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Peripheral and proximal lung ventilation in asthma; short-term variation and response to bronchodilator

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Abstract

Background: The relative involvement of the large and small airways in asthma is not clear. Hyperpolarised gas MRI provides high resolution three-dimensional images of ventilation distribution which can be quantified by the ventilated volume percentage of the lungs (VV%).

Objective: To (1) quantify the baseline reproducibility of VV%, (2) assess the ventilation distribution between the proximal and peripheral lungs and (3) investigate regional ventilation response to bronchodilator inhalation in a cohort of patients with asthma.

Methods: 33 patients with poorly controlled, moderate-to-severe asthma were scanned with hyperpolarised ^{3}He MRI. Two image datasets were acquired at baseline, and one image dataset was acquired after bronchodilator inhalation. Images were divided into proximal and peripheral regions for analysis.

Results: Bland-Altman analysis showed strong reproducibility of VV% (bias = 0.12%, LOA = -1.86, 2.10%). VV% variation at baseline was greater in the periphery than in the proximal lung. The proximal lung was better ventilated than the peripheral lung. Ventilation increased significantly in response to bronchodilator, globally and regionally, and the ventilation increase in response to bronchodilator was greater in the peripheral lung than in the proximal lung. Hyperpolarised gas MRI was more sensitive to changes in response to bronchodilator (58%) than spirometry (33%).

Conclusion: The peripheral lung showed reduced ventilation and a greater response to bronchodilator than the proximal lung. The high level of baseline reproducibility and sensitivity of hyperpolarised gas MRI to bronchodilator

reversibility suggests that it is suitable for low subject number studies of therapy response.

Key Messages:

- The peripheral lung was the main site of ventilation obstruction and had greater response to bronchodilator when compared to the proximal lung in a cohort of patients with moderate-to-severe asthma.
- Hyperpolarised gas ventilation MRI is highly reproducible and sensitive to bronchodilator therapy, allowing the use of small sample sizes for studies of therapy response.

Capsule summary:

In patients with poorly-controlled moderate-to-severe asthma, the peripheral lung was more poorly ventilated and showed a greater response to bronchodilator than the proximal lung, and ventilation MRI was highly reproducible and sensitive to bronchodilator response.

Keywords: Hyperpolarised gas MRI, ventilation, asthma, proximal, peripheral, reproducibility, bronchodilator response

Abbreviations:

MRI = magnetic resonance imaging

MDCT = multi-detector computed tomography

PET = positron emission tomography

VV% = ventilated volume percentage

COPD = chronic obstructive pulmonary disease

GINA = global initiative for asthma

ICS = inhaled corticosteroids

LABA = long acting beta agonist

^{3}He = helium-3

VV = ventilated volume

TLV = total lung volume

VDP = ventilation defect percentage

FEV_1 = forced expiratory volume in one second

SEM = standard error of measurement

SDD = smallest detectable difference

LOA = limits of agreement

FVC = forced vital capacity

EIB = exercise induced bronchoconstriction

MCID = minimal clinically important difference

ACQ = asthma control questionnaire

Introduction

Much about the pathology of asthma has been learnt from post-mortem studies [1, 2], as well as several transbronchial and endobronchial studies [3, 4], and several lines of evidence point towards the involvement of both large and small airways in asthma [1, 5, 6]. However, the relative involvement of the large and small airways in disease expression is not so well understood, and the ability to study the small airways *in vivo* is limited, driving the need for repeatable imaging techniques which are sensitive to small airways disease.

There is a body of evidence to suggest that the small airways (<2mm diameter) are the main site of airflow limitation in asthma [7-10], and yet other studies conclude that narrowing of the large airways is the primary cause of airflow limitation [11, 12]. Hyperpolarised gas MRI provides high resolution three-dimensional images of lung ventilation. Regions without ventilation signal in such images, termed ventilation defects, are due to airway obstruction which may be caused by mucous plugging[13], smooth muscle constriction[14] or airway remodelling[15]. It has been suggested that larger ventilation defects are the result of closure of segmental or sub-segmental bronchi [16], and increased distal airway wall thickness measured on MDCT has been observed proximal to these regions without signal [15, 17]. However, analysis of PET data in patients with asthma has shown some lung units with normal ventilation levels within large ventilation defects, consistent with the defect being caused by clusters of constricted small airways rather than exclusive constriction of large airways [18]. Further modelling concluded that ventilation defects only formed when both small and large airways throughout the branching tree were allowed to constrict. A relationship between abnormal peripheral airway function measured using multiple

breath washout and more extensive airway closure during bronchoconstriction on PET has also been observed [19].

Hyperpolarised gas images are sensitive to ventilation changes in response to therapy [20-22] and challenge [16, 23]. Lung ventilation can be simplistically quantified as the ventilated percentage of the total lung volume (VV%) [24] and is most commonly assessed as a global value. Lobar analyses have found differences in ventilation distribution within the lungs of patients with asthma [25, 26], and both anterior-to-posterior and apical-to-basal ventilation dependences have been observed in patients with exercise-induced bronchoconstriction [21]. Previously the lung has been divided into proximal and peripheral regions (core and rind) to investigate the distribution of emphysema in COPD [27] and to perform automated feature analysis of hyperpolarised gas images in patients with asthma [28]. As proximal lung regions contain the majority of the large airways and peripheral regions contain predominantly small airways, we hypothesised that regional analysis of hyperpolarised gas images in this manner may help to elucidate the relative involvement of the large and small airways in ventilation obstruction in asthma.

The aim of this work was to:

(1) quantify the baseline reproducibility of ventilated volume percentage (VV%)
(2) assess ventilation distribution between the proximal and peripheral lungs
(3) investigate ventilation response to bronchodilator inhalation in the proximal and peripheral lung

in a cohort of patients with poorly controlled, moderate-to-severe asthma.

Methods

33 adults with moderate-to-severe asthma who were taking part in the Fevipiprant trial[29] (EudraCT Number: 2011-004966-13) were recruited in Leicester and scanned in Sheffield. Patients had moderate-to-severe asthma (Global Initiative for Asthma (GINA) step 2-5 [30]) and sputum eosinophilia (count $\geq$ 2%), and were symptomatic and incompletely controlled on their current therapy (inhaled corticosteroids (ICS) or ICS-long acting beta agonist (LABA) therapy). The study was approved by the national research ethics committee and all patients provided written informed consent.

Imaging took place before treatment with Fevipiprant or placebo[29]. Baseline scans and spirometry were performed after patients had withheld short-acting bronchodilators for at least 6 hours. Post-bronchodilator measurements took place 20 minutes after bronchodilator inhalation (400µg Salbutamol).

MRI acquisition

Patients were positioned supine in a ^{3}He transmit-receive vest coil (Clinical MR Solutions, Brookfield, WI) and scanned using a 1.5T whole body MRI system (GE HDx, WI). Two ^{3}He ventilation image sets were acquired at baseline within 5 minutes of each other; the patient remained in the same supine position for both acquisitions. Patients exited the scanner room to inhale their bronchodilator in an upright position and were repositioned in the scanner after a 10 minute break during which they were in an upright posture. A third set of ^{3}He ventilation images were acquired 20 minutes after bronchodilator inhalation. Ventilation images were acquired using a 2D multi-slice coronal spoiled gradient echo sequence with full lung coverage and voxel size = 3 x 3 x 10mm. Anatomical images of the same imaging volumes were also acquired. Further details are in the online repository.

MRI analysis

The ventilation images were segmented to measure ventilated volume (VV) and the anatomical images were segmented to measure total lung volume (TLV). The total lung volume was divided into proximal and peripheral regions. The proximal region represented the central two thirds (by volume) of the lungs containing the conducting airways, small airways and alveolar airspaces. The peripheral region represented the distal third (by volume) of the lungs containing small airways and alveolar airspaces; although it should be noted that small airways in the periphery are supplied by larger airways such that a peripheral ventilation defect may be caused by obstruction of a larger supplying airway. This division into proximal and peripheral regions adopted the approach previously used in the segmentation of CT images [27] but defined the regions according to two thirds and one third of the total lung volume rather than an even split between the two regions to ensure that the majority of the large airways would lie in the proximal region. The ventilated percentage of the lungs (VV%) was calculated as (VV/TLV) x 100 [24], globally and for the proximal and peripheral regions. VV% is negatively proportional to the ventilation defect percentage (VDP) by the relation; VV% = 100 – VDP. Ventilation defects that spanned both proximal and peripheral regions contributed unventilated volume to the appropriate regions according to the defined boundary between proximal and peripheral. Further details are in the online repository. The smallest detectable difference [31] in VV% for the whole lung calculated from the baseline images was used as the threshold for MRI response to bronchodilator.

Spirometry

Spirometry was performed according to American Thoracic Society / European Respiratory Society guidelines [32] using a rolling seal spirometer (Vitalograph, Buckingham, England). Both z-scores [33] and percent predicted values were reported. FEV_1 response to bronchodilator was classed as improvement in $FEV_1 \geq$ 12% and increase in volume $\geq$ 200ml [34].

Statistical analysis

Statistical analysis was performed in GraphPad Prism. Data were assessed for normality using the D'Agostino and Pearson normality test, and treated accordingly. To assess repeatability between the baseline ventilation images, Bland-Altman analysis was performed, and the Spearman or Pearson correlation, intra-class correlation, coefficient of variation, standard error of measurement (SEM) and smallest detectable difference (SDD) were calculated [31] for whole lung, proximal and peripheral VV% values. T-tests and Wilcoxon signed rank tests were used to assess response to bronchodilator and the ventilation distribution between lung regions, with $p < 0.05$ considered significant. Spearman correlations were performed between MRI and spirometry metrics with p-values corrected for multiple comparisons according to the method proposed by Benjamini and Hochberg [35]. In addition, Bland-Altman analysis of absolute ventilated volume (VV) at baseline was performed, and a t-test was also used to assess VV response to bronchodilator of the different lung regions.

Results

Patients were aged between 21 and 73, on a median GINA treatment step of 4 and had a median prior smoking exposure of 0 pack years, full demographics are given

in table 1. Spirometry and MRI metrics are given in table 2. Figure 1 shows example ventilation images from three patients; two images at baseline and one image after bronchodilator inhalation, and also the segmented images.

VV% reproducibility

Bland-Altman analysis showed strong reproducibility of VV% between repeated baseline images (bias = 0.12%, LOA = -1.86, 2.10% for the whole lung VV%, bias = 0.04%, LOA = -2.22, 2.31% for proximal lung VV%, and bias = 0.53%, LOA = -4.71, 5.77% for peripheral lung VV%) (figure 2) and strong correlations were observed between repeated VV% measures made at baseline (table 3). Ventilation variation at baseline was greater in the periphery than in the proximal lung (mean magnitude change in proximal VV% = 0.82% when compared to mean magnitude change in peripheral lung VV% = 2.10, $p<0.0001$). The minimum difference that was required to be confident that any given change in VV% was real and not due to baseline variations (smallest detectable difference [31]) was 2.0% for the whole lung, 2.3% for proximal lung and 5.2% for peripheral lung. Bland-Altman results of absolute ventilated volume (VV) for repeated baseline images are shown in the online repository (figure OR3, table OR1).

Ventilation distribution

The proximal lung was significantly better ventilated than the peripheral lung, both at baseline (VV% = 95.9% and 79.6% respectively) and after bronchodilator (VV% = 98.1% and 87.0% respectively, both $p<0.0001$).

Response to bronchodilator

Ventilation increased significantly in response to bronchodilator in the lungs as a whole (VV% = 90.8% to 94.1%, p=0.0002, 3.6% relative increase), in the proximal lung (VV% = 95.9% to 98.1%, p=0.0006, 2.3% relative increase) and in the peripheral lung (79.6% to 87.0%, p<0.0001, 9.3% relative increase) (figure 3). The magnitude of these changes in VV% after bronchodilator inhalation were significantly greater than baseline variability, over the whole lung (p=0.0001), proximally (p<0.0001) and peripherally (p=0.0001). Additionally, the VV% increase in response to bronchodilator was significantly greater in the peripheral lung than the proximal lung (p=0.0218) (figure 3d). The mean change in ventilated volume, VV, (i.e. not normalised by the total lung volume) in response to bronchodilator was 0.057L in the peripheral lung and 0.047L in the proximal lung (p=0.84) (figure OR4). Spirometric indices also changed significantly after bronchodilator inhalation (FEV_1 z-score -2.07 to -1.54, p<0.0001, FEV_1 % predicted 69.0% to 77.7%, p<0.0001, FVC z-score -0.95 to -0.56, p=0.0008, FVC % predicted 87.3% to 92.4%, p=0.0003 and FEV_1/FVC 67.7 to 71.6, p<0.0001).

11 patients (33%) had a FEV_1 response to bronchodilator. 19 patients (58%) had a significant increase in whole lung VV% (>2.0%) after bronchodilator while 3 patients (9%) had a significant decrease in VV% after bronchodilator. Of the 3 patients with a significant decrease in VV% after bronchodilator, 1 had a FEV_1 response to bronchodilator while 2 did not, but none had reduced FEV_1 after bronchodilator.

Correlations between MRI and spirometry

Moderate statistically significant correlations were observed between VV% and spirometric outcome metrics both at baseline and post-bronchodilator (table 4).

There were no significant correlations between change in VV% and change in spirometry metrics after bronchodilator.

Discussion

The regional analysis of ventilation images performed in this study found that proximal lung was significantly better ventilated than peripheral lung, and that ventilation increase in response to bronchodilator was significantly greater in the peripheral lung than in the proximal lung. Due to the greater proportion of small airways in the peripheral than the proximal lung, a possible interpretation would support a propensity towards small airway involvement in ventilation obstruction and the associated response of lung ventilation to short acting bronchodilator inhalation in this cohort of patients with moderate-to-severe asthma. However, for larger ventilation defects, the observation of reduced ventilation in the periphery could be a result of more central obstruction of the airway tree or clusters of constricted small airways as hypothesised by Venegas et al [18]. As such, in the instance where no tracer gas is imaged in the small airways of the periphery, the ventilation MRI data alone cannot determine whether this is due to narrowing / obstruction of the small airways themselves [18] or of a larger airway upstream. In further work, combination of this approach with a high resolution structural assessment of obstruction and remodelling of the larger airways from CT [15, 17] might help isolate the two mechanisms. Smaller ventilation defects are likely caused by obstruction of the small airways, whether located in the proximal or peripheral lung, as blockage of a large airway would obstruct airflow to a larger segment of the lungs that contains small airways and alveolar airspaces. A limitation of the regional analysis performed

in this study is that the proximal and peripheral regions do not contain exclusively large and small airways respectively due to the difficulty distinguishing them from each other using hyperpolarised gas MRI. However, the vast majority of the large airways (>2mm diameter) were located within the proximal region. A previous study supporting peripheral lung involvement in airway obstruction observed that the extent of airway closure induced by methacholine challenge visible on PET images was greater with increasing peripheral airways disease measured by multiple breath washout [19]. Another study which divided the lung into proximal and peripheral regions found that features of the outer peripheral lung ranked highly for relevance when distinguishing the lungs of patients with asthma when compared to healthy volunteers [28]. Lobar analysis has previously shown greater ventilation in the lower lobes than the right middle and upper lobes in patients with mild-to-moderate asthma, and in the lower lobe than the upper lobe of the right lung in patients with severe asthma [26]. Lower ventilation in the anterior compared to the posterior in mild-to-moderate asthma, and compared to the middle of the lungs in both severity groups was also observed in the same study.

The measurement of ventilated percentage of the lung showed a high level of reproducibility between repeated baseline images, with a smallest detectable difference of 2.0%. This is consistent with a previous study which found the number of ventilation defects present on images acquired on the same day to be highly reproducible [36]. The repeatability of global VV% between baseline images (ICC = 0.995) is higher than that reported between imaging sessions that were performed 7-14 days apart in 13 patients with exercise induced bronchoconstriction (EIB) (ICC ranged from 0.74 to 0.89 for independent readers) [37]. This could be due to several factors including different patient cohorts and periods between imaging. In the study

of patients with EIB, measurements from post exercise challenge and post recovery were incorporated in the repeatability metrics, and there were also methodological differences including no co-registered proton images from which to measure total lung volume for post exercise and recovery time points and the inclusion of partially ventilated regions in defect volume. The smallest detectable difference of 2.0% was considerably less than the minimal clinically important difference (MCID) of 4.0% [38] calculated based on the Asthma Control Questionnaire (ACQ) score MCID and the linear relationship between ACQ score and ventilation defect percentage observed in 18 patients with severe, poorly controlled asthma [39]. The MCID is the smallest measurement difference that patients perceive as beneficial, so this implies that hyperpolarised gas ventilation MRI is repeatable enough to detect clinically important changes with sufficient measurement precision. As VV% is linearly proportional to VDP, the reproducibility and change metrics for VV% are the same as if they had been reported for VDP. The difference in VV% between baseline time-points includes any errors introduced by the image acquisition and processing techniques (measurement error) and also the natural physiological variability in ventilation between imaging time-points, which is likely higher in this cohort than in most patient groups due to the inherent reversibility of air-flow limitation in asthma. Repositioning patients between baseline and post-bronchodilator scans is an additional potential source of error that was not taken into account by the baseline repeatability measurements, which were performed with the patient in the same position. Therefore, the smallest detectable difference for VV% may be higher when assessing differences when the patient has been repositioned between scans.

The higher variability of ventilation in the peripheral lung at baseline when compared to the proximal lung should be interpreted with some caution due to the different

absolute lung volumes of the two regions and because quantitative measurement of lung ventilation at the lung periphery has additional sources of error. Misregistration due to differing lung inflation levels between the constituent ventilation and anatomical images, cardiac motion, partial volume effects when a voxel contains both lung and non-lung tissues and any magnetic susceptibility artefact at the diaphragm, all can affect the fidelity of quantitative peripheral lung ventilation measurement more so than in the proximal lung. It is also worth noting that when large airways or vessels extended into the lung parenchyma within a coronal slice, the automatic algorithm used to separate proximal and peripheral lung sometimes misclassified the lung tissue at the borders of the central airways and vessels as peripheral lung, as seen in figure 1. This depended on if there was a gap on the inner edge of the lung caused by the airway or vessel segmentation and would also have contributed to the apparent ventilation variation between scans in some cases. An additional consideration when comparing peripheral and proximal change in VV% is that for the same change in absolute lung volume (measured in millilitres), the relative change in VV% for the peripheral one third of the lungs would be twice that for the proximal two thirds of the lungs. When considering the baseline repeatability of absolute ventilated volume (VV), the relative variability for the peripheral lung (8.0%) was only slightly higher than for the proximal lung (7.6%) which could be due to the additional sources of error in the peripheral lung when measuring ventilated volume. Consequently, the balance of true physiological ventilation variation at baseline between the proximal and peripheral lung is difficult to determine from these data. The baseline variability of VV was substantially greater than that of VV% due to the lack of normalisation for changes in lung volume between breaths. Both proximal and peripheral ventilation improved significantly after bronchodilator, as did

global VV% and spirometric indices. This is consistent with a previous study of seven patients with asthma that found significant improvements in global VV% after bronchodilator inhalation [20]. Peripheral lung ventilation was more impaired than proximal lung ventilation both before and after bronchodilation, so while VV% increase in response to bronchodilator was greater in the peripheral than the proximal lung, there was more potential for resolution of airway obstruction in the periphery than proximally. Considering that there was twice the volume of lung in the proximal region than the peripheral region, the finding that the mean increase in absolute ventilated volume was similar for the peripheral and proximal lung regions also supports a hypothesis of greater response to bronchodilator in the periphery than proximally. 67% of patients showed a significant change in VV% after bronchodilator inhalation whereas 33% of patients met the criteria for FEV_1 response to bronchodilator. The high reproducibility of VV% allows the threshold for meaningful change in VV% to be much smaller than for FEV_1.

A limitation of the study was that MRI and spirometry were performed on different days, albeit within a period of at most one week, and this may have influenced the correlations observed between VV% and spirometry. However, MRI and spirometry measure different aspects of lung function, and the spatially localised nature of MRI allows it greater sensitivity to regional ventilation changes. A significant reduction in VV% was observed after bronchodilator inhalation in 9% of patients, which, while counter-intuitive, may be the cumulative result of altered airflow patterns throughout the lungs, i.e. bronchodilation may have caused gas to enter a region which was already ventilated at baseline in preference to a region which was poorly ventilated at baseline, leading to reduced VV%. More advanced regional analyses of ventilation change, such as treatment response mapping [40], could be used to

highlight such areas for clinical interpretation. Treatment response mapping or 3D analysis of individual ventilation defects [41] might also offer additional insight into regional bronchodilator response. The discordance of change in VV% and change in FEV_1 in these three patients, along with the lack of significant correlations between change in VV% and change in spirometric indices after bronchodilator, also underscore that MRI and spirometry measure lung function differently. The differing nature of FEV_1 and MRI measurements required different definitions of response to bronchodilator for the two methods. The clinical definition of FEV_1 response was used (FEV_1 improvement $\geq$ 200mL and $\geq$ 12%) [34], which is considered to suggest significant bronchodilation while changes of < 150mL or < 8% are likely to be within measurement variability [42]. The smallest detectable difference in VV% was used as the threshold for MRI response (VV% improvement > 2.0%), defined as the minimum change needed to be confident that the change in VV% was real and not due to baseline variability [31]. The choice of threshold influences the apparent sensitivity to bronchodilator response of the measurement, but in the absence of MRI clinical response guidelines the smallest detectable difference provides a well-established, unsubjective threshold calculated from baseline measurement variability. A further limitation is that this study assessed patients who were chosen to enter a clinical trial and therefore the findings may not be generalised to a wider population.

In conclusion, the peripheral lung showed reduced ventilation and greater response to bronchodilator when compared to the proximal lung. The high level of baseline reproducibility and sensitivity to bronchodilator response of hyperpolarised gas MRI suggests that it is suitable for low subject number studies of therapy response.

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Figure captions

Figure 1

Ventilation image examples (left) and segmented images (right) from 3 different patients with asthma; (left) baseline 1, (centre) baseline 2 and (right) after bronchodilator inhalation. Segmentations show ventilation defects in dark grey and ventilated regions in light grey and white (see key), with proximal and peripheral regions highlighted. Top row; 5.8% increase in total VV% post BD, centre row; 2.0% increase in total VV% post BD, and bottom row; 2.8% decrease in total VV% post BD.

Figure 2

Baseline repeatability of VV% measurement. Bland-Altman plots of; (a) whole lung VV% (bias = 0.12%, limits of agreement (LOA) = -1.86, 2.10%), (b) proximal VV% (bias = 0.04%, LOA = -2.22, 2.31%) and (c) peripheral VV% (bias = 0.53%, LOA = -4.71, 5.77%).

Figure 3

VV% response to bronchodilator. (a) proximal VV% ($p=0.0006$), (b) peripheral VV% ($p<0.0001$), (c) whole lung VV% ($p=0.0002$) and (d) change in VV% for proximal and peripheral lung ($p=0.0218$).

Tables

Table 1: Patient demographics, given as mean ± standard deviation or median (minimum, maximum)

Subjects n (% female)	33 (48)
Age (years)	51.8 ± 12.5
Height (cm)	166 ± 8
Weight (kg)	83.6 ± 19.4
Body Mass Index	29.2 (21.9, 40.3)
Subjects on GINA treatment step 2	1
Subjects on GINA treatment step 3	1
Subjects on GINA treatment step 4	24
Subjects on GINA treatment step 5	7
Prior smoking exposure (pack years)	0 (0, 9)

Table 2: Spirometry and MRI metrics, values at baseline and after bronchodilator inhalation, given as mean ± standard deviation or median (minimum, maximum). All showed significant difference between baseline and post-bronchodilator values.

	Baseline	**After Bronchodilator**	**Change**	**p-value**
FEV_1 z-score	-2.07 ± 1.65	-1.54 ± 1.70	0.46 (-1.18, 2.26)	<0.0001
FEV_1 % predicted	69.0 (26.3, 110.3)	77.7 ± 24.3	6.8 (-6.8, 29.6)	<0.0001
FVC z-score	-0.95 ± 1.40	-0.56 ± 1.24	0.26 (-0.52, 2.65)	0.0008
FVC % predicted	87.3 ± 18.6	92.4 ± 16.7	3.9 (-3.8, 34.4)	0.0003
FEV_1/FVC	67.7 (30.7, 85.2)	71.6 (33.6, 87.8)	3.7 + 3.7	<0.0001
Whole lung VV%	90.8 (57.5, 99.2)	94.1 (60.6, 99.3)	3.0 + 3.8	0.0002
Proximal VV%	95.9 (61.7, 99.9)	98.1 (62.7, 99.9)	2.0 + 3.2	0.0006
Peripheral VV%	79.6 ± 12.2	87.0 (55.7, 98.1)	4.8 + 5.8	<0.0001

Table 3: Baseline repeatability of whole lung, proximal and peripheral VV%. Spearman's / Pearson's correlations between baseline values were all significant ($p<0.0001$).

Measure	Whole lung VV%	Proximal VV%	Peripheral VV%
Spearman or Pearson Correlation (r)	0.98	0.97	0.98
Intra-class correlation (ICC)	0.995	0.992	0.976
Coefficient of variation CoV (%)	0.69	0.67	1.94
Standard error of measurement SEM (%)	0.7	0.8	1.9
Smallest detectable difference SDD (%)	2.0	2.3	5.2

Table 4: Correlations between MRI and spirometry at baseline and after bronchodilator inhalation, all were significant $p<0.01$.

measure 1	measure 2	baseline r	after bronchodilator r
Whole lung VV%	FEV_1 z-score	0.64	0.70
Whole lung VV%	FEV_1 % predicted	0.69	0.70
Whole lung VV%	FVC z-score	0.56	0.53
Whole lung VV%	FVC % predicted	0.56	0.57
Whole lung VV%	FEV_1/FVC	0.56	0.65
Proximal VV%	FEV_1 z-score	0.55	0.67
Proximal VV%	FEV_1 % predicted	0.59	0.66
Proximal VV%	FVC z-score	0.53	0.50
Proximal VV%	FVC % predicted	0.52	0.50
Proximal VV%	FEV_1/FVC	0.46	0.65
Peripheral VV%	FEV_1 z-score	0.63	0.66
Peripheral VV%	FEV_1 % predicted	0.68	0.66
Peripheral VV%	FVC z-score	0.54	0.51
Peripheral VV%	FVC % predicted	0.54	0.57
Peripheral VV%	FEV_1/FVC	0.59	0.59