Supplementary Material

Hyperpolarised xenon MRI in difficult asthma; initial experience in a clinical setting

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Methods

MRI acquisition

Patients were scanned using a 1.5T whole body MRI system (GE HDx, Milwaukee, WI, USA) equipped for hyperpolarised gas imaging. Patients were positioned in a ^{129}Xe transmit-receive vest coil (Clinical MR Solutions, USA) and scanned by an experienced radiographer. The same chest volume was imaged with both proton and xenon MRI, with the field of view (FOV) and number of slices adjusted to ensure full lung coverage.

Xenon (^{129}Xe) was polarised (1) on site under regulatory licence. Mean ^{129}Xe polarisation = 27 % with a SD of +/- 6 % (where the units of the SD are in percentage polarisation). The dose of xenon and inhaled volume were titrated based upon patient height. In people >160cm, 500ml of hyperpolarised ^{129}Xe was mixed with nitrogen to give a total volume of 1 litre. In people 150-160cm, 450ml of hyperpolarised ^{129}Xe was mixed with nitrogen to give a total volume of 800ml. No subjects were below 150cm in height. The gas was transported to the patient in a Tedlar bag, with a tube connected to it, from which the patient could breathe in the gas via a filtered mouthpiece. The patient was asked to breathe in and out twice by the instructor. On the second expiration, the mouthpiece was given to the patient and they were instructed to breathe in the contents of the bag and then hold their breath. During breath hold, ventilation images were acquired using a 3D steady state free precession (SSFP) sequence (parameters in the table below).

Proton (^{1}H) anatomical images were acquired during a separate breath hold using a three-dimensional (3D) spoiled gradient echo (SPGR) sequence, after the patient had inhaled the bag volume from functional residual capacity (FRC). Images were acquired using the scanner body coil (GE, WI), with the sequence parameters outlined below.

Scan	Matrix	Field of view (FOV)	Slice thickness	Number of slices	Bandwidth (BW)	Echo time (TE)	Repetition time (TR)	Flip angle	Scan time
^{1}H	100x100	40-48cm	5mm	~48	167kHz	0.6ms	1.9ms	5°	4s
^{129}Xe	100x100	40-	10mm	~24	16kHz	2.2ms	6.7ms	10°	15s

		48cm							

Processing of the MR images

All images were reviewed by radiologists. Image metrics were calculated using semi-automated segmentation (2) for both the ^{1}H and ^{129}Xe images. The ^{129}Xe images were segmented in order to calculate the ventilated lung volume (VV) and the ^{1}H images were used to calculate the total lung cavity volume (TCV). From these values the ventilation defect percentage (VDP) was calculated as the proportion of TCV without ventilation. The ^{129}Xe segmentation was used to generate a map of the ventilation heterogeneity and corresponding histogram. This is calculated based upon the coefficient of variation in the signal intensity from neighbouring ventilated voxels (3). From this, the ventilation heterogeneity index (VH_I) was calculated from the interquartile range of these values (4). All image segmentation was performed by the first author (G.T.M.) after training from a member of the POLARIS group with extensive experience of ventilation image segmentation gained over the previous 3 years (L.J.S.).

Pulmonary function tests

25 patients underwent spirometry on the day of the MRI scan, and spirometry was performed before the MRI scan. There were 3 patients who had the MRI scan on an alternative day to spirometry due to pulmonary function lab availability; with intervals of 15 days, 19 days and 9 days.

Interpreting spirometry results using predicted values, as is done in clinical practice, can

introduce age and height related bias. FEV_1 has a wide normal range, particularly in older adults and using a threshold of 80% predicted to define an abnormal FEV_1 results in a high percentage of false positives in the elderly. Similarly, FEV_1/FVC declines with age and the lower limit of normal falls below 0.7, therefore using a cut off of <0.7 to identify abnormal airways obstruction leads to overestimation in the elderly (5,6). Z-scores demonstrate how many standard deviations a measured value is from a predicted value. Ninety percent of healthy subjects will have spirometry within $\pm$1.64 z-scores, therefore 1.64 z-scores is the cut off used to identify patients outside of the normal range. Z-scores are independent of age, height, gender and ethnicity, which allows lung function to be compared amongst individuals regardless of these factors (6). As a result, in this research analyses related to pulmonary function tests have used z-scores.

Reversibility testing

Reversibility was examined at the request of the referring clinician in 18 of the cohort. Prior to testing patients were advised to withhold all inhalers on the morning of the scan. Following baseline spirometry and MRI, these patients inhaled 400μg of salbutamol from a metered-dose inhaler via a spacer, whilst supervised by a physician or physiologist. After approximately 20 minutes, MRI was repeated followed by spirometry. The remaining 10 patients of the study did not have reversibility testing, so their spirometry results are only post-bronchodilator.

Other clinical information

Medications of interest were long-acting and short-acting beta-agonists, long- acting muscarinic antagonists, leukotriene receptor antagonists, theophyllines, inhaled and oral

corticosteroids, azithromycin (an anti-inflammatory macrolide used to reduce asthma exacerbation frequency) and biological therapies. All patients were prescribed a short-acting beta-agonist, in addition to this, 25 patients were prescribed a combined long-acting beta-agonist and inhaled corticosteroid inhaler. Eighteen patients were also prescribed a long-acting muscarinic antagonist. Ten patients were taking long term corticosteroids (between 5 and 10mg). Six patients were taking biological therapies (5 taking mepolizumab and 1 taking omalizumab).

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