The Use of Hyperpolarised Xenon (HP $^{129}$Xe-MRI) for Assessing Collateral Ventilation

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Aims and objectives

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Emphysema is a component of COPD that can be effectively treated with lung volume reduction in selected patients. Lung volume reduction therapy (LVRT) can be performed via a surgical or bronchoscopic approach and aims to induce collapse of hyperinflated regions of the lung. Greater emphysema heterogeneity [1,2] and interlobar fissure completeness, a surrogate for collateral ventilation, are predictors for successful LVRT outcome [1-3].

Currently, potential LVRT subjects are assessed for the presence of collateral ventilation either indirectly with computed tomography or directly via a commercially available bronchoscopic system, the Chartis system (Pulmonx) [4,5]. There is a need for alternative non-invasive functional imaging methods to directly visualise collateral ventilation as the Chartis system is highly invasive and CT provides no functional information and identification of interlobar fissures in subjects with grossly distorted lung architecture can prove challenging.

$^{133}$Xe scintigraphy [6] and xenon-enhanced dynamic dual-energy CT [7-9] have previously been employed to obtain images of collateral ventilation but incur exposure to ionising radiation. Hyperpolarised gas imaging has emerged as a promising technique to evaluate intralobar, interlobar collateral ventilation and delayed ventilation. It offers the advantage of enabling assessment of gas diffusion to comprehensively evaluate both emphysema distribution and collateral ventilation. Hyperpolarised $^3$He MRI has successfully demonstrated collateral ventilation directly [10] and long-range diffusion measurements with $^3$He may indicate that collateral ventilation is taking place [11,12].

The aim of this study was to determine the feasibility of time-resolved HP $^{129}$Xe MRI to assess delayed ventilation in subjects with COPD and obtain proof of principle that the technique could be further investigated in patients undergoing LVRT.
Methods and materials

The study was approved by the National Research Ethics Service (NRES) Committee and written informed consent was obtained from study participants.

Twelve patients diagnosed with COPD were prospectively enrolled between November 2014 and June 2015 from a tertiary referral centre with the following inclusion criteria:

- At least mild disease (stage II-IV on GOLD criteria classification, forced expiratory volume in 1 second (FEV₁)<80% predicted and FEV₁/forced vital capacity (FVC) <70%)
- Significant smoking history (>15 pack years) or other definite cause of COPD
- Over the age of 18 and able to give informed consent.

Study exclusion criteria included the presence of co-existent cardio-pulmonary disease that predominated over COPD and might confound result interpretation (e.g. asthma, bronchiectasis, cystic fibrosis, lung cancer, uncontrolled heart failure, frequent unstable angina, respiratory muscle weakness).

Patients underwent static and time-resolved breath-hold HP $^{129}$Xe-MR ventilation imaging, and quantitative computed tomography (QCT) at a single time point. Study measures were completed during disease stability.

$^{129}$Xe polarisation and delivery

Isotopically enriched $^{129}$Xe gas (80% $^{129}$Xe, Spectra Gases Inc., Alpha NJ, USA, supplied by Littleport, Cambridgeshire, UK) was polarised to 4-12% by rubidium vapour spin-exchange optical pumping (SEOP), and cryogenically accumulated in 1 L doses using a commercial polariser (Polarean Xenospin, Durham, NC, USA). Hyperpolarised $^{129}$Xe was then thawed into a Tedlar bag (Jensen Inert Products, Coral Springs, FL, USA), and administered to patients who were lying supine in the MRI scanner. Patients were instructed to exhale to functional residual capacity (FRC) and then inhale the 1 L contents of the Tedlar bag. Images were acquired over a breath-hold of up to 20 seconds. Study participants were provided training and instruction for breath-hold imaging, performing practice breath holds beforehand, to ensure lung volumes were as reproducible as possible for all imaging.

HP $^{129}$Xe-MRI
HP $^{129}$Xe-MRI was performed on a 1.5 Signa HDx whole-body MR system (GE Healthcare, Milwaukee, USA). Subjects were fitted with a flexible twin Helmholtz quadrature transmit-receive coil (Clinical MR solutions, Brookfield, WI) resonating at the $^{129}$Xe Larmour frequency (17.7 MHz).

Following initial localisers, HP $^{129}$Xe-MR ventilation images were acquired using a broadbanded 2D spoiled gradient echo sequence. Pulse sequence parameters were: 15 mm coronal slices covering the whole lung, FOV of 40 cm x 40 cm, resolution of 96 x 96 matrix, BW of 4 kHz, TE/TR of 4.2/20 ms, flip angle of 9°. Static HP $^{129}$Xe-MR ventilation imaging enabled identification of up to 4 coronal slices containing ventilation defects.

Time-resolved HP $^{129}$Xe-MR ventilation imaging adopted the same sequence parameters as static imaging with 3 second delays; the selected coronal slices were imaged up to five times during a single breath-hold with a flip angle of 4°.

Anatomical proton MR images were acquired during a separate 15 second breath-hold after HP $^{129}$Xe-MRI. These images were acquired using a steady-state free precession sequence and image location copied from the preceding HP $^{129}$Xe-MRI for co-registration purposes.

**QCT**

QCT was performed on a 16-slice GE Discovery 670 scanner (GE Healthcare, Milwaukee, USA). Images were acquired with a 1.25 mm slice thickness during suspended tidal inspiration following inhalation of 1 L oxygen via a Tedlar bag from FRC to ensure lung volumes were as similar to HP $^{129}$Xe-MRI as possible. Subjects underwent breath-hold training by radiographer instruction to ensure reproducibility.

**Image data analyses**

Analysis of time-resolved HP $^{129}$Xe-MR ventilation data was performed using Pulmonary Toolkit (PTK), an open-source image processing kit that runs in the Matlab® environment (Mathworks, Natick, MA). The software performs semi-automated non-rigid registration of HP $^{129}$Xe-MR with proton MR and QCT to determine lobar ventilation level (signal intensity). The image processing algorithm is illustrated in Figure 1.
Fig. 1: Flowchart showing the incorporation of various imaging data leading to the computation of lobar collateral ventilation data. Steps involving the use of Pulmonary Toolkit (PTK) are highlighted in red.

References: University of Oxford - Oxford/UK

HP $^{129}$Xe signal decay due to the imaging procedure and natural $T_1$ relaxation processes were accounted for by normalisation of images at each time point using a region of fully ventilated lung.

Delayed ventilation was defined as the quantifiable increase in ventilation level (signal intensity) in a lobe showing ventilation defects at baseline. The total number and percentage of pulmonary lobes demonstrating delayed ventilation with time-resolved HP $^{129}$Xe-MRI were determined.

The corresponding co-registered CT coronal image slices were reviewed for discernable structural differences that may contribute to collateral ventilation.
**Fig. 1:** Flowchart showing the incorporation of various imaging data leading to the computation of lobar collateral ventilation data. Steps involving the use of Pulmonary Toolkit (PTK) are highlighted in red.

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Results

Time-resolved breath-hold HP $^{129}$Xe-MR ventilation images were successfully acquired in all patients with no serious adverse events.

Delayed ventilation was observed visually and quantified by an increase in ventilation level signal intensity in 11 of the 12 imaging sets acquired. Within the imaging sets where delayed ventilation was shown, an increase in ventilation level signal intensity was present in at least two and up to all five pulmonary lobes. In total, delayed ventilation was demonstrated in 38 pulmonary lobes.

Example static and time-resolved HP $^{129}$Xe-MR ventilation imaging and data analyses are shown in Figures 2-5.

Fig. 2: Time-resolved breath-hold HP 129Xe-MR ventilation imaging from a 57 year-old female with COPD (GOLD III). a)-c) show three coronal slices with incremental
increase in ventilation level (signal intensity) best appreciated in the right and left lower zones.

References: University of Oxford - Oxford/UK

Figure 2 shows time-resolved HP\textsuperscript{129}Xe-MR ventilation imaging from a 57 year-old female ex-smoker with a 26 pack-year history (GOLD stage III). There is incremental increase in ventilation signal intensity over time, best appreciated in the right and left lower zones. The observed change in ventilation level within each pulmonary lobe has been quantified (Figure 3).

![Diagram showing ventilation levels over time for each lobe.](image)

**Fig. 3:** Lobar ventilation levels measured at baseline, 3s and 6s. Note the incremental change at 3s in all five lobes demonstrating delayed ventilation in those lobes, this decreases at 6s after the maximum ventilation is reached. RUL: Right Upper Lobe, RML: Right Middle Lobe, RLL: Right Lower Lobe, LUL: Left Upper Lobe, LLL: Left Lower Lobe.

References: University of Oxford - Oxford/UK
Figure 3 highlights the presence of delayed ventilation in all five pulmonary lobes. For improved illustration of regional information, a time-resolved HP $^{129}$Xe-MR ventilation map has been generated (Figure 4). This clearly depicts the regions where delayed ventilation has occurred (yellow and red areas).

Fig. 4: a)-c) Time-resolved HP 129Xe-MR ventilation maps of the three coronal slices shown in Figure 2. The maps generated allow better appreciation of regional change according to specific time points. An increase in ventilation level is depicted by the yellow and red areas at 3 and 6 seconds respectively.

References: University of Oxford - Oxford/UK

The corresponding coronal QCT slices from the same patient (Figure 5) do not show any definitive structural abnormality, specifically incomplete pulmonary fissures to suggest that delayed and collateral ventilation should be expected.
**Fig. 5:** a)-c) Corresponding coronal QCT slices from the same patient with no definitive structural abnormality to suggest presence of collateral ventilation.

**References:** University of Oxford - Oxford/UK

To better illustrate our findings, dynamic time-resolved ventilation maps are shown in Figure 6, for a 74 year-old female ex-smoker with a 22 pack year history (GOLD III). Note that delayed ventilation is most easily appreciated in the right and left lower zones.
Fig. 6: Dynamic time-resolved breath-hold HP 129Xe-MR ventilation maps for a 74 year-old female ex-smoker, 22 pack year history (GOLD III); delayed ventilation is most easily appreciated in the right and left lower zones.

References: University of Oxford - Oxford/UK

The corresponding QCT image slice and lobar ventilation levels are given in Figure 8. Note that although delayed ventilation is most visibly appreciated in the right and left lower zones, it was measured in all five pulmonary lobes.
Fig. 7: a) Corresponding QCT coronal view and b) measured ventilation level changes for the patient whose ventilation maps are shown in Figure 6. Note although delayed ventilation is most visibly appreciated in the right and left lower zones, it was measured in all five lobes. In a), regions where delayed ventilation is most visible are highlighted by blue arrows.

References: University of Oxford - Oxford/UK

As a second example, the dynamic ventilation maps for a 53 year-old male ex-smoker, 111 pack year history (GOLD IV) are shown in Figure 8. In this case, delayed ventilation is most easily appreciated in the left lower zone.
**Fig. 8**: Dynamic time-resolved breath-hold HP 129Xe-MR ventilation maps for a 53 year-old male ex-smoker, 111 pack year history (GOLD IV); delayed ventilation is most easily appreciated in the left lower zone.

*References*: University of Oxford - Oxford/UK

The corresponding QCT image slice and lobar ventilation levels are given in Figure 10. Likewise, delayed ventilation was measured in all five lobes.
Fig. 9: a) Corresponding QCT coronal view and b) measured ventilation level changes for the patient whose ventilation maps are shown in Figure 8. Note although delayed ventilation is most visibly appreciated in the left lower field, it was measured in all five lobes. In a), region where delayed ventilation is most visible is highlighted by the blue arrow.

References: University of Oxford - Oxford/UK
**Fig. 2:** Time-resolved breath-hold HP 129Xe-MR ventilation imaging from a 57 year-old female with COPD (GOLD III). a)-c) show three coronal slices with incremental increase in ventilation level (signal intensity) best appreciated in the right and left lower zones.

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**Fig. 3:** Lobar ventilation levels measured at baseline, 3s and 6s. Note the incremental change at 3s in all five lobes demonstrating delayed ventilation in those lobes, this decreases at 6s after the maximum ventilation is reached. RUL: Right Upper Lobe, RML: Right Middle Lobe, RLL: Right Lower Lobe, LUL: Left Upper Lobe, LLL: Left Lower Lobe.

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**Fig. 4:** a)-c) Time-resolved HP 129Xe-MR ventilation maps of the three coronal slices shown in Figure 2. The maps generated allow better appreciation of regional change according to specific time points. An increase in ventilation level is depicted by the yellow and red areas at 3 and 6 seconds respectively.

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**Fig. 5:** a)-c) Corresponding coronal QCT slices from the same patient with no definitive structural abnormality to suggest presence of collateral ventilation.

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Fig. 6: Dynamic time-resolved breath-hold HP 129Xe-MR ventilation maps for a 74 year-old female ex-smoker, 22 pack year history (GOLD III); delayed ventilation is most easily appreciated in the right and left lower zones.

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**Fig. 7:** a) Corresponding QCT coronal view and b) measured ventilation level changes for the patient whose ventilation maps are shown in Figure 6. Note although delayed ventilation is most visibly appreciated in the right and left lower zones, it was measured in all five lobes. In a), regions where delayed ventilation is most visible are highlighted by blue arrows.

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Fig. 8: Dynamic time-resolved breath-hold HP 129Xe-MR ventilation maps for a 53 year-old male ex-smoker, 111 pack year history (GOLD IV); delayed ventilation is most easily appreciated in the left lower zone.

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Fig. 9: a) Corresponding QCT coronal view and b) measured ventilation level changes for the patient whose ventilation maps are shown in Figure 8. Note although delayed ventilation is most visibly appreciated in the left lower field, it was measured in all five lobes. In a), region where delayed ventilation is most visible is highlighted by the blue arrow.

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Conclusion

This study has shown that time-resolved breath-hold HP $^{129}$Xe-MR ventilation imaging is feasible in patients with COPD.

Delayed ventilation was demonstrated in 92% of the time-resolved HP $^{129}$Xe-MR imaging sets completed. The delayed ventilation observed visually and objectively quantified may represent a number of processes including collateral ventilation, partial obstruction, gas trapping, narrowing of the peripheral airways or a combination of these. If the delayed ventilation observed does represent collateral ventilation, this may be due to gas moving freely between pulmonary lobules (intralobar) or between lobes (interlobar).

The current findings are consistent with the 8 out of 10 patients with COPD previously reported to show delayed ventilation with HP $^3$He-MRI [10]. In contrast to previous methodology, we have quantified delayed ventilation according to specific pulmonary lobes rather than within regions-of-interest (ROI). The rationale behind this was to providing stronger evidence of interlobar collateral ventilation. Arguably, interlobar collateral ventilation is of greatest significance in treatment planning for lung volume reduction. HP $^{129}$Xe-MRI is non-invasive, exposes the patient to no radiation and may be performed repeatedly, potentially immediately after LVRT to determine its efficacy. This may allow early treatment modifications or allow clinicians to inform patients of the likely success of their intervention.

There are a number of limitations associated with the study. The sample size was small and the HP $^{129}$Xe-MR delayed ventilation observed cannot be confirmed to exclusively represent collateral ventilation. Future work is needed to determine whether the delayed ventilation demonstrated with HP $^{129}$Xe-MR corresponds to collateral ventilation as measured directly with the Chartis system.

In conclusion, time-resolved breath-hold HP $^{129}$Xe-MR ventilation imaging is a feasible technique to demonstrate delayed ventilation in patients with COPD. Future work may confirm that the observed delayed ventilation represents collateral ventilation and subsequently identify a potential role for HP $^{129}$Xe-MRI to improve patient selection and treatment efficacy evaluation in LVRT.
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