



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/142131/>

Version: Accepted Version

Article:

Tahir, B.A., Marshall, H., Hughes, P.J.C. et al. (2019) Comparison of CT ventilation imaging and hyperpolarised gas MRI: effects of breathing manoeuvre. *Physics in Medicine and Biology*, 64 (5). 055013. ISSN: 0031-9155

<https://doi.org/10.1088/1361-6560/ab0145>

This is an author-created, un-copyedited version of an article accepted for publication/published in *Physics in Medicine and Biology*. IOP Publishing Ltd is not responsible for any errors or omissions in this version of the manuscript or any version derived from it. The Version of Record is available online at <https://doi.org/10.1088/1361-6560/ab0145>

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

ACCEPTED MANUSCRIPT

Comparison of CT ventilation imaging and hyperpolarised gas MRI: effects of breathing manoeuvre

To cite this article before publication: Bilal A Tahir *et al* 2019 *Phys. Med. Biol.* in press <https://doi.org/10.1088/1361-6560/ab0145>

Manuscript version: Accepted Manuscript

Accepted Manuscript is “the version of the article accepted for publication including all changes made as a result of the peer review process, and which may also include the addition to the article by IOP Publishing of a header, an article ID, a cover sheet and/or an ‘Accepted Manuscript’ watermark, but excluding any other editing, typesetting or other changes made by IOP Publishing and/or its licensors”

This Accepted Manuscript is © 2018 Institute of Physics and Engineering in Medicine.

During the embargo period (the 12 month period from the publication of the Version of Record of this article), the Accepted Manuscript is fully protected by copyright and cannot be reused or reposted elsewhere.

As the Version of Record of this article is going to be / has been published on a subscription basis, this Accepted Manuscript is available for reuse under a CC BY-NC-ND 3.0 licence after the 12 month embargo period.

After the embargo period, everyone is permitted to use copy and redistribute this article for non-commercial purposes only, provided that they adhere to all the terms of the licence <https://creativecommons.org/licenses/by-nc-nd/3.0>

Although reasonable endeavours have been taken to obtain all necessary permissions from third parties to include their copyrighted content within this article, their full citation and copyright line may not be present in this Accepted Manuscript version. Before using any content from this article, please refer to the Version of Record on IOPscience once published for full citation and copyright details, as permissions will likely be required. All third party content is fully copyright protected, unless specifically stated otherwise in the figure caption in the Version of Record.

View the [article online](#) for updates and enhancements.

Comparison of CT ventilation imaging and hyperpolarised gas MRI: Effects of breathing manoeuvre

Bilal A Tahir^{1,2}, Helen Marshall¹, Paul JC Hughes¹, Christopher E Brightling³, Guilhem Collier¹, Rob H Ireland^{1,2}, Jim M Wild¹

¹POLARIS, Academic Radiology, University of Sheffield, UK

²Academic Unit of Clinical Oncology, University of Sheffield, UK

³Institute for Lung Health, University of Leicester, UK

Abstract

Image registration of lung CT images acquired at different inflation levels has been proposed as a surrogate method to map lung 'ventilation'. Prior to clinical use, it is important to understand how this technique compares with direct ventilation imaging modalities such as hyperpolarised gas MRI. However, variations in lung inflation level have been shown to affect regional ventilation distributions. Therefore, the aim of this study was to evaluate the impact of lung inflation levels when comparing CT ventilation imaging to ventilation from ³He-MRI.

7 asthma patients underwent breath-hold CT at total lung capacity (TLC) and functional residual capacity (FRC). ³He-MRI and a same-breath ¹H-MRI were acquired at FRC+1L and TLC. Percentage ventilated volumes (%VVs) were calculated for FRC+1L and TLC ³He-MRI. TLC-CT and registered FRC-CT were used to compute a surrogate ventilation map from voxel-wise intensity differences in Hounsfield unit values, which was thresholded at the 10th and 20th percentiles. For direct comparison of CT and ³He-MRI ventilation, FRC+1L and TLC ³He-MRI were registered to TLC-CT indirectly via the corresponding same-breath ¹H-MRI data. For ³He-MRI and CT ventilation comparison, Dice similarity coefficients (DSCs) between the binary segmentations were computed.

The median (range) of %VVs for FRC+1L and TLC ³He-MRI were 90.5 (54.9-93.6) and 91.8 (67.8-96.2), respectively ($p=0.018$). For MRI versus CT ventilation comparison, statistically significant improvements in DSCs were observed for TLC ³He MRI when compared with FRC+1L, with median (range) values of 0.93 (0.86-0.93) and 0.86 (0.68-0.92), respectively ($p=0.017$), for the 10-100th percentile and 0.87 (0.83-0.88) and 0.81 (0.66-0.87), respectively ($p=0.027$), for the 20-100th percentile.

Correlation of CT ventilation imaging and hyperpolarised gas MRI is sensitive to lung inflation level. For ventilation maps derived from CT acquired at FRC and TLC, a higher correlation with gas ventilation MRI can be achieved if the MRI is acquired at TLC.

Keywords: CT ventilation imaging, functional lung imaging, hyperpolarised gas MRI, lung inflation, lung diseases, pulmonary image registration

Novelty & Significance

CT ventilation imaging derived from lung CT images acquired at different inflation levels has been proposed as a surrogate method to map lung ventilation. However, it is important to understand how the technique compares with established ventilation modalities such as hyperpolarised gas MRI. Direct comparison of CT ventilation imaging and gas ventilation MRI requires consideration of the sensitivity of both modalities to lung inflation state. To date, CT ventilation has not been compared against an established ventilation imaging modality acquired at different inflation states. Here, we report the first study to evaluate the impact of lung inflation level when comparing gas MRI and CT ventilation.

1. Introduction

The primary function of the human lungs is gas exchange of which ventilation is an essential component. Although normal lungs exhibit a degree of ventilation heterogeneity (Crawford *et al.*, 1985), a marked increase has been shown in patients with respiratory diseases (Mugler *et al.*, 2010). In current clinical practice, ventilation is normally evaluated using global measures of lung function. Assessment of the regional heterogeneity of respiratory disease, however, requires imaging techniques, which are able to visualise and quantify the spatially varying extent of ventilation.

Several respiratory diseases are characterised by impaired lung function on a regional basis with anatomically specific propensity of lung obstruction. In particular, obstructive lung diseases such as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) exhibit marked increases in ventilation heterogeneity when compared with normal subjects due to airway narrowing or closure. For asthmatics, the impact of regionally specific therapeutic interventions such as bronchial thermoplasty may benefit from the regional and quantitative information yielded by ventilation imaging from treatment planning to the assessment of regional pathophysiology response to treatment (Thomen *et al.*, 2015). For COPD patients, regional ventilation can help assess the impact of lung volume reduction surgery (Kurose *et al.*, 2004). For paediatric patients with cystic fibrosis, an early detection of ventilation dysfunction may enable bronchoscopy or physiotherapy for regionally specific mucus clearance to prevent the onset of lung disease irreversibility (Thomen *et al.*, 2015). Regional lung ventilation imaging techniques including single photon emission computed tomography (SPECT) (Seppenwoolde *et al.*, 2000; Christian *et al.*, 2005) and hyperpolarised gas magnetic resonance imaging (Ireland *et al.*, 2007) have also been applied to lung cancer patients undergoing radiotherapy to spatially assist in preferential sparing of functional lung during the treatment planning process (Ireland *et al.*, 2016). Thus, the ability to visualise and quantify regional lung ventilation is highly desirable. However, current regional ventilation modalities suffer from some

1
2
3 or all of the following: poor spatial and temporal resolution, requirement of inhaled contrast agents
4 and specialised equipment inaccessible to most centres.
5
6
7

8 Computed tomography (CT) images of the lungs are routinely utilised in the clinic for the radiological
9 assessment of respiratory diseases and radiotherapy treatment planning. Over the past decade, CT-
10 based methods of mapping regional ventilation, sometimes referred to as 'CT ventilation imaging',
11 which are based on image registration of non-contrast lung CT images acquired at two different
12 inflation levels, have been proposed as a surrogate method to image lung 'ventilation' (Guerrero *et*
13 *al.*, 2005; Reinhardt *et al.*, 2008). Although the technique has gained considerable interest, relatively
14 few papers have addressed the issue of validation against established direct ventilation imaging
15 modalities such as hyperpolarised gas MRI (Mathew *et al.*, 2012; Tahir *et al.*, 2016; Tahir *et al.*,
16 2018). However, direct comparison of CT ventilation imaging and gas ventilation MRI requires
17 consideration of the potential sensitivity of both methods to lung inflation state. For example,
18 hyperpolarised gas ventilation MRI has been shown to be sensitive to lung inflation state; in elite
19 divers, marked decreases in ventilation were demonstrated at sub-residual volumes (Muradyan *et*
20 *al.*, 2010), and in patients with asthma, increased and more homogeneous ventilation was visualised
21 in images acquired at total lung capacity (TLC) when compared to those acquired at functional
22 residual capacity (FRC) + 1L (Marshall *et al.*, 2013).
23
24
25
26
27
28
29
30
31
32

33 Similarly, CT-based surrogates of ventilation have been shown to be sensitive to inflation state;
34 previously, Mistry *et al.* (2013) evaluated the effects of different breathing manoeuvres during CT
35 imaging and observed marked differences in the distribution of the computed CT ventilation images.
36 To date, CT-based surrogates of ventilation have not been compared against an established direct
37 ventilation imaging modality acquired at different inflation states.
38
39
40
41
42

43 The primary aim of this study, therefore, was to evaluate the impact of inflation levels when CT-
44 based surrogate maps of ventilation are compared against an established direct measure of regional
45 ventilation. To this end, we employed ³He hyperpolarised gas MR ventilation imaging acquired at
46 breath-hold at two different lung volumes and performed spatial overlap comparison between each
47 inflation state and the CT ventilation surrogate. A secondary aim was to evaluate the differences in
48 ³He ventilation with lung inflation state.
49
50
51
52
53
54
55
56
57
58
59
60

2. Methods

2.1. Subjects

The study was performed with national research ethics committee approval. Between September 2012 to February 2013, seven patients with sputum eosinophilia and moderate-to-severe asthma gave written informed consent to participate in this study. The inclusion criteria were greater than 18 years of age, physician diagnosis of asthma, currently on Global Initiative for Asthma (GINA) step 2 to 5 asthma therapies, sputum eosinophil count greater than or equal to 2%. The exclusion criteria included other acute illnesses, recent or current lower respiratory tract infection, contra-indication to MRI, body mass index <17 or >40 kg/m², women of child-bearing potential and patients who have been hospitalized or required high-dose (>10mg prednisolone/day) oral corticosteroid (OCS) therapy within 6 weeks of the screening visit. The characteristics of these patients can be found in Table 1.

Table 1 Summary of patient characteristics and lung function parameters.

	Age	Sex	FEV ₁ (L)	FEV ₁ (% predicted)	FEV ₁ /FVC (%)
1	41	Male	3.35	89.10	68.65
2	51	Female	0.80	33.81	45.71
3	45	Male	3.85	104.42	67.54
4	64	Female	2.10	107.03	72.41
5	62	Male	2.30	69.21	50.00
6	52	Female	2.10	99.81	74.73
7	42	Male	3.30	99.97	77.65
Mean	51	N/A	2.54	86.19	65.24
SD	9.20	N/A	1.03	26.40	12.42

FEV₁ = forced expiratory volume in the first second of expiration, FVC = forced vital capacity, L = litres.

2.1. Image acquisition

All patients underwent CT and MRI. MRI was performed within 4 days of CT with a mean±SD interval of 1.5±0.8 days and range of 1 to 4 days.

Breath-hold CT scans were acquired at TLC and FRC on a Sensation 16 scanner (Siemens, Forchheim, Germany). The following CT settings were used: tube voltage, 120kV; tube current,

1
2
3 120mAs; rotation time, 0.5s; pitch, 1.5. Where available, a B30f reconstruction kernel was used or
4 the next kernel closest to it (e.g. B35f, B60 etc.). CT in-plane resolution was approximately
5 0.86×0.86mm with a pixel matrix of 512×512. CT slice thickness was 1 mm with approximately 600
6 slices for each patient.
7
8

9
10
11 ³He MR ventilation images were acquired at two lung inflation states, namely, FRC+1L and TLC,
12 during separate breath-holds in a manner similar to Smith *et al.* (2018) described briefly as follows.
13 In the same breath-hold as ³He MRI, anatomical ¹H MR images were also acquired on a GE HDx
14 1.5T whole body MRI system (GE Healthcare, Milwaukee, WI, USA) (Wild *et al.*, 2011). For the ³He
15 MR ventilation images acquired at FRC+1L, patients exhaled to FRC and then inhaled a mixture of
16 350ml ³He and 650ml N₂. For the ³He MR ventilation images acquired at TLC, patients exhaled to
17 FRC and then inhaled a mixture of 400ml ³He and 600ml N₂ followed by inhalation of room air until
18 TLC was reached. The increase in ³He dose was to account for the gas dilution with increase in lung
19 volume at TLC. Ventilation images at TLC were acquired within six minutes of those at FRC+1L.
20
21
22
23
24

25
26
27 Helium was polarised on-site to approximately 25% using a rubidium spin exchange polariser (GE
28 Healthcare, Amersham, UK). A transmit-receive quadrature ³He vest coil (Clinical MR Solutions,
29 Brookfield, WI, USA) was used to acquire ³He images with the following sequence: 2D spoiled
30 gradient-echo, 3x3mm in-plane resolution, 10mm slice thickness, 38.4cm field of view, 1.1ms echo
31 time, 3.6ms repetition time, 8° flip angle, 62.5kHz bandwidth and full lung coverage (20 to 24 slices).
32
33

34
35 Same-breath ¹H images from the same coronal slices were acquired using the ¹H body coil of the
36 scanner with the following sequence; 2D steady state free precession, 3x6mm in-plane resolution,
37 38.4cm field of view, 0.7ms echo time, 2.4ms repetition time, 50° flip angle, and 167kHz bandwidth.
38
39

40
41 The MRI acquisition protocol was described in Smith *et al.* (2018) and Hughes *et al.* (2018).
42
43

44 45 *2.3. Image segmentation*

46
47 Medical image segmentation software (Mimics; Materialise, Leuven, Belgium) was used to segment
48 the lungs of the inspiratory and expiratory CT scans. ³He and ¹H MR lung parenchyma were
49 segmented in Matlab (MathWorks, Natick, MA) using a modified version of the Spatial Fuzzy C-
50 means (FCM) algorithm presented by Chuang *et al.* (2006) as recently described (Hughes *et al.*,
51 2017). Prior to segmentation, images were pre-processed using a bilateral filter (Tomasi and
52 Manduchi, 1998). Segmented images were manually inspected and large airways including the
53 trachea were removed.
54
55
56
57
58
59
60

2.4. Inspiratory and expiratory breath-hold CT image registration validation and algorithmic optimisation

CT ventilation imaging is highly sensitive to the image registration technique (Yamamoto *et al.*, 2011; Latifi *et al.*, 2013). In order to generate robust maps, accurate registration of inspiratory and expiratory CT images is essential. The vast majority of CT ventilation validation studies to date have utilised 4D-CT data, acquired during tidal breathing (Mathew *et al.*, 2012; Castillo *et al.*, 2012; Castillo *et al.*, 2010). However, the spatial displacement magnitudes between the maximum inhale and exhale phases of normal tidal breathing are significantly lower than those of paired breath-hold CT images acquired at the extremes of inflation (Castillo *et al.*, 2013). As such, inspiratory and expiratory breath-hold CT pose significant challenges for deformable image registration. Although several pulmonary CT datasets for validation of deformable registration exist (Vandemeulebroucke *et al.*, 2011), given the large differences between inspiratory and expiratory breath-hold CT used in this study, image registration was validated by computing the mean target registration error (TRE) of 300 corresponding expert landmarks on inspiratory and expiratory breath-hold image pairs from a separate validation cohort consisting of CT images from ten COPD patients. The paired images were acquired at the same inflation levels as the breath-hold CT scans used for this study (TLC and FRC). These data sets were obtained from the DIR-lab (www.dir-lab.com), a publicly available reference dataset acquired from the National Heart Lung Blood Institute COPDgene study archive for the validation of pulmonary deformable registration algorithms (Castillo *et al.*, 2013). The in-plane resolution of the images ranged from 0.586x0.586 to 0.742x0.742 mm. Slice thickness was always 2.5 mm. The TRE was computed by taking the Euclidean distance between the corresponding landmark on the fixed and warped moving image.

In this study, the choice of registration software used was based on the best performing algorithm at the time of writing during a recent pulmonary image registration competition (EMPIRE10, <http://empire10.isi.uu.nl/>), which forms part of the MICCAI Grand Challenges in image analysis. The results of this challenge were reported in Murphy *et al.* (2011) where the Greedy symmetric normalization (SyN) algorithm implemented within the Advanced Normalization Tools (ANTs) registration framework (Avants *et al.*, 2011) attained first place.

To find the optimal parameters for this dataset, a number of parameters were varied, and the mean TRE per patient was calculated. Initial parameters used were based on the developers' own submissions to the EMPIRE10 challenge (<http://empire10.isi.uu.nl/mainResults.php>) where two variants of their Symmetric Normalization (SyN) algorithm were used, one with Gaussian regularization and the other with B-splines. These two settings are referred to here as 'EMPIRE10_Syn' and 'EMPIRE10_BSplineSyn', respectively. Numerous experiments were undertaken to find the optimal parameters for the reference datasets with respect to minimising TRE.

1
2
3 In this study, we compare the results of these two scripts with that of an empirically validated
4 optimised parameter script, referred to here as 'Optimised'.
5
6

7 All three methods are discussed in brief below:
8

9
10 *1. EMPIRE10_Syn*
11

- 12 – A coarse pre-alignment rigid transform was applied to align the centres of mass of the
13 fixed and moving image intensities.
- 14 – The resulting transform was then applied to rigid and affine stages using the mutual
15 information similarity metric with 32 histogram bins optimised via the gradient descent
16 algorithm with a step size of 0.1.
- 17 – A multi-resolution Gaussian pyramid with 4 levels was used with down-sampling factors
18 8x4x2x1 and corresponding smoothing Gaussian sigmas of 3x2x1x0 mm.
- 19 – A maximum of 10,000 iterations was set for each resolution level to ensure convergence
20 (Glocker *et al.*, 2011).
- 21 – For the non-rigid stage, the SyN diffeomorphic transform was used with a Gaussian
22 regularization kernel width of 3 voxels for smoothing of the update transform field.
- 23 – A 4-level multi-resolution pyramid with down-sampling factors of 6x4x2x1 and
24 corresponding smoothing Gaussian sigmas of 3x2x1x0 mm and the normalized
25 correlation coefficient similarity metric with a radius of 4 voxels were used.
- 26 – A step size of 0.1 was selected for the gradient descent optimisation algorithm.
27
28
29
30
31
32
33
34
35
36
37

38 *2. EMPIRE10_BSplineSyn*
39

- 40 – For the rigid and affine stages, the same parameters as above were employed.
- 41 – An additional diffeomorphic transformation with explicit B-spline regularization (Tustison
42 and Avants, 2013) that copes with larger deformations than the familiar SyN algorithm
43 (Avants *et al.*, 2008) was applied instead to the resulting transform of the affine pipeline
44 with a knot spacing for the update field of 40 mm.
- 45 – The same 4-level multi-resolution strategy was employed.
46
47
48
49
50
51

52 *3. Optimised*
53

- 54 – The empirically optimised script used identical rigid and affine parameters as
55 EMPIRE10_Syn and EMPIRE10_BSplineSyn.
- 56 – For the deformable stage, the explicit B-spline regularization was applied to the resulting
57 transform of the affine pipeline.
58
59
60

- A knot spacing for the update field of 65 mm provided optimal results.
- Additionally, a 5-level multi-resolution pyramid was used (instead of 4 levels) with down-sampling factors of 10x6x4x2x1 and corresponding smoothing Gaussian sigmas of 5x3x2x1x0 mm and the normalized correlation coefficient similarity metric with a radius of 2 voxels instead of 4.
- A step size of 0.2 was selected for the gradient descent optimisation algorithm.

To reduce the computational times in performing the three registration pipelines above, 8 cores via an Intel Xeon E5-2670 eight-core processor @ 2.60 GHz were run in parallel on a 64-bit high performance Linux server (Iceberg, University of Sheffield) using the multi-threading options available in ITK⁴.

2.5. CT ventilation computation

For the CT ventilation calculation, FRC-CT was registered to TLC-CT using the optimised script. Next, TLC-CT and registered FRC-CT were used to compute a surrogate ventilation image from voxel-wise intensity differences in Hounsfield unit (HU) values based on a modified version of the original formulation of Guerrero *et al.* (2005) to account for the computation being performed in the inhalation CT spatial domain:

$$\frac{\Delta V}{V_{exp}} = 1000 \frac{HU_{ins} - \overline{HU}_{exp}}{\overline{HU}_{exp}(1000 + HU_{ins})}$$

where \overline{HU}_{exp} is the HU of the voxels in the moving deformed expiration image which spatially correspond to the voxels in the fixed inspiration image and HU_{insp} is the HU of the inspiratory voxel. The metric purports to be a measure of change in fractional content of air per voxel between respiratory phases.

For subsequent analysis, the CT ventilation surrogate image needed to be segmented. Here, we employed the percentile threshold technique used in several studies (Castillo *et al.*, 2010; Castillo *et al.*, 2012; Kipritidis *et al.*, 2014; Yamamoto *et al.*, 2014) to discern ventilated from non-ventilated lung. To assess the effect of using different percentile values, we thresholded the CT ventilation surrogate to the 10-100th and 20-100th percentile ranges which were assumed to be ventilated.

2.6. Comparison of ^3He MRI and CT

The percentage ventilated volume (%VV) was calculated for each patient by taking the ratio of the binary lung segmentations of ^3He and ^1H MRI. For spatial comparison of ^3He MRI and CT ventilation, for each patient, MR images were registered to the TLC-CT image's spatial domain via the anatomical same-breath ^1H MRI as previously described (Tahir *et al.*, 2014) and Dice similarity coefficients (DSCs) were computed separately for the binary segmentations of both CT ventilation percentiles with that of FRC+1L and TLC ^3He MRI. The workflow for the comparison method of FRC+1L and TLC ^3He MRI with CT ventilation is shown in Figure 1.

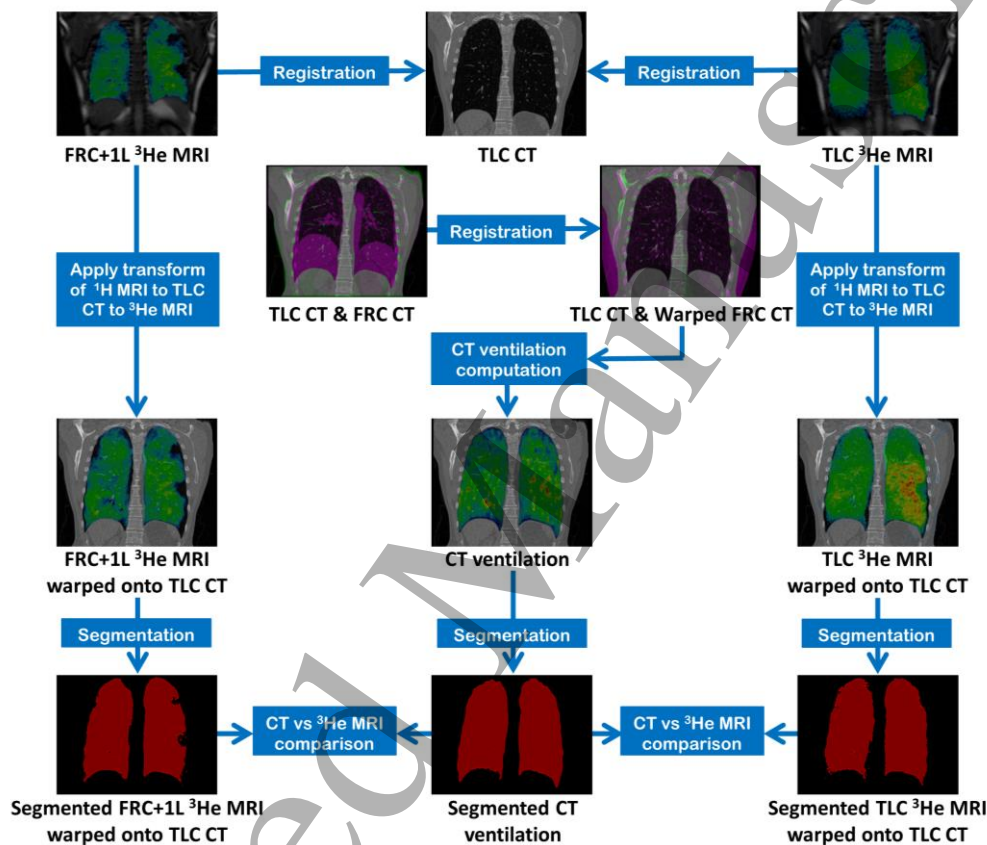


Figure 1 Workflow for comparison of FRC+1L and TLC ^3He MRI with CT ventilation. CT ventilation images were generated on TLC-CT geometry by deformably registering FRC-CT to TLC-CT. For each patient, ^3He MR images were registered to the TLC-CT image's spatial domain via the anatomical same-breath ^1H MRI. For spatial comparison, Dice similarity coefficients were computed separately for the binary segmentations of the CT ventilation images with that of the warped FRC+1L and TLC ^3He MR images.

2.7. Statistical analysis

Statistical analysis was performed by using IBM SPSS software (version 20.0; Chicago, IL, USA). A p value less than 0.05 was considered statistically significant. The Wilcoxon signed-ranks test was used to test statistical significance in differences.

3. Results

3.1. Breath-hold CT image registration accuracy

Figure 2 shows example coronal slices for the moving exhalation image overlaid with the fixed inhalation image for patient 10 of the DIR lab dataset before and after performing each of the three registration pipelines. There is a notable improvement in diffeomorphic registration accuracy with B-spline regularisation for both the EMPIRE10_BSplineSyn and Optimised pipelines and subtle improvements for the Optimised pipeline. The mean TREs before registration and for the registration pipelines are displayed in Table 2. The results show that B-spline regularisation improves registration accuracy compared with that of Gaussian regularisation ($p < 0.05$). The optimised script proposed in this study outperformed all other methods ($p < 0.05$).

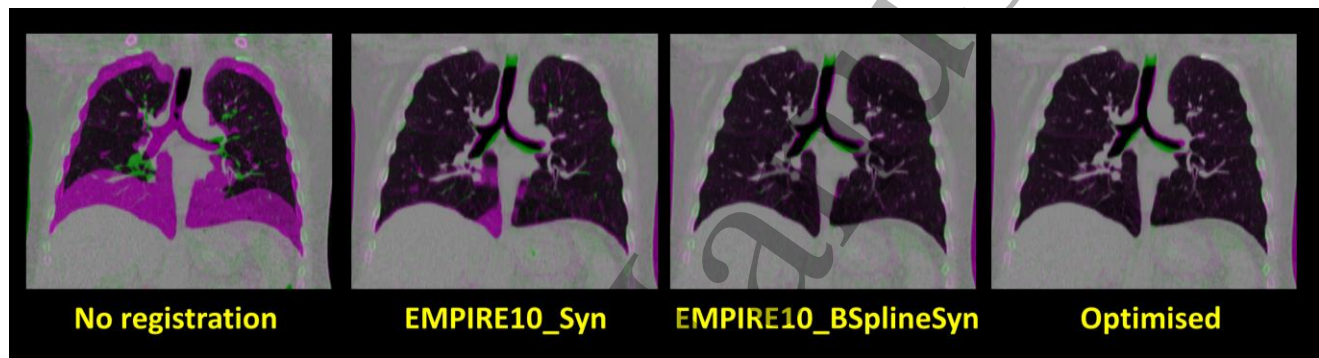


Figure 2 Example coronal slices for the moving exhalation image overlaid with the fixed inhalation image for patient 10 of the DIR lab dataset before and after performing each of the three registration pipelines.

Table 2 Registration accuracy results. Mean and standard deviation of the TREs of the 300 expert landmarks for breath-hold CT reference dataset. Values are given in mm. Summary statistics are shown for the registration methods compared in this study. Euclidian distances between landmarks when no registration was performed are provided for reference.

Registration method	Mean TRE \pm SD (mm)
0. No registration	23.36 \pm 10.11
1. EMPIRE10_Syn	7.98 \pm 3.49
2. EMPIRE10_BSplineSyn	3.09 \pm 1.53
3. Optimised	1.26 \pm 0.27

3.1. FRC+1L versus TLC ^3He MRI

All patients complied with the imaging procedures and were able to perform breath-holds at both FRC+1L and TLC. TLC ^3He MRI exhibited increased and more homogenous ventilation than FRC+1L ^3He MRI. Frequently, defects observed at FRC+1L would either partially or completely resolve at TLC. The spatial extent and location of these ventilation defects were confirmed by same-breath anatomical ^1H MRI as shown in Figure 3, indicating increased airway opening at the higher inflation state. The median (range) of %VV for FRC+1L and TLC ^3He MRI were 90.5 (54.9-93.6) and 91.8 (67.8-96.2), respectively ($p=0.018$). This is also displayed graphically in Figure 4.

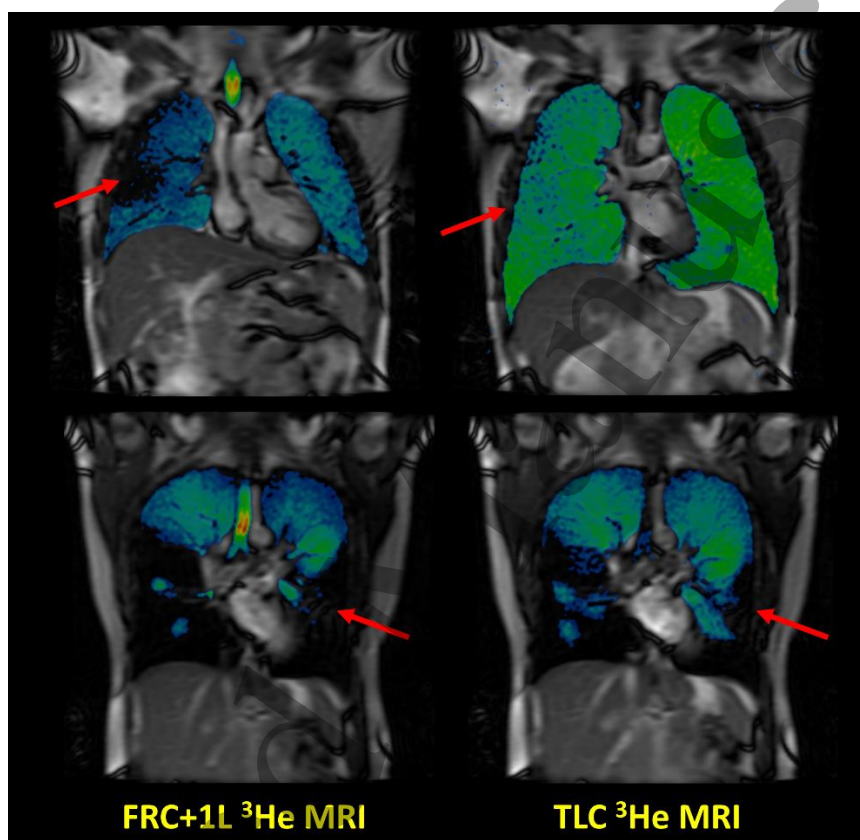


Figure 3 Corresponding coronal slices of patient 1 (top) and 2 (bottom) showing ^3He MRI acquired at FRC+1L (left) and TLC (right) fused with same-breath anatomical ^1H MRI. Some ventilation defects observed at FRC+1L resolve at TLC (red arrows), indicating increased

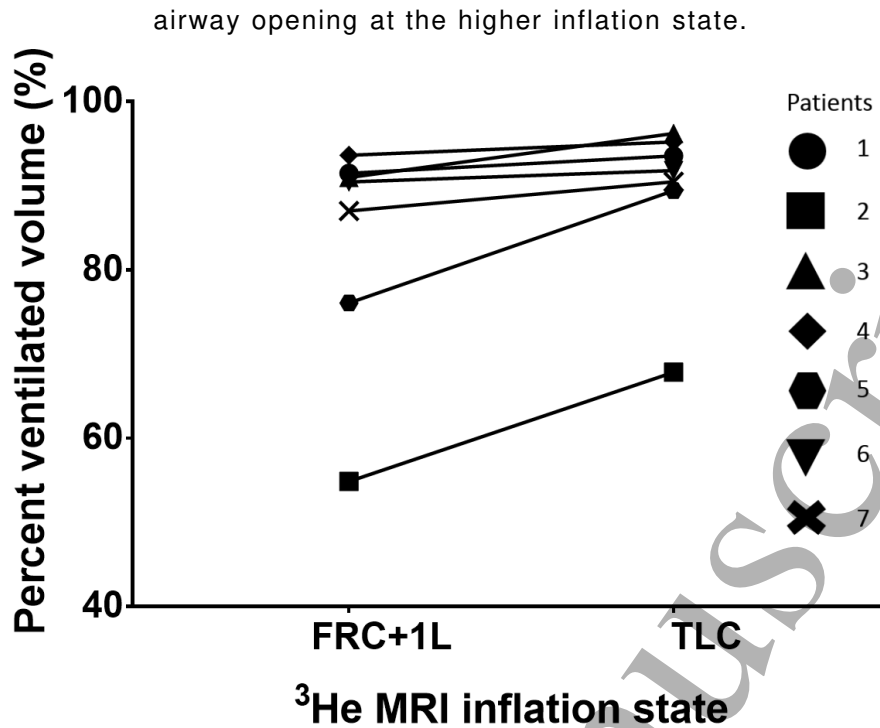


Figure 4 A comparison of percent ventilated volumes of ^3He MRI acquired at FRC+1L and TLC. Individual data points are shown for all patients.

3.2. CT ventilation vs FRC+1L and TLC ^3He MRI

Figure 5 shows corresponding coronal slices of registered FRC+1L and TLC ^3He MRI and CT ventilation for two patients in the study. The CT ventilation images are visually more similar to those of the TLC ^3He MRI. This was confirmed by quantitative spatial overlap results, whereby statistically significant improvements in DSCs were observed between CT ventilation and TLC ^3He MRI compared with FRC+1L ^3He MRI, with median (range) values of 0.93 (0.86-0.93) and 0.86 (0.68-0.92) respectively, for the 10-100th percentile ($p=0.017$) and 0.87 (0.83-0.88) and 0.81 (0.66-0.87) respectively, for the 20-100th percentile ($p=0.027$). Statistically significant improvements in DSCs were observed with the 10-100th compared with the 20-100th percentile CT ventilation masks for both FRC+1L ($p = 0.026$) and TLC ^3He MRI ($p = 0.017$). The results for each patient are displayed in Table 3.

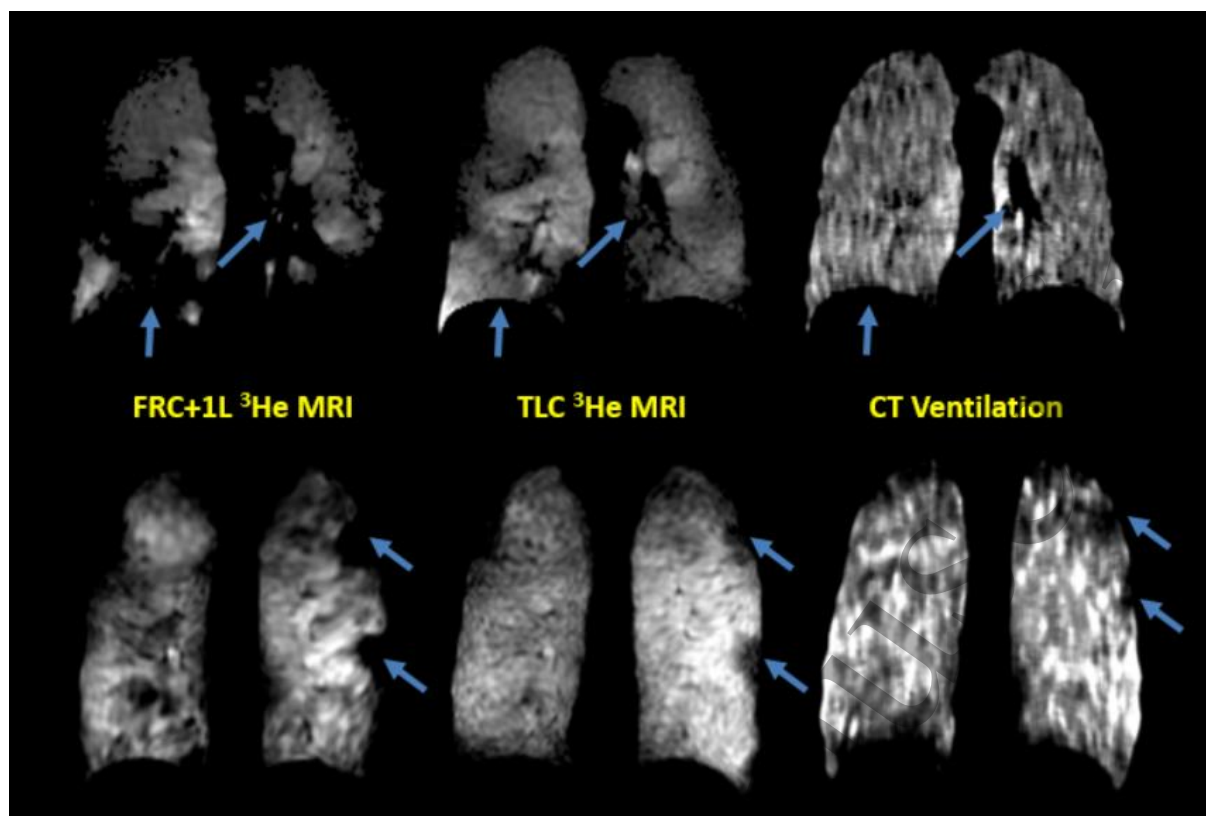


Figure 5 Corresponding coronal slices for two representative patients of registered FRC+1L ^3He MRI, TLC ^3He MRI and CT ventilation. The blue arrows indicate defects and regions that are more visually similar for CT ventilation and TLC ^3He MRI compared with FRC+1L ^3He MRI. Note that the lower defect observed in the left lung of the second patient (bottom row) is spatially offset.

Table 3 Dice similarity coefficients for CT ventilation thresholded at two different percentile ranges with FRC+1L and TLC ^3He MRI.

Patients	CT 10 to 100% percentile		CT 20 to 100% percentile	
	^3He MRI FRC+1L	^3He MRI TLC	^3He MRI FRC+1L	^3He MRI TLC
1	0.86	0.93	0.81	0.87
2	0.78	0.86	0.78	0.84
3	0.92	0.93	0.87	0.88
4	0.92	0.93	0.87	0.87
5	0.68	0.87	0.66	0.83
6	0.92	0.93	0.86	0.87
7	0.85	0.91	0.81	0.86
Mean \pm SD	0.85 \pm 0.09	0.91 \pm 0.03	0.81 \pm 0.07	0.86 \pm 0.02
Median (range)	0.86 (0.68-0.92)	0.93 (0.86-0.93)	0.81 (0.66-0.87)	0.87 (0.83-0.88)
<i>P</i> value	0.017		0.027	

4. Discussion

Seven adults with asthma were evaluated in the first study to compare CT-based surrogates of ventilation with an established ventilation modality acquired at multiple inflation levels. CT ventilation images were more similar to ^3He MR ventilation images that were acquired at TLC than at FRC+1L, with significantly higher DSCs between ventilation masks generated from the different modalities when MR images were acquired at TLC. ^3He MRI exhibited increased and more homogenous ventilation at TLC than FRC+1L, with several ventilation defects observed at FRC+1L either completely or partially resolved at TLC. The registration of all images to the TLC CT images in this study enabled spatial comparison of ventilation masks generated from the different modalities to examine their similarity on a truly regional basis.

4.1. Breath-hold CT image registration accuracy

The 'EMPIRE10_Syn' pipeline was consistently outperformed by its B-spline analogue. The parameters of both scripts were identical with the exception of regularisation methods for the deformable stage; 'EMPIRE10_Syn' employed Gaussian convolution for regularization whilst 'EMPIRE10_BsplineSyn' employed B-spline functions. These results are in line with that of a previous study in the context of brain registration, where the B-spline Syn algorithm was shown to yield statistically significant improvements in DSCs compared with the well-known Syn algorithm (Tustison and Avants, 2013). Tustison and Avants (2013) have speculated that the improvement could be due to the continuous nature of B-spline regularization when compared to the discrete approximation offered by Gaussian smoothing.

A significant improvement in registration accuracy when compared with the developers' settings was shown for the optimised pipeline developed in this study. Although the developers' settings provided excellent results for the EMPIRE10 challenge data, which comprised of a range of data including 4D-CT and breath-hold, it was not specifically optimised for paired breath-hold CT with extreme motion amplitudes. This demonstrates the importance of problem-specific parameterisation for new registration applications.

4.2. Effect of lung inflation state on distribution of ventilation

Visual evaluation of ventilation-weighted ^3He MRI demonstrated increased and more homogenous ventilation at TLC when compared with FRC+1L. In several cases, ventilation defects observed at FRC+1L resolved completely at TLC. This was confirmed by quantitative results where we observed statistically significant improvements in the percent ventilated volumes at the higher inflation state. As lung inflation increases, the increased ventilation homogeneity observed may be attributable to

1
2
3 airway opening and release of trapped air. Brown and Mitzner (1996) used high resolution CT to
4 quantify the effect of lung inflation on airway diameter in canine subjects and observed significant
5 increases at increased inflation levels. Thus, airways that were narrowed or closed at FRC+1L could
6 have opened at the higher inflation state, resolving some of the ventilation defects, as observed in
7 this study.
8
9
10

11
12 The results of this study are consistent with other findings suggesting potential bronchodilatory
13 effects of deep inspiration (Scichilone and Toggias, 2004). Deep inspirations may enable distribution
14 of gas to hypoventilated regions affected by narrowed or closed airways. Although a degree of
15 ventilation heterogeneity is observed in normal subjects in the form of a vertical gradient due to
16 gravity and other effects, these effects are significantly reduced at TLC where much more
17 homogenous ventilation is observed (Milic-Emili, 2011). Recent work with multi-inflation
18 hyperpolarised gas MRI in healthy subjects and patients with CF has confirmed this hypothesis
19 where increased ventilation heterogeneity was observed at the lower lung volumes with the least
20 ventilation heterogeneity observed at TLC (Hughes *et al.*, 2018; Smith *et al.*, 2018). These results
21 and those observed in the present study suggest that imaging at lower inflation levels is more
22 sensitive at detecting ventilation defects and may be more appropriate to use in routine clinical
23 practice. Notwithstanding, we do believe that there may be a role for multi-inflation hyperpolarised
24 gas MR ventilation imaging by providing information on the nature of reversible airway obstruction
25 in asthma i.e. it may allow discernment of regions of volume-reversible and non-reversible ventilation
26 abnormalities.
27
28
29
30
31
32
33
34
35
36
37

38 Such improvements in ventilation were not observed in this study for all ventilation defects seen,
39 demonstrated by the fact that the percent ventilated volume at TLC was still lower than 100%, despite
40 exhibiting statistically significant improvements from FRC+1L. As such, numerous defects observed
41 at FRC+1L persisted at TLC which we believe to be indicative of less reversible focal airway
42 obstruction. Thus, other factors may have a greater impact on the formation of ventilation defects in
43 asthma including small and large airway closure due to airway inflammation, obstruction and
44 remodelling (Brightling *et al.*, 2012). Importantly, inflammation in the airway smooth muscle bundles
45 has been shown to be a key factor contributing to impaired airway dilation of asthmatics during deep
46 inspiration (Slats *et al.*, 2007).
47
48
49
50
51
52
53

54 4.3. Impact of ^3He MR inflation level on correlation with CT ventilation

55

56 Using DSCs, statistically significant improvements in spatial overlap were observed between CT
57 ventilation and ^3He MRI acquired at the higher inflation level of TLC. This might be attributable to the
58 CT acquisition protocol for this study. As the CT-based surrogates were derived from breath-hold
59
60

1
2
3 CT acquired at FRC and TLC and thus represent local volume change between these two inflation
4 levels, they would more closely depict the distribution of ^3He gas at TLC than at FRC+1L. As
5 mentioned earlier, imaging at FRC+1L appears to be more sensitive at detecting ventilation defects
6 than at TLC and may thus undermine the use of CT ventilation in clinical practice. Whilst we can say
7 that CT ventilation derived from TLC and FRC may not provide measures of ventilation which are as
8 sensitive as FRC+1L ^3He MRI at depicting ventilation defects, we cannot say that this will be the
9 case for CT ventilation derived from a different pair of inflation levels. For example, we recently
10 demonstrated that CT ventilation maps derived from FRC and FRC+1L show moderate correlations
11 with hyperpolarised gas MRI and marked ventilation defects (Tahir *et al.*, 2018). To comprehensively
12 answer this question, we require CT acquired at more than two inflation levels (e.g. FRC, FRC+1
13 and TLC) in order to compare the ventilation distributions of CT ventilation between e.g. FRC &
14 FRC+1L and FRC & TLC to see if there is indeed an increase in ventilation defects with the former.
15 Unfortunately, the acquisition of CT at more than 2 inflation levels was outside the scope of the
16 current imaging protocol but we hope that such a study can be performed in the near future.
17
18
19
20
21
22
23
24
25

26
27 Despite notable similarities between CT ventilation and ^3He MRI acquired at TLC, perfect correlation
28 was not observed. Visual evaluation demonstrated that some ventilation defects observed on MRI
29 were spatially offset on CT (figure 5). The differences observed between CT and ^3He MRI are
30 ultimately attributable to the fact that both modalities provide distinct physiologic measurements; CT-
31 based surrogates of ventilation measure the local change in air volume between two lung inflation
32 states, whilst static ventilation-weighted ^3He MR images represent a snapshot of the concentration
33 of ^3He gas within the air in the lungs at a given inflation level. As such, the primary purpose of this
34 study was to compare both techniques rather than to validate the CT-based surrogates of ventilation.
35 A more appropriate modality to use for the purpose of validation may be a multiple-breath washout
36 imaging technique such as that described by Horn *et al.* (2014a) which uses ^3He MRI as the tracer.
37 By correcting for T1 decay, RF depolarisation and RF coil sensitivity, this technique has the
38 advantage of providing fractional ventilation maps that are fully quantitative. However, this technique
39 is not as widely used and requires more complicated breathing manoeuvres for the patient and much
40 higher doses of hyperpolarised ^3He to match the resolution of static ventilation images. This is
41 particular pertinent in the current climate where there is a worldwide paucity of ^3He gas. ^{129}Xe is a
42 naturally-abundant isotope for hyperpolarised gas MRI and has demonstrated good correlations with
43 ^3He in static lung ventilation and diffusion-weighted MRI (Stewart *et al.*, 2018). We have recently
44 compared both gases with CT ventilation imaging in lung cancer patients and demonstrated
45 moderately low correlations of CT at the voxel-level against both gases, increasing with larger
46 regional analysis, while strong correlations were observed between ^3He and ^{129}Xe (Tahir *et al.*,
47 2018). Technical developments in the field of multiple-breath washout imaging with ^{129}Xe may pave
48 the way for improved comparative studies with CT ventilation imaging.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5 The findings of this study not only imply the importance of careful volumetric control of lung inflation
6 for CT ventilation validation studies but also for longitudinal studies to monitor disease progression
7 and treatment response. It is, therefore, essential that consistent repeatable breathing manoeuvres
8 are employed as variations can alter the ventilation distributions.
9
10

11 12 13 4.4. Study limitations 14

15 This study has several limitations. Firstly, a relatively small number of patients were studied; thus,
16 further comprehensive testing on a larger sample size would be beneficial. Nonetheless, we note
17 that the increase in ventilation defects observed at FRC+1L compared with TLC and the increased
18 spatial correlation of CT ventilation imaging with ^3He MRI TLC for both percentiles were observed
19 consistently for all subjects studied. Thus, the results are very promising and we believe that it is
20 very likely that these results will be observed for a larger cohort. A larger cohort could also facilitate
21 reliable subgroup analysis, which may aid in understanding the impact of inflation level on the nature
22 and pattern of ventilation defects seen on hyperpolarised gas MR images, across the spectrum of
23 asthma disease, and will allow for a greater understanding of whether the correlations observed
24 between CT and MRI are reproducible across all subgroups.
25
26
27
28
29
30
31
32

33 Furthermore, this study only included patients with asthma. Thus, caution must be exercised when
34 extending these results to other respiratory diseases. For example, although improved airway
35 distention at higher lung inflations has been observed in patients with asthma, albeit to a lower
36 degree than normal subjects (Jensen *et al.*, 2001), comparisons of the effect of deep-inspiration
37 induced changes in airway response between asthma and COPD patients indicate that
38 bronchodilatory effects are less effective in the latter disease (Slats *et al.*, 2007). Therefore, a larger
39 scale study of the effect of inflation level as measured by ^3He MRI and its impact on spatial correlation
40 with CT-based ventilation in other respiratory diseases is warranted. Likewise, to further reassure
41 that methods are correlated, it would be useful to perform this study in healthy subjects.
42
43
44
45
46
47
48

49 Moreover, CT and MRI were performed several days apart (range: 1 to 4 days); it is well known that
50 asthma symptoms vary over time (Zhang *et al.*, 2002) and thus the degree of airway narrowing and
51 inflammation may have changed between CT and MRI sessions. The present investigation was part
52 of a multi-centre study where patients underwent CT in another city than their MRI scans. Four days
53 was the maximum achievable time for coordinating and organising such a study. Notwithstanding,
54 several patients underwent MRI within a day of CT. To minimise errors associated with
55 reproducibility, we did not recruit patients who had been hospitalized or required high-dose (>10mg
56 prednisolone/day) OCS therapy within 6 weeks of the screening visit. This would have excluded
57
58
59
60

1
2
3 patients with unstable disease or those who may not have been able to cope with the study
4 procedures, thus ensuring that the patients included in the study were more likely to have stable
5 disease, with less airflow variability over time. We also note that the reproducibility of ^3He MRI
6 ventilation distributions in asthma has shown some persistence and reproducibility on the order of a
7 few months (de Lange *et al.*, 2009). However, the authors of this work agree that the comparison of
8 the two imaging modalities might be more appropriately conducted in subjects with relatively fixed
9 ventilation defects such as COPD or stable CF.
10
11
12
13
14

15
16 Different breath-hold procedures were used for the FRC+1L and TLC ^3He MRI acquisitions. For the
17 TLC scans, inhalation of room air would increase the time for the ^3He gas to ventilate “slow filling”
18 regions of the lung and may have contributed to the fewer ventilation defects observed at TLC. In
19 previous work with 3D time resolved ^3He MRI at breath-hold, we studied the effects of delayed
20 ventilation due to diffusion with time and used this effect to assess co-lateral ventilation pathways
21 due to emphysema (Marshall *et al.*, 2012). In more recent work, we studied the effect of ^3He inflation
22 level (TLC and FRC+1L with a similar acquisition protocol to this study) on patients with CF. For that
23 study, we also had collateral ventilation performed for the same patients and demonstrated that no
24 significant changes in ventilation distributions occur within the timescale of 1-3 seconds. However,
25 we appreciate that asthma is a different disease and the effects of delayed ventilation on this
26 timescale are yet to be studied in this patient population and higher homogeneity of ventilation
27 distribution may occur during the additional time for gas to diffuse within 1-3 s. Although this may
28 result in a methodological bias, we believe that this effect is likely to be small.
29
30
31
32
33
34
35
36
37

38 For determination of ventilated volume, there exists some possibility for erroneous segmentation.
39 For CT ventilation segmentation, numerous techniques have been employed in the literature, most
40 notably, percentile thresholding. Functional percentile ranges used have included 0-20%, 21-40%,
41 41-60%, 61-80%, 81-100% (Castillo *et al.*, 2010) and 21-100% (Kipritidis *et al.*, 2014). Here, we
42 employed two percentile ranges and observed that the 10-100th functional percentile range exhibited
43 greater correlation with the ^3He MRI segmentation than that of the 20-100th range, suggesting that
44 spatial correlation between modalities is sensitive to CT ventilation segmentation technique.
45 Similarly, with the relative infancy of hyperpolarised gas MRI as a tool to assess pulmonary
46 ventilation distribution, no definitive consensus yet exists regarding best practice on segmentation
47 and delineation of ventilated volume. In particular, similar to Kirby *et al.* (2012), we classified regions
48 of hypointense signal as part of ventilated volume. This will inevitably lead to reduced defect volumes
49 when compared to other groups who classify hypointense signal as a defect.
50
51
52
53
54
55
56
57

58 DSCs provide a measure of overlap between two binary segmentations and do not account for
59 subtler differences in the intensity distributions within the boundaries of these segmentations. A more
60

1
2
3 robust method of comparing the images would be to perform voxel-wise spatial correlations as has
4 been performed for Galligas PET and CT ventilation images which were acquired on the same
5 scanner and were thus inherently co-registered (Kipritidis *et al.*, 2014). However, in this study, no
6 strict patient immobilization protocol was observed when acquiring ^3He MRI and CT, leading to
7 significant postural differences and images were acquired several days apart. Furthermore, ^3He MRI
8 resolution was significantly lower than that of CT, especially in the z direction (10mm vs. 1mm). The
9 CT and MRI registration accuracy, computed via TRE, has previously been assessed for this cohort
10 to be on order of > 10 mm (Tahir *et al.*, 2014). As such, these significant differences in acquisition
11 settings between CT and MRI precluded us from performing a meaningful voxel-wise correlation. An
12 improved acquisition strategy such as that proposed by Ireland *et al.* (2008) where MRI and CT are
13 acquired on the same day with matching subject immobilisation palettes may mitigate these
14 limitations. Moreover, recent advancements in MR image acquisition have led to improved resolution
15 and image quality of same-breath ^3He and ^1H MRI (Horn *et al.*, 2014b).

25 For ^3He MRI, patients inhaled the noble gas from a starting point of FRC until they reached the
26 desired inflation level. Inhalation from residual volume has been shown to provide different gas
27 distributions (Milic-Emili *et al.*, 1966) and may result in different correlations. Similarly, CT breathing
28 manoeuvre has been shown to alter the resulting ventilation distribution (Mistry *et al.*, 2013). In this
29 study, we did not acquire CT at FRC+1L. Given our findings, we hypothesise that CT acquired at
30 FRC and FRC+1L would lead to ventilation surrogates more closely matched to ^3He MRI acquired
31 at FRC+1L, compared with ventilation computed from CT acquired at FRC and TLC.

38 5. Conclusion

41 This study demonstrates that comparison of CT ventilation and hyperpolarised gas MRI varies with
42 inflation state during gas MRI. If CT is acquired at FRC and TLC, a higher correlation with gas
43 ventilation MR imaging can be achieved if the latter is acquired at TLC. This study also provides
44 further evidence that ventilation abnormalities are sensitive to inflation level and that imaging at lower
45 lung volumes may be more sensitive at depicting ventilation defects. Imaging at multiple inflation
46 levels may facilitate discernment of regions of volume-reversible and non-reversible ventilation
47 defects. Further work is needed to determine the optimal inflation levels for CT ventilation imaging.

53 Acknowledgements

55 This work was supported by the University of Sheffield James Morrison Fund, Sheffield Hospitals
56 Charity, Weston Park Hospital Cancer Charity, National Institute of Health Research, AirPROM (EU
57 FP7) and Novartis.

References

- Avants B B, Epstein C L, Grossman M and Gee J C 2008 Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain *Med Image Anal* **12** 26-41
- Avants B B, Tustison N J, Song G, Cook P A, Klein A and Gee J C 2011 A reproducible evaluation of ANTs similarity metric performance in brain image registration *Neuroimage* **54** 2033-44
- Brightling C E, Gupta S, Gonem S and Siddiqui S 2012 Lung damage and airway remodelling in severe asthma *Clin Exp Allergy* **42** 638-49
- Brown R H and Mitzner W 1996 Effect of lung inflation and airway muscle tone on airway diameter in vivo *J Appl Physiol (1985)* **80** 1581-8
- Castillo R, Castillo E, Fuentes D, Ahmad M, Wood A M, Ludwig M S and Guerrero T 2013 A reference dataset for deformable image registration spatial accuracy evaluation using the COPDgene study archive *Phys Med Biol* **58** 2861-77
- Castillo R, Castillo E, Martinez J and Guerrero T 2010 Ventilation from four-dimensional computed tomography: density versus Jacobian methods *Phys Med Biol* **55** 4661-85
- Castillo R, Castillo E, McCurdy M, Gomez D R, Block A M, Bergsma D, Joy S and Guerrero T 2012 Spatial correspondence of 4D CT ventilation and SPECT pulmonary perfusion defects in patients with malignant airway stenosis *Phys Med Biol* **57** 1855-71
- Christian J A, Partridge M, Nioutsikou E, Cook G, McNair H A, Cronin B, Courbon F, Bedford J L and Brada M 2005 The incorporation of SPECT functional lung imaging into inverse radiotherapy planning for non-small cell lung cancer *Radiother Oncol* **77** 271-7
- Chuang K-S, Tzeng H-L, Chen S, Wu J and Chen T-J 2006 Fuzzy c-means clustering with spatial information for image segmentation *Computerized Medical Imaging and Graphics* **30** 9-15
- Crawford A B, Makowska M, Paiva M and Engel L A 1985 Convection- and diffusion-dependent ventilation maldistribution in normal subjects *J Appl Physiol (1985)* **59** 838-46
- de Lange E E, Altes T A, Patrie J T, Battiston J J, Juersivich A P, Mugler J P, 3rd and Platts-Mills T A 2009 Changes in regional airflow obstruction over time in the lungs of patients with asthma: evaluation with ³He MR imaging *Radiology* **250** 567-75
- Glocker B, Sotiras A, Komodakis N and Paragios N 2011 Deformable Medical Image Registration: Setting the State of the Art with Discrete Methods *Annu Rev Biomed Eng* **13** 219-44
- Guerrero T, Sanders K, Noyola-Martinez J, Castillo E, Zhang Y, Tapia R, Guerra R, Borghero Y and Komaki R 2005 Quantification of regional ventilation from treatment planning CT *Int J Radiat Oncol Biol Phys* **62** 630-4
- Horn F C, Deppe M H, Marshall H, Parra-Robles J and Wild J M 2014a Quantification of regional fractional ventilation in human subjects by measurement of hyperpolarized ³He washout with 2D and 3D MRI *J Appl Physiol (1985)* **116** 129-39
- Horn F C, Tahir B A, Stewart N J, Collier G J, Norquay G, Leung G, Ireland R H, Parra-Robles J, Marshall H and Wild J M 2014b Lung ventilation volumetry with same-breath acquisition of hyperpolarized gas and proton MRI *NMR Biomed* **27** 1461-7
- Hughes P J C, Horn F C, Collier G J, Biancardi A, Marshall H and Wild J M 2017 Spatial fuzzy c-means thresholding for semiautomated calculation of percentage lung ventilated volume from hyperpolarized gas and (1) H MRI *J Magn Reson Imaging*
- Hughes P J C, Smith L, Chan H F, Tahir B A, Norquay G, Collier G J, Biancardi A M, Marshall H and Wild J M 2018 Assessment of the influence of lung inflation state on the

- 1
2
3 quantitative parameters derived from hyperpolarized gas lung ventilation MRI in
4 healthy volunteers *J Appl Physiol* (1985)
- 5 Ireland R H, Bragg C M, McJury M, Woodhouse N, Fichelle S, van Beek E J, Wild J M and
6 Hatton M Q 2007 Feasibility of image registration and intensity-modulated
7 radiotherapy planning with hyperpolarized helium-3 magnetic resonance imaging for
8 non-small-cell lung cancer *Int J Radiat Oncol Biol Phys* **68** 273-81
- 9 Ireland R H, Tahir B A, Wild J M, Lee C E and Hatton M Q 2016 Functional Image-guided
10 Radiotherapy Planning for Normal Lung Avoidance *Clin Oncol (R Coll Radiol)* **28** 695-
11 707
- 12 Ireland R H, Woodhouse N, Hoggard N, Swinscoe J A, Foran B H, Hatton M Q and Wild J
13 M 2008 An image acquisition and registration strategy for the fusion of hyperpolarized
14 helium-3 MRI and x-ray CT images of the lung *Phys Med Biol* **53** 6055-63
- 15 Jensen A, Atileh H, Suki B, Ingenito E P and Lutchen K R 2001 Selected contribution: airway
16 caliber in healthy and asthmatic subjects: effects of bronchial challenge and deep
17 inspirations *J Appl Physiol* (1985) **91** 506-15; discussion 4-5
- 18 Kipritidis J, Siva S, Hofman M S, Callahan J, Hicks R J and Keall P J 2014 Validating and
19 improving CT ventilation imaging by correlating with ventilation 4D-PET/CT using
20 ⁶⁸Ga-labeled nanoparticles *Med Phys* **41** 011910
- 21 Kirby M, Heydarian M, Svenningsen S, Wheatley A, McCormack D G, Etemad-Rezai R and
22 Parraga G 2012 Hyperpolarized ³He magnetic resonance functional imaging
23 semiautomated segmentation *Acad Radiol* **19** 141-52
- 24 Kurose T, Okumura Y, Sato S, Yamamoto Y, Akaki S, Takeda Y, Kanazawa S, Ando A,
25 Date H, Shimizu N and Hiraki Y 2004 Functional evaluation of lung by Xe-133 lung
26 ventilation scintigraphy before and after lung volume reduction surgery (LVRS) in
27 patients with pulmonary emphysema *Acta Med Okayama* **58** 7-15
- 28 Latifi K, Forster K M, Hoffe S E, Dilling T J, van Elmpst W, Dekker A and Zhang G G 2013
29 Dependence of ventilation image derived from 4D CT on deformable image
30 registration and ventilation algorithms *J Appl Clin Med Phys* **14** 4247
- 31 Marshall H, Deppe M H, Parra-Robles J, Hillis S, Billings C G, Rajaram S, Swift A, Miller S
32 R, Watson J H, Wolber J, Lipson D A, Lawson R and Wild J M 2012 Direct
33 visualisation of collateral ventilation in COPD with hyperpolarised gas MRI *Thorax* **67**
34 613-7
- 35 Marshall H, Siddiqui S, Leung G, Parra-Robles J, Xu X, Brightling C and Wild J 2013 Imaging
36 The Effect Of Airway Opening In Asthma Due To Inflation State With ³He MRI *Am J*
37 *Respir Crit Care Med* **187** A3744
- 38 Mathew L, Wheatley A, Castillo R, Castillo E, Rodrigues G, Guerrero T and Parraga G 2012
39 Hyperpolarized (³He) magnetic resonance imaging: comparison with four-
40 dimensional x-ray computed tomography imaging in lung cancer *Acad Radiol* **19**
41 1546-53
- 42 Milic-Emili J 2011 *Comprehensive Physiology*: John Wiley & Sons, Inc.)
- 43 Milic-Emili J, Henderson J A, Dolovich M B, Trop D and Kaneko K 1966 Regional distribution
44 of inspired gas in the lung *J Appl Physiol* **21** 749-59
- 45 Mistry N N, Diwanji T, Shi X, Pokharel S, Feigenberg S, Scharf S M and D'Souza W D 2013
46 Evaluation of fractional regional ventilation using 4D-CT and effects of breathing
47 maneuvers on ventilation *Int J Radiat Oncol Biol Phys* **87** 825-31
- 48 Mugler J P, 3rd, Altes T A, Ruset I C, Dregely I M, Mata J F, Miller G W, Ketel S, Ketel J,
49 Hersman F W and Ruppert K 2010 Simultaneous magnetic resonance imaging of
50 ventilation distribution and gas uptake in the human lung using hyperpolarized xenon-
51 ¹²⁹ *Proc Natl Acad Sci U S A* **107** 21707-12
- 52
53
54
55
56
57
58
59
60

- 1
2
3 Muradyan I, Loring S H, Ferrigno M, Lindholm P, Topulos G P, Patz S and Butler J P 2010
4 Inhalation heterogeneity from subresidual volumes in elite divers *J Appl Physiol*
5 (1985) **109** 1969-73
6
7 Murphy K, van Ginneken B, Reinhardt J M, Kabus S, Ding K, Deng X, Cao K, Du K,
8 Christensen G E, Garcia V, Vercauteren T, Ayache N, Commowick O, Malandain G,
9 Glocker B, Paragios N, Navab N, Gorbunova V, Sporring J, de Bruijne M, Han X,
10 Heinrich M P, Schnabel J A, Jenkinson M, Lorenz C, Modat M, McClelland J R,
11 Ourselin S, Muenzing S E, Viergever M A, De Nigris D, Collins D L, Arbel T, Peroni
12 M, Li R, Sharp G C, Schmidt-Richberg A, Ehrhardt J, Werner R, Smeets D, Loeckx
13 D, Song G, Tustison N, Avants B, Gee J C, Staring M, Klein S, Stoel B C, Urschler
14 M, Werlberger M, Vandemeulebroucke J, Rit S, Sarrut D and Pluim J P 2011
15 Evaluation of registration methods on thoracic CT: the EMPIRE10 challenge *IEEE*
16 *Trans Med Imaging* **30** 1901-20
17
18 Reinhardt J M, Ding K, Cao K, Christensen G E, Hoffman E A and Bodas S V 2008
19 Registration-based estimates of local lung tissue expansion compared to xenon CT
20 measures of specific ventilation *Med Image Anal* **12** 752-63
21
22 Scichilone N and Togias A 2004 The role of lung inflation in airway hyperresponsiveness
23 and in asthma *Curr Allergy Asthma Rep* **4** 166-74
24
25 Seppenwoolde Y, Engelsman M, De Jaeger K, Muller S, Belderbos J, Boersma L and
26 Lebesque J 2000 Optimising radiation treatment plans for lung cancer using
27 functional information *Radiotherapy and Oncology* **56**
28
29 Slats A M, Janssen K, van Schadewijk A, van der Plas D T, Schot R, van den Aardweg J G,
30 de Jongste J C, Hiemstra P S, Mauad T, Rabe K F and Sterk P J 2007 Bronchial
31 inflammation and airway responses to deep inspiration in asthma and chronic
32 obstructive pulmonary disease *Am J Respir Crit Care Med* **176** 121-8
33
34 Smith L J, Collier G J, Marshall H, Hughes P J C, Biancardi A M, Wildman M, Aldag I, West
35 N, Horsley A and Wild J M 2018 Patterns of regional lung physiology in cystic fibrosis
36 using ventilation magnetic resonance imaging and multiple-breath washout *Eur*
37 *Respir J* **52**
38
39 Stewart N J, Chan H F, Hughes P J C, Horn F C, Norquay G, Rao M, Yates D P, Ireland R
40 H, Hatton M Q, Tahir B A, Ford P, Swift A J, Lawson R, Marshall H, Collier G J and
41 Wild J M 2018 Comparison of (3) He and (129) Xe MRI for evaluation of lung
42 microstructure and ventilation at 1.5T *J Magn Reson Imaging* **0**
43
44 Tahir B A, Hughes P J C, Robinson S D, Marshall H, Stewart N J, Norquay G, Biancardi A,
45 Chan H F, Collier G J, Hart K A, Swinscoe J A, Hatton M Q, Wild J M and Ireland R
46 H 2018 Spatial comparison of CT-based surrogates of lung ventilation with
47 hyperpolarized Helium-3 and Xenon-129 gas MRI in patients undergoing radiation
48 therapy *International Journal of Radiation Oncology*Biophysics*
49
50 Tahir Bilal A, Swift Andrew J, Marshall H, Parra-Robles J, Hatton Matthew Q, Hartley R, Kay
51 R, Brightling Christopher E, Vos W, Wild Jim M and Ireland Rob H 2014 A method
52 for quantitative analysis of regional lung ventilation using deformable image
53 registration of CT and hybrid hyperpolarized gas/ 1 H MRI *Phys Med Biol* **59** 7267
54
55 Tahir B A, Van Holsbeke C, Ireland R H, Swift A J, Horn F C, Marshall H, Kenworthy J C,
56 Parra-Robles J, Hartley R, Kay R, Brightling C E, De Backer J, Vos W and Wild J M
57 2016 Comparison of CT-based Lobar Ventilation with 3He MR Imaging Ventilation
58 Measurements *Radiology* **278** 585-92
59
60 Thomen R P, Sheshadri A, Quirk J D, Kozlowski J, Ellison H D, Szczesniak R D, Castro M
and Woods J C 2015 Regional ventilation changes in severe asthma after bronchial
thermoplasty with (3)He MR imaging and CT *Radiology* **274** 250-9

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- Tomasi C and Manduchi R 1998 Bilateral Filtering for Gray and Color Images. In: *Proceedings of the Sixth International Conference on Computer Vision: IEEE Computer Society*) p 839
- Tustison N J and Avants B B 2013 Explicit B-spline regularization in diffeomorphic image registration *Front Neuroinform* **7** 39
- Vandemeulebroucke J, Rit S, Kybic J, Clarysse P and Sarrut D 2011 Spatiotemporal motion estimation for respiratory-correlated imaging of the lungs *Med Phys* **38** 166-78
- Wild J M, Ajraoui S, Deppe M H, Parnell S R, Marshall H, Parra-Robles J and Ireland R H 2011 Synchronous acquisition of hyperpolarised ^3He and ^1H MR images of the lungs - maximising mutual anatomical and functional information *NMR Biomed* **24** 130-4
- Yamamoto T, Kabus S, Klinder T, von Berg J, Lorenz C, Loo B W, Jr. and Keall P J 2011 Four-dimensional computed tomography pulmonary ventilation images vary with deformable image registration algorithms and metrics *Med Phys* **38** 1348-58
- Yamamoto T, Kabus S, Lorenz C, Mitra E, Hong J C, Chung M, Eclov N, To J, Diehn M, Loo B W, Jr. and Keall P J 2014 Pulmonary ventilation imaging based on 4-dimensional computed tomography: comparison with pulmonary function tests and SPECT ventilation images *Int J Radiat Oncol Biol Phys* **90** 414-22
- Zhang J, Yu C, Holgate S T and Reiss T F 2002 Variability and lack of predictive ability of asthma end-points in clinical trials *Eur Respir J* **20** 1102-9

Accepted Manuscript