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Direct Visualisation of Collateral Ventilation in COPD with Hyperpolarised Gas MRI

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What is the key question? Is it possible to visualise collateral ventilation in COPD during a single breathold using a non-invasive, non-ionising imaging technique?

What is the bottom line? We demonstrate direct imaging of delayed gas filling in what we believe to be collateral ventilation in COPD patients, using hyperpolarised gas MRI.

Why read on? The ability to image and quantify collateral ventilation pathways directly may help the understanding of patho-physiology in COPD and aid assessment for therapies.

ABSTRACT

Background Collateral ventilation has been proposed as a mechanism of compensation of respiratory function in obstructive lung diseases but limited observations of it *in vivo* have been demonstrated. The assessment of collateral ventilation with an imaging technique could help gain insight into lung physiology and aid with the planning of new bronchoscopic techniques for treating emphysema.

Objective To image delayed ventilation that may be related to collateral ventilation over the period of a single breath-hold in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods Time-resolved hyperpolarised ^{3}He Magnetic Resonance Imaging was used to image the progressive influx of polarised gas into initially non-ventilated defects.

Results A time-series of images showed ^{3}He moving into lung regions which were initially non-ventilated. Ventilation defects with delayed-filling were observed in eight of the ten patients scanned.

Conclusions A method for direct imaging of delayed ventilation within a single breath-hold has been demonstrated in COPD patients. We present images of what we believe to be collateral ventilation and slow-filling of peripheral airspaces due to increased flow resistance. The technique provides 3D whole lung coverage with sensitivity to regional information, and is non-invasive and non-ionising.

INTRODUCTION

Collateral ventilation pathways have been proposed as a mechanism of increased tolerance to obstructive lung diseases by enabling alternative respiratory pathways to carry out gas exchange (1,2), see the schematic in figure 1. In addition to gaining insight into lung physiology, the assessment of collateral ventilation with an imaging technique could help with the planning of new bronchoscopic techniques for treating emphysema (2,3). In bronchoscopic lung volume reduction, collateral ventilation from adjacent lobes prevents the target atelectasis (4), whereas in airway bypass treatment the presence of collateral ventilation can be advantageous (5).

Catheter-based techniques (6) have been used to measure collateral ventilation but a non-invasive method is desirable. Radiological Computed Tomography (CT) scores of emphysema are significantly linked to inter-lobar collateral ventilation (7), and ^{133}Xe scintigraphy (8) and xenon-enhanced dynamic dual-energy CT (9-11) have been used to image collateral ventilation. However these techniques monitor the wash-in and wash-out of a tracer gas over multiple breathing cycles, and both use ionising radiation. Long-range diffusion measurements with hyperpolarised ^{3}He Magnetic Resonance Imaging (MRI) are also potentially sensitive to collateral ventilation (12-14). Lung structure at the acinar level influences the long-range apparent diffusion coefficient (ADC), which is related to the path of gas through the peripheral airways. High long-range ADC values suggest the presence of collateral pathways because the gas has diffused more quickly than it could have done by navigating healthy airways (13). However, the measurement of long-range ADC is indirect and as such can only imply that collateral ventilation is taking place.

Here we present direct visual evidence of delayed gas ventilation at breath-hold in what we believe to be collateral ventilation in Chronic Obstructive Pulmonary Disease (COPD). Images were acquired over the period of a single breath-hold using a non-invasive and non-ionising imaging modality. Delayed-filling of peripheral regions was also observed in some patients, which is thought to be due to increased resistance in the small airways. Time-resolved hyperpolarised ^{3}He MRI was used to image delayed ventilation in COPD patients with whole lung coverage.

METHODS

Ten COPD patients were scanned using a 1.5T whole body MRI system (GE HDx, Milwaukee, WI) equipped for hyperpolarised ^{3}He imaging. The inclusion criteria were: COPD without other significant respiratory disease as diagnosed by a respiratory physician, post-bronchodilator ratio of Forced Expiratory Volume in 1 second (FEV1) to Forced Vital Capacity (FVC) < 0.7, post-bronchodilator FEV1 $\geq$ 30% and $\leq$ 80% of predicted, cigarette smoking history of $\geq$ 10 pack years, and resting pulse oximeter oxygen saturation (SpO_2) of > 90% on room air.

^{3}He was polarised on site to 25% using rubidium spin-exchange (15) apparatus (GE Healthcare, Amersham, UK) under a regulatory approved licence. Imaging was performed with ethics committee approval and written consent. Subjects were positioned in a ^{3}He quadrature transmit-receive vest coil (Clinical MR Solutions, USA). A mix of 200ml hyperpolarised ^{3}He and 800ml N_2 was inhaled from a state of relaxed expiration, and ^{3}He

images were acquired during the breath-hold. A 3D coronal spoiled gradient echo sequence (16) with full lung coverage was used for imaging with parameters: field of view = 35cm^2, in-plane matrix = 64 x 32, 16 x 20mm slices, flip angle = 1^o, bandwidth = 62kHz, echo time (TE) = 0.8ms, and repetition time (TR) = 2.5ms. This 3D volume was acquired at six time-points during the single breathold; at 0, 1.3, 5.8, 10.3, 14.8 and 19.3 seconds.

The time-course images were analysed for any ventilation defects present in the first time-point image which subsequently filled with gas during the breathold. A pattern of gas filling with gas moving gradually from the edges of the defect towards the centre was identified as being suggestive of collateral ventilation.

RESULTS

The COPD patients scanned (5 male, 5 female) had a mean age of 60.6 years, a mean smoking history of 39.5 pack years and a mean FEV1 % predicted of 49.6%. Ventilation defects with delayed-filling were observed in eight of the ten COPD patients scanned (table 1). These examples varied in defect size, number and fill-rate from the most visibly striking case shown in figure 2 to much more subtle effects such as those seen in patient 3 in figure 3. Fifteen slow-filling ventilation defects were identified, 8 of these were seen to fill from the edge(s) of the defect and 7 were too small to determine the gas fill pattern.

Figure 2(a-f) shows a single coronal image slice acquired from one of the patients at the 6 time-points. Two initially non-ventilated defects, which gradually filled with ^{3}He over the

time-course of the breath-hold are highlighted with arrows. The largest defect is magnified in the top row. The images are all displayed with the same colour scale, the magnitude of which is proportional to the density of ^{3}He in that pixel. Hyperpolarised ^{3}He MR signal is non-renewable and diminishes over time due to both the imaging procedure and natural T_1 relaxation processes due to the presence of oxygen (16). In normally ventilated regions of the lung this expected signal decay over time is observed and has been used to infer lung oxygen partial pressure (17). However, in the regions indicated the signal *increases* over time, with a progressive influx of polarised gas from the edge of the defects towards the centre. Sagittal reformats through the right lung at time-points t=0s (g) and t=19.3s (h) illustrate the 3D nature of the upper lobe ventilation defect and the related wash-in of gas. The delay to signal onset map (figure 2i) shows the time taken in seconds from the start of the data acquisition until gas arrived at each pixel. The gas-filling pattern from both of the defect edges towards the centre is not consistent with the defects being ventilated via their feeding bronchi. This suggests that gas is entering the defects via collateral pathways at the defect edges.

High-resolution computed tomography (HRCT) images (e.g. figure 2(j)) show that this patient has severe bilateral emphysema, in particular pan-lobar disease affecting the right upper and lower lobes. The two ventilation defects in the right lung seen in figure 2 correspond to more severe disease than the surrounding tissue. There is no difference in lung structure discernable by HRCT between the slow-ventilated upper defect and the defect in the lower right lung, which does not ventilate at all.

Figure 3 shows examples of slow-filling ventilation defects in two other patients. In one patient (top row) several wedge-shaped defects along the peripheral edge of the right lung are filled over the course of the breathold. In another patient (bottom row) delayed ventilation of a wedge defect on the outside edge of the left lung is seen.

An example of delayed-filling of a peripheral ventilation defect is shown in figure 4. The slow-filling of the defect at the lower left lung edge, with a front of gas progressing slowly towards the lung edge, may be due to increased resistance to air-flow in the peripheral airways.

DISCUSSION

Ventilation defects with delayed filling in a pattern consistent with collateral ventilation were observed in 40% of the patients scanned. Delayed-filling ventilation defects were present in 80% of the patients but some were too small to imply which mechanism might cause the delayed ventilation.

Delayed-filling of ventilation defects may be due to collateral ventilation, partial obstruction, lung hyperinflation (air-trapping), narrowing of the peripheral airways or a mixture of such mechanisms. However, in cases where the pattern of ^{3}He filling is visibly seen to progress from the defect edges towards the centre (e.g. figure 2) we believe that the slow filling is due to collateral ventilation. The example shown in figure 4 with peripheral delayed filling

could represent sensitivity to peripheral airways flow resistance in the 'quiet zone' (18) of the lungs.

Collaterally-ventilated defects may arise from centrilobular emphysema (19), where centrilobular spaces form in lobules with obliterated terminal bronchioles (20) and may become ventilated via collateral pathways (thanks to Professor Jim Hogg at the University of British Columbia for useful comments on this possible mechanism in the review process). The larger collaterally-ventilated defects might be networks of lobules with inter-connecting centrilobular spaces.

High-resolution ^{3}He ventilation images, which were acquired as a single time frame snapshot during the same scanning sessions (figures 2(k), 3(d, h) and 4(h)) show no information about the collateral wash-in of gas. A whole breathold is needed for a single acquisition of the lung volume with high-resolution multi-slice imaging, meaning that there is no time-resolved aspect to the data and changes over time cannot be detected. The slice acquisition timing of a high-resolution ventilation dataset will change the appearance of defects with delayed-ventilation. For example, if a slow-filling defect is imaged near the start of a breathold it will appear as a signal void (e.g. figure 2(k)) but if the same defect is imaged later in the multi-slice acquisition, after gas has entered it, the ventilation defect will contain some signal (e.g. figure 3(h)).

The case of collateral ventilation presented here appears to be inter-segmental which is consistent with previously reported collateral ventilation in COPD detected using xenon-enhanced dual-energy CT (21).

By virtue of its low atomic mass ^{3}He in air is more diffusive than xenon in air or pure air alone, so it is likely to show a faster and potentially amplified effect, allowing delayed/collateral ventilation to be visualised directly over the period of a single breath-hold (within 20 seconds). The use of this technique with hyperpolarised ^{129}Xe MRI may also allow visualisation of delayed/collateral ventilation, although the lower diffusivity of ^{129}Xe may slow the process to beyond a realistic single breath-hold time in patients.

The imaging sequence used is simple and available on all MRI systems equipped for hyperpolarised gas lung imaging. The sequence is readily adaptable, and from this initial data a breathold of 15 seconds with 4 evenly spaced data acquisition time-points should be sufficient to capture delayed ventilation effects similar to those seen here, with the potential for an associated increased spatial resolution in the images.

In conclusion, a method is demonstrated for direct imaging of delayed ventilation within a single breath-hold, which is able to visualise what we believe to be collateral ventilation in COPD. The technique gives 3D full lung coverage allowing global assessment of delayed and collateral ventilation pathways with regional sensitivity.

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FIGURE LEGENDS

Figure 1

A graphical representation of collateral ventilation, adapted from Hogg et al (1).

Figure 2

Images tracking collateral ventilation in a COPD patient. Images (a) to (f) show the same coronal slice at six different time points during a single breath-hold. The colour scale is the same for all images (a) to (f). The arrows indicate two collaterally-ventilated defects, and the top row shows magnifications of the largest defect. (g) is a sagittal reformat of the first time-point data and (h) is a sagittal reformat of the last time-point data with the coronal slice position indicated with a dashed white line. (i) shows a delay to signal onset map for the coronal slice with timescale in seconds. (j) is a HRCT image of a similar slice, and (k) is a high-resolution ^{3}He MRI ventilation image of the same coronal slice acquired in the same scanning session.

Figure 3

Images showing delayed ventilation in two other COPD patients; (top row) patient 2, (bottom row) patient 3. (a) is the first time-point data and (b) is the last time-point data, arrows highlight ventilation defects which fill with gas during the course of the breathold. (c) is the delay to signal onset map and (d) a high resolution ventilation image of the same slice. (e) to (h) show the same respectively for patient 3.

Figure 4

Images showing slow filling of a peripheral ventilation defect. Images (a) to (f) show a coronal slice at six time-points during the breathold. (g) is the delay to signal onset map and (h) is the high-resolution ventilation image of the same slice.

TABLE 1

Patient demographics, lung function and delayed-filling ventilation defect information.

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	Smoking history (pack years)	FEV1 (L)	FEV1 % predicted	FEV1/FVC (%)	TLCO (mmol/kPa.min)	TLCO % predicted	Number of defects with delayed-filling	Volumes of defects (cm^3)	Defect fills from the edge(s)?
1	55	F	155	62	30	0.83	39	29	1.8	25	2	173.3, 81.2	Y, Y
2	64	F	160	97	50	0.72	34	33	3.7	51	4	16.2, 15.6, 2.3, 0.8	Y, Y, U, U
3	64	M	163	53	25	1.50	56	34	3.4	44	1	6.6	Y
4	62	M	183	98	35	1.08	30	30	5.0	49	2	46.1, 65.9	Y, Y
5	68	M	169	83	90	1.54	55	49	3.4	41	1	4.9	U
6	64	M	170	87	20	1.39	47	37	7.0	81	0	0	n/a
7	63	F	157	70	50	0.72	35	44	2.5	36	2	15.4, 4.3	Y, U
8	58	M	172	99	35	2.61	81	54	5.0	54	0	0	n/a
9	50	F	156	89	40	1.69	74	62	5.5	73	2	0.9, 0.7	U, U
10	58	F	159	77	20	0.99	45	45	3.1	42	1	1.5	U

Y = yes, U = unsure (defects are too small to determine gas fill pattern)

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Competing Interest: None to declare.