Appendix 1: Dyspnoea-12 questionnaire

This questionnaire is designed to help us learn more about how your breathing is troubling you.

Please read each item and then tick in the box that best matches your breathing during the past few days. If you do not experience an item tick the “none” box.
Please respond to all items.

	None	Mild	Moderate	Severe
My breath does not go in all the way	☐	☐	☐	☐
My breathing requires more work	☐	☐	☐	☐
I feel short of breath	☐	☐	☐	☐
I have difficulty catching my breath	☐	☐	☐	☐
I cannot get enough air	☐	☐	☐	☐
My breathing is uncomfortable	☐	☐	☐	☐
My breathing is exhausting	☐	☐	☐	☐
My breathing makes me feel depressed	☐	☐	☐	☐
My breathing makes me feel miserable	☐	☐	☐	☐
My breathing is distressing	☐	☐	☐	☐
My breathing makes me agitated	☐	☐	☐	☐
My breathing is irritating	☐	☐	☐	☐

Appendix 2: WHO performance status

World Health Organisation (WHO) performance status classification categorises patients as: -

Grade	Activity
0	Able to carry out all normal activity without restriction
1	Restricted in strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Symptomatic and in a chair or in a bed for greater than 50% of the day but not bedridden
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Appendix 3: Study protocol for healthy volunteers

Oxford Biomedical Research Centre

Oxford Radcliffe Hospitals NHS Trust | UNIVERSITY OF OXFORD | NHS National Institute for Health Research

Regional lung imaging and modelling to quantify anatomy, ventilation and perfusion using hyperpolarized xenon gas MR and thoracic CT imaging.

Short title: Regional lung imaging using hyperpolarised xenon gas MR
Ethics Ref: 11/SC/0487
EudraCT Number: 2011-002027-17
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Date and Version No: PROTOCOL Version 6 17 December 2013

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee. Within the terms of an existing confidentiality agreement, information may be disclosed to GE Healthcare.

1. ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
AE	Adverse event
AR	Adverse reaction
BRC	Biomedical Research Centre
cm^2s^{-1}	Square centimetres per second (measure of ADC)
CRF	Case Report Form
CT	Computed Tomography
COPD	Chronic Obstructive Pulmonary Disease
ECG	Electrocardiogram
EPI	Echo Planar Imaging
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FiXe	Fraction of inhaled xenon
FXe	Fraction of xenon
GCP	Good Clinical Practice
GP	General Practitioner
He	Helium
ICH	International Conference on Harmonisation
L	Litre
LPV	Lobar Perfusion Value
MAC	Minimum Alveolar Concentration
MHRA	Medicines and Healthcare products Regulatory Agency
MRI/MR	Magnetic Resonance Imaging
NIHR	National Institute for Health Research
PET	Positron Emission Tomography
PO_2	Partial Pressure of Oxygen
PV	Perfusion Values
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation
SAR	Serious Adverse Reaction
SPECT	Single photon emission computed tomography
SPV	Segmental Perfusion Value
S\V	Alveolar surface area per unit volume of gas
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSG	Oxford University Hospitals Trust / University of Oxford Trials Safety Group
VPV	Ventilation Perfusion Volume
VDV	Ventilation Defect Volume
Xe	Xenon
XTC	Xenon Transfer Contrast

2. RATIONALE

Chronic respiratory disease is an important condition for patients as it leads to disabling symptoms that impair quality of life, with breathlessness, reduced exercise tolerance, social isolation and dependence. The commonest of these diseases is chronic obstructive pulmonary disease (COPD), which is responsible for about 25-30% of the chronic lung disease burden, affecting 10% of adults in the UK aged over 40 years (1).

Overall, chronic lung disease is responsible for one in five of all UK deaths, one of the highest mortality rates in the European Union (1). It kills more people than ischaemic heart disease and leads to about 25 million certified sickness days taken from work each year (1). The estimated annual NHS cost for chronic respiratory disease is £ 6.6 billion (1). COPD alone is responsible for a quarter of all emergency respiratory admissions, occupies more than one million hospital bed days per annum, and generates 40 million prescriptions each year in England (1).

Currently, the gold standard for assessment of lung function in chronic respiratory disease is spirometry. This is combined with anatomical imaging (chest x-ray and computed tomography) for structural assessment. Spirometry only measures global lung function. It provides no information regarding the different regions of the lung or about the supporting "framework" of the lung itself, the parenchyma. In addition, changes in lung function as measured with spirometric indices do not correlate coherently with the symptoms experienced by patients, nor reflect their decline in health. This is particularly disappointing, since symptomatic disability is a much stronger predictor of mortality than spirometry alone (2). This weak relationship is probably because the lung is a complex regional organ where localized disturbances of a variety of factors including gas flow (ventilation), blood flow (perfusion) and gas transfer all combine to impair respiratory function.

To address these issues we aim to use hyperpolarized xenon gas magnetic resonance imaging (MRI) and computed tomography to develop a new technique capable of objectively and quantitatively describing regional and structural lung abnormality in patients with chronic respiratory disease. Since this is a relatively novel technique, we first need to acquire imaging and clinical data from a group of participants with normal lungs. We hope to generate an "atlas" of normality, which will form the foundation of future studies to compare with patients suffering from chronic respiratory disease. We also aim to validate the new technique in terms of intra-subject reproducibility.

MRI has the advantage of being free from ionizing radiation making it safe and practical for diseases such as asthma and obstructive lung disease where repeated follow-up scans are necessary. Hyperpolarized xenon, in the doses given for imaging has been shown to be safe (3). In conventional MRI, the signal originates principally from the protons in water molecules of tissues limiting its use in respiratory disease, because the lung has a very low density of protons, instead being largely composed of air spaces that do not generate MR signal. Hyperpolarized noble gases can resolve this problem. Helium (He-3) and xenon (Xe-129) are unreactive or inert noble gases. Both have a nuclear spin of ½, which generates a signal enabling use in MR imaging.

The study will focus on hyperpolarized Xe-129 MR imaging as xenon is more abundant and has certain additional properties to He-3 for lung MRI including solubility. Using GE Healthcare's xenon hyperpolarization system Xenospin, Xe-129 will be hyperpolarized, that is to say the nuclear spin within the atoms is increased. Hyperpolarization increases the MR signal enabling the Xe-129 gas to show up on the MR scan. In portions of the lung

that have good airflow, the hyperpolarized Xe-129 gas will show up more and be seen more quickly. In addition Xe-129 readily dissolves in blood where it emits different MR signal characteristics. This property may be exploited to regionally quantify both ventilation and perfusion within the lung providing a comprehensive assessment of lung function. These techniques have been developed by GE Healthcare, whose imaging technology group (Dr Chris Buckley and Dr Jan Wolber) and the University of Sheffield (Prof Wild) who are part of this collaboration.

In conclusion there is a need for improved functional lung imaging to inform the assessment of chronic respiratory disease better than current global lung function tests. Hyperpolarized xenon gas MR imaging offers the potential to assess regional functional abnormalities of the lung. Furthermore, establishing this new technique would open the possibility to multiple applications in clinical care including: -

- Functional assessment of response to different therapies in the clinic such as bronchodilators. This would assist in tailoring treatments better to the individual. It would also allow enable analysis of expensive therapies such as biologics for asthma and provide a biomarker surrogate for drug development.
- Selection of patients for regional lung therapies, such as lung reduction surgery.
- Prediction of the lung function consequences of destructive therapy such as resection at thoracic surgery and radiotherapy.
- Clinical research to describe the pathophysiology of regional lung disease (asthma, COPD, pulmonary fibrosis).

3. BACKGROUND

Current pulmonary assessment techniques
Spirometry involves assessment of forced expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC). FEV_1 only reflects the calibre of large airways but does not provide information about the support 'framework' of the lung itself (the parenchyma). Spirometry and other pulmonary function measures give an indication of global lung function but do not indicate regional lung function. This is important in respiratory disease where significant variations in air and blood flow exist between different portions of the lungs.

Computed tomography (CT) has been the main imaging modality for morphological evaluation of lung diseases. Structural information may be achieved with high spatial resolution. However, attempts to establish dynamic CT imaging for functional evaluation, with either standard multidetector CT or xenon enhanced electron beam CT, have not succeeded. This is largely due to technical constraints (4-8). Exposure to ionizing radiation also renders CT an unfavourable modality for diseases requiring multiple follow-up scans.

Nuclear medicine is able to provide functional information regarding lung ventilation and perfusion but with considerable limitations in spatial and temporal resolution. Single photon emission computed tomography (SPECT) offers improved structural detail, but still has poor temporal resolution (9). Positron emission tomography (PET) may be employed but requires special tracers not widely available. Both SPECT and PET also expose patients to ionizing radiation.

Hyperpolarized gas MR imaging
The first hyperpolarized gas MR images were obtained using Xe-129 in a mouse heart

lung preparation by Albert et al. (10), followed shortly by hyperpolarized He-3 images of human lungs by MacFall et al. (11). In subsequent years, hyperpolarized He-3 MR imaging became the focus of investigation due to inherent advantageous physical properties. He-3 has a larger magnetic moment than Xe-129 giving an increased signal to noise ratio. Also, until recently polarization methods were capable of achieving 30-50% polarization levels for He-3 but only 10 % for Xe-129 (12, 13). Both of these factors contributed to a stronger MR signal for He-3 compared with Xe-129. However, over recent years new modified polarization methods have been described enabling up to 55% polarization levels of Xe-129 to be achieved (14). These levels of polarization are comparable to those previously published for He-3, making Xe-129 an increasingly attractive agent given its large natural abundance and wider availability.

Methods of hyperpolarization

In their natural form, noble gases (Xe-129 and He-3) have low magnetic moments generating a weak MR signal. Compared to protons, which are abundant throughout the body, there is a limit to the amount of noble gas that can be administered into the lungs. Laser optical pumping is a technique employed to enhance the nuclear polarization of noble gases via a process called hyperpolarization. This technique was developed over 50 years ago and has been extensively applied within the field of physics research (15). Hyperpolarization results in the polarization of noble gases 100,000 times greater than the polarization of hydrogen nuclei in conventional MRI. This large net polarization gives rise to a large MR signal. In this way hyperpolarization compensates for the low physical density of noble gases introduced to the lungs permitting good visualization of the airspaces. The polarization that is generated by the hyperpolarization of He-3/Xe-129 and is completely independent of the field strength, unlike conventional MRI (16, 17). It is therefore possible to perform hyperpolarized Xe-129 MR imaging at a lower field strength with the benefit of reduced susceptibility artefacts. However most studies to date have been undertaken with 1.5T systems due to availability.

Comprehensive details of hyperpolarization methods have been previously published (18-23). There are two methods of laser optical pumping including alkali-metal spin exchange (24) and metastability exchange (25). Hyperpolarization of Xe-129 can only be performed by the spin exchange technique. Both methods employ circularly polarized light at different wavelengths. In brief, the spin exchange technique involves heating a glass cell containing He-3 or Xe-129 and rubidium metal to produce rubidium vapour. The rubidium atoms absorb circularly polarized laser light illuminating the cell, resulting in high polarization of rubidium by “optical pumping”. Collision between the polarized rubidium atoms and noble gas atoms transfers the polarization by “spin exchange”. The product is hyperpolarized He-3 or Xe-129 atoms.

Challenges faced when imaging hyperpolarized noble gases include the following: -

1. The hyperpolarization generating the MR signal is “non-renewable”. Some polarization will be consumed during image acquisition and may only be replenished by the introduction of additional hyperpolarized gas.
2. The paramagnetic properties of oxygen within the lungs lead to a loss of polarization and decay of MR signal. However, this characteristic can be utilized beneficially to measure intrapulmonary PO_2.
3. He-3 and Xe-129 are highly diffusive resulting in MR signal loss.

MR pulse sequences have been developed to account for these factors and enable regional imaging of lung structure and function down to the level of the secondary pulmonary lobule.

Hyperpolarized Helium MR Imaging
To date, hyperpolarized helium (He-3) gas MRI has been the focus of ventilation imaging research. However He-3 is expensive and limited in world supply necessitating further investigation into other suitable gases, namely Xe-129. The techniques and findings from previous research with hyperpolarized He-3 MR imaging form the basis of the current study. A summary of the current literature has therefore been included.

In normal individuals, the inhaled hyperpolarized He-3 gas is distributed homogenously throughout the lung airspaces. In contrast, localized regions deficient in hyperpolarized gas and therefore MR signal represent ventilation defects. These have been shown in a range of lung pathologies e.g. asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (26) and bronchiolitis obliterans (27, 28). The size and extent of ventilation defects demonstrated with hyperpolarized gas MR correlate with spirometry (26, 29). Furthermore, hyperpolarized gas MRI has shown increased sensitivity in detecting ventilation abnormalities compared with spirometry and lung ventilation scintigraphy (12, 30).

"Dynamic ventilation images" may be obtained with hyperpolarized gas MRI by employing ultrafast pulse sequences (31-34). Dynamic ventilation imaging allows the distribution and severity of air trapping to be assessed directly (33, 34) and has been performed to evaluate air trapping in patients with bronchial asthma (33) and cystic fibrosis (34).

Several methods for the quantitative measurement of regional lung ventilation using hyperpolarized He-3 MRI have been suggested in experimental animal studies (35-37). In a rat model of emphysema, the ventilation abnormalities detected preceded the histological changes seen in lung alveoli (38). This study, demonstrated detectable lung functional changes before structural abnormalities and further supports hyperpolarized gas MR functional imaging for earlier diagnosis in pathological disease processes.

The diffusion coefficient of a particular gas determines the average distance its atoms move in a given period of time. The lung microstructure acts to restrict the diffusion of hyperpolarized noble gas atoms enabling the average short time diffusion coefficient, (apparent diffusion coefficient, ADC) to be measured with MRI (39). Increased ADC values have been reported with hyperpolarized He-3 MR imaging in emphysema, reflecting the increased free movement of He-3 gas atoms permitted by alveolar tissue destruction (39-42). In this way, regional ADC values can be used as a surrogate measure of alveolar airspace size. Precise correlations between hyperpolarized gas MRI ADC measurements and histological measurements of alveolar size have been reported (43-45). ADC values with hyperpolarized He-3 MR imaging have proven highly reproducible (46, 47), and been shown to correlate strongly with lung function tests (40). Another potential application of ADC measurements is the assessment of radiation induced lung injury. Post radiation therapy, lower hyperpolarized He-3 ADC values may represent reduced alveolar volumes associated with fibrosis of the interstitium (48).

In the presence of oxygen within the lung, hyperpolarized noble gases undergo hastened loss of polarization resulting in a predicted reduced MR signal (49). This known paramagnetic effect of oxygen on He-3 gas may therefore be utilized to quantitatively measure intrapulmonary PO_2 (50, 51). Reproducibility of intrapulmonary PO_2 measurements has been confirmed.

Hyperpolarized Xenon MR Imaging
Xenon (Xe) is an inert, non-toxic noble gas. Atmospheric air contains approximately 0.04 mol% of xenon. The xenon isotope Xe-129 is employed for hyperpolarized xenon MR

imaging. The natural abundance of Xe-129 in atmospheric Xe is 26%, and it can be extracted relatively easily.

Previous applications of xenon include use as an anaesthetic at much higher concentrations (> 3 times, and at larger volumes) than employed in this study. Xenon has also been used in scintigraphic and CT brain perfusion studies and as an inhaled contrast agent in CT (52, 53). Xe-129 is ten times more soluble than He-3 in water and one hundred times more soluble in lipid-rich tissue. Xenon's vastly increased solubility in blood and lipid-rich tissue demonstrates a partition coefficient of approx 0.1 (54). This property of Xe-129 may be exploited to evaluate gas exchange between alveoli and capillaries, and to provide information regarding the diffusion capacity (14, 55-60). In addition to assessment of ventilation and ADC in the gas spaces possible with He-3, Xe-129 allows for dissolved-phase imaging (10).

Following inhalation, approximately only 2% of Xe-129 is dissolved into the lung parenchyma or blood. The blood circulation distributes dissolved Xe-129 throughout the body enabling perfusion imaging in different organs. The MR signal characteristics of Xe-129 are strongly influenced by its environment such that the signal from dissolved-phase Xe-129 is significantly different to that of the gas-phase. A chemical shift of signal in the dissolved-phase is seen of approximately 200 parts per million from that of the gas-phase. Chemical shifting imaging in the lungs and other body organs has been demonstrated in rat models (61, 62). Investigation of hyperpolarized Xe-129 MR signal characteristics has revealed different signals corresponding to Xe-129 compartmentalized within fat, tissue and red blood cells. Simultaneous ventilation perfusion studies of the lung are possible through collection of gas and dissolved-phase signal within a single acquisition of images.

Initially Albert *et al.* demonstrated imaging of the lung airspaces using hyperpolarized Xe-129 introduced into the trachea of a mouse heart-lung model (10). High signal intensity was achieved using 25ml (3atm) of Xe-129 polarized to approximately 25%. This was followed by a combined imaging and spectroscopic approach by Mugler *et al.* (58). Comparison was made between hyperpolarized Xe-129 and conventional H^1 MR images in two human volunteers following inhalation of hyperpolarized Xe-129, polarized to 2%. Significant correlation was shown between the gas space signal absence in conventional MRI and the gas space signal in hyperpolarized Xe-129 images (58).

The dynamics of Xe-129 within the chest have been further studied in a dog (13). This study demonstrated a decay of the Xe-129 MR signal within the gas-phase. This was observed to provide a measure of Xe-129 absorption into the tissue. Time constants for saturation were determined as 61ms and 70ms for tissue and red blood cells respectively.

Hyperpolarized Xe-129 MR imaging may be applied as a non-invasive measure of lung function parameters specific to emphysema. The alveolar surface area per unit volume of gas (S/V) represents a primary measure of emphysema that may be evaluated using the chemical shift saturation recovery method (14, 55, 63). Another strategy using hyperpolarized Xe-129 MR is the xenon transfer contrast (XTC) method that may be adapted to derive values of S/V (14, 63). In addition, the XTC method has been used successfully to measure lung septal thickness in animals (59, 64) and humans (14) and evaluate the severity and progression of emphysema (43).

ADC values may also be determined with hyperpolarized Xe-129 MR imaging. However, Xe-129 has a much lower diffusivity than He-3 and demonstrates a lower diffusion

coefficient. This offers potential advantages over He-3 since for measurement of alveolar and small airways dimensions with weighted imaging (65).

Hyperpolarized Xe-129 is also susceptible to the paramagnetic effect of oxygen within the pulmonary airspaces. The resultant loss of polarization and predicted decay in MR signal may be used to measure intrapulmonary PO_2. However, this is slightly more complex than when measuring with He-3 because additional signal loss due to diffusion of Xe-129 into alveolar tissue needs to be taken into account (14). An equivalent PO_2 is determined accounting for signal decay due to the presence of oxygen and Xe-129 diffusion.

4. OBJECTIVES

4.1 Primary Objective

- To develop hyperpolarized Xe-129 MR imaging as an objective and quantifiable method of regional lung assessment.

4.2 Secondary Objectives

- Following inhalation of xenon gas, a very small fraction dissolves into the blood stream where it emits different MR signal characteristics. This property allows us to potentially look at gas transfer and perfusion (blood flow within different regions of the lung) in addition to structure and ventilation (flow of gas). The main secondary objective is to determine normal regional lung perfusion parameters in hyperpolarized xenon gas magnetic resonance imaging.
- We will compare the scans with CT scans taken no more than one year apart.

5. STUDY DESIGN

5.1 Summary of Study Design

This will be an open, non-comparative study. The study group will include 40 participants from a cohort of patients with a prior history of testicular germ cell tumours. These patients commonly present aged 20 to 40 years, although there is also a slightly older cohort that may develop the disease. They very often have no or little associated comorbidity, and for early stage disease, the treatment is limited to either resection alone, or resection plus abdominal para-aortic radiotherapy. They will not have received chemotherapy or thoracic radiotherapy at study entry, will have no significant smoking history (≤10 pack years) or respiratory history, and will have normal spirometry (FEV_1 ≥80% predicted for age and height), normal arterial oxygen saturations (SaO_2), no reported exercise limitation and a normal chest CT (the CT chest is carried out as part of their usual clinical care). A normal CT will be defined as: subjectively normal according to a Consultant Thoracic Radiologist and with no evidence of emphysema on CT lung density mapping, taken not more than one year before the proposed hyperpolarized Xe-129 MR scan. At the time of the routine oncology follow-up clinic appointment, participants will be offered the opportunity of participating in this study. The patients will be identified from the Regional Germ cell database by the Oncology Consultant and Specialist Cancer Nurse. Patients with a spread of ages will be recruited enabling comparisons between age groups.

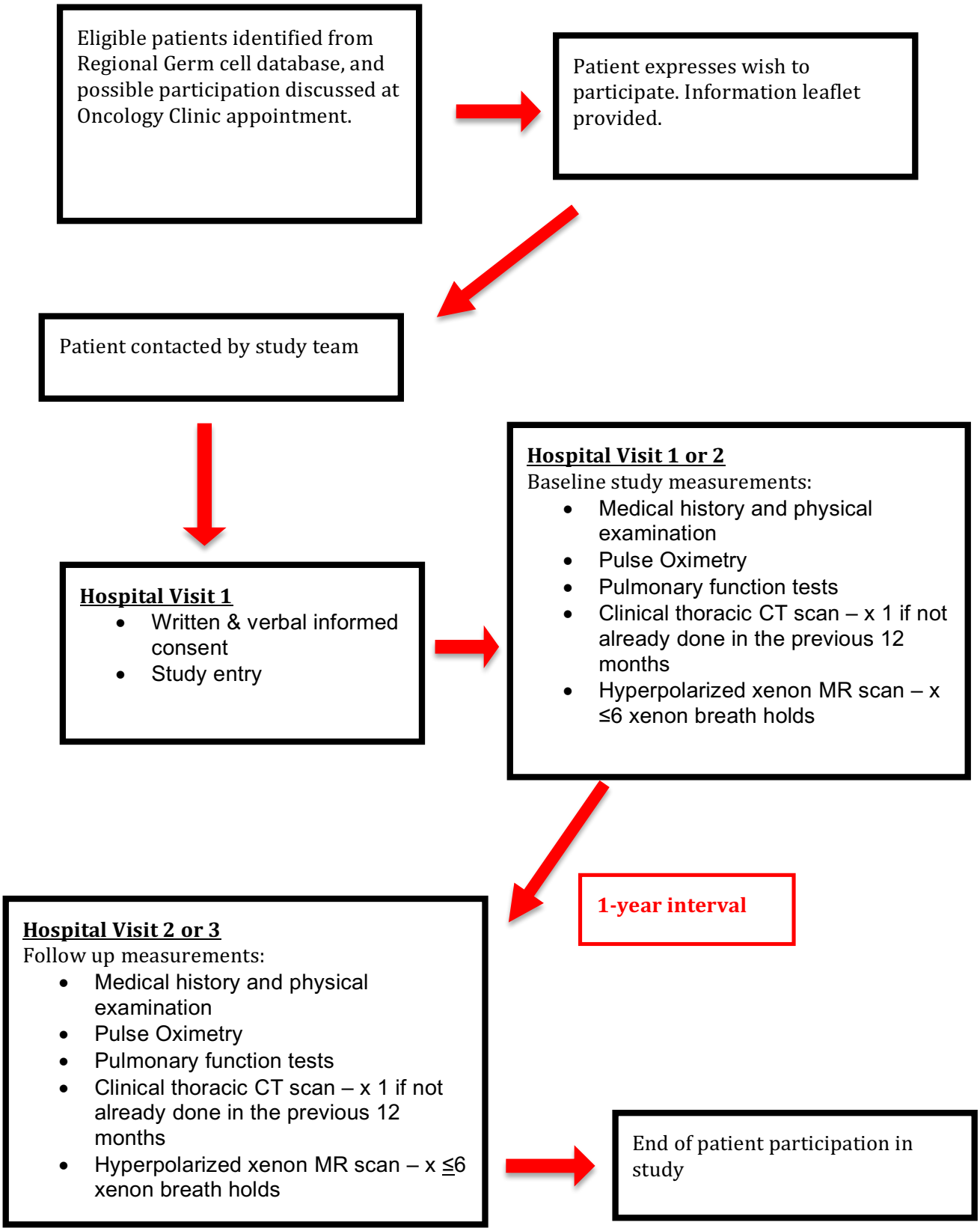
Hyperpolarized xenon MR imaging will be carried out at baselineand again after a one year interval to assess reproducibility. Hyperpolarized xenon MR imaging involves acquisition of up to four MR sequences during one scanning session. These may be different sequences or the same sequence may be repeated to assess reproducibility on the same day. In the event that breathing and scanning are not entirely synchronised, one or two xenon breath holds may need to be repeated. The participant will undergo up to a maximum of six hyperpolarized xenon breath holds during each visit. The sequences may be acquired with the patient lying supine or prone at the baseline visit. Previous studies have shown that the signal from each xenon breath hold clears within seconds of exhalation. Some patients will also undergo a follow-up thoracic CT at the one-year interval, which forms part of their normal clinical care. Patients will only be included in the study if the baseline thoracic CT is found to be normal, but the CT scan may have been performed up to one year before the proposed hyperpolarized Xe-129 MR scan. During each visit, patients are scheduled to undergo up to six hyperpolarized Xe-129 breath holds to complete MRI scanning. so in total, each participant will undergo up to a maximum of twelve hyperpolarized Xe-129 breath holds over the 1 year study period.

All patients will undergo clinical assessment involving full pulmonary function tests, which form part of standard best care at the time of baseline and follow-up imaging. Non-invasive detailed pulmonary function testing consists of:

- Pulmonary function tests – to include spirometry, static lung volumes and carbon monoxide transfer factor. Predicted values are determined from standard published data.
- Arterial oxygen saturations (SaO_2) – measured at the end of the history during which the patient has been sitting quietly, but before clinical examination. The patient sits without talking with eyes closed and hands resting comfortably whilst SaO_2 is observed. The average reading over a two-minute period is recorded.

Participation in enrolment and annual follow-up visits will take up to a day. Lung imaging (including thoracic CT and hyperpolarized Xe-129 MRI) and pulmonary function tests will take up to five hours, less if a patient does not need a CT scan, which will be the case if he has had a thoracic CT scan in the previous 12 months, including a period of observation after scanning.

5.2 Summary Flow Chart of Study Design



Primary and Secondary Endpoints/Outcome Measures

Primary Endpoint

- Production of Xe-129 ADC maps co-registered to CT and objective measures of regional lung anatomy, ventilation and perfusion in normals with hyperpolarized Xe-129 MR imaging (ADC quantification in cm^2s^{-1}). Derivation of reproducibility data.

Secondary Endpoints

- Measure of blood perfusion in the lung from the dissolved fraction of Xe-129
- Compare the MRI scans with routine CT in the same patient
- Look at the repeatability of the scans, comparing scans on the same day with the patient prone and supine and comparing scans taken one year apart

5.3 Study Participants

5.3.1 Overall Description of Study Participants

Study participants with a prior history of testicular germ cell tumours will be recruited. They will not have received chemotherapy or radiotherapy, will be non-smokers with no significant smoking history (≤10 pack years), no significant respiratory history, and will have entirely normal lungs according to spirometry indices, arterial oxygen saturations (SaO_2) and appearances on CT.

5.3.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male, aged > 18 years.
- Patients with previous histologically verified testicular germ cell tumour who have successfully undergone resection and do not and have never had metastatic disease.
- Normal chest CT, confirmed subjectively by a Consultant Thoracic radiologist (Dr F. Gleeson or R. Benamore or their nominated representative), and no evidence of emphysema on CT density mapping to have been performed no more than one year prior to proposed hyperpolarized Xe-129 MR scan.
- Normal spirometry indices (>80% predicted FEV1 for age and height) and normal arterial oxygen saturations (SaO_2), normal carbon monoxide transfer factor, and generally in good health with no subjective exercise limitation.
- Current non-smokers with no significant smoking history (≤10 pack years) and no history of respiratory disease.
- WHO performance status 0.
- Able (in the Investigators opinion) and willing to comply with all study requirements.
- Willing to allow his General Practitioner and consultant, if appropriate, to be notified of participation in the study.

5.3.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Inability to give written informed consent.
- Patients with a history of nodal or metastatic germ cell tumour.
- Patients with a prior history of chemotherapy or radiotherapy at study entry.
- Prior history of thoracic surgery or significant chest trauma

- Prior history of significant smoking or respiratory disease.
- The presence of another malignancy, where the extent of disease or treatment for that condition may interfere with the study endpoints.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- Inability to lie flat for imaging.
- Contra-indications to receiving iodine-based contrast during thoracic CT – those with marked renal failure not on dialysis, known allergy to contrast medium, history of anaphylaxis, known or suspected thyroid carcinoma and inability to gain intra-venous access.
- Contraindications to MRI examination including indwelling pacemaker, non-MRI compatible metallic implant, severe claustrophobia, intra-ocular foreign body.
- Epilepsy requiring on-going medical treatment, or a seizure within the past year.

5.4 Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate.
Participants will be offered a small payment of approximately £30 as a 'thank you' for their time.

5.5 Study Procedures

5.5.1 Informed Consent

Documented informed consent will be obtained prior to registration and any study procedures being undertaken. This will be done in accordance with the national and local regulatory requirements.

Patients who express an interest in participating in the study when their Oncologist mentions it will be provided with a brief verbal explanation and a patient information leaflet to take away. The leaflet will explain that they will be contacted in due course, by one of the study co-investigators.

The participant information and Informed consent will be presented by the doctor taking informed consent and the written version will be given to the patient. This will detail no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information (usually around a week with written information), and the opportunity to discuss the study with the Investigator, their GP or other independent parties to decide whether they wish to participate. The informed consent procedure will conform to the ICH (International Conference on Harmonisation) guidelines on Good Clinical Practice (GCP). This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representatives". A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

The person who obtained the consent will be suitably qualified and experienced with up to date GCP/informed consent training, and have been authorised to do so by the Chief Investigator.

5.5.2 Screening and Eligibility Assessment

Potential participants will be identified from the Regional Germ cell database and approached by their Oncologist within the hospital setting. Any potential participant fulfilling the inclusion criteria with previous successfully resected testicular germ cell tumour will be informed of the study by their Oncologist. If a patient expresses an interest in the study, they will be given a patient information leaflet.

Prior to registration or any study measures being undertaken, documented informed consent will be completed as detailed in section 5.6.1.

All participants will undergo clinical assessment including history, physical examination and baseline study measures over 1 -2 hospital visits as outlined below: -

Demographics
The date of birth, gender and smoking history will be recorded.

Medical History & Physical Examination
These will be performed as part of the participants' normal clinical care.

Arterial oxygen saturations (SaO_2) – measured at the end of the history during which the patient has been sitting quietly, but before clinical examination. The patient sits without talking with eyes closed and hands resting comfortably whilst SaO_2 is observed. The average reading over a two-minute period is recorded.

5.5.3 Baseline Assessments

Pulmonary Function Tests
Pulmonary function tests will be carried out, including spirometry, lung volumes and carbon monoxide transfer factor. Recordings will be compared to predicted values determined from standard published data.

Computed Tomography
Thoracic CT will be performed on the 64-slice GE Lightspeed scanner. A slice thickness of 0.675mm will be used. All images will be acquired during a single breath hold performed triggered to lung volume. The patient lies on their back, whilst scanning takes place. Intravenous contrast will be administered and scanning performed 50-60 seconds post injection as per standard imaging for routine germ cell tumour follow up. It is not necessary to conduct this scan at the study visit if the patient has already had a thoracic CT scan less than one year before the Xe-129 MR scan.

Hyperpolarized Xe-129 MR Imaging
The patient lies on their back in an MR scanner, and has conventional safety monitoring throughout (direct visual observation, arterial oxygen saturations and heart rate monitoring). They wear a lightweight vest containing the imaging coils over their clothes that is necessary for acquiring images.

Before the first Xe-129 MR scan involving inhalation of up to 1L of xenon, patients will be asked to breath in a small volume of xenon of approximately 100mL mixed with medical grade nitrogen for a total volume of 1L. The patient will be instructed to perform a standard breath hold for a short period of time (approximately 2 seconds). This is a set-up procedure for the scan enabling optimization of Xe-129 MR parameters according to patient height and weight, as well as a practice run for the patient. The

output from calibration (flip angle measurement) enables the best quality Xe-129 MR images to be acquired for each individual and is not be used to evaluate the study endpoints.

The patient breathes out, and then breathes in up to 1L of xenon from a bag. The total volume of gas participants are given for Xe-129 MRI scans is 1L, however this may consist of a mixture of 50-100% hyperpolarized xenon and up to 50% nitrogen i.e. 500 mL to 1L of hyperpolarized xenon is mixed with medical grade nitrogen to make up a total volume of 1L. Breathing in xenon is challenging for some people because it has a density 4.55 times greater than air, which increases airways resistance (66). Therefore patients are sometimes given assistance with the respiratory manoeuvre by physically compressing the bag during inhalation. The patient receives a bag full of air to practice this breathing manoeuvre before breathing xenon. Scanning then takes place during a breath hold for up to a maximum of 20 seconds. If the patient fails to breathe in sufficient xenon at the required time, the investigator may suggest that the procedure is repeated. One patient will not exceed six inhalations of xenon in a single day. In the unlikely occurrence of an adverse event, a radiographer will be able to access the participant immediately.

No intravenous contrast will be administered for MR imaging. Patients are given an MRI safety leaflet, and a contact number to discuss any aspect of the visit and scanning prior to giving consent.

During the study, it may be necessary to perform a small number of scans to validate changes in the scanning technique, or updates in software. These scans may also be required to check the quality of hyperpolarized Xe-129 for inhalation, following faults that may occur in the manufacturing system. These technical development scans will be performed with the help of consenting members of hospital staff, in order to not cause inconvenience to a study participant. Scanning of staff members will also be used if it should be necessary to train radiographers specifically for hyperpolarized gas MRI scanning. The procedure for this is included in Appendix C.

Hyperpolarized Xe-129 MR imaging will be performed using xenon hyperpolarized by a Xenospin hyperpolarizer (GE Healthcare 2000) and imaged on a 1.5T MRI scanner. A dedicated Xe-129 chest coil will be used. Images will be obtained in any plane, coronal, axial or sagittal. This manoeuvre with scanning will be repeated up to six times to enable acquisition of all Xe-129 MRI sequences. If the patient time allows and the maximum number of inhalations has not be exceeded, images may be acquired to assess reproducibility on the same day. There are currently three confirmed sequences that patients will undertake (ventilation, ADC and dissolved phase) with further sequences under technical development that may be introduced during the course of the study. During each scanning session, up to six hyperpolarized Xe-129 MR sequences will be acquired with the participant undergoing up to six separate xenon breath holds. Participants may be imaged both supine and prone at baseline to assess positional reproducibility. Participants will be imaged supine only at the 1-year follow up, as sufficient data to evaluate positional reproducibility will have already been collected at baseline. Total scanning time will be approximately 1 hour. Image acquisition strategy will follow the protocol tested in healthy normal volunteers in Sheffield and will consist of: -

- Short echo time proton MRI for co-registration purposes.
- Static ventilation – conventional 3D gradient echo based pulse sequences with small flip angles to produce static ventilation images of the lung. Parameters

repetition time 8-10ms, echo time 3-5ms, flip angle 5-15^0, section thickness 10mm, matrix 96 x 96, and field of view 32-50cm.

- Dynamic ventilation – Dynamic spoiled gradient echo imaging to capture respiratory airflow.
- Diffusion Imaging (ADC) – Gradient echo-pulse sequences to collect 2 or more images at each position with different diffusion weighting gradients.
- Intrapulmonary PO2 – determined from rate of decay of MR signal over successive images obtained during two separate breath holds varying the RF-pulse flip angle or the inter-image delay time.
- Dissolved phase xenon imaging.

Some patients have reported drowsiness in earlier research work. The patient will be carefully observed and asked about adverse events up to 30 minutes after the scan. If the study doctor believes that the patient is not fit to drive home, the research team will arrange another way for the patient to get home safely, without additional cost to him.

If the study team fails to acquire all the required Xe-129 MRI sequences during a single scanning session as a result of technical difficulties or non-synchronisation of patient breathing and scanning, the patient may be requested to return within a few days to complete Xe-129 lung MRI scanning and ensure acquisition of all sequences for that study visit. This may take up to half a day and may involve repeating one or two Xe-129 MR sequences previously acquired since these cannot be analysed accurately if they have not all been performed at the same time point.

Analysis

All analyses will be performed by two experienced Thoracic Radiologists (FVG & RB or an approved deputy) and an MR physicist. All analyses will be blinded to clinical data and all other investigation results to avoid bias.

1. Visual analysis, and subjective and objective confirmation of normality. The visual analysis, will include assessment of each pulmonary segment, both CT, and Xe-129 ventilation, diffusion and perfusion. The objective analysis will include calculation of mean attenuation values and percentage volumes in different ranges of attenuation values (in Hounsfield units), per lobe.

2. Non-rigid alignment with hyperpolarized Xe-129 MR imaging – expertise Computational Biology Group, Oxford University. This alignment will be scored as per prior lung scoring systems. Perfect alignment, up to 5% deviation, 10% deviation, > 10% deviation, per lung.

3. Accurate co-registration of *global* and *regional* data from hyperpolarized Xe-129 MRI and CT chest, by correlating lung masks obtained from CT and proton MRI scans. Analysis of the correlation of MRI ADCs with CT lung tissue density (measured in Hounsfield units).

At least the following quantitative analyses will be calculated:

i) Ventilation defect volumes (VDV)

ii) Ventilation perfusion volumes (VDP)

iii) Lobar and segmental perfusion values (LPV, SPV)

Whole lung histogram analyses of ADC, and Perfusion values (PV),

iv) VDV, VDP, LPV, SPV, PV reproducibility of Xe-129 lung MRI imaging in participants over time.

5.6 Subsequent assessments

At the time of follow-up imaging, study patients will be asked whether they have had any:

- Hospitalisations
- Consultations with other medical practitioners
- Disability or incapacity or other adverse event that has occurred since their last visit

All study measures will be performed and analysed as detailed previously in sections 5.6.2 and 5.6.3 of this document.

Assessments to be performed at the time of follow-up (one year after baseline): -

- Clinical assessment
- Full pulmonary function tests
- Arterial oxygen saturation (SaO_2)
- Thoracic CT (already scheduled as part of routine care to monitor for testicular germ cell tumour relapse). It is not necessary to conduct this scan at the study visit if the patient has already had a thoracic CT scan within one year before the Xe-129 MR scan.
- Hyperpolarized Xe-129 MR imaging

5.7 Definition of End of Study

The "end of study" is defined as the last visit of the last patient undergoing the study. It is estimated that this will be three years after initiation of the study. It is the responsibility of the Chief Investigator to inform the Trust R&D (the Sponsor) within 90 calendar days of the "end of study" that the study has closed. Enrolment in the study will be stopped when:

- The stated number of patients to be recruited (40) is reached

The sponsor and Chief Investigator reserve the right to terminate the study at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the patient's best interests.

6.9 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- An adverse event which results in inability to continue to comply with study procedures
- Disease progression which results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

Withdrawal from the study will not result in exclusion of the data for that participant from analysis provided all baseline study measures have been completed.
The reason for withdrawal will be recorded in the Case Report Form (CRF).
If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5.10 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). In this study the CRF will be used as the source document for clinical assessment at baseline and follow-up.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the identification code list and the signed consent, the participant will be referred to by the study participant number/code, not by name.

6. TREATMENT/ INTERVENTION

6.1 Description of Treatments/ Interventions

No treatments are given as a part of the proposed study.
Hyperpolarized Xe-129 lung MRI requires breathing in an investigational medical product, hyperpolarized xenon gas, Xe-129, which is described in detail below. There are no other interventions, and all assessments are detailed in Section 6.6..

6.2 Description of Xe-129

Xenon is an inert gas that is present in the atmosphere in low concentrations. It has no smell or taste. Breathing xenon or undergoing an MRI scan does not involve exposure to ionising radiation.

Physiological effects At low concentrations such as those that will be used in this study, Xenon has effects similar to nitrous oxide (laughing gas). Nine out of 10 patients experience light-headedness, paraesthesia, euphoria or a mild 'drunk' feeling, which is short lived and resolves within 2-3 minutes of breathing the gas (67-69).

Side effects Xenon has been found to be extremely safe and well tolerated, both during single breath-hold experiments such as ours (n=26 (70)and n=44 (66)) and during 4 minute 20 second continuous breathing (n=1,830) (68). In a prospective study examining safety and tolerability of xenon, 32% of 44 volunteers experienced mild gastrointestinal symptoms (66). One volunteer experienced drowsiness, sleepiness and numbness, which resolved in about 7 minutes (66). She had considerable co-morbidity, including multiple sclerosis, B12 deficiency and Graves' disease. In a large retrospective study involving breathing xenon for cerebrovascular imaging during a 4 minutes 20 seconds period (in contrast to our single breath exposure), the incidence of pauses in breathing for >15 seconds was 0.6%, headache (usually mild) 0.4%, nausea or vomiting 0.2%, change in sensorium 0.1% and 0.05% hallucinations (68). 0.2% of patients had a

seizure, but 3 of 4 of these patients were being investigated for unexplained seizures, and diagnostic information was not available for the fourth patient. Patients with multiple sclerosis had increased emotional lability. These side effects nearly all occurred towards the end of the exposure period. Pauses in breathing almost invariably were terminated by an instruction to take a breath.

Safety considerations At high concentrations xenon has anaesthetic properties. The minimum alveolar concentration (MAC) of xenon at sea level is 70% (71). Participants will breathe an FiXe considerably lower than this, and will inhale a single breath and therefore not approach the gas equilibrium that is required when defining MAC. Participants will inhale up to 1L from residual volume, resulting in an approximate FXe of 10-30%. The alveolar FXe would tend to be marginally lowered due to Xe in the anatomical deadspace of the large airways, and marginally raised due to Xe not entering non- or slowly communicating air spaces within the lungs. Thus the FXe that participants will be exposed to is considerably below the dose required to induce anaesthesia, and well within safe limits. It is not possible for participants to breathe more than 1 L of xenon, since they are given a single 1L bag of the gas.

A further safety consideration is participants' oxygenation, since they will be inhaling 1 L of anoxic gas, followed by a breath hold. However, participants will only be exposed to this low oxygen fraction for a single breath hold. The breath hold is up to a maximum of 20 seconds, although participants are free to take another breath sooner if they cannot manage this long. The amount of oxygen available in 3.5 L of 11% oxygen is 385 mL, which is considerably more than the oxygen requirement for the duration of the breath hold (assuming oxygen use is 250 mL/ min). These calculations assume all gas within the lungs is in communication with inhaled gas, which is often not the case in respiratory disease, however the safety margins are extremely large. Reassuringly, studies in chronic obstructive pulmonary disease (COPD) patients using this breathing technique observed a mean fall in oxygen saturations of only 1.2 % of baseline during observation at 2 minute intervals for 10 minutes (66), and all the participants included in this study will have entirely normal lungs as a criteria for entry.
Participants will be carefully observed and monitored throughout the study, including heart rate, respiratory rate and arterial oxygen saturations. In the event of any untoward medical event occurring mid-scan, staff can reach the participant immediately.

6.3 Xe-129 production, storage and dispensing

Xe-129 will be isolated from a gas mixture of 1.0% xenon, 10% nitrogen and 89% helium, manufactured in the USA and supplied by Spectra Gases Ltd, Littleport Cambridgeshire. The gas mix will be shipped to the hospital and will be delivered to the Radiology Department where it will be polarised via spin exchange optical pumping by laser, using the GE Healthcare Xenospin hyperpolarisation system. The hyperpolarisation will take approximately one hour. Xe-129 will then isolated from other gases and sublimated into Tedlar plastic bags in Radiology for administration to participants via inhalation in the MR suite. The gas is labelled in accordance with Annexe 13 according to EU trial directive requirements. There are clear SOPs for each stage of this manufacturing process. The maximum storage time before administration to a participant is 30 minutes.

Each batch of Xe-129 will be tested using a GE Healthcare 1651 polarisation measurement system to ensure sufficient xenon gas is hyperpolarised to enable lung imaging.

Calibration doses, given before the first Xe-129 MR scan, contain a small volume of xenon of approximately 100mL mixed with medical grade nitrogen for a total volume of 1L. These are not IMP controlled batches and are not tested for quality control.

The total volume of gas in each bag is 1L, however this may consist of a mixture of 50-100% hyperpolarized xenon and up to 50% nitrogen i.e. 500 mL to 1L of hyperpolarized xenon is mixed with medical grade nitrogen to make up a total volume of 1L.

All staff involved in the process of Xe-129 manufacture will be trained using GE Healthcare's training programme to ensure that the manufacture is conducted safely to the correct technical specification. The manufacturing facility will be licensed by the MHRA and each batch (excluding the calibration doses) will be manufactured to GMP standard and certified for release to the investigator by a qualified person according to the approved Standard Operating Procedures.

6.4 Randomisation codes/ unblinding

This study is not a randomised trial. All patients undergoing hyperpolarized MR imaging will breathe Xe-129.

6.5 Modification of trial treatment

Following a serious adverse event (SAE) by regulatory criteria (see section 7) treatment may be interrupted at the discretion of the chief investigator and restarted if clinically appropriate to complete the proposed treatment course.

6.6 Accountability

Medical grade xenon will be supplied by Spectra Gases Ltd, Littleport Cambridgeshire to the polariser installed at the Oxford Thoracic Imaging Centre. Xenon will undergo hyperpolarisation up to an hour prior to use. The xenon manufacturing unit will keep records of the batches and dispense xenon directly from the unit.

6.7 Measures of compliance/ adherence

It will only be possible to give one xenon dose per MR scan. The xenon dose is only given by radiographers/ radiologists during the MR regional lung imaging itself.

6.8 Treatment data collection

MR Image data will be collected as for routine radiology procedures. The data will be anonymised before exporting to the Oxford University department of Computer Science. Safety outcome data for the study will be recorded on the case report forms.

6.9 Non-trial treatment

The only investigational medicinal product employed during this study is hyperpolarised Xe-129. All other non-study treatment will continue throughout and following study completion as part of best patient care.

6.10 Data on concomitant medications

Patients' medications will be recorded at baseline and at each follow-up visit.

6.11 Co-enrolment guidelines

Patients may enter into other clinical trials with ethical approval and informed consent.

6.12 Post Study Treatment

The proposed study is an observational study. All participants will receive best standard care throughout and this will continue without interference following study completion.

7. SAFETY AND ADVERSE EVENTS AND REACTIONS

7.1 Adverse Events

An adverse event (AE) is defined as 'any untoward occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this product'; in this study it is Xe-129. These may include side effects, injury, toxicity or hypersensitivity reactions. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

An adverse event (AE) includes:

1. An exacerbation of a pre-existing illness
2. An increase in frequency or intensity of a pre-existing episodic event/condition
3. A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
4. Continuous persistent disease or symptoms present at baseline that worsen following the administration of the trial treatment
5. Expected physiological effects that are caused by breathing xenon, as described in section 5.2

An adverse event does not include:

1. Medical or surgical procedures: the condition which leads to the procedure is the adverse event
2. Pre-existing disease or conditions present before treatment that do not worsen
3. Situations where an untoward medical occurrence has occurred e.g. elective surgery
4. Overdose of medication without signs or symptoms (although such events should be reported on the relevant CRFs.
5. Underlying disease associated symptoms/ signs unless more severe than expected for the patient's condition

Adverse events (AEs) should be reported on the routine CRFs. For this study, AEs occurring during, or within 24 hours of breathing xenon will be recorded. Since xenon is not expected to have any pharmacological activity beyond a few minutes after a single breath, subsequent AE reporting will be limited to any adverse event having a reasonable possibility of being attributable to breathing xenon (that is an adverse reaction), as judged by the local investigator, and any other adverse event considered to be of medical interest/ importance by the chief investigator.

All other adverse events will be provided in a written report once a year throughout the clinical trial and at the end of the study or on request, to the sponsor, Competent Authority (MHRA) and the REC.

7.2 Adverse Reaction (AR)

This is defined as all untoward and unintended responses to a medicinal product related to any dose. The phrase 'responses to a medicinal product' means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

7.3 Expected Adverse Drug Reactions

After breathing gas containing xenon, feelings of light-headedness, paraesthesia, euphoria or mild 'drunk' feeling are common, occurring in 9 out of 10 people. These symptoms last for just a few minutes, just like breathing 'laughing gas'. The expected Adverse Drug Reactions are described in the Investigators' Brochure.

7.4 Unexpected Adverse Reaction

An unexpected adverse reaction is an event having a reasonable possibility of being related to trial medication and which is of a nature or severity that is not consistent with the expected adverse reaction profile of the trial medication. Unexpected adverse reactions are recorded on the case report forms. The expected profile is as in Section 7.3 and detailed in the Investigators' Brochure.

7.5 Reporting of Adverse Events

All AEs observed by the investigator or reported by the patient during and for 24 hours after Xe-129 lung MRI are reported on the case report forms. Thereafter only adverse events where there is a reasonable possibility of a relationship to inhaled xenon (adverse reactions) as judged by the chief investigator, and any adverse event considered by the chief investigator to be of medical interest/ importance are reported. These events will be reported on the case report forms.

AEs considered related to inhaled xenon (adverse reactions) are followed until resolution, or the event is considered stable. The following attributes are recorded by the investigator: description, date of onset and resolution date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. The investigator may be asked to provide follow-up information.

All adverse reactions that result in a patient's withdrawal from the study or are present at the end of the study should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE/ AR is of sufficient severity to require the patient's removal from Xe-129 MRI scanning. A patient may also voluntarily withdraw from study procedures if they tolerate it poorly. Further details of withdrawal are presented in Section 5.9.

In the event of symptoms arising, patients will be given appropriate care and medical supervision until symptoms resolve, or the condition becomes stable. Every effort will be made to gather outcome data on patients through study follow-up, or general practitioner/ hospital staff unless the patient is specifically withdrawn consent to such efforts.

7.6 Serious Adverse Events

7.6.1 Serious Adverse Events (SAE) and Reactions

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:
The term '*severe*' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as '*serious*', which is based on patient/ event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Subject to the specific reporting procedures for this trial, a serious adverse event (SAE) occurring to a research participant during or within 24 hours following Xe-129 lung MRI will be reported to the Oxford University Hospitals Trust R&D Department within one working day of discovery or notification of the event. Subsequent to this, only events that are thought likely to be related to the inhalation will be reported as SAEs as above.

The regulatory definitions (by ICH criteria) by which an AE/ R should be classified as 'serious' are listed below. The reporting of these events in this trial is subject to the specific reporting procedures for this trial (see section 7.1, 7.5).

1. Results in death
2. Is life-threatening (i.e. with an immediate, not hypothetical, risk of death at the time of the event)
3. Requires hospitalisation or prolongs existing hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included)
4. Results in persistent or significant disability or incapacity such that the patient is unable to conduct normal daily life functions
5. Is a congenital anomaly (i.e. the outcome of pregnancy involving a patient). A pregnancy undetected at entry would constitute a protocol violation [Not applicable].
6. Any other important medical events. This, though not included in the above, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed (e.g. include allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias which did not result in hospitalisation or development of drug dependency). Medical and scientific judgment should be exercised in deciding whether an adverse event is serious in other situations.

Serious (regulatory) adverse events occurring during or within 24 hours following Xe-129 lung MRI scanning should be reported to the Oxford University Hospitals Trust R&D Department within one working day. R&D will perform an initial check of the report, request any additional information and ensure it is reviewed by the Medical Monitor on a weekly basis. R&D will also ensure that it is reviewed at the next Trial Safety Group meeting. All SAE information must be recorded on an SAE form and faxed to R&D. Additional information received for a SAE (follow-up or corrections to the original case) need to be detailed on a new SAE form and faxed to R&D. It will be clearly stated on the SAE form whether or not, in the opinion of the chief investigator, the SAE has a reasonable suspected causal relationship to the trial medications.

All SAEs from Xenospin will be reported to the sponsor (the Oxford University Hospitals NHS Trust) within standard regulatory timelines for the reporting of SAEs and SUSARS, consistent with the MHRA regulations for clinical trials.

7.6.2 Trial Safety Group

The Oxford University Hospitals Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the study reported during the quarter and cumulatively. The aims of this review include:

- To ensure the safety of each patient in the trial
- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary
- To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment

The Trial Safety Group will also, as required:

- Request Provision of training specific groups within the Trusts or University
- Request internal audits either in the Trust or University, where necessary

7.6.3 SUSAR's

In collaboration with R&D and TSG Medical Monitor, the Chief Investigator will report all SUSARs to the MHRA and the REC. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARS within 15 days. The Chief Investigator will also inform all investigators concerned of relevant information about SUSARS that could adversely affect the safety of participants.

7.7 Outcome grading of Adverse Events

Graded as either: resolved, resolved with sequelae, persisting, worsening or fatal.

7.8 Relationship to trial treatment

The relationship between the trial treatment and the adverse event will be graded as: Definitely, probably, possibly, unlikely or not related.

7.9 Follow-up after Adverse Events

Participants experiencing SAEs or AEs will receive the appropriate medical treatment. After recovery these participants will be followed up in the normal study follow-up sequence.

7.10 Annual Reports

In addition to the expedited reporting above, the Chief Investigator shall submit once a year throughout the trial, or on request, a Development Safety Update Report and an annual progress report to the Competent Authority (MHRA), Ethics Committee, Sponsor and Host NHS Trust in collaboration with University of Oxford Cohort COPD study.

8. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification 'serious breaches' to the MHRA within seven days of the sponsor becoming aware of the breach. A serious breach is defined as 'A breach of GCP or the trial protocol which is likely to affect to a significant degree –

a) The safety or physical or mental integrity of the subjects of the trial; or
b) The scientific value of the trial'

In the event that a serious breach is suspected R&D must be contacted as soon as possible.

9. STATISTICS

Early studies (67, 72), including work from our own group (73), using hyperpolarized helium MRI have demonstrated that this technique provides valuable information regarding pulmonary parenchymal apparent diffusion coefficients (ADCs – measures of increased air spaces), demonstrating important differences compared to age matched controls or young, healthy volunteers. This study will enable accurate mapping and quantification of variation in ventilation, diffusion and perfusion in normals, with the determination of subjective and objective values, VDV, VDP, LPV, SPV, with comparison of baseline and follow-up, and supine and prone scans.
We will also carry out the following completely novel analysis:

- Assessments of detailed regional data, with regional ventilation, ADCs, and perfusion.
- Accurate co-registration of *global* and *regional* data from Xe-129 lung MRI and CT chest, by correlating by correlating lung masks obtained from CT and proton MRI scans. Analysis of the correlation of MRI ADCs with CT lung tissue density (measured in Hounsfield units).
- Development of perfusion data (blood flow through the lungs) obtained using Xe-129 lung MRI.

9.1 Description of Statistical Methods

Statistical methods for comparison between baseline and follow up will be Wilcoxon matched-pairs two-tailed t test.
Observer reproducibility will be evaluated using the interclass correlation coefficient of variation and linear regression.
Relationships with pulmonary function tests and age will be by linear regression and Spearman correlation coefficients
The Wilcoxon test will also be used to establish statistical significance of the anterior-posterior, superior-inferior, differences between lobes and change on supine and prone scanning

9.2 The Number of Participants

The total sample size will be 40.

This is an observational study of normal, designed to provide a normal map for Xe-129 MRI and objective values. It is not possible to perform a detailed power calculation regarding sample size because this is the first time regional lung imaging with hyperpolarized Xe-129 has been formally investigated.

To date most studies employing hyperpolarized Xe-129 have been on animal models and healthy volunteers and have reported it as a viable functional lung imaging modality (14, 63). The sample size proposed for this trial will be sufficient to be informative in our planned analyses and direct future investigation.

9.3 The Level of Statistical Significance

This is an observational non-blinded trial to provide both an atlas of normal ventilation, diffusion and perfusion in patients with normal lungs, and to determine variability on

repeat measurements, prone and supine, and at 1 year follow up. It also provides the opportunity to measure changes in these measurements with age, and measure variations in the normal population. A p value of <0.05 and a correlation coefficient of > 0.5 will be regarded as significant.

9.4 Criteria for the Termination of the Trial.

The study will terminate following full recruitment and completion of follow-up or significant safety concern according to the safety reporting protocol and review as stated in section 6.

9.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

Efforts to measure all data as outlined in the trial protocol will be made. If a patient provides data from only one Xe-129 MRI scan, this will be included in analysis for mapping, but not for reproducibility. The data will be reviewed by F Gleeson, to confirm that it is robust, and any deviation from expected results will be reviewed to determine if this is due to scanning error, or other artefact.

9.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

This is an observational study; exploratory analyses in addition to those above may be conducted to further the development of the technique. These will be described in full in the final study report. Patient observations will cease at the time of termination of the trial.

9.7 Inclusion in Analysis

All evaluable participants will be included in the analysis. Participants will be deemed not to be evaluable for reproducibility if either or both baseline scans are not assessable or if the patient withdraws from the trial before completion of follow-up.

10. MONITORING

The sponsor will monitor the study according to the monitoring plan for the trial.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The Sponsor is responsible for monitoring the trial in order to verify that:

(1) The rights and wellbeing of the human subjects are protected
(2) The reported trial data are accurate, complete and verifiable from source documents
(3) The conduct of the trial is in compliance with the approved protocol and GCP

Monitoring will be performed in accordance with the applicable ORH policies and guidelines. These may include activities designed to:

- Initiate the study and check progress periodically
- Review the essential trial documentation and study data collected
- Conduct source document verification if required
- Identify any issues and address their resolution
- Confirm proper closure of the clinical study site at the end of the clinical phase

Control of Data Consistency
The research staff will check all CRFs for completeness, consistency and accuracy

Completeness
Research staff will ensure all relevant variables are completed on CRFs at the time of the participant's hospital visit and checked again before data entry

Consistency
The research staff will check CRFs manually.

Accuracy
Endpoint variables will be checked for all patients

The sponsor or the BRC may conduct a quality assurance audit to assure compliance with protocol and ICH-GCP. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and host institution agree to allow auditors/inspectors direct access to all relevant documents and to allocate his/her time and the time of his/her staff to discuss the findings and any relevant issues.

The study data will be held for at least five years. Thereafter the data will be archived according to the Radiology Department and Oxford University Hospitals NHS Trust policies.

13. ETHICS

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

13.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.5 Other Ethical Considerations

This type of imaging research raises several ethical issues. The proposed hyperpolarized Xe-129 MR will be provided in addition to any routine scans. Additional imaging may or may not add any information that will benefit the individual patient. These issues will be addressed as follows:

- There is no additional exposure to ionizing radiation or risk associated with administration of iodinated contrast above and beyond that already involved in routine follow-up CT scans scheduled as part of standard care for all participants.
- Patient Information Sheets will be provided describing the study and what it involves in non−technical language, as far as possible.
- Written informed consent will be obtained in an appropriate setting. The study will be introduced to the patient by a member of staff already known to the patient although consent will be performed by one of the study investigators.
- Potential hazards of hyperpolarized Xe-129 and CT will be explained to the patient.
- Patient inconvenience will be minimised by scheduling study investigations on the same day as routine clinic appointments, as far as possible. If a separate visit is necessary the patient will be compensated for any travel expenses.
- Patients will be informed that findings from the study may not benefit them directly but will be used to improve future assessment of lung function and monitoring of treatment response.
- As the MRI will only image the lungs and the subjects chosen have healthy lungs no additional information of clinical significance will be identified from scanning, so incidentally discovered abnormalities will not occur.

14. DATA HANDLING AND RECORD KEEPING

All study data will be entered on a password secured database. The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file. The Data Protection Act will be adhered to at all times.

All data will be checked for missing or unusual values (range checks) and for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be reviewed for checking and confirmation or correction, as appropriate. Any data, which are changed, will be crossed through with a single line, initialled and dated.

15. FINANCE AND INSURANCE

The trial sponsor will be the Oxford University Hospitals NHS Trust, Joint Research Office, Block 60, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ.

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The funder for this study will be the Oxford Biomedical Research Centre. GE Healthcare has provided support for the trial by installing the Xenospin hyperpolarizer and providing modifications to the Churchill Hospital MRI scanner to enable reading of the hyperpolarized xenon signal.

The chief investigator is responsible for applying for local Trust management approval to conduct the trial in accordance with local arrangements and policies. Trust approval and indemnity must be confirmed in writing before patient recruitment commences on the Investigator site.

The Oxford University Hospitals NHS Trust will authorize trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place.

Trial insurance

There are no special compensation arrangements for this study. The NHS Litigation Authority covers standard clinical negligence of NHS employees, staff and health professionals under its Clinical Negligence scheme for Trusts.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a patient is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

16. PUBLICATION POLICY

The final results of the trial will be submitted to a peer-reviewed journal for publication. Authors will be the Chief Investigator, the Co-Investigators and other members of the research team. No data on individual patients will be published without the permission of the Chief Investigator. Authors shall acknowledge that the study was sponsored by and performed with the support of the NIHR Oxford Biomedical Research Centre.

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Appendix 4: Data analysis in healthy volunteers

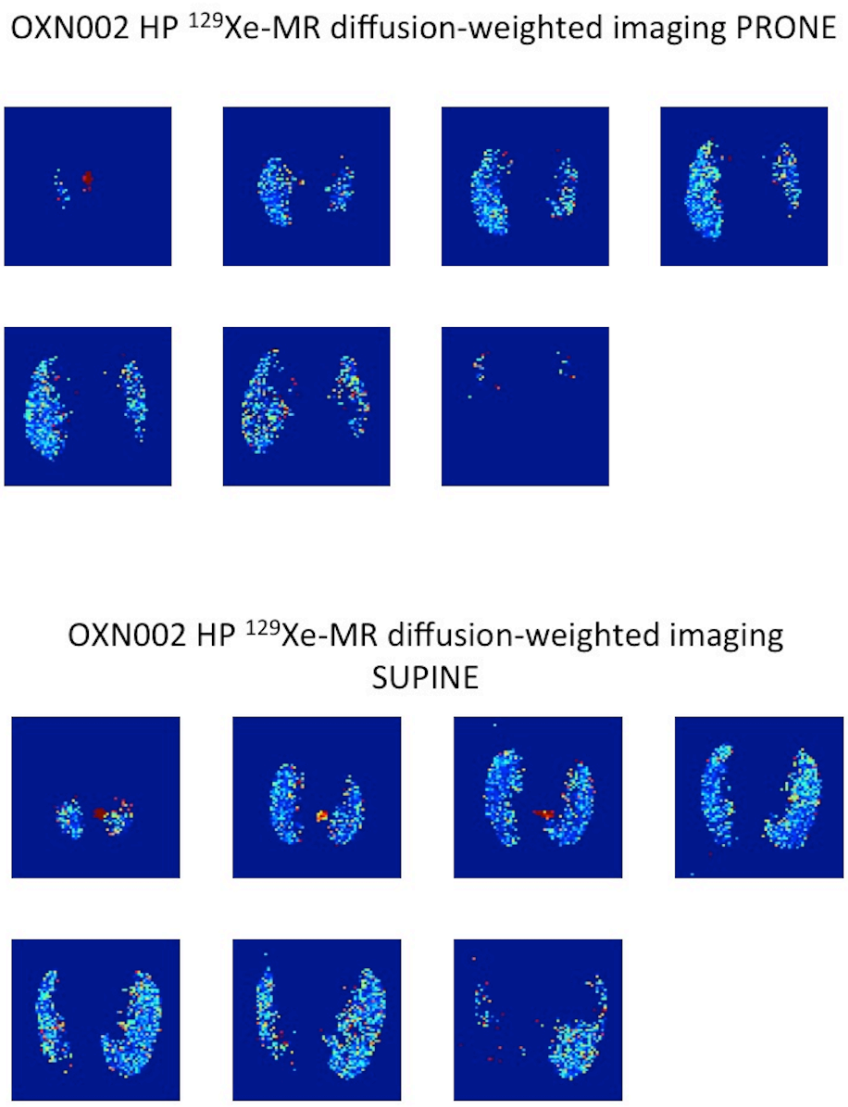


Figure A4.1a: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN002 in the prone and supine posture.

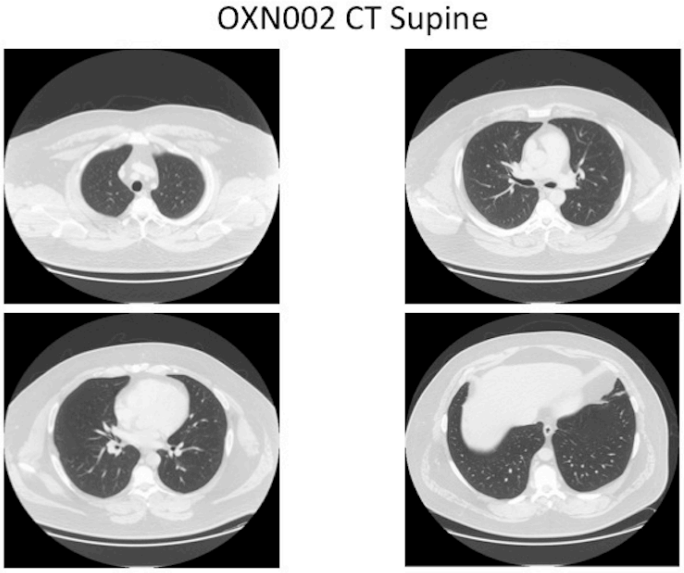


Figure A4.1b: Axial thoracic QCT from OXN002 in the supine posture.

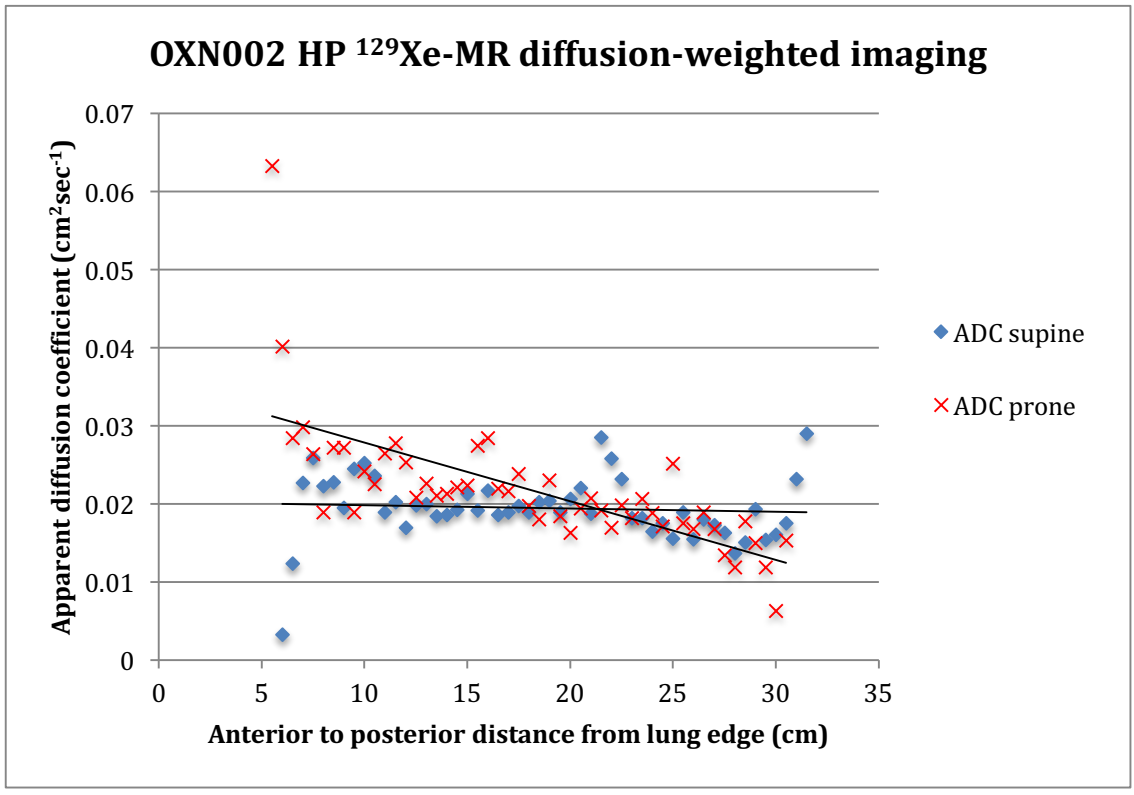


Figure A4.1c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN002 in the prone and supine posture.

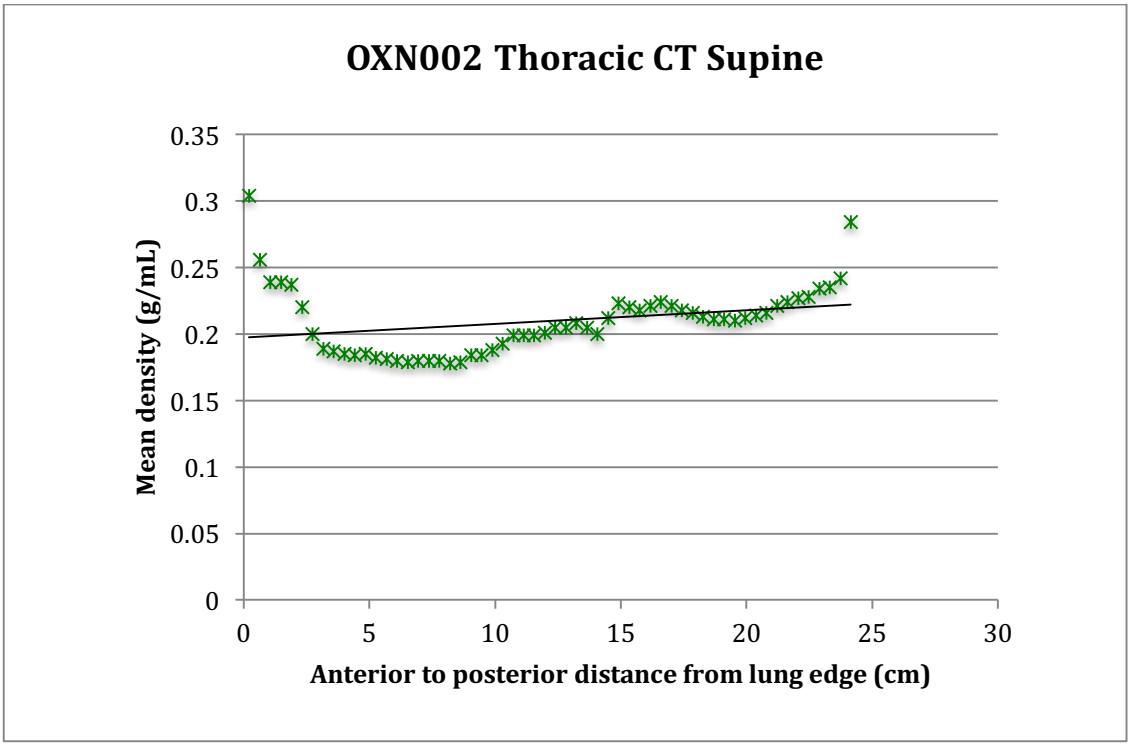
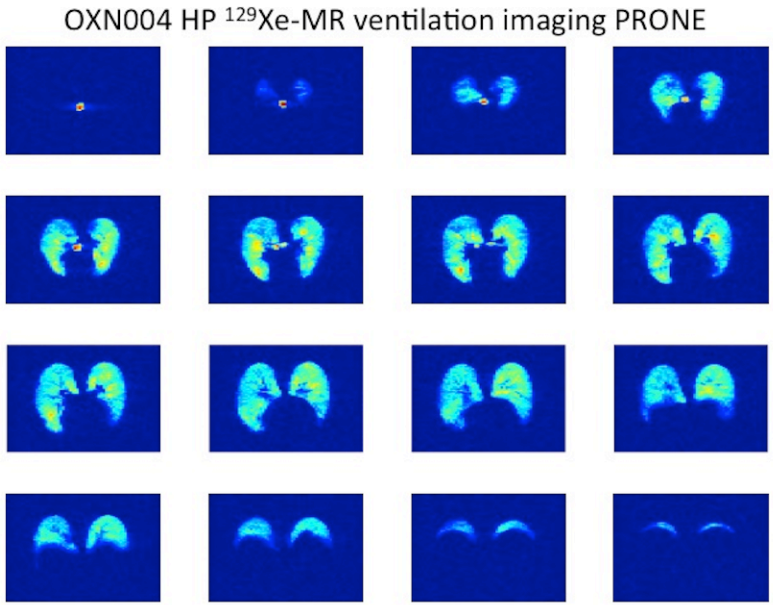


Figure A4.1d: Graph showing mean density in the AP direction for QCT acquired from OXN002 in the supine posture.



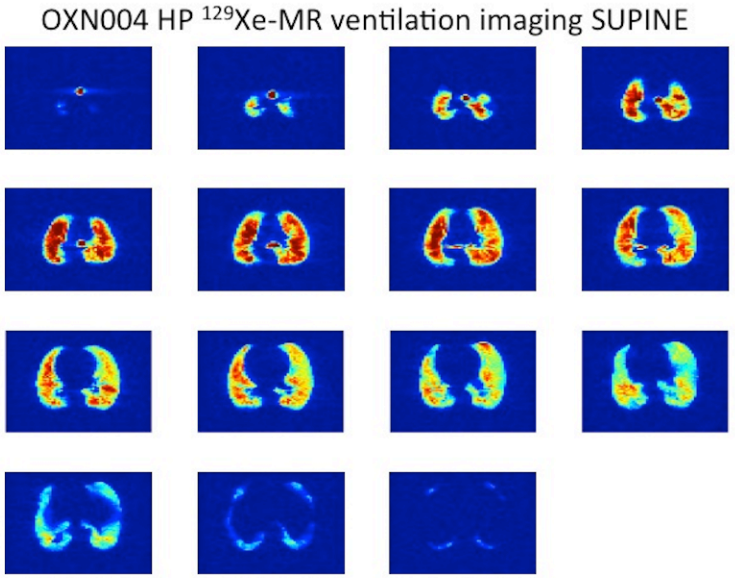


Figure A4.2a: Axial HP ^{129}Xe-MR ventilation imaging from OXN004 in the prone and supine posture.

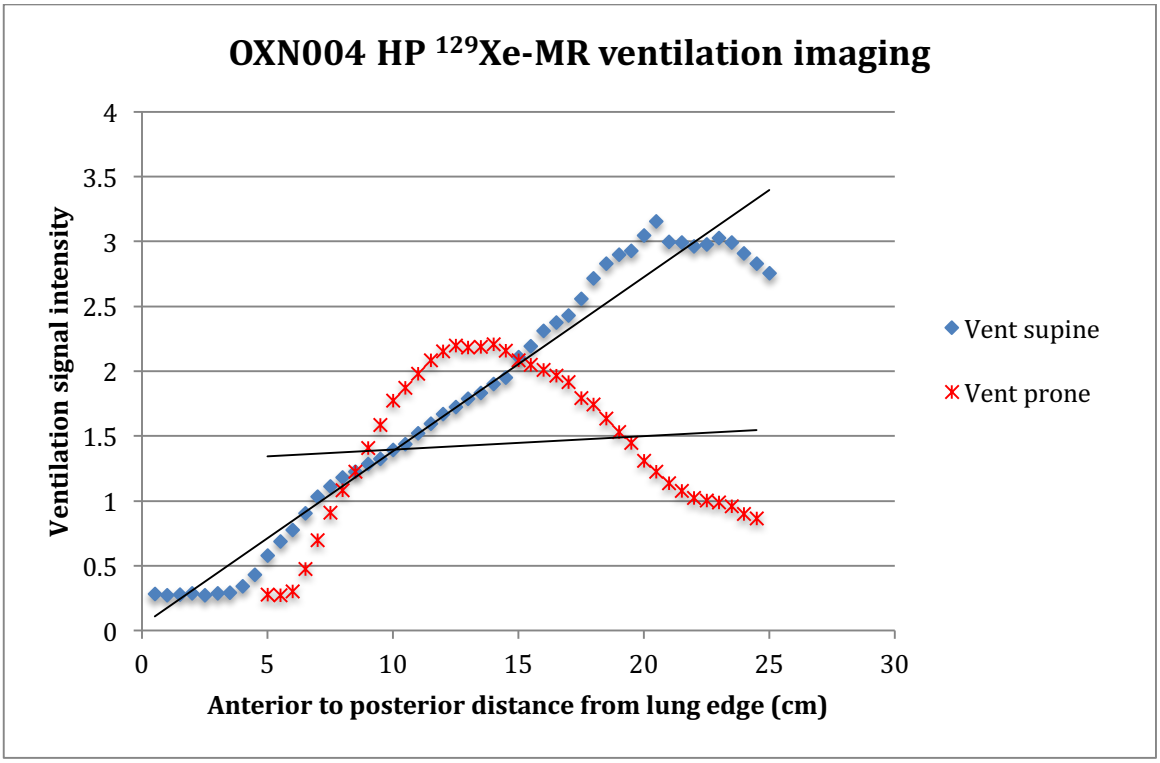


Figure A4.2b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN004 in the prone and supine posture.

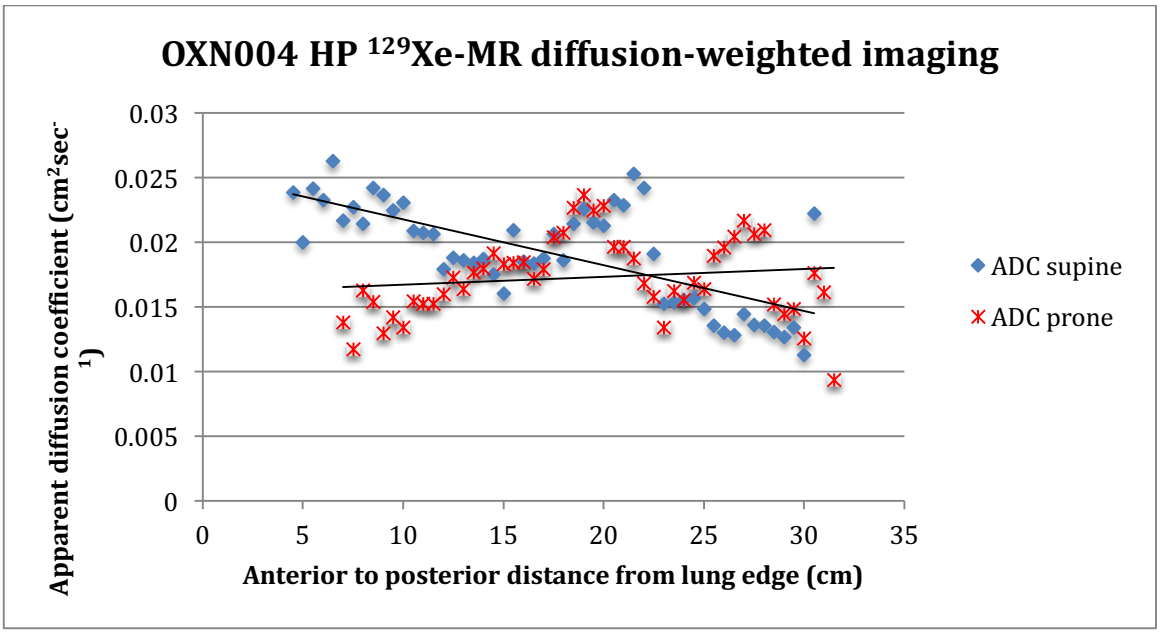


Figure A4.2c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN004 in the prone and supine posture.

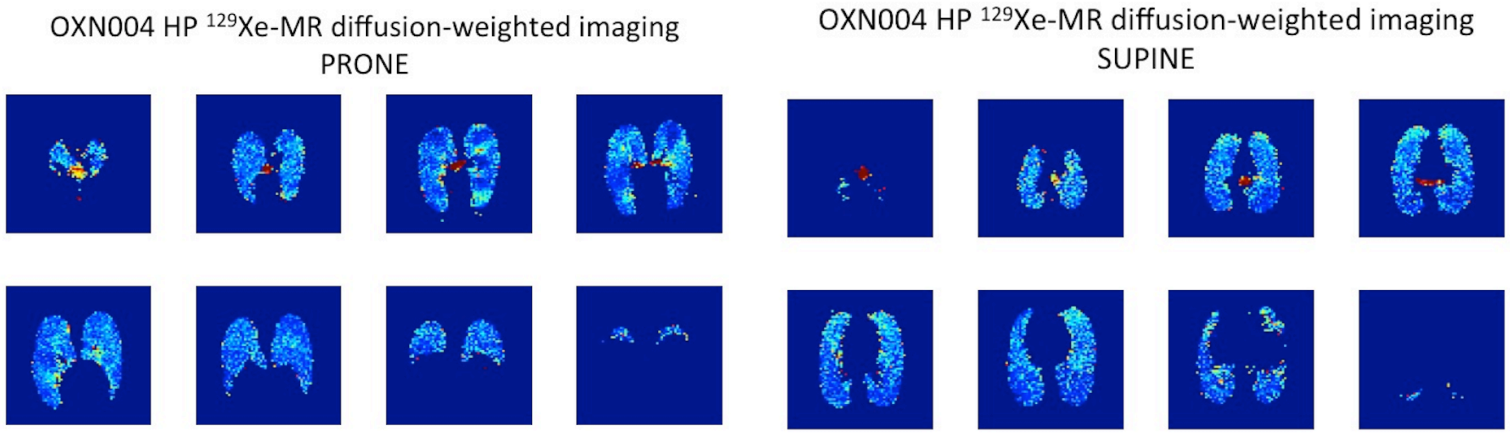


Figure A4.2d: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN004 in the prone and supine posture.

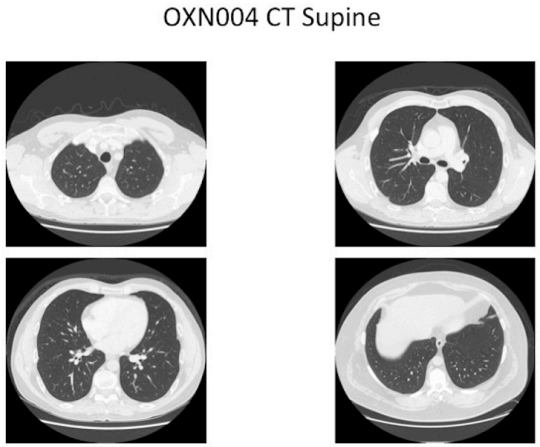


Figure A4.2e: Axial thoracic QCT from OXN004 in the supine posture.

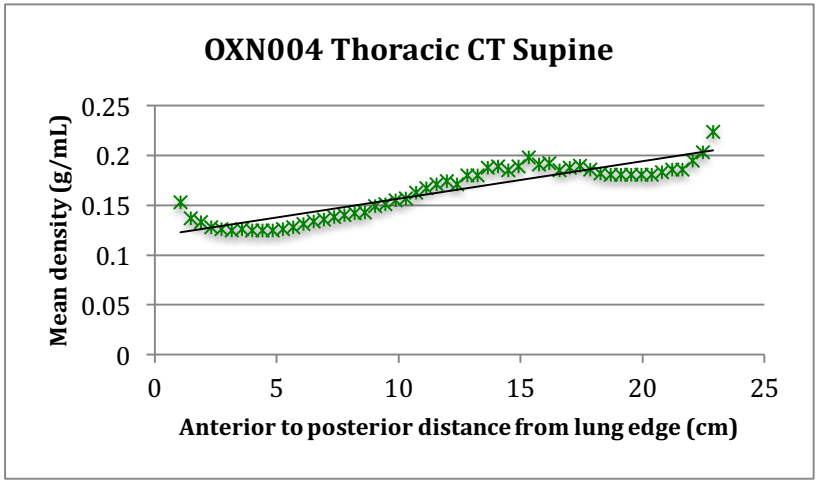


Figure A4.2f: Graph showing mean density in the AP direction for QCT acquired from OXN004 in the supine posture.

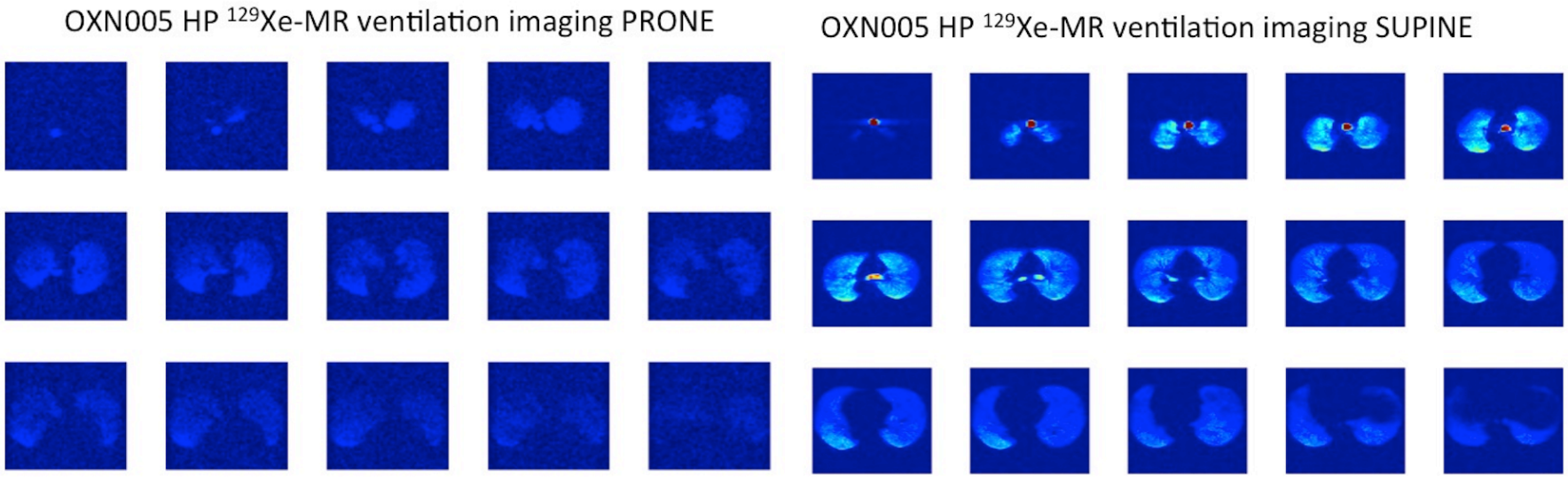


Figure A4.3a: Axial HP ^{129}Xe-MR ventilation imaging from OXN005 in the prone and supine posture.

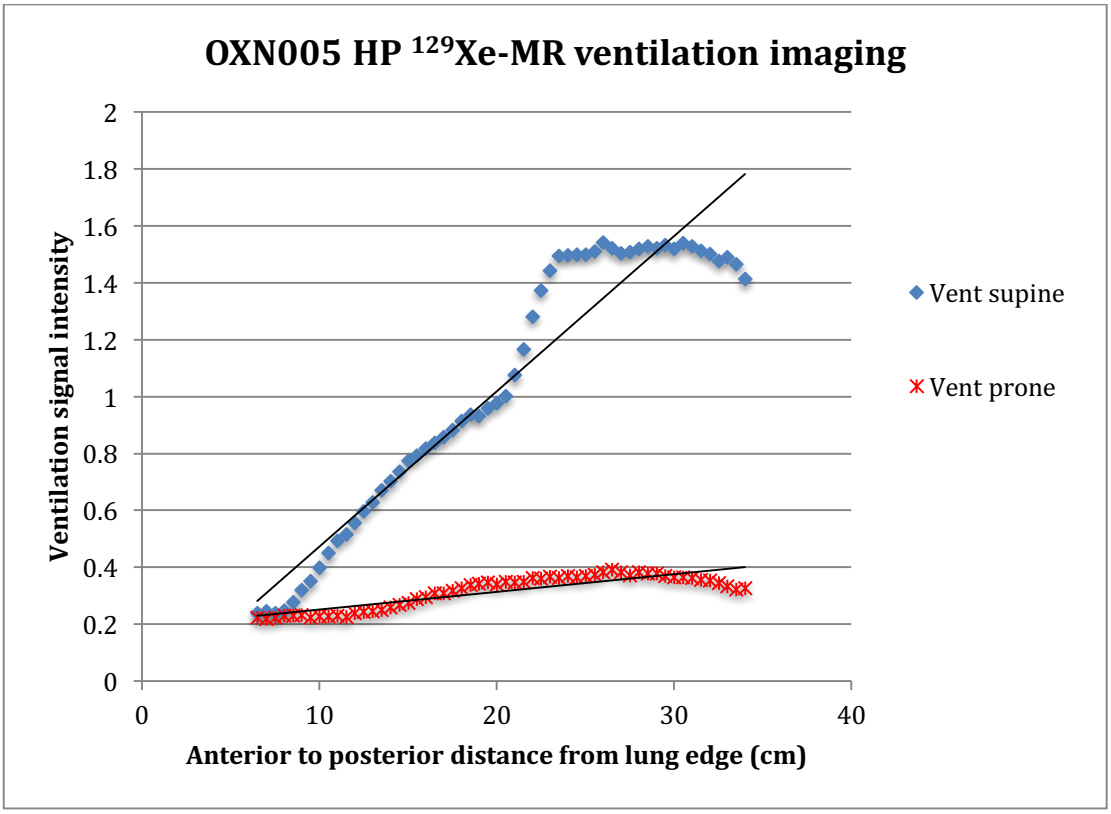


Figure A4.3b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN005 in the prone and supine posture.

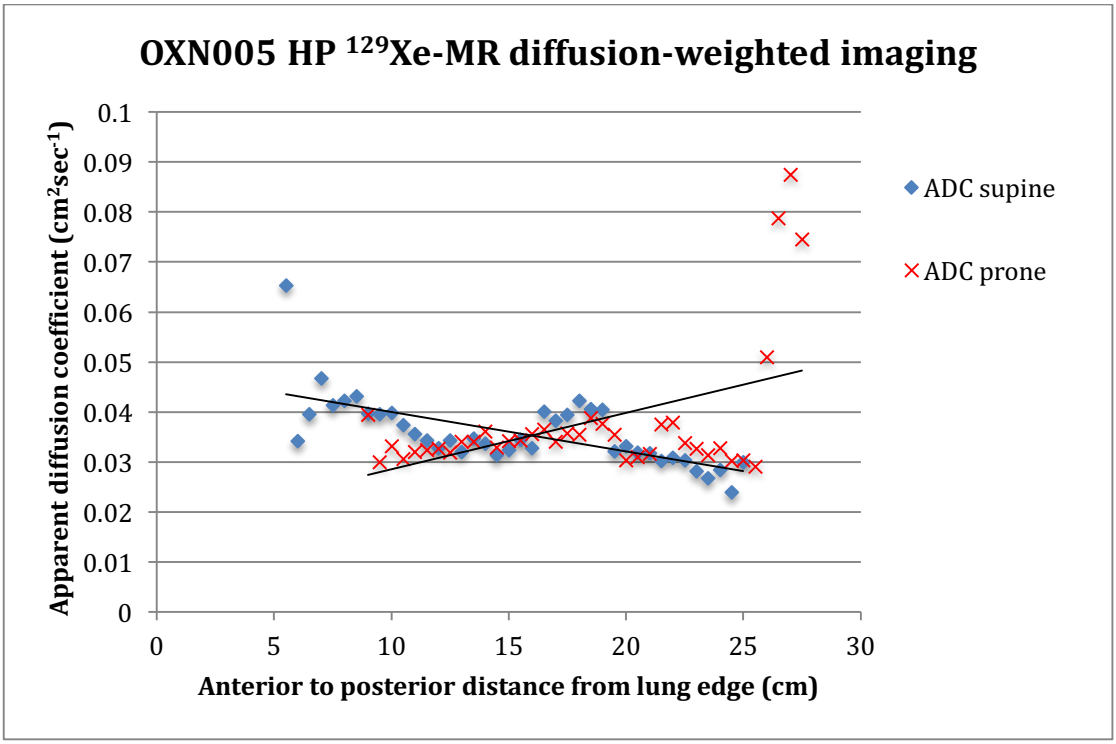


Figure A4.3c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN005 in the prone and supine posture.

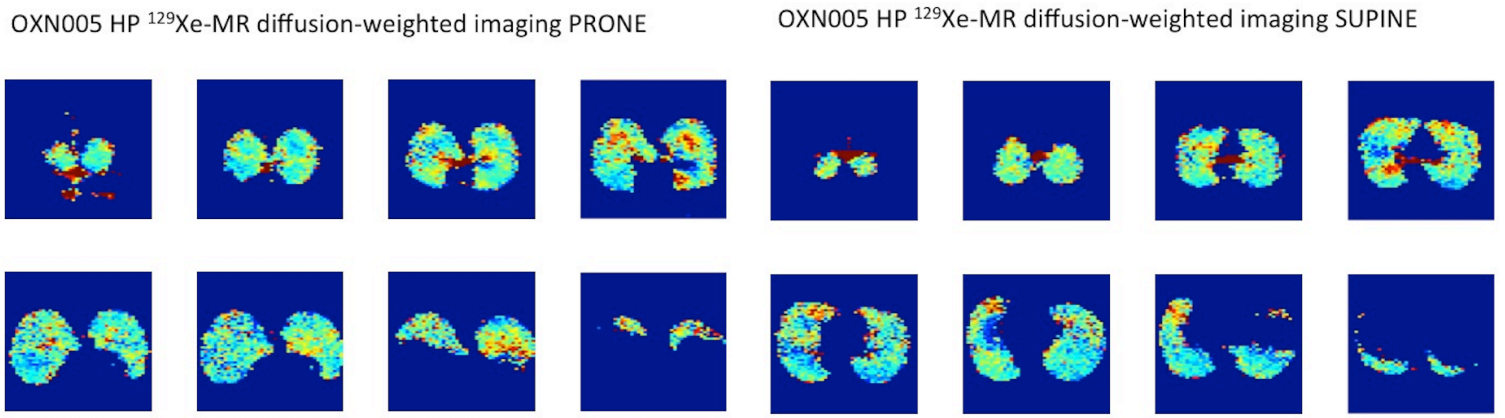


Figure A4.3d: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN005 in the prone and supine posture.

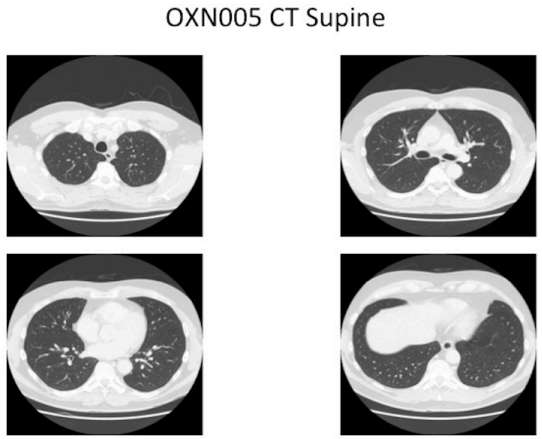


Figure A4.3e: Axial thoracic QCT from OXN005 in the supine posture.

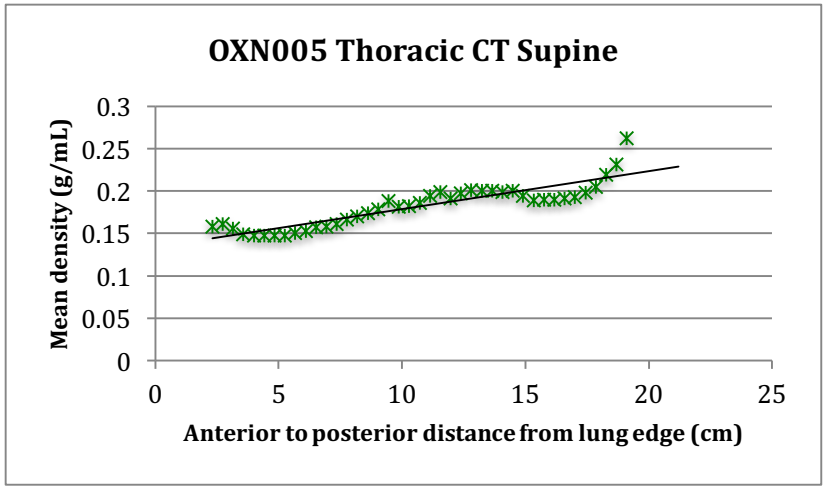


Figure A4.3f: Graph showing mean density in the AP direction for QCT acquired from OXN005 in the supine posture.

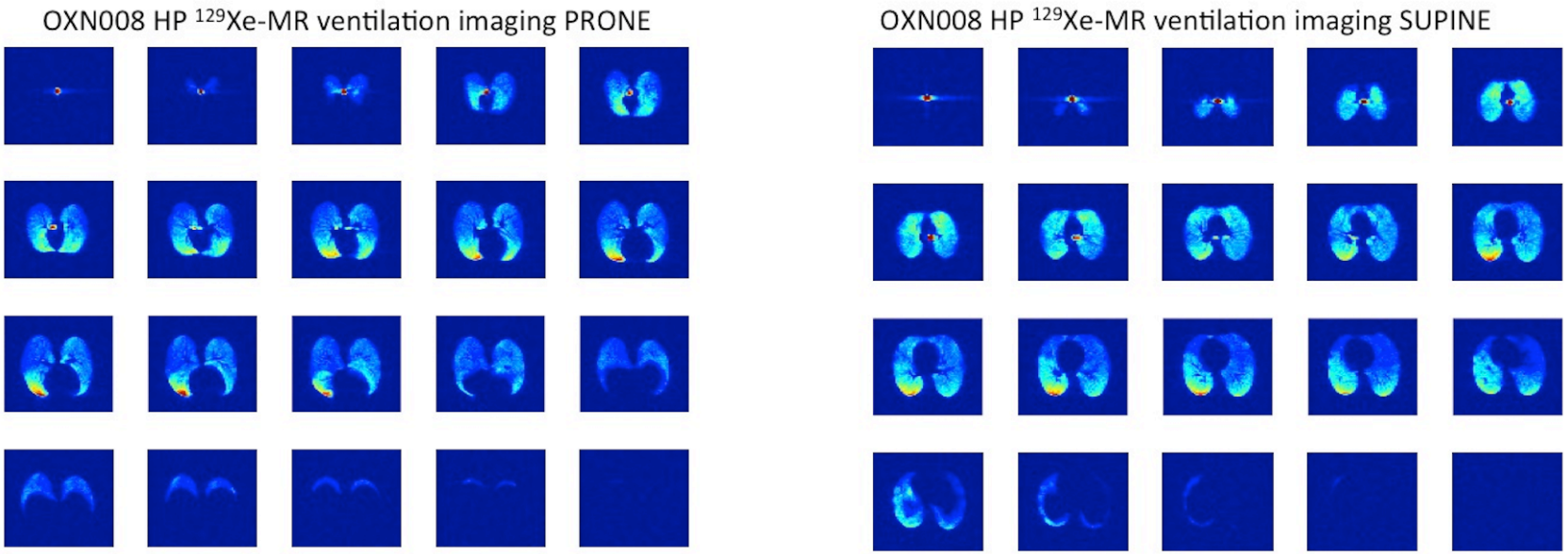


Figure A4.4a: Axial HP ^{129}Xe-MR ventilation imaging from OXN008 in the prone and supine posture.

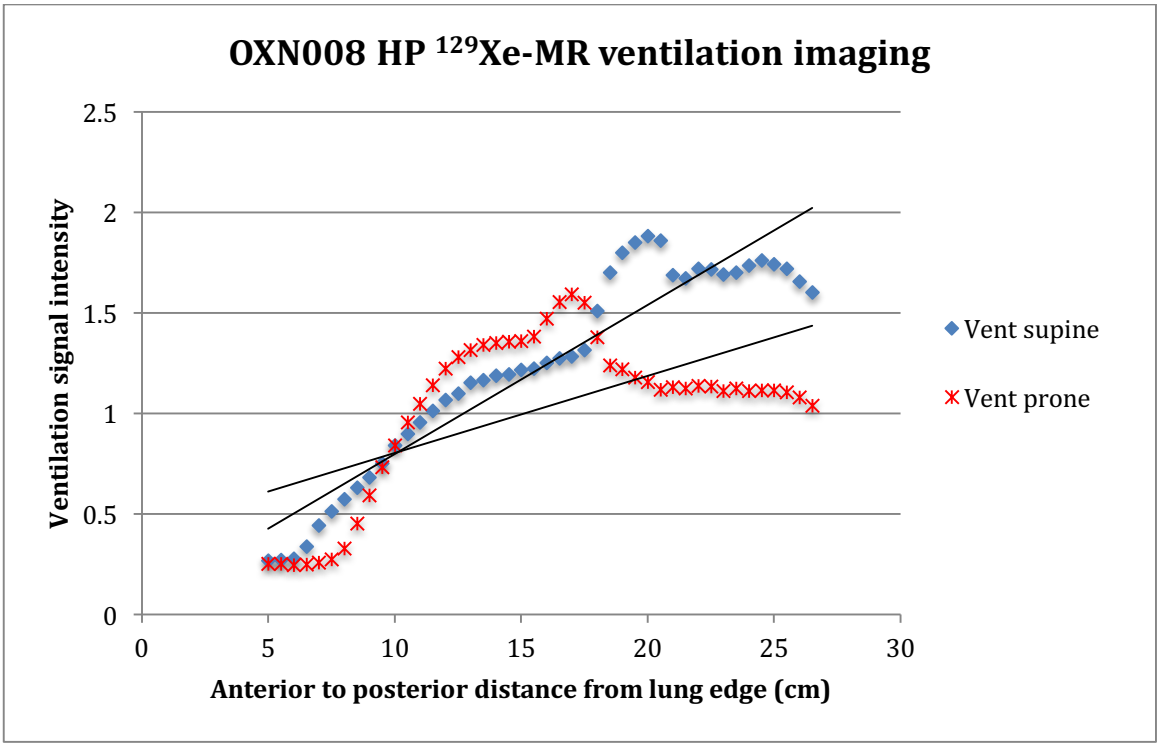


Figure A4.4b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN008 in the prone and supine posture.

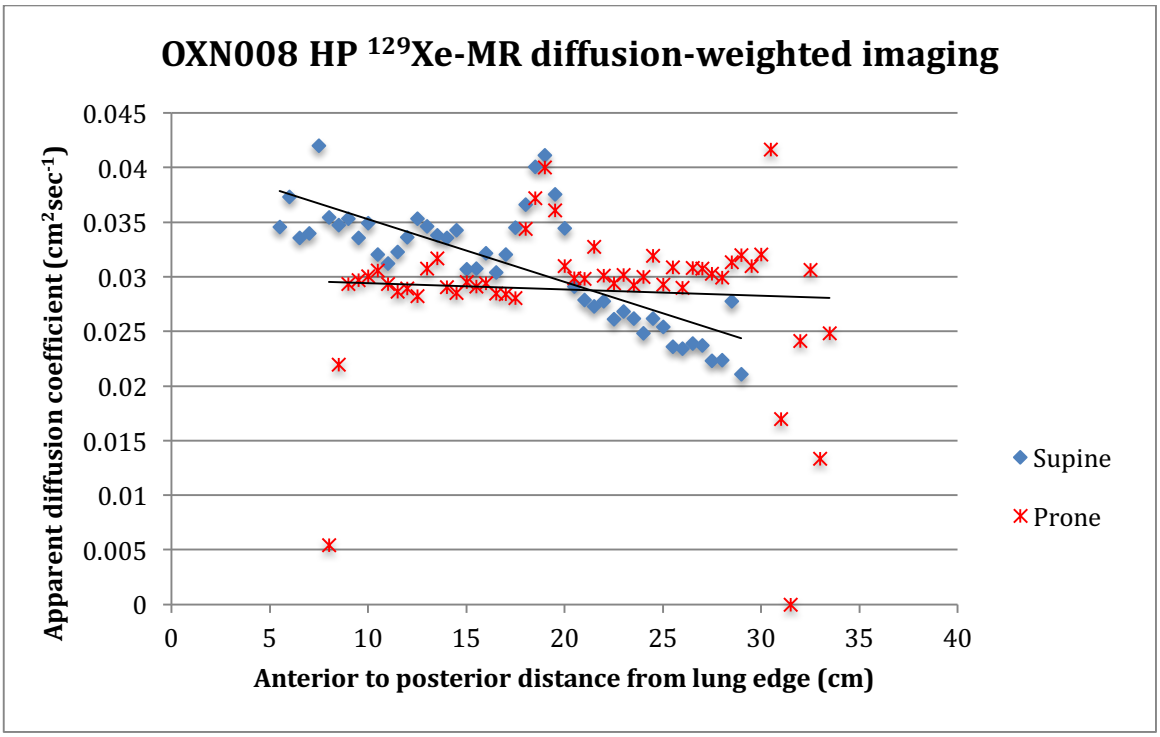


Figure A4.4c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN008 in the prone and supine posture.

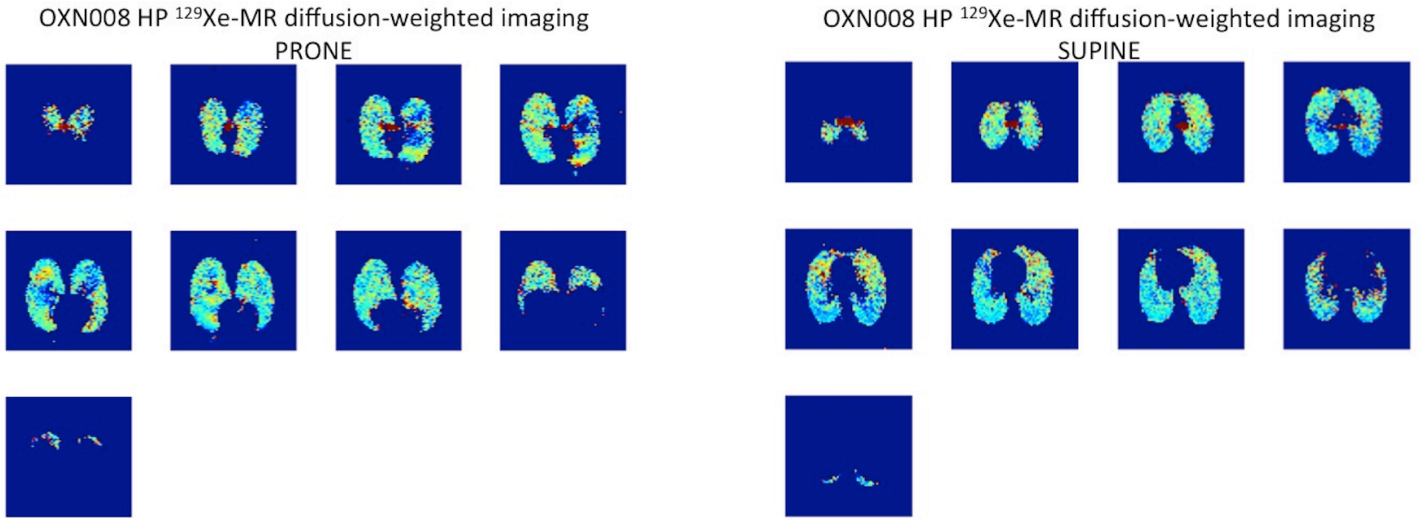


Figure A4.4d: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN008 in the prone and supine posture.

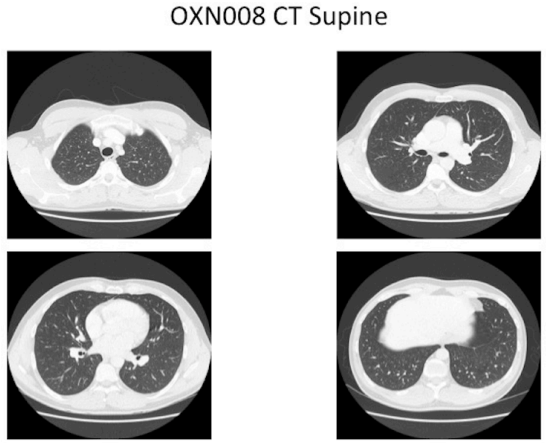


Figure A4.4e: Axial thoracic QCT from OXN008 in the supine posture.

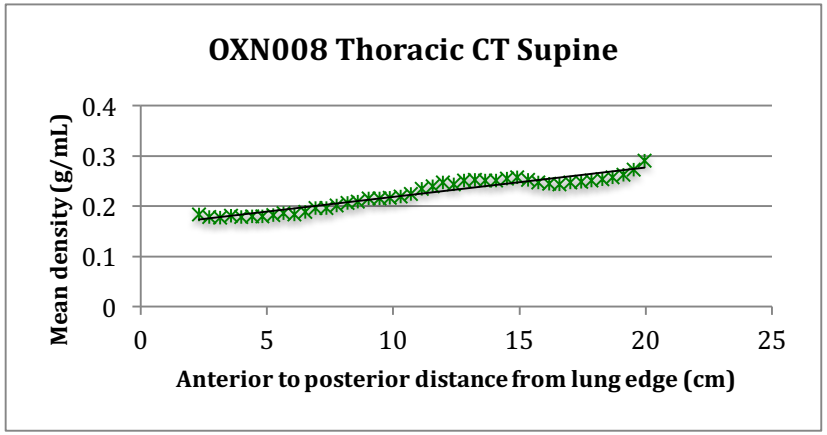


Figure A4.4f: Graph showing mean density in the AP direction for QCT acquired from OXN008 in the supine posture.

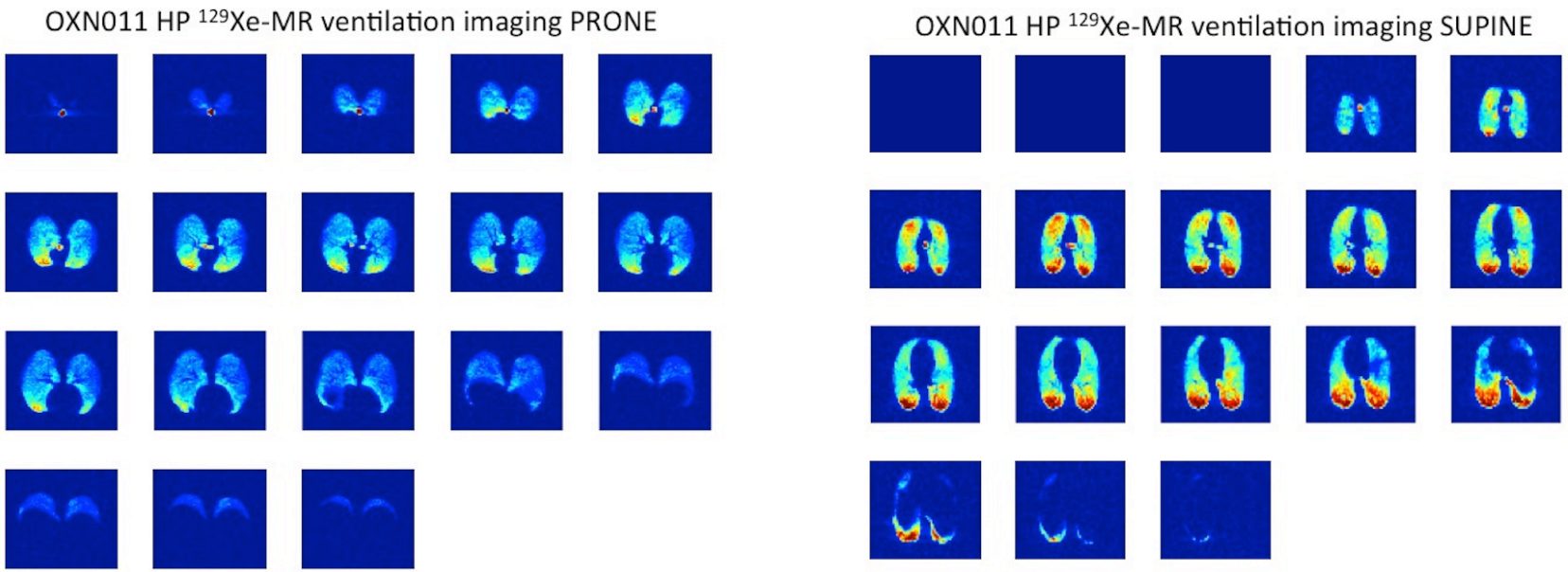


Figure A4.5a: Axial HP ^{129}Xe-MR ventilation imaging from OXN011 in the prone and supine posture.

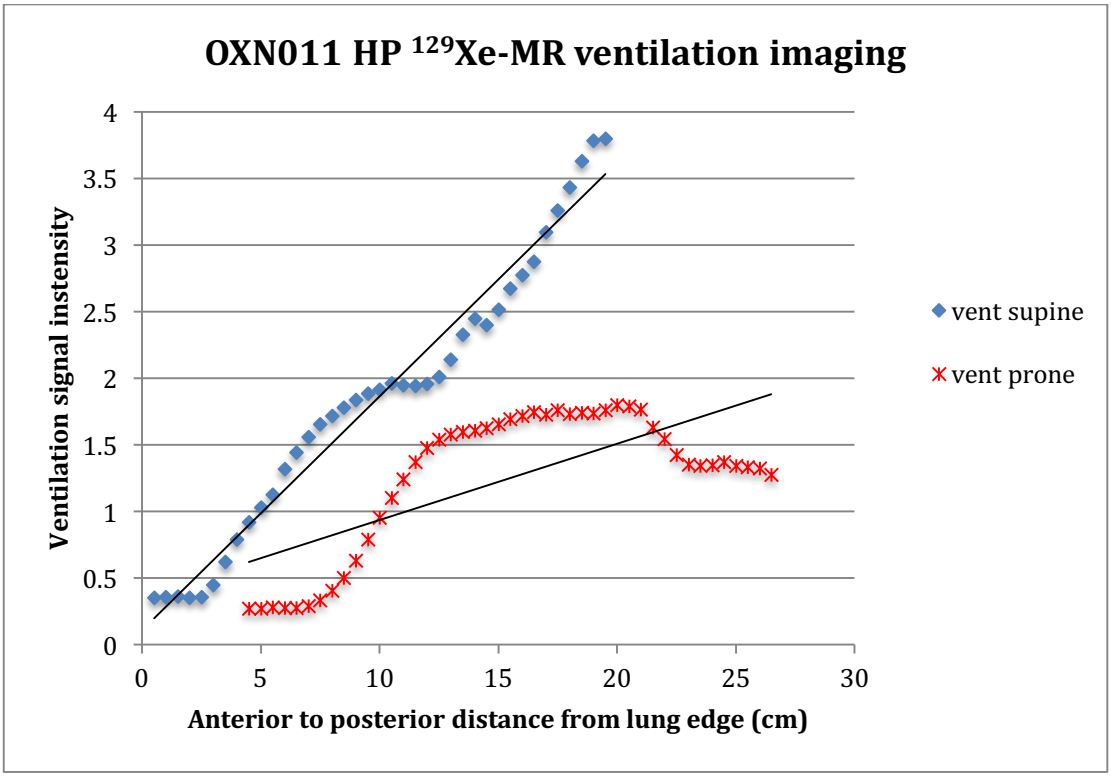


Figure A4.5b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN011 in the prone and supine posture.

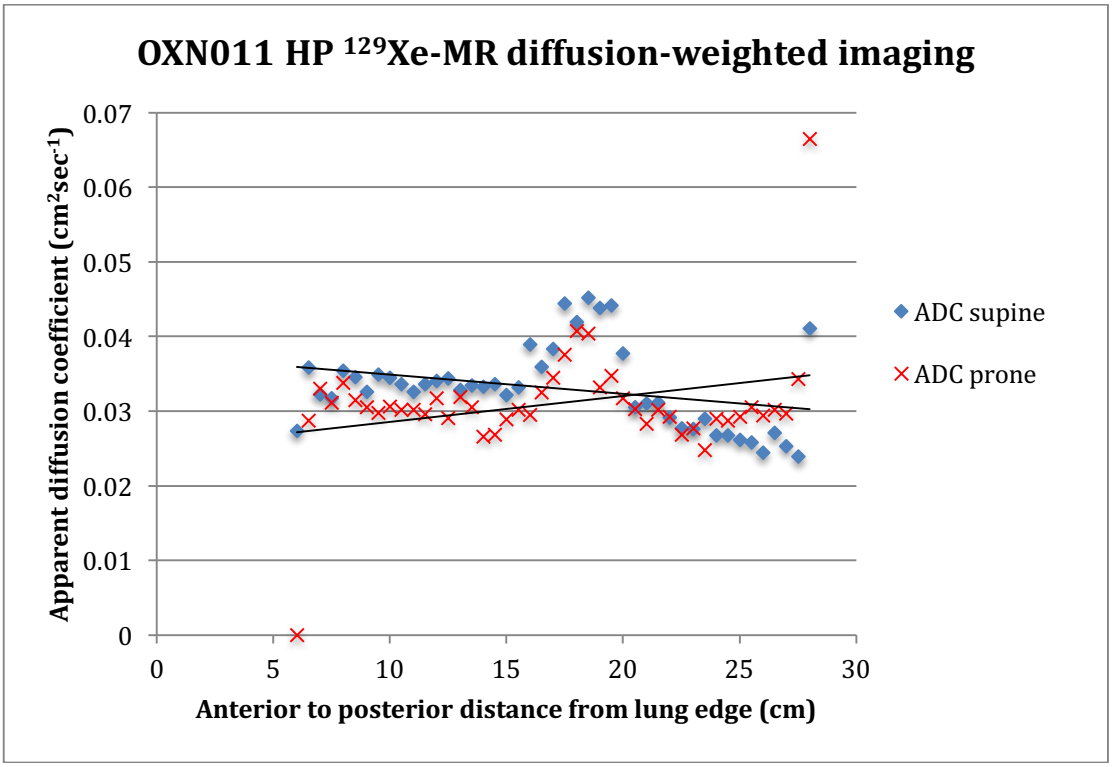


Figure A4.5c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN011 in the prone and supine posture.

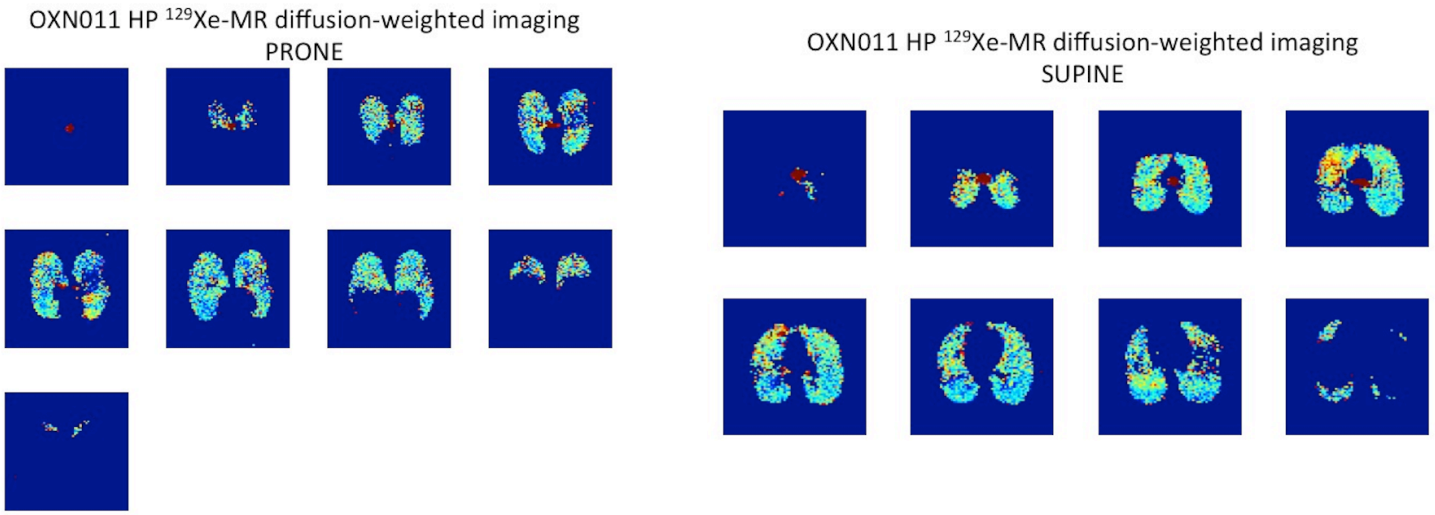


Figure A4.5d: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN011 in the prone and supine posture.

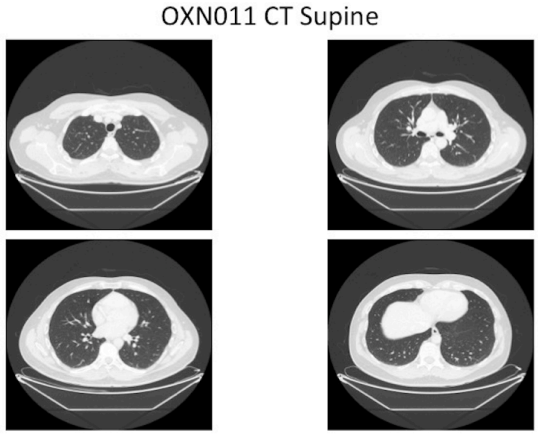


Figure A4.5e: Axial thoracic QCT from OXN011 in the supine posture.

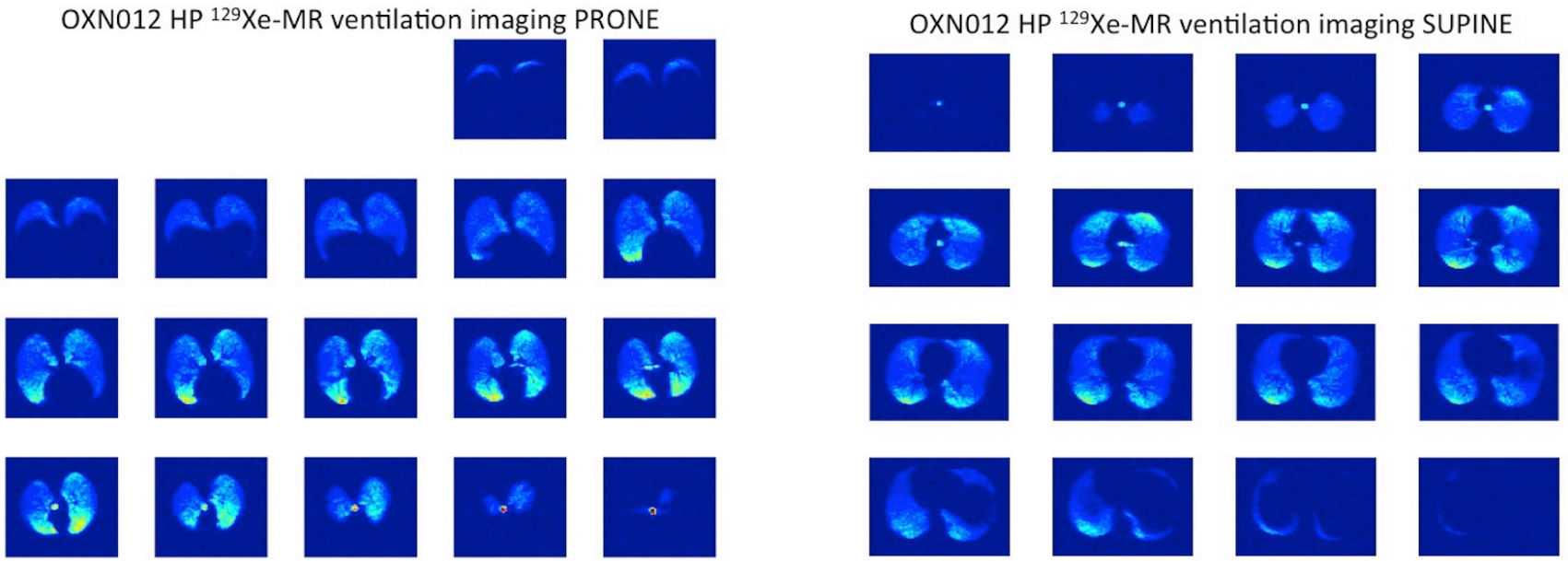


Figure A4.6a: Axial HP ^{129}Xe-MR ventilation imaging from OXN012 in the prone and supine posture.

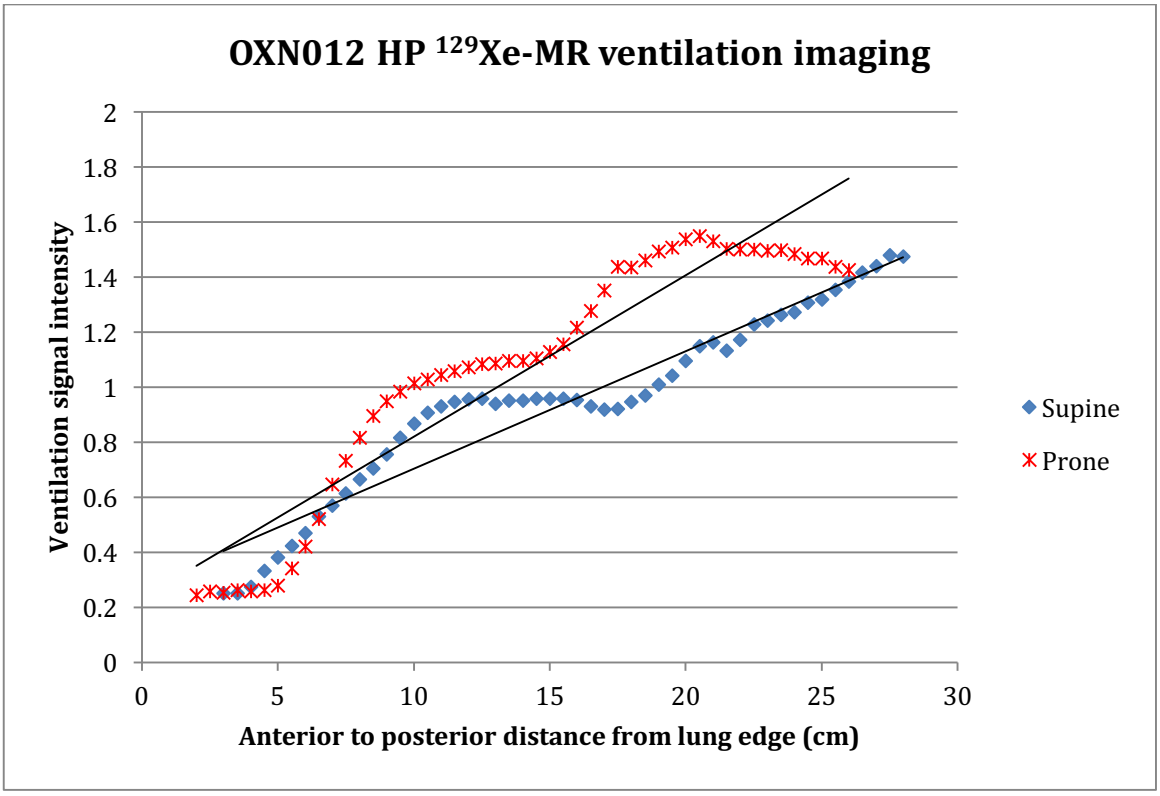


Figure A4.6b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN012 in the prone and supine posture.

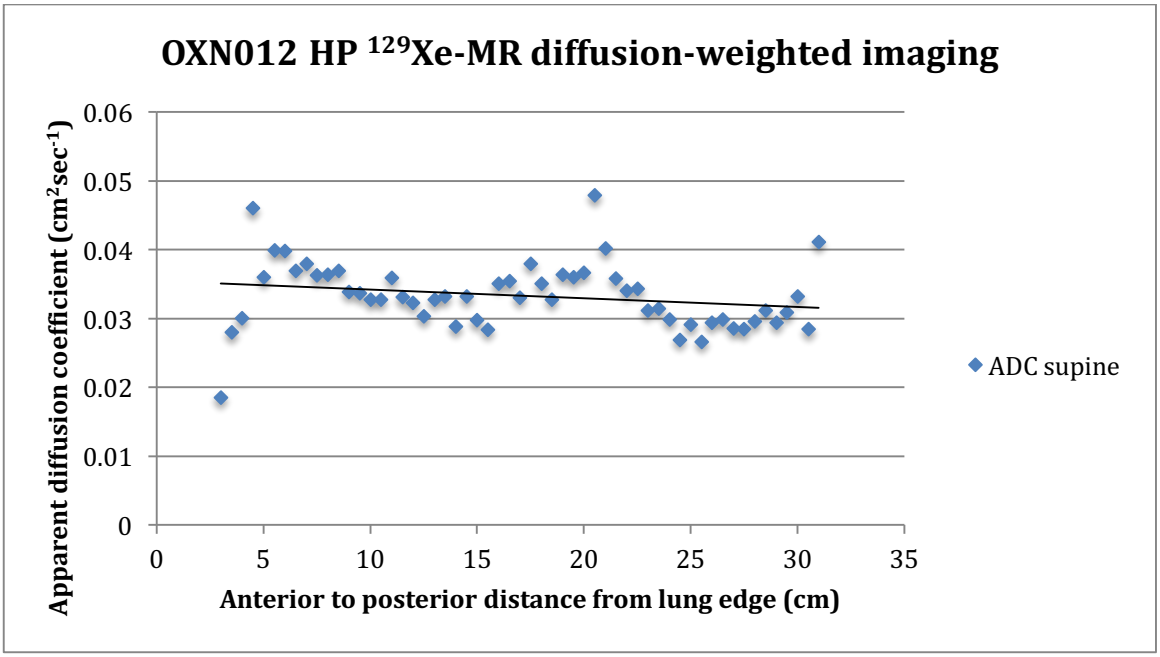


Figure A4.6c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN012 in the supine posture.

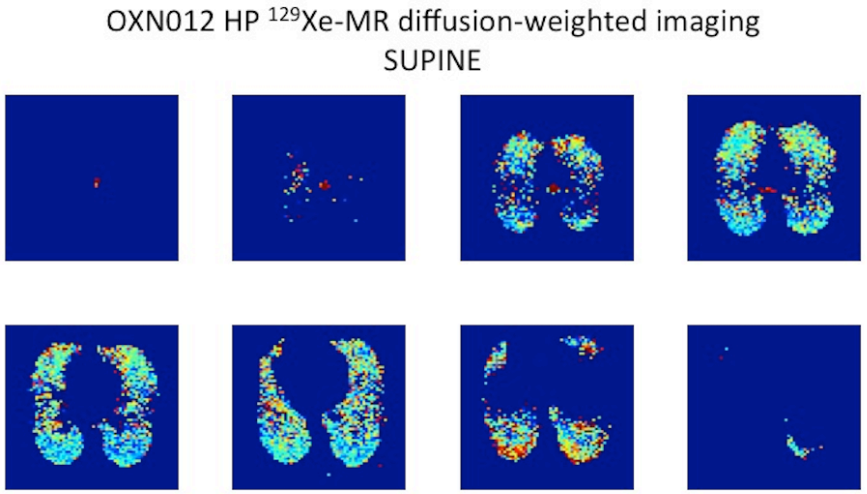


Figure A4.6d: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN012 in the supine posture.

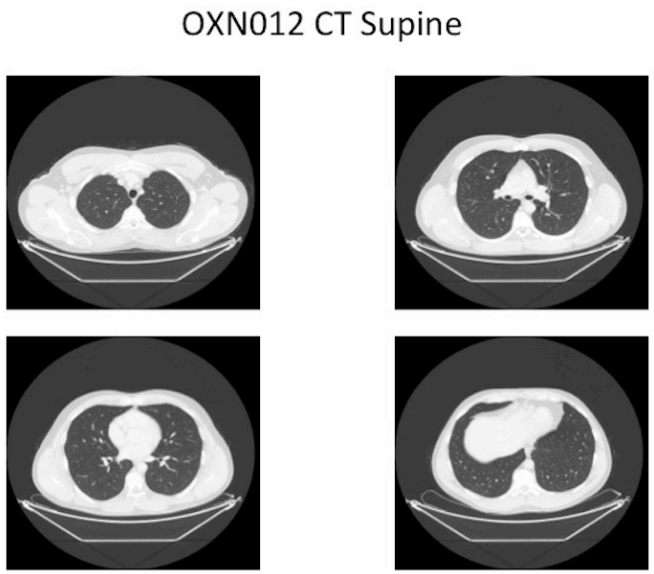


Figure A4.6e: Axial thoracic QCT (supine) from OXN012.

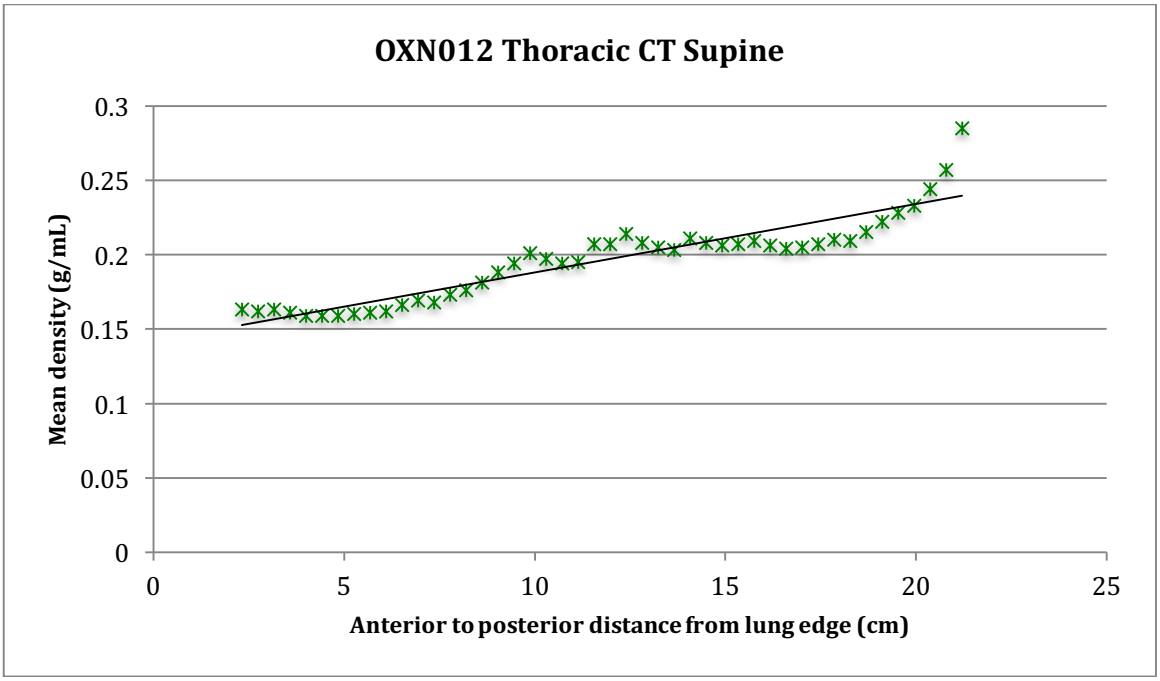


Figure A4.6f: Graph showing mean density in the AP direction for QCT acquired from OXN012 in the supine posture.

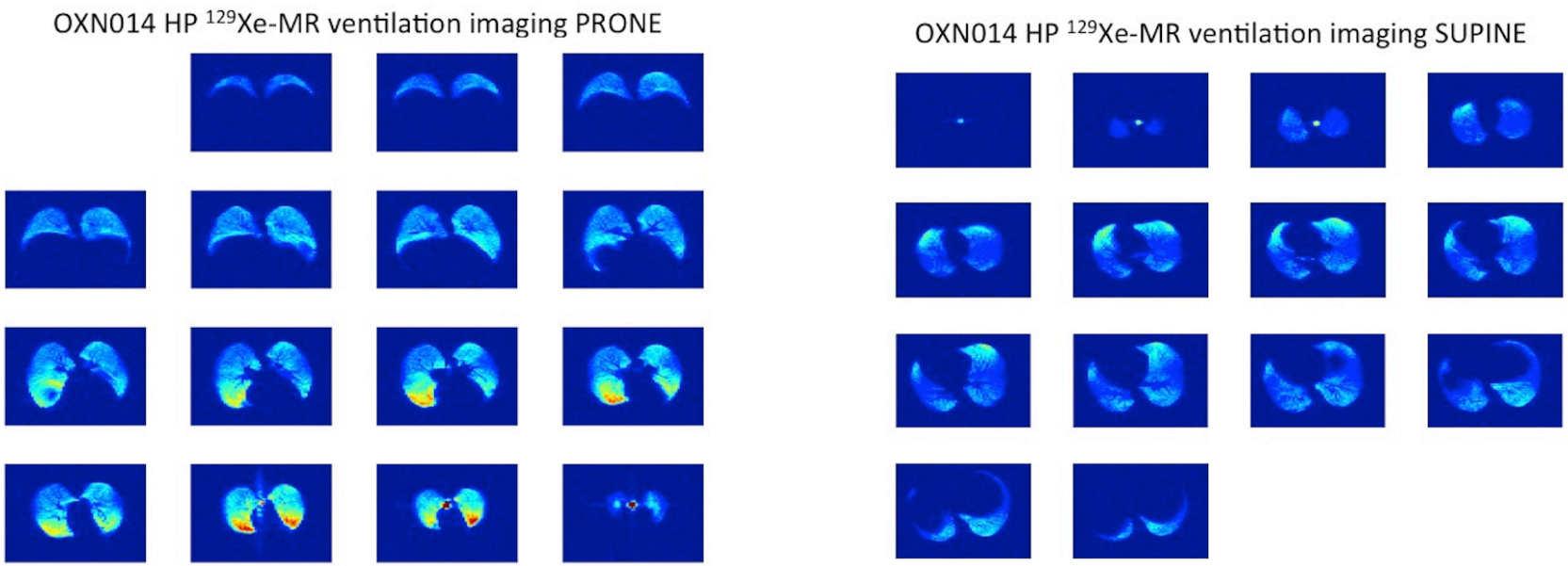


Figure A4.7a: Axial HP ^{129}Xe-MR ventilation imaging from OXN014 in the prone and supine posture.

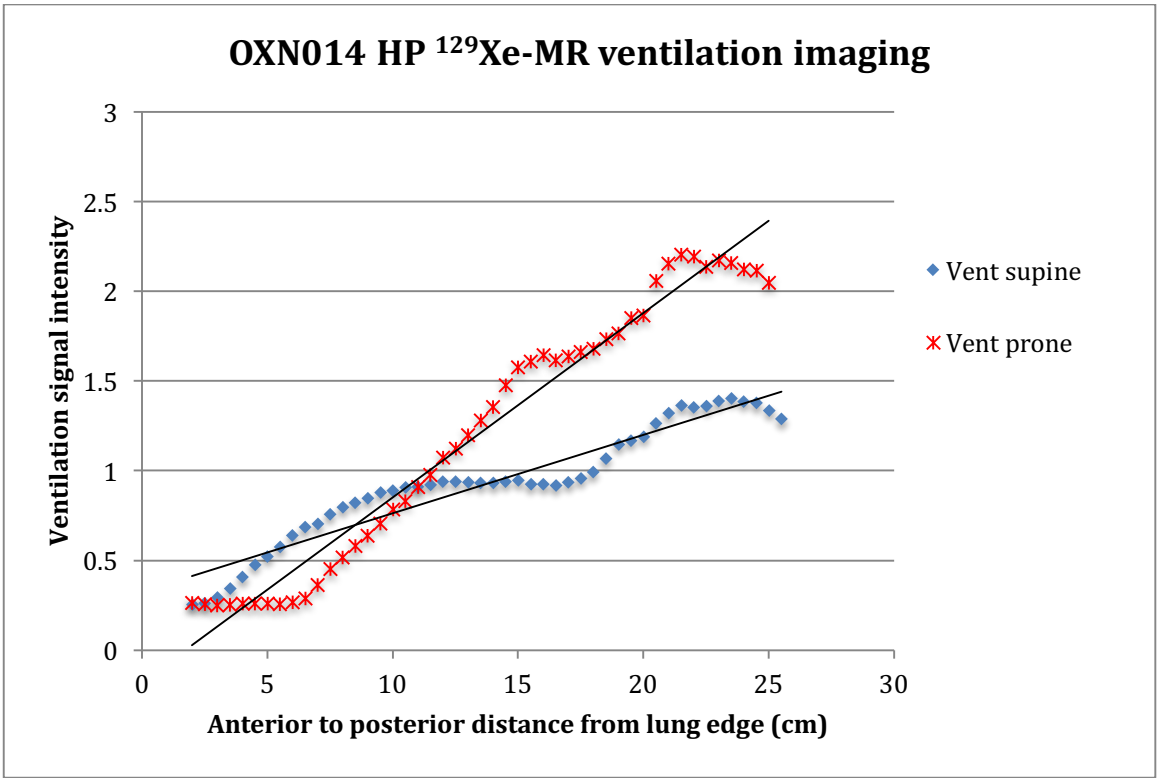


Figure A4.7b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN014 in the prone and supine posture.

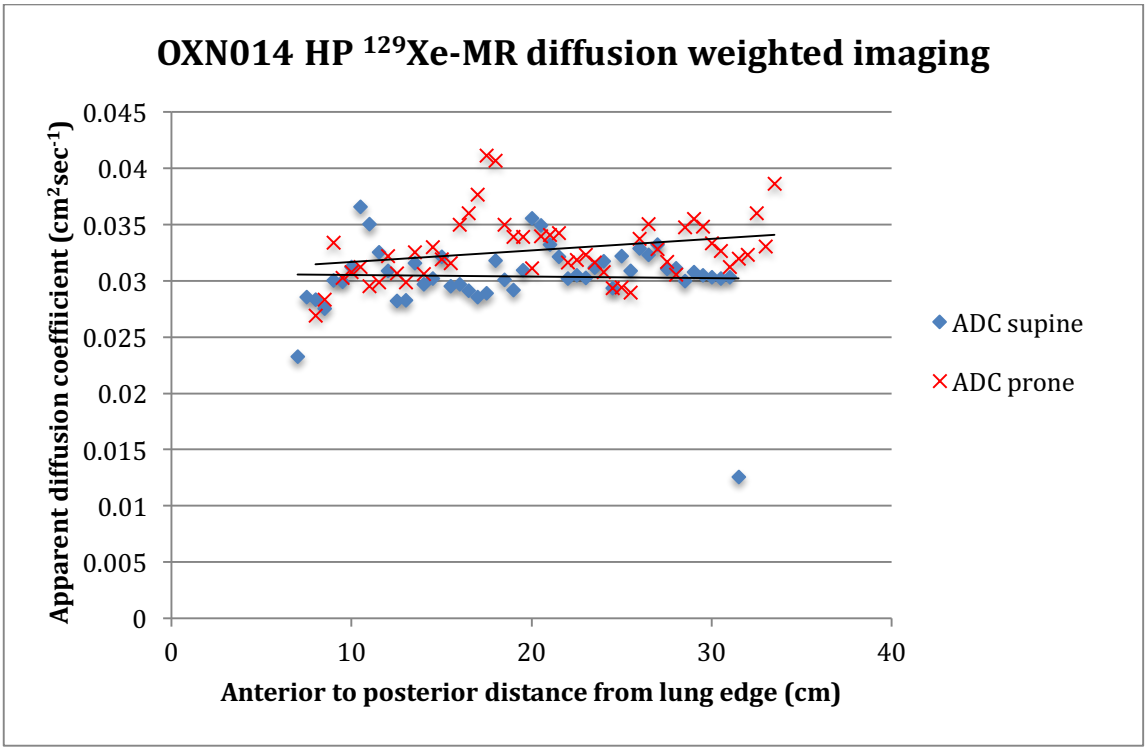


Figure A4.7c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN014 in the prone and supine posture.

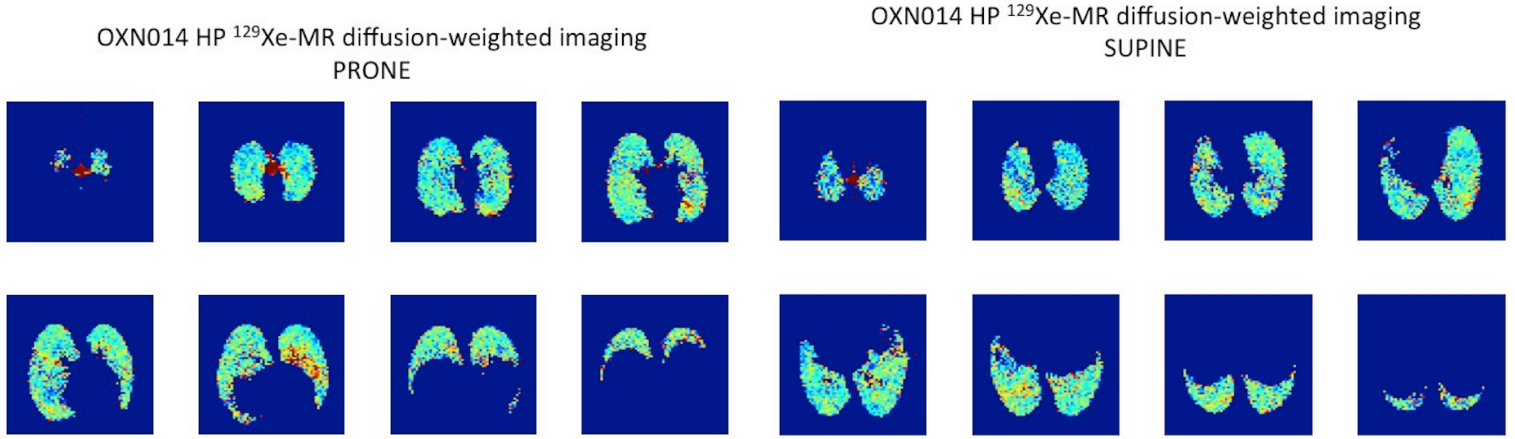


Figure A4.7d: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN014 in the prone and supine posture.

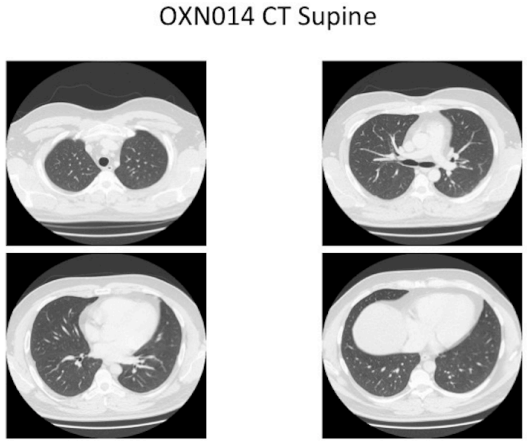


Figure A4.7e: Axial thoracic QCT from OXN014 in the supine posture.

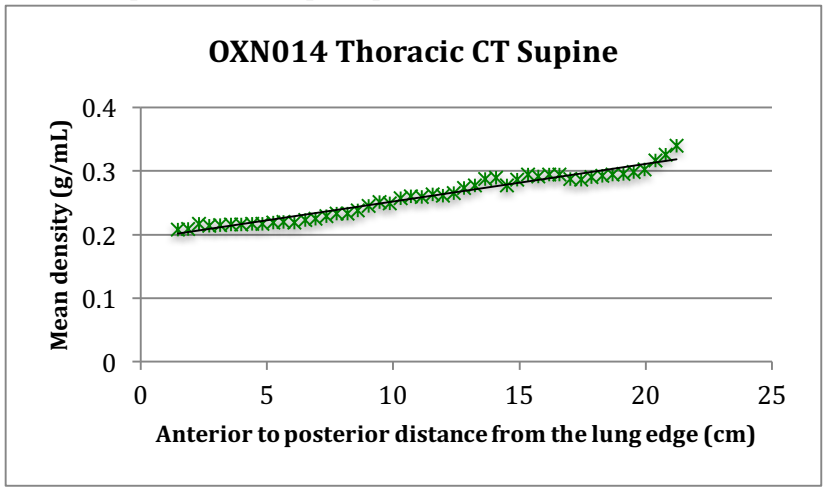


Figure A4.7f: Graph showing mean density in the AP direction for QCT acquired from OXN014 in the supine posture.

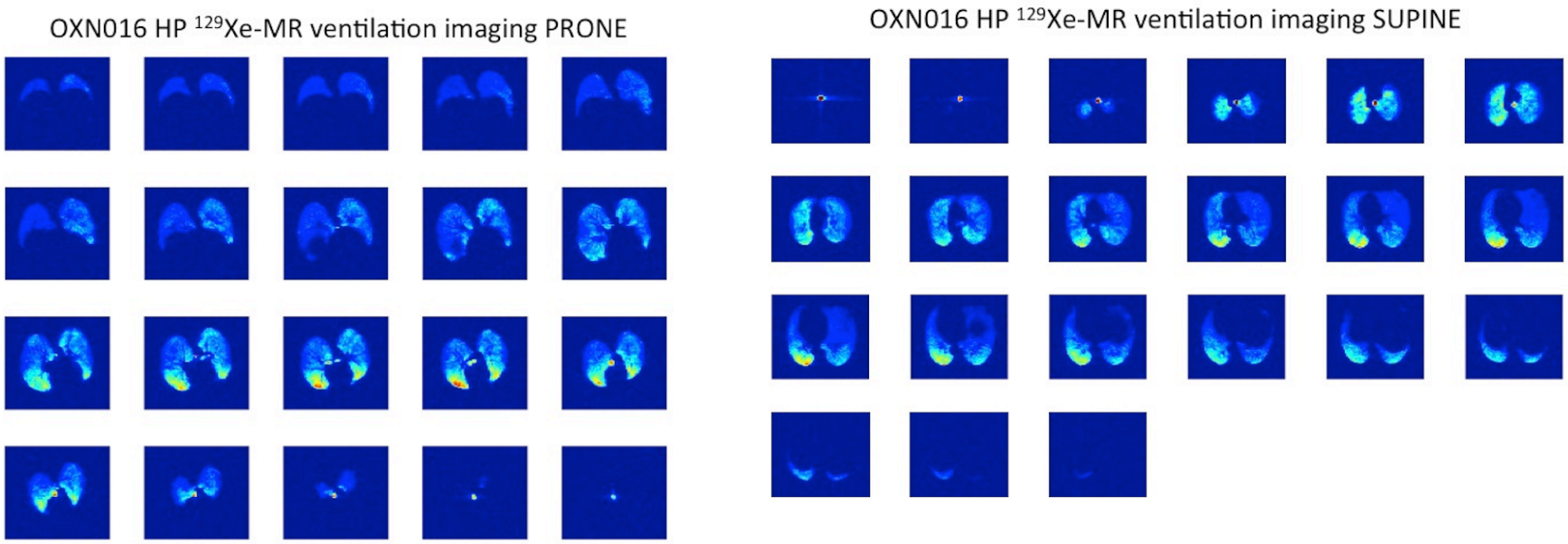


Figure A4.8a: Axial HP ^{129}Xe-MR ventilation imaging from OXN016 in the prone and supine posture.

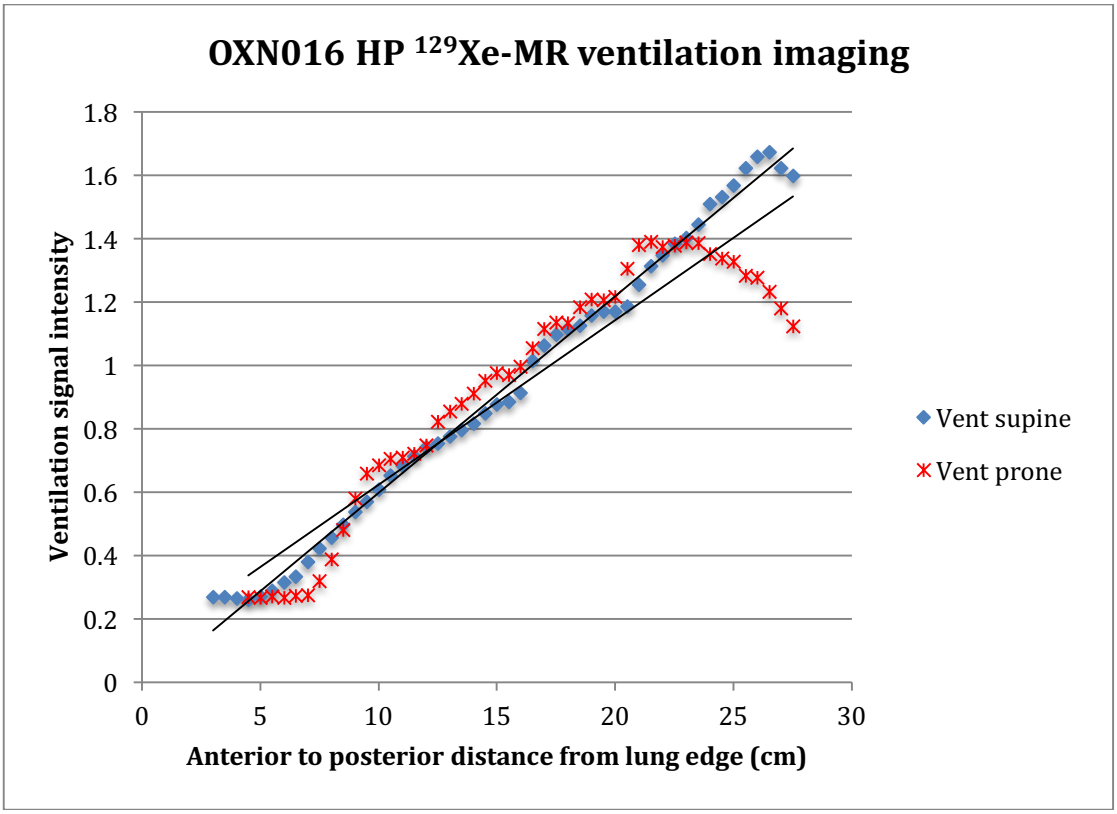


Figure A4.8b: Graph showing ventilation signal intensity in the AP direction for HP ^{129}Xe-MR ventilation imaging acquired from OXN016 in the prone and supine posture.

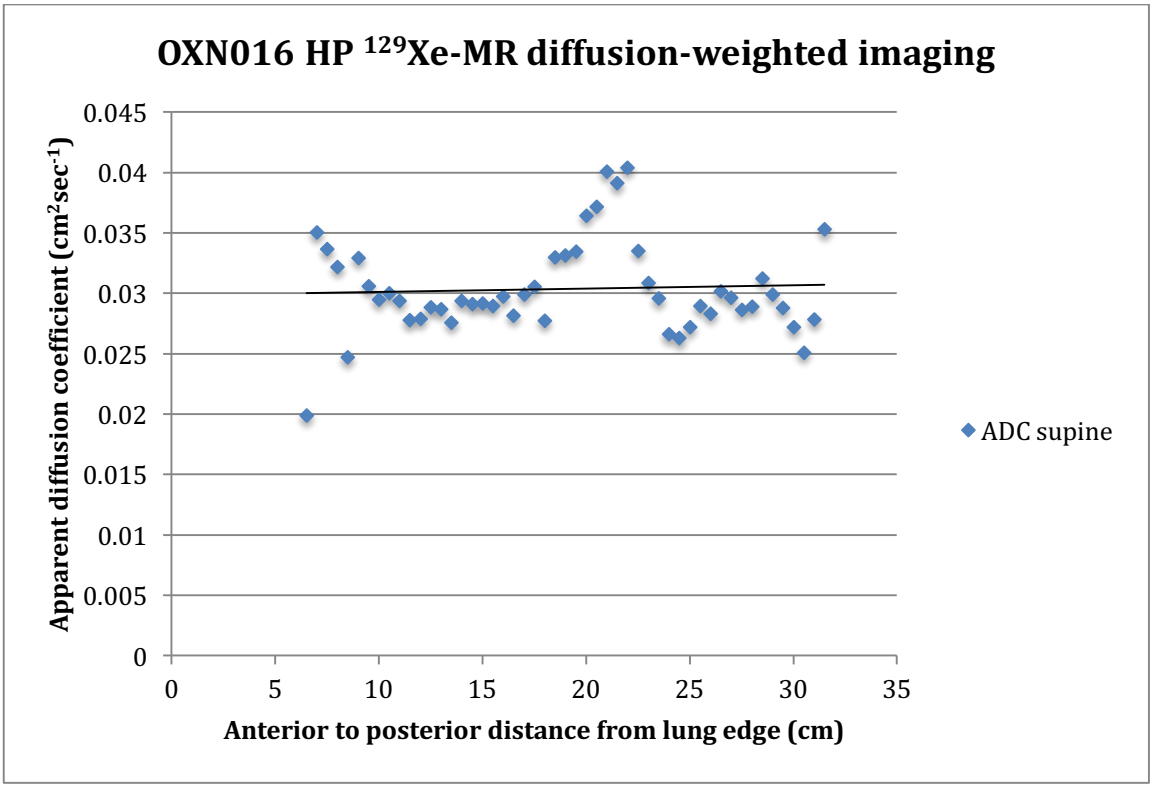


Figure A4.8c: Graph showing mean ADC values in the AP direction for HP ^{129}Xe-MR diffusion-weighted imaging acquired from OXN016 in the supine posture.

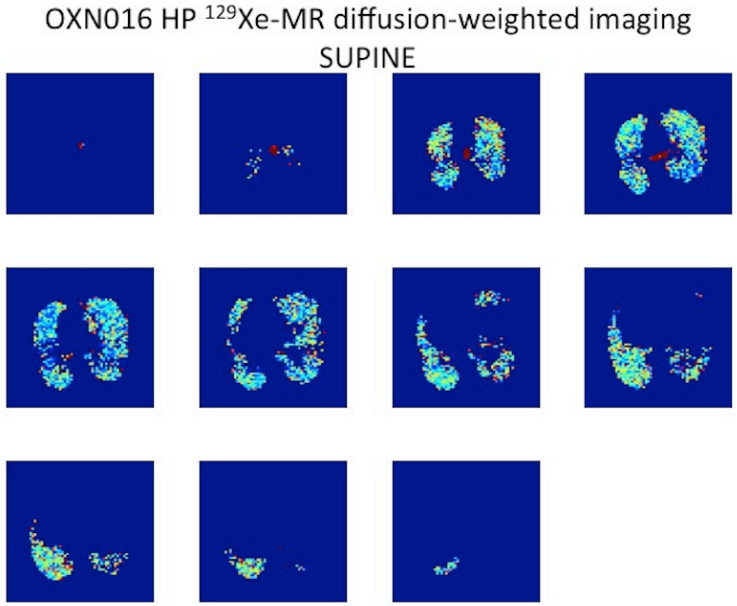


Figure A4.8b: Axial HP ^{129}Xe-MR diffusion-weighted imaging from OXN016 in the supine posture.

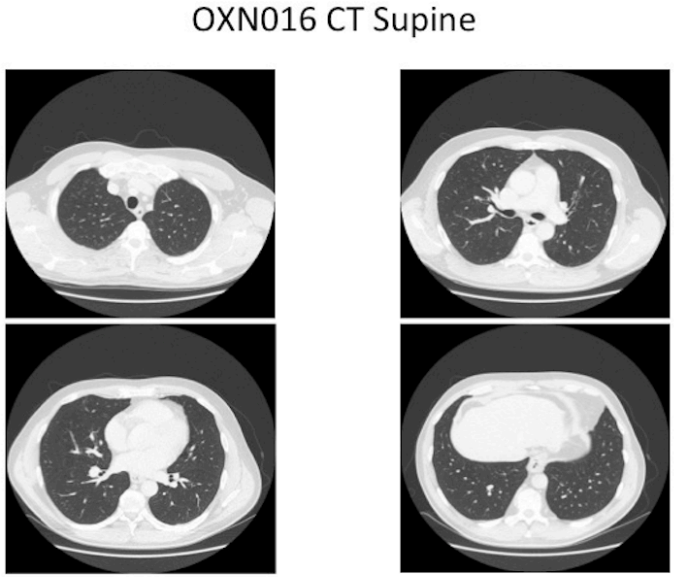


Figure A4.8c: Axial thoracic QCT from OXN016 in the supine posture.

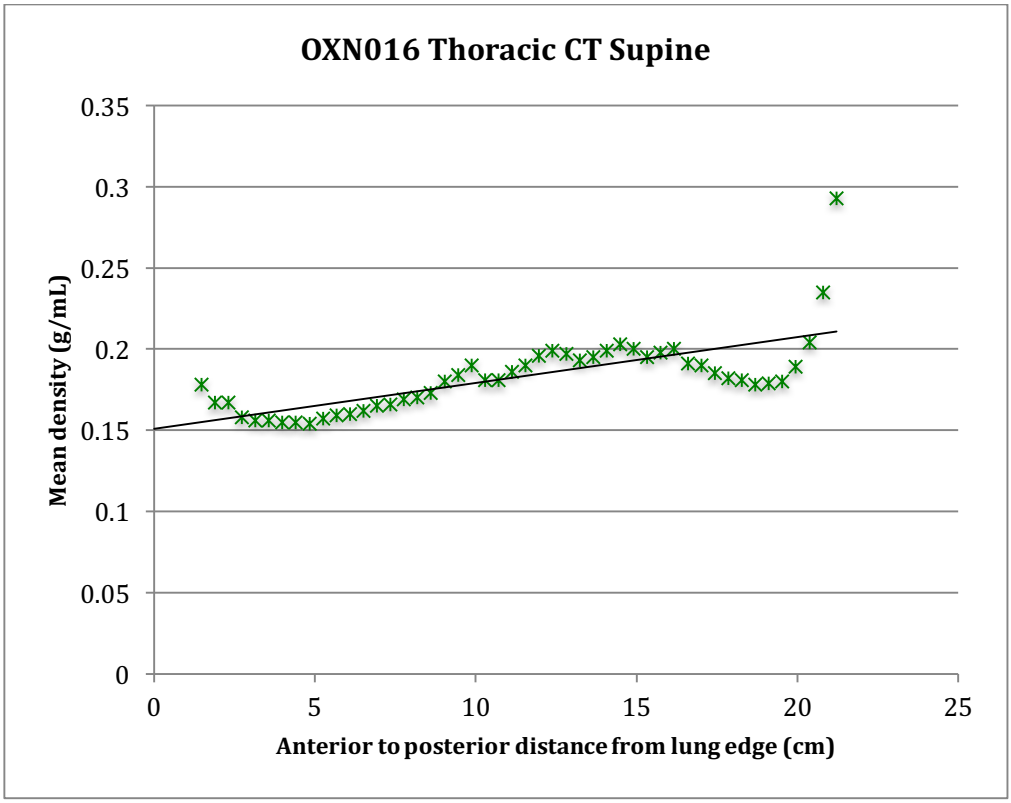


Figure A4.8d: Graph showing mean density in the AP direction for QCT acquired from OXN016 in the supine posture.

Appendix 5: GOLD classification

Global initiative for chronic obstructive lung disease (GOLD) classification of severity of airflow limitation in COPD

In patients with $FEV_1/FVC < 0.70$: -

GOLD I:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD II	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD III	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD IV	Very severe	$FEV_1 < 30\%$ predicted

Appendix 6: Study protocol for patients with COPD

Oxford Respiratory Trials Unit (ORTU)

UNIVERSITY OF OXFORD

Oxford Biomedical Research Centre
Enabling translational research through partnership

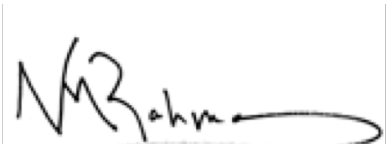
NHS National Institute for Health Research

Hyperpolarised xenon MRI (Xe-129 MRI) lung imaging in COPD clinical trial protocol

REC Reference:11/SC/0488

Protocol version number	6.0
Protocol date	8th May 2015
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Authorised by:

Name:	Dr Najib Rahman [1]	Role:	Chief Investigator
Signature:		Date:	8th May 2015

Confidentiality Statement
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1. SUMMARY

1.1 Lay summary

Hyperpolarised xenon magnetic resonance imaging (Xe-129 MRI) of the lungs is a technique in use in a limited number of centres world-wide, and now available in Oxford. Unlike any other assessment tool, it has the ability to determine detailed lung anatomy and function simultaneously. It has enormous potential to advance understanding and treatment of the lung condition, chronic obstructive pulmonary disease (COPD). COPD is a progressive condition usually caused by smoking, in which airways are irreversibly narrowed, with excess mucous production. It is an important condition for patients as it leads to disabling symptoms that impair quality of life, with reduced exercise tolerance, shortness of breath during daily activities, cough and sputum production and frequent chest infections. It is also an important condition for health-care providers as it is common, (10% in adults over 40 in the UK), and accounts for a large number of hospital bed-days and prescriptions. Current treatments for COPD make only a small difference to symptoms and rate of disease progression. One of the problems in improving treatment is that there are large differences in symptoms between patients, which are not adequately explained by severity of airway narrowing as evaluated using currently available techniques. Up until now, COPD assessment tools have only been able to look separately at overall lung function (e.g. forced expiratory volume in one second (FEV_1), or exercise tolerance), or anatomy (e.g. computerised tomographic scanning). These techniques may miss important localised changes within the lungs that determine patients' symptoms and response to treatment.

Xe-129 MRI lung imaging will enable the anatomy and function of small areas within the lung to be examined simultaneously in detail, thereby increasing the potential to understand the great variation in symptoms and functional performance between individuals, and tailor treatments accordingly. The current proposal (1) further develops technical aspects of this imaging modality in COPD, (2) tests the hypothesis that it is a better predictor of exercise ability and shortness of breath than current assessment methods, (3) evaluates changes in lung imaging post salbutamol and (4) evaluates longitudinal changes in imaging that occur with time.

Patients will be recruited from a range of settings that treat COPD patients, which will include Respiratory out-patient clinics in-patient wards and pulmonary rehabilitation. Potential participants will initially be approached by a member of their clinical team and informed about the study. Their permission is sought to be contacted regarding taking part by a member of the study team. Potential participants are provided with a patient information sheet which includes contact details for the study team should they wish to initiate contact themselves.

2. BACKGROUND AND RATIONALE

Xe-129 MRI lung imaging in COPD

COPD is a chronic, progressive condition characterised by irreversible airway narrowing, and usually caused by smoking. It is very common, with a prevalence of 4-10%[1], and accounts for 27,000 death per annum in the UK[2]. It leads to disabling symptoms with cough, sputum production, dyspnoea, and impaired quality of life[3-5]. Current therapies have only a modest impact on symptom burden and disease progression[6]. One of the challenges of improving care for patients with COPD is that it is a heterogeneous condition, in which current assessment tools such as forced expiratory volume in one second, FEV_1, only explain a small proportion of the variability in symptoms[7], exercise tolerance[8 9] and disease progression. We propose inviting COPD

patients to undergo Xe-129 MRI lung imaging. Xe-129 MRI lung imaging studies have been established as part of the Biomedical Research Centre's initiative, in partnership with the NIHR Clinical Research Network (NIHR CRN) and Oxford Respiratory Trials Unit.

Limitations of current assessment tool in COPD

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are simple and readily available, and so have been widely adopted as an objective assessment tool for COPD, indicating disease severity, responses to drug treatment[10 11] and helping predict mortality[12 13]. However they have several limitations; COPD is characterised by *lack* of airway reversibility, and airway collapse during forced expiration reduces FEV_1[14]. Furthermore, whilst FEV_1 may reflect *airway* calibre, the main target for COPD drugs to date, it is not a good measure of disease affecting the support 'framework' of the lung or *parenchyma*, and is therefore not the optimal measure to assess drugs aimed at the parenchyma such as α1-antitrypsin augmentation therapy. Like other pulmonary function measures, FEV_1 only reflects *global* lung function. The lung is however a complex regional organ where *localised* disturbances of gas flow (ventilation), blood flow (perfusion), and transfer of gases between alveoli (air spaces) and blood occurs. CT scanning does not reflect function, and whilst it has good spatial resolution of 0.5 mm, it is unable to depict the significance of structural change in relation to function and measureable physiologic change.

Conventional MRI is not an ideal modality for assessing lung structure, but may have advantages when coupled with hyperpolarised gas imaging. In conventional MRI the signal originates principally from the protons in water molecules of tissues. It is therefore not particularly useful in assessing the lungs, which are composed largely of air spaces rather than water.

Xe-129 MRI lung imaging

The hyperpolarised noble gases, helium (He-3) and xenon (Xe-129) overcome this problem of using MR for lung imaging, as they have a nuclear spin speed of ½ which generates a signal on MR imaging. This technique, including production of hyperpolarised noble gases, has been reviewed previously[15]. We will use Xe-129 rather than He-3, as it is available in unlimited supply. We anticipate that, like He-3 lung MRI, it will show sensitivity of ventilation and apparent diffusion coefficient (ADC) to change, for example post salbutamol[16], but additionally has the potential to provide valuable information regarding perfusion and diffusion due to its greater lipid solubility than He-3. Xe-129 will be hyperpolarised, that is tosay that the nuclear spin within the atoms will be increased, using GE Healthcare's xenon hyperpolarisation system 2000. This enables the Xe-129 gas to show up on the MR scan. Hyperpolarised Xe-129 gas shows up most in portions of the lung with the greatest airflow. Additionally, Xe-129 readily dissolves in blood, where it emits different MR signal characteristics. Thus Xe-129 MRI enables information regarding anatomy, air flow and blood flow to be evaluated simultaneously. These techniques have been developed by GE Healthcare, who have supported installation of Xe-129 imaging.

Xe-129 lung MRI is an imaging modality that is used in a limited number of centres world-wide, and is now available in Oxford. It has the advantage of involving no ionising radiation. Previous studies have been carried out in animals, and in small numbers of healthy volunteers and patients. Our aim is to use Xe-129 MRI, computed tomography (CT) and perfusion lung imaging to develop a new technique capable of objectively and quantitatively describing regional and structural lung abnormalities in COPD. We will (1) further develop Xe-129 MRI lung imaging in COPD including comparison with conventional clinical imaging modalities, (2) test the hypothesis that it has a closer relationship to symptoms (dyspnoea) and functional ability (exercise capacity) in

patients with COPD than other currently available methods (spirometry, blood gases chest CT and perfusion imaging), (3) evaluate changes in lung imaging post salbutamol, and (4) determine its changes over time.. Xe-129 lung MRI promises to be a useful research tool for assessing effects of new pulmonary drugs, and enabling prediction of anatomical and functional changes following clinical interventions such as lung volume reduction surgery, lung resection or thoracic radiotherapy. It may provide an intermediate surrogate outcome measure for drug development uses, and increase understanding of the pathophysiology of regional lung disease.

3. OBJECTIVES

Our objective is to develop and use Xe-129 lung MRI, a regional non-ionising radiation based functional imaging tool for the evaluation of COPD. Specific aims are:

(1) Technique development

- To assess detailed regional data with regional ventilation, apparent diffusion coefficient (ADC) and bronchial wall thickness measurements.
- To accurately co-register *global* and *regional* data from Xe-129 lung MRI and chest CT by correlating lung masks obtained from CT and proton MRI scans, and analyse the correlation of MRI ADCs with CT lung tissue density (measured in Hounsfield units).
- To develop perfusion data (blood flow through the lungs) obtained using Xe-129 lung MRI, and validate against the current gold-standard –ventilation/perfusion nuclear medicine scan.
- To develop techniques to assess collateral and delayed ventilation.
- To develop novel and automated analysis methods, based on computational models of lung function and combined anatomical and functional information from CT and MRI scans, following current work at the Computational Biology Group, University of Oxford.

(2) Comparison to standard COPD assessment tools

- To carry out multivariate analysis to correlate global and regional ADC data from Xe-129 lung MRI with key patient-centred outcome measures – dyspnoea assessment using the Dyspnoea-12 score[17] and MRC breathlessness score, and exercise tolerance using distance walked in the modified shuttle walk test. We will test the hypothesis that Xe-129 lung MRI has a close correlation with standard methods of assessment of lung function such as FEV_1 or CT derived measures.

(3) Effects of salbutamol

- To test the effects of salbutamol on Xe-129 lung MRI imaging post-inhaled salbutamol.

(4) Interval imaging

- To evaluate changes in Xe-129 lung MRI imaging occurring in patients over time.

4. STUDY DESIGN

4.1 Study Design Overview

All patients with a diagnosis of COPD, Gold classification II to IV, will be eligible for inclusion in Xe-129 lung MRI imaging trials. Those willing to be contacted as suggested by the treating clinician may be contacted by the research team regarding taking part in the Xe-129 MRI lung imaging study. If they are interested, they will be given a patient

information sheet. If they choose to take part, they will be invited to undergo an assessment appointment and lung imaging. Lung imaging visits take up to a day. These visits are described in detail below. As this is a new procedure, patients will be observed carefully for adverse events during and for at least 30 minutes after the Xe-129 scan.

4.2 Lung imaging visit schedule:

Lung imaging involves at least three visits, which are enrolment (visit 1), baseline imaging (visit 2), longitudinal imaging at year 1 (visit 3), and optional salbutamol intervention imaging prior to but on the same day as baseline imaging (see Figure 1). Each imaging visit takes up to a day in length..All visits take place during disease stability (defined as exacerbation free for at least 2weeks). All visits comprise at least a history review (check disease stability, other medical events and any medication changes), dyspnoea questionnaires (MRC breathlessness score, Likert scale, Dyspnoea 12 & VAS), simple observations (pulse oximetry, heart rate and blood pressure), pulmonary function tests and Xe-129 lung imaging.

Enrolment (visit 1) All potential participants undergo an *enrolment visit*. This can take place at any time. This is an opportunity to discuss the study in more detail. It comprises

- Gaining written, informed consent – patients will be provided with information on the study when initially approached and therefore have sufficient time to consider their participation.
- Review of eligibility criteria
- A 'dummy run' of Xe-129 lung MRI imaging, during which the patient lies on a couch similar to that used during the MRI, and practice the manoeuvre required when breathing in xenon from a 1L bag during subsequent lung imaging. During the dummy run this will simply be air or oxygen in the 1L bag.
- Medical history including detailed smoking history
- Lung function testing
- Dyspnoea questionnaires (MRC breathlessness score, VAS, Likert scale and Dyspnoea-12)
- Exercise test.(please refer to section 4.3 for details)
- Renal function will be checked with a blood test (gfr) to ensure safety for use of CT and MRI contrast if no bloods conducted for other clinical reasons are available within the previous 3 months (or within the past two weeks for those with a history of renal impairment).

Baseline Imaging (Visit 2)

All participants take part in this visit, which lasts up to a day. For convenience, this visit may be carried out on the same day as the enrolment visit (visit 1).

The imaging visit is carried out when exacerbation free for at least two weeks. It involves a review of history and simple observations (pulse oximetry, heart rate, andblood pressure -.

Imaging to be completed at this visit includes: -

- Ventilation /perfusion nuclear medicine scan (SPECT/CT),
- Conventional-dose CT chest with contrast,

- Xe-129 lung MRI and gadolinium enhanced lung MRI.

These images enable co-registration between imaging modalities and correlation with physiological variables.
During each scanning visit, patients are scheduled to undergo up to four hyperpolarised Xe-129 breath holds to complete Xe-129 lung MRI scanning. In the event that breathing and scanning are not entirely synchronised, one or two xenon breath holds may need to be repeated; so in total, each participant will undergo up to a maximum of 12 hyperpolarised Xe-129 breath holds during the 2 imaging visits over the study period.

The *salbutamol intervention* component (Visit 2):
This may be completed prior to any other baseline imaging study measures but on the same day and is an optional component. Participants may decide whether they wish to complete the salbutamol intervention component depending on their personal preference and/or their reliance on bronchodilators. If participants decide not to complete the salbutamol intervention component, they will complete all other baseline study measures as described above.
Participants who choose to complete the optional interventional salbutamol component of the study will undergo additional study measures pre-inhaled salbutamol. They will all receive ten puffs of inhaled salbutamol via a MDI and spacer and then complete baseline study measures as described in section 4.2 and 4.3.

The salbutamol intervention component involves Xe-129 lung MRI pre-inhaled salbutamol, then 10 puffs of inhaled salbutamol will be administered by a MDI and volumatic spacer. The post-inhaled salbutamol Xe-129 lung MRI will be completed within 25 minutes of salbutamol inhalation. Non-imaging study measures are simple observations (pulse oximetry, heart rate and blood pressure), spirometry and dyspnoea questionnaires (VAS, Likert scale, Dyspnoea 12). For participants completing the salbutamol intervention component, the dyspnoea 12 questionnaire is only carried out pre- salbutamol and not repeated as all other dyspnoea questionnaires are for baseline (post-salbutamol) imaging. In addition, spirometry is repeated post-salbutamol along with other standard baseline imaging study measures.

Nearly all patients will be taking long acting bronchodilators regularly and most will have short-acting bronchodilators available to take when required (for example many patients take them prior to/ during exercise, or during exacerbations). Participants who wish to complete the salbutamol intervention component will be asked to omit long-acting bronchodilators (such as serevent and tiotropium) from 24 hours prior to study visit 2 (baseline imaging), and short-acting beta agonists (such as salbutamol and atrovent) on the day of visit 2 up until the salbutamol intervention study measures described above are complete i.e. simple observations, spirometry and dyspneoa questionnaires and pre-inhaled salbutamol Xe-129 lung MRI. This temporary omission of long acting bronchodilators and delay in short acting bronchodilators is safe and well tolerated in patients with stable COPD (for example see Kirby[16]), given that this is a condition characterized by minimal airways reversibility. The patient is invited to take their usual short acting bronchodilator (such as salbutamol) after the study measures are complete.

Longitudinal Imaging at year 1 (Visit 3): this involves examining change from baseline data with time.
This visit occurs 1 year post-baseline , ± 1 month when exacerbation free for at least 2 weeks. The visit involves a review of history and simple observations (oximetry, heart rate and blood pressure), lung function tests, dyspnoea questionnaires (MRC, VAS,

Likert scale, Dyspnoea 12) and an exercise test. Renal function will be checked with a blood test (gfr) to ensure safety for use of CT and MRI contrast if no bloods are available within the previous 3 months (or within the past two weeks for those with a history of renal impairment).
Lung imaging comprises

- Ventilation /perfusion nuclear medicine scan (SPECT/CT),
- Low dose CT chest without contrast
- 129-Xe lung MRI and gadolinium enhanced lung MRI.

Patients undergoing endobronchial valve placement or lung volume reduction surgery

Some patients with COPD undergo endobronchial valve placement or lung volume reduction surgery as part of their usual clinical care. For this sub-group of patients only, the longitudinal follow-up visit (visit 3) will be at six months post-procedure rather than at one year post base-line (as stated above), please see figure 2. The exercise test will be completed at both baseline and 6-months follow up visit and will involve a 6-minute walk test rather than an incremental shuttle walk test. This choice has been made so that data gathered from this sub-group of patients can be meaningfully compared with the existing literature for patients undergoing lung volume reduction surgery. These patients will not be invited to participate in the salbutamol intervention component.

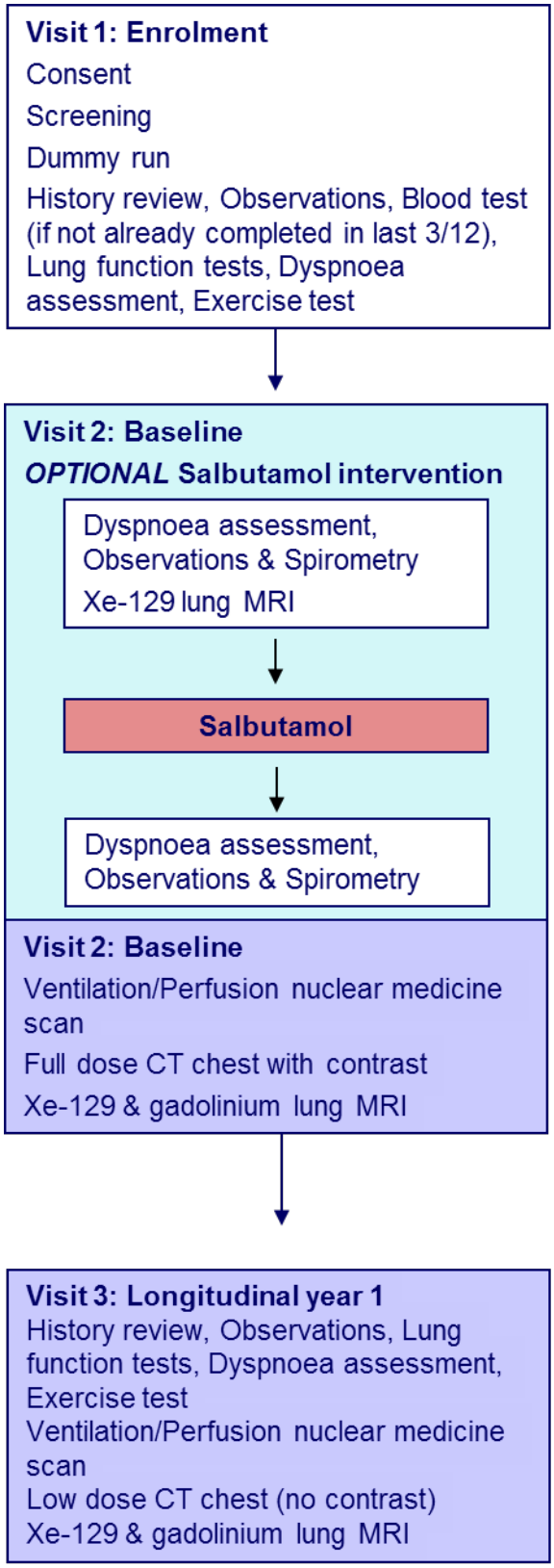


Figure 1: Flow sheet of study visits. Study visits are enrolment (visit 1), baseline imaging (visit 2) and longitudinal imaging at year 1 (visit 3). Participants may choose to take part in the optional salbutamol intervention component completed prior to but on the same day as baseline imaging (visit 2). All these visits take place during disease stability.

Patients undergoing endobronchial valve placement or lung volume reduction surgery

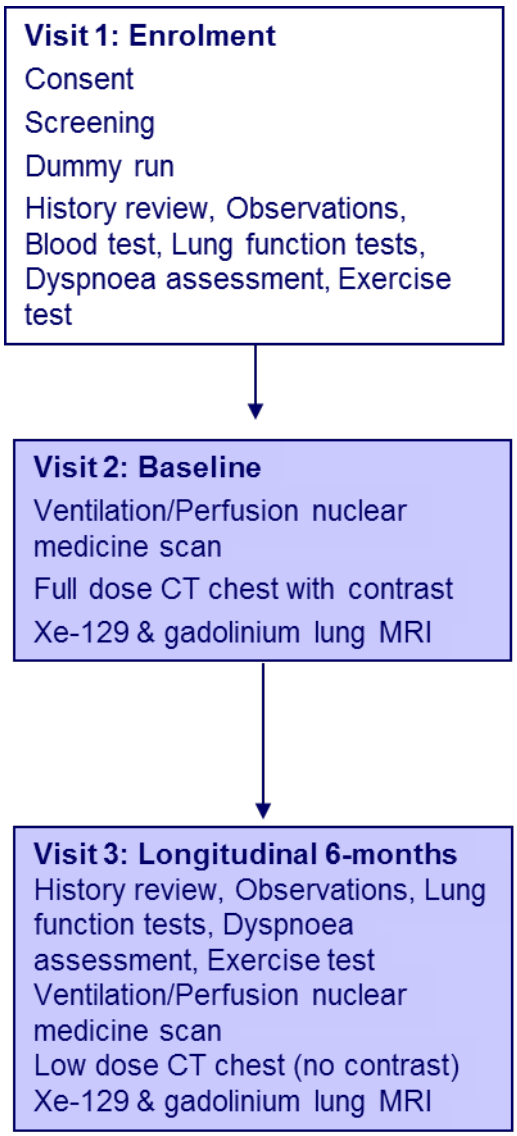


Figure 2: Flow sheet of study visits. Study visits are enrolment (visit 1), baseline imaging (visit 2) and longitudinal imaging at year 1 (visit 3). All these visits take place during disease stability

4.3 Study Treatment/ Intervention

Dyspnoea questionnaires – the MRC dyspnoea score, visual assessment score, Likert score and the Dyspnoea 12[17] questionnaires will be completed.

Exercise testing – Most patients taking part in this study undergo an **incremental shuttle walk test**. Patients walk up and down a 10m course delineated by two cones set 0.5m from either end, whilst oxygen saturations and heart rate are monitored. The speed at which the patient walks is dictated by an audio-signal played on a tape cassette. Every minute the speed of walking is increased by a small increment. The only verbal contact with the supervisor is advice given each minute to increase the walking speed slightly. The test is terminated either by (a) the patient when they are too breathless to maintain the required speed, (b) the therapist if the patient fails to complete a shuttle in

the time allowed, or (c) attainment of their predicted maximum heart rate derived from the formula [210-(0.65*Age)][18].
The sub-group of patients who are undergoing valve placement or lung volume reduction surgery as part of their clinical care will do a **six-minute walk test[19]** instead of an incremental shuttle walk test. This involves the patient walking up and down a corridor as far as they feel able over the course of six minutes. Their total walking distance is recorded.
The exercise test is carried out twice, and the better of the two tests said to be the walk-distance.
Lung function – spirometry, static lung volumes and carbon monoxide transfer factor are carried out. Predicted values are determined from standard published data[20].

CT chest and ventilation/perfusion nuclear medicine scan (SPECT/CT)
This is performed using the 16-slice GE Discovery 670 scanner with a slice thickness of 0.625mm. A cannula will be inserted and an injection of iodinated contrast will be given for the first CT chest completed at visit 2 (baseline only). Low-dose CT chest scans will be completed without contrast at the longitudinal imaging visit at year 1.
CT images are acquired during an inspiratory breath hold of up to 23 seconds to reduce movement artefact. The patient lies supine, whilst computerised scanning takes place. A normal dose CT chest (6mSv) is carried out once, and a low dose CT chest (1.7 mSv) is carried out at the longitudinal follow-up imaging visit at year 1. Software will be used to determine areas of lung attenuation, such as delineating areas < -950 HU validated by visual inspection by an experienced thoracic radiologists, and/ or other measures of local texture in CT imaging. Comparisons with manual region of interest performed on an image display software (OsiriX) will be made.
Participants will be screened for hypersensitivity/allergy to injection of iodinated contrast prior to completion of this study measure. Iodinated contrast will be given for the first conventional CT chest scan during visit 2 only. If hypersensitivity/allergy to iodinated contrast is identified all CT chest scans will be performed without contrast. This will not exclude the patient from participating in the study.
At the baseline visit (visit 2), patients will have a ventilation/perfusion nuclear medicine scan. The ventilation component involves the patient breathing in a gaseous radioactive tracer in aerosol form e.g. technetium-labeled diethylenetriamine pentaacetate (99mTc-DTPA) via a mouthpiece or face mask.
The perfusion component involves insertion of a cannula (the same cannula inserted for the CT chest with contrast can be used), and an injection of a small volume, < 5 mls, of radioactive technetium labelled macro aggregates of albumin (99mTc-MAA). A gamma camera acquires both ventilation and perfusion images. The ventilation/ perfusion nuclear medicine scan will be repeated at longitudinal follow-up at year 1 (visit 3. Patients do not have to move to a different bed between the CT and nuclear medicine scans, so it is associated with minimum disruption.
Xe-129 MRI lung imaging
Patients are given an MRI safety leaflet, and a contact number to discuss any aspect of the visit and scanning prior to giving consent. The patient lies supine in an MR scanner, and has conventional safety monitoring throughout the scan (direct visual observation, arterial oxygen saturations and heart rate monitoring). They wear a lightweight vest containing the imaging coils over their clothes that is necessary for acquiring images. Before the first Xe-129 MR scan involving inhalation of up to 1L of xenon, patients will be asked to breath in a small volume of xenon of approximately 100mL mixed with medical grade nitrogen for a total volume of 1L. The patient will be instructed to perform a standard breath hold for a short period of time (approximately 2 seconds). This is a set-up procedure for the scan enabling optimization of Xe-129 MR parameters according to patient height and weight as well as a practice run for the patient. The output from calibration (flip angle measurement) enables the best quality Xe-129 MR

images to be acquired for each individual and is not be used to evaluate the study endpoints.
For the actual Xe-129 MRI scan, the patient breathes out, and then breathes in vigorously from a 1L bag containing up to 1L xenon, balance nitrogen. Breathing in xenon may be hard work for some people with airway narrowing due to COPD, because it has a density 4.55 time greater than air, which increases airways resistance[22]. Therefore patients are sometimes helped with this breathing manoeuvre by physically compressing the bag during the breath in.
The patient receives a bag full of air or oxygen to practice the breathing manoeuvre before breathing xenon. Scanning then takes place during a breath hold for approximately 20 seconds, or during an inhalation – exhalation manoeuvre. This manoeuvre with scanning will be repeated three times to enable acquisition of all Xe-129 MRI sequences e.g. ventilation, ADC and collateral ventilation. For the optional salbutamol intervention component, pre-salbutamol Xe-129 lung MRI involves acquisition of one sequence i.e. ventilation only. If the patient fails to breathe in sufficient xenon at the required time, the investigator may suggest that the manoeuvre is repeated. One patient will not exceed sixinhalations of xenon in a single day. The time interval between repeat manoeuvres with scanning may be around an hour, since this is the time required to polarise a litre of xenon.
If the study team fails to acquire all the required Xe-129 MRI sequences during a single scanning session as a result of technical difficulties or non-synchronisation of patient breathing and scanning, the patient may be requested to return within a few days to complete Xe-129 lung MRI scanning and ensure acquisition of all sequences for that study visit. This may take up to half a day and may involve repeating one or two Xe-129 MR sequences previously acquired since these cannot be analysed accurately if they have not all been performed at the same time point.
The mean apparent diffusion coefficient (ADC) will be determined for each scan in a global (per lung) and regional (per lobe, following lobe segmentation in the CT scan and co-registration CT-MRI). This is a measure of the size of airspaces, and has been show to be increased in COPD[23]. Different investigators will carry out analysis of imaging data (MRI, CT and perfusion) from those carrying out other physiological measures, such as spirometry and exercise tests or questionnaires to ensure investigators are blind to results that will be cross-correlated, so avoiding bias. Patients are observed for at least 30 minutes post Xe-129 MRI lung imaging.
Gadolinium enhanced lung MRI – an intravenous cannula is inserted at the start of the study visit. This may be the same cannula used for CT Chest and nuclear medicine scans. An injection containing gadolinium is given via the cannula and lung MRI carried out during a short breath hold. Since patients do not need to move from the bed following Xe-129 lung MRI there is minimal inconvenience and disruption for the patient.
Inhaled salbutamol component – as part of this component, patients will be invited to complete additional study measures pre-inhaled salbutamol. This will be completed prior to but on the same day as baseline imaging (visit 2, (figure 1) to determine the effects of salbutamol on Xe-129 lung MRI images. Salbutamol is a beta-agonist that aids bronchodilation. It is a central component of treatment in asthma exacerbations. Although beta-agonists are given as part of routine care to patients with COPD, their role is less important in this condition, since COPD is characterised by minimal airways reversibility.
Volunteers wishing to complete this optional component, will be asked to omit long acting beta-agonists (e.g. serevent) and antimuscarinics (e.g. tiotropium) for 24 hours in advance of study visit 2 (baseline imaging), and short acting beta agonists (e.g. salbutamol and atrovent) on the actual study day . A short period of omitting beta agonists is well tolerated without adverse symptoms in patients with stable COPD, given the minimal airway reversibility in this patient group[16].

Ten puffs of salbutamol will be delivered as a multi-dose inhaler (MDI) via a volumatic spacer. This is the usual MDI delivery method for most patients. The effects of salbutamol itself are not being tested in this study; salbutamol is simply being used as a tool to demonstrate sensitivity of imaging techniques to change.
Other measures – For participants who opt to complete the salbutamol intervention component, spirometry and dyspnoea assessment will be carried out twice during the baseline imaging visit i.e. before and after inhaled salbutamol.

4.4 Time commitment and duration of study

Lung imaging
Visits take up to a day, which includes observation of at least 30 minutes after the last inhalation of xenon. The study comprises up to threevisits over a duration of up to two years depending upon patient preference for study participation.

5. SELECTION OF RESEARCH PATIENTS

5.1 Inclusion Criteria

- Patients with a diagnosis of COPD with at least mild disease (stage II – IV on GOLD criteria classification, FEV_1 <80% predicted and FEV_1/ FVC <70%[24])
- Significant smoking history (>15 pack years, where a pack year is the product of [average number of cigarettes smoked per day] and [number of years smoked for] divided by 20) or other definite cause of COPD
- Patients over the age of 18 who are willing and able to give informed consent to participate in the study.

5.2 Exclusion Criteria

- Co-existent cardio-pulmonary disease that predominates over COPD and might confound results interpretation (for example asthma, bronchiectasis, cystic fibrosis, lung cancer, uncontrolled heart failure, frequent unstable angina, respiratory muscle weakness)
- Other major co-morbidity such that life expectancy is less than 24 months due to a cause other than COPD
- Pregnancy

Exclusion criteria for CT scanning

- Inability to lie flat

Exclusion criteria for MR imaging

- Inability to lie flat
- Severe claustrophobia

- Presence of a cardiac pace-maker or non-MRI compatible metallic implant
- Intra-ocular foreign body
- Epilepsy requiring on-going medical treatment, or a seizure within the past year

Exclusion criteria for gadolinium enhanced lung MRI scanning

- Known hypersensitivity/ allergy to the injection of MultiHance that is given as part of this scanning or an adverse reaction to an injection given during previous MRI scanning. MultiHance contains gadobenate dimeglumine and small quantities of benzyl alcohol.
- Severe renal impairment

Exclusion criteria for ventilation/perfusion nuclear medicine scanning

- Known hypersensitivity to albumin or preference to avoid blood donation product

Exclusion criteria for salbutamol intervention component of study

- Known hypersensitivity to salbutamol or to any of the excipients
- Inability to omit long acting bronchodilators for 24 hours prior to the start of the study, and short acting bronchodilators on the day of the study until measurements are complete.

6. TREATMENT/ INTERVENTION

6.1 Description of Treatments/ Interventions

At patients' initial clinical review it is anticipated their medications will be optimised, in accordance with the GOLD guidelines[5] as part of their normal best medical practice. No treatments are given as a part of the COPD Cohort study.
Xe-129 lung MRI requires breathing in an investigational medical product, hyperpolarised xenon, Xe-129, which is described in detail below.
Participation in the salbutamol intervention component of the study requires inhaling salbutamol. Salbutamol itself is not being tested since almost all patients will already be taking it as part of their routine care. It is simply the sensitivity of Xe-129 to change that is being evaluated.
From the patients' perspective, participation in this component of the study simply means delaying their first salbutamol dose of the day, and omitting long-acting bronchodilators for 24 hours prior to the start of the baseline study visit (visit 2). Temporarily omitting bronchodilators in COPD during disease stability is safe and well tolerated, since it is a condition characterised by minimal airway reversibility.

6.2 Description of Xe-129

6.2.1 The Investigational medicinal Product (IMP) tested in this study is Xenon (Xe-129). Xenon is an inert gas that is present in the atmosphere in low concentrations. It has no smell or taste. Breathing xenon or undergoing an MRI scan does not involve exposure to ionising radiation.

6.2.2 Physiological effects At low concentrations such as those that will be used in this study, Xenon has effects similar to nitrous oxide (laughing gas). Nine out of 10 patients experience light headedness, paraesthesia, euphoria or a mild 'drunk' feeling, which is short lived and resolves within 2-3 minutes of breathing the gas[23 25 26]. Due to its increased density compared to air, it leads to a brief change in voice quality when breathing the gas out.

6.2.3 Side effects Xenon has been found to be extremely safe and well tolerated, both during single breath-hold experiments such as ours (n=26[15], n=27[23] and n=44[22]) and during 4 minute 20 second continuous breathing (n=1,830)[25]. In a prospective study examining safety and tolerability of xenon, 32% of 44 volunteers experienced mild gastrointestinal symptoms[22]. One volunteer experienced drowsiness, sleepiness and numbness, which resolved in about 7 minutes[22]. She had considerable co-morbidity, including multiple sclerosis, B12 deficiency and Graves' disease. In a large retrospective study involving breathing xenon for cerebrovascular imaging during a 4 minutes 20 seconds period (in contrast to our single breath exposure), the incidence of pauses in breathing for >15 seconds was 0.6%, headache (usually mild) 0.4%, nausea or vomiting 0.2%, change in sensorium 0.1% and 0.05% hallucinations[25]. 0.2% of patients had a seizure, but 3 of 4 of these patients were being investigated for unexplained seizures, and diagnostic information was not available for the fourth patient. Patients with multiple sclerosis had increased emotional liability. These side effects nearly all occurred towards the end of the exposure period. Pauses in breathing almost invariable were terminated by an instruction to take a breath.

6.2.4 Safety considerations At high concentrations xenon has anaesthetic properties. The minimum alveolar concentration (MAC) of xenon to achieve this at sea level is 70%[27]. Our patients will breathe a Xe concentration considerably lower than this. Xe is transferred from the source to the patient in an isolated bag, which is 1L in volume. Thus the patient is not in continuity with the Xe supply, and it is not possible to inhale more than 1L. They simply inhale a single breath, and therefore do not approach the gas equilibrium that is required when defining MAC. They inhale this 1L breath from residual volume. The mean residual volume of the first 73 patients entering our COPD Cohort is 4.4 L (SD 1.2 L) with a range of 2.5 to 6.5 L. This would result in an average FXe of 19%, with a range of 29 – 13%. The alveolar FXe would tend to be marginally lowered due to Xe in the anatomical deadspace of the large airways, and marginally raised due to Xe not entering non- or slowly communicating air spaces within the lungs. Thus the FXe that our patients will be exposed to is considerably below the dose required to induce anaesthesia, and well within safe limits. It is not possible for patients to breathe more than 1 L of xenon at a time, since they are given a single 1 L bag of the gas. This procedure may be repeated up to three times during one imaging session, with time to rest of around half an hour in-between manoeuvres. In the event that breathing and scanning are not entirely synchronised, one or two xenon breath holds may need to be repeated; so in total, each participant will undergo up to a maximum of 40 hyperpolarised Xe-129 breath holds during the 8 imaging visits over the 2 year study period.

A further safety consideration is patients' oxygenation, since they will be inhaling 1 L of anoxic gas, followed by a breath hold. If we consider the 'worst case' scenario of our patient with the lowest residual volume of 2.5 L, if they inhaled 1 L of xenon and the mean FiO_2 in the lungs before inhalation was 15%, then immediately after the xenon breath in this would fall to 11%. This is not dissimilar to the degree of hypoxic exposure of COPD patients with severe COPD given 15% FiO_2 to breathe for 20 minutes when assessing their 'fitness to fly', and is considered quite safe. We will only be exposing patients to this low oxygen fraction for a single breath hold. The breath hold is up to a maximum of 20 seconds, although patients are free to take another breath sooner if they cannot manage this long. It is likely that patients with advanced lung disease will only be able to hold their breath for shorter periods, however the majority of the imaging is

complete within 6-10 seconds. The amount of oxygen available in 3.5 L of 11% oxygen is 385 mls, which is considerably more than the oxygen requirement for the duration of the breath hold (assuming oxygen use is 250 mls/ min). These calculations assume all gas within the lungs is in communication with inhaled gas, which will not be the case in COPD, however the safety margins are extremely large. Reassuringly, studies in COPD patients using this breathing technique observed a mean fall in oxygen saturations of only 1.2% of baseline during observation at 2 minute intervals for 10 minutes[22]. In the unlikely event that a patient desaturates by more than 10% immediately following Xe inhalation, this manoeuvre will not be repeated. This level of desaturation is commonly experienced by some patients with COPD undergoing exercise or during sleep. Such patients are accustomed, and therefore partially acclimatised, to such fluctuations in oxygen.

Our patients will be carefully observed and monitored throughout the study, including direct visual observation, heart rate, respiratory rate and arterial oxygen saturations. The minimum number of people in attendance during a scan is two. This includes a doctor or allied health care professional such as a nurse or radiographer, who is solely responsible for patient monitoring, safety and well-being. They will be aware of potential risks of Xe, and appropriately trained in how to respond to any adverse sequelae arising. It also includes a technician/ radiologist who is responsible for acquiring images. In the event of any untoward medical event occurring mid-scan, staff can reach the patient immediately. As in all clinical areas throughout the Oxford University Hospitals NHS Trust, emergency drugs and equipment are readily available and staff are trained in their use. This includes supplementary oxygen and resuscitation equipment.

A 'Physician information sheet' documenting possible effects of Xe and appropriate medical responses has been drawn up, and will be provided to all those involved in Xe imaging.

Description of inhaled salbutamol

Ten puffs of salbutamol, 100 micrograms each, will be given from a multi-dose inhaler via a volumatic spacer. Salbutamol is a short acting selective β2 adrenergic bronchodilator, that is used routinely for patients with asthma and COPD. It provides short-acting (4-6 hour) bronchodilatation with a fast onset (within 5 minutes). When salbutamol is taken by the inhalation route only about 10% - 20% of the dose is deposited in the airways, with the remainder either being retained in the delivery system or swallowed. Salbutamol does not appear to be metabolised in the lung. The swallowed part of the salbutamol dose is absorbed from the gastrointestinal tract and is subject to first-pass metabolism in the liver; about half is excreted in the urine as an inactive sulphate conjugate.

<u>Safety considerations for salbutamol</u>

Salbutamol is safe and well tolerated in COPD. Almost all patients will already be taking it as part of their routine clinical care, and so will be known to tolerate it well. As part of participation in this study component, they will simply be delaying their first dose of the day. Patients who are unable to tolerate salbutamol will not take part in this optional component of the lung imaging study. Recognised adverse effects of salbutamol that might lead a patient not to tolerate it are paradoxical bronchoconstriction, tachycardia, palpitations, headache and mouth or throat irritation. Such effects would occur from when salbutamol is first introduced as part of patients' routine clinical care, and would not be expected to arise *de novo* due to participation in this study.

Description of MultiHance (gadolinium injection)

MultiHance contains gadolinium, which is a rare earth metal that improves images of pulmonary arteries during lung MRI. Gadolinium is given in the form of gadobenate dimeglumine. The dose of MultiHance is around 0.2 ml/ kg body weight.

Safety considerations for MultiHance

MultiHance is commonly used in clinical practice for perfusion imaging during MRI where it is safe and well tolerated. Common side effects (more than 1/100 but fewer than 1/10) are headache, nausea, feeling hot and local reactions such as swelling or pain at the injection site. Rarely (more than 1/ 10,000 but fewer than 1/ 1,000) allergic reactions can arise leading to shock, itching, skin rashes, urticarial, fainting, a swollen face and neck and wheezing, or other serious effects including tinnitus, pancreatitis, pulmonary oedema, intracranial hypertensions or hemiparesis.

6.3 Xe-129 production, storage and dispensing

Xe-129 will be isolated from a gas mixture of 1.0% xenon, 10% nitrogen and 89% helium, manufactured in the USA and supplied by Spectra Gases Ltd, Littleport Cambridgeshire. The gas mix will be shipped to the hospital and will be delivered to the Radiology Department where it will be polarised via spin exchange optical pumping by laser, using the GE Healthcare Xenospin hyperpolarisation system.

The hyperpolarisation will take approximately one hour. Xe-129 will then isolated from other gases and sublimated into Tedlar plastic bags in Radiology for administration to participants via inhalation in the MR suite. The gas is labelled in accordance with Annexe 13 according to EU trial directive requirements. There are clear SOPs for each stage of this manufacturing process. The maximum storage time before administration to a participant is 30 minutes.

Each batch of Xe-129 will be tested using a GE Healthcare 1651 polarisation measurement system to ensure sufficient xenon gas is hyperpolarised to enable lung imaging. All staff involved in the process of Xe-129 manufacture will be trained using GE Healthcare's training programme to ensure that the manufacture is conducted safely to the correct technical specification. The manufacturing facility will be licensed by the MHRA and each batch will be manufactured to GMP standard and certified for release to the investigator by a qualified person according to the approved Standard Operating Procedures.

Calibration

Calibration involves the patient breathing a small volume of xenon of approximately 100mL mixed with medical grade nitrogen for a total volume of 1L. The patient will be instructed to perform a standard breath hold for a short period of time (approximately 2 seconds). This is a set-up procedure for the scan enabling optimization of Xe-129 MR parameters according to patient height and weight as well as a practice run for the patient. The output from calibration (flip angle measurement) enables the best quality Xe-129 MR images to be acquired for each individual and is not be used to evaluate the study endpoints.

For calibration, hyperpolarisation will take up to 10 minutes. The same manufacturing process as clearly described by SOPs to produce up to 1L of hyperpolarised Xe-129 will be adhered to. The only difference is the length of hyperpolarisation time resulting in a much smaller volume (100mL) of hyperpolarised xenon gas being produced. Xe-129 will be isolated from other gases and sublimated into Tedlar plastic bags in Radiology for administration to participants via inhalation in the MR suite. These small calibration doses are not considered to be IMPs and do not require QP release.

6.4 Randomisation codes/ unblinding

The Xe-129 lung MRI imaging study is not randomised. All patients undergoing regional lung imaging will breathe Xe-129 gas.

6.5 Modification of trial treatment

Following a serious adverse event (SAE) by regulatory criteria (see section 8) treatment may be interrupted at the discretion of the Chief Investigator and restarted if clinically appropriate to complete the proposed treatment course.

6.6 Accountability and unused drugs

Medical grade xenon will be purchased from Spectra Gases Ltd, Littleport, Cambridgeshire, and stored at the Oxford Thoracic Imaging Centre. Xenon will undergo hyperpolarisation up to an hour prior to use, and there will be no unused gas.

6.7 Measures of compliance/ adherence

Compliance auditing is not relevant to use of hyperpolarised xenon: a dose is only given by radiographers/ radiologists during the MR regional lung imaging itself. Xenon inhalation will simply be recorded on the case report forms.

6.8 Treatment data collection

The data collected for this study will include the imaging data that will be stored electronically and sent for analysis at the University of Oxford Computing Laboratory. Safety data, for example Adverse Event data related to Xe-129 exposure, will be recorded on the CRFs for this study.

6.9 Non-trial treatment

At the initial clinical review it is anticipated patients' medications will be optimised, in accordance with the GOLD guidelines[5] as part of normal best medical practice. Other treatments, such as antibiotics, steroids and oxygen will be given as indicated clinically, as part of standard care. The only interventional medical product for this study is hyperpolarised Xe-129.

6.10 Data on concomitant medications

Patients' medications will be recorded at each follow-up visit.

6.11 Co-enrolment guidelines

Patients participating in theis lung imaging study may enter into other clinical trials.

6.11.1 Definition of End of Study

The "end of study" is defined as the last visit of the last patient undergoing the study. It is estimated that this will be up to three years after initiation of the study. It is the responsibility of the Chief Investigator to inform the University of Oxford CTRG (the Sponsor) within 90 calendar days of the "end of study" that the study has closed. The sponsor and Chief Investigator reserve the right to terminate the study at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the patient's best interests.

6.12 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may withdraw a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- An adverse event which results in inability to continue to comply with study procedures
- Disease progression which results in inability to continue to comply with study procedures
- Consent withdrawal
- Lost to follow up

Withdrawal from the study will not result in exclusion of the data for that participant from analysis provided the patient has not refused consent for further use of the data (see Section 4.4). The reason for withdrawal will be recorded in the Case Report Form (CRF).

6.13 Patient withdrawal

Patients can withdraw from this lung imaging study at any time without giving a reason and without affecting their quality of future medical care. Consent can be withdrawn at three levels:

No further contact – means that the COPD research team no longer contacts the patient directly, but still has their permission to use information, samples and to obtain further information from health records.

No further access – means that the COPD team no longer contacts the patient or obtains information from their health records, but still has permission to use the information and samples already collected.

No further use –means that the COPD team no longer contacts the patient or obtains further information, aims to destroy all samples already collected (though tracing previously distributed samples may not always be possible), does not use either data or samples for further analyses, but is not able to remove data from analyses already carried out. Data already entered on to the database cannot be deleted, but will be excluded from analysis.

If the participant is withdrawn due to an adverse event, the investigator will arrange for visits or telephone calls to collect follow-up information on the adverse event until the adverse event has resolved or stabilised.

7. ASSESSMENTS

7.1 Outcome measures

Assessments to (1) further develop technical aspects of Xe-129 lung MRI, (2) compare with standard COPD assessment tools (3) evaluate changes in lung imaging post salbutamol and (4) evaluate interval changes in imaging are described in detail in section 10.

7.2 Procedure for assessing safety

Details of adverse event (AE) and serious adverse event (SAE) reporting are presented in Section 7. AEs should be reported on each attendance to follow up with the study

team, and there is 'free text' on the case report forms (CRFs) for staff to document any adverse events reported by patients.

8. SAFETY REPORTING

Definitions

8.1 Adverse Events

An adverse event (AE) is defined as 'any untoward occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this product'; in this study it is Xe-129. These may include side effects, injury, toxicity or hypersensitivity reactions. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

8.2 Adverse Drug Reaction (ADR)

This is defined as all untoward and unintended responses to a medicinal product (Xe-129) related to any dose. The phrase 'responses to a medicinal product' means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.3 Expected Adverse Drug Reactions

After breathing gas containing xenon, feelings of light headedness, paraesthesia, euphoria or a mild 'drunk' feeling are common, occurring in 9 out of 10 people. These symptoms last for just a few minutes, just like breathing 'laughing gas'. A normal expected effect of breathing xenon is a change in voice quality, but this will last for only a few seconds until the xenon is exhaled. Reference safety information is provided in the Investigator's brochure.

Salbutamol may cause a fine tremor of skeletal muscle, usually the hands are most obviously affected. This effect is dose-related and is common to all β- adrenergic stimulants. Tachycardia, with or without peripheral vasodilatation, may rarely occur. All patients will already be taking beta-agonists such as salbutamol as part of their standard care, and so will be familiar with this side-effect (or if known to be intolerant of side effects will not participate in this component of the study).

8.4 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is an adverse event having a reasonable possibility of being related to a study medication, but which is of a nature or severity that is not consistent with the expected adverse reaction profile of the trial medication. The expected profile is described in the Investigators' brochure.

8.5 Reporting of Adverse Events

8.5.1 All adverse events (AEs), whether serious or not, should be reported on an Adverse Event form as part of the patients' routine CRF data capture. For this study, AEs occurring during, or within a day of breathing xenon will be recorded. Since xenon is not expected to have any pharmacological activity beyond a few minutes after a single breath, subsequent AE reporting will be limited to any adverse event having a reasonable possibility of being attributable to breathing xenon (that is an adverse

reaction), and any other adverse event considered to be of medical interest/ importance by the investigator. AEs will be followed until resolution, or the event is considered stable.
The following attributes are recorded by the investigator: description, date of onset and resolution date, severity, assessment of relatedness to study medication (Xenon), other suspect drug or device and action taken. The investigator may be asked to provide follow-up information.
It will be clearly stated on the AE form whether or not, in the opinion of the Chief Investigator, the AE has a reasonable suspected causal relationship to the trial medication.

8.5.2 Patient withdrawal

All AEs that result in a patient's withdrawal from the study or are present at the end of the study should be followed up until a satisfactory resolution occurs. It will be left to the investigator's clinical judgment whether or not an AE/ AR are of sufficient severity to require the patient's removal from Xe-129 MRI scanning. A patient may also voluntarily withdraw from study procedures if they tolerate it poorly. Further details of withdrawal are presented in Section 6.12 In the event of symptoms arising, patients will be given appropriate care and medical supervision until symptoms resolve, or the condition becomes stable. Every effort will be made to gather outcome data on patients through study follow-up, or general practitioner/ hospital staff unless the patient has specifically withdrawn consent to such efforts.

8.5.3 Pregnancy reporting

If a patient becomes pregnant during the study, the pregnancy will be monitored and followed up until the outcome is known. The pregnancy will be reported to the ORTU team, and documented on an adverse event form.

8.6 Serious Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:
The term '*severe*' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).
This is not the same as '*serious*', which is based on patient/ event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.
The regulatory definitions (by ICH E2A criteria) by which an AE/ R should be classified as 'serious' are listed below.

7. Results in death
8. Is life-threatening (i.e. with an immediate, not hypothetical, risk of death at the time of the event)
9. Requires hospitalisation or prolongs existing hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included)
10. Results in persistent or significant disability or incapacity such that the patient is unable to conduct normal daily life functions
11. Is a congenital anomaly (i.e. the outcome of pregnancy involving a patient). A pregnancy undetected at entry would constitute a protocol violation.
12. Any other important medical events. This, though not included in the above, may jeopardise the patient and may require medical or surgical intervention to prevent

one of the outcomes listed (e.g. include allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias which did not result in hospitalisation or development of drug dependency). Medical and scientific judgment should be exercised in deciding whether an adverse event is serious in other situations.

8.7 Reporting of Serious Adverse Events (SAEs)

All SERIOUS adverse events occurring during or within 24 hours of Xe-129 lung MRI scanning should be reported within 24 hours of the PI/research team's awareness to the sponsor (CTRG) via fax and a copy of the SAE form also sent to the Oxford Respiratory Trials Unit. The sponsor (CTRG) will perform an initial check of the report, request any additional information and ensure it is reviewed by the Medical Monitor. CTRG will also ensure that it is reviewed at the next Trial Safety Group (TSG) meeting. Additional information received for a case (follow-up or corrections to the original case) will need to be added to the original SAE form and faxed to CTRG.

8.8 SUSAR reporting

In collaboration with the sponsor (CTRG) and the TSG Medical Monitor, the CI will report all SUSARs to the Competent Authorities (MHRA in the UK), the Research Ethics Committee concerned and Host NHS Trusts. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

8.9 Outcome grading of Adverse Events

Graded as either: recovered, recovered with sequalae, continuing, change in SAE, Patient died, unknown.

8.10 Relationship to study intervention

The relationship between the trial treatment and the adverse event will be graded as: Definitely, probably, possibly, unlikely or not related.

8.11 Follow-up after Adverse Events

Participants experiencing SAEs or AEs will receive the appropriate medical treatment. After recovery these participants will be followed up in the normal study follow-up sequence.

8.11 Developmental Safety Update Report

In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial or on request a Development Safety Update Report (DSUR) to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and sponsor.

9. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of 'serious breaches' to the MHRA within seven days of the sponsor

becoming aware of the breach. A serious breach is defined as 'A breach of GCP or the trial protocol which is likely to affect to a significant degree –

c) The safety or physical or mental integrity of the subjects of the trial; or
d) The scientific value of the trial

In the event that a serious breach is suspected the sponsor (University of Oxford) must be contacted as soon as possible.

10. STATISTICS AND OUTCOME MEASURE

Early studies[23 28], including work from our own group[29], using Xe-129 lung MRI have demonstrated that this technique provides valuable information regarding *global* pulmonary parenchymal apparent diffusion coefficients (ADCs – measures of increased air spaces) in COPD, demonstrating important differences compared to age matched controls or young, healthy volunteers. Our scanner has excellent anatomical resolution compared to those used in most previous work, enabling us to perform *regional* analysis, down to the level of the secondary pulmonary lobule, and to determine bronchial wall thickness. These observations are of particular interest in COPD, which is a heterogeneous condition affecting different regions of the lung to differing extents, and with potential airway thickening and mucus plugging.

This study comprises (1) a baseline study, (2) a longitudinal study, and (3) optional salbutamol intervention component. For each of these study components determining Xe-129 lung MRI changes within patients, the primary outcome measure is change in *ventilation and ADC maps*. A detailed analysis plan will be constructed prior to analysis of the full dataset.

We will also compare *global* Xe-129 lung MRI ADC measures between COPD patients and other diagnostic groups (initially patients with lung cancer and patients with normal lungs who are well, but who are having chest CT imaging due to a prior testicular malignancy: these studies are covered by separate consent). We will carry out the following completely novel analyses:

Technique development

- Assessments of detailed regional data, with regional ADC and bronchial wall thickness measurements.
- Accurate co-registration of *global* and *regional* data from Xe-129 lung MRI and chest CT, by correlating lung masks obtained from CT and proton MRI scans. Analysis of the correlation of MRI ADCs with CT lung tissue density (measured in Hounsfield units).
- Development of perfusion data (blood flow through the lungs) obtained using Xe-129 lung MRI, and validation against the current gold standard – ventilation/perfusion nuclear medicine scanning.
- Development of a technique to assess collateral and delayed ventilation.
- Development of novel and automated analysis methods, based on computational models of lung function and combined anatomical and functional information from CT and MRI scans, following current work at the Computational Biology Group.

Comparison with standard COPD assessment tools

- Multivariate analysis to correlate global and regional (lobar) ADC data from Xe-129 lung MRI with key patient-centred outcome measures – dyspnoea assessment using the Dyspnoea-12 score[17] and MRC breathlessness score, and exercise tolerance using distance walked in the incremental shuttle walk test or the six-minute walk test in subjects undergoing endobronchial valve

placement/lung volume reduction surgery. We will test the hypothesis that Xe-129 lung MRI has a closer correlation with these measures than FEV_1.

Interval imaging

- Changes over time in Xe-129 lung MR imaging at 1 year follow-up will be determined. Rate of change dependent upon the number of exacerbations as defined by patient reporting will be determined.
- Changes in Xe-129 lung MRI imaging from pre- to post- salbutamol -.
- All patients with Gold classification II to IV COPD will be invited to undergo lung imaging. It is not yet possible to do a detailed power calculation regarding the sample size needed for exploration of correlation between Xe-129 MRI indices and the severity of patient dyspnoea in COPD as this is the first time they will have been compared. However, in our development work with this technology, we have shown that in 24 patients with COPD, regional lung MR imaging identifies more lung regions affected by emphysema (defined from apparent diffusion coefficient > 0.34 cm^2/s, an MRI index of the presence of emphysema) than does the severity of emphysema quantified by thoracic CT (defined from a lung attenuation <960 HU, a standard CT index). The percentage of lung voxels affected by emphysema on MRI was 38% (IQR 20-80), and the percentage of lung voxels affected by emphysema on CT was 10% (IQR 6-19, $p<0.01$ Mann-Whitney). Recent correlation work has shown clinically significant correlations between measured lung function and MRI functional lung imaging in COPD in sample size of 22 subjects[30].

10.1 Number of participants

It is not possible to perform a detailed power calculation regarding sample size because this is the first time regional lung imaging with hyperpolarized Xe-129 has been formally investigated. We aim for 100 patients to be recruited and complete baseline studies, of whom a substantial proportion will complete the, longitudinal 1 year follow-up and optional salbutamol intervention components of the study. This sample size enables sub-set analysis, such as comparing patients with different disease severity. To date most studies employing hyperpolarized Xe-129 have been on animal models and healthy volunteers and have reported it as a viable functional lung imaging modality. The sample size proposed for this trial will be sufficient to be informative in our planned analyses and direct future investigation.

10.2 The level of statistical significance

This is a study to provide both an atlas of ventilation, diffusion and perfusion in patients with COPD, and to determine sensitivity to decline in lung function with long-term follow-up. A p value of <0.05 and a correlation coefficient of > 0.5 will be regarded as significant.

10.3 Criteria for the Termination of the Trial

The study will terminate following full recruitment and completion of follow-up of at least 30 patients, or should a significant safety concern emerge. More than 30 patients will be observed provided this is found to be a useful technique for regional lung imaging in these patients.

10.4 Procedure for Accounting for Missing, Unused, and Spurious Data

Efforts to measure all data as outlined in the trial protocol will be made. If a patient provides data from only one Xe-129 MRI scan, this will be included in analysis for

mapping, but not for longitudinal evaluation. The data will be reviewed by the research team, to confirm that it is robust, and any deviation from expected results will be reviewed to determine if this is due to scanning error, or other artefact.

10.5 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Exploratory analyses in addition to those above may be conducted to further the development of the technique. These will be described in full in the final study report. Patient observations will cease at the time of termination of the trial.

10.6 Inclusion in Analysis

All evaluable participants will be included in the analysis. Participants will be deemed not to be evaluable if baseline scans are not assessable.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The Sponsor University of Oxford (CTRG) is responsible for monitoring the trial in order to verify that:

(4) The rights and wellbeing of the human subjects are protected
(5) The reported trial data are accurate, complete and verifiable from source documents
(6) The conduct of the trial is in compliance with the approved protocol and GCP

Monitoring will be performed in accordance with the applicable SOPs and monitoring plan. These will include activities designed to:

- Initiate the study and check progress periodically
- Review the essential trial documentation and study data collected
- Conduct source document verification if required
- Identify any issues and address their resolution
- Confirm proper closure of the clinical study site at the end of the clinical phase

The Competent Authority (MHRA) may conduct an Inspection to assure compliance with the protocol and ICH-GCP. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and host institution agree to allow auditors/inspectors direct access to all relevant documents and to allocate his/her time and the time of his/her staff to discuss the findings and any relevant issues.
The study data will be held for at least five years. Thereafter the data will be archived according to the Radiology Department and Oxford University policies.

13. ETHICS

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

13.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.5 Other Ethical Considerations

This type of imaging research raises several ethical issues. The proposed hyperpolarised Xe-129 MR will be provided in addition to any routine scans. Additional imaging may or may not add any information that will benefit the individual patient. These issues will be addressed as follows:

- There is minimal exposure to ionizing radiation. There is a small but quantifiable risk associated with administration of iodinated contrast. All additional exposure will be formally justified.
- Patient Information Sheets will be provided describing the study and what it involves in non−technical language, as far as possible.
- Written informed consent will be obtained in an appropriate setting. The study will be introduced to the patient by a member of staff already known to the patient although consent will be performed by one of the study investigators.
- Potential hazards of hyperpolarised Xe-129, gadolinium-enhanced lung MRI, ventilation/perfusion nuclear medicine scans and CT will be explained to the patient.
  Patient inconvenience will be minimised by scheduling study assessments to suit patient preference as far as possible. Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate.
- Patients will be informed that findings from the study may not benefit them directly but will be used to improve future assessment of lung function and monitoring of treatment responses.
- One of the risks of undergoing lung imaging is the new finding of a possible or definite serious condition other than COPD, such as a pulmonary nodule of uncertain significance, or a lung cancer. In such incidences the findings would be discussed with the patient, and further investigation and/ or treatment arranged locally, in keeping with usual best clinical practice, and not impinged upon by enrolment in this study.
- It is acknowledged that intensive and rigorous investigation may emphasise the presence of COPD to patients and their families, and its impact on their lives.

Study investigators will be empathetic to this occurrence, and there will be the opportunity to discuss any such issues that arise with the investigators, or other clinicians who are experienced in the management of COPD.

13.6 Informed Consent

The patient information leaflets describe the objectives of the research, the procedures involved and any discomfort or risks that relate to participation in the study. All patients are given copies of the information leaflets and have sufficient time to read these, ask any questions arising from the written information or accompanying verbal information and to discuss the possibility of taking part in the research with family members or health professionals. The information leaflet confirms that patients or subjects are free to withdraw from the study at any time and for any reason without any effects on future medical care and without being obliged to give a reason for their withdrawal. Consent withdrawal is discussed in section 3.4. Written informed consent is obtained by means of patient dated signature, signature of the person who presented the informed consent and, if different, the Chief Investigator (or named Co-Investigator). A copy of the signed informed consent is given to the patient, a copy is filed in the patients' notes and a copy is stored securely in the coordinating centre (ORTU).

13.7 Patient Confidentiality

Confidentiality and patient data protection are vital elements of this study. The investigators take responsibility for this. All participating patients give informed consent for their data to be stored on the research database. The methods for achieving security of this electronic database are described in section 14. All paper documents recording patient information will be stored securely in compliance with the Data Protection Act. Patients give informed consent to be registered with the NHS Information Centre, requiring their identifying data only to be passed on for this purpose.

14. DATA HANDLING AND RECORD KEEPING

Security of data collection, handling, transfer, storage and use is a key component of studies such as this, and central to the continuing integrity and viability of these research projects. The study database will be bespoke and hosted on the University of Oxford server with services provided through the University's Information Management Services Unit (IMSU). The IMSU Virtual Server service provides dependable and resilient application servers for research groups utilising industry-leading software and high-quality server and storage components. The server and database are protected by a number of measures including anti-virus and anti-spyware applications, firewalls, encryption technology and permissions. The database will be backed up on a daily basis. ORTU remains the owner of all data stored on the database in relation to this study.

Data will be collected in the Oxford Centre for Respiratory Medicine and Radiology department by staff trained in high quality handling and secure procedures. Paper CRFs will be stored in a designated locked filing cabinet in a locked room and protected against damp and fire. All other information and data will be stored electronically. The security of the database is maintained by the following principles:

1) Access to clinical and personal data in the database is limited to the Chief Investigator and named research staff and clinicians (typically research fellows, research nurses and data entry staff). Access is secure, requiring personal usernames and passwords. The research individuals will maintain confidentiality and be trained in database care.

2) All patient identifiable data (name, hospital number and address) are stored in one database and all clinical and research data are stored in a physically separate database. The databases are linked by specific study patient identifiers. When data is downloaded for research purposes patient identifiable data will not be included and individuals are only identified by their study number, although age and sex can be downloaded.

The number of staff who have access to all fields of the database is limited. It is also permitted for appropriate regulating bodies, ethics committees and a limited number of collaborating researchers (who may or may not be Oxford based) to have direct access to the source documents and data.

15. INSURANCE/ INDEMNITY

Indemnity and/ or compensation for negligent harm arising specifically from an accidental injury, for which the University is legally liable as the Research Sponsor, will be covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

Indemnity and/ or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the Research Subject's participation in the study for which the University is the Research Sponsor, will be covered by the University of Oxford.

The funder for this study will be the Oxford Biomedical Research Centre. GE Healthcare has provided support for the trial by installing the Xenospin hyperpolariser and providing modifications to the Churchill Hospital MRI scanner to enable reading of the hyperpolarized xenon signal.

The Chief Investigator is responsible for applying for local Trust management approval to conduct the trial in accordance with local arrangements and policies. Trust approval and indemnity must be confirmed in writing before patient recruitment commences on the Investigator site.

16. PUBLICATION POLICY

The final results of the trial will be submitted to a peer-reviewed journal for publication. Authors will be the Chief Investigator, the Co-Investigators and other members of the research team. No data on individual patients will be published without the permission of the Chief Investigator. Authors shall acknowledge that the study was sponsored by the University of Oxford and performed with the support of the NIHR Oxford Biomedical Research Centre.

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Appendix 7: Data analysis from patients with COPD

Data analysis from COPD patient OXF0093

Table A7.1: Lobar imaging parameters acquired from OXF0093

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	45.31	60.94	76.58	61.75	61.38
HP ^{129}Xe-MRI$_R$ % ventilated volume	36.01	47.05	59.52	48.33	48.83
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.047	0.053	0.054	0.045	0.064
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.046	0.053	0.055	0.045	0.064
QCT-derived % LAA	22.7	22.6	24.1	22.3	34.9
QCT-derived Pi10 (mm)	5.1	4.6	6.6	5.7	5.6
NM-Q SPECT relative % perfusion	20.2	15.2	37.4	15.6	11.6

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

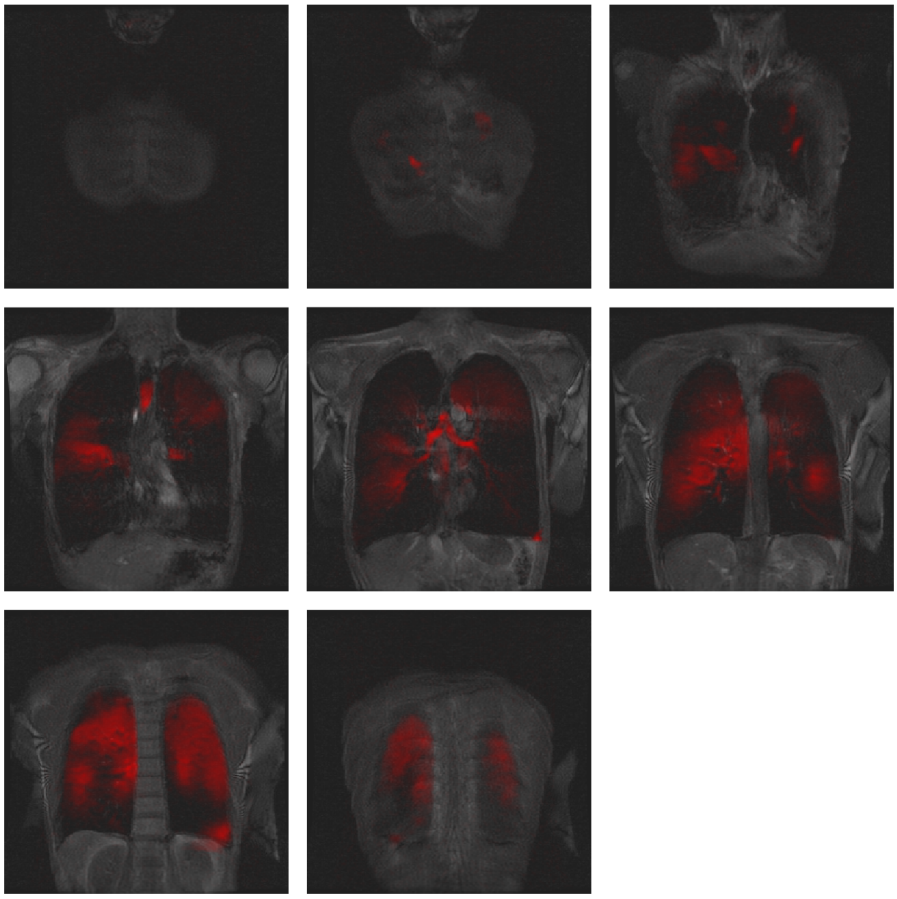


Figure A7.1a: Coronal HP ^{129}Xe-MR ventilation imaging co-registered to proton MRI from COPD patient OXF0093. Co-registration to proton MRI enables the lung boundaries to be defined.

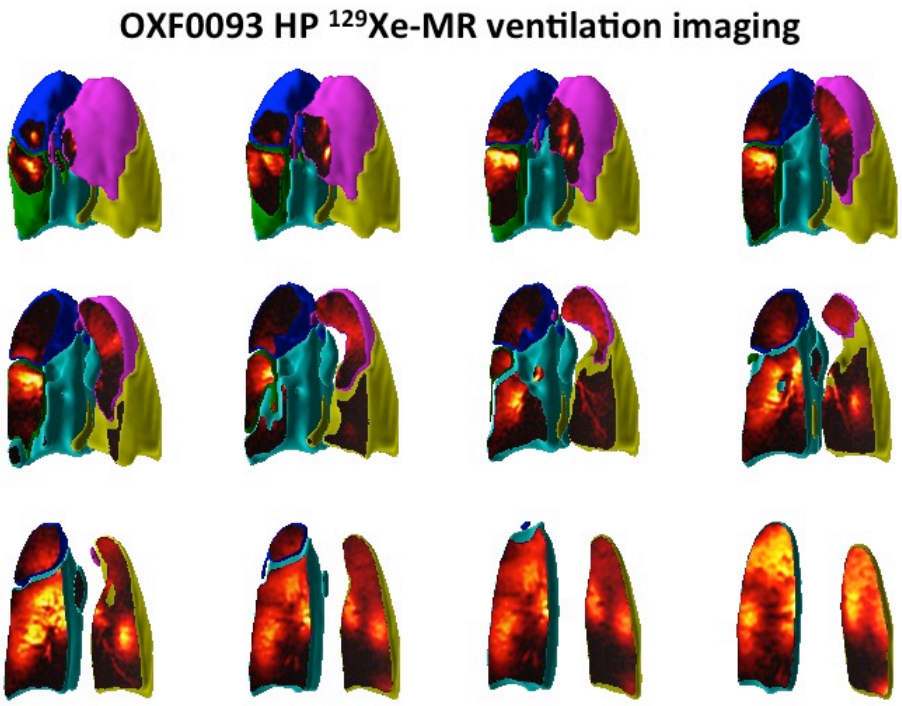


Figure A7.1b: 3-D HP ^{129}Xe-MRI lobar ventilation imaging from OXF0093. Low signal intensity in the right upper lobe (blue) indicates relatively reduced ventilation compared with the middle (green) and left upper (pink) lobes where signal intensity and therefore ventilation is greater.

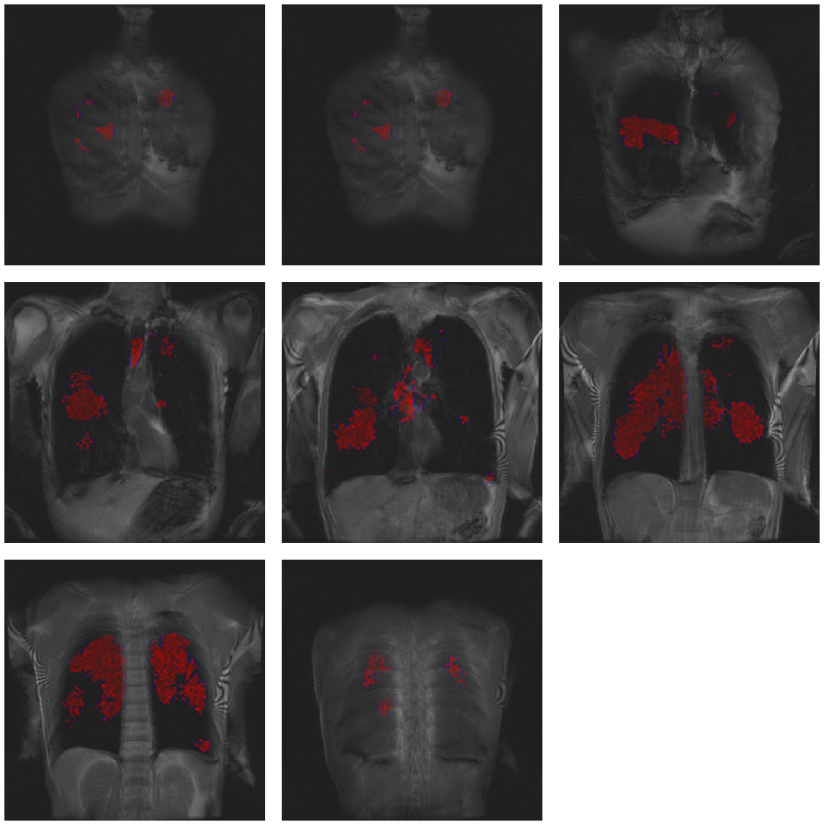


Figure A7.1c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from COPD patient OXF0093.

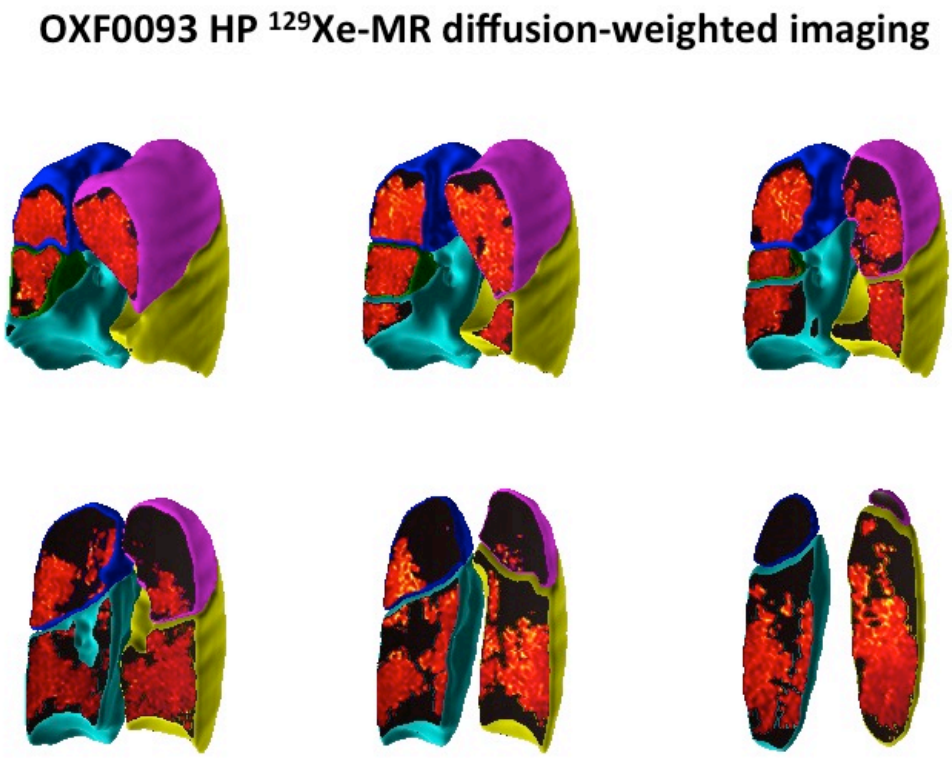


Figure A7.1d: 3-D HP ^{129}Xe-MRI lobar diffusion-weighted imaging from OXF0093. Regions of increased signal intensity correspond to higher HP ^{129}Xe-MRI ADC values and indicate emphysematous tissue destruction.

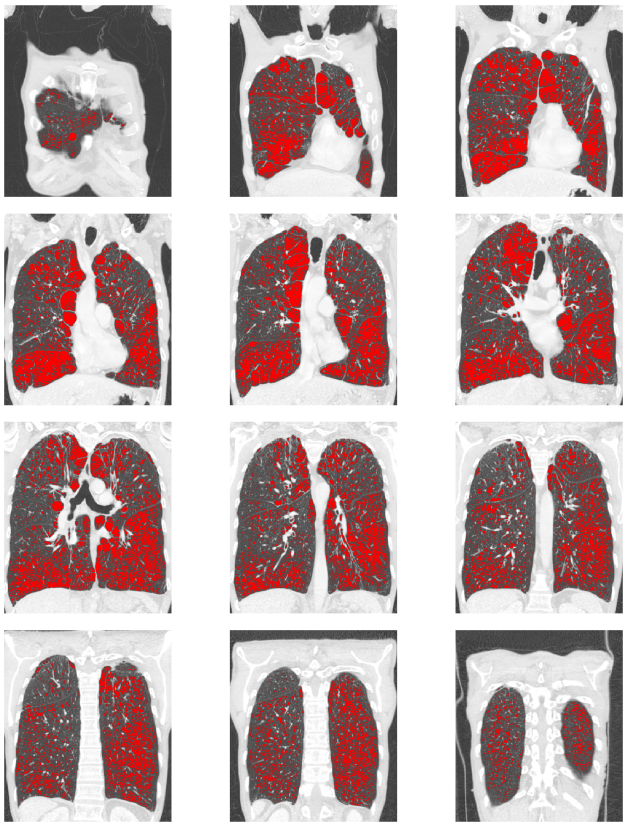


Figure A7.1e: QCT-derived emphysema (% LAA) from COPD patient OXF0093. Red areas correspond to regions with attenuation less than -950 HU. Images show moderate emphysema with relative homogeneous distribution.

Data analysis from COPD patient OXF0127

Table A7.2: Lobar imaging parameters acquired from OXF0127

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	65.44	96.22	56.67	95.08	78.26
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.063	0.050	0.054	0.058	0.052
QCT-derived % LAA	23.1	14.1	26.4	16.4	16.7
QCT-derived Pi10 (mm)	4.9	4.5	4.8	5.3	6.6
NM-Q SPECT relative % perfusion	16.1	10.3	19.9	33.5	20.1

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

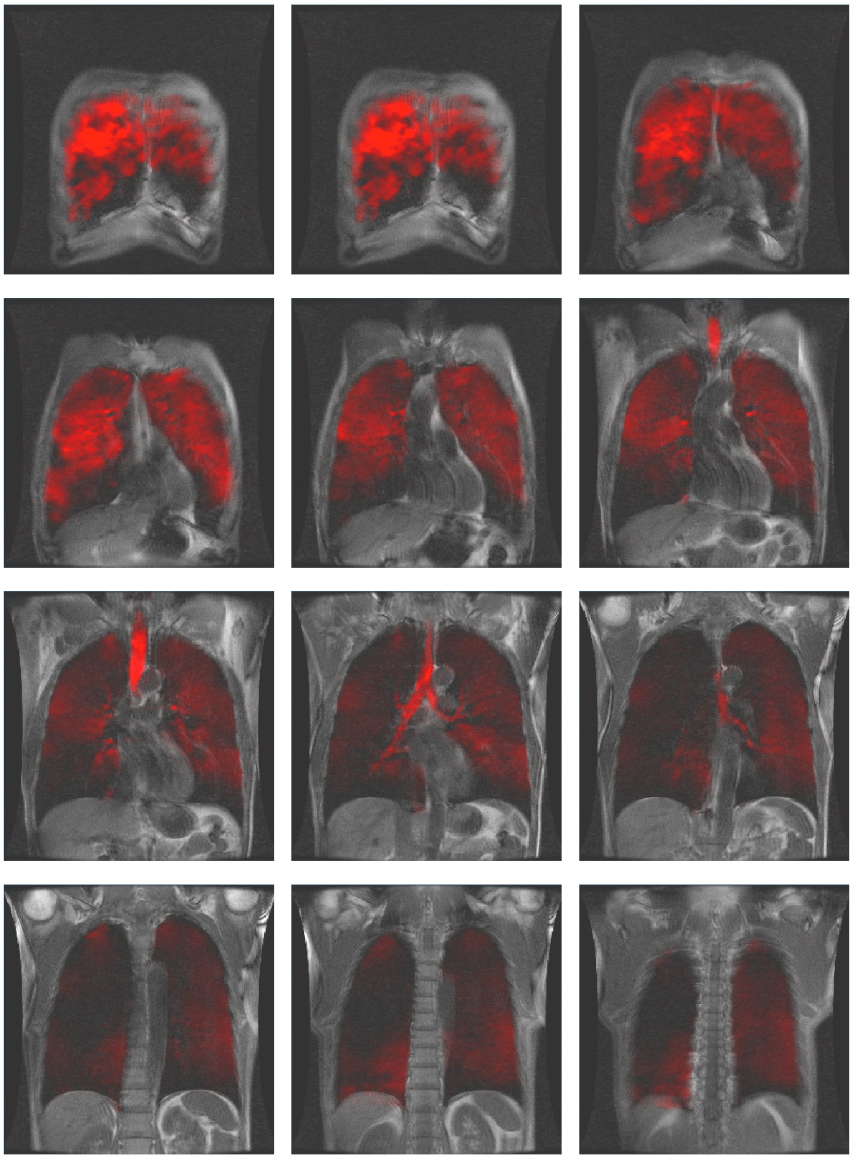


Figure A7.2a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI from OXF0127. Regions of increased signal intensity correspond to good ventilation. The proton MRI enables lung boundaries to be determined which is particularly relevant in the lower lobes where ventilation defects are present.

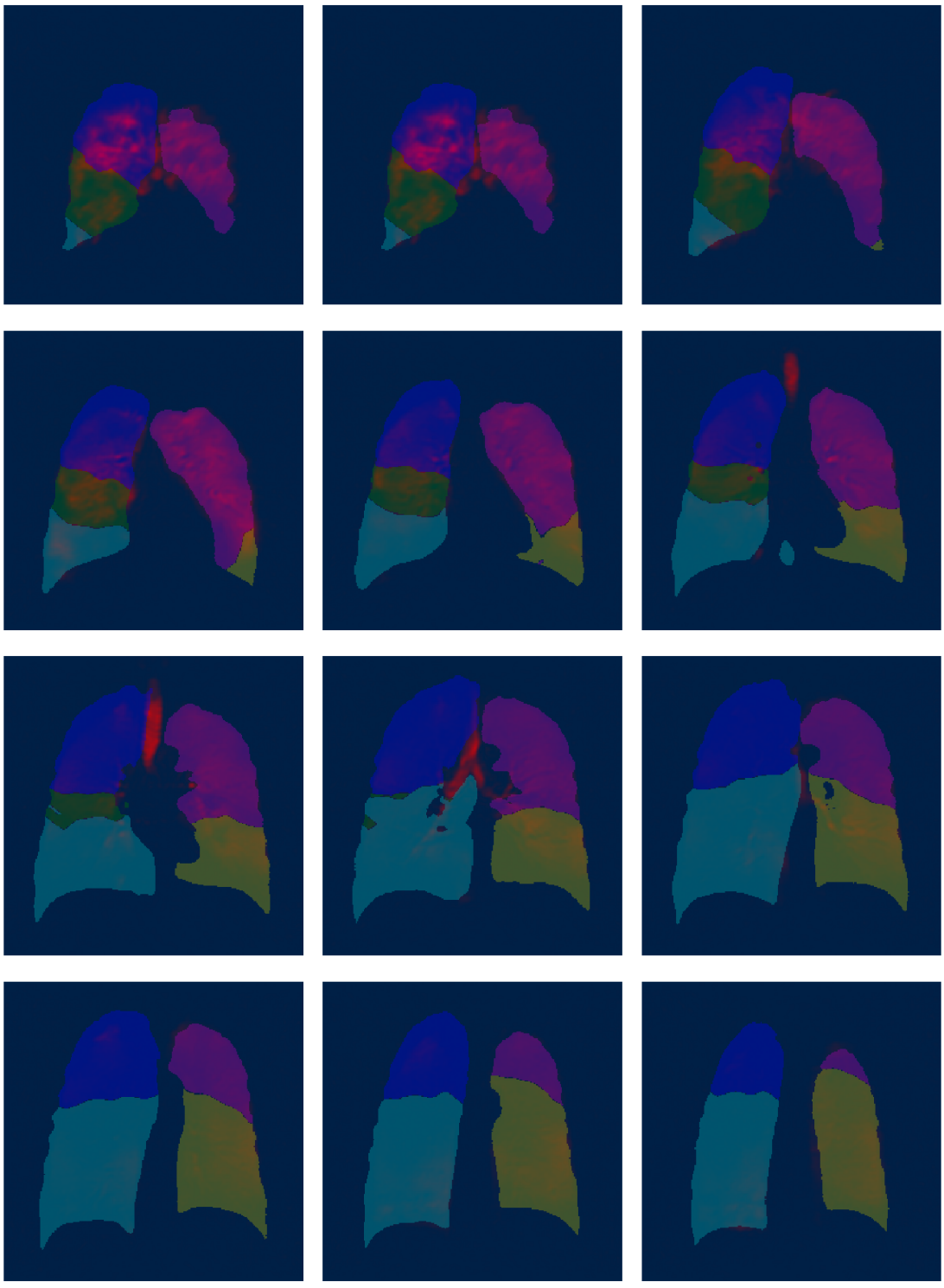


Figure A7.2b: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0127. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

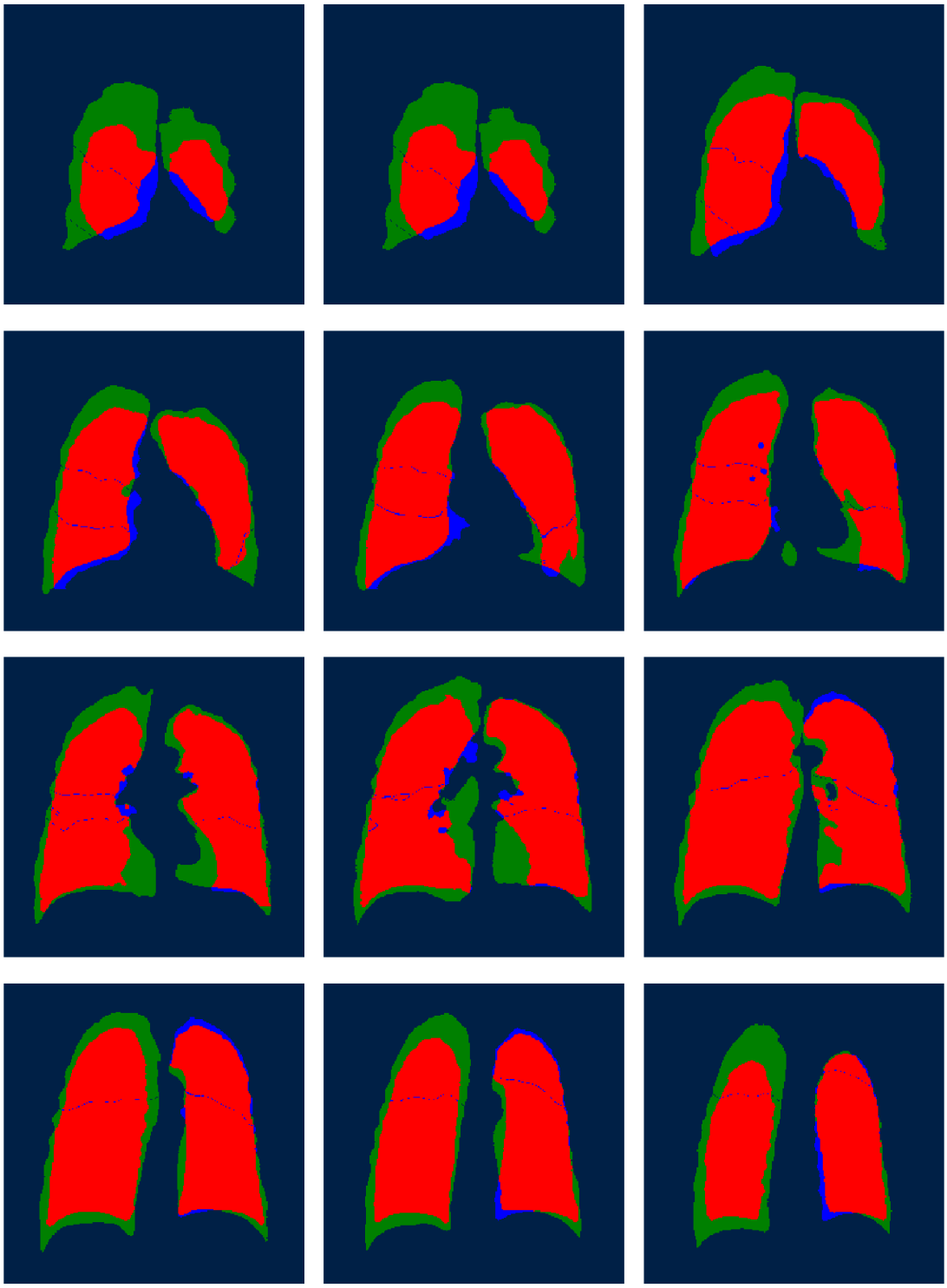


Figure A7.2c: Coronal co-registered lung masks from multi-modality imaging acquired from COPD patient OXF0127. Lung masks are from HP ^{129}Xe-MR ventilation imaging (blue), proton MRI (green) and QCT (red).

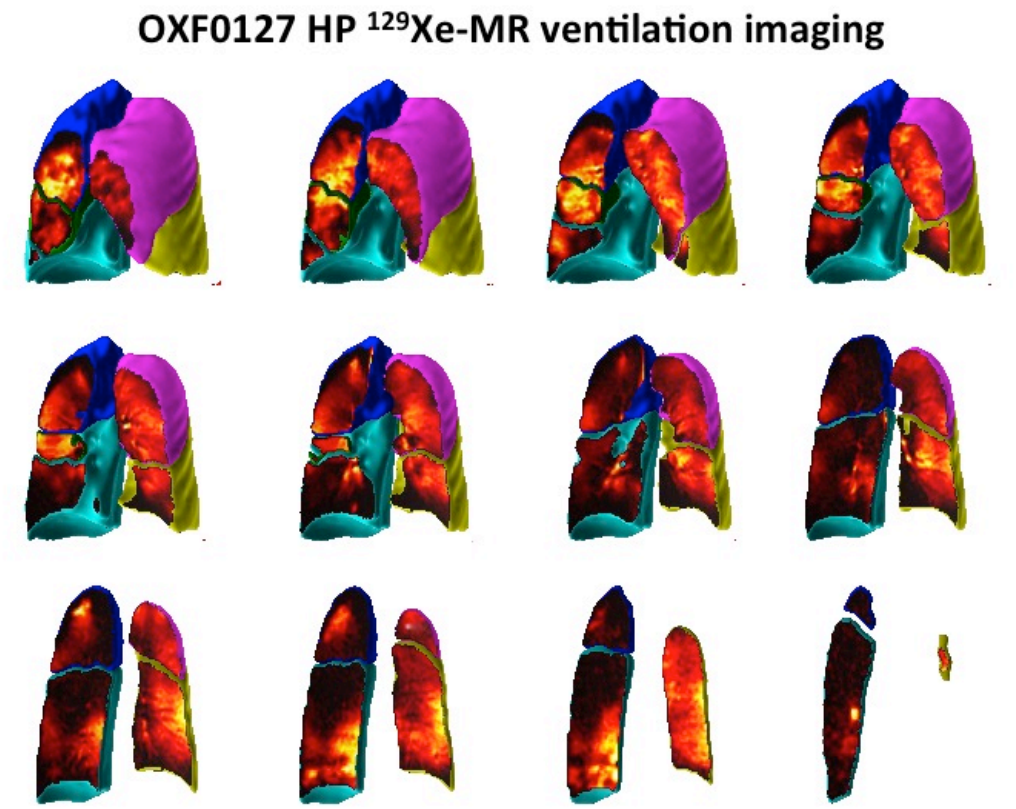


Figure A7.2d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0127. Low signal intensity is appreciated in the right upper (blue) and lower (cyan) lobes posteriorly indicating poor ventilation.

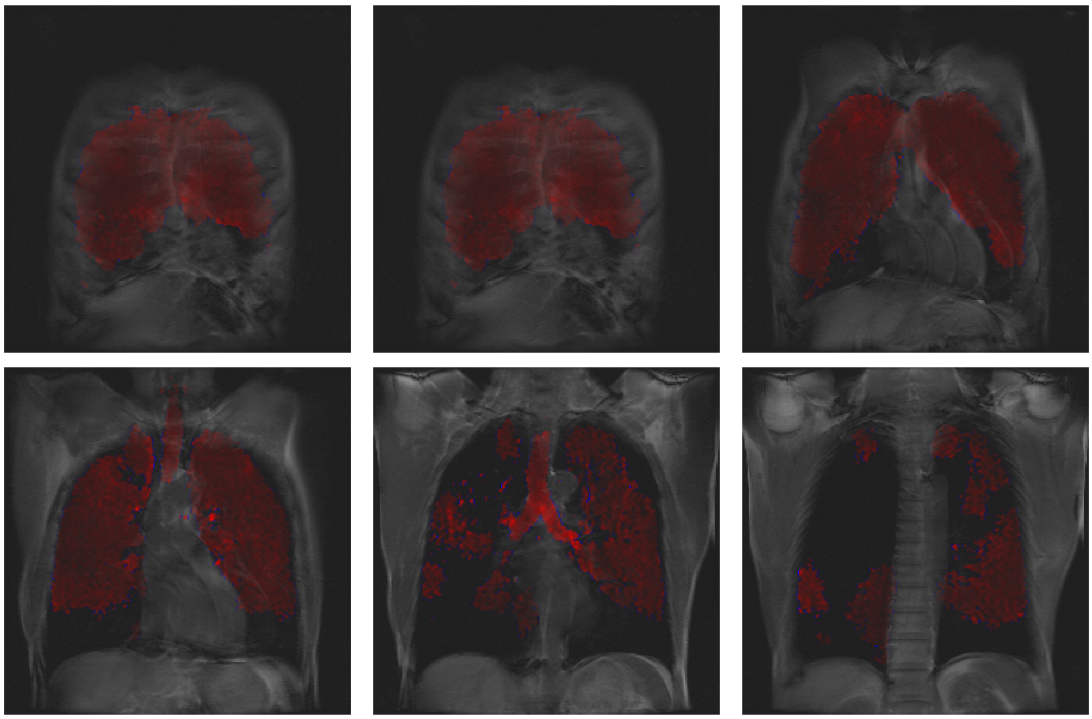


Figure A7.2e: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0127.

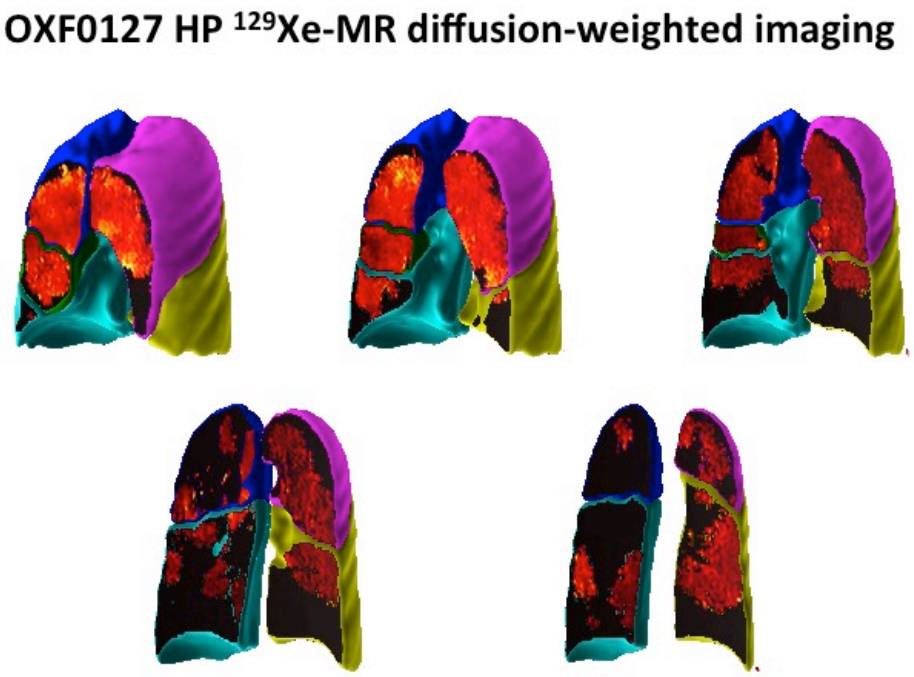


Figure A7.2f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0127. There is increased signal intensity in the right upper (blue) lobe corresponding to higher ADC values and increased emphysema.

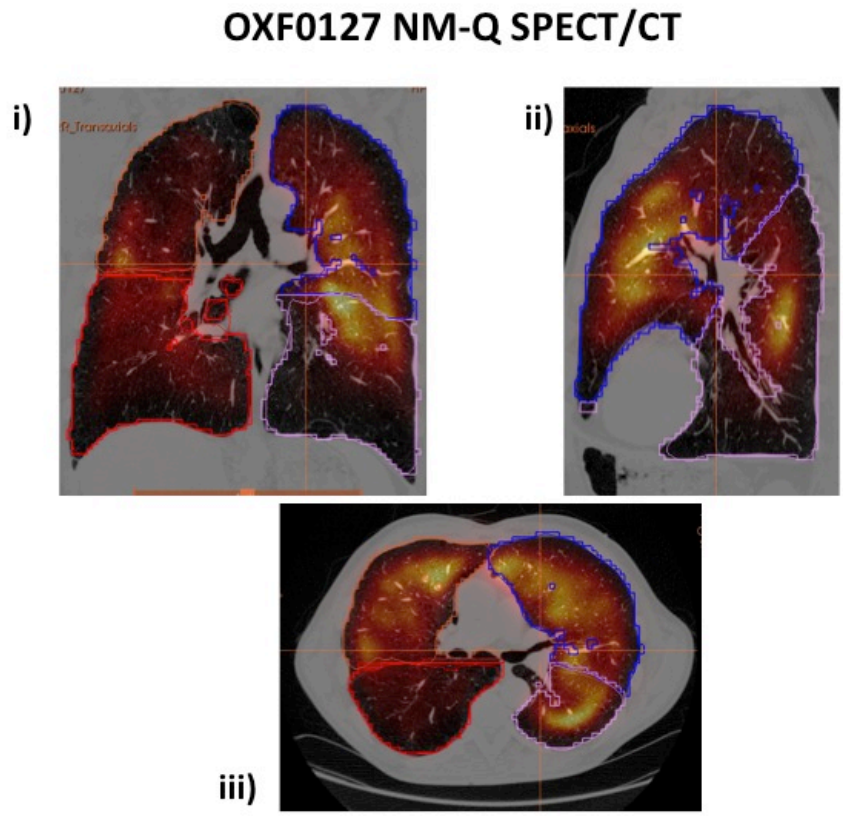


Figure A7.2g: Selected NM-Q SPECT/CT images from OXF0127. Images are in the i) coronal, ii) sagittal and iii) axial plane.

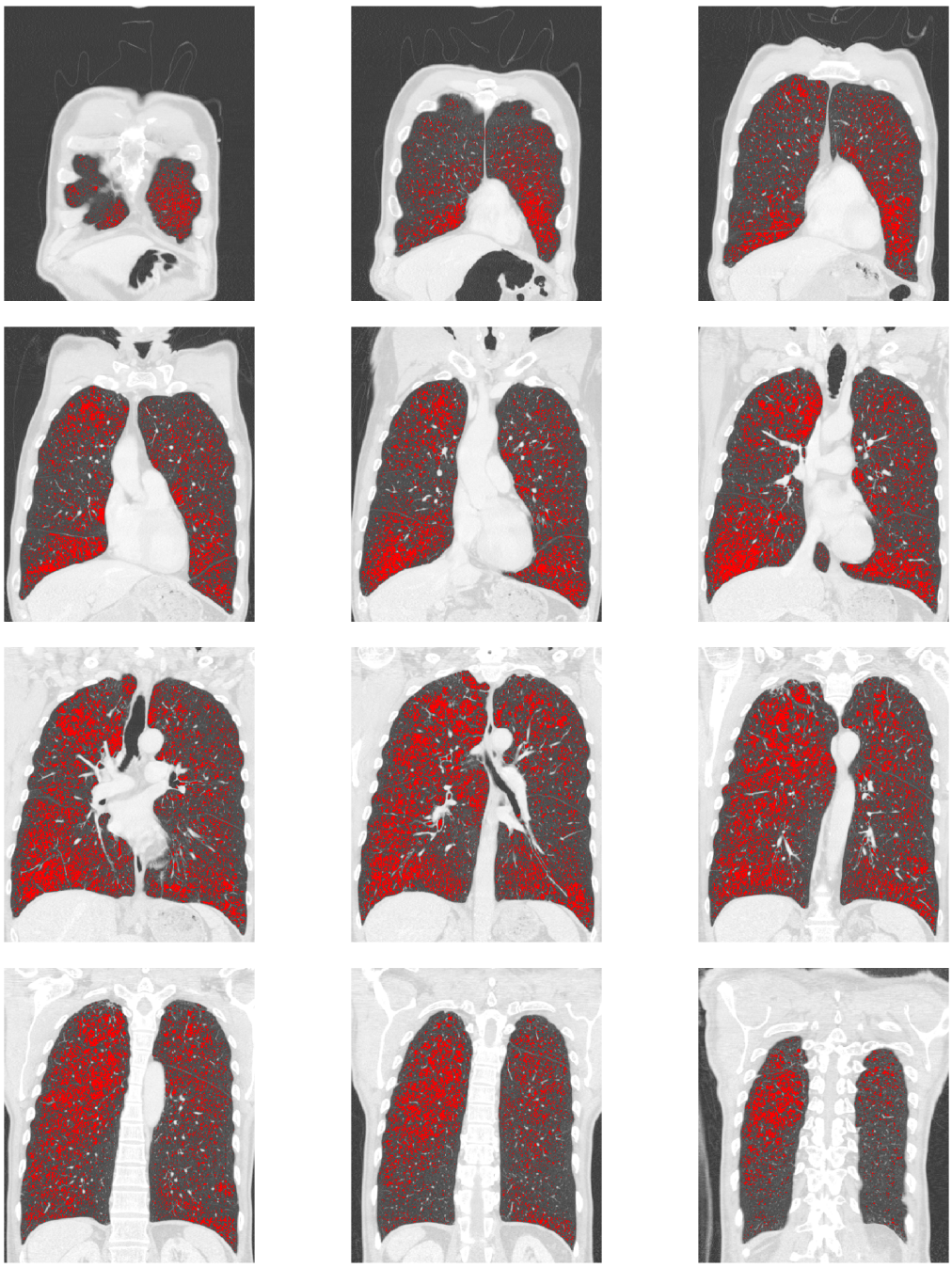


Figure A7.2h: QCT-derived emphysema (% LAA) in COPD patient OXF0127. Red areas correspond to regions with attenuation less than -950 HU. Images show moderate emphysema with no lobar predominance.

Data analysis from COPD patient OXF0131

Table A7.3: Lobar imaging parameters acquired from OXF0131

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	79.77	87.29	91.28	77.15	87.07
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.067	0.052	0.049	0.065	0.054
QCT-derived % LAA	24.9	15.3	7.9	27.9	20.8
QCT-derived Pi10 (mm)	4.7	4.5	4.9	4.0	3.8
NM-Q SPECT relative % perfusion	17	6.3	36.2	18.7	21.8

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

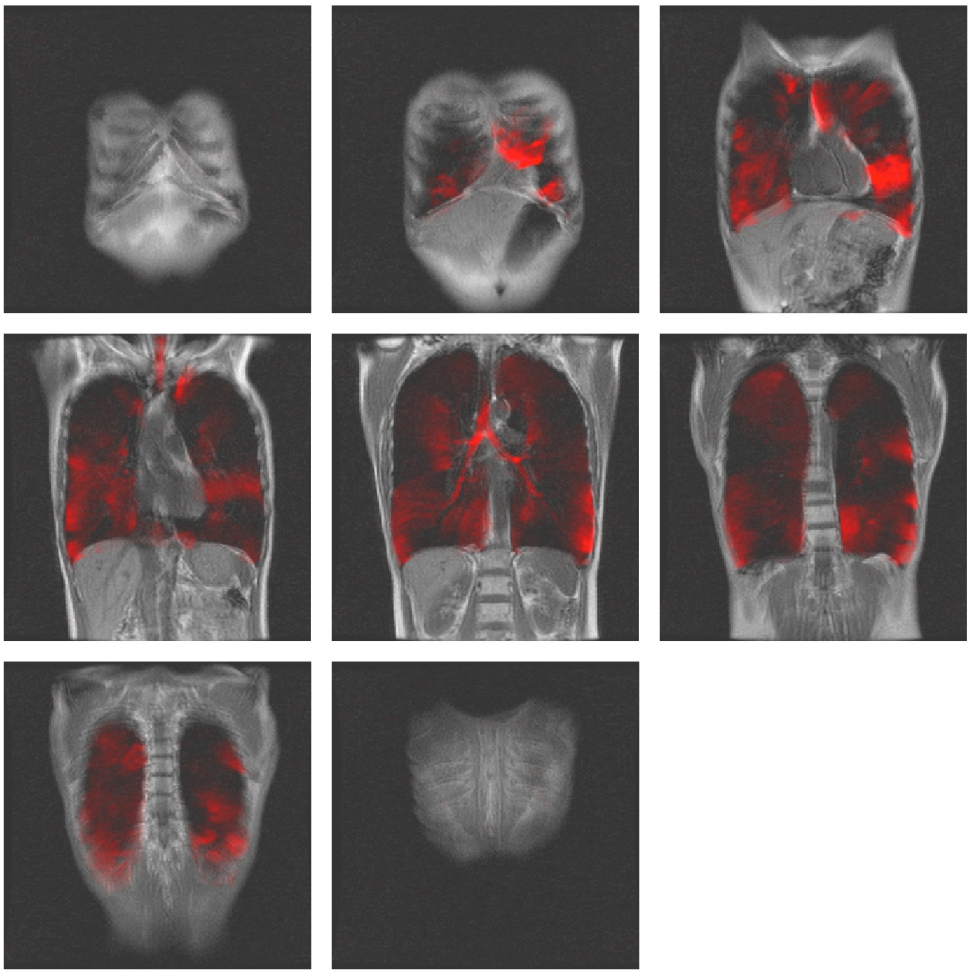


Figure A7.3a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0131. Co-registration to proton MRI enables the lung boundaries to be defined.

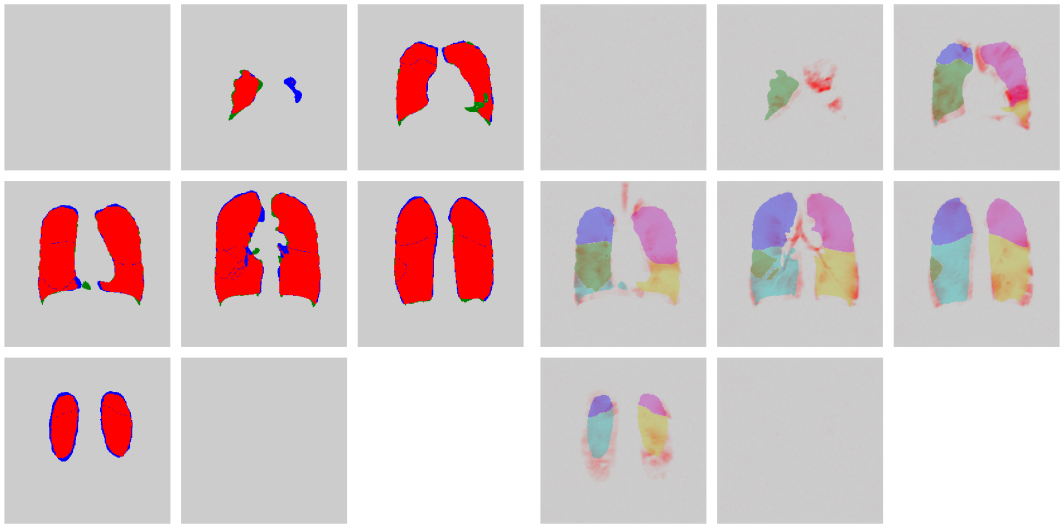


Figure A7.3b: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0131. Lung masks are from HP ^{129}Xe-MR ventilation imaging (blue), proton MRI (green) and QCT (red).

Figure A7.3c: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0131. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

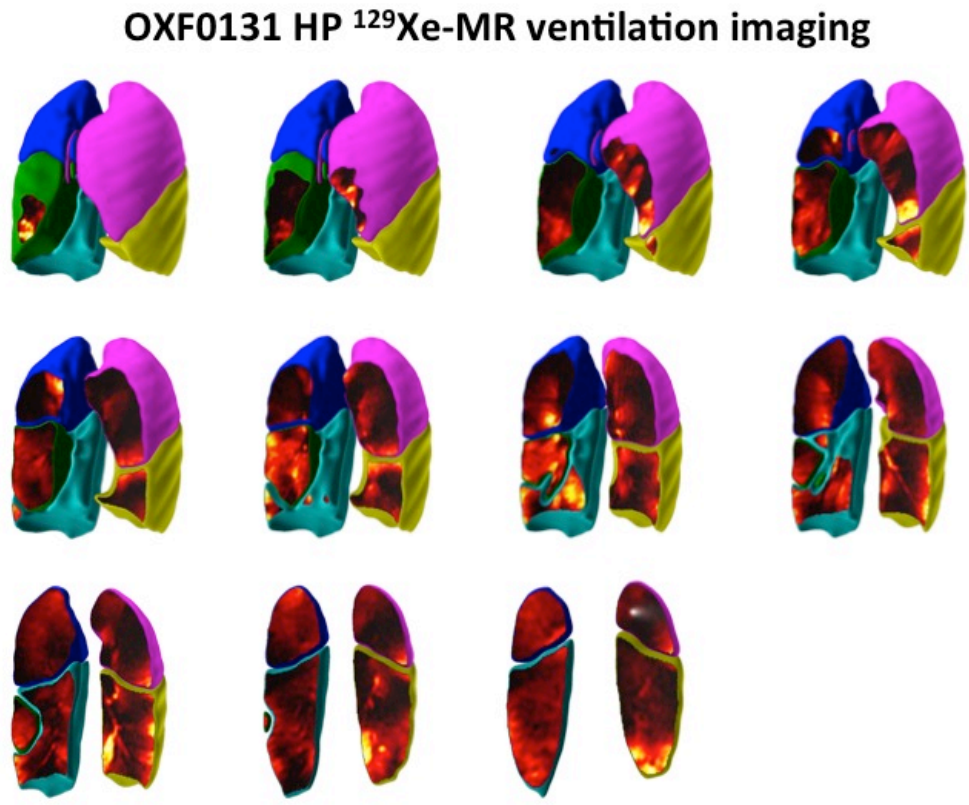


Figure A7.3d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0131. Low signal intensity is appreciated in the right upper (blue) and middle (green) lobes anteriorly in keeping with poor ventilation.

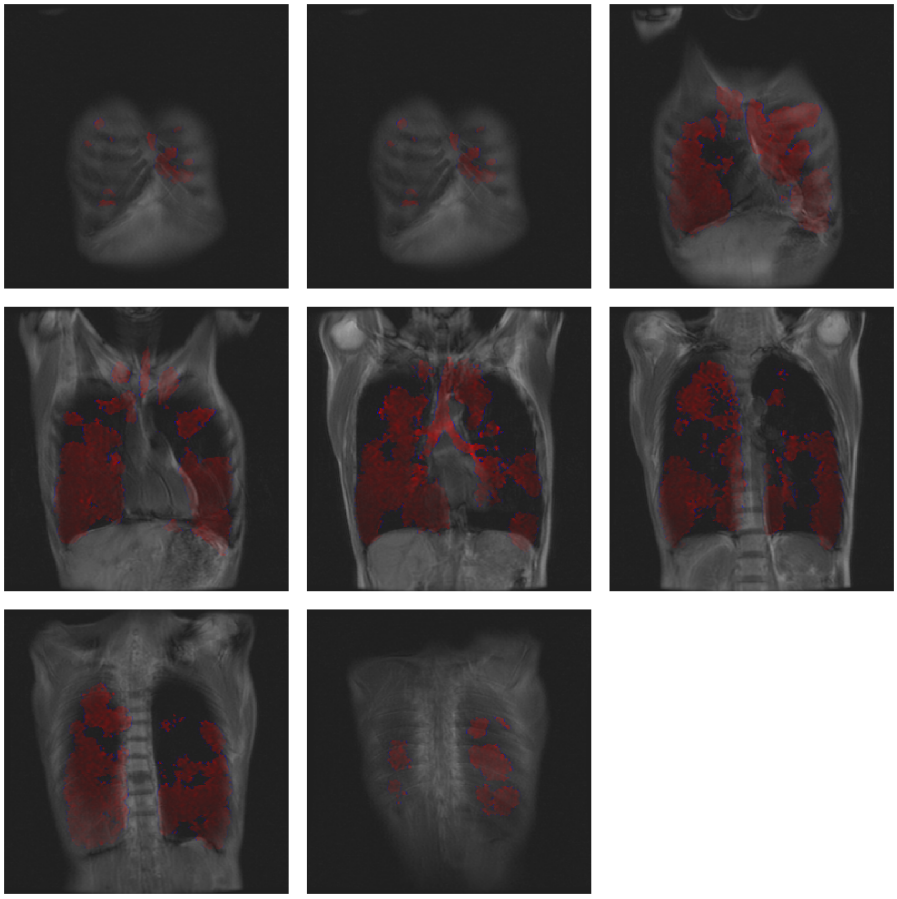


Figure A7.3e: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0131.

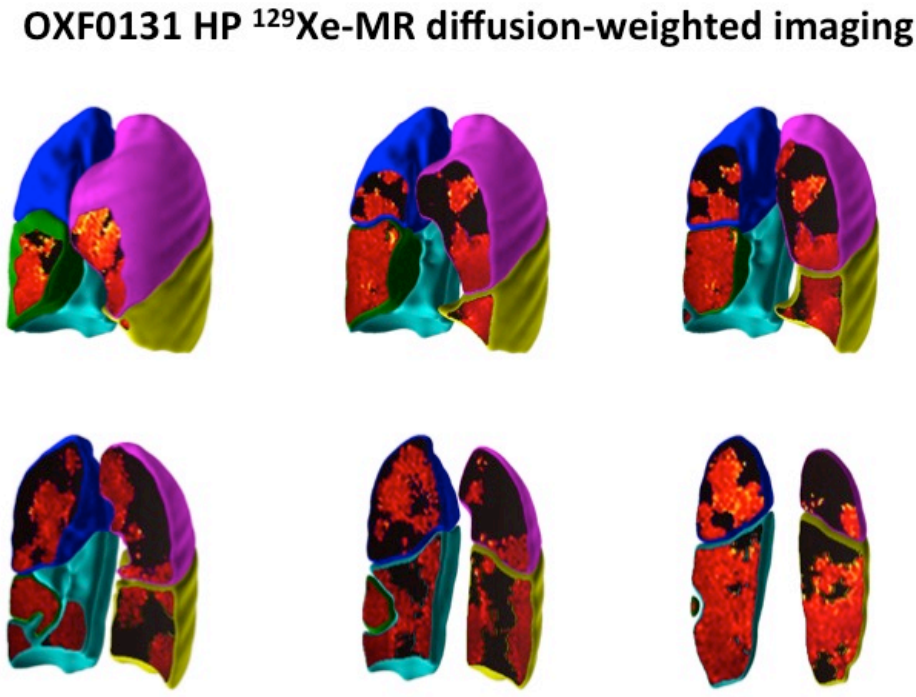


Figure A7.3f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0131. There is increased signal intensity in the left upper (pink) lobe anteriorly corresponding to elevated ADC values and increased emphysema in this region.

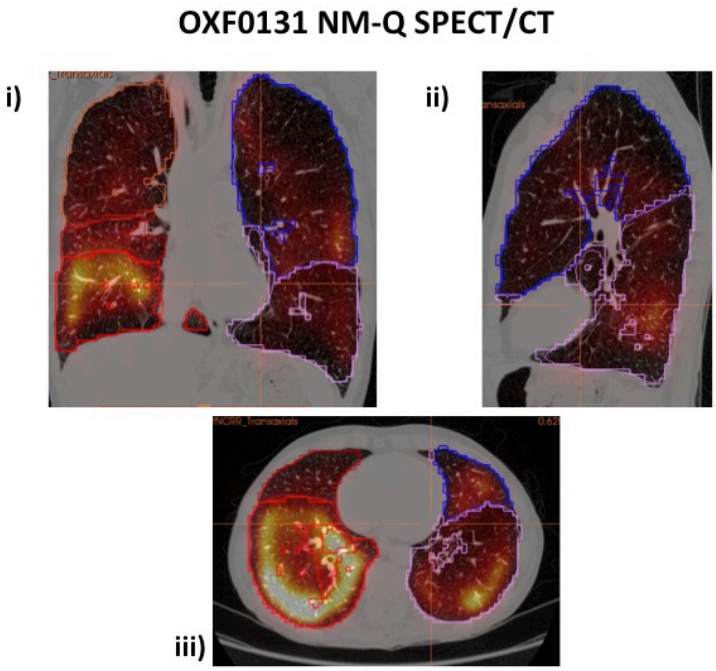


Figure A7.3g: Selected NM-Q SPECT/CT images from OXF0131. Images are in the i) coronal, ii) sagittal and iii) axial plane.

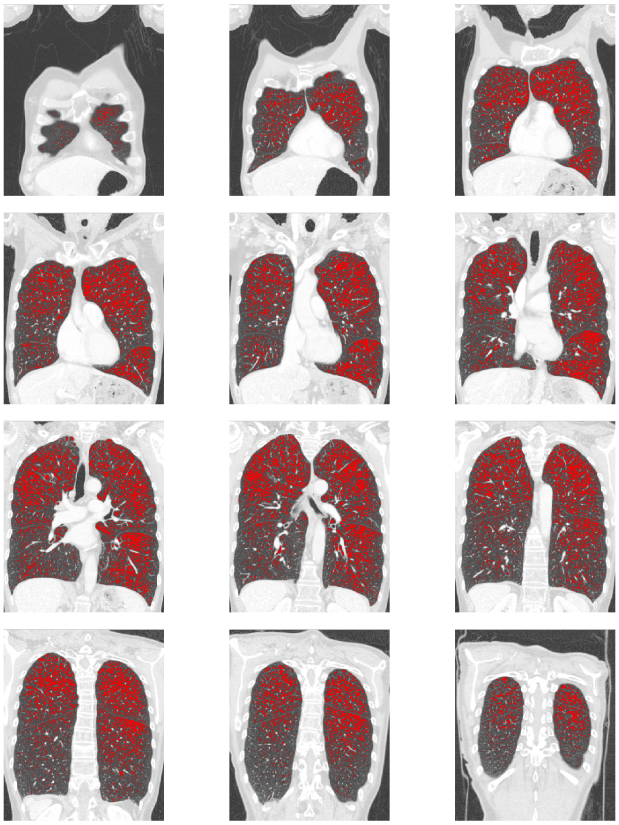


Figure A7.3h: QCT-derived emphysema (% LAA) from patient OXF0131. Red areas correspond to regions with attenuation less than -950 HU. Images show moderate emphysema with upper lobe predominance on the right but homogeneous distribution on the left.

Data analysis from COPD patient OXF0121

Table A7.4: Lobar imaging parameters acquired from OXF0121

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	96.11	95.68	95.45	96.42	96.42
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.034	0.032	0.029	0.029	0.029
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.036	0.033	0.031	0.033	0.028
QCT-derived % LAA	33.7	14.4	33.1	27.1	8.1
QCT-derived Pi10 (mm)	6.0	6.3	7.7	6.1	6.3
NM-Q SPECT relative % perfusion	33.2	10.8	8.6	34.5	12.9

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility
RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

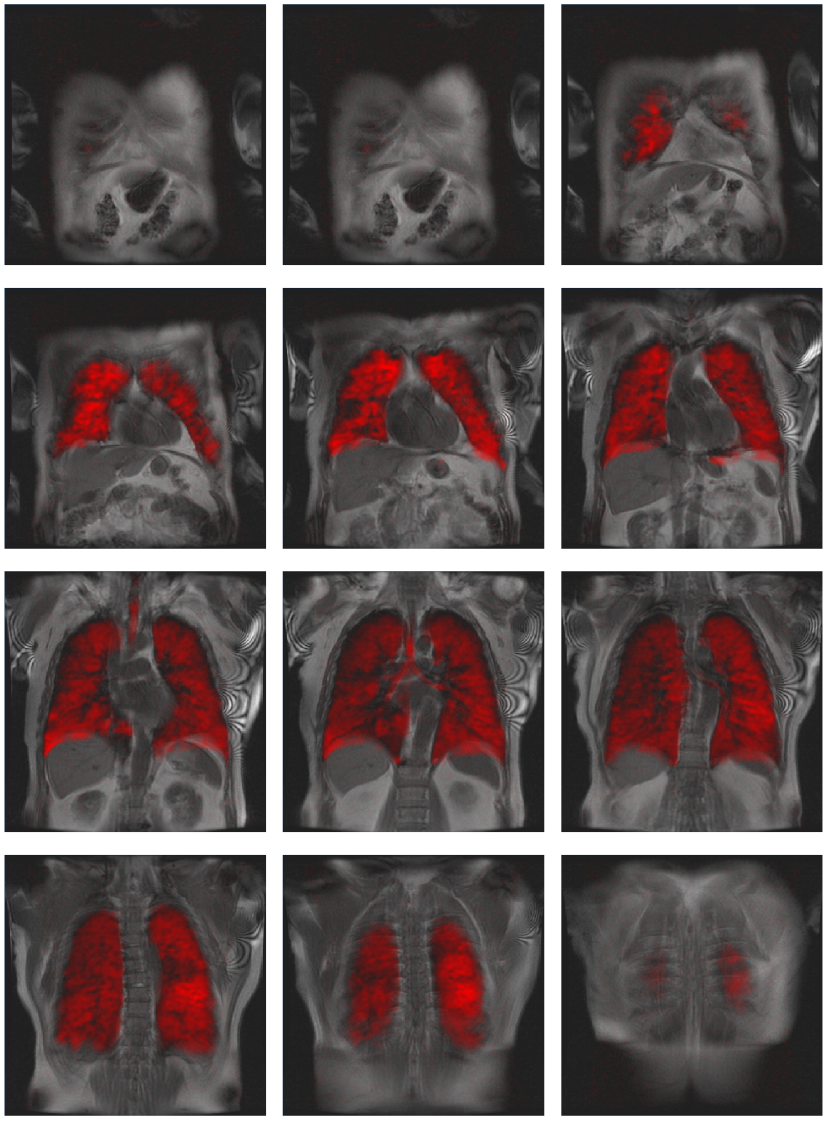


Figure A7.4a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0121. Co-registration to proton MRI enables the lung boundaries to be defined.

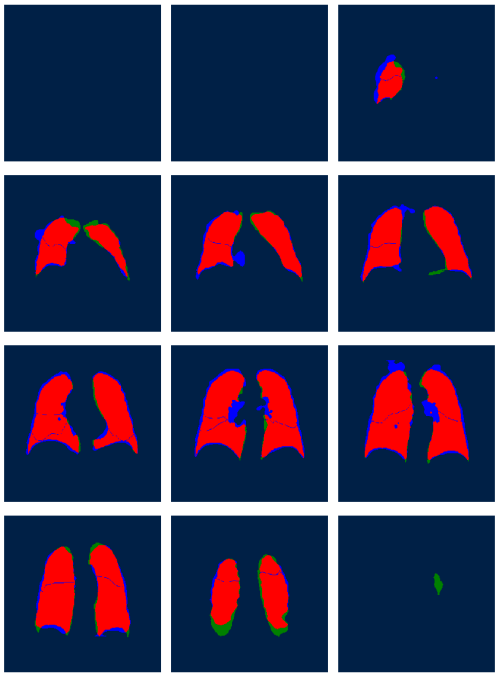


Figure A7.4b: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0121. Lung masks are from HP ^{129}Xe-MR ventilation imaging (blue), proton MRI (green) and QCT (red).

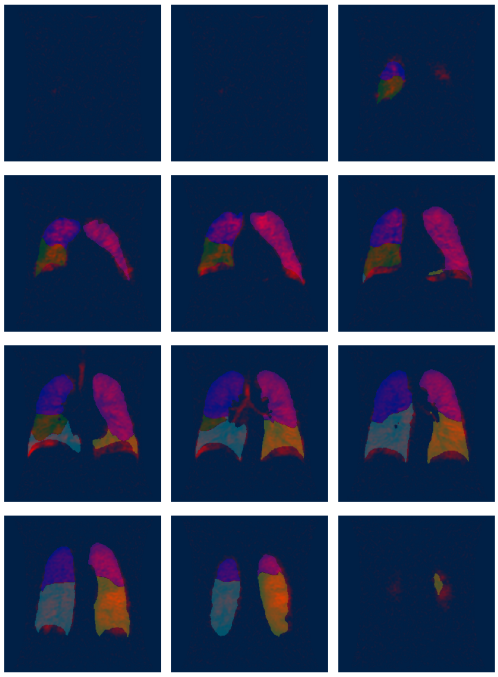


Figure A7.4c: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0121. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

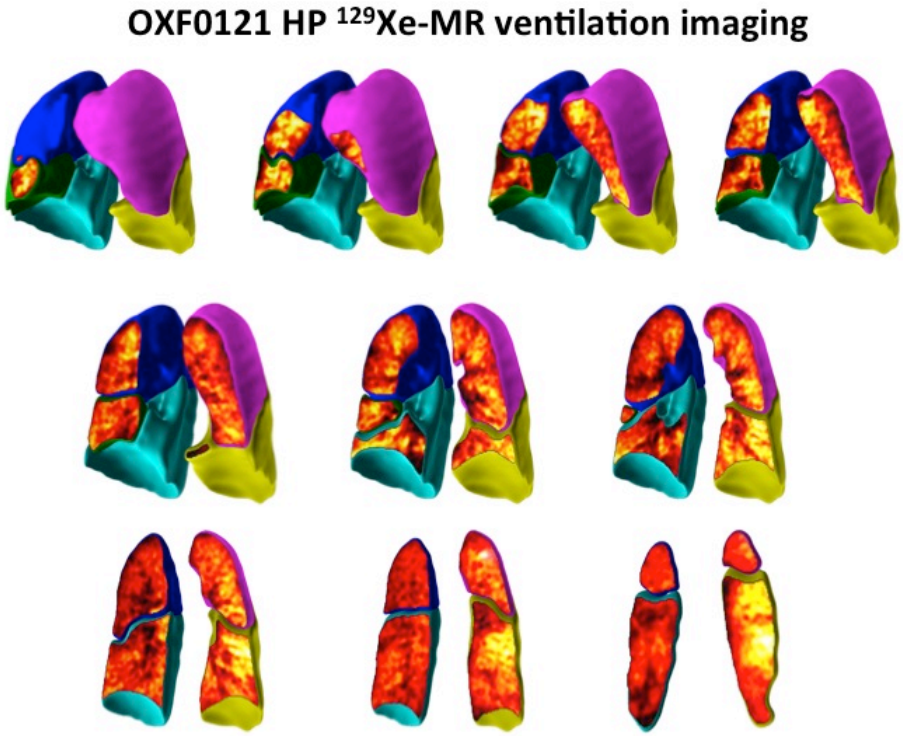


Figure A7.4d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0121. Images show relatively good ventilation signal in all lobes with small peripheral ventilation defects, most marked in the right lung.

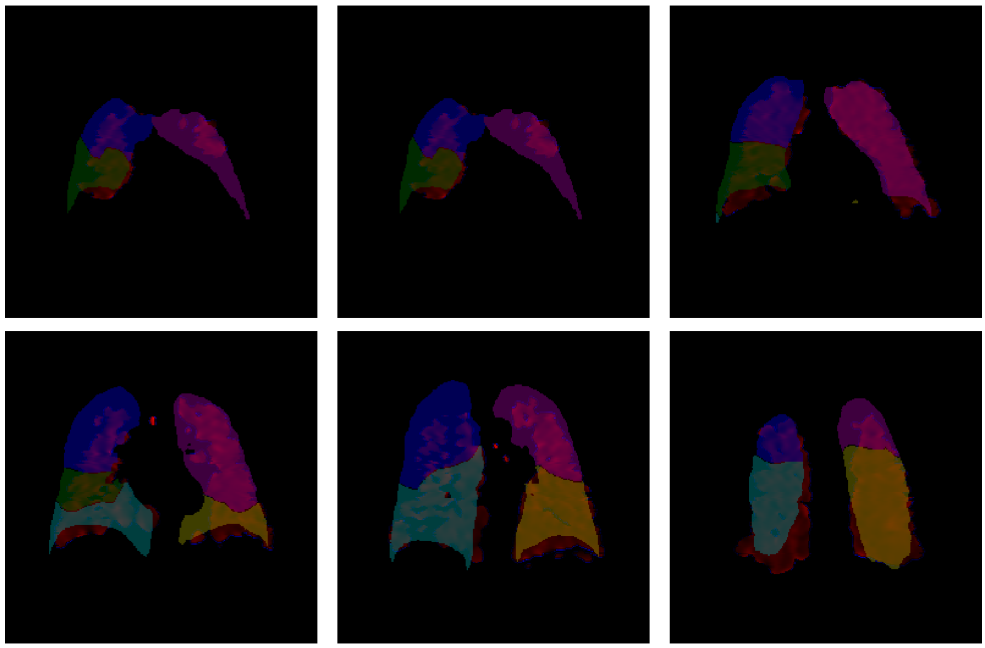


Figure A7.4e: Non-rigid co-registration of HP ^{129}Xe-MR diffusion-weighted imaging and QCT from OXF0121. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MRI ADC values.

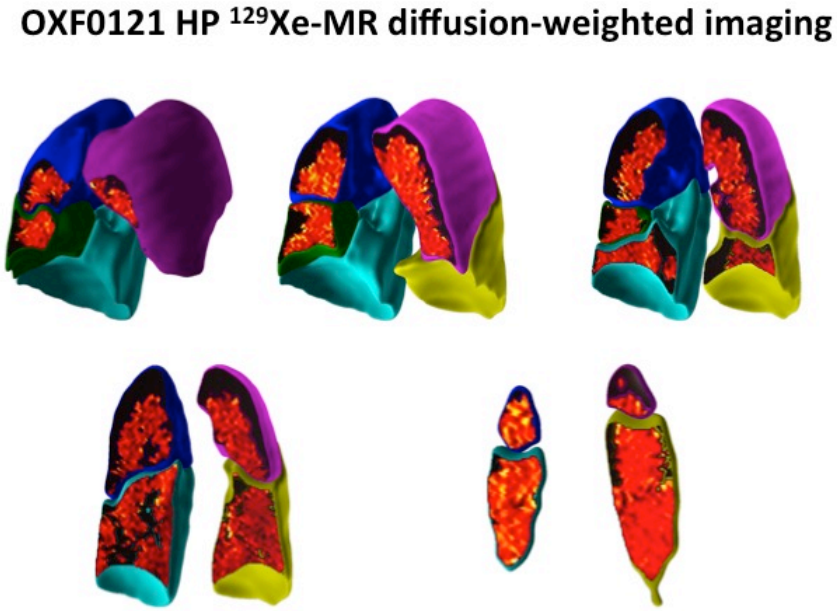


Figure A7.4f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0121. Images show increased signal in the right upper and lower lobes posteriorly corresponding to elevated ADC values and increased emphysema in these regions.

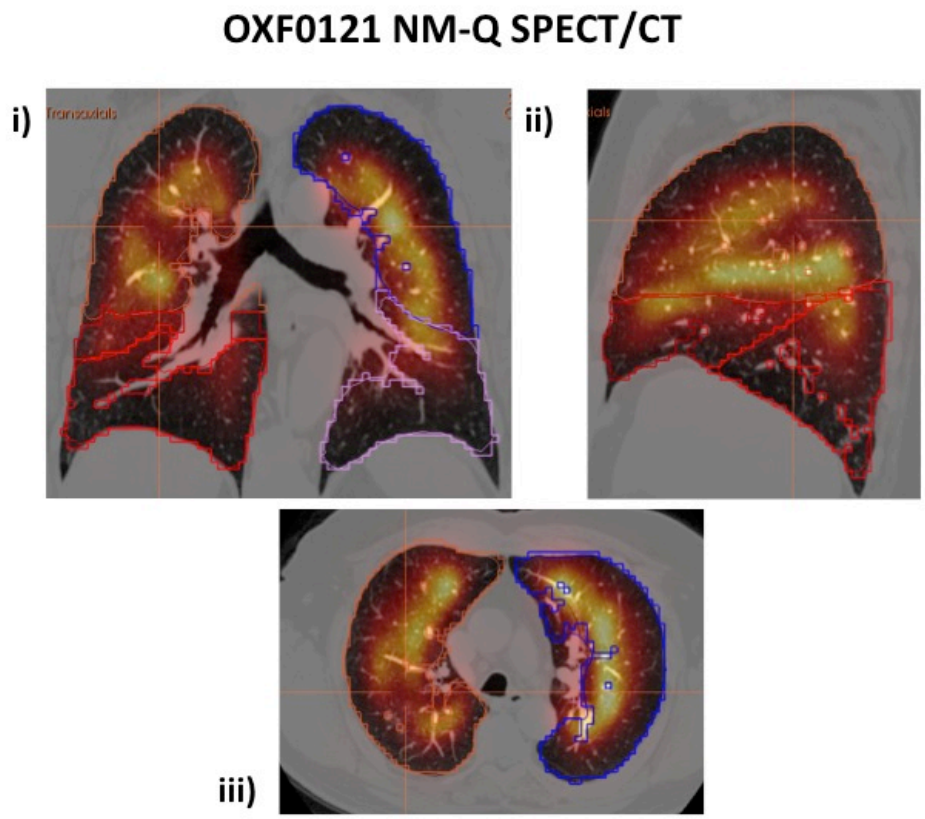


Figure A7.4g: Selected NM-Q SPECT/CT images from OXF0121. Images are in the i) coronal, ii) sagittal and iii) axial plane.

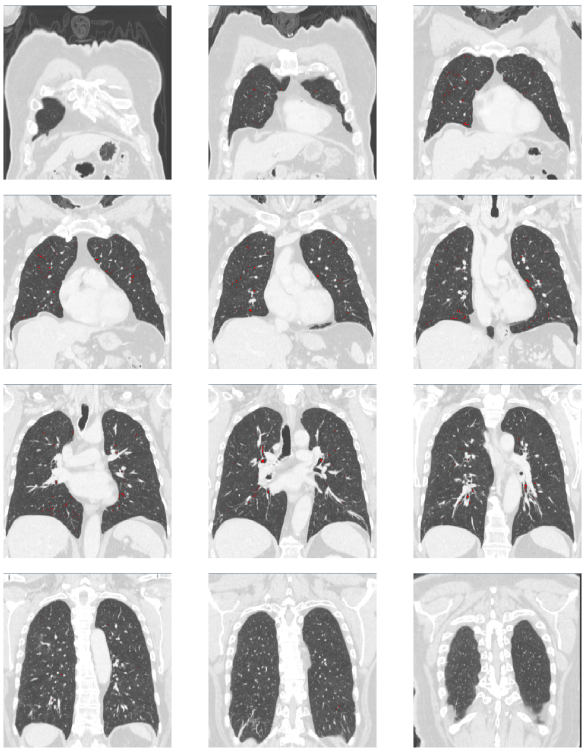


Figure A7.4h: QCT-derived emphysema (% LAA) for patient OXF0121. Red areas correspond to regions with attenuation less than -950 HU. Images show very mild emphysema.

Data analysis from COPD patient OXF0104

Table A7.5: Lobar imaging parameters acquired from OXF0104

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	53.74	90.37	84.79	87.48	89.19
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.072	0.073	0.080	0.066	0.070
QCT-derived % LAA	37.9	24.5	39.8	33.4	
QCT-derived Pi10 (mm)	6.9	7.2	6.7	7.4	5.1
NM-Q SPECT relative % perfusion	4.5	10.1	31.1	7.9	46.4

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

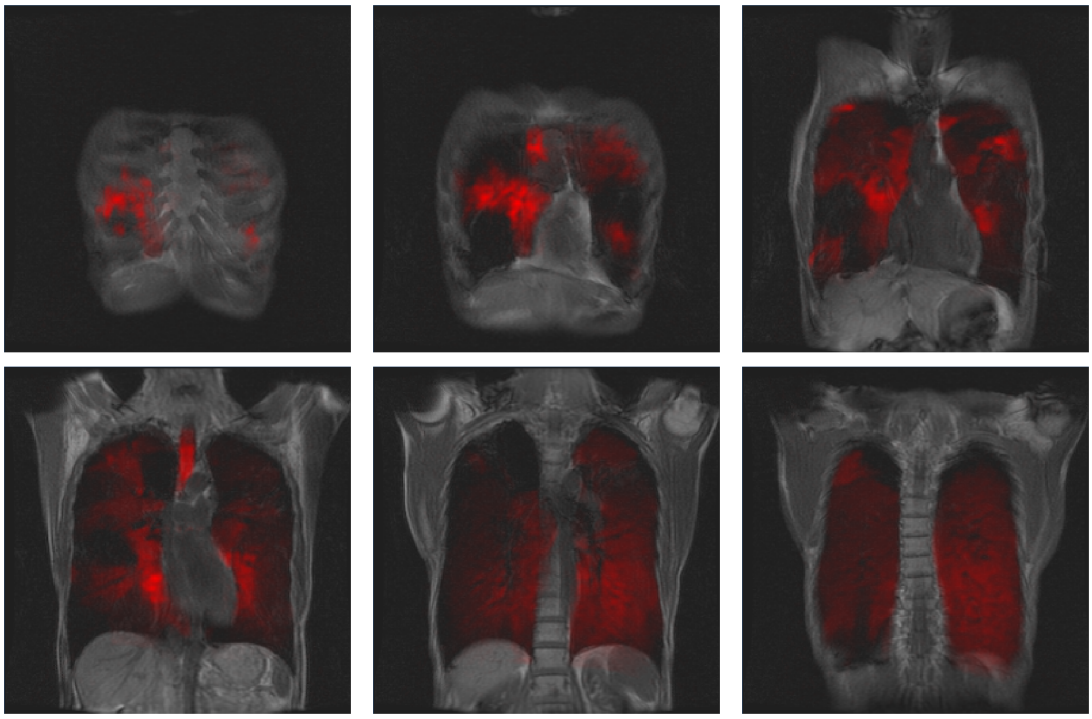


Figure A7.5a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0104. Co-registration to proton MRI enables the lung boundaries to be defined.

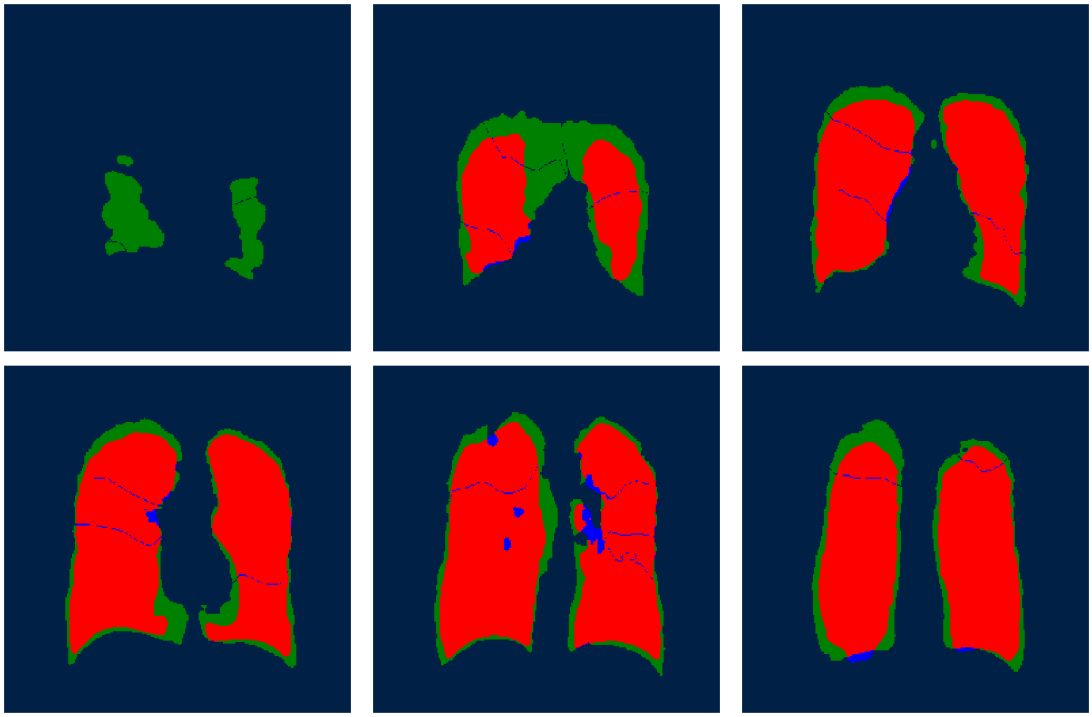


Figure A7.5b: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0104. Lung masks are from HP ^{129}Xe-MR ventilation imaging (blue), proton MRI (green) and QCT (red).

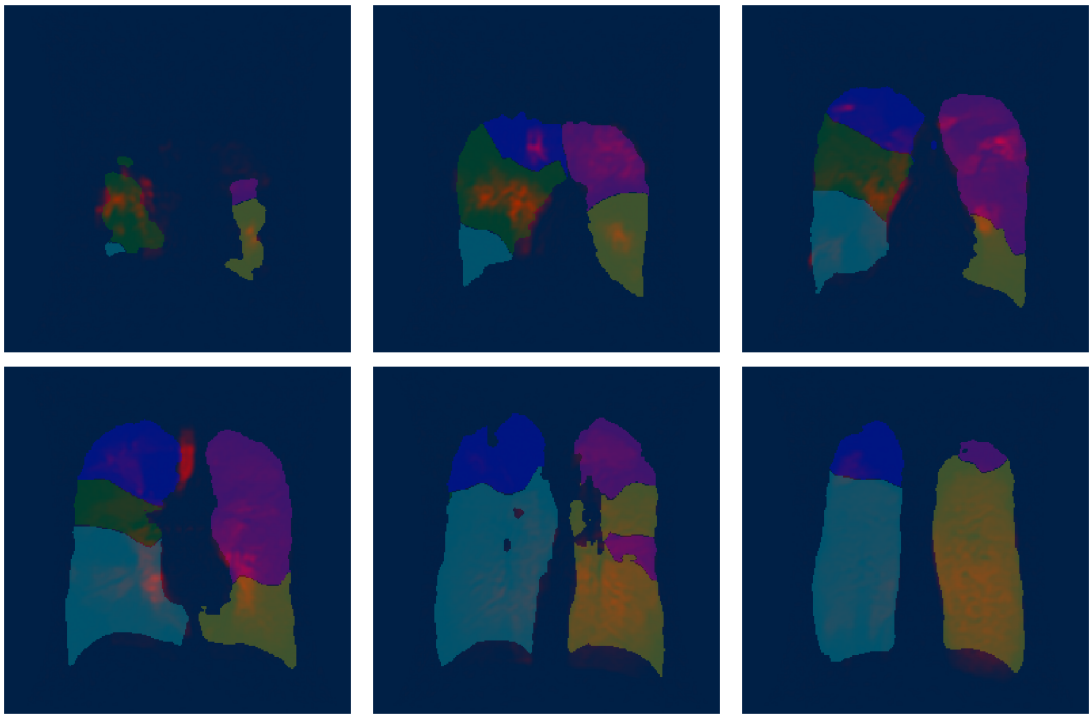


Figure A7.5c: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0104. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

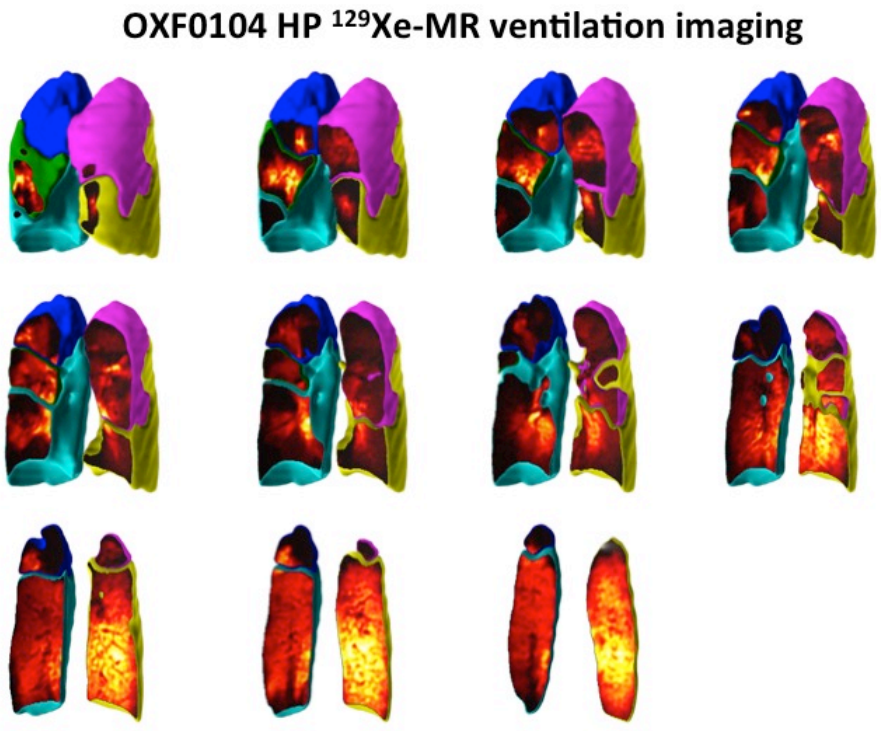


Figure A7.5d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0104.
Ventilation defects are present in the right upper (blue), middle (green) and lower (cyan) lobes anteriorly.

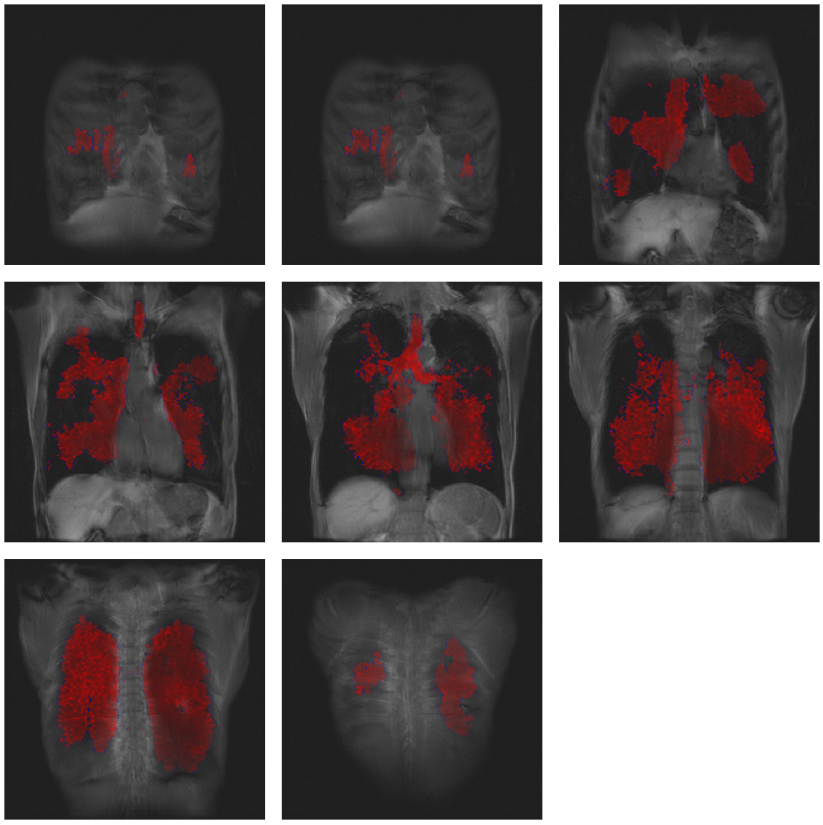


Figure A7.5e: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0104.

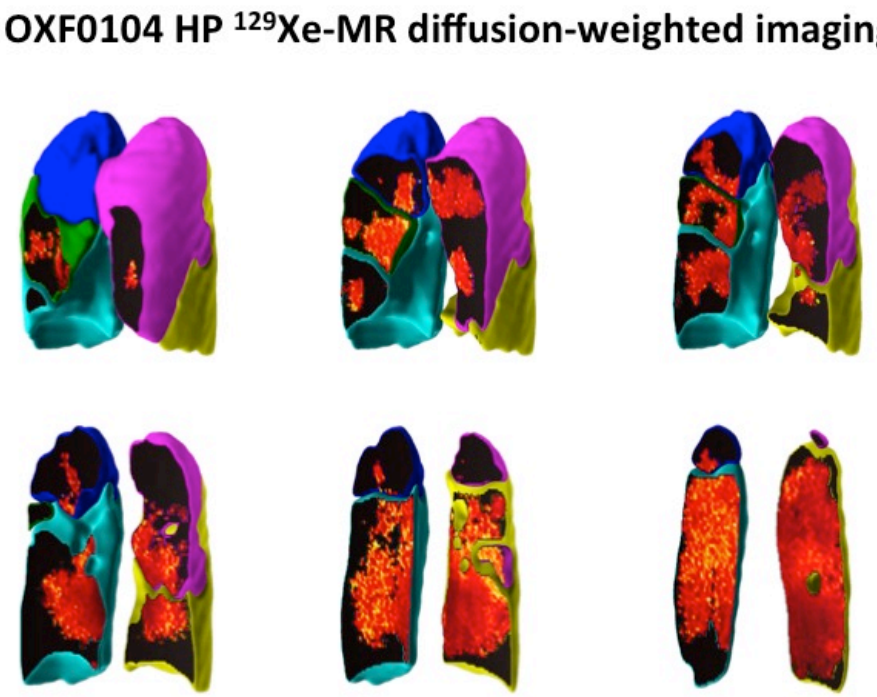


Figure A7.5f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0104. There is increased signal intensity in the right lower (cyan) lobe posteriorly corresponding to higher ADC values and increased emphysematous tissue destruction.

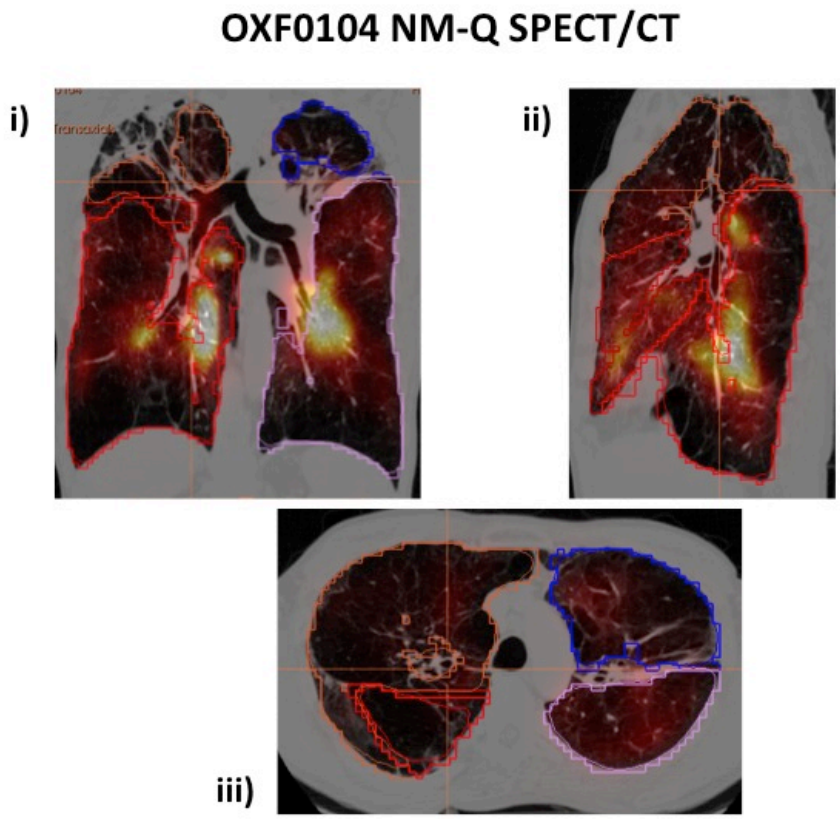


Figure A7.5g: Selected NM-Q SPECT/CT images from OXF0104. Images are in the i) coronal, ii) sagittal and iii) axial plane. Images show perfusion signal predominantly within the lower lobes only.

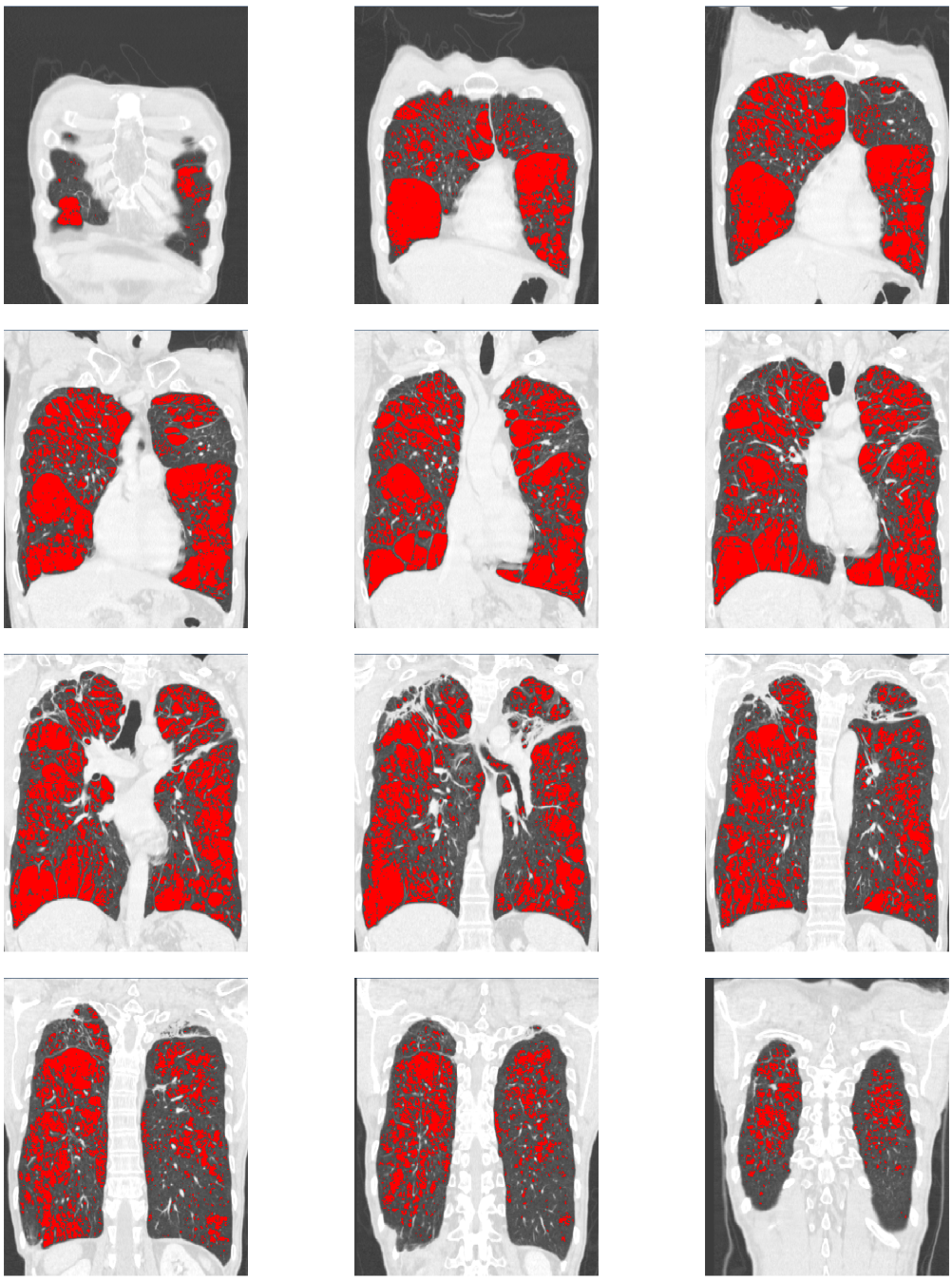


Figure A7.5h: QCT-derived emphysema (% LAA) in COPD patient OXF0104. Red areas correspond to regions with attenuation less than -950 HU. Images show homogeneous distribution of severe emphysema.

Data analysis from COPD patient OXF0106

Table A7.6: Lobar imaging parameters acquired from OXF0106

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	79.35	90.58	94.58	79.34	94.14
HP ^{129}Xe-MRI$_R$ % ventilated volume	86.53	94.86	86.39	81.73	76.39
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.073	0.062	0.054	0.066	0.058
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.024	0.020	0.017	0.019	0.016
QCT-derived % LAA	15.9	7	9.8	12.7	9.7
QCT-derived Pi10 (mm)	6.5	6.9	5.5	5.9	5.3

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

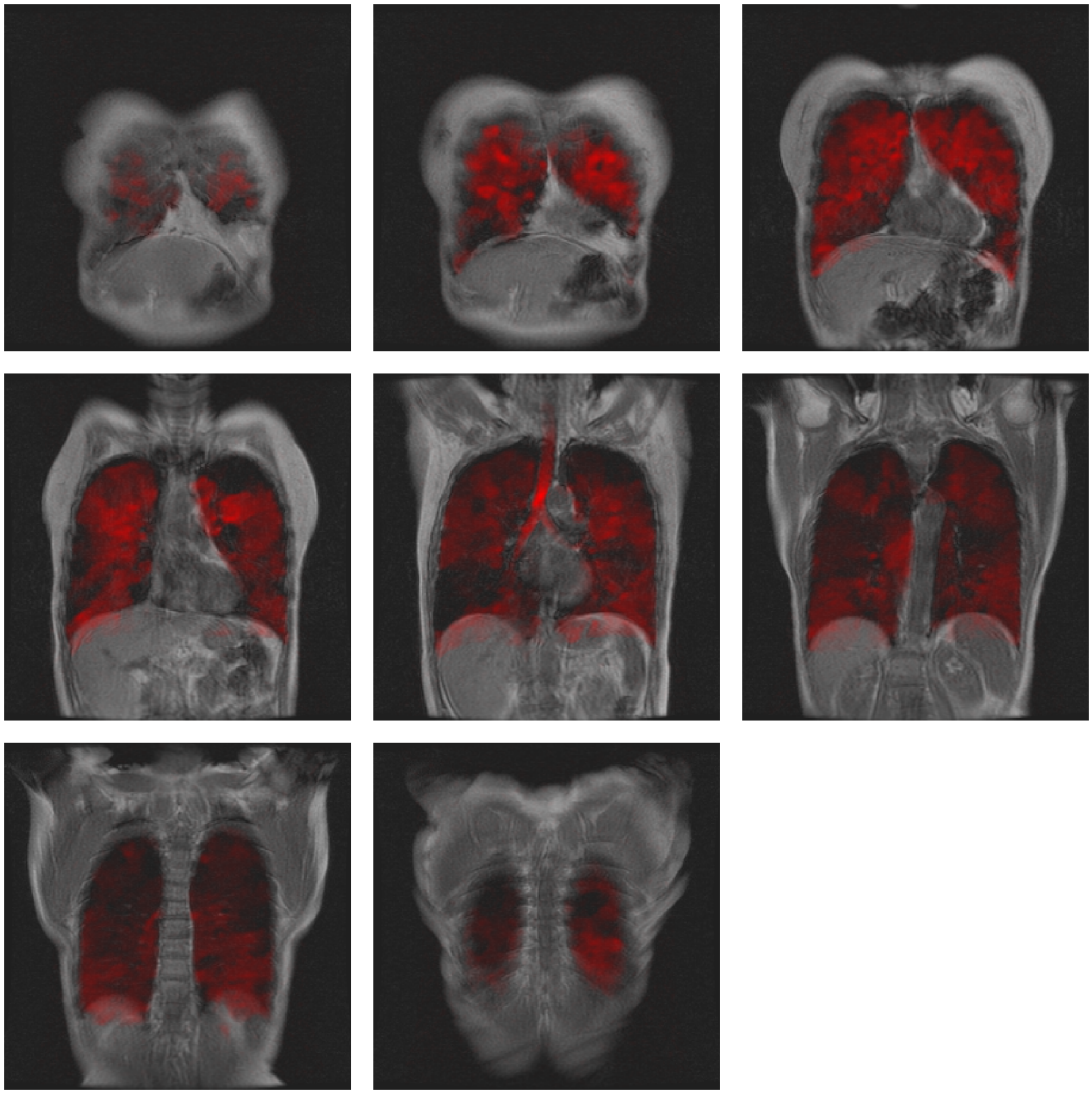


Figure A7.6a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0106. Co-registration to proton MRI enables the lung boundaries to be defined.

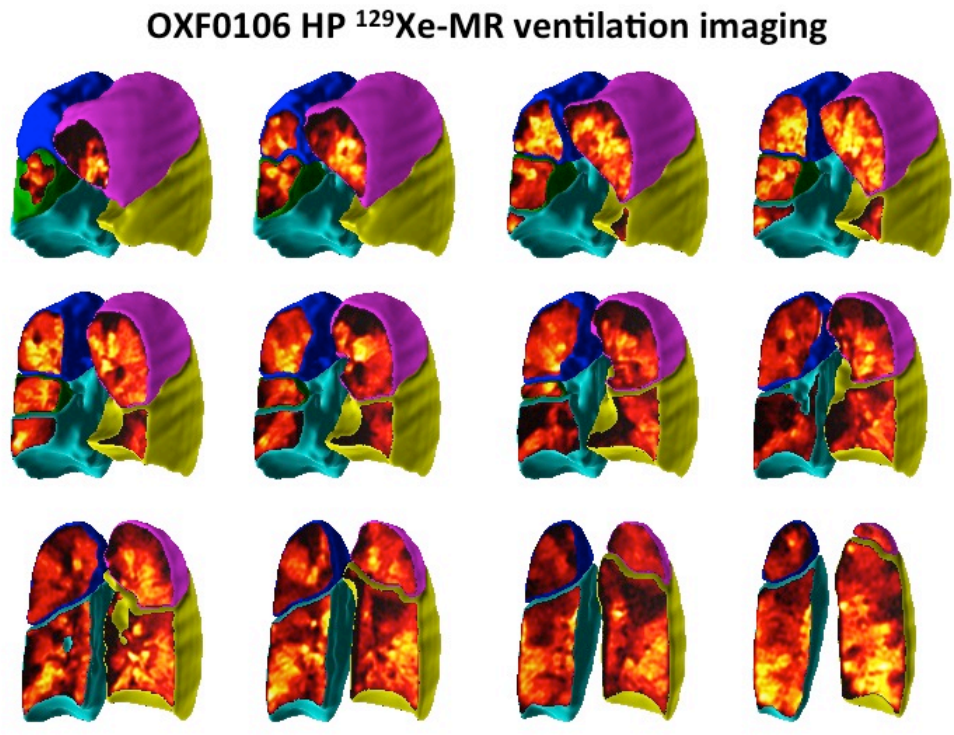


Figure A7.6b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0106. Images show peripheral ventilation defects most marked in the left upper (pink) and right lower (cyan) lobes.

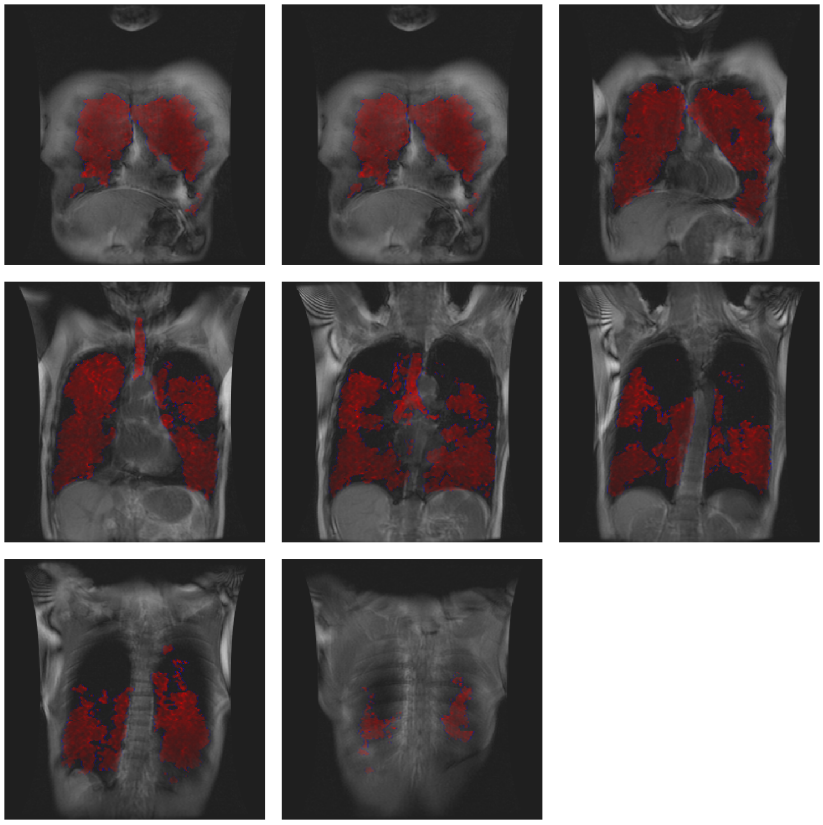


Figure A7.6c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0106.

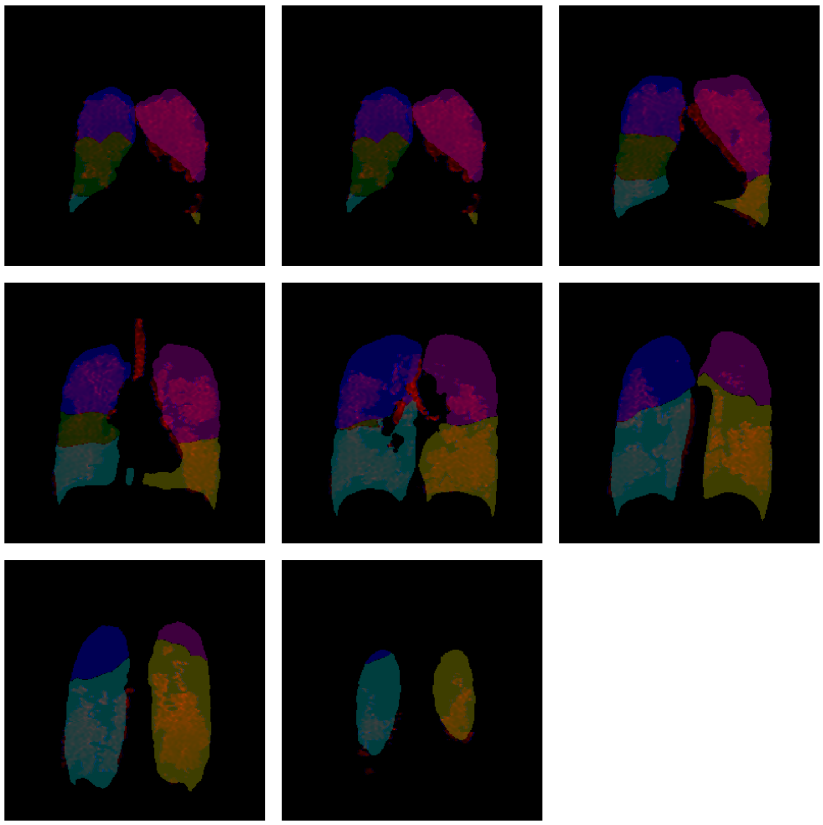


Figure A7.6d: Non-rigid co-registration of HP ^{129}Xe-MR diffusion-weighted imaging and QCT from OXF0106. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MRI ADC values.

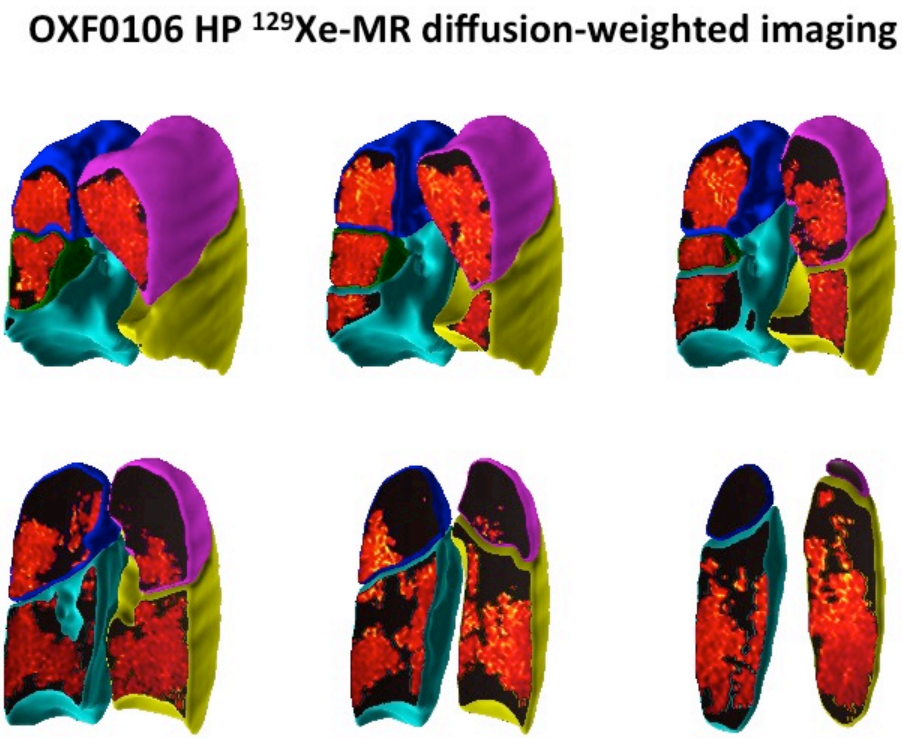


Figure A7.6e: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0106. There is increased signal intensity in the upper lobes corresponding to higher ADC values and increased emphysematous tissue destruction.

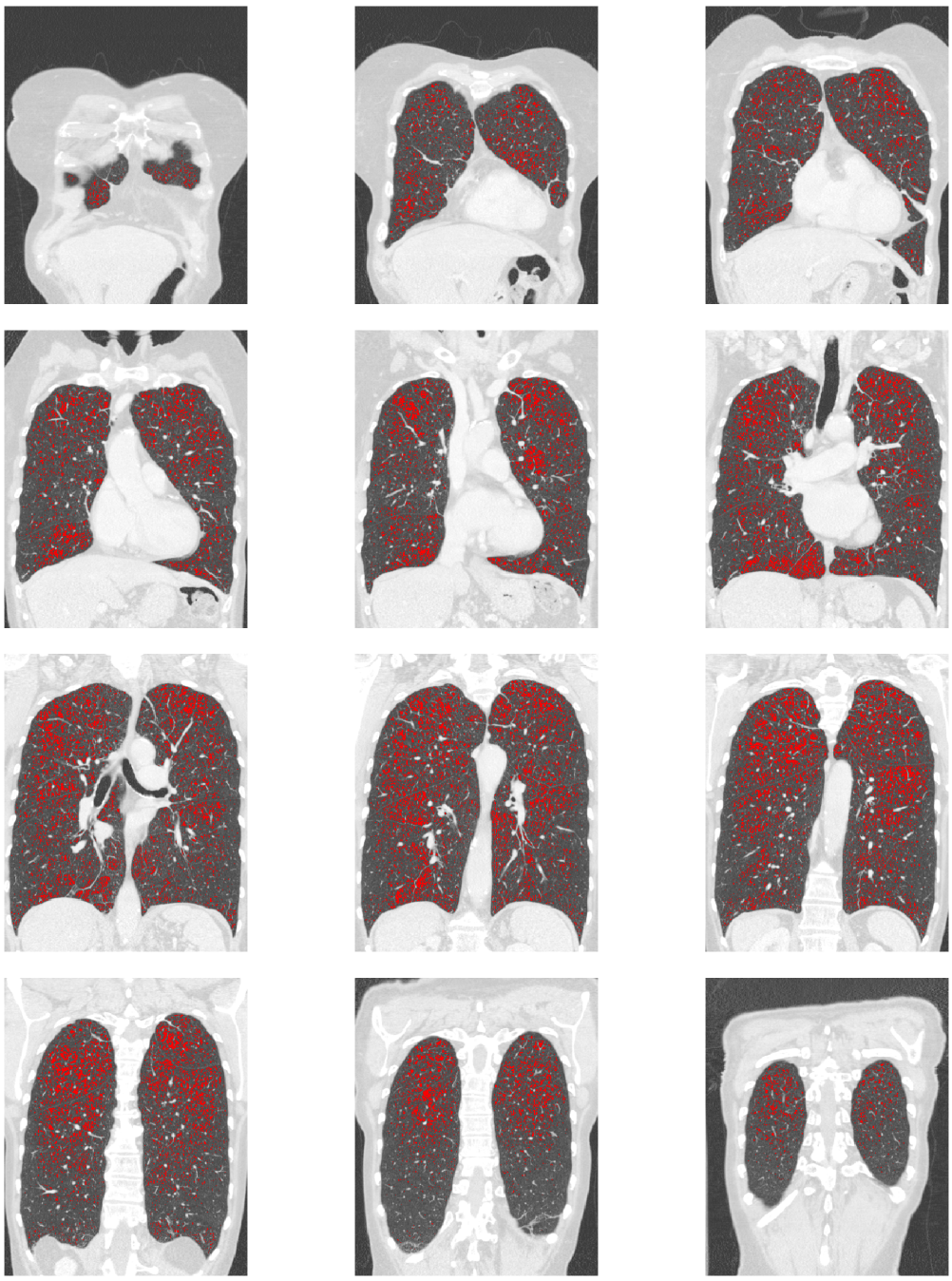


Figure A7.6f: QCT-derived emphysema (% LAA) from OXF0106. Red areas correspond to regions with attenuation less than -950 HU. Images show mild emphysema with no lobar predominance.

Data analysis from COPD patient OXF0109

Table A7.7: Lobar imaging parameters acquired from OXF0109

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	79.64	95.57	78.69	88.84	79.26
HP ^{129}Xe-MRI$_R$ % ventilated volume	89.50	92.41	67.26	84.52	73.23
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.045	0.040	0.040	0.048	0.041
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.041	0.038	0.023	0.044	0.028
QCT-derived % LAA	3.3	3.2	3.6	6.3	3.6
QCT-derived Pi10 (mm)	6.0	11.6	6.9	6.7	5.9
NM-Q SPECT relative % perfusion	22	11.8	16.4	28.7	21

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

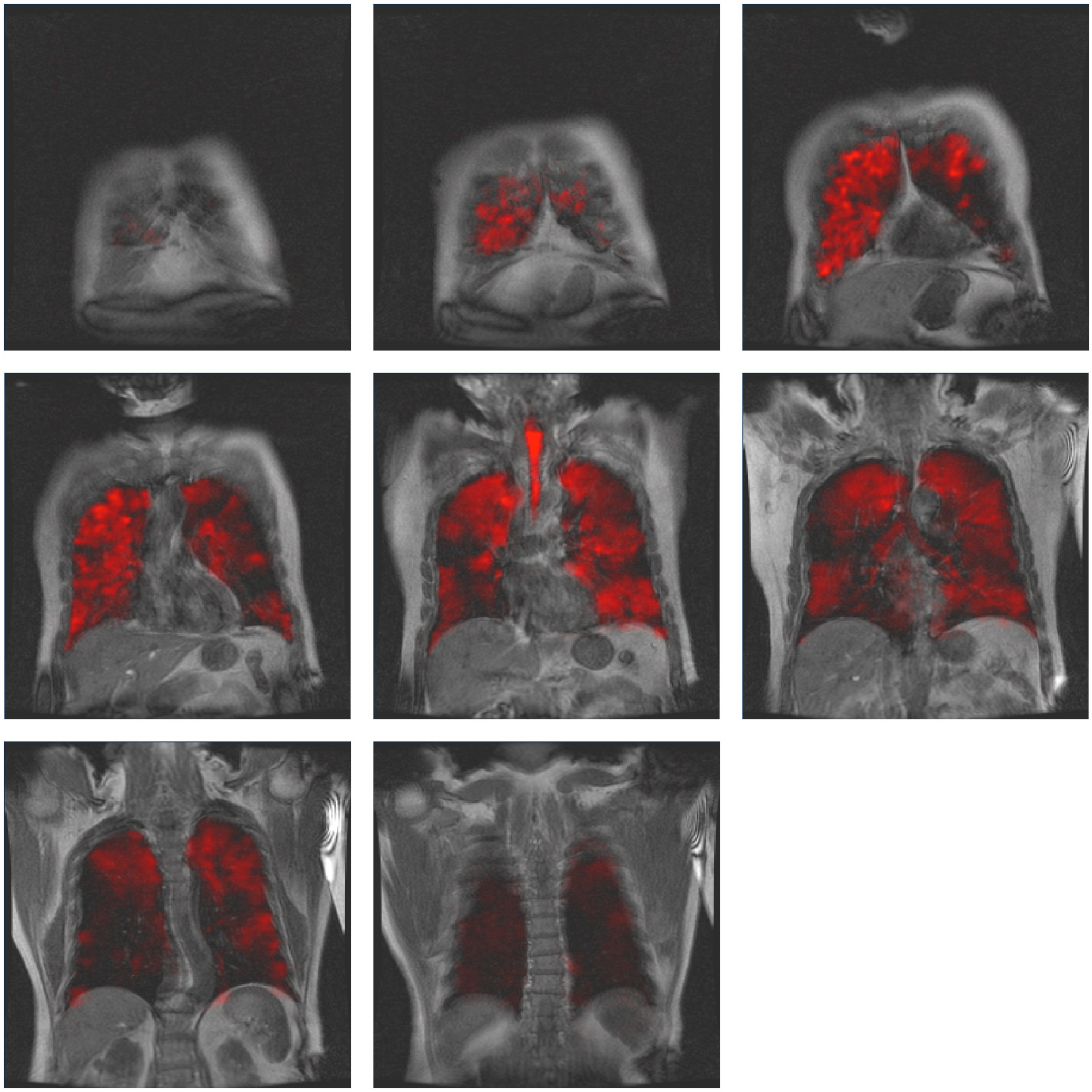


Figure A7.7a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI from COPD patient OXF0109. Co-registration to proton MRI enables the lung boundaries to be defined.

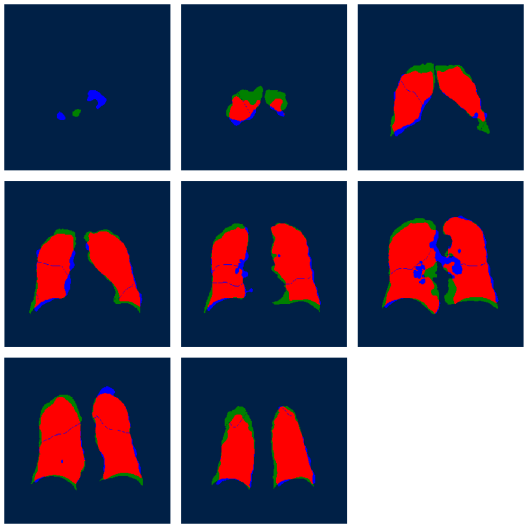


Figure A7.7b: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0109. Lung masks are from HP ^{129}Xe-MR ventilation imaging (blue), proton MRI (green) and QCT (red).

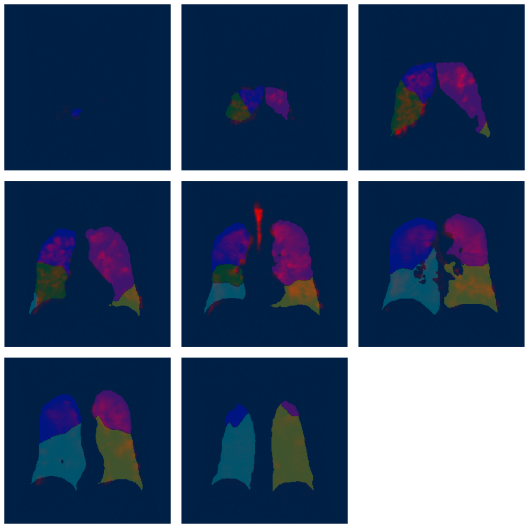


Figure A7.7c: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0109. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

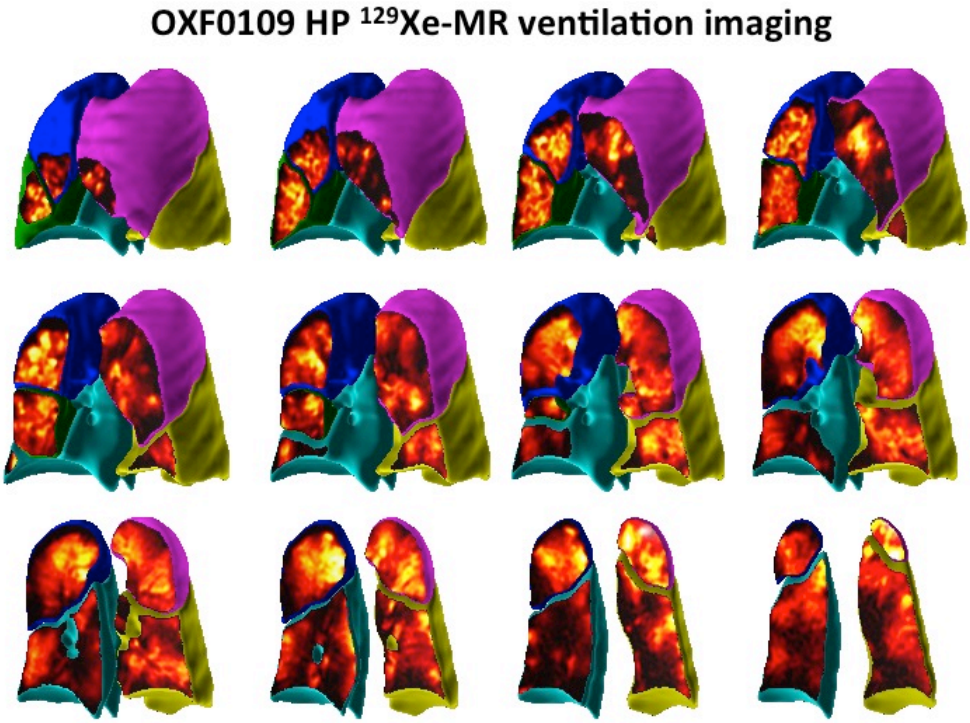


Figure A7.7d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0109. Images show several peripheral ventilation defects in the left upper (pink) lobe anteriorly and in the right lower lobe (cyan).

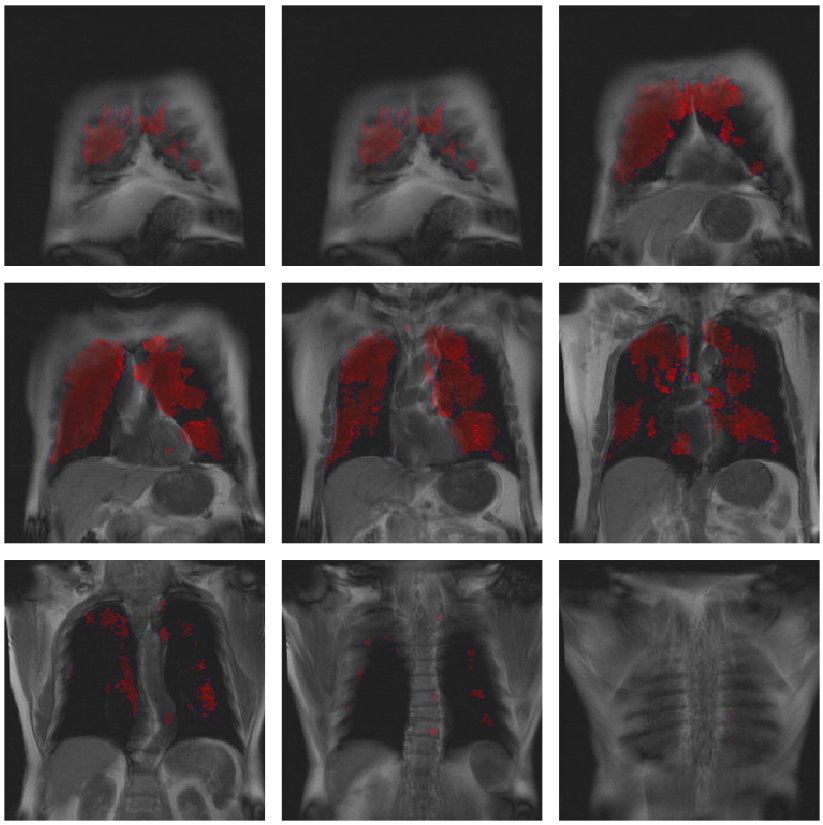


Figure A7.7e: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI in COPD patient OXF0109.

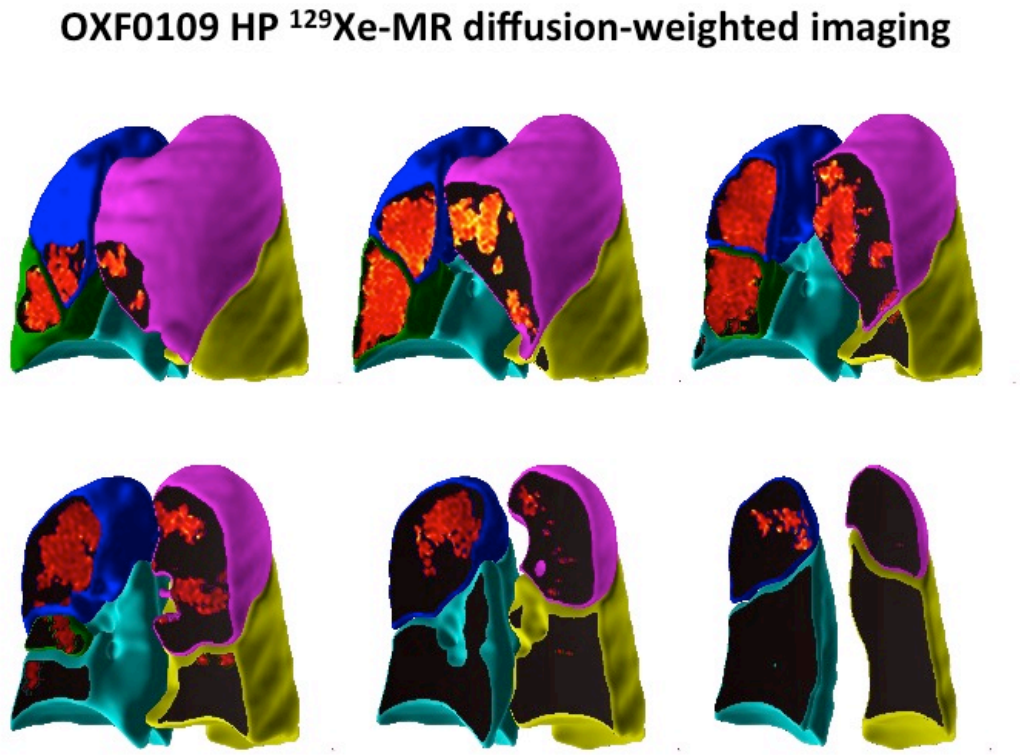


Figure A7.7f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0109. There is increased signal intensity in the left upper (pink) lobe anteriorly corresponding to higher ADC values and increased emphysematous tissue destruction.

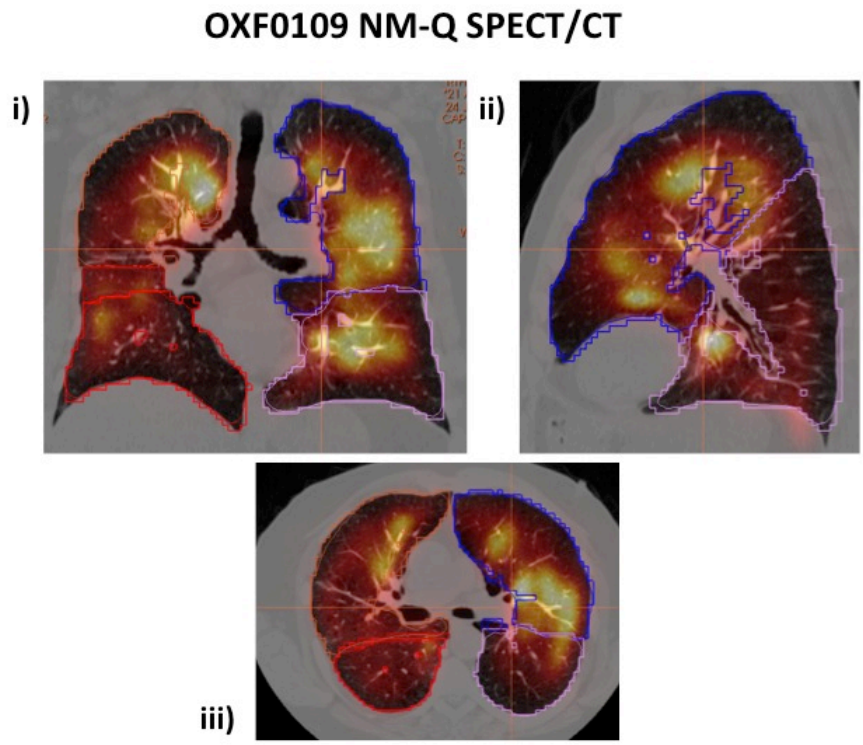


Figure A7.7g: Selected NM-Q SPECT/CT images acquired from OXF109. Images are in the i) coronal, ii) sagittal and iii) axial plane and show relatively increased perfusion signal in the left lung.

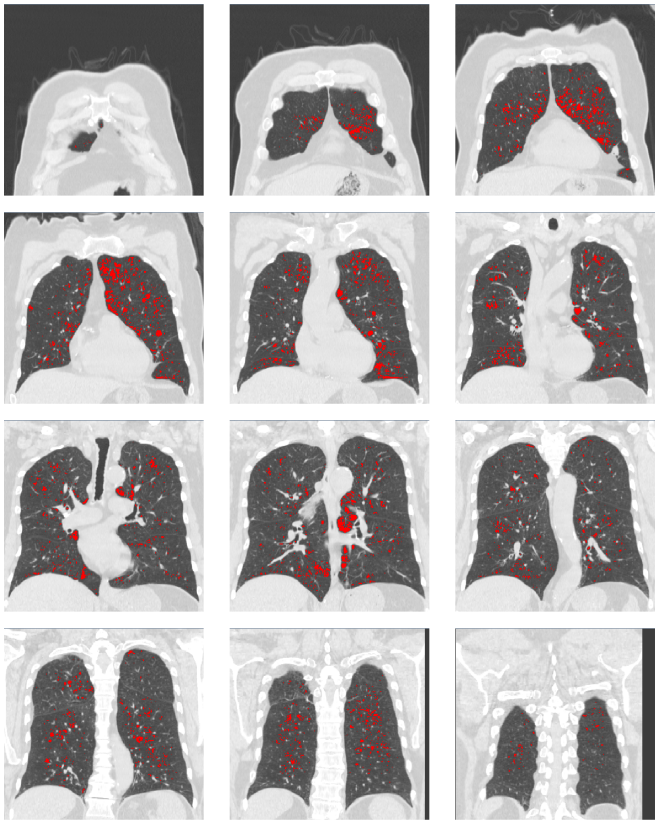


Figure A7.7h: QCT-derived emphysema (% LAA) from COPD patient OXF0109. Red areas correspond to regions with attenuation less than -950 HU. Images show mild emphysema.

Data analysis from COPD patient OXF0141

Table A7.8: Lobar imaging parameters acquired from OXF0141

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	80.1	58.2	36.9	36.8	51.6
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.046	0.049	0.053	0.065	0.048
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.046	0.049	0.053	0.065	0.048
QCT-derived % LAA	2.4	8.9	6.6	6.0	6.8
QCT-derived Pi10 (mm)	6.0	7.8	6.9	4.5	4.9
NM-Q SPECT relative % perfusion	32.9	8.0	10.2	37.3	11.6

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility
RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

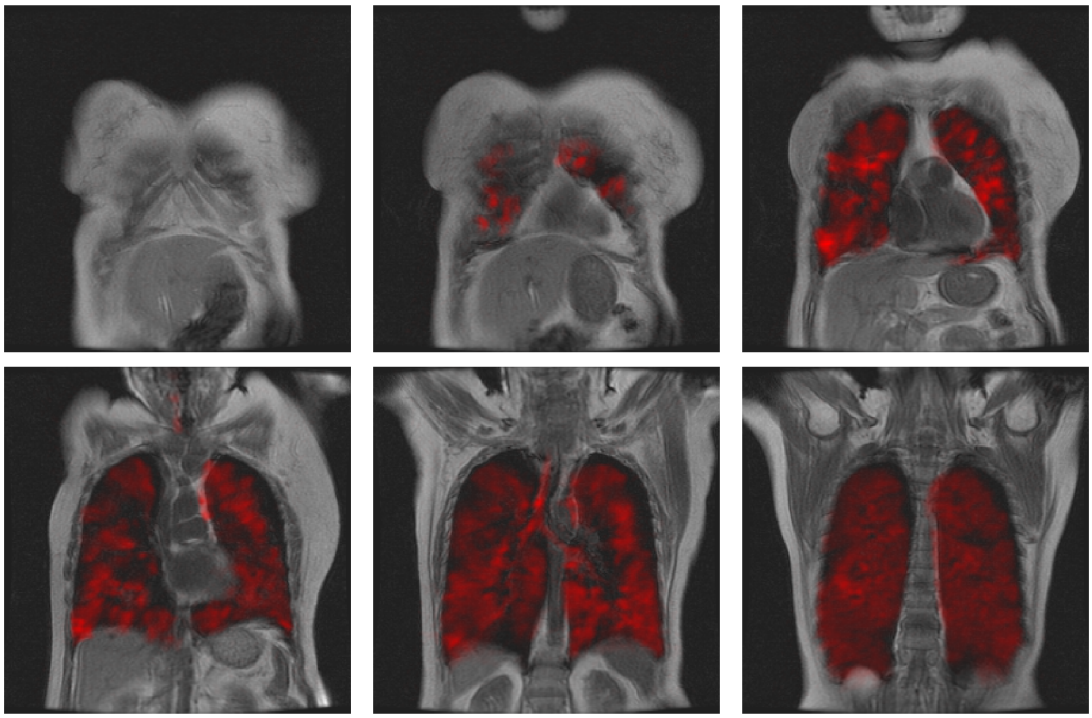


Figure A7.8a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0141. Co-registration to proton MRI enables the lung boundaries to be defined.

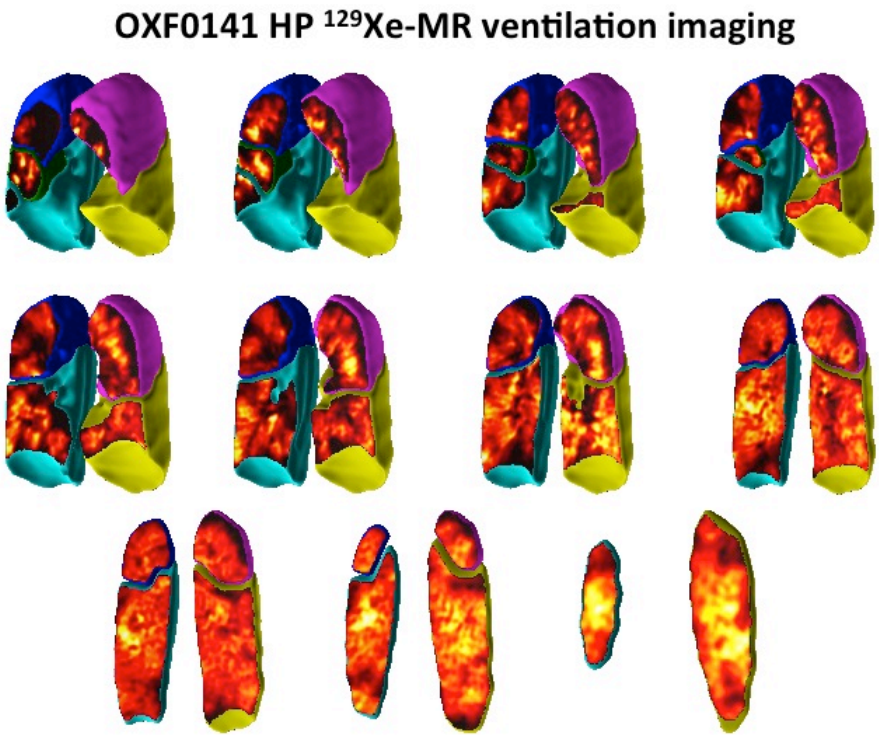


Figure A7.8b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0141. Images show peripheral ventilation defects most marked in the right upper lobe (blue).

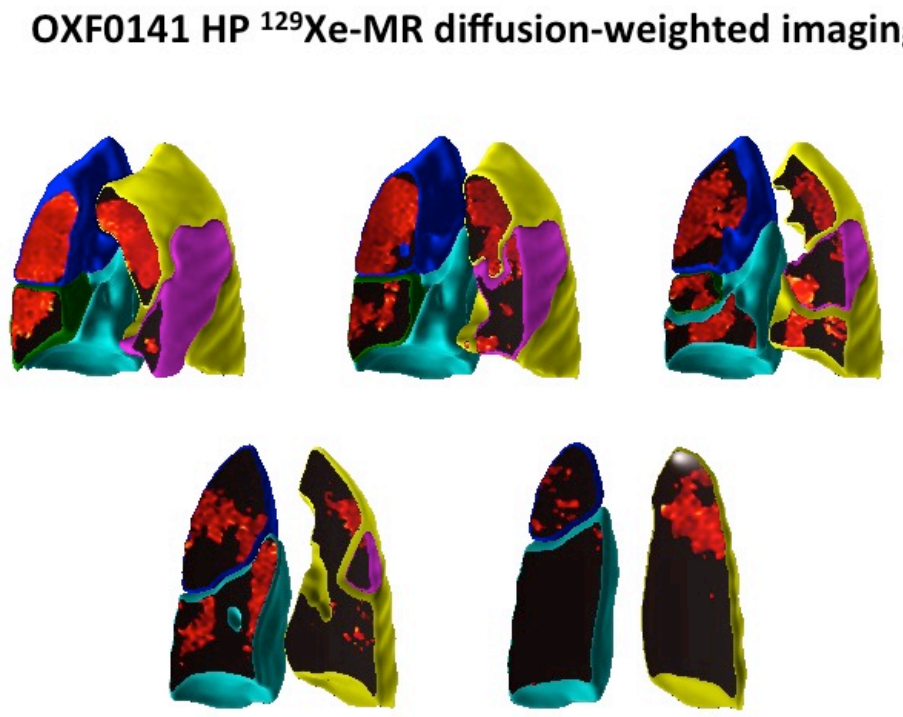


Figure A7.8c: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0141. Images show absent signal in the lower lobes posteriorly indicating poor ventilation of these regions and consequent lack of ^{129}Xe diffusion.

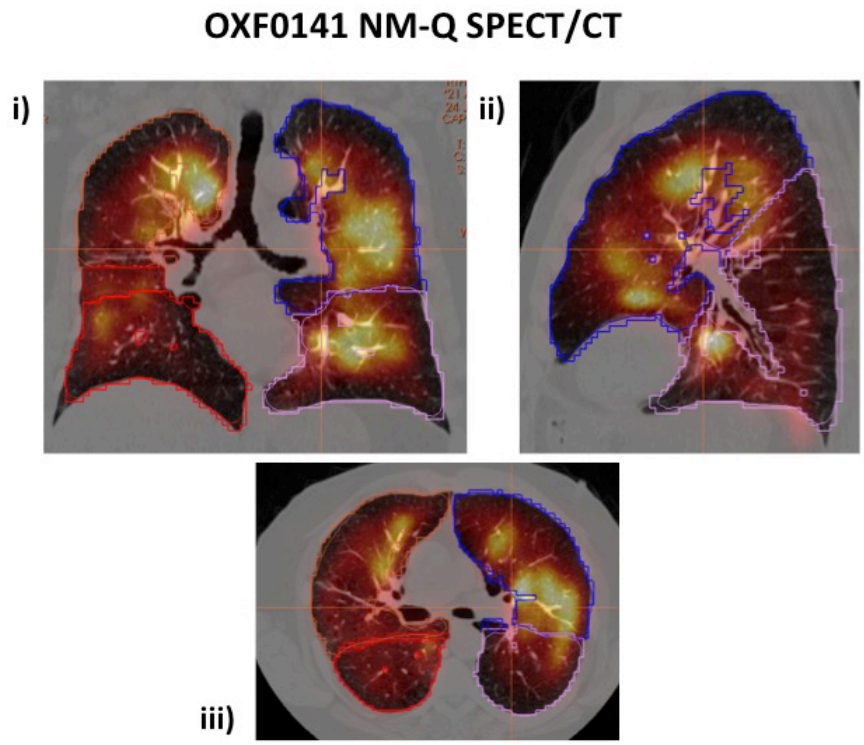


Figure A7.8d: Selected NM-Q SPECT/CT images from OXF0141. Images are in the i) coronal, ii) sagittal and iii) axial plane and show relative increased perfusion in the right upper lobe and left lung.

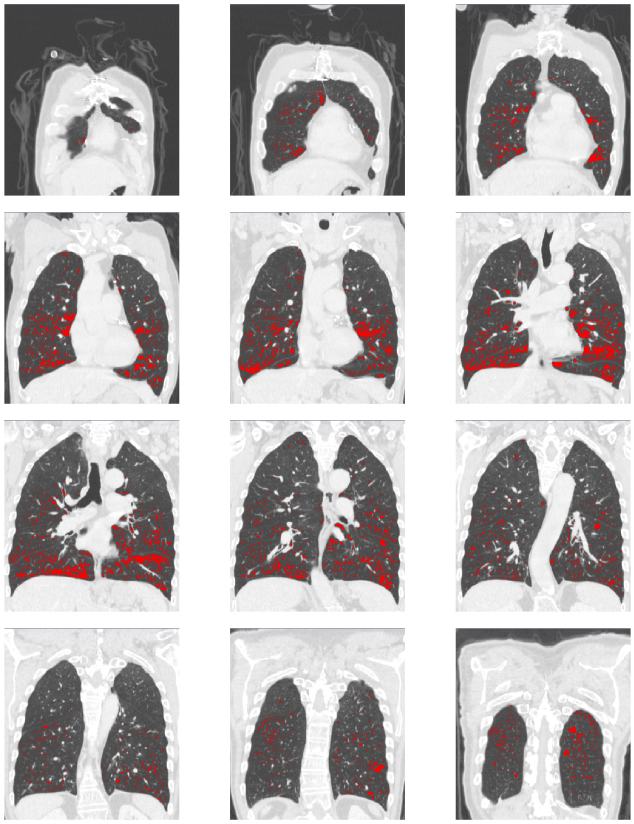


Figure A7.8e: QCT-derived emphysema (% LAA) for patient OXF0141. Red areas correspond to regions with attenuation less than -950 HU. Images show mild lower zone predominant emphysema.

Data analysis from COPD patient OXF0129

Table A7.9: Lobar imaging parameters acquired from OXF0129

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	81.33	97.02	91.16	88.22	91.16
HP ^{129}Xe-MRI$_R$ % ventilated volume	80.94	84.40	79.29	89.72	82.75
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.038	0.040	0.039	0.037	0.035
QCT-derived % LAA	0.2	0.5	0.6	0.6	0.7
QCT-derived Pi10 (mm)	5.8	6.6	5.6	6.0	5.9
NM-Q SPECT relative % perfusion	17.1	11.5	25.6	21.3	24.5

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

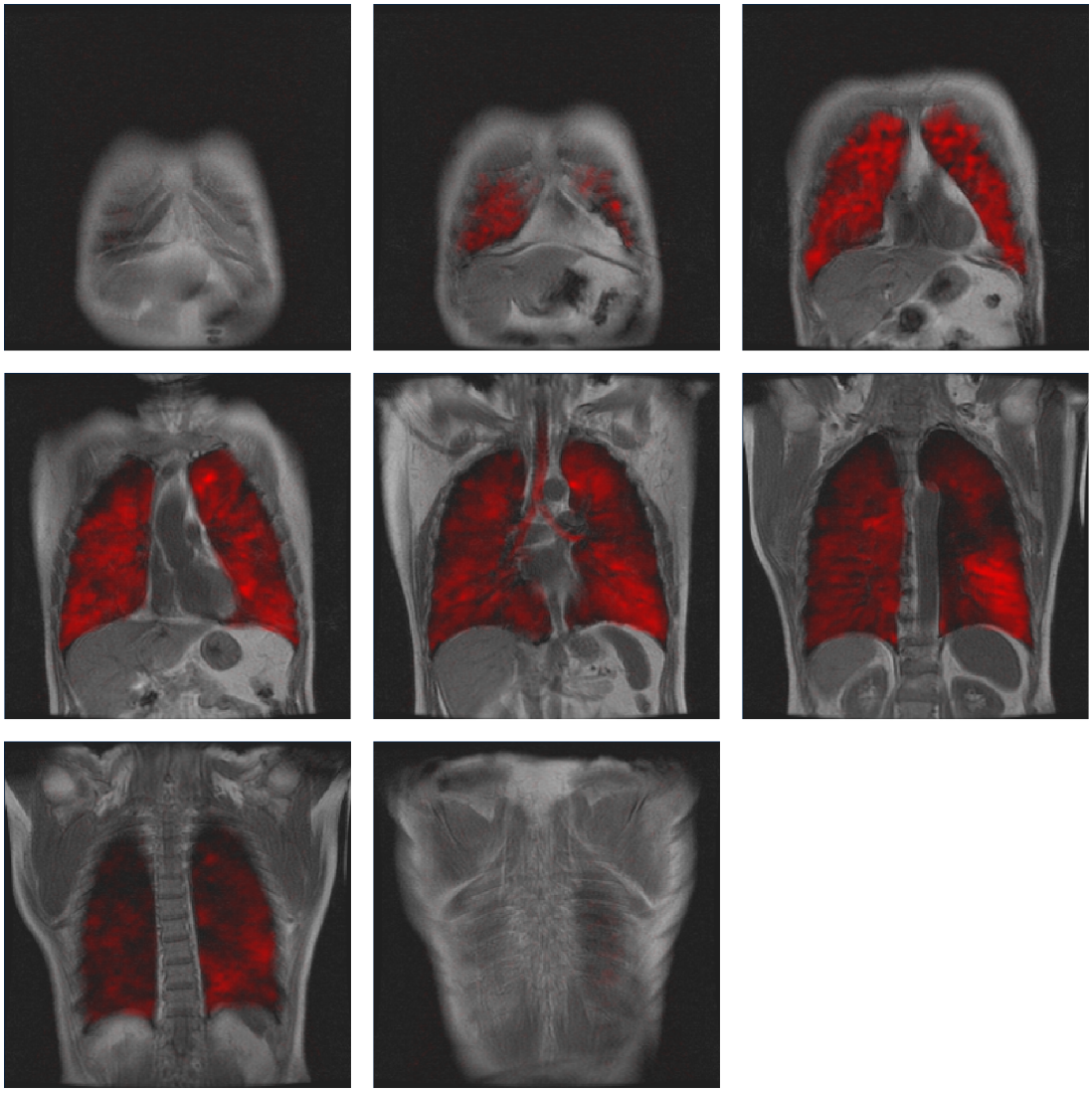


Figure A7.9a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0129. Co-registration to proton MRI enables the lung boundaries to be defined.

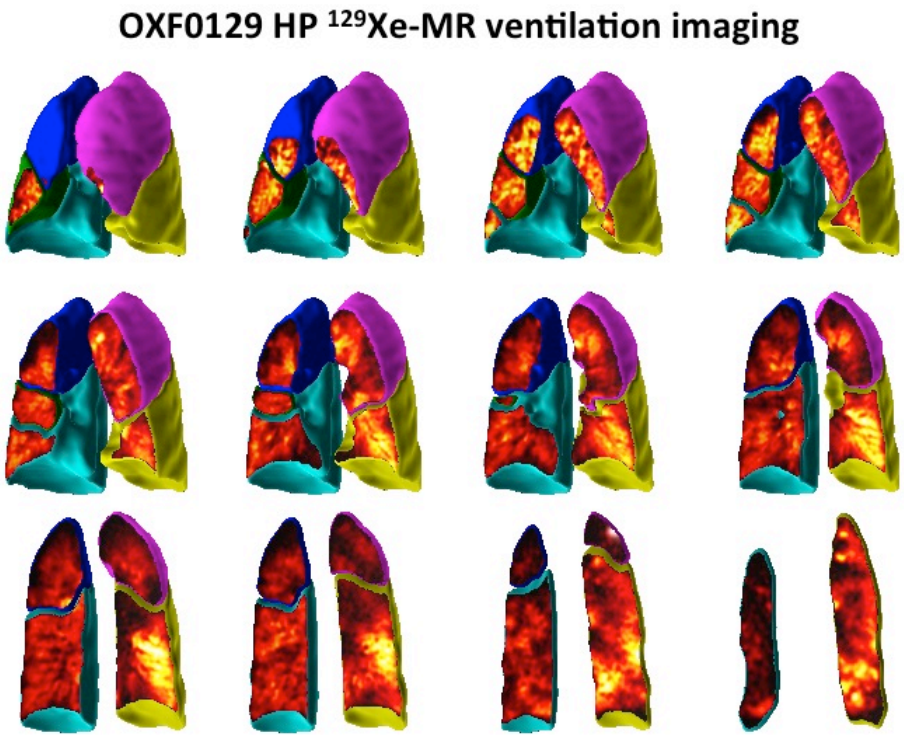


Figure A7.9b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0129. Images show small peripheral ventilation defects predominantly in the right upper (blue) and lower (cyan) lobes posteriorly.

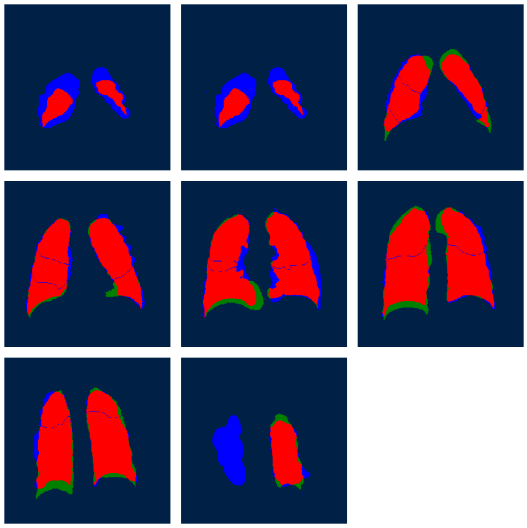


Figure A7.9c: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0129. Lung masks are from HP ^{129}Xe-MR diffusion-weighted imaging (green), proton MRI (blue) and QCT (red).

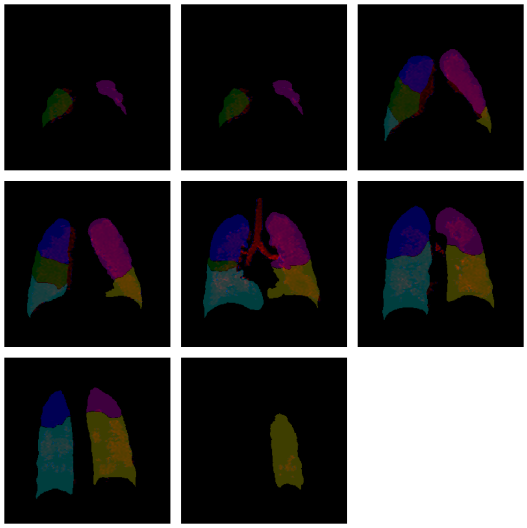


Figure A7.9d: Non-rigid co-registration of HP ^{129}Xe-MR diffusion-weighted imaging and QCT from OXF0129. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

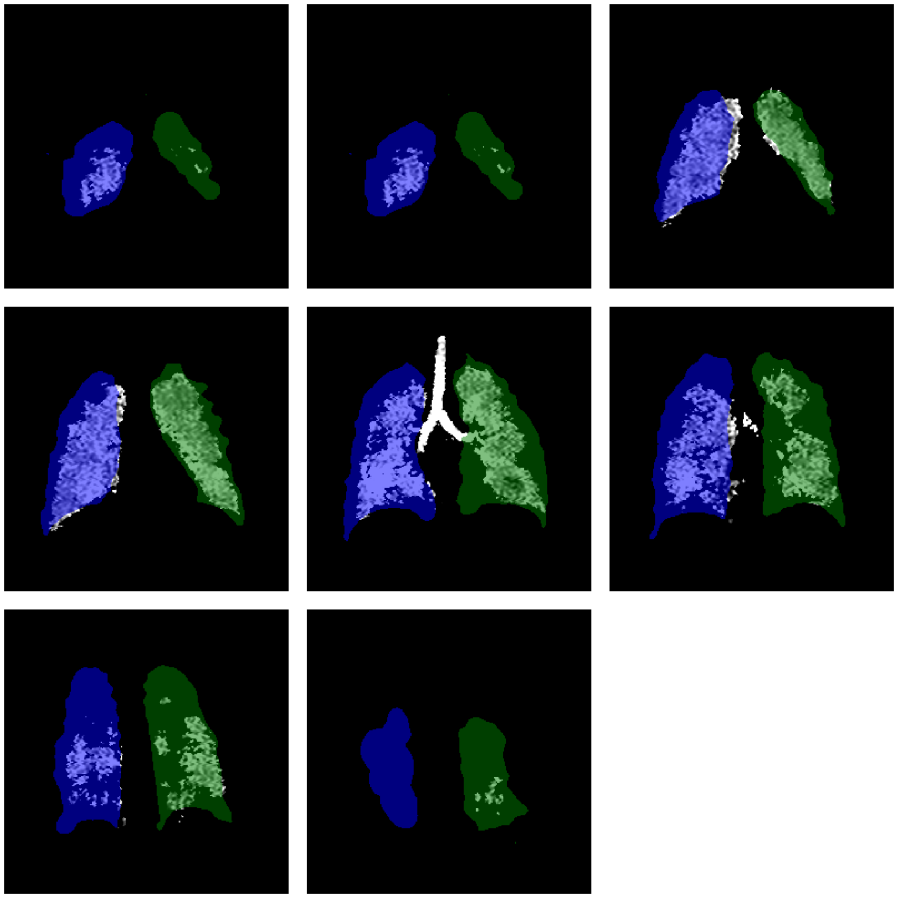


Figure A7.9e: Rigid co-registration of coronal proton MRI and HP ^{129}Xe-MR diffusion-weighted imaging (ADC maps) from OXF0129. ADC maps are shown in grey-scale with overlying proton MRI (right lung = blue, left lung = green).

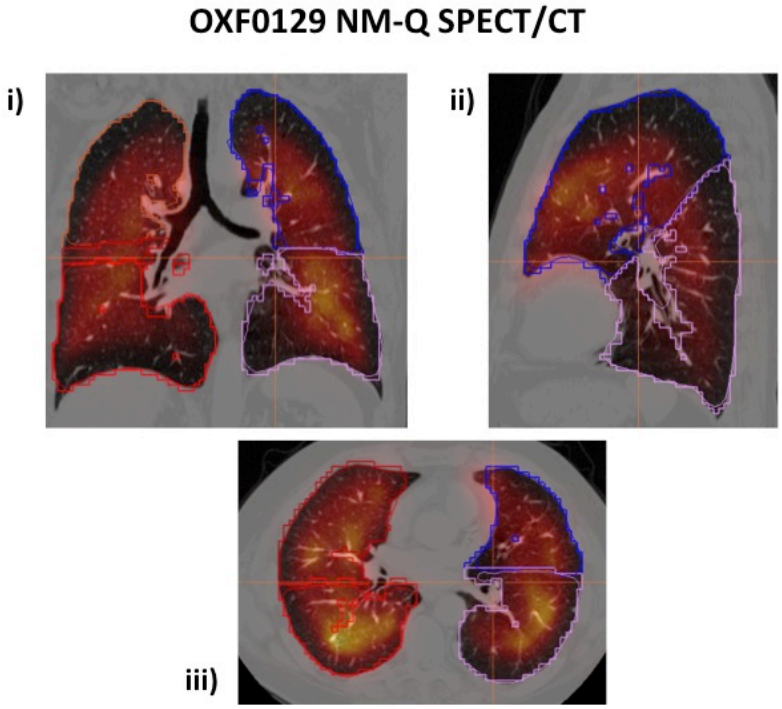


Figure A7.9f: Selected NM-Q SPECT/CT images from OXF0129. Images are in the i) coronal, ii) sagittal and iii) axial plane.

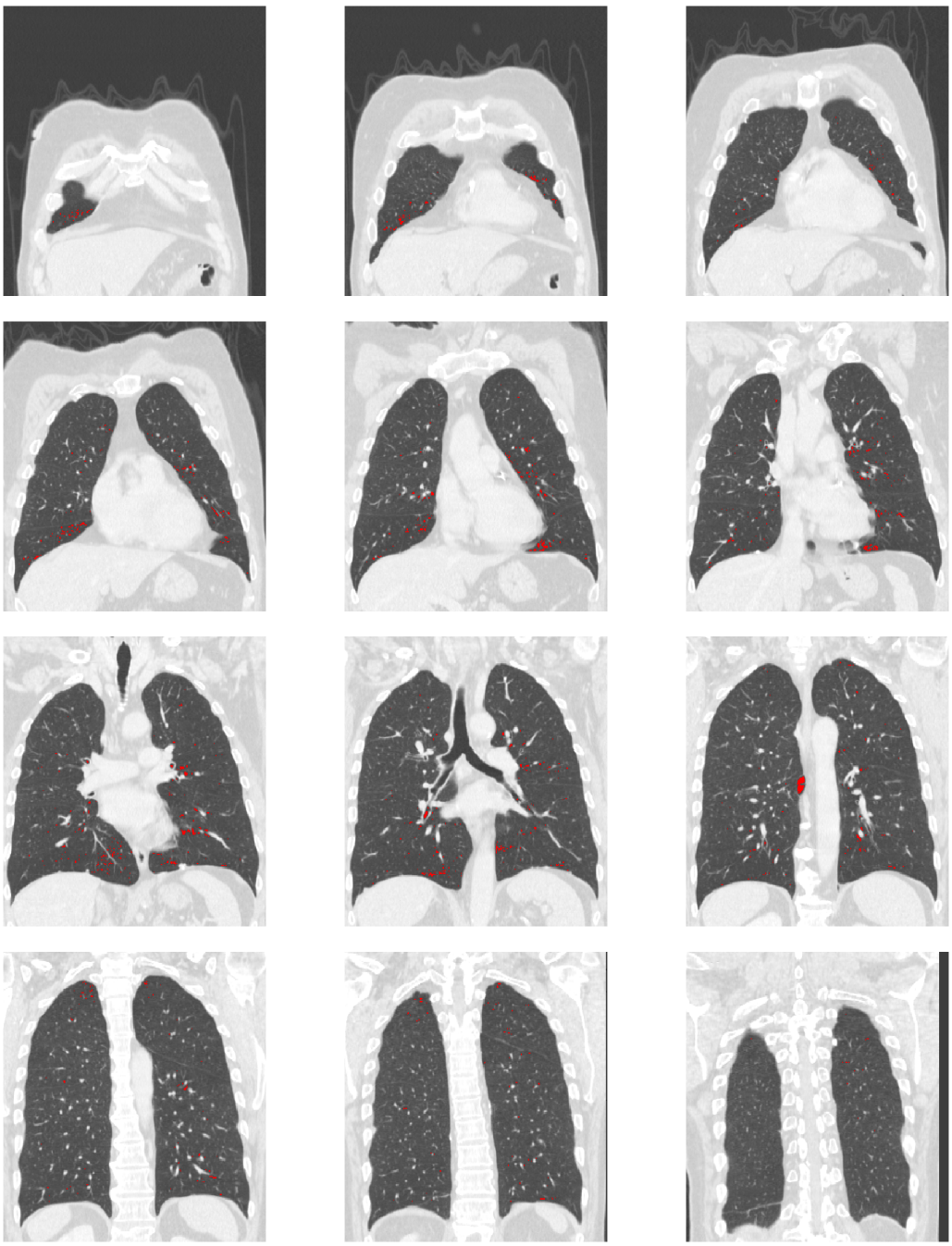


Figure A7.9g: QCT-derived emphysema (% LAA) for patient OXF0129. Red areas correspond to regions with attenuation less than -950 HU. Images show very mild emphysema.

Data analysis from COPD patient OXF0041

Table A7.10: Lobar imaging parameters acquired from OXF0041

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	73.87	88.66	88.85	76.26	77.32
HP ^{129}Xe-MRI$_R$ % ventilated volume	75.76	83.59	73.07	75.07	48.25
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.029	0.034	0.030	0.032	0.028
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.020	0.019	0.020	0.019	0.015
QCT-derived % LAA	0.1	0.4	0.4	0.4	0.4
QCT-derived Pi10 (mm)	4.9	3.1	5.8	5.8	7.0
NM-Q SPECT relative % perfusion	24.3	11.6	29.4	20.3	14.3

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

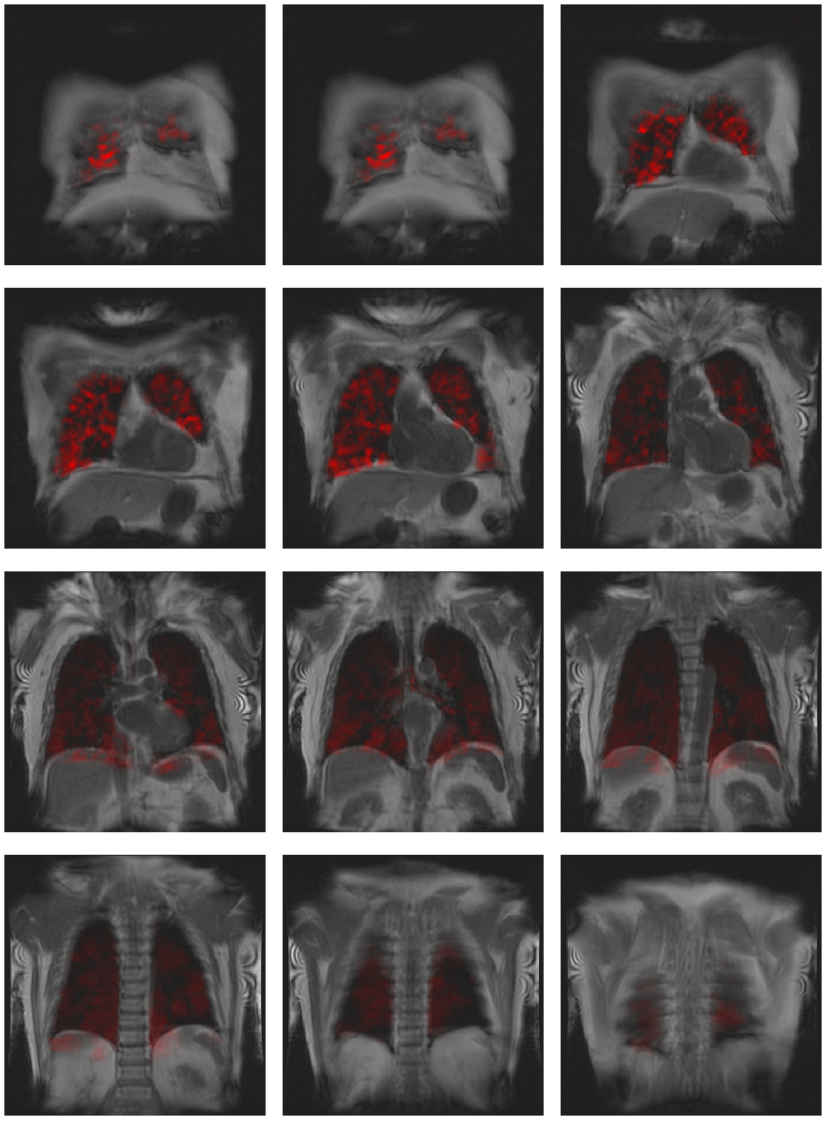


Figure A7.10a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0041. Co-registration to proton MRI enables the lung boundaries to be defined.

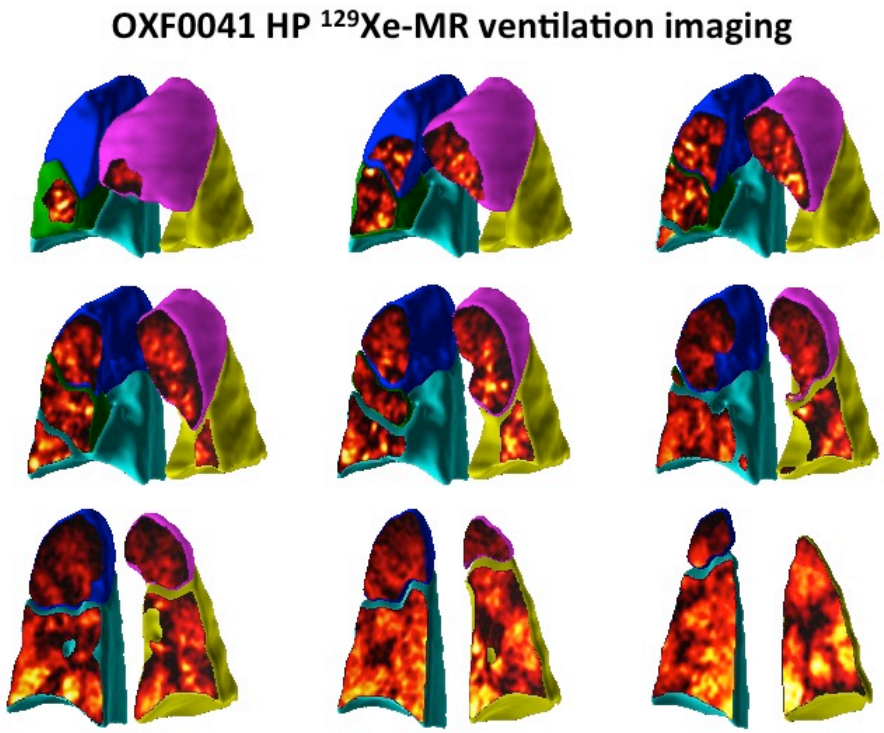


Figure A7.10b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0041. Images show patchy heterogeneous ventilation signal throughout the lungs.

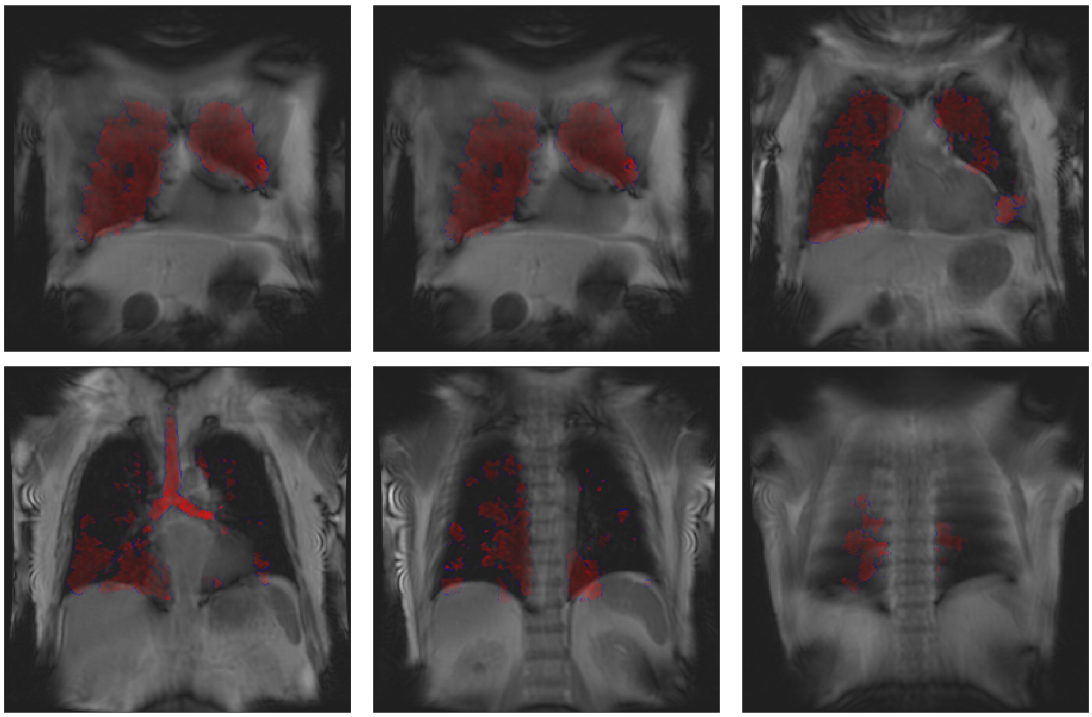


Figure A7.10c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0041.

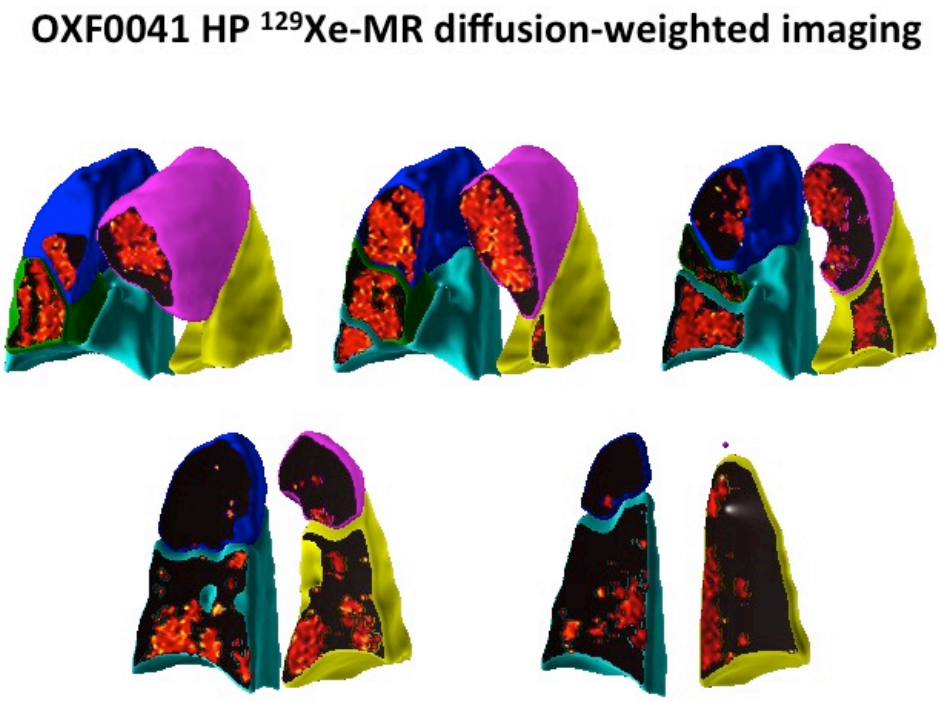


Figure A7.10d: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0041. There is increased signal intensity in the upper lobes corresponding to higher ADC values and increased emphysematous tissue destruction.

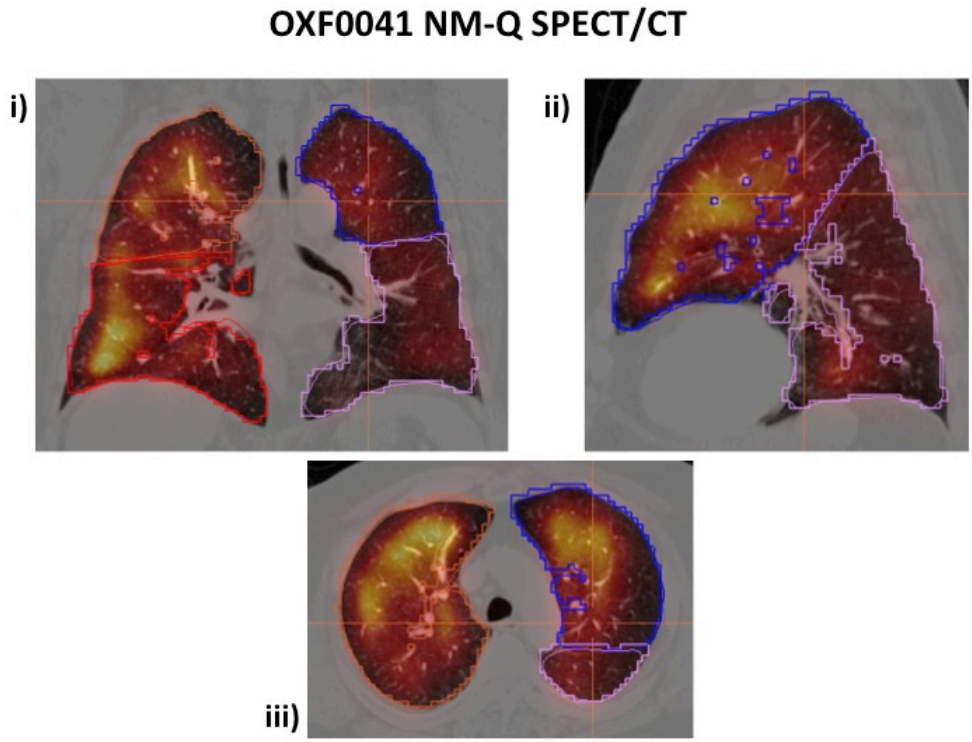


Figure A7.10e: Selected NM-Q SPECT/CT images from OXF0041. Images are in the i) coronal, ii) sagittal and iii) axial plane.

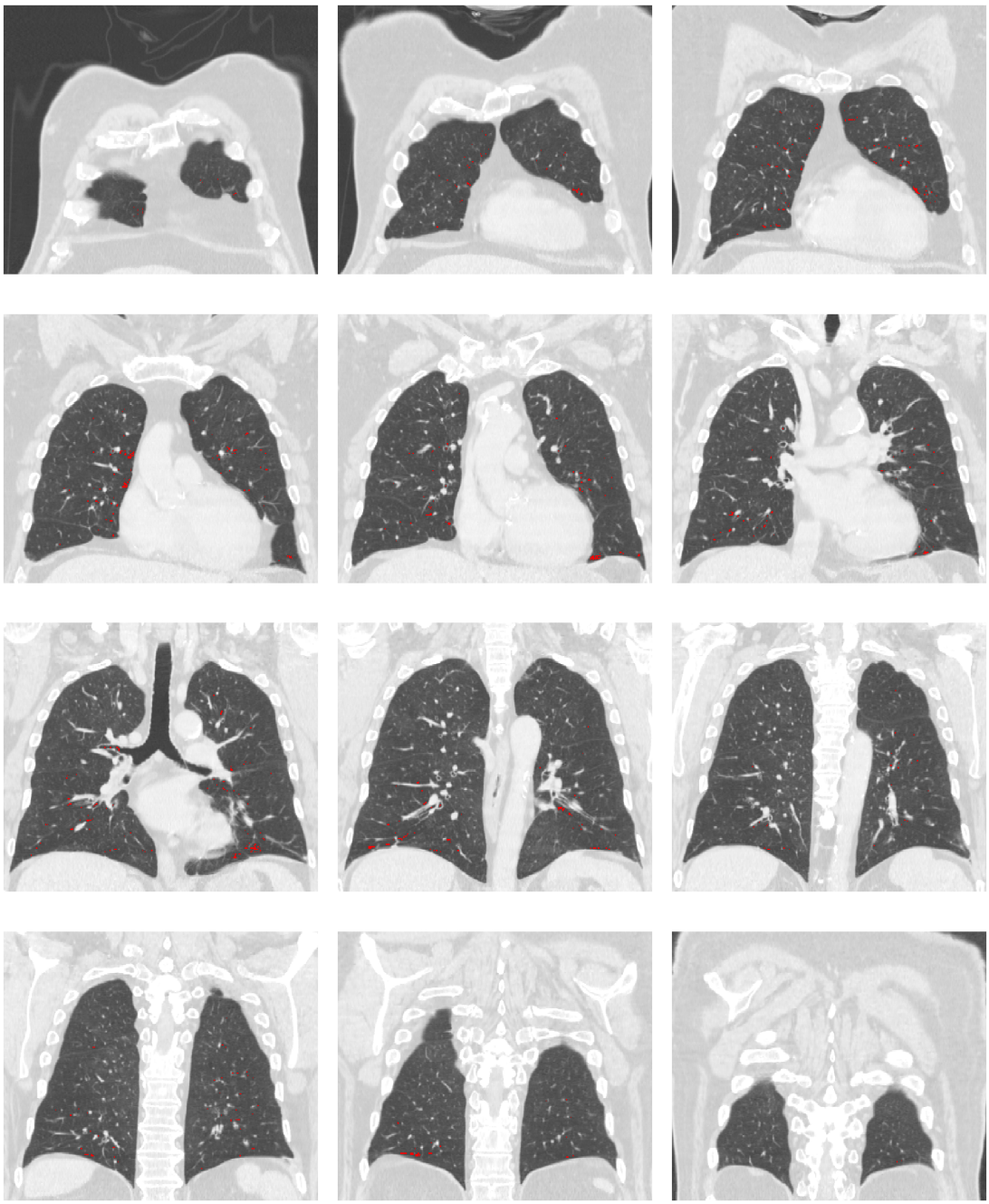


Figure A7.10f: QCT-derived emphysema (% LAA) for patient OXF0041. Red areas correspond to regions with attenuation less than -950 HU.

Data analysis from COPD patient OXF0113

Table A7.11: Lobar imaging parameters acquired from OXF0113

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	90.09	87.50	91.60	81.87	87.87
HP ^{129}Xe-MRI$_R$ % ventilated volume	80.33	67.27	87.96	72.67	82.81
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.044	0.039	0.042	0.056	0.047
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.042	0.034	0.039	0.046	0.046
QCT-derived % LAA	0.8	0.1	0.2	5.4	0.7
QCT-derived Pi10 (mm)	5.9	6.9	6.4	6.5	6.4
NM-Q SPECT relative % perfusion	18.7	8.6	14.9	30.2	27.5

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

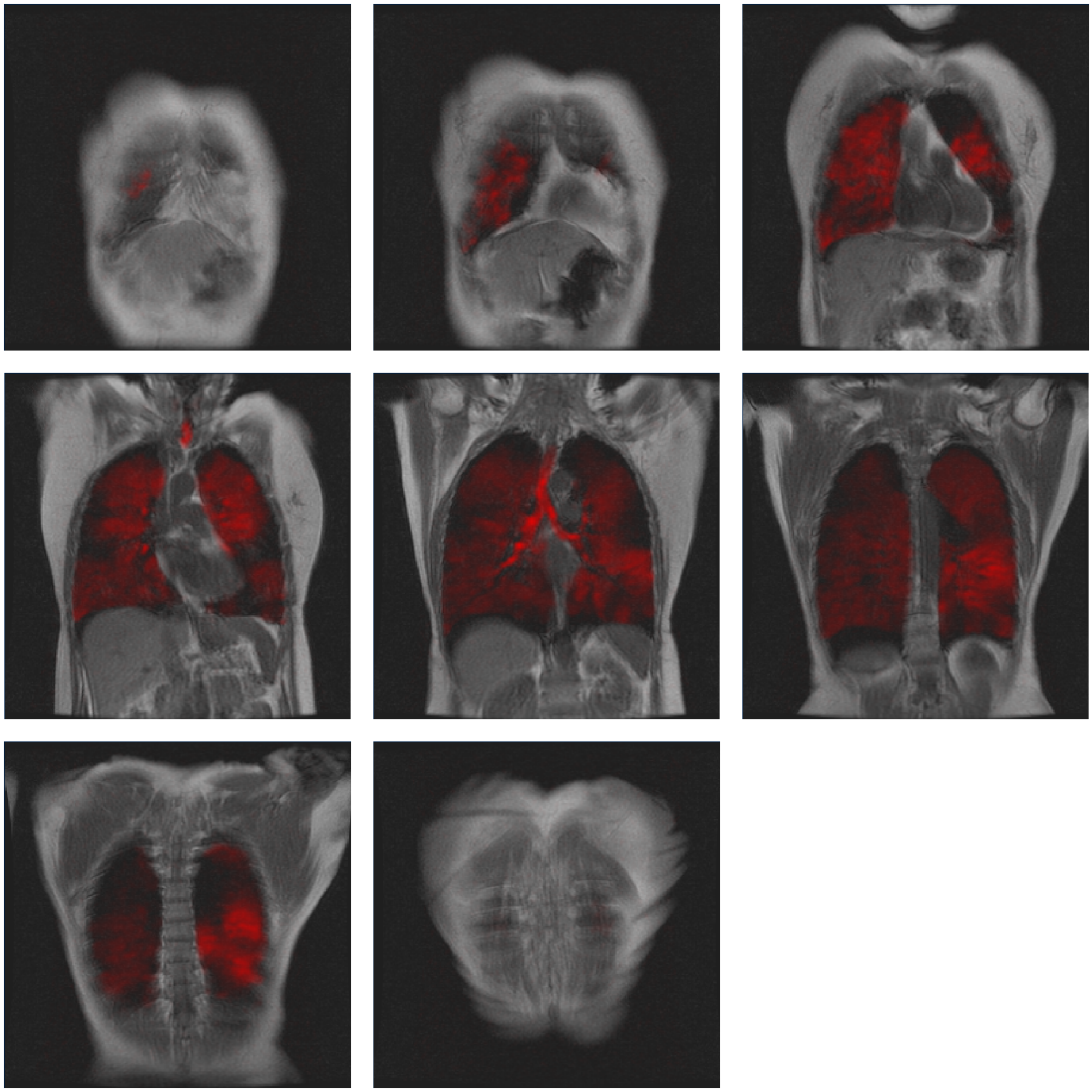


Figure A7.11a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0113. Co-registration to proton MRI enables the lung boundaries to be defined.

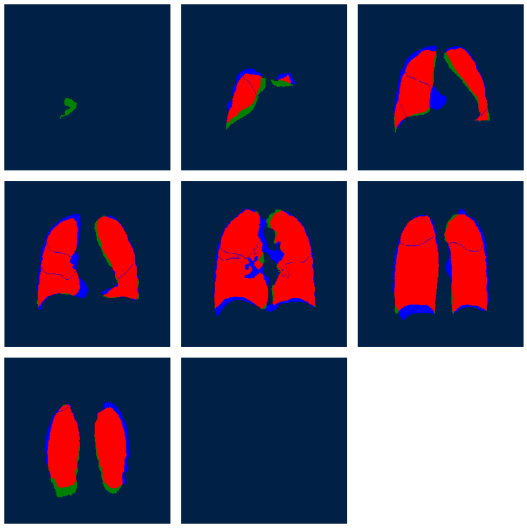


Figure A7.11b: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0113. Lung masks are from HP ^{129}Xe-MR ventilation imaging (green), proton MRI (blue) and QCT (red).

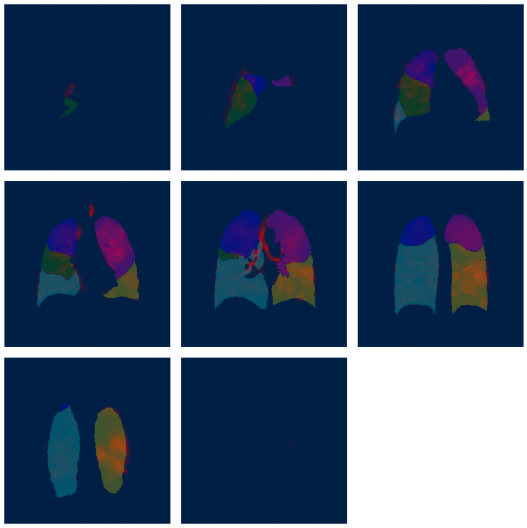


Figure A7.11c: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0113. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

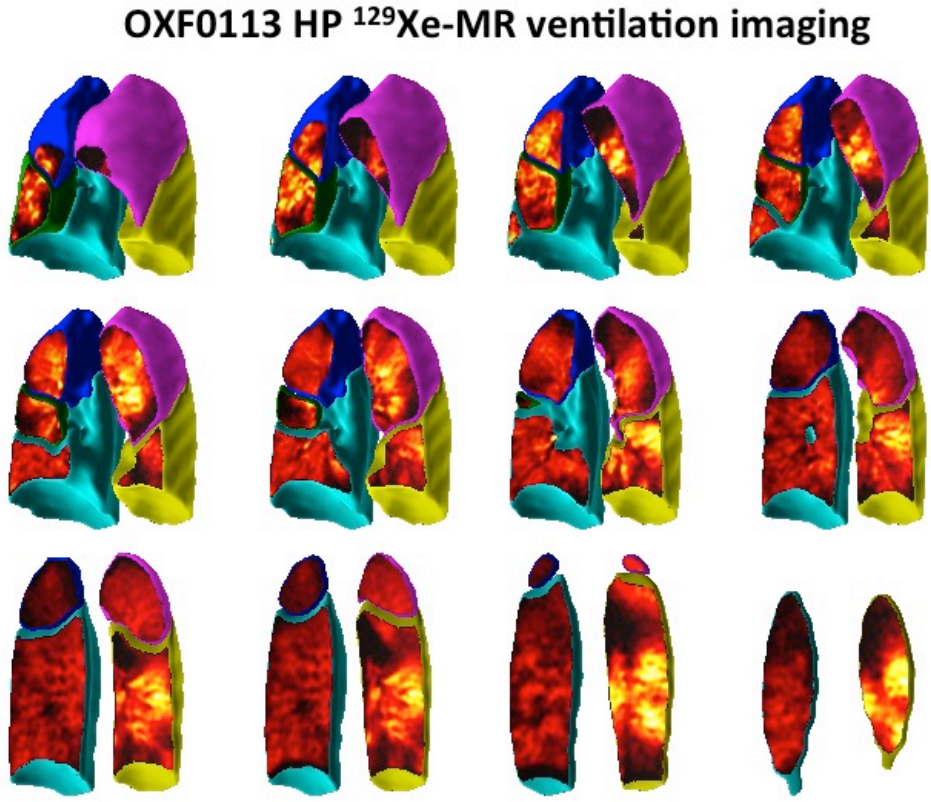


Figure A7.11d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0113. Images show a ventilation defect in the left upper lobe (pink) anteriorly and both lower lobes posteriorly.

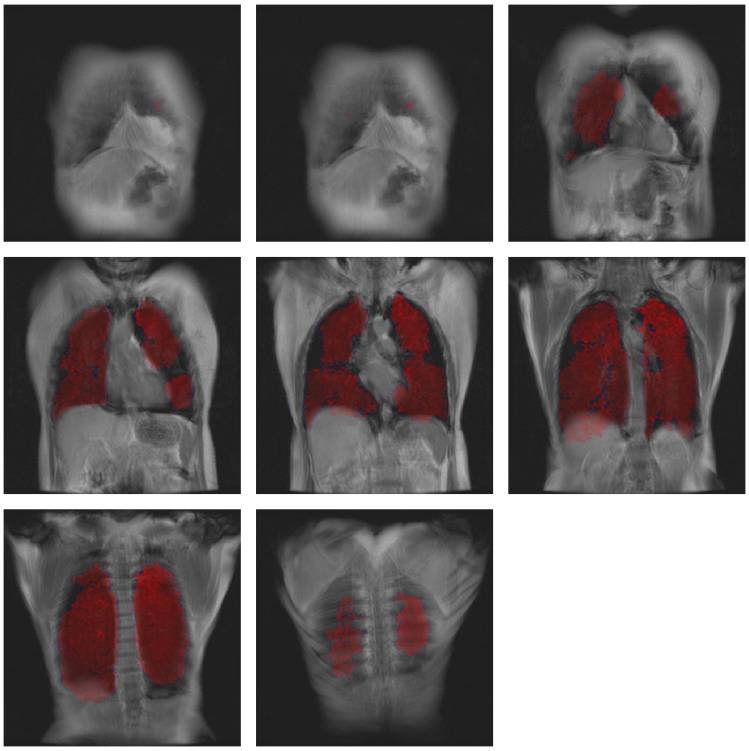


Figure A7.11e: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0113.

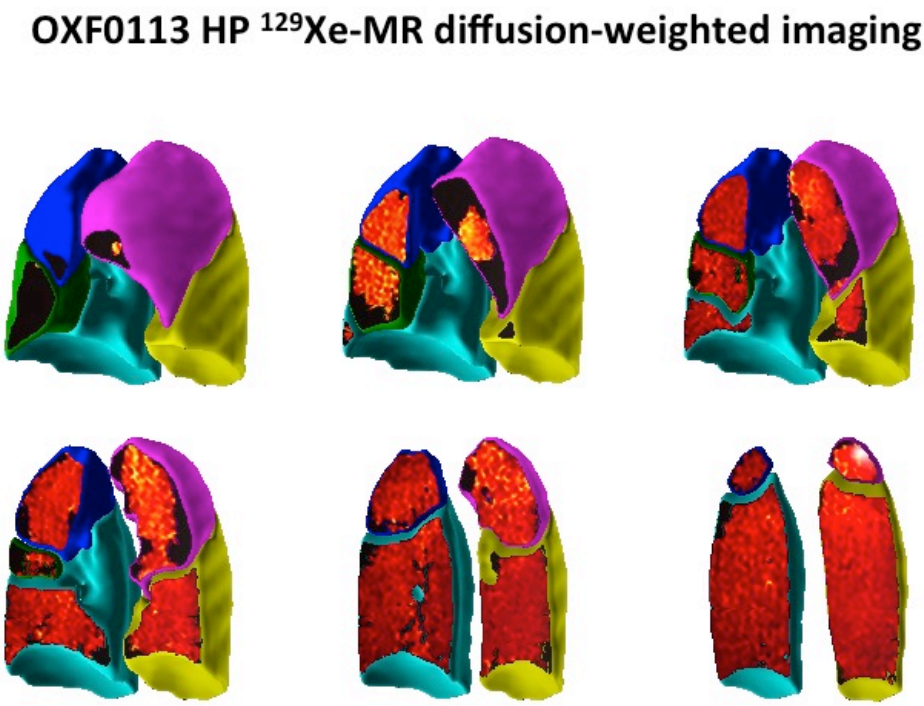


Figure A7.11f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0113. There is increased signal intensity in the left upper (pink) lobe corresponding to higher ADC values and increased emphysema in this region.

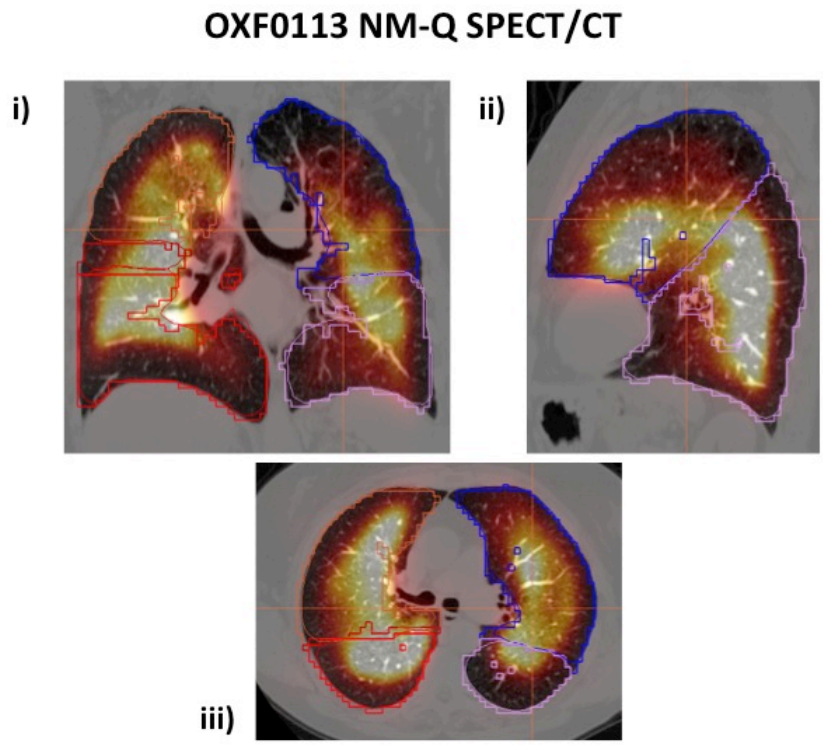


Figure A7.11g: Selected NM-Q SPECT/CT images from OXF0113. Images are in the i) coronal, ii) sagittal and iii) axial plane.

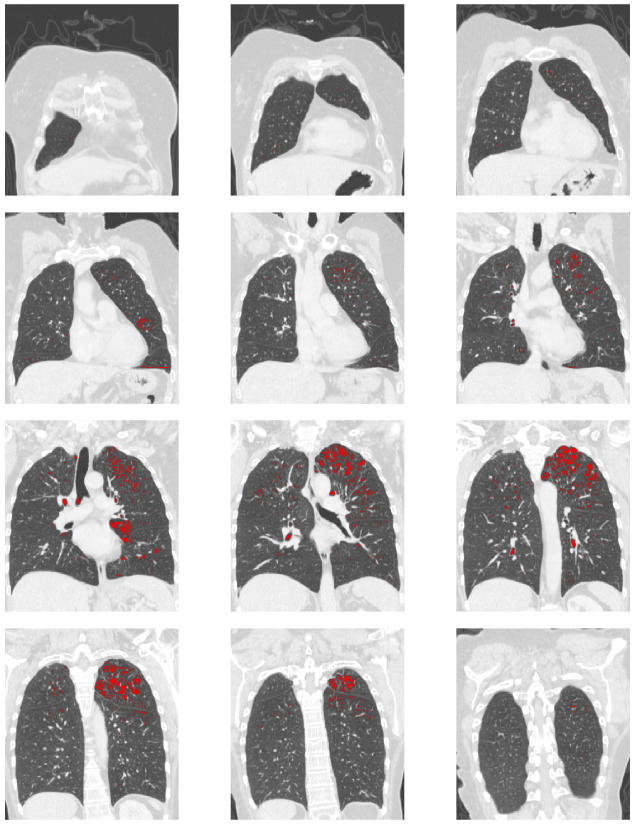


Figure A7.11h: QCT-derived emphysema (% LAA) for patient OXF0113. Red areas correspond to regions with attenuation less than -950 HU. Images show mild paraseptal and centilobular emphysema in the left upper lobe.

Data analysis from COPD patient OXF0144

Table A7.12: Lobar imaging parameters acquired from OXF0144

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	92.26	86.87	20.54	98.07	76.46
HP ^{129}Xe-MRI$_R$ % ventilated volume	91.93	86.09	19.62	97.61	75.78
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.047	0.045	0.054	0.050	0.053
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.048	0.050	0.046	0.047	0.051
QCT-derived % LAA	4.5	7.1	12.5	1.1	4.3
QCT-derived Pi10 (mm)	6.9	6.6	6.9	5.1	5.6
NM-Q SPECT relative % perfusion	19.8	11.9	9.7	41.4	17.2

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

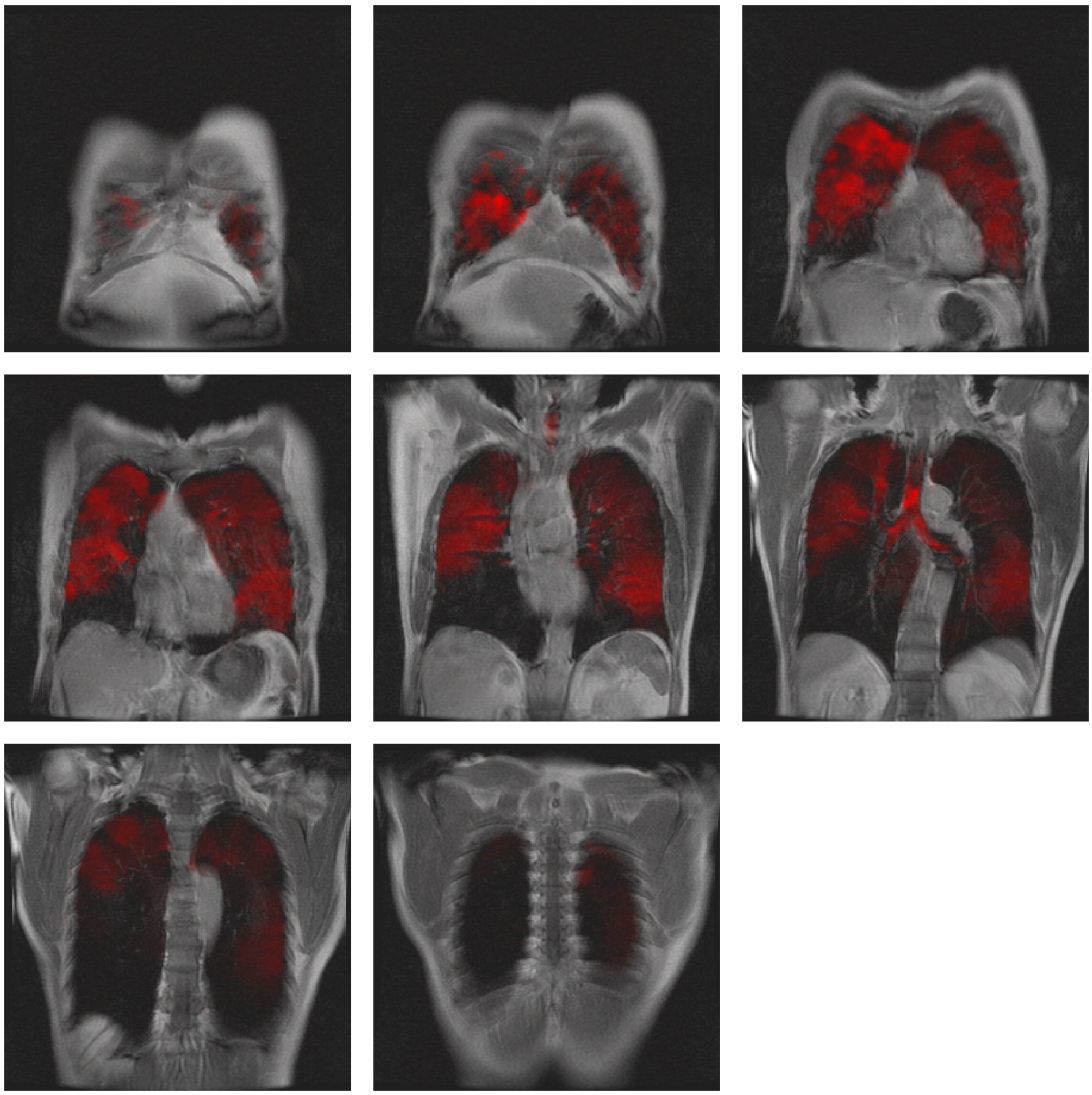


Figure A7.12a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0144. Co-registration to proton MRI enables the lung boundaries to be defined.

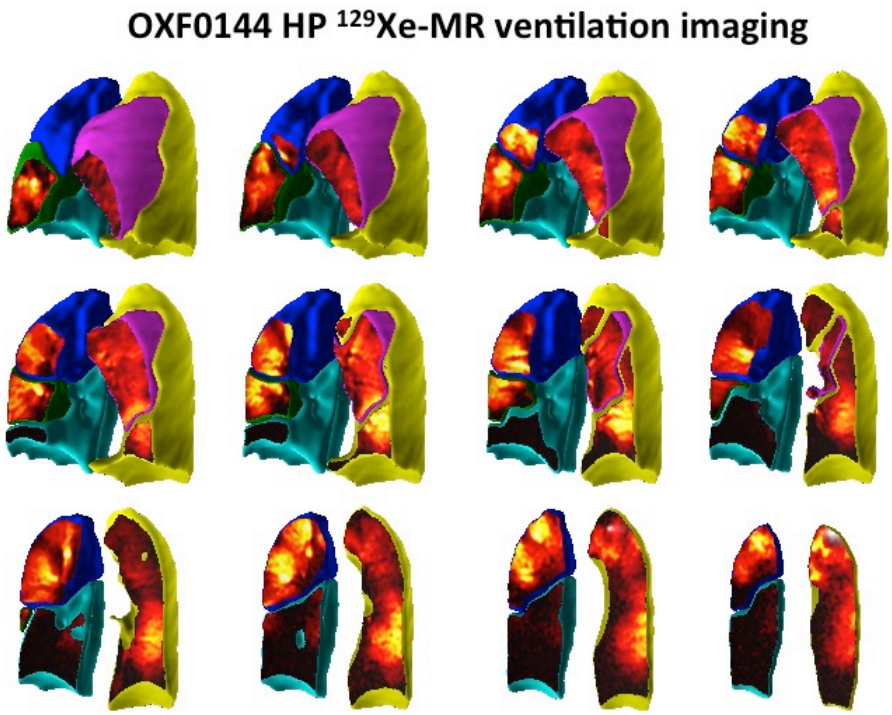


Figure A7.12b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0144. Low signal intensity is appreciated in the lower lobes, more on the right (cyan) in keeping with poor ventilation in these lobes.

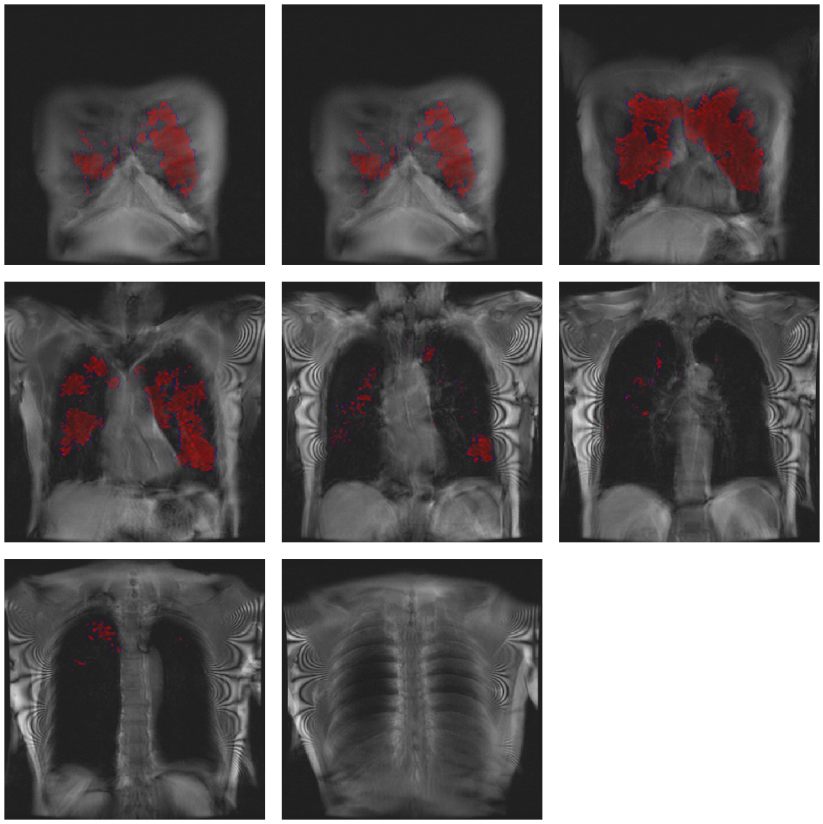


Figure A7.12c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0144.

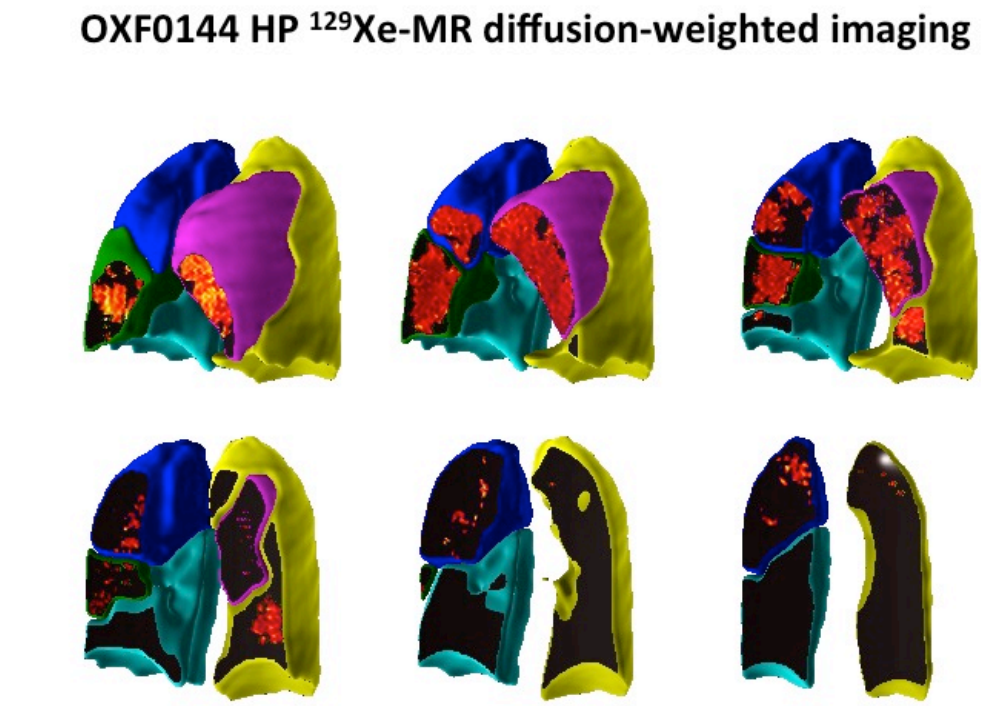


Figure A7.12d: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0144. There is increased signal intensity in the left upper lobe (pink) anteriorly corresponding to higher ADC values and increased emphysema.

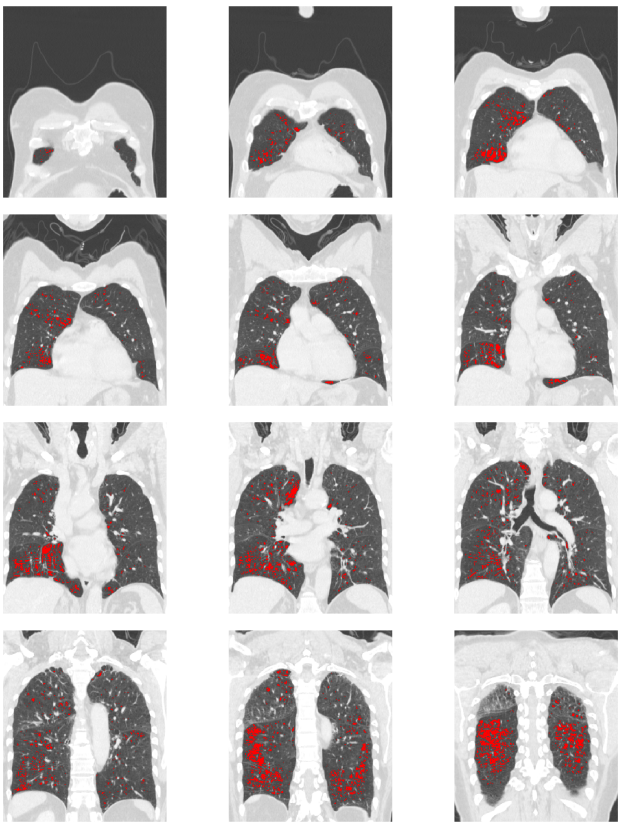


Figure A7.12e: QCT-derived emphysema (% LAA) for patient OXF0144. Red areas correspond to regions with attenuation less than -950 HU.

Data analysis from COPD patient OXF0086

Table A7.13: Lobar imaging parameters acquired from OXF0086

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	94.17	72.28	99.85	84.09	85.14
HP ^{129}Xe-MRI$_R$ % ventilated volume	77.77	57.23	87.03	85.27	74.50
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.069	0.046	0.049	0.058	0.030
HP ^{129}Xe-MRI$_R$ ADC (cm^2sec^{-1})	0.042	0.024	0.027	0.036	0.019
QCT-derived % LAA	11.4	0	0.3	14.3	0.07
QCT-derived Pi10 (mm)	6.4	9.6	8.2	6.8	5.7
NM-Q SPECT relative % perfusion	40	7.5	4.4	45.5	2.6

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

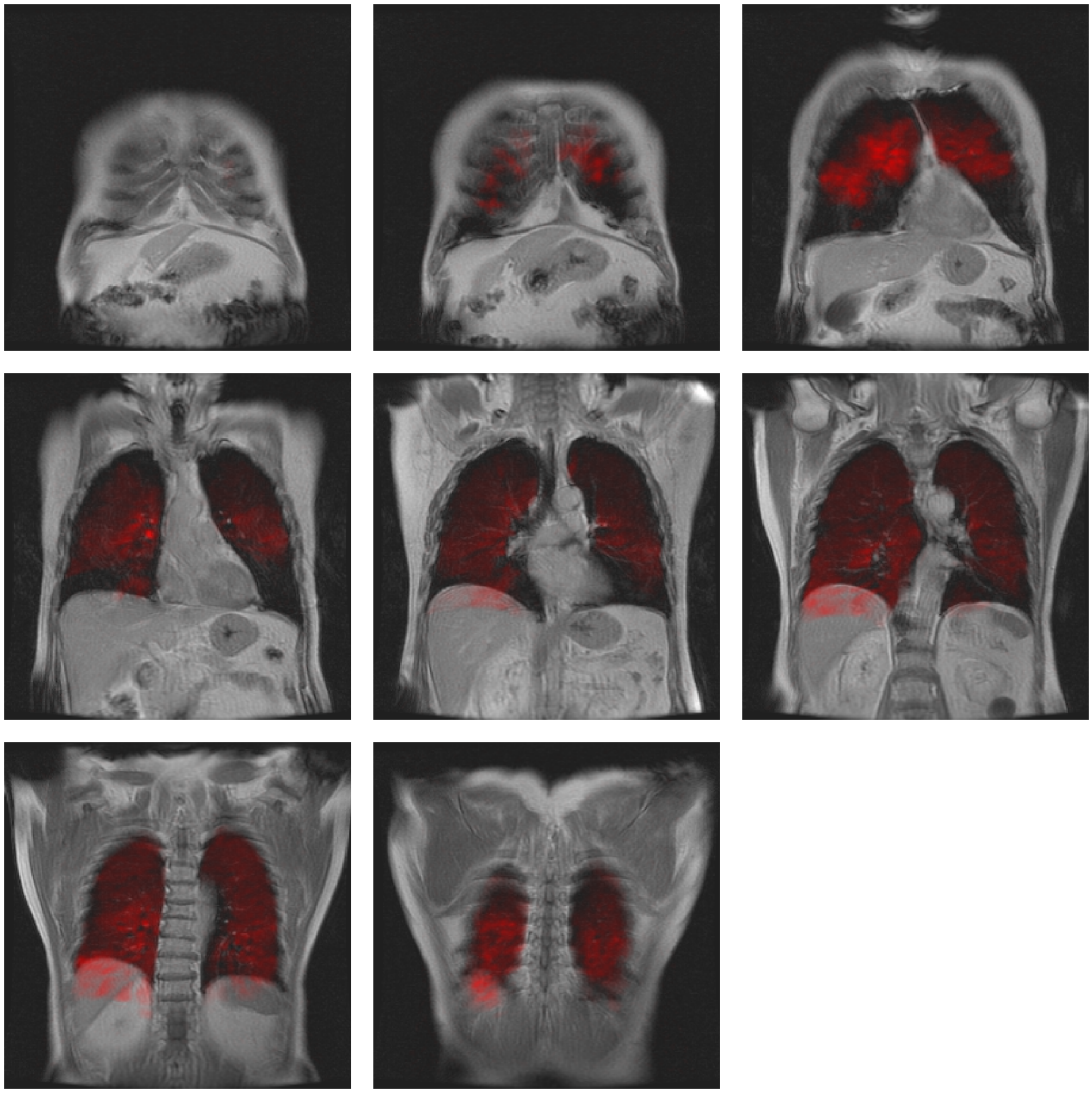


Figure A7.13a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0086. Co-registration to proton MRI enables the lung boundaries to be defined.

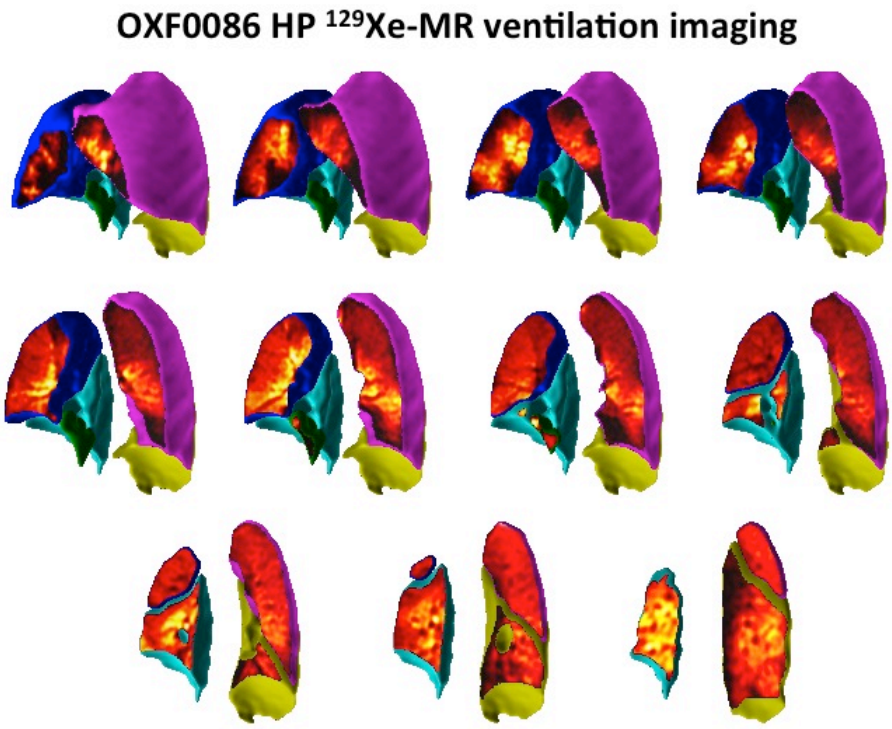


Figure A7.13b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0086. Images show peripheral ventilation defects in both upper lobes (right – blue, left – pink).

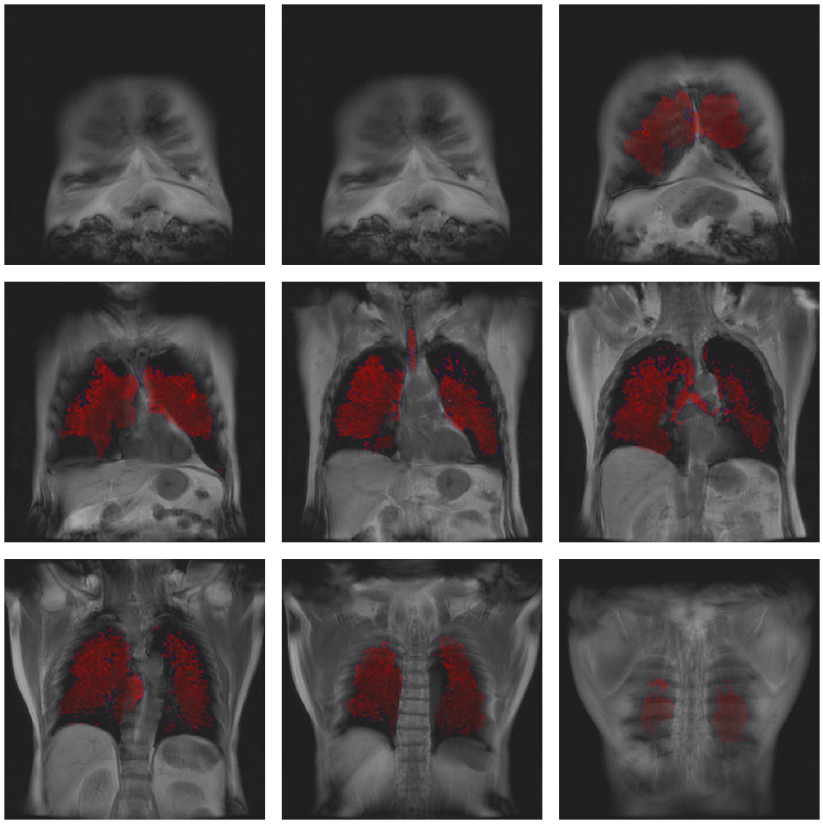


Figure A7.13c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0086.

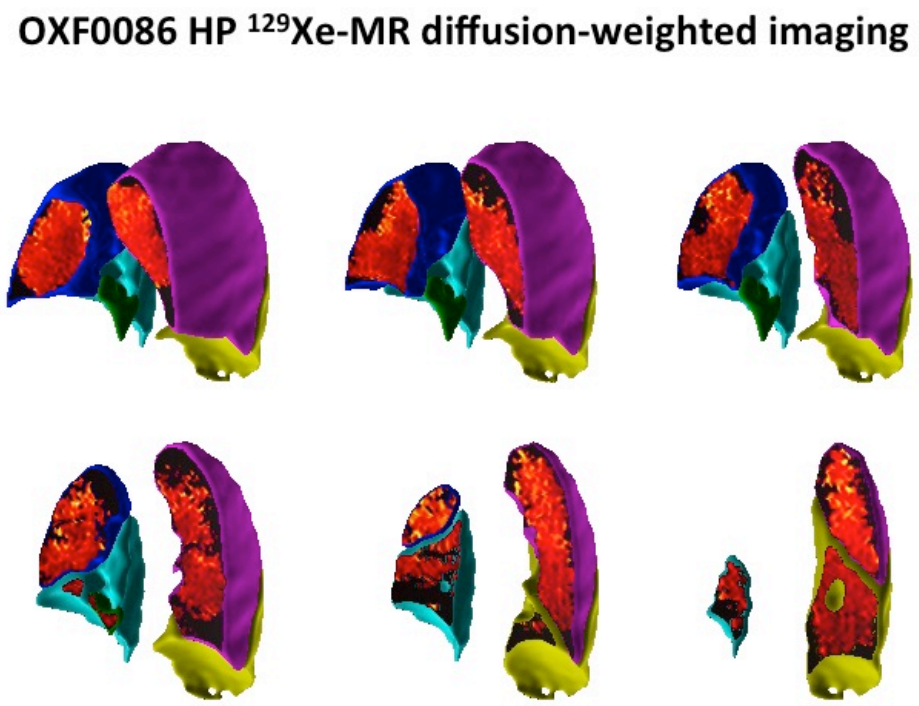


Figure A7.13d: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0086. Images show increased signal intensity in the left upper lobe (pink) indicating elevated ADC values.

Data analysis from COPD patient OXF0136

Table A7.14: Lobar imaging parameters acquired from OXF0136

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	69.92	90.22	66.59	58.07	70.19
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.032	0.027	0.028	0.027	0.027
QCT-derived % LAA	8.8	8.6	4.8	7.5	6.0
QCT-derived Pi10 (mm)	7.9	7.0	7.4	5.4	5.1
NM-Q SPECT relative % perfusion	28.1	6.8	14.1	33.7	17.2

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

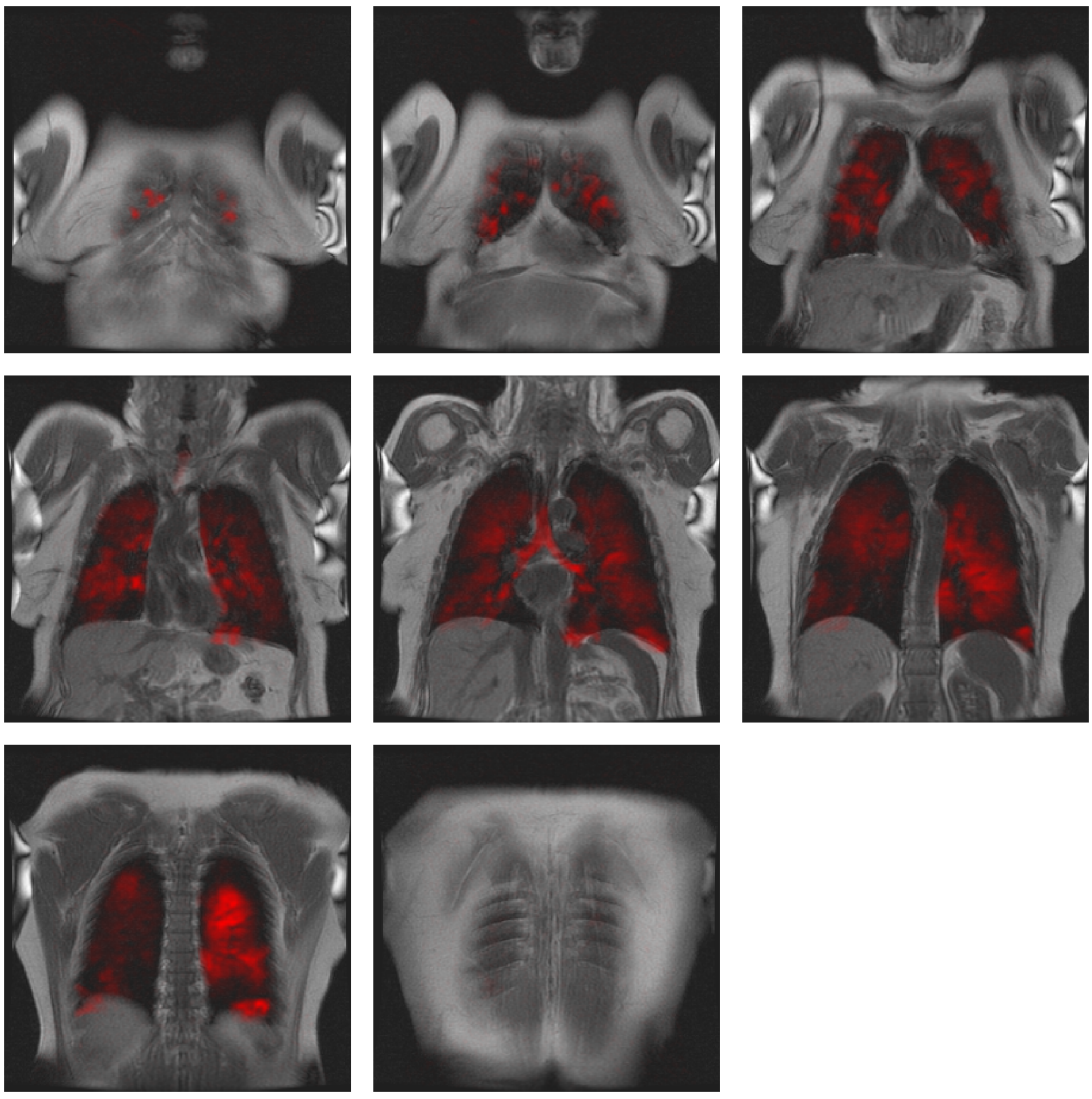


Figure A7.14a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0136. Co-registration to proton MRI enables the lung boundaries to be defined.

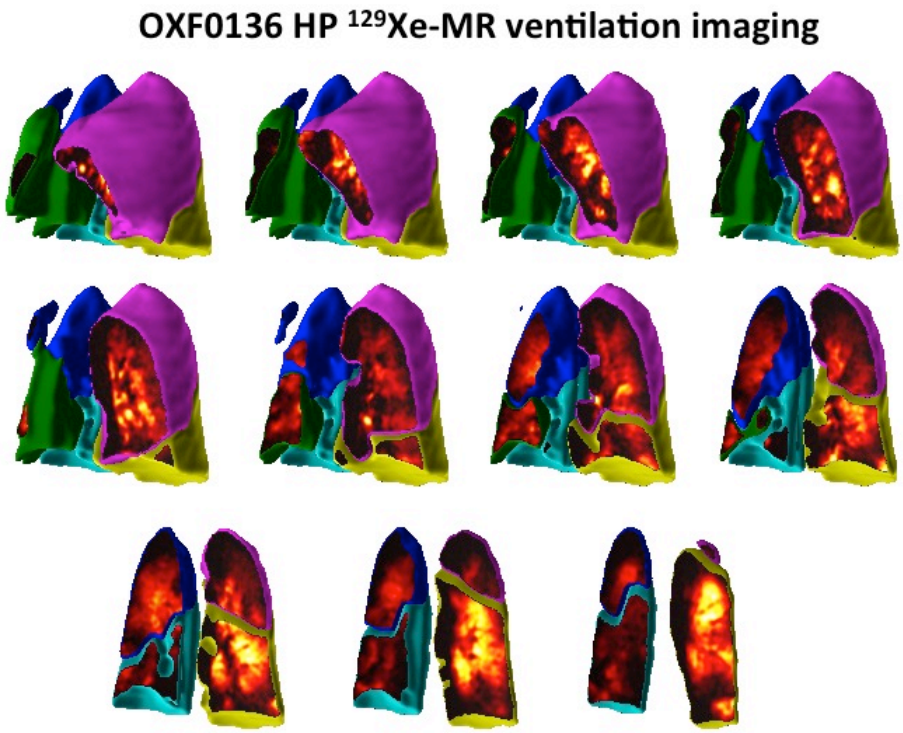


Figure A7.14b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0136. Images show multiple ventilation defects in all lobes.

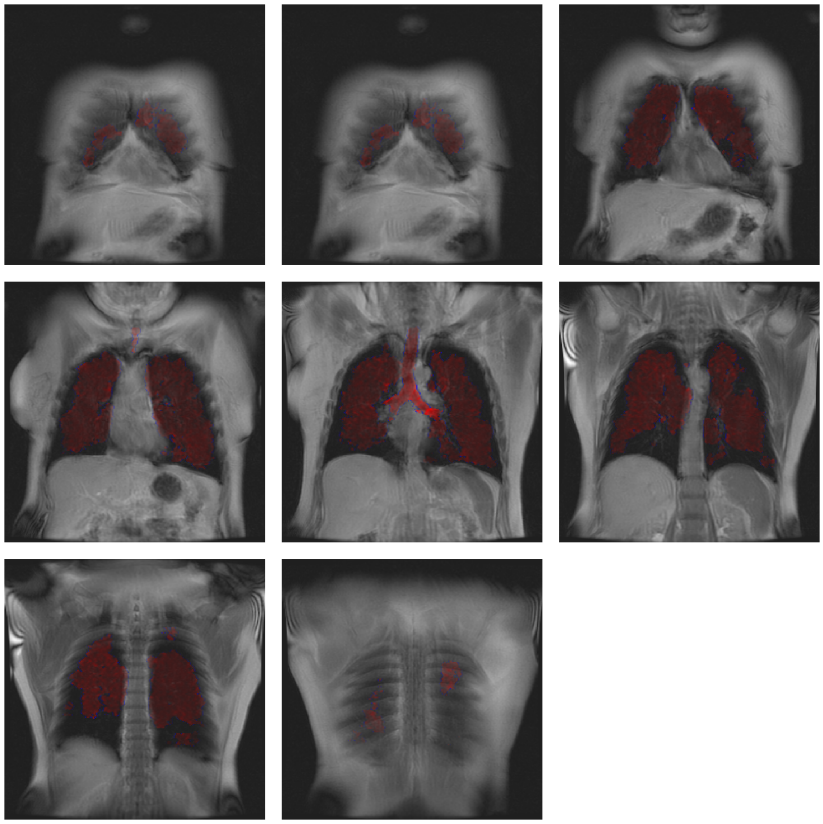


Figure A7.14c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0136.

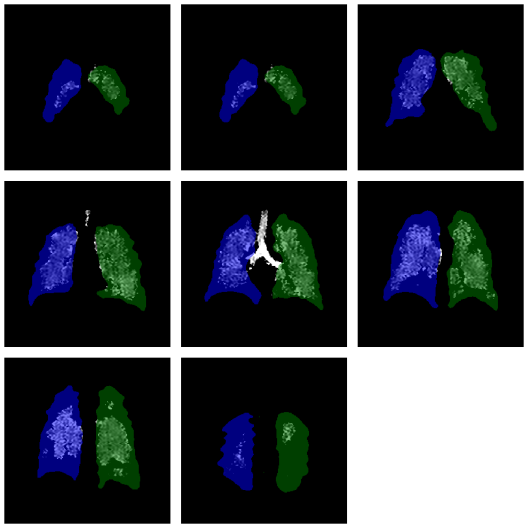


Figure A7.14d: Coronal co-registered lung masks from proton MRI and HP ^{129}Xe-MRI diffusion-weighted imaging in OXF0136. Lung masks are from HP ^{129}Xe-MRI ADC maps (grey-scale) and proton MRI (right lung – blue, left lung - green).

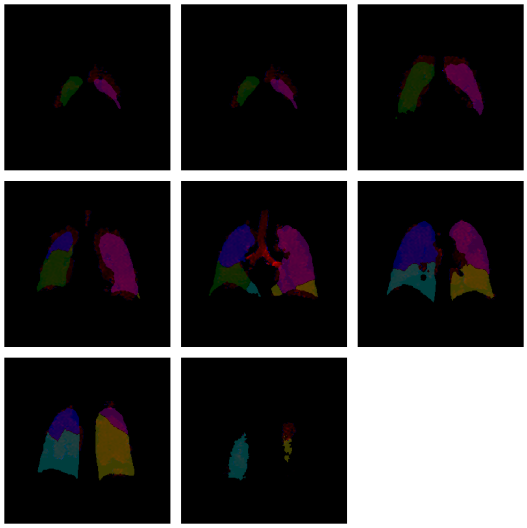


Figure A7.14e: Non-rigid co-registration of HP ^{129}Xe-MR diffusion-weighted imaging and QCT from OXF0136. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MRI ADC values.

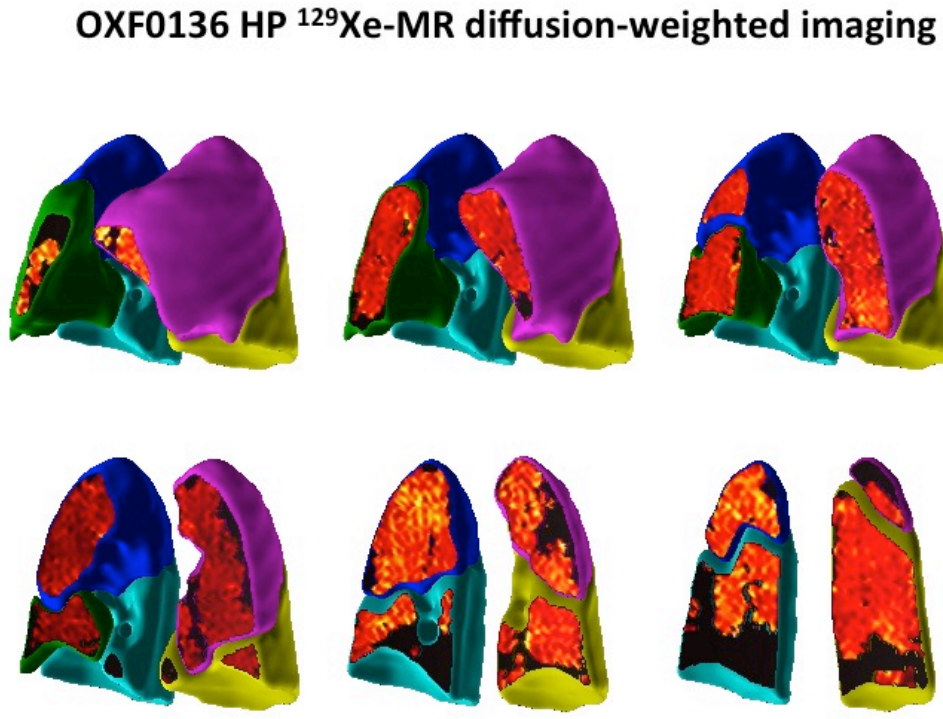


Figure A7.14f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0136. There is increased signal intensity in the right upper (blue) and left upper (pink) lobes consistent with elevated ADC values.

Data analysis from COPD patient OXF0052

Table A7.15: Lobar imaging parameters acquired from OXF0052

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	61.3	95.9	96.4	77.9	94.3
QCT-derived % LAA	29.7	12.03	2.2	12.4	2.3
QCT-derived Pi10 (mm)	7.3	9.0	9.1	6.9	8.5
NM-Q SPECT relative % perfusion	13.2	11.3	29	30.7	15.8

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

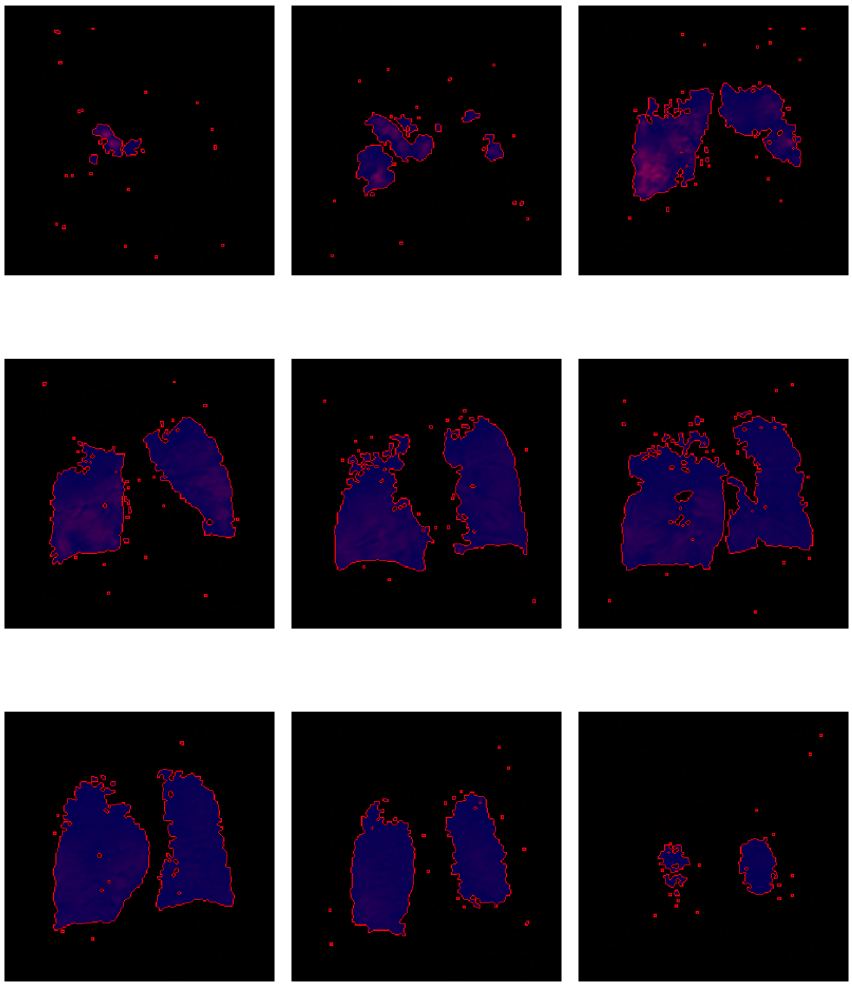


Figure A7.15a: Coronal lung masks from HP ^{129}Xe-MR ventilation imaging in OXF0052. Lung masks are from HP ^{129}Xe-MR ventilation imaging (blue). The lung boundaries have been outlined in red. Background noise signal (red dots) is excluded from analysis.

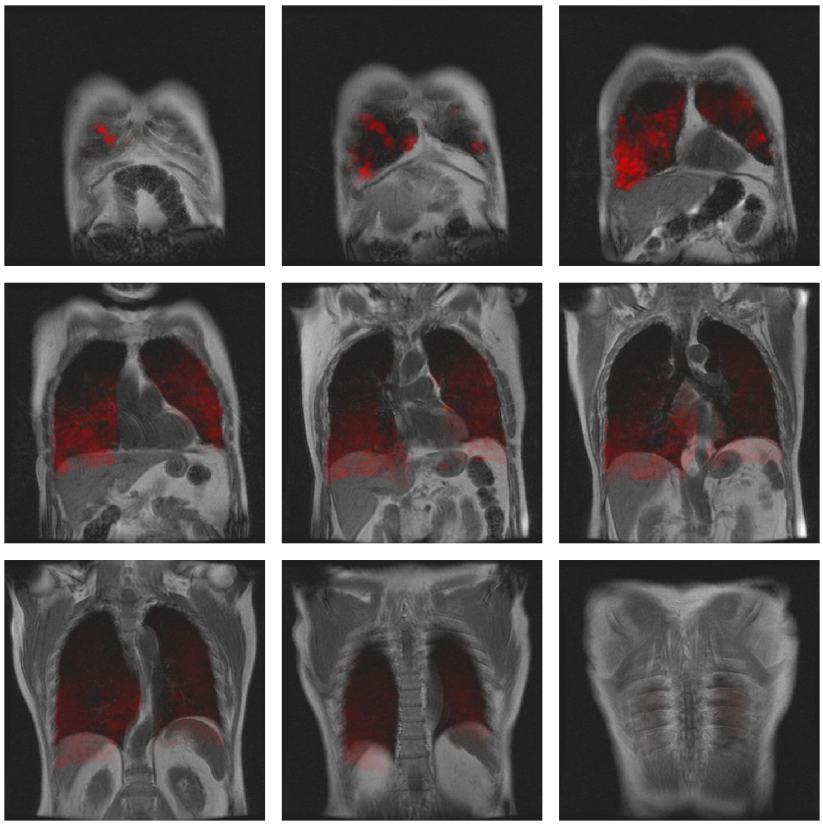


Figure A7.15b: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0052. Co-registration to proton MRI enables the lung boundaries to be defined.

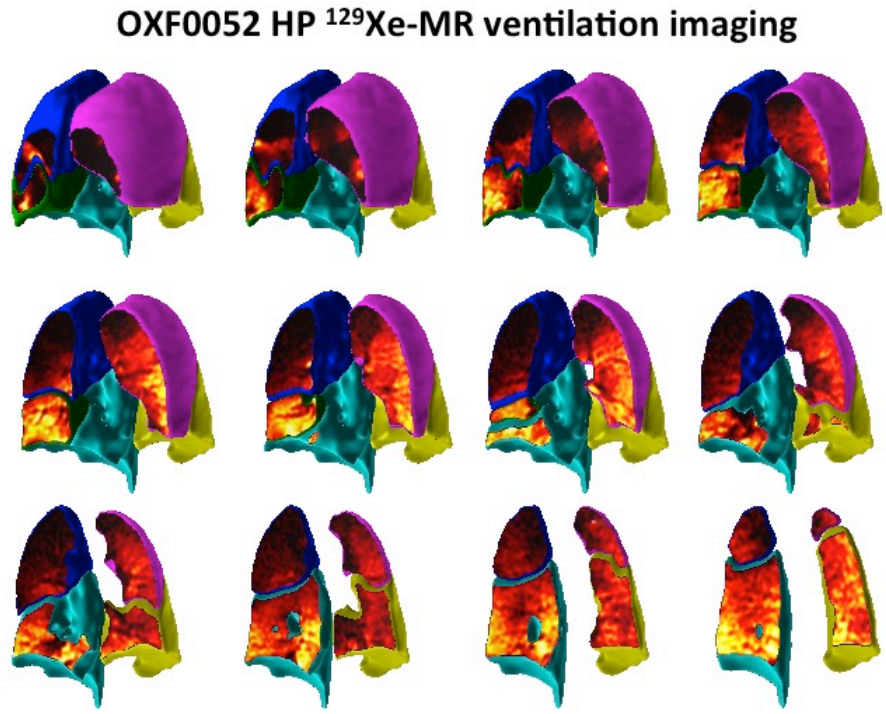


Figure A7.15c: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0052. Low signal intensity is appreciated in the right upper lobe (blue) in keeping with poor ventilation.

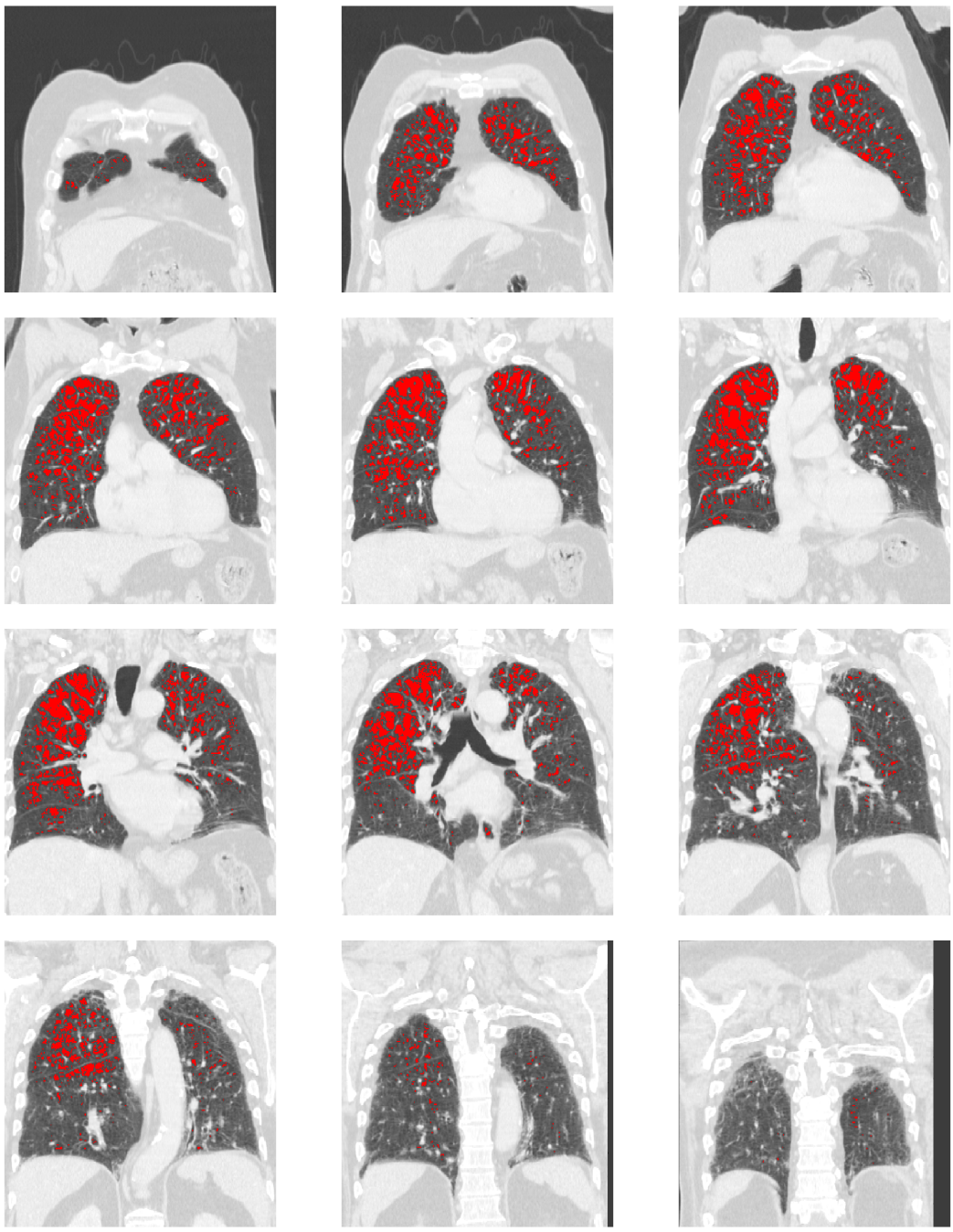


Figure A7.15d: QCT-derived emphysema (%LAA) from patient OXF0052. Red areas correspond to regions with attenuation less than -950 HU. Images show moderate upper lobe predominant emphysema.

Data analysis from COPD patient OXF0151

Table A7.16: Lobar imaging parameters acquired from OXF0151

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	63.2	72.0	87.7	75.5	90.6
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.036	0.028	0.028	0.034	0.027
QCT-derived % LAA	4.2	0.1	0	2.5	0.1
QCT-derived Pi10 (mm)	6.8	5.9	6.4	5.9	5.8

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

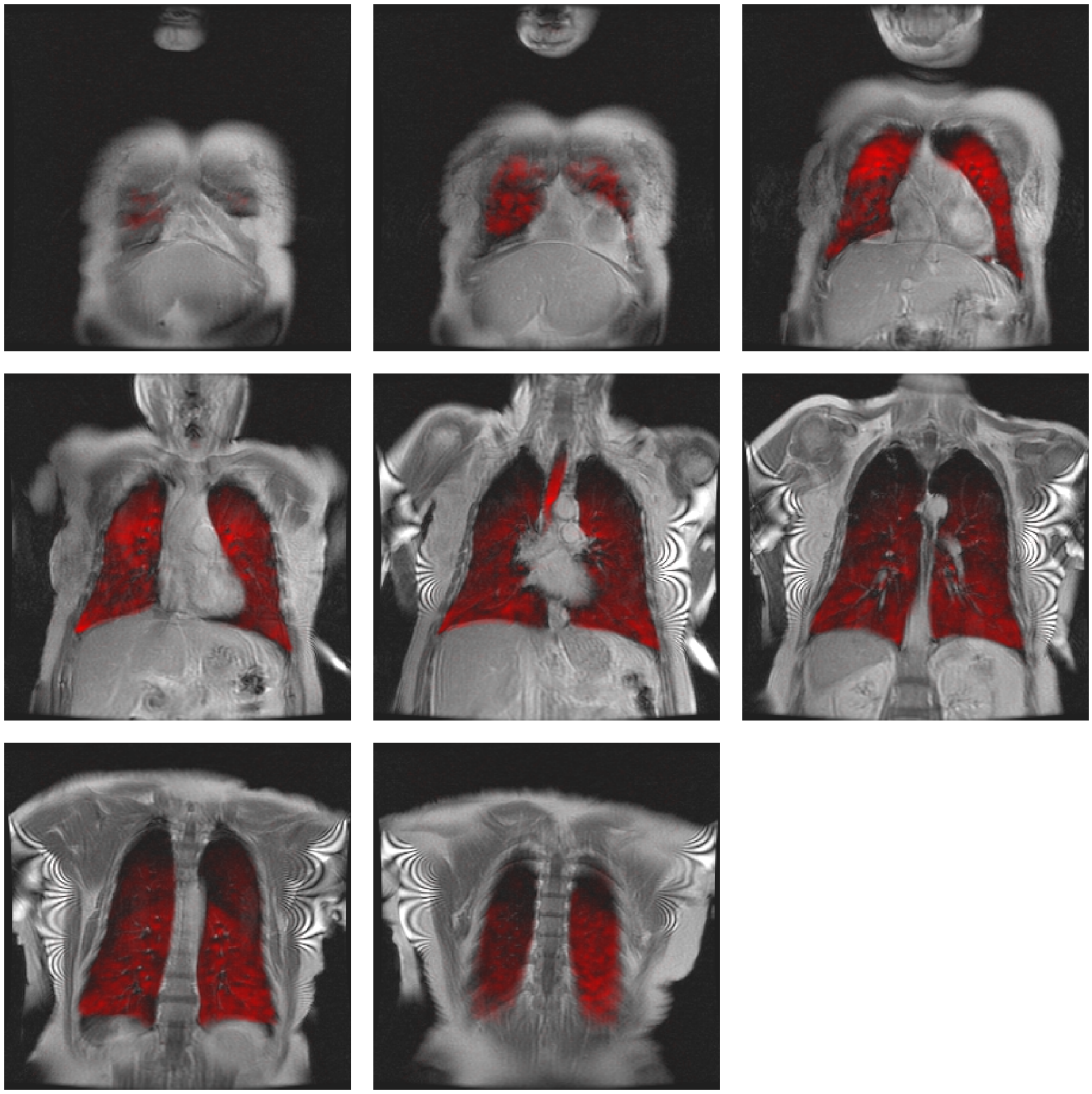


Figure A7.16a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0151. Co-registration to proton MRI enables the lung boundaries to be defined.

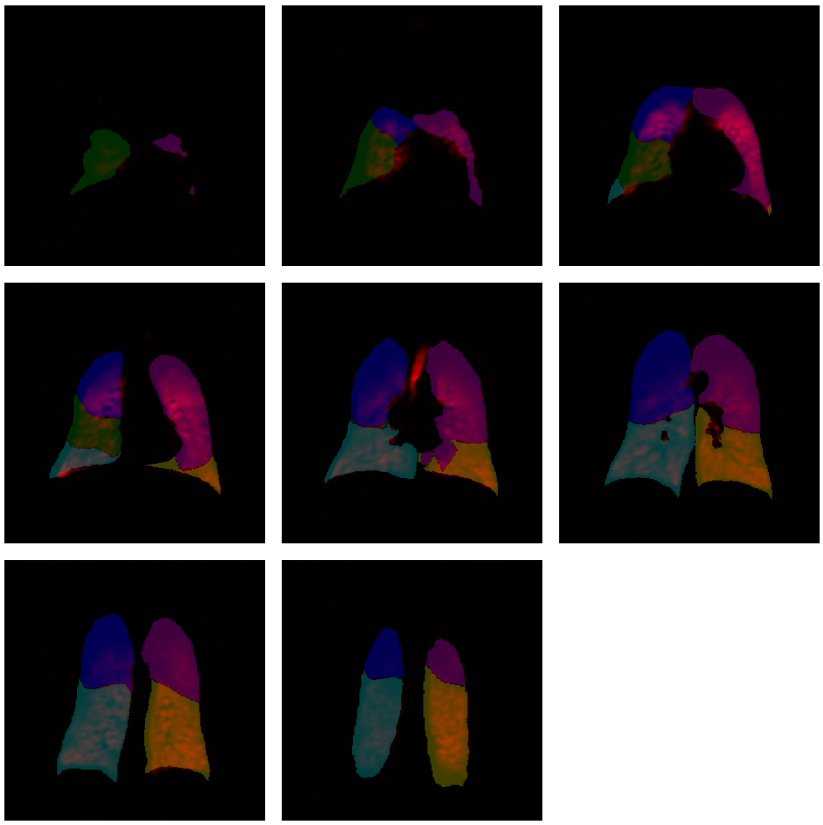


Figure A7.15b: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0151. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

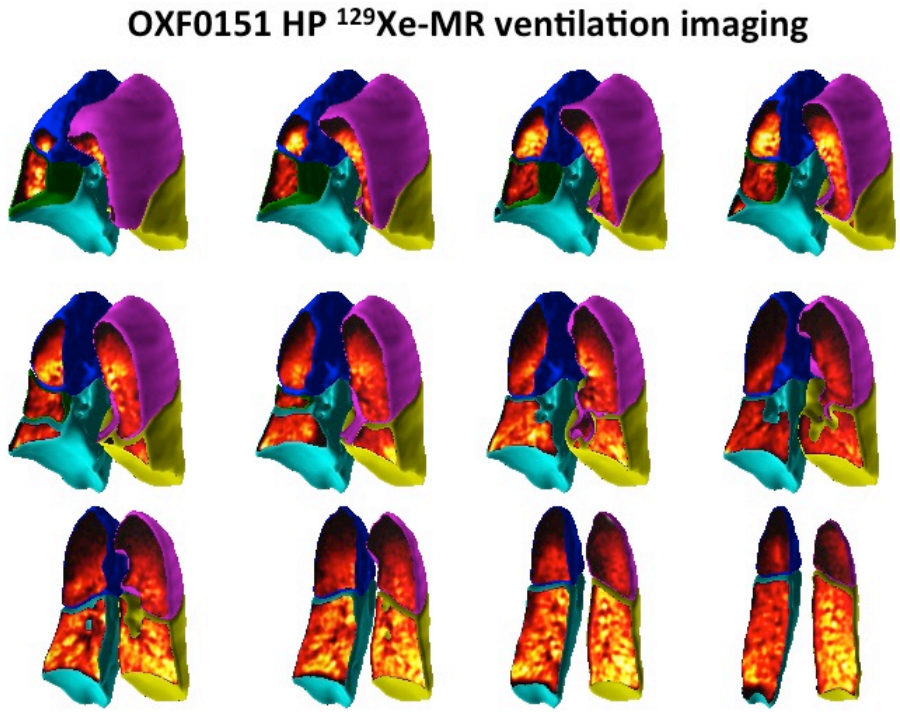


Figure A7.15c: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0151. Images show peripheral ventilation defects in both upper lobes (right – blue, left - pink).

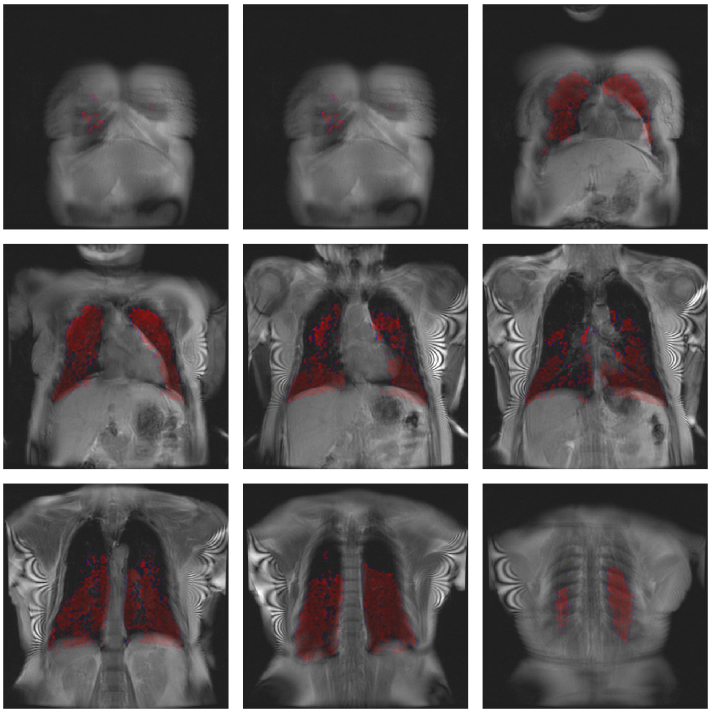


Figure A7.15d: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0151.

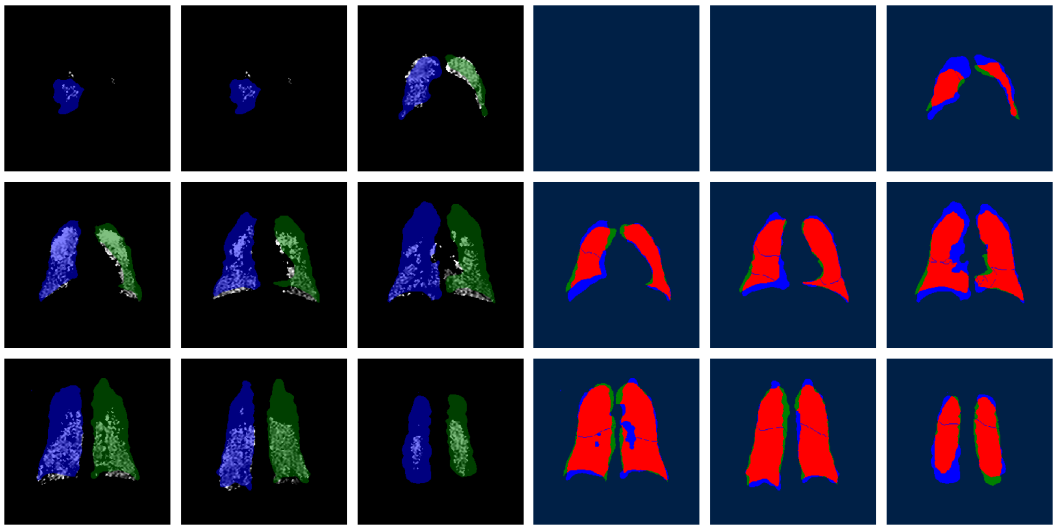


Figure A7.15e: Rigid co-registration of proton MRI and HP ^{129}Xe-MR diffusion-weighted imaging in OXF0151. HP ^{129}Xe-MRI maps are shown in grey-scale with overlying proton MRI lung masks (right – blue, left – green).

Figure A7.15f: Coronal non-rigid co-registered lung masks from multi-modality imaging acquired in OXF0151. Lung masks are from HP ^{129}Xe-MR diffusion-weighted imaging (green), proton MRI (blue) and QCT (red).

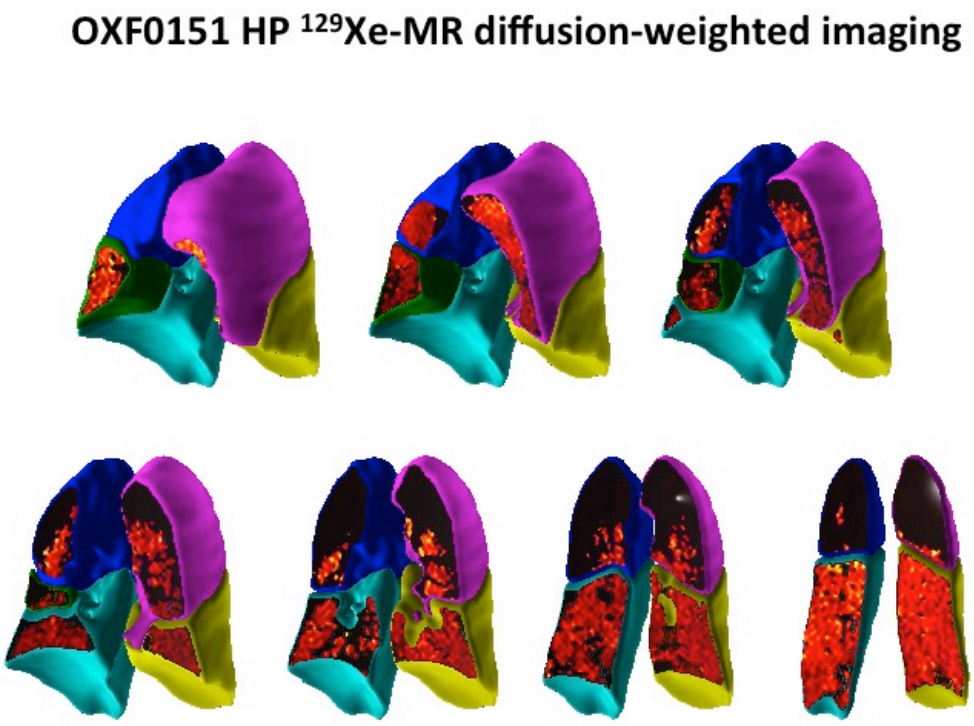


Figure A7.15g: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0151. Increased signal intensity in the left lower lobe (yellow) corresponds to elevated ADC values.

Data analysis from COPD patient OXF0098

Table A7.16: Lobar imaging parameters acquired from OXF0098

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	88.3	90.2	80.3	89.0	77.6
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.063	0.053	0.052	0.062	0.049
QCT-derived % LAA	12.7	4.4	1	10.4	0
QCT-derived Pi10 (mm)	6.0	6.0	6.0	5.5	6.8
NM-Q SPECT relative % perfusion	16.1	10.8	12.4	40.2	20.5

R Repeat HP ^{129}Xe-MRI measures to evaluate reproducibility
RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

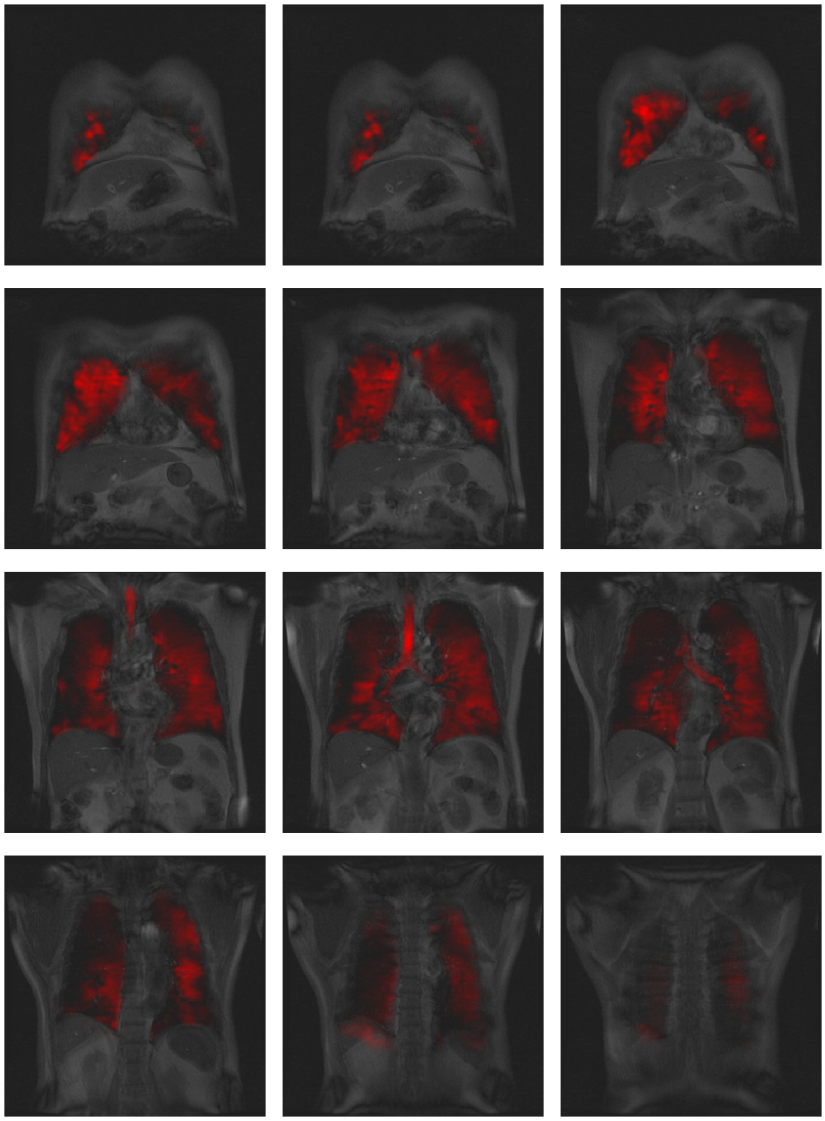


Figure A7.16a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0098. Co-registration to proton MRI enables the lung boundaries to be defined.

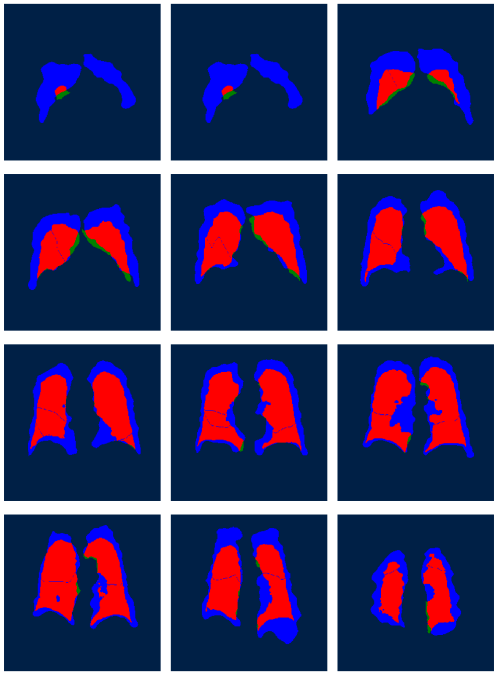


Figure A7.16b: Coronal co-registered lung masks from multi-modality imaging acquired in OXF0098. Lung masks are from HP ^{129}Xe-MR ventilation imaging (green), proton MRI (blue) and QCT (red).

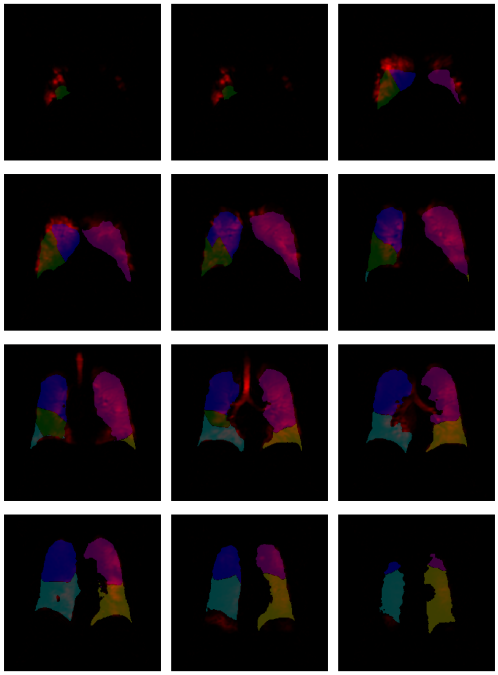


Figure A7.16c: Non-rigid co-registration of HP ^{129}Xe-MR ventilation imaging and QCT from OXF0098. QCT enables definition of the lobar boundaries (pulmonary fissures) to allow lobar quantification of HP ^{129}Xe-MR ventilation.

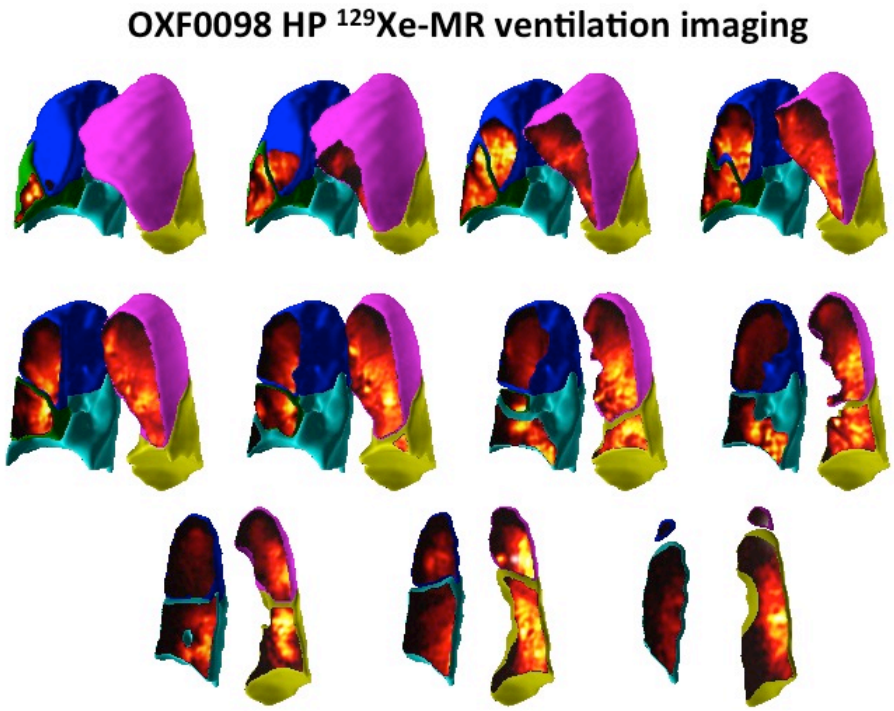


Figure A7.16d: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0098. Low signal intensity is appreciated in the right upper (blue) and lower (cyan) lobes posteriorly indicating poor ventilation.

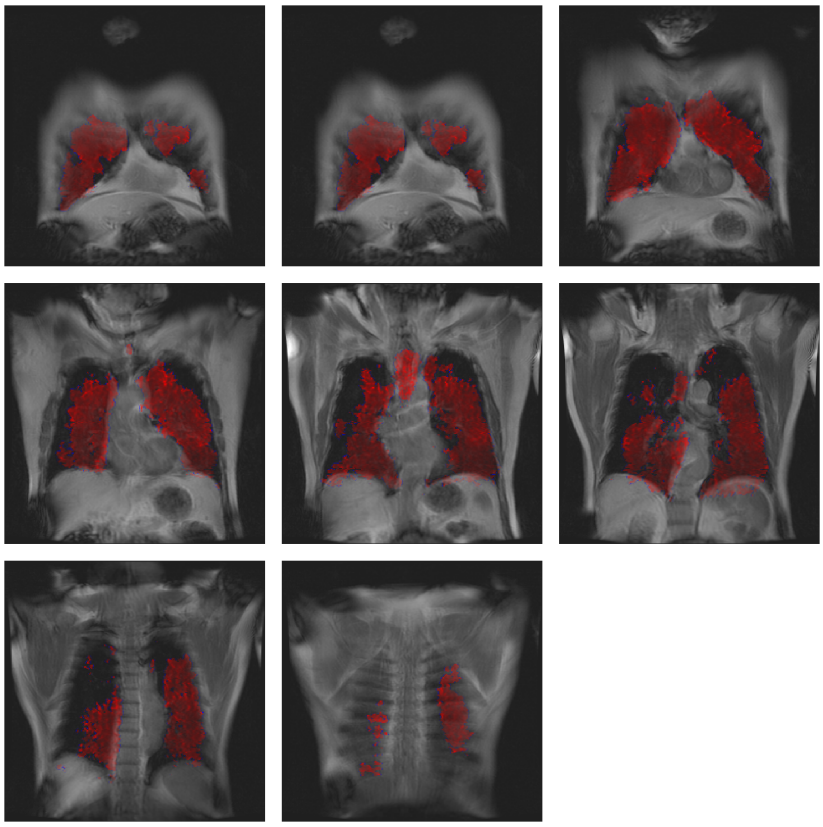


Figure A7.16e: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0098.

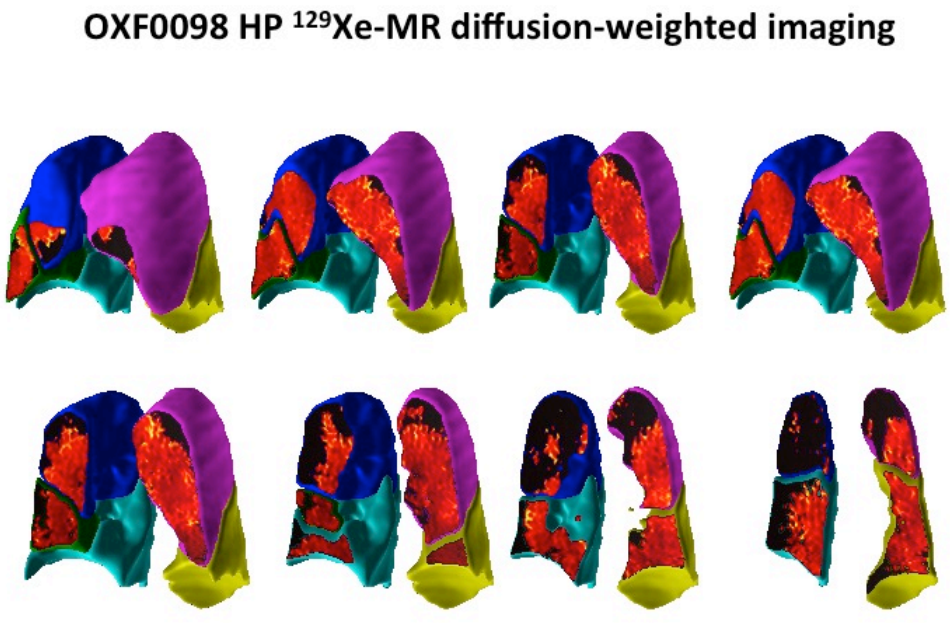


Figure A7.16f: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0098. There is increased signal intensity in the left upper lobe (pink) corresponding to higher ADC values.

Data analysis from COPD patient OXF0009

Table A7.17: Lobar imaging parameters acquired from OXF0009

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	60.81	59.44	98.78	81.31	46.58
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.047	0.046	0.052	0.041	0.055
QCT-derived % LAA	0.3	4.5	10.6	1	2.8
QCT-derived Pi10 (mm)	5.0	6.6	5.2	7.7	5.6

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

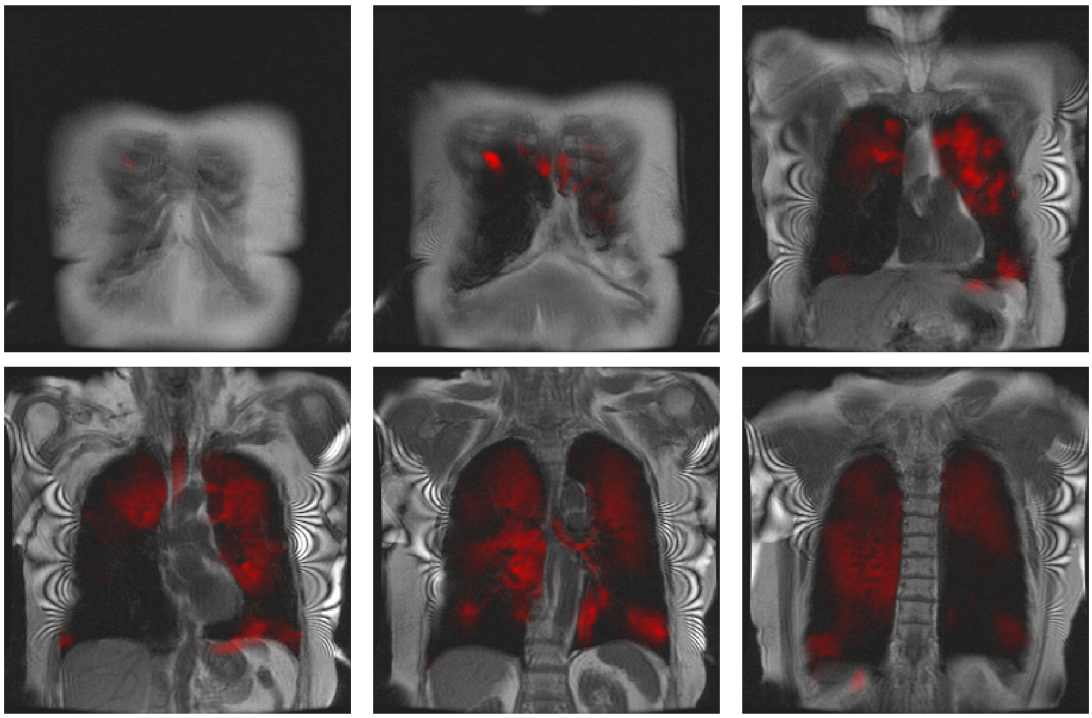


Figure A7.17a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0009. Co-registration to proton MRI enables the lung boundaries to be defined.

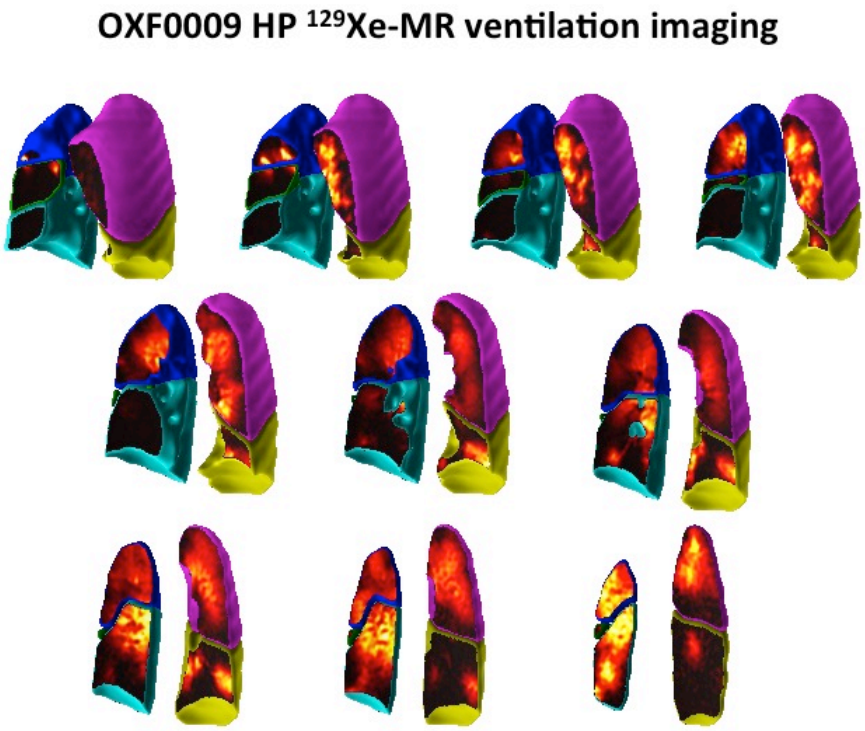


Figure A7.17b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0098. Images show a large ventilation defect in the right lower lobe (cyan).

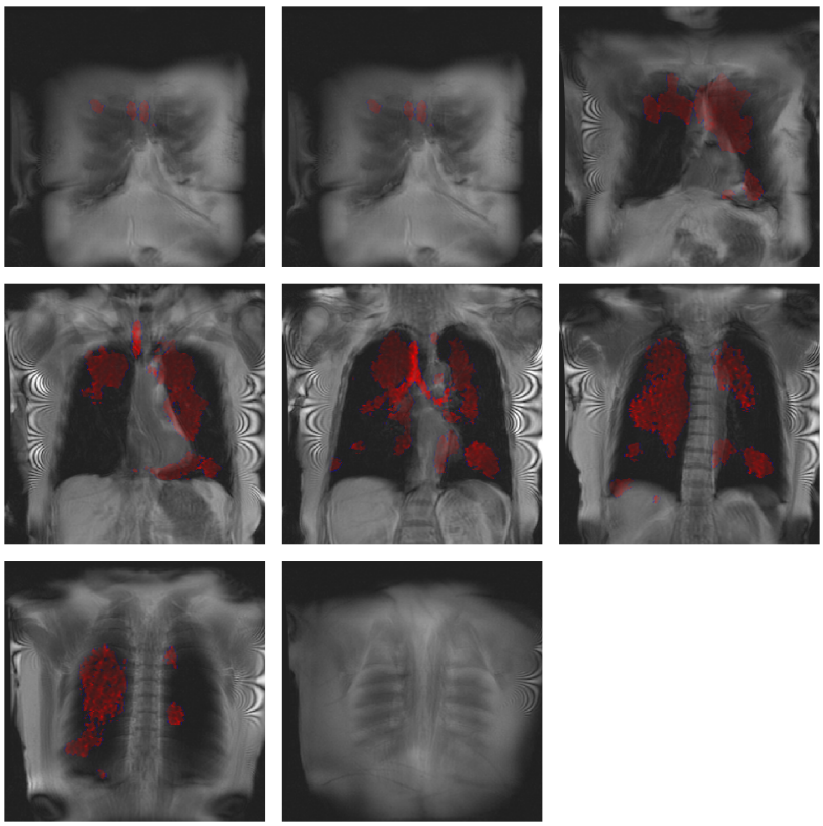


Figure A7.17c: Coronal HP ^{129}Xe-MR diffusion-weighted imaging (red) co-registered to proton MRI from OXF0009.

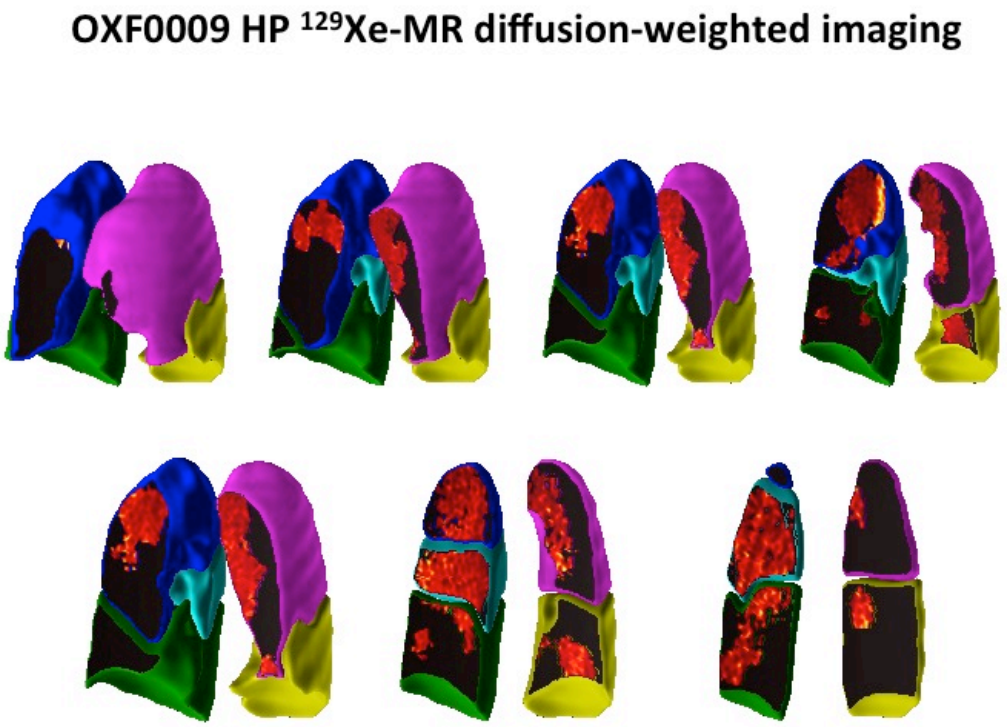


Figure A7.17d: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0009.

Data analysis from COPD patient OXF0153

Table A7.18: Lobar imaging parameters acquired from OXF0153

Imaging parameter	Pulmonary lobe				
	RUL	RML	RLL	LUL	LLL
HP ^{129}Xe-MRI % ventilated volume	82.56	76.75	83.65	62.19	76.55
HP ^{129}Xe-MRI ADC (cm^2sec^{-1})	0.039	0.038	0.040	0.039	0.036
QCT-derived % LAA	0.1	0.2	0.3	0.2	0.02
QCT-derived Pi10 (mm)	7.4	7.9	7.6	7.5	6.9

RUL = Right upper lobe, RML = Right middle lobe, RLL = Right lower lobe, LUL = Left upper lobe, LLL = Left lower lobe, %LAA = Percentage low-attenuation areas less than -950 HU, Pi10 = Square root of bronchial wall area for a "theoretical airway" with an internal perimeter of 10 mm

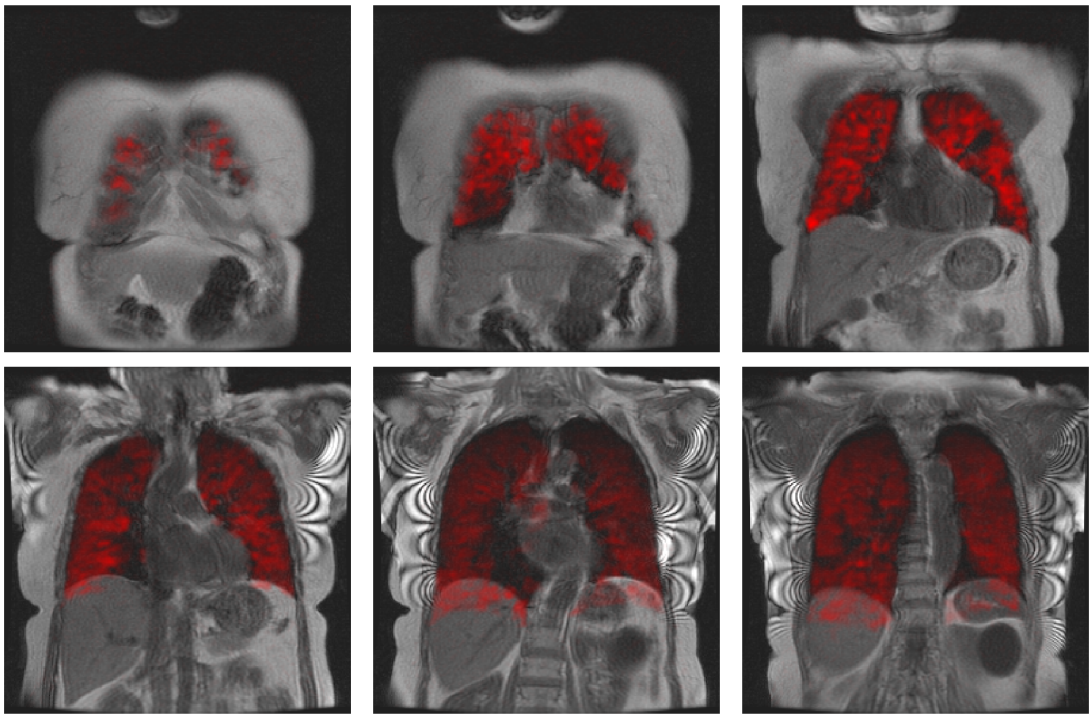


Figure A7.18a: Coronal co-registered HP ^{129}Xe-MR ventilation imaging (red) and proton MRI acquired from OXF0153. Co-registration to proton MRI enables the lung boundaries to be defined.

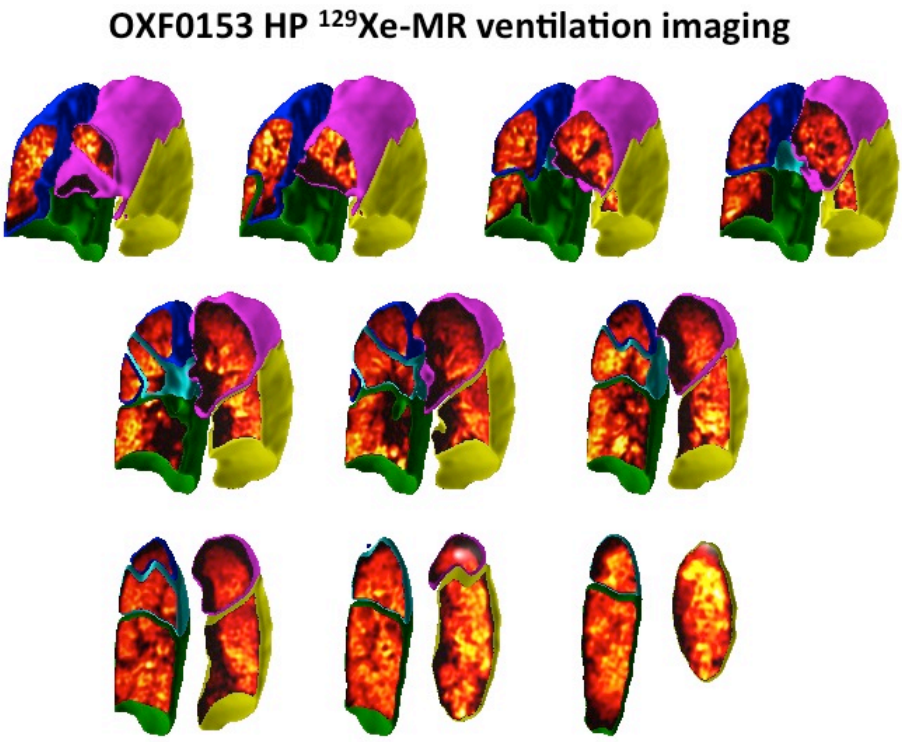


Figure A7.18b: 3-D lobar HP ^{129}Xe-MR ventilation imaging from OXF0153. Images show peripheral ventilation defects most marked in the left upper lobe (pink).

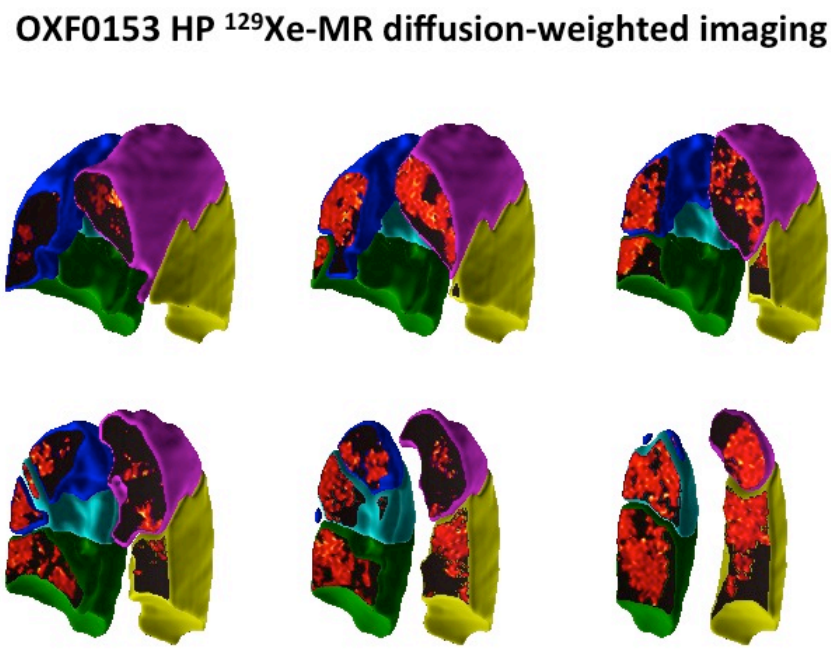


Figure A7.18c: 3-D lobar HP ^{129}Xe-MR diffusion-weighted imaging from OXF0153. Images show increased signal intensity in the left upper lobe (pink) corresponding to elevated ADC values.

Appendix 8: Data analysis of time-resolved HP ^{129}Xe-MRI ventilation imaging

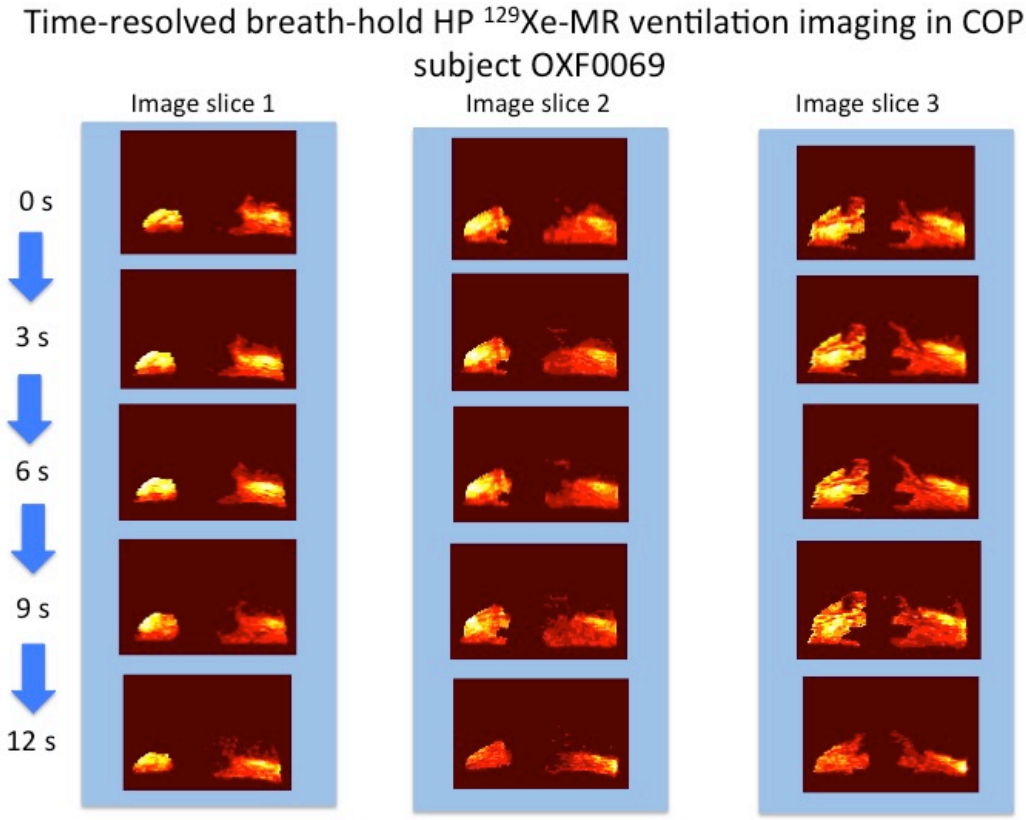


Figure A8.1a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0069. Delayed ventilation is not easily appreciated visually.

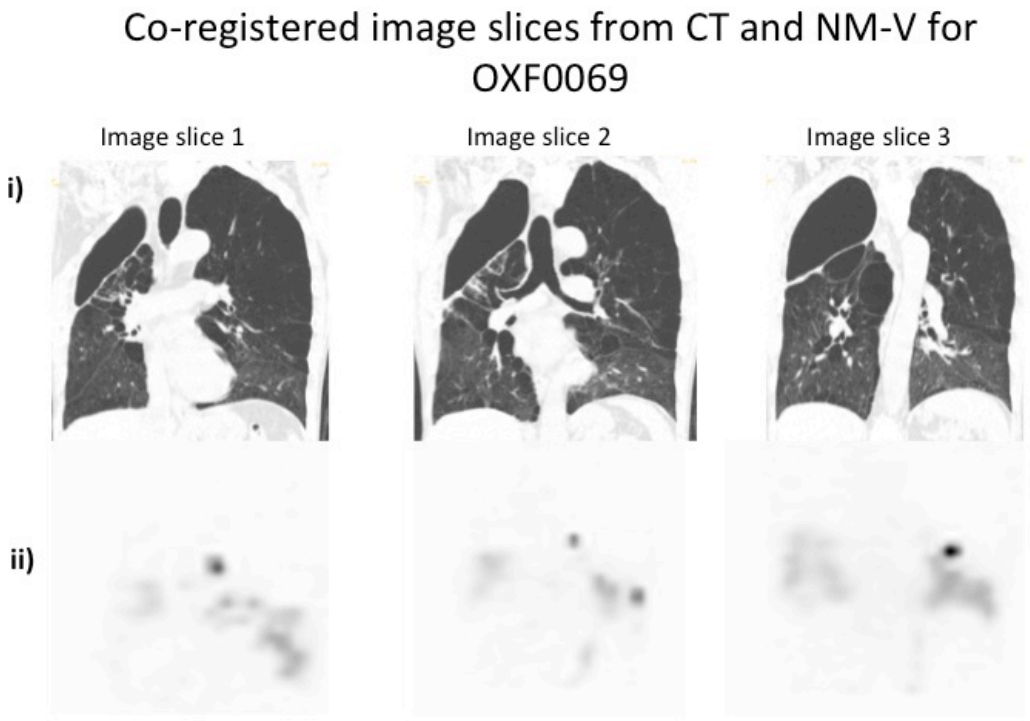


Figure A8.1b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0069. The CT images show a large right apical pleural cavity and severe upper zone emphysema.

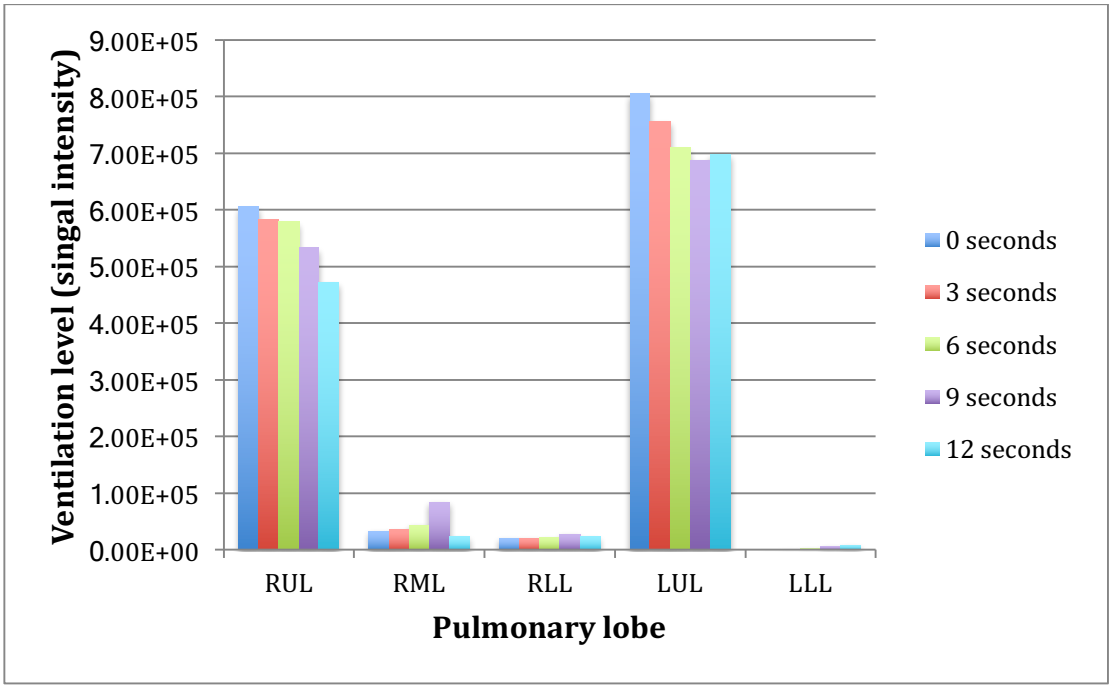


Figure A8.1c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0069. These data demonstrate delayed ventilation in the right middle and lower and left lower lobes.

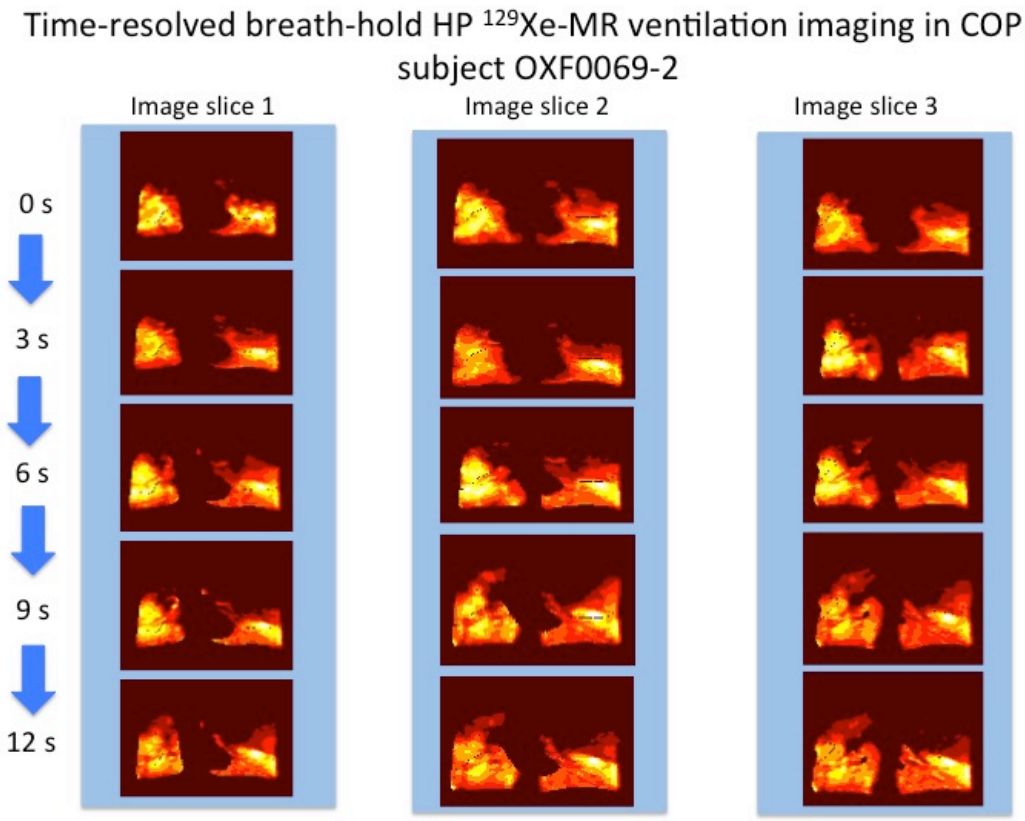


Figure A8.2a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0069-2.

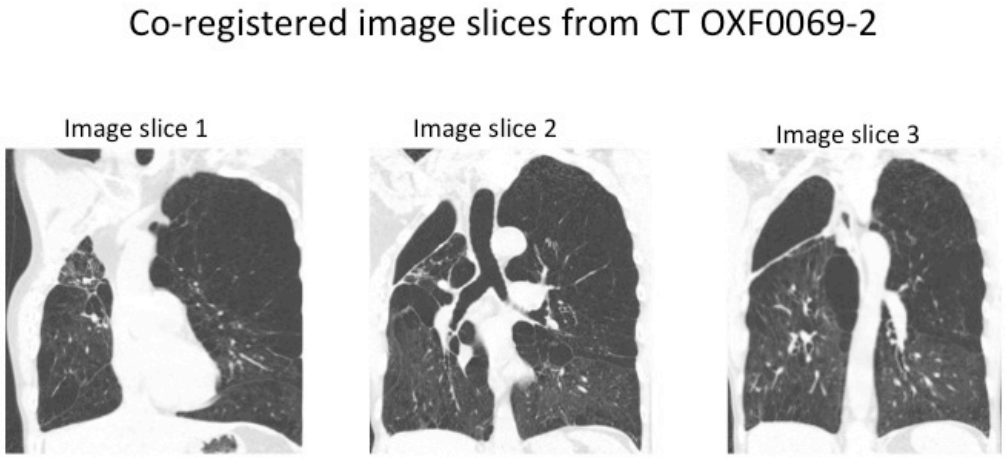


Figure A8.2b: Coronal thoracic CT images acquired from OXF0069-2. Images acquired post-endobronchial valve insertion into the right apical bronchi showing modest reduction in size of the right apical pleural cavity.

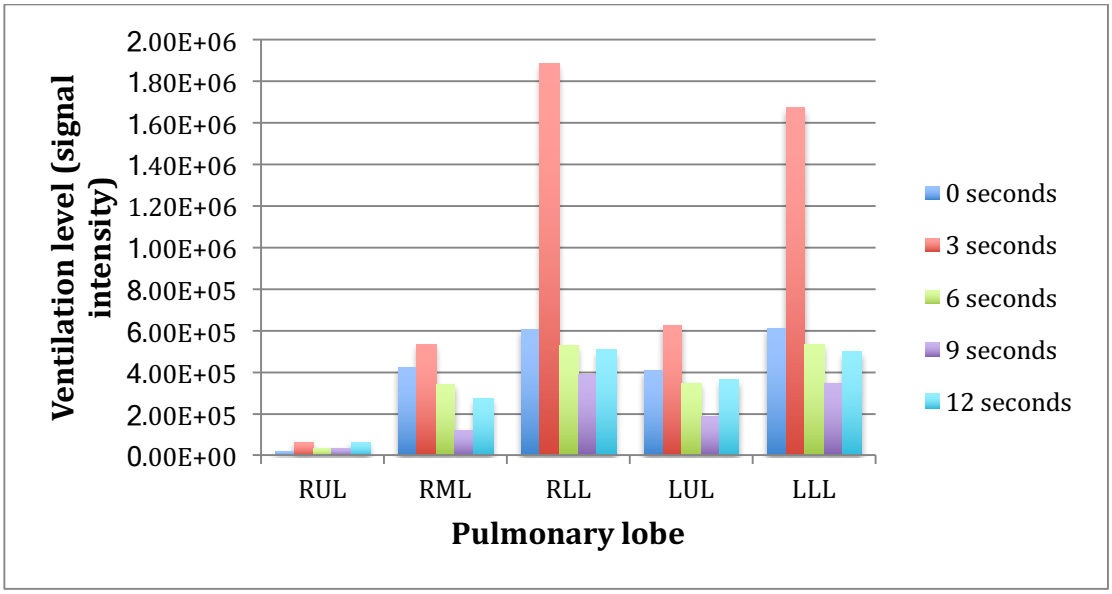


Figure A8.2c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0069-2. These data demonstrate delayed ventilation in all pulmonary lobes.

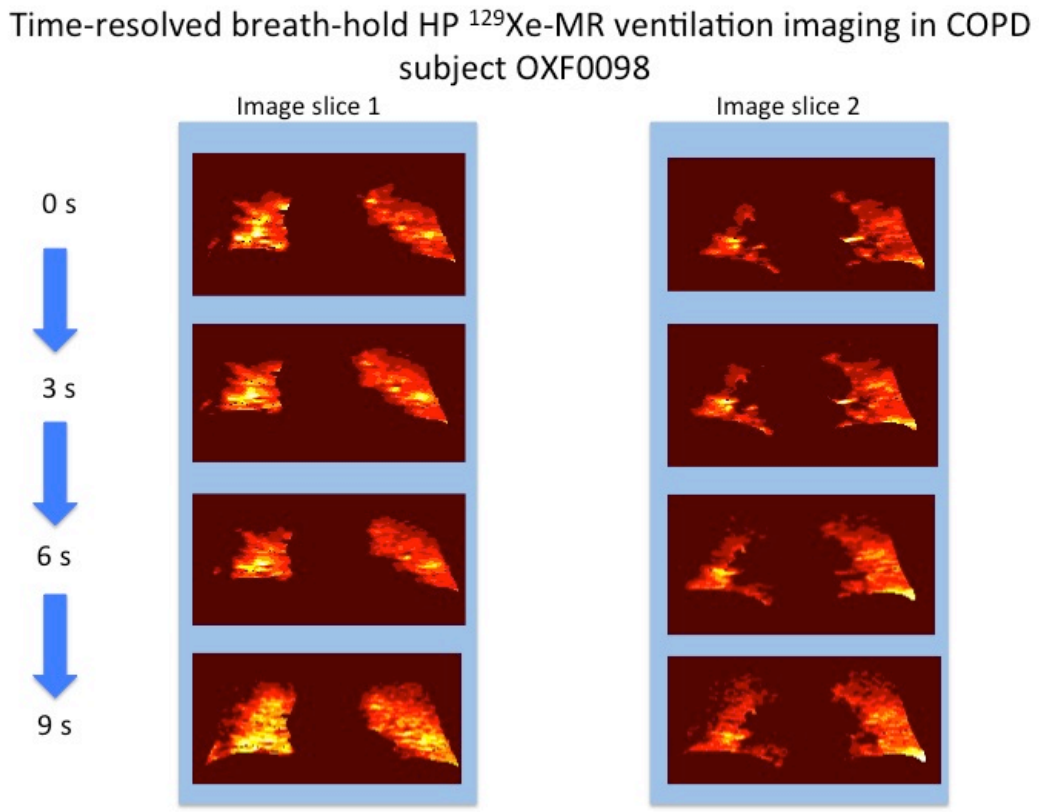


Figure A8.3a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0098.

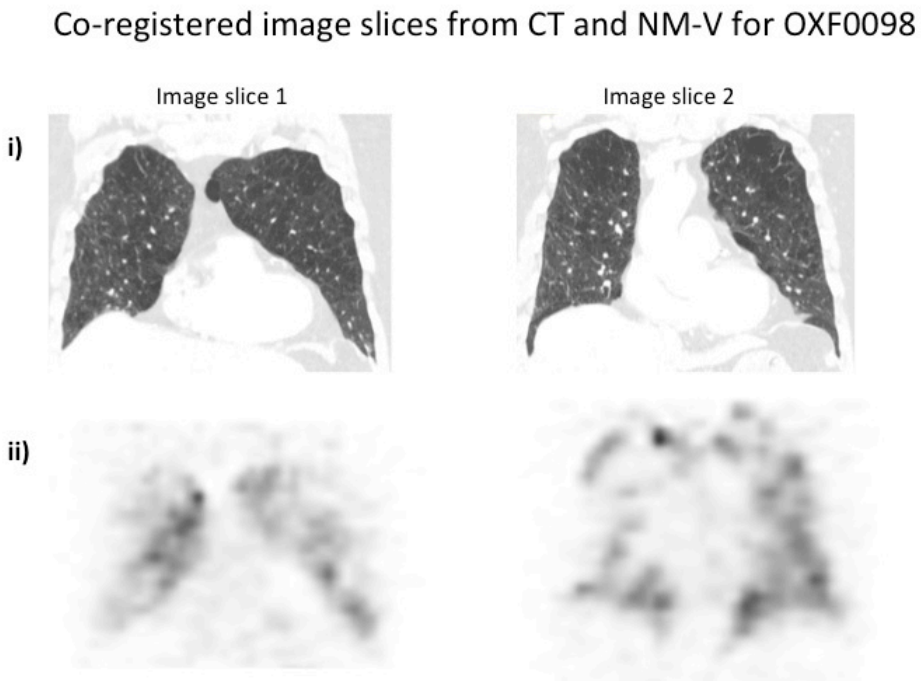


Figure A8.3b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0098. CT shows moderate centilobular emphysema with a homogeneous distribution.

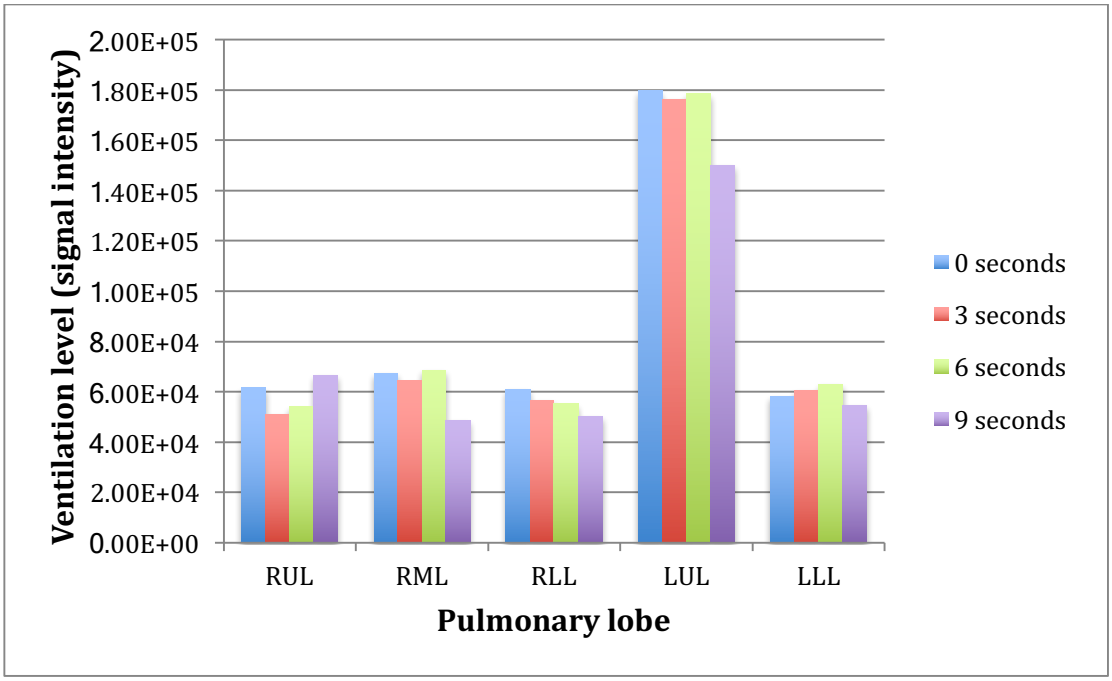


Figure A8.3c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0098. These data demonstrate delayed ventilation in the right upper and left lower lobe.

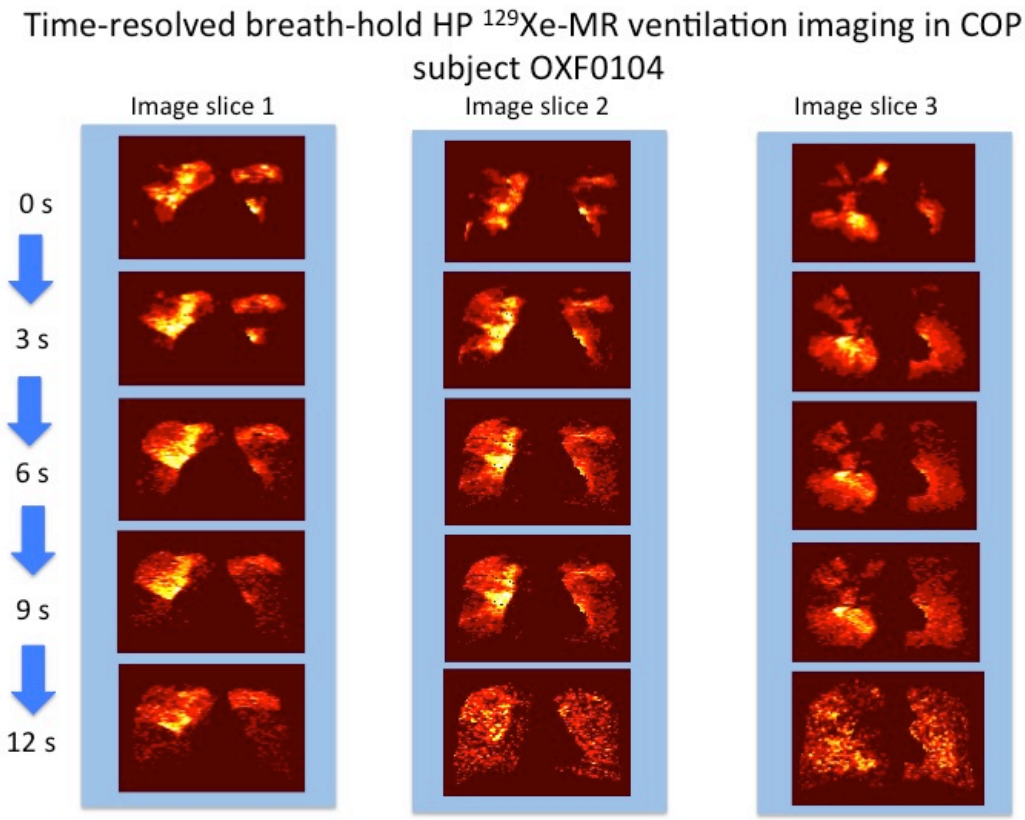


Figure A8.4a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0104. Delayed ventilation is observed in the right mid and left lower zones.

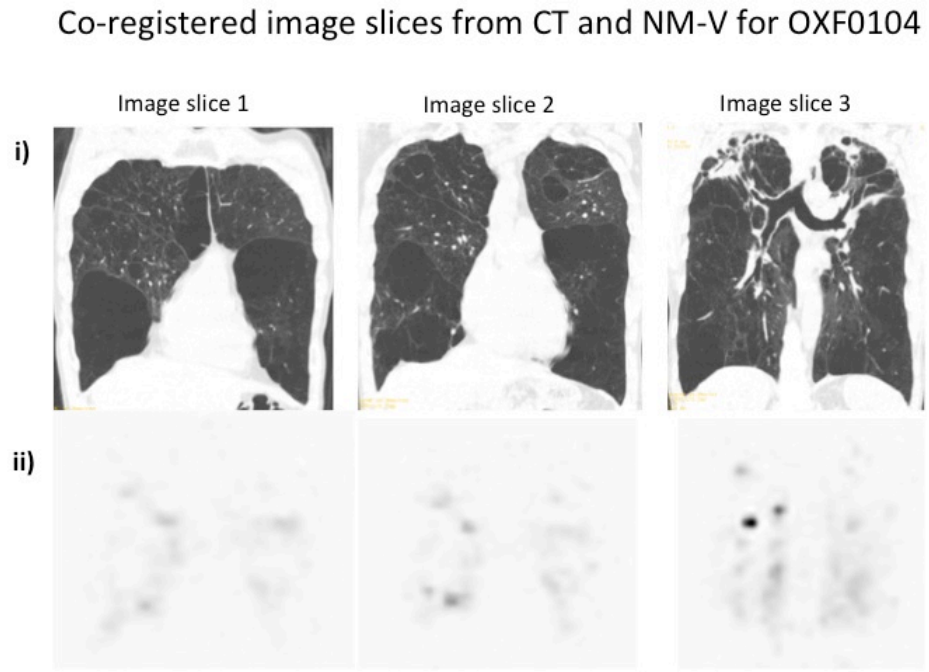


Figure A8.4b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0104. CT images show severe paraseptal and centrilobual emphysema. Delayed ventilation is not observed with NM-V SPECT.

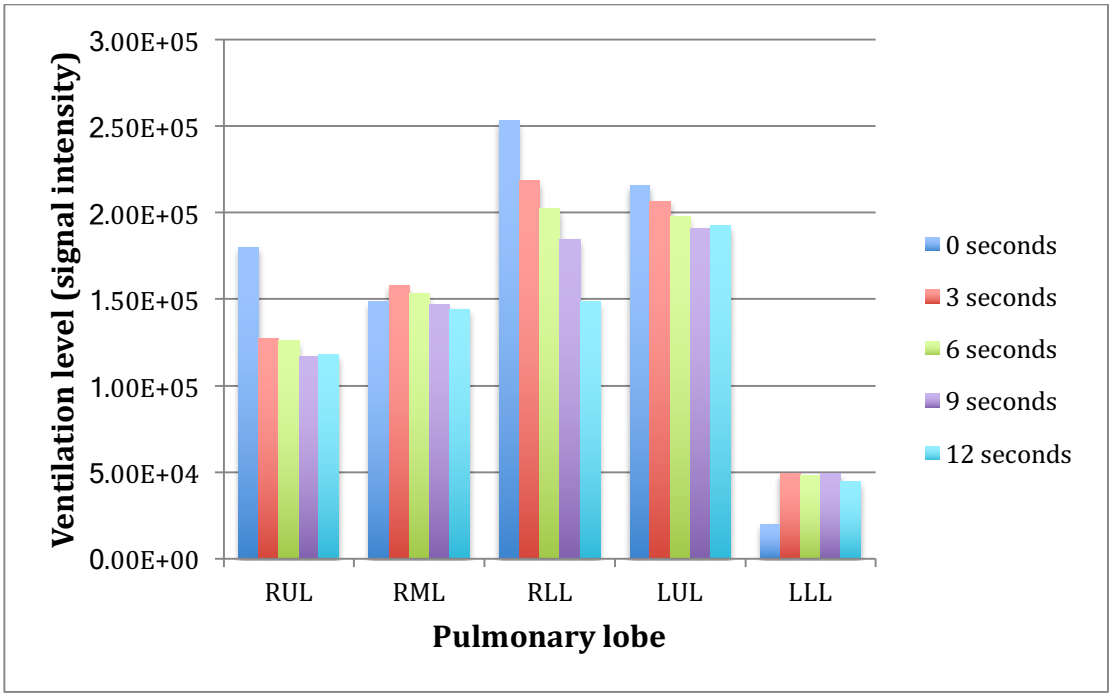


Figure A8.4c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0104. These data demonstrate delayed ventilation in the right middle and left lower lobes.

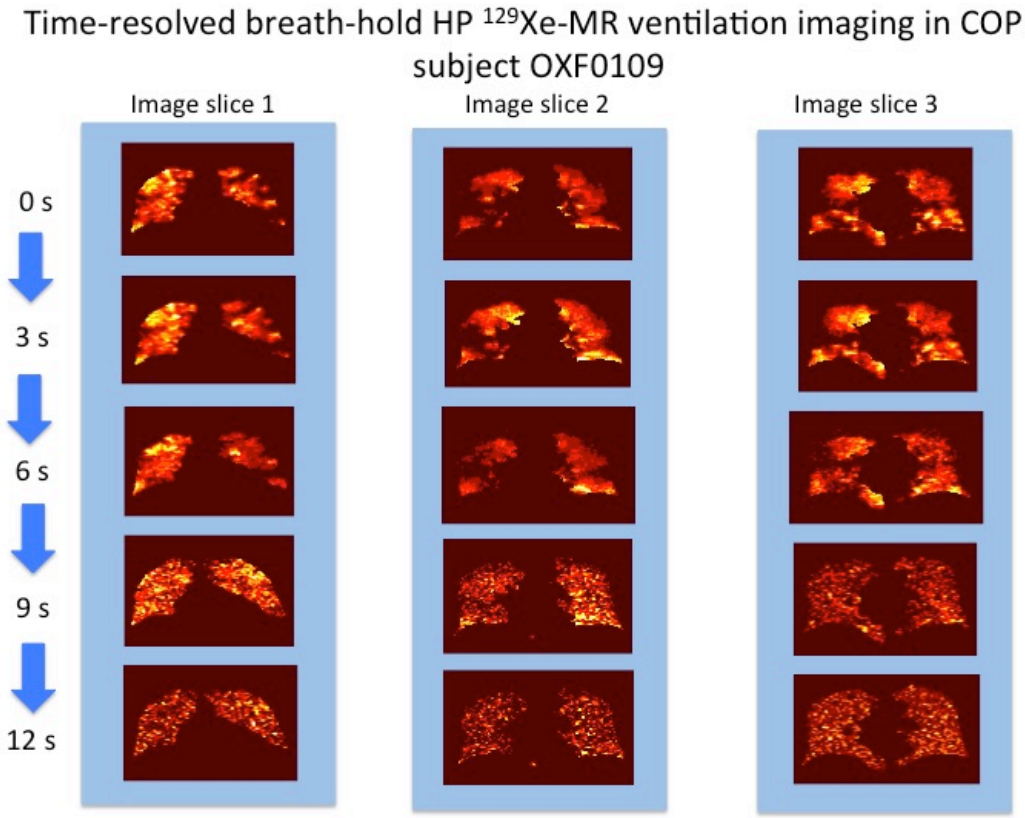


Figure A8.5a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0109. Delayed ventilation is observed in both lower zones.

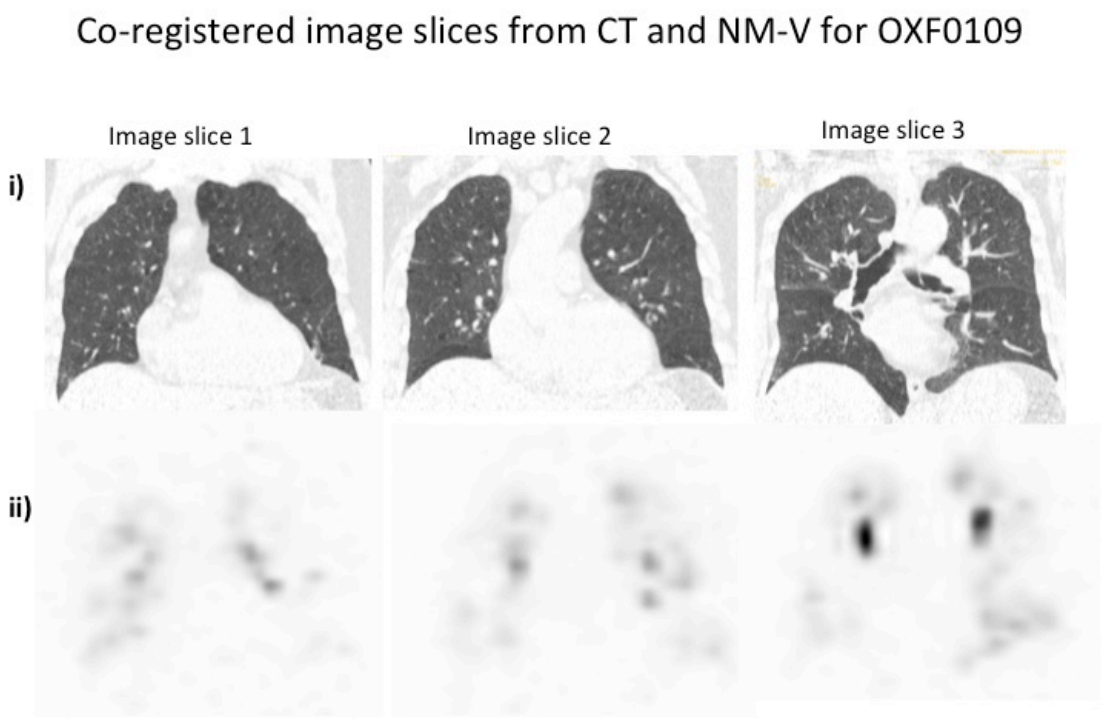


Figure A8.5b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0109. Delayed ventilation is not observed with NM-V SPECT.

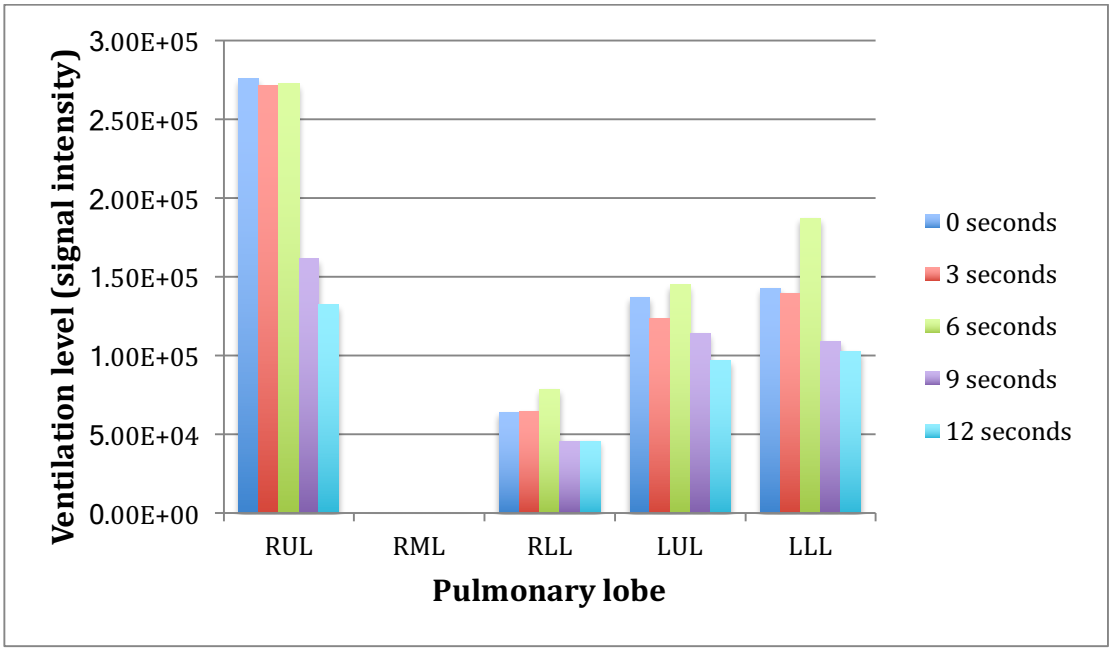


Figure A8.5c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0109. These data demonstrate delayed ventilation in the right lower, left upper and lower lobes.

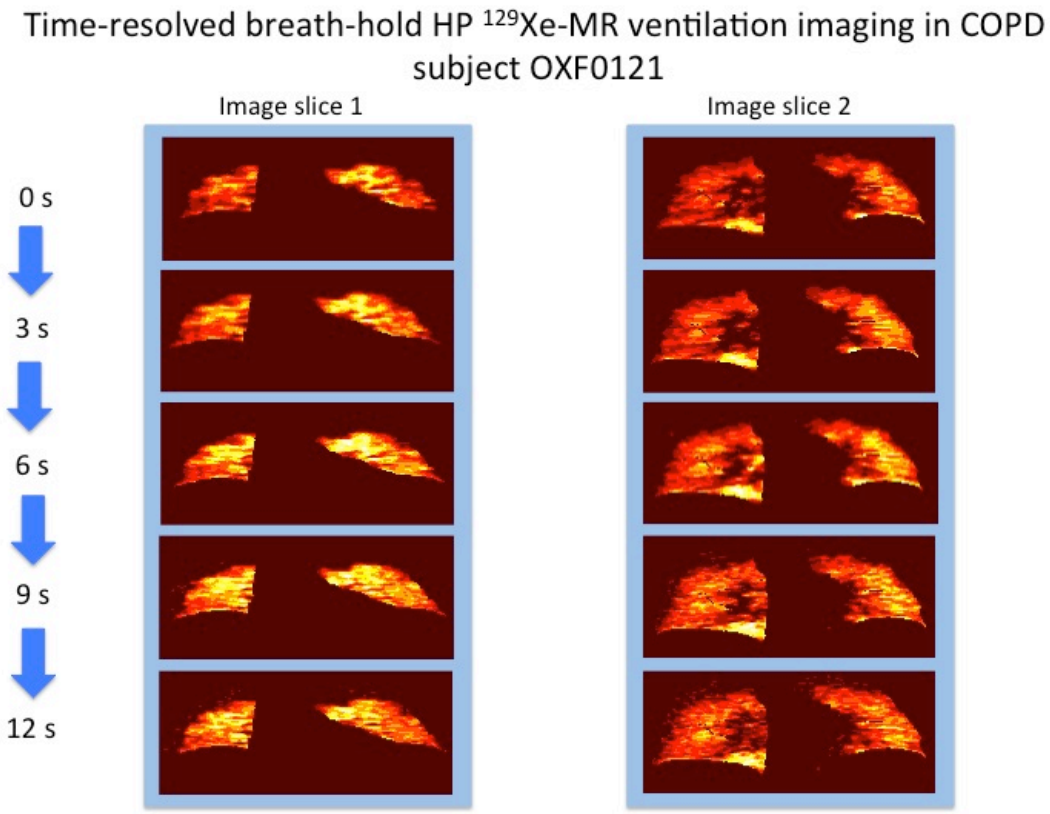


Figure A8.6a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0121. Delayed ventilation is not easily appreciated visually.

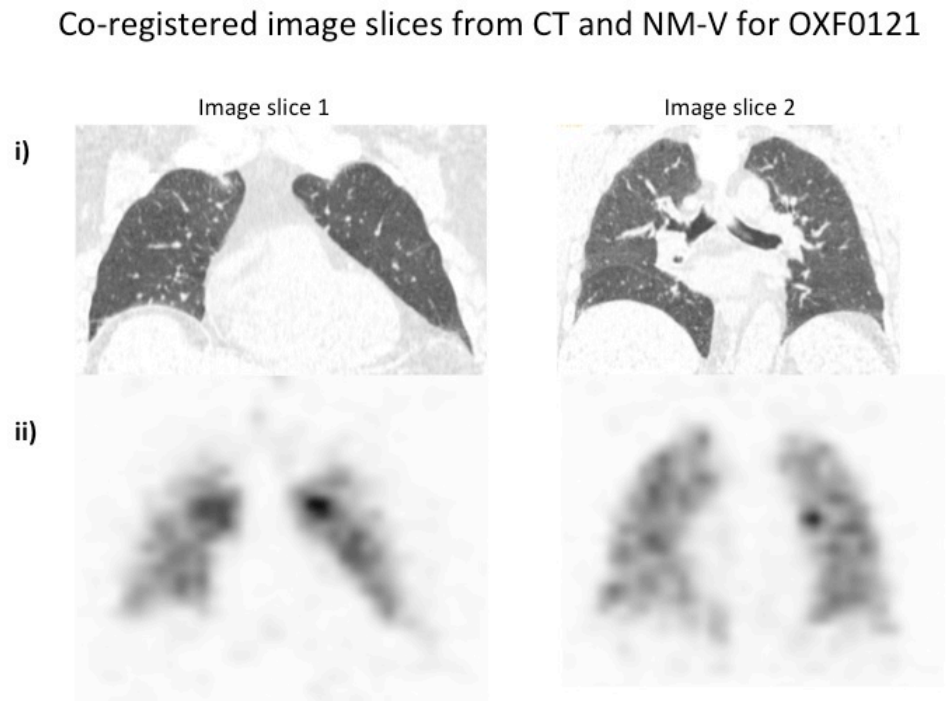


Figure A8.6b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0121.

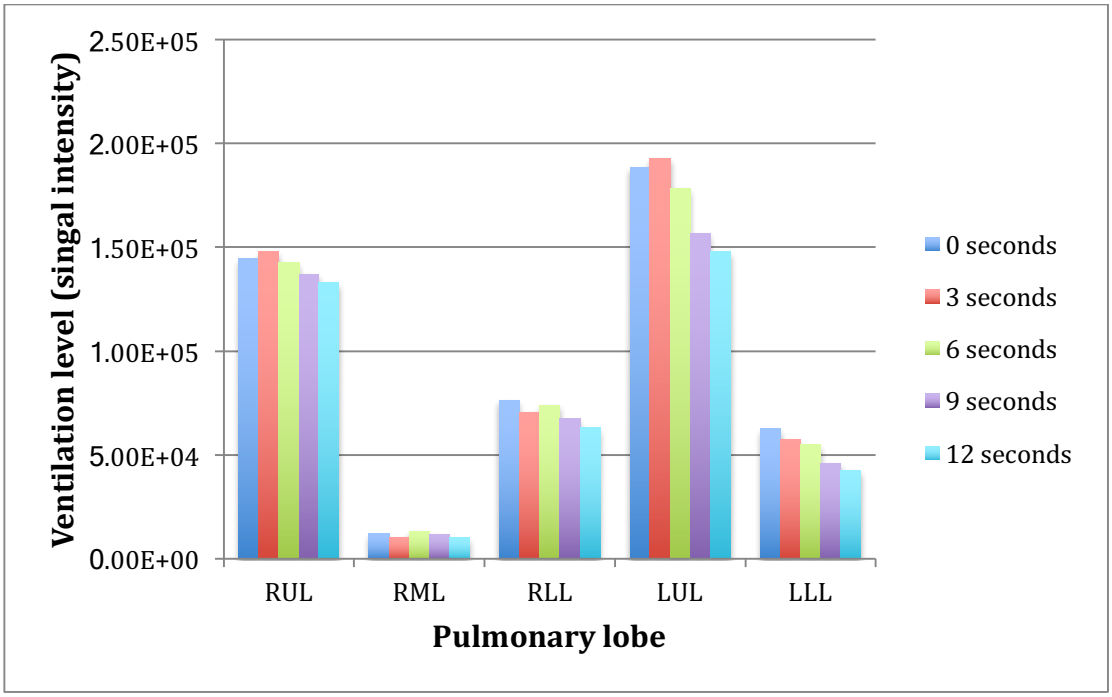


Figure A8.6c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0121. These data demonstrate delayed ventilation in the right upper and left upper lobe.

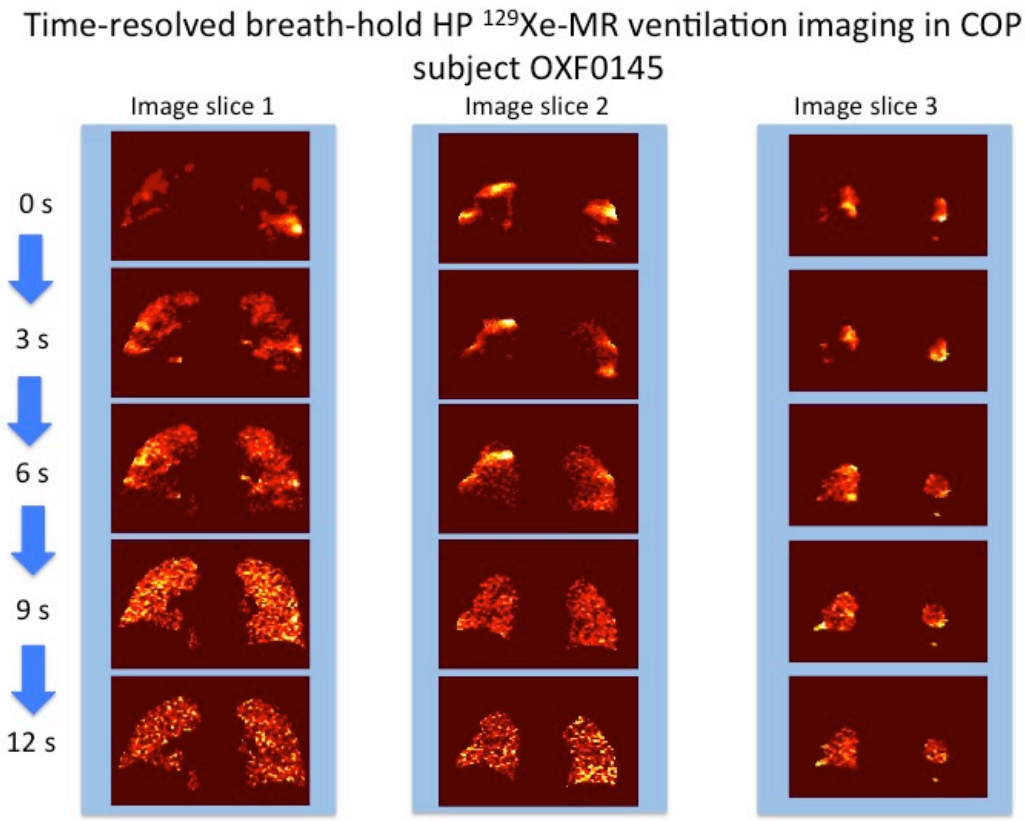


Figure A8.7a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0145.

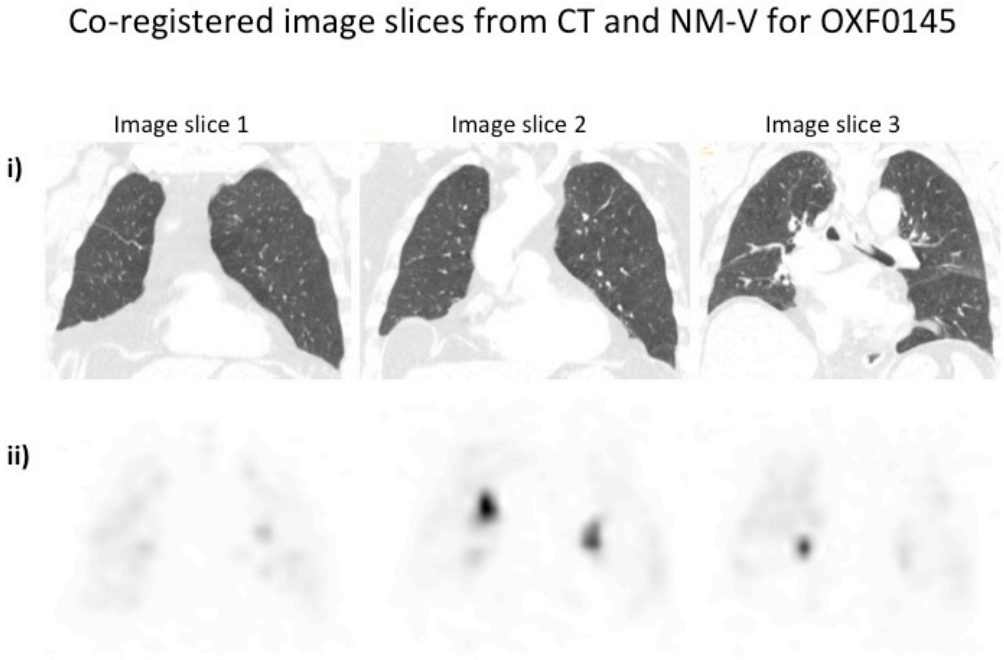


Figure A8.7b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0145.

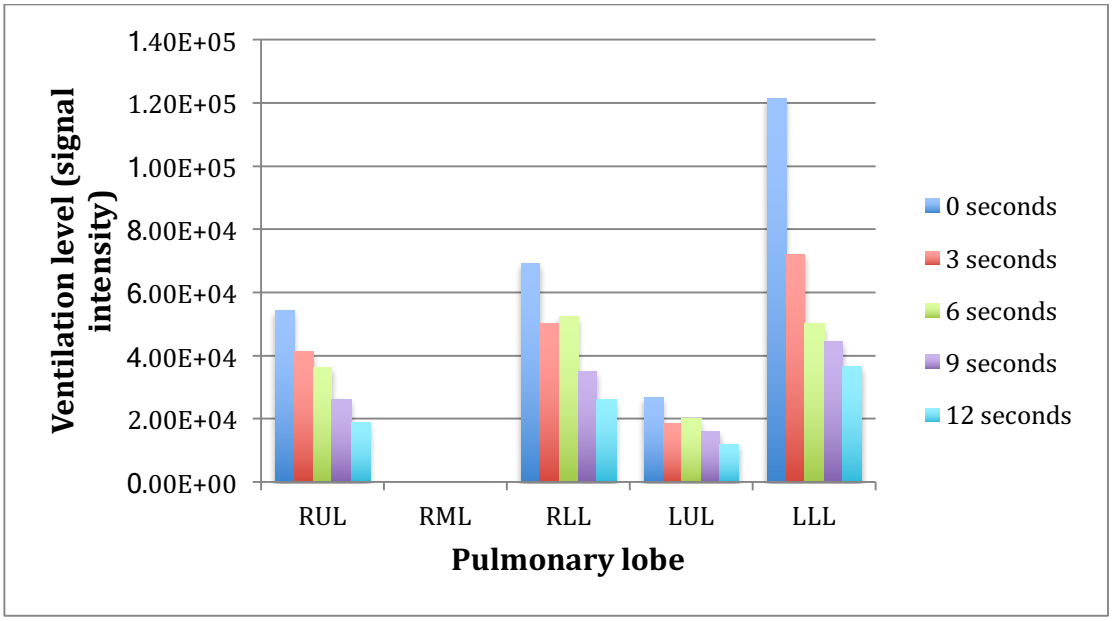


Figure A8.7c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0145. These data demonstrate no delayed ventilation in any lobe.

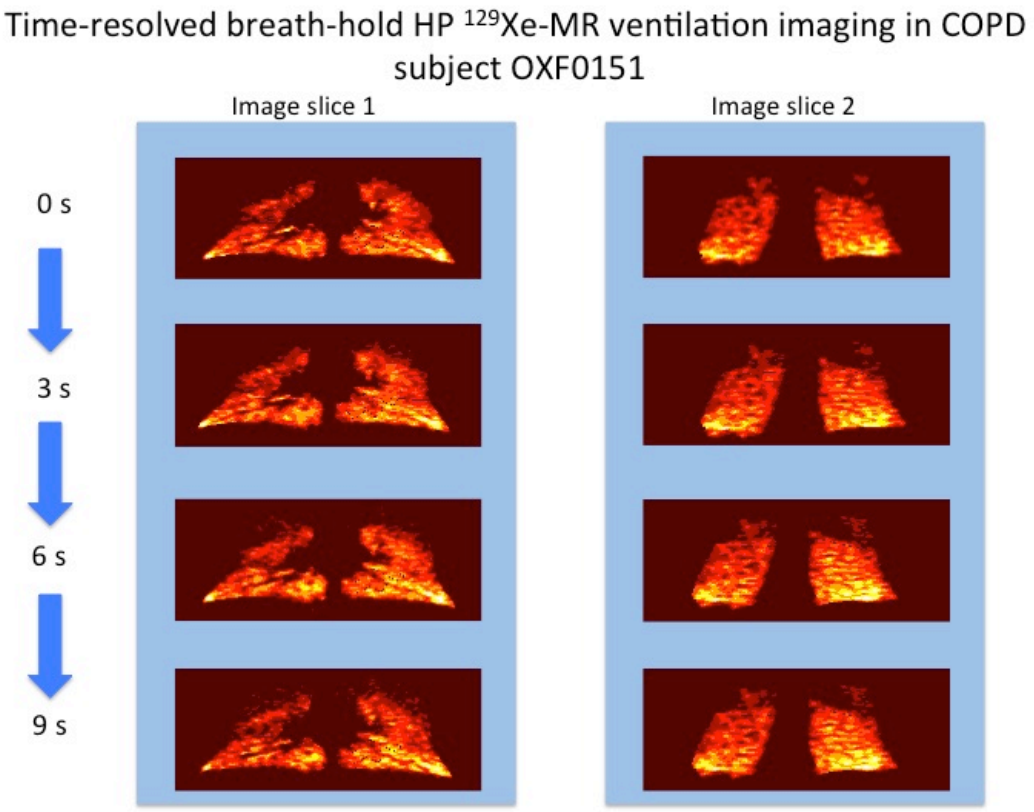


Figure A8.8a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0151. Delayed ventilation is not easily appreciated visually on these images.

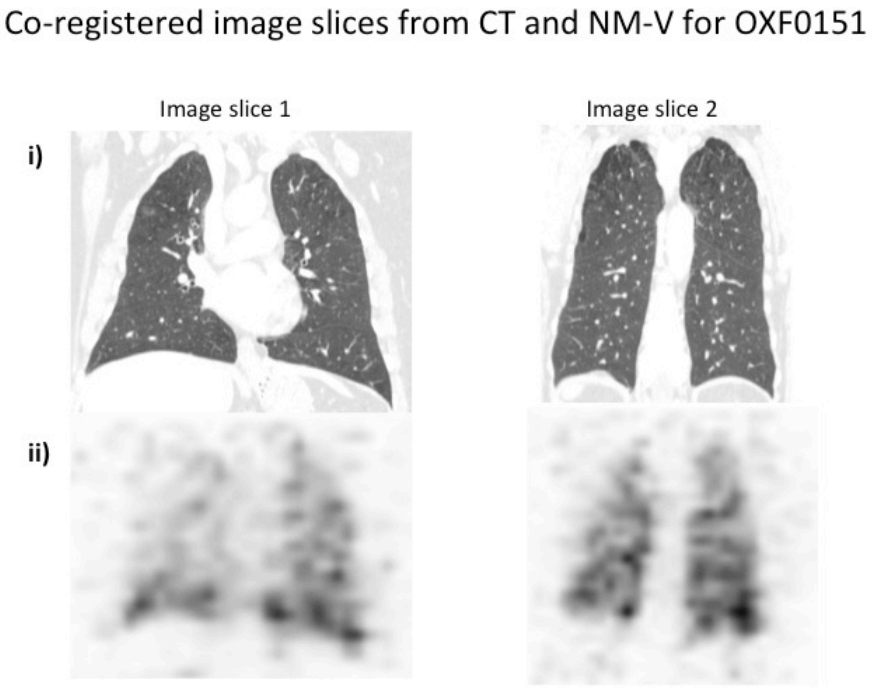


Figure A8.8b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0151.

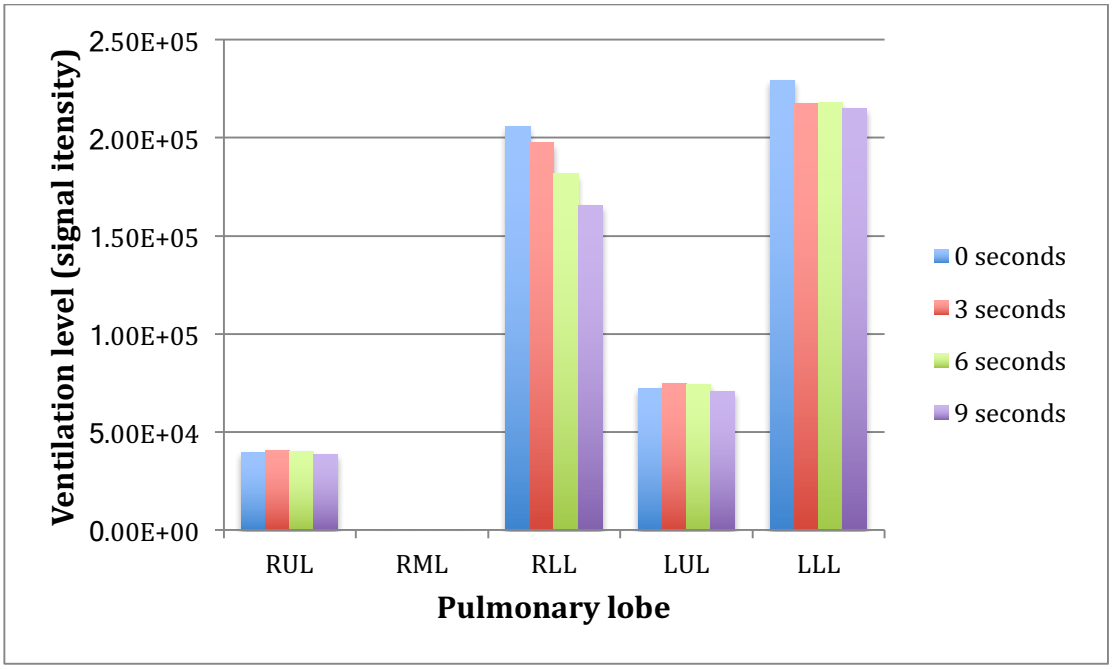


Figure A8.8c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0151. These data show delayed ventilation in the right upper and left upper lobes.

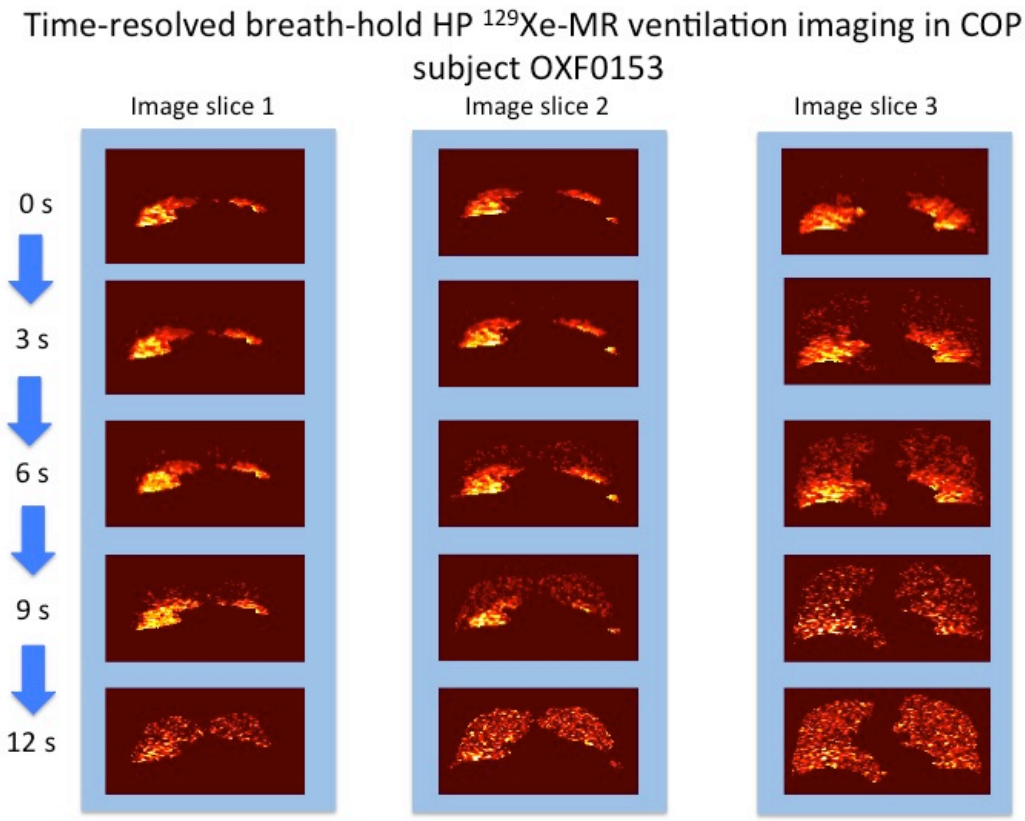


Figure A8.9a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0153. Delayed ventilation is observed in the left lower zone.

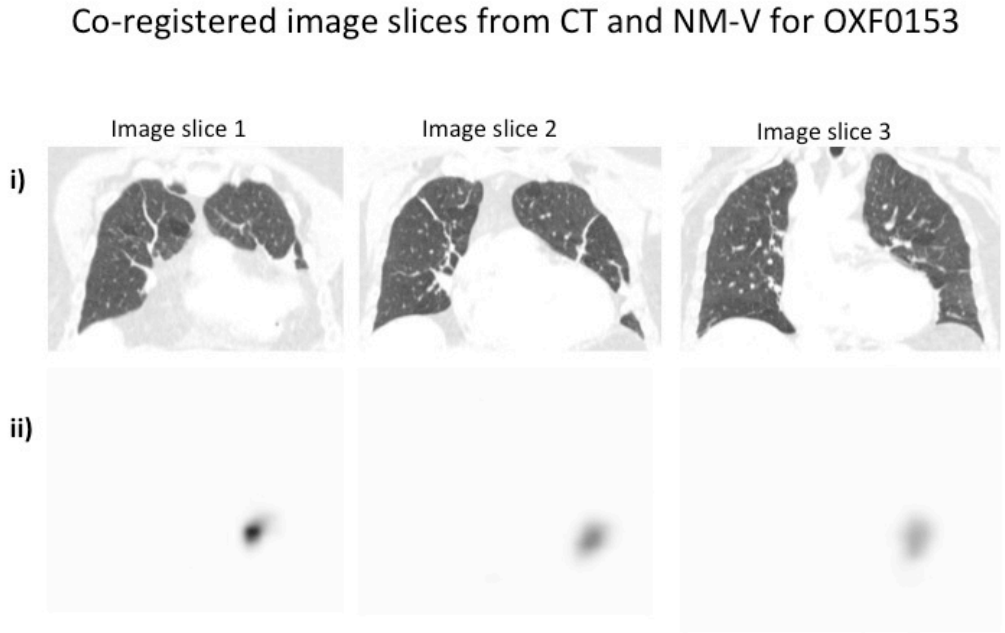


Figure A8.9b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0153. NM-V SPECT images demonstrate a focal region of counts in the left mid/lower zone likely due to poor patient technique failing to inhale the radiotracer.

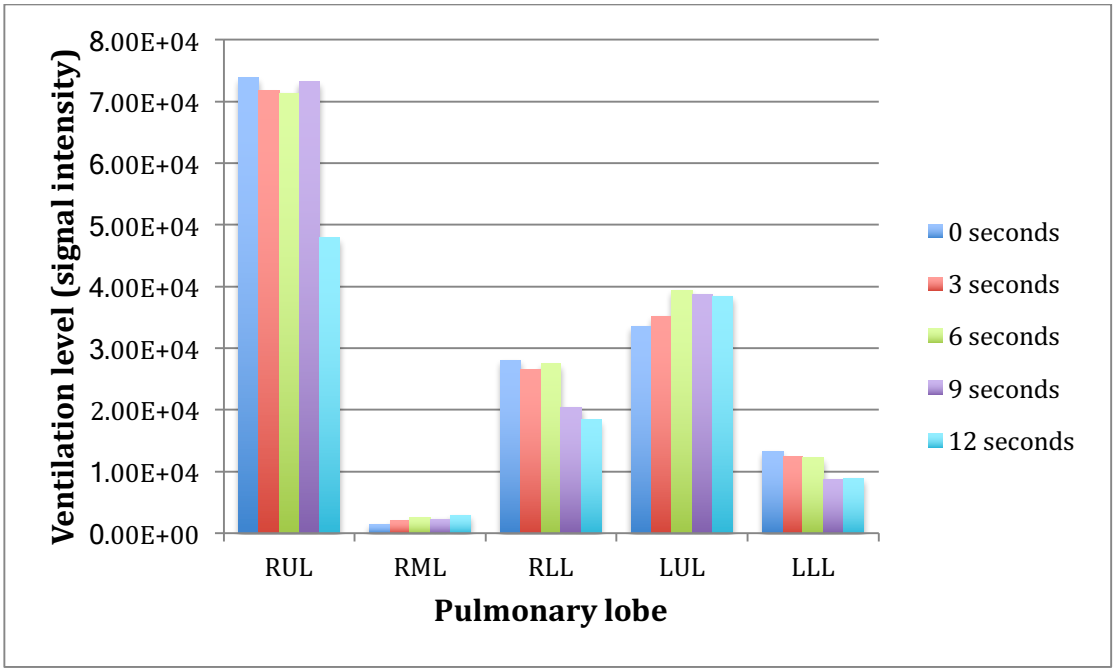


Figure A8.9c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0153. These data show delayed ventilation in the right middle and left upper lobes.

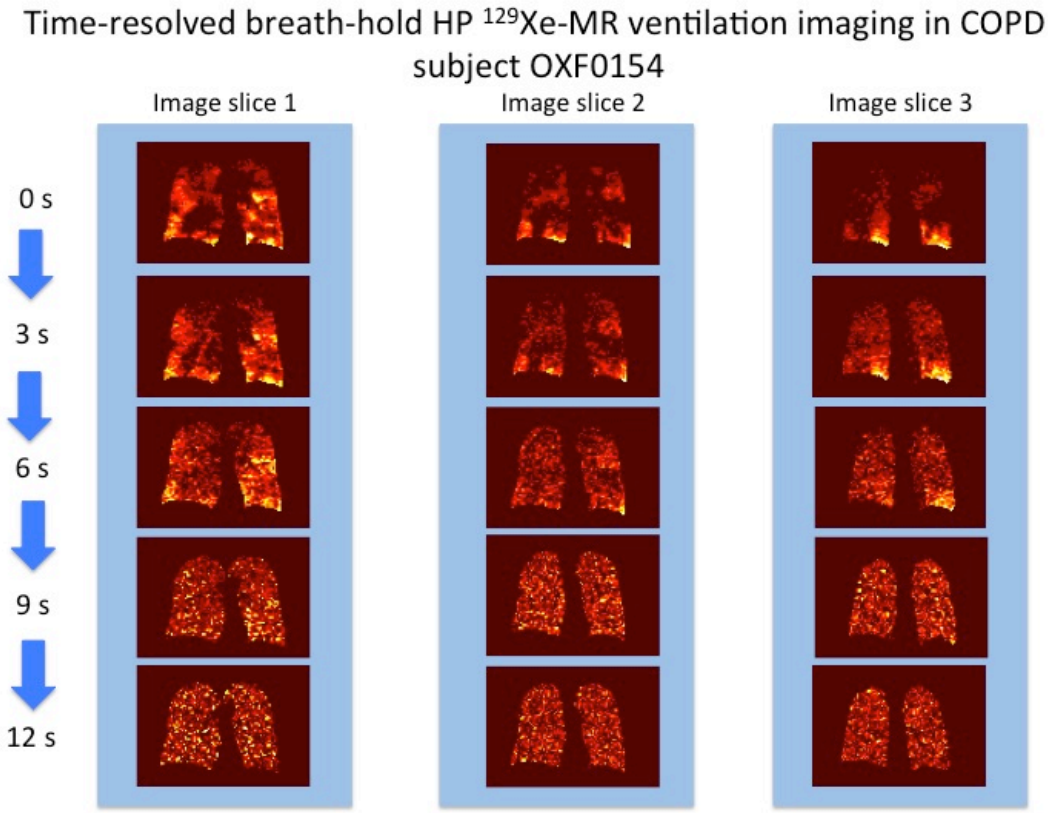


Figure A8.10a: Coronal time-resolved breath-hold HP ^{129}Xe-MR ventilation imaging acquired from OXF0154. Delayed ventilation is observed in all lobes.

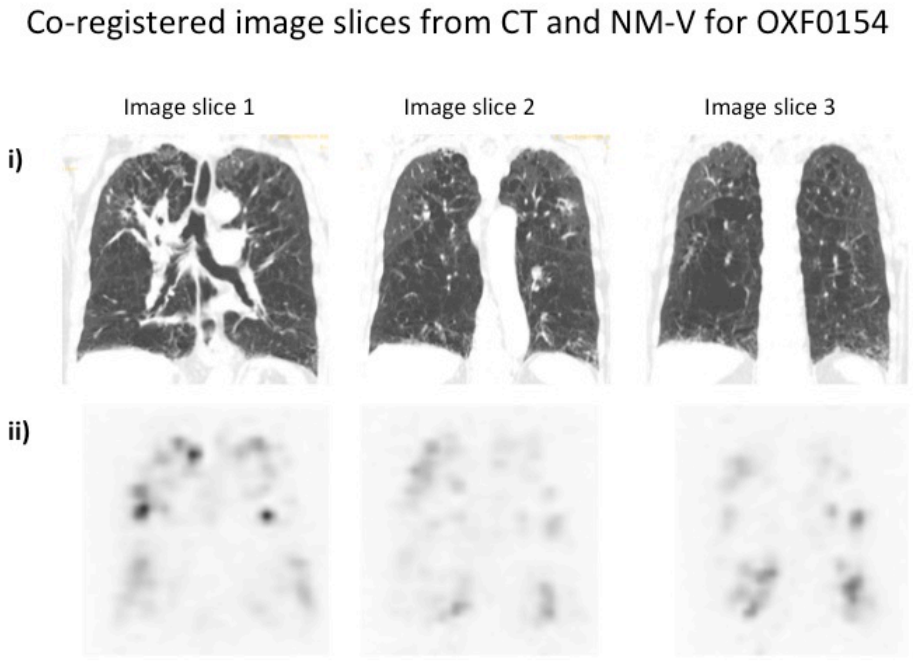


Figure A8.10b: Coronal i) thoracic CT and ii) NM-V SPECT images acquired from OXF0154. CT images show severe centrilobular and paraseptal emphysema with lower zone predominance. Delayed ventilation is not observed with NM-V SPECT

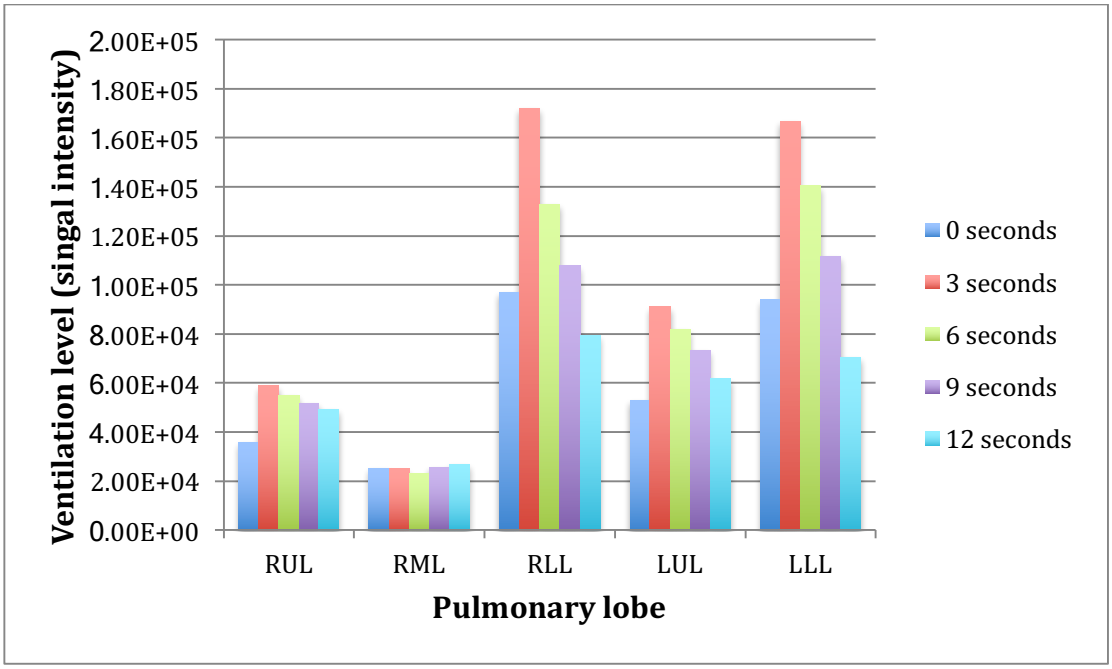


Figure A8.10c: Histogram showing change in ventilation level signal intensity per pulmonary lobe during time-resolved breath-hold HP ^{129}Xe-MRI acquired from OXF0154. These data demonstrate delayed ventilation in all pulmonary lobes.