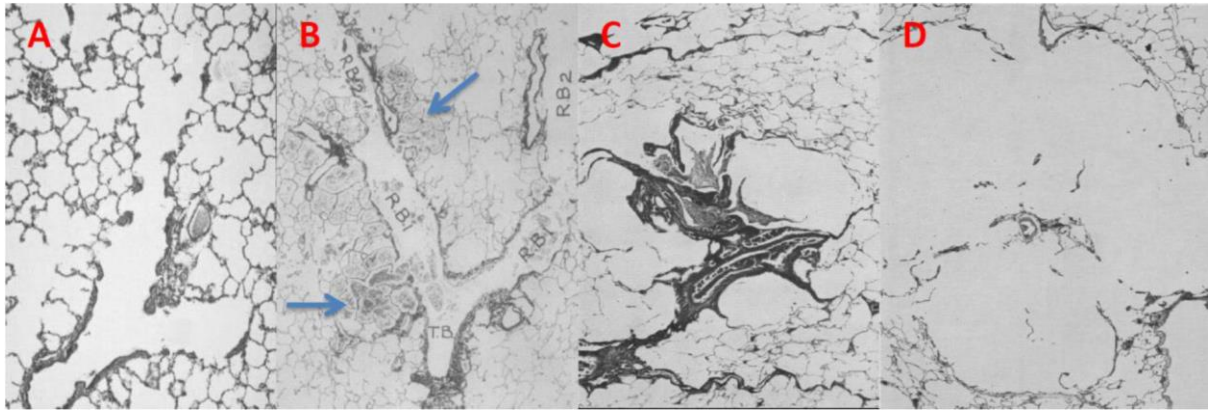
Never-smoker: 64-year-old female, $\text{FEV}_1=124\%_{\text{pred}}$, $\text{FEV}_1/\text{FVC}=85\%$, $\text{RV}/\text{TLC}=73\%_{\text{pred}}$, $\text{DL}_{\text{CO}}=78\%_{\text{pred}}$, 6MWD not performed, pack-years <0.5, MRI VDP=1%, MRI ADC=0.22 cm^2/s , $\text{RA}_{950}=0\%$.

Mild-Moderate COPD: 76-year-old male, $\text{FEV}_1=77\%_{\text{pred}}$, $\text{FEV}_1/\text{FVC}=57\%$, $\text{RV}/\text{TLC}=117\%_{\text{pred}}$, $\text{DL}_{\text{CO}}=70\%_{\text{pred}}$, $6\text{MWD}=357\text{m}$, pack years=72, MRI VDP=7%, MRI ADC=0.30 cm^2/s , $\text{RA}_{950}=2\%$.

Severe COPD: 69-year-old female, $\text{FEV}_1=33\%_{\text{pred}}$, $\text{FEV}_1/\text{FVC}=39\%$, $\text{RV}/\text{TLC}=166\%_{\text{pred}}$, $\text{DL}_{\text{CO}}=28\%_{\text{pred}}$, $6\text{MWD}=366\text{m}$, pack years=106, MRI VDP=34%, MRI ADC=0.51 cm^2/s , $\text{RA}_{950}=33\%$

Figure 4. Ex-smoker without CT or spirometry evidence of COPD and low DL_{CO}

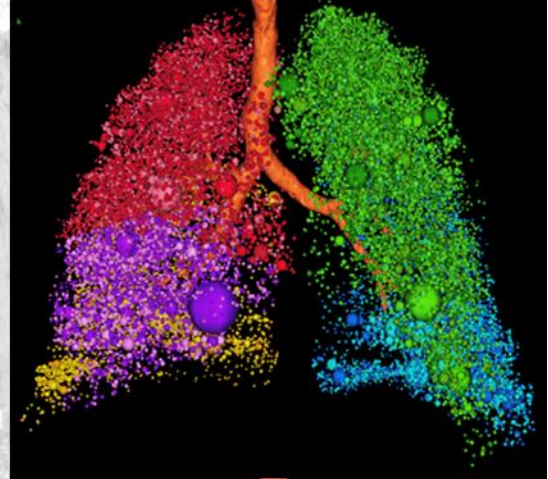
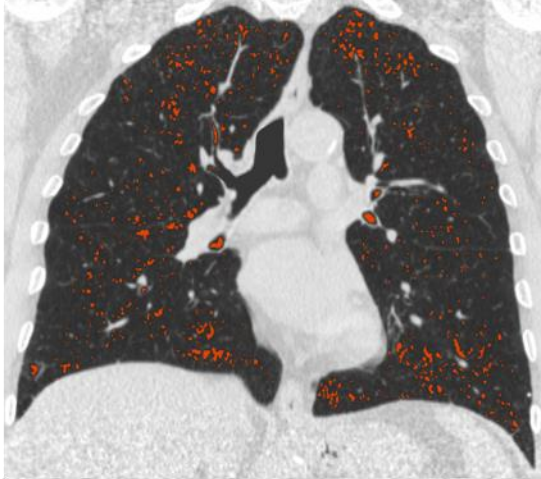
74-year-old male ex-smoker, $\text{FEV}_1=89\%_{\text{pred}}$, $\text{FEV}_1/\text{FVC}=77\%$, $\text{RV}/\text{TLC}=109\%_{\text{pred}}$, $\text{DL}_{\text{CO}}=41\%_{\text{pred}}$, $6\text{MWD}=299\text{m}$, pack years=50, MRI VDP=5%, MRI ADC=0.31 cm^2/s , $\text{RA}_{950}=2\%$, $\text{LAC}=-2.1$



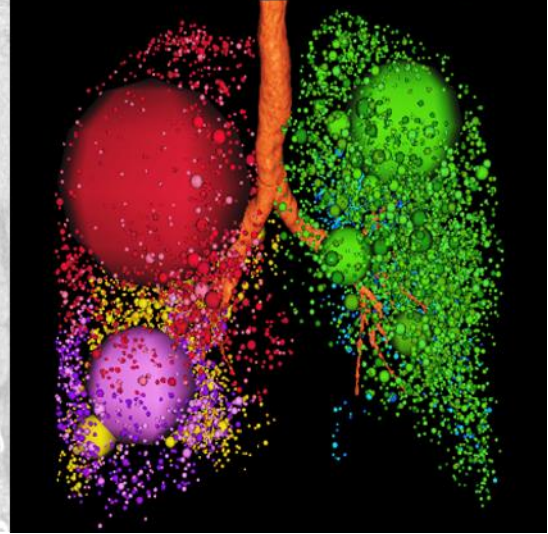
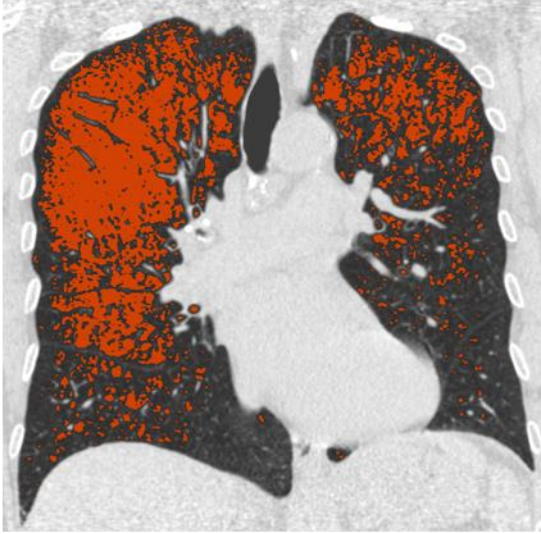
CT RA₉₅₀

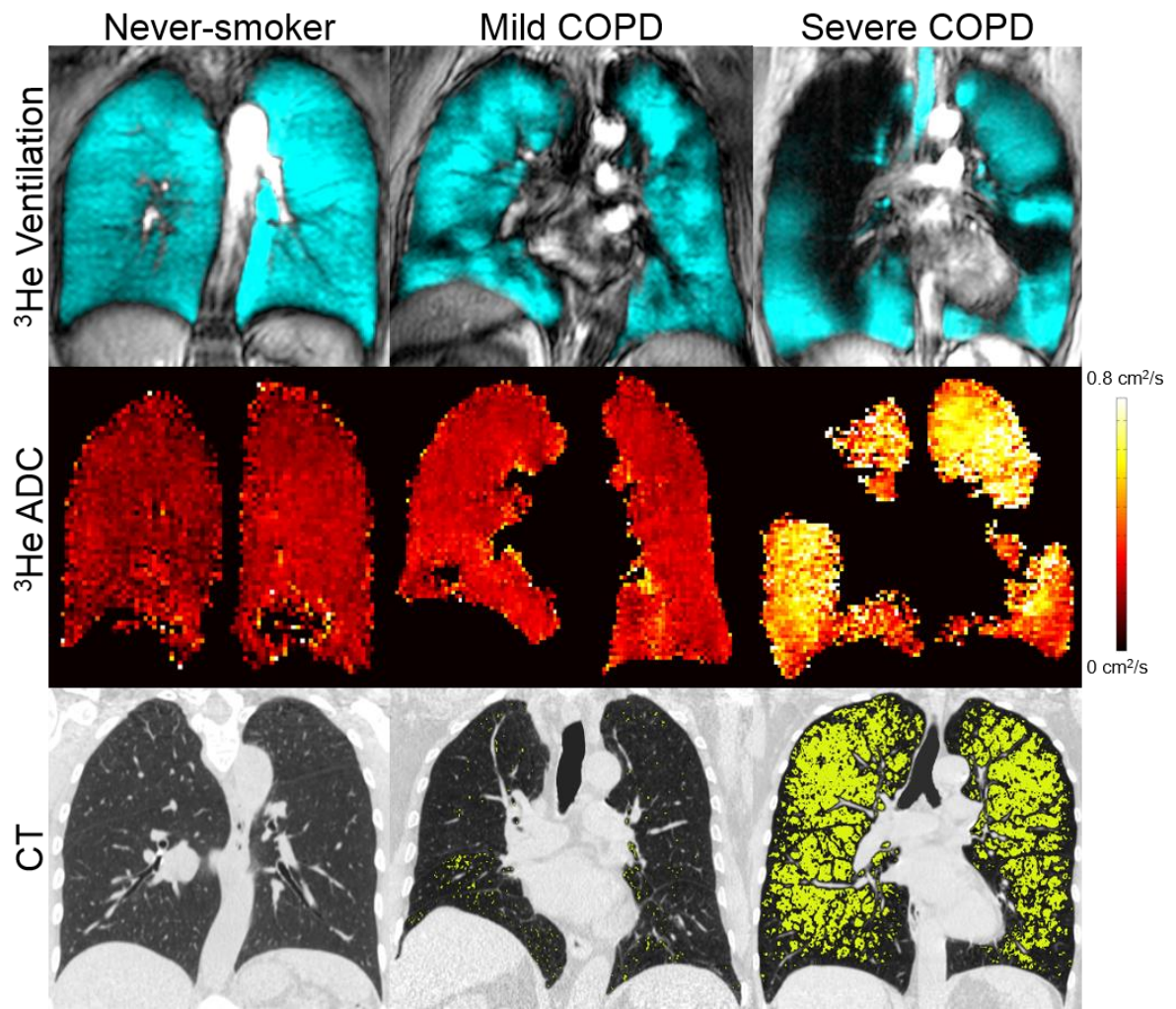
3D LAC

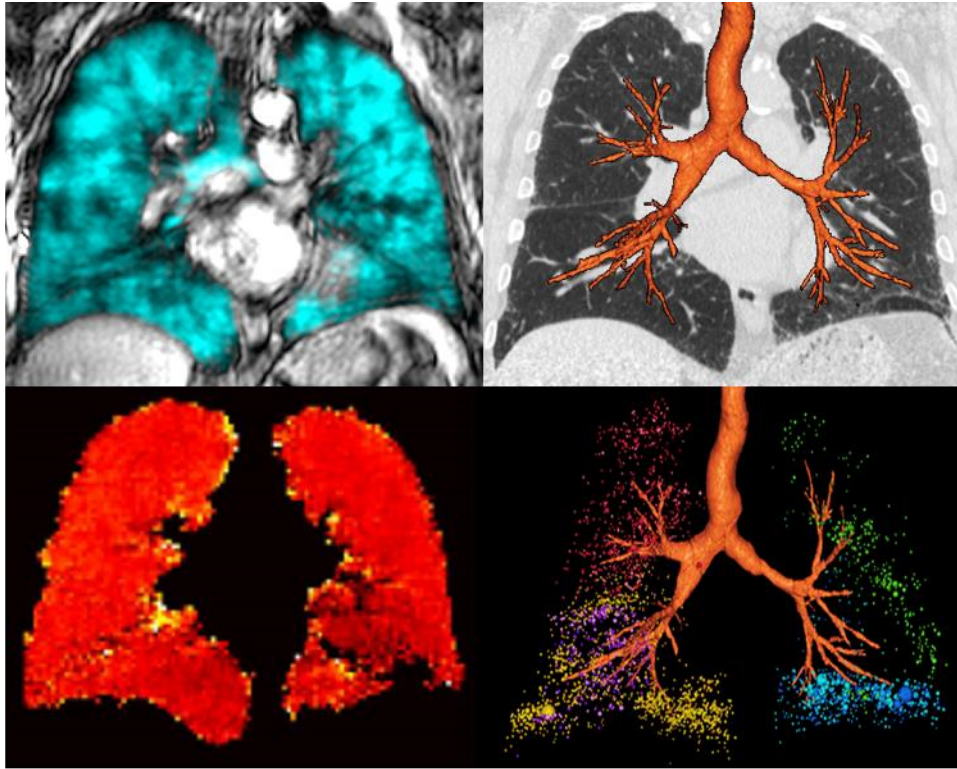
Mild/Early COPD



Severe/Advanced COPD







0 cm²/s  0.8 cm²/s