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Online Supplementary Material

Patterns of regional lung physiology in cystic fibrosis using ventilation MRI and MBW

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Methods

The MR images were acquired in a 10-12 second breath-hold, during which, both the ventilation image and a ^{1}H anatomical co-registered image were acquired [1]. The end-inspiratory tidal volume (EIVt) scans were always acquired prior to the total lung capacity (TLC) scans, with an interval of 2-5 minutes between. The inhaled bag volumes used for ventilation MRI were titrated based on the patient's standing height. The calculations were based on predicted functional residual capacity (FRC) and TLC volumes in children [2] in an attempt to ensure that children would not be near their TLC when inhaling the EIVt dose. For each height interval of 10cm we calculated the volumes based on the middle of each bracket (i.e. 125cm for the interval 120-130cm). For each height interval we looked at the mean predicted FRC and TLC values. We subtracted 20% off the FRC value to compensate for the effect of posture and then titrated the inhaled bag volume to give a total predicted EIVt volume (FRC + bag volume) of approximately 60% of TLC. The inhaled bag volume consisted of a scaled dose of helium-3 (^{3}He) balanced with nitrogen (N_2). The total bag volume inhaled for TLC was the same as for the EIVt scan but it contained an increased proportion of ^{3}He in order to provide sufficient image signal-to-noise ratio, due to the effect of gas concentration dilution at the higher lung volume. The bag volume height chart can be seen in E-Table 1.

E-Table 1: *Hyperpolarised ^{3}He MR imaging bag volume chart.*

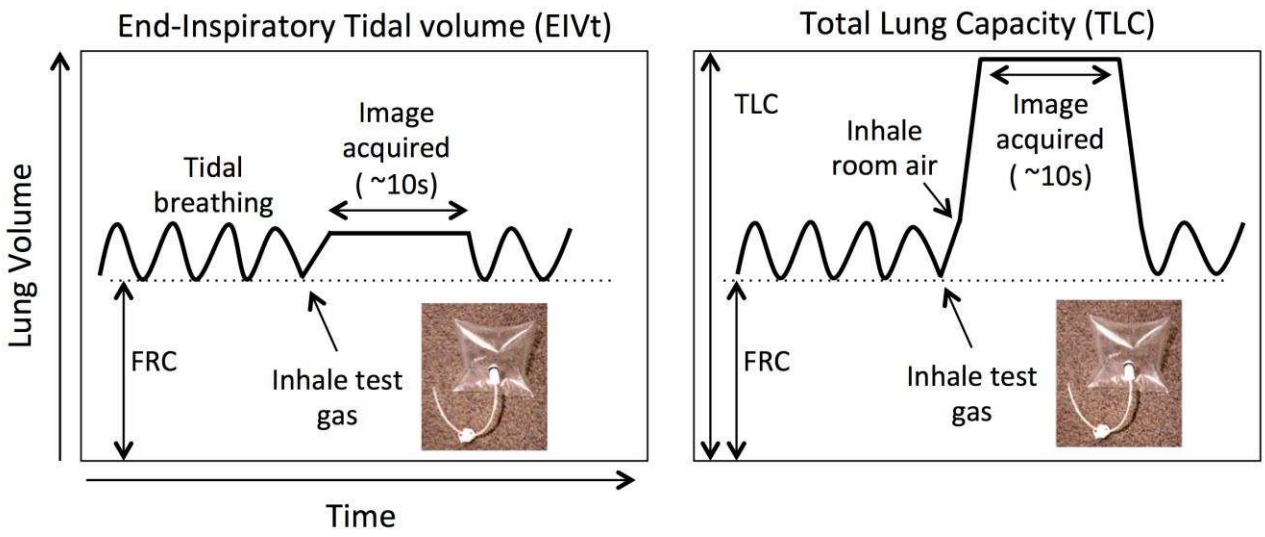
Patient Height	Total Bag Volume	Gas doses	
		EIVt	TLC
160cm +	1.0 L	150 ml ^{3}He + 850 ml N_2	200 ml ^{3}He + 800 ml N_2
150-160cm	800 ml	140 ml ^{3}He + 660 ml N_2	180 ml ^{3}He + 620 ml N_2
140-150cm	650 ml	130 ml ^{3}He + 520 ml N_2	160 ml ^{3}He + 490 ml N_2
130-140cm	500 ml	120 ml ^{3}He + 380 ml N_2	140 ml ^{3}He + 360 ml N_2
120-130cm	400 ml	110 ml ^{3}He + 290 ml N_2	120 ml ^{3}He + 280 ml N_2

Ventilation imaging breathing manoeuvre

In order to deliver the inhaled gas to the patient, the gas was transported in a Tedlar bag (maximum volume = 1.5L), which has a locking ratchet system in place to stop ambient air mixing with the contents. The Tedlar bag had tubing to which a respiratory bacterial filter was placed for the patient to breathe through when required. Prior to performing ventilation imaging the patient was trained on the breathing manoeuvres required. The breathing instructions were given by a respiratory physiologist, specialising in paediatrics.

The instructions were straightforward; the patient was first required to acknowledge that they were ready to proceed before a nose-clip was placed. The patient was then required to gently breathe in and out, at least twice, with each inspiratory and expiratory breath performed at the instructor's request. This ensured that the patient was at a true FRC prior to breathing back in. The instructor assessed this by watching the patient's chest move during respiratory

manoeuvres. After the second gentle expiration to FRC, the filter was lowered into the patient's mouth where they were instructed to inhale the full volume of the bag (as soon as the patient began to make an inspiratory effort the release mechanism on the Tedlar back was activated to allow the inhalation of ^{3}He and N_2). For the EIVt image the patient was then instructed to hold their breath for approximately 10 seconds while the image was acquired. For the TLC image, after the full bag volume was inhaled, the filter was immediately removed from the patient's mouth by the instructor and then immediately instructed to take a big breath in to TLC, where they then held their breath for approximately 10 seconds whilst the image was acquired (E-Figure 1).



E-Figure 1: *Schematic detailing the breathing sequence performed for both EIVt and TLC ventilation imaging highlighting the difference in the lung volumes for the two MR image acquisitions.*

MR image processing

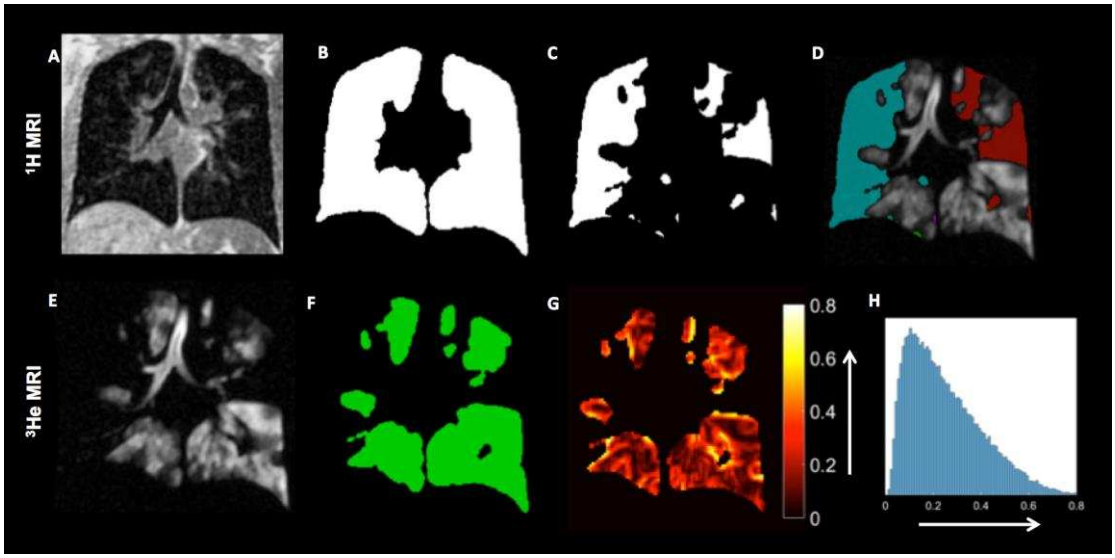
For both the EIVt and TLC ^{3}He and ^{1}H images, image metrics were calculated from a semi-automated segmentation [3]. The ^{3}He images were segmented in order to calculate the ventilated lung volume (VV) and the ^{1}H images were used to calculate the thoracic cavity volume (TCV). From these two segmentations the ventilation defect percentage (VDP) was defined as the proportion of the TCV without ventilation. The ^{3}He VV segmentation was also utilized to generate a map and histogram distribution of local ventilation heterogeneity, which corresponds to the coefficient of variance of signal intensity from neighbouring ventilated voxels only [4]. From the resulting distribution, the ventilation heterogeneity index (VH_I) was defined as the inter-quartile range of values. The inter-quartile range was reported due to non-normally distributed histograms and best reflects the increased spread of values seen in disease. VH_I for a hypothetical perfectly ventilated lung would be 0, with increasing values representing increased ventilation heterogeneity.

To investigate the size and nature of the distribution of local ventilation defects, a mask of ventilation defects, corresponding to areas of the TCV without ventilation was created, i.e areas contributing to VDP. Contiguous individual ventilation defects were assessed using the software Simplewhere ScanIP (Synopsys, Mountain View, USA). A 3D flood fill algorithm was implemented on this mask to isolate and partition defects. Defects that contributed to less than 1% of total VDP were discarded. The number of remaining defects ($N_{defects}$), as well as the volume

of individual defects were calculated. A workflow of image analysis can be found in E-Figure 2.

MRI post-processing workflow

The image workflow analysis can be seen in E-Figure 2, which demonstrates that the ventilation and anatomical images are segmented to create three masks. A ventilation mask, a thoracic cavity mask and a defect mask.

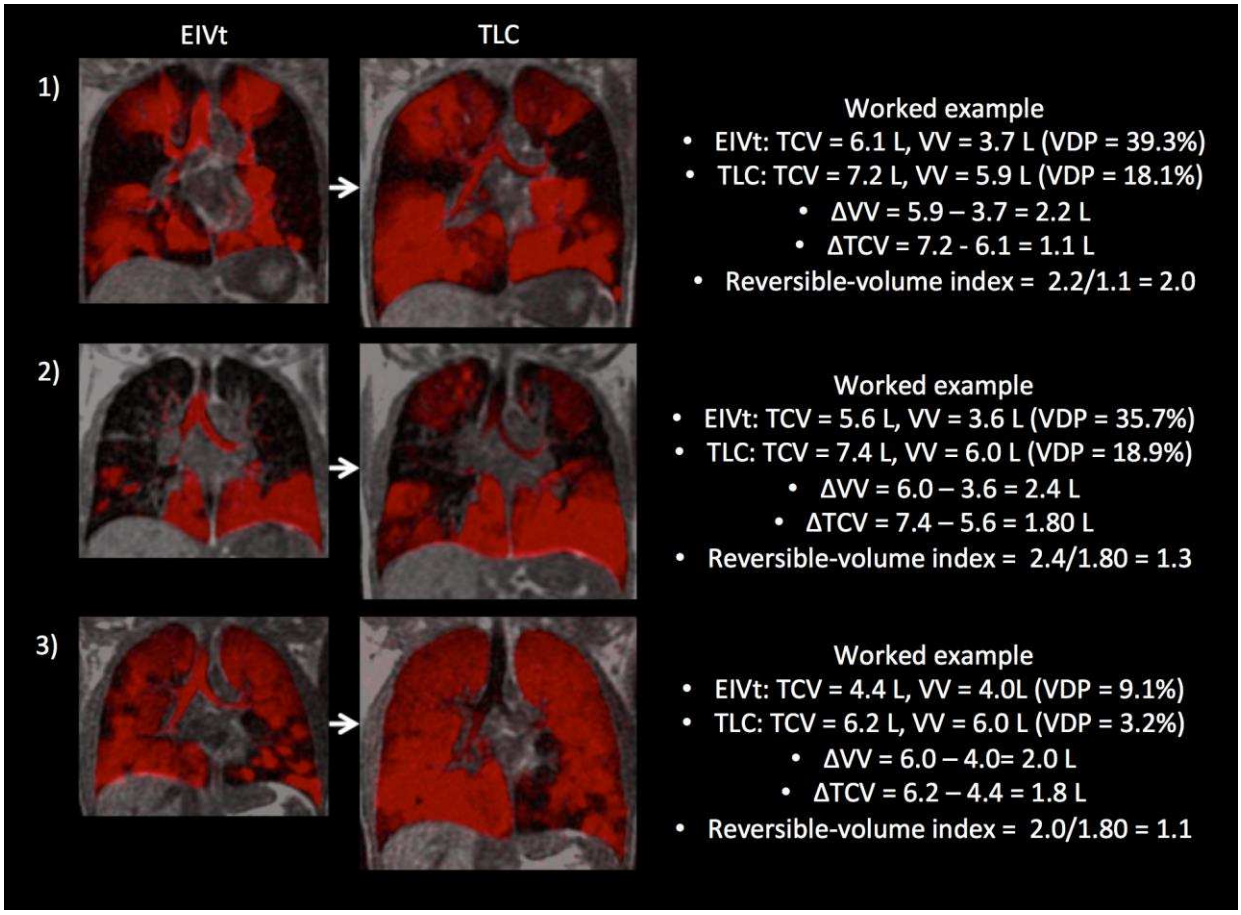


E-Figure 2: *Workflow of ventilation image analysis from one patient. The ^{1}H anatomical image (image A) and the ^{3}He ventilation image (E) are segmented to create a thoracic cavity mask (B) and a ventilation mask (F). Ventilation defect percentage is calculated from the resulting mask volumes. The ventilation defect mask (C) is created as the inverse of the ventilation mask within the thoracic cavity mask (B) and is used to assess the number and volume of contiguous ventilation defects (D). Individual contiguous ventilation defects are shown in different colours in D. The ventilation mask (F) is used to define the area over which the local coefficient of variation is calculated from a 3*3 moving window centred on each*

voxel, before being displayed in a heat map (G) and in histogram form (H). The ventilation heterogeneity index (VH_I) is the inter-quartile range of the local coefficient of variation histogram for the whole lung. Each image or plot (A-H) represents the same coronal central lung slice.

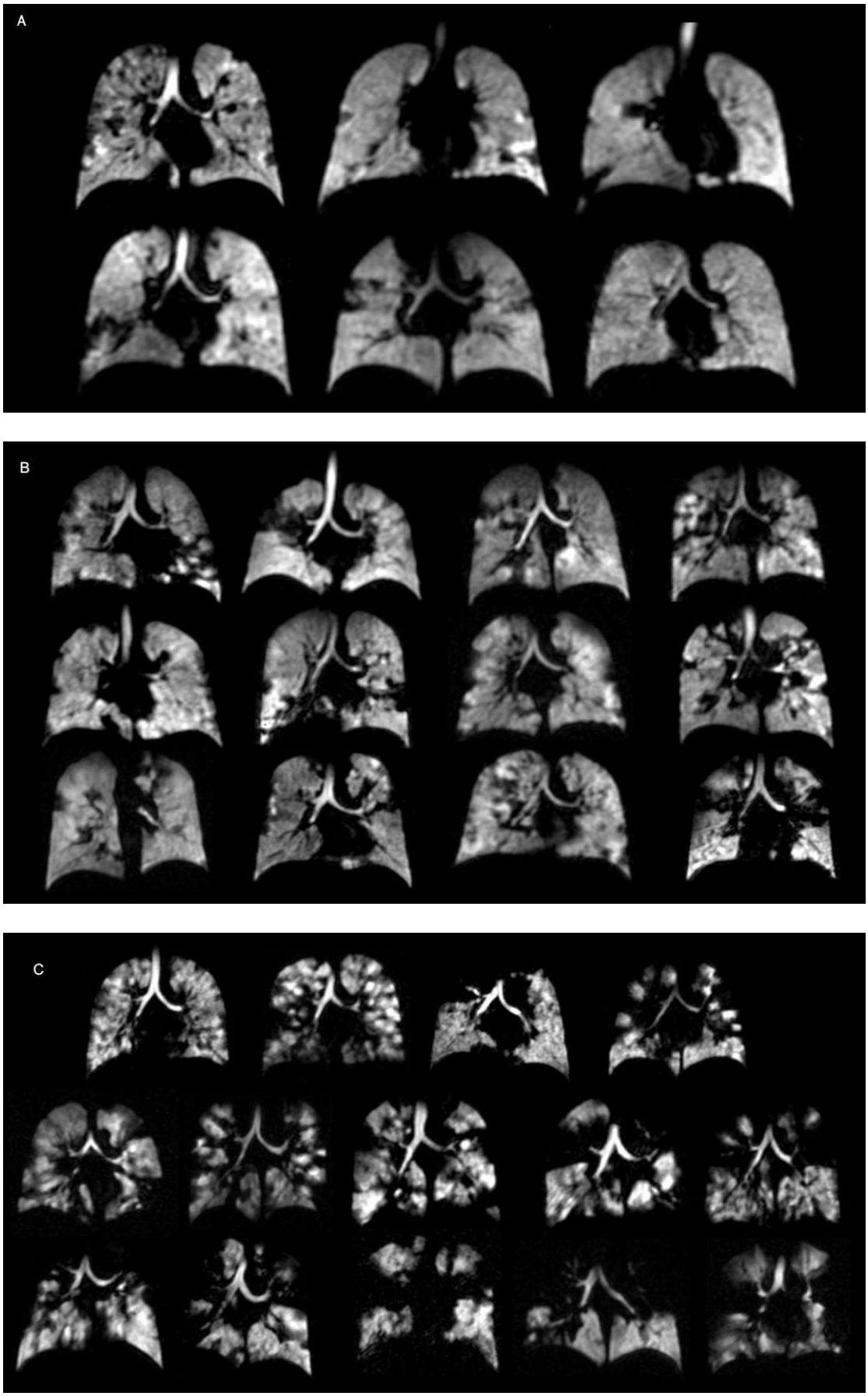
Reversible-volume index

The reversible-volume index is quantitatively derived from the EIVt and TLC ^{3}He and ^{1}H MR images and describes the relative change in ventilated volume when compared to the increase in thoracic cavity volume. The reversible-volume index in a healthy subject with no ventilation defects would equal 1.0, as the increase in ventilated volume would be the same as the increase in thoracic cavity volume when comparing EIVt to TLC images. The reversible-volume index in a patient with non-reversible ventilation defects (resulting from complete obstruction) would also equal 1.0. The reversible-volume index in a subject with CF with significant ventilation defects at EIVt, which at least partially resolve at TLC would have a reversible-volume index >1.0. This is caused by ventilation defects at EIVt becoming ventilated at TLC and therefore the increase in ventilated volume is larger than the increase in thoracic cavity volume. E-Figure 3 gives some worked examples from three patients within this cohort.



E-Figure 3: *Worked reversible-volume index examples from different patients (1-3) within the study. Representative EIVt and TLC ventilation image slices (red) are overlaid onto the ^{1}H MRI acquired during the same breath-hold (grey). The ventilated volume (VV) is calculated from the segmentation of the ^{3}He ventilation image and the thoracic cavity volume (TCV) is calculated from the segmentation of the ^{1}H image. Both the TCV and VV are measured in litres (L).*

Results



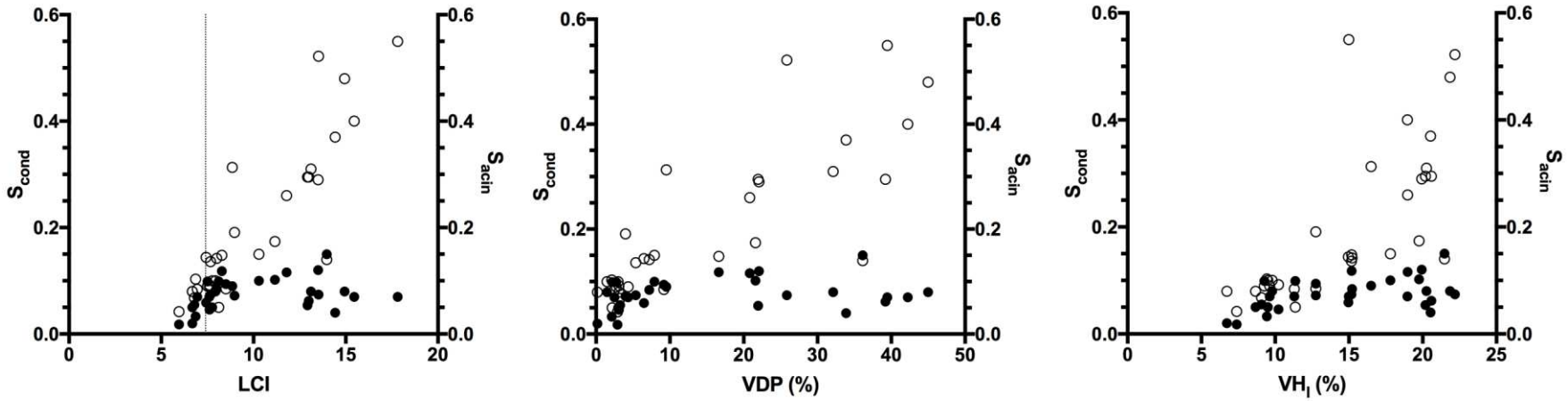
E-Figure 4: *Three panels demonstrating representative ^{3}He ventilation MR images from all CF patients within the study. The first panel (A) is group 1 who have normal FEV_1 and LCI. The second panel (B) is group 2 who have normal FEV_1 but abnormal LCI. The third panel is group 3 (C) who have abnormal FEV_1 and LCI.*

Comparison of seated vs supine MBW data.

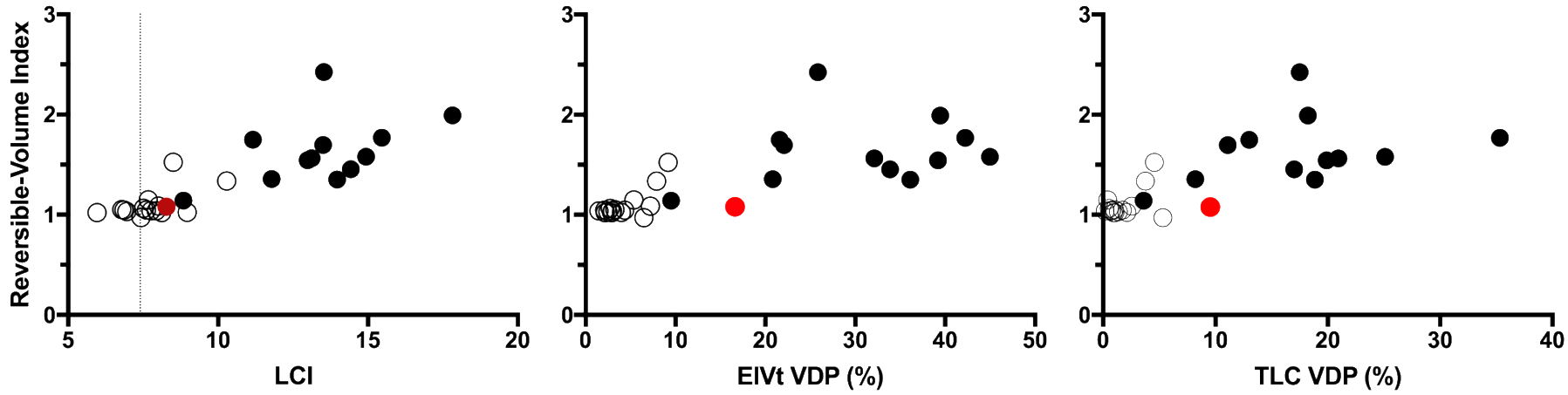
Paired t-test analysis of LCI, FRC, S_{cond} and S_{acin} in the seated versus the supine posture was performed as previously described [5]. LCI was significantly lower in the seated position compared to supine (median LCI of 8.4 vs 9.6 respectively, $p<0.001$). FRC was significantly lower supine compared to seated (mean FRC of 1.4 vs 1.8 litres respectively, $p<0.001$). Despite this there was no significant difference for S_{cond} and S_{acin} between postures.

E-Table 2: *Spearman correlations of supine MBW values against ventilation MRI metrics at EIVt. All significant correlations (p<0.001) are highlighted by *.*

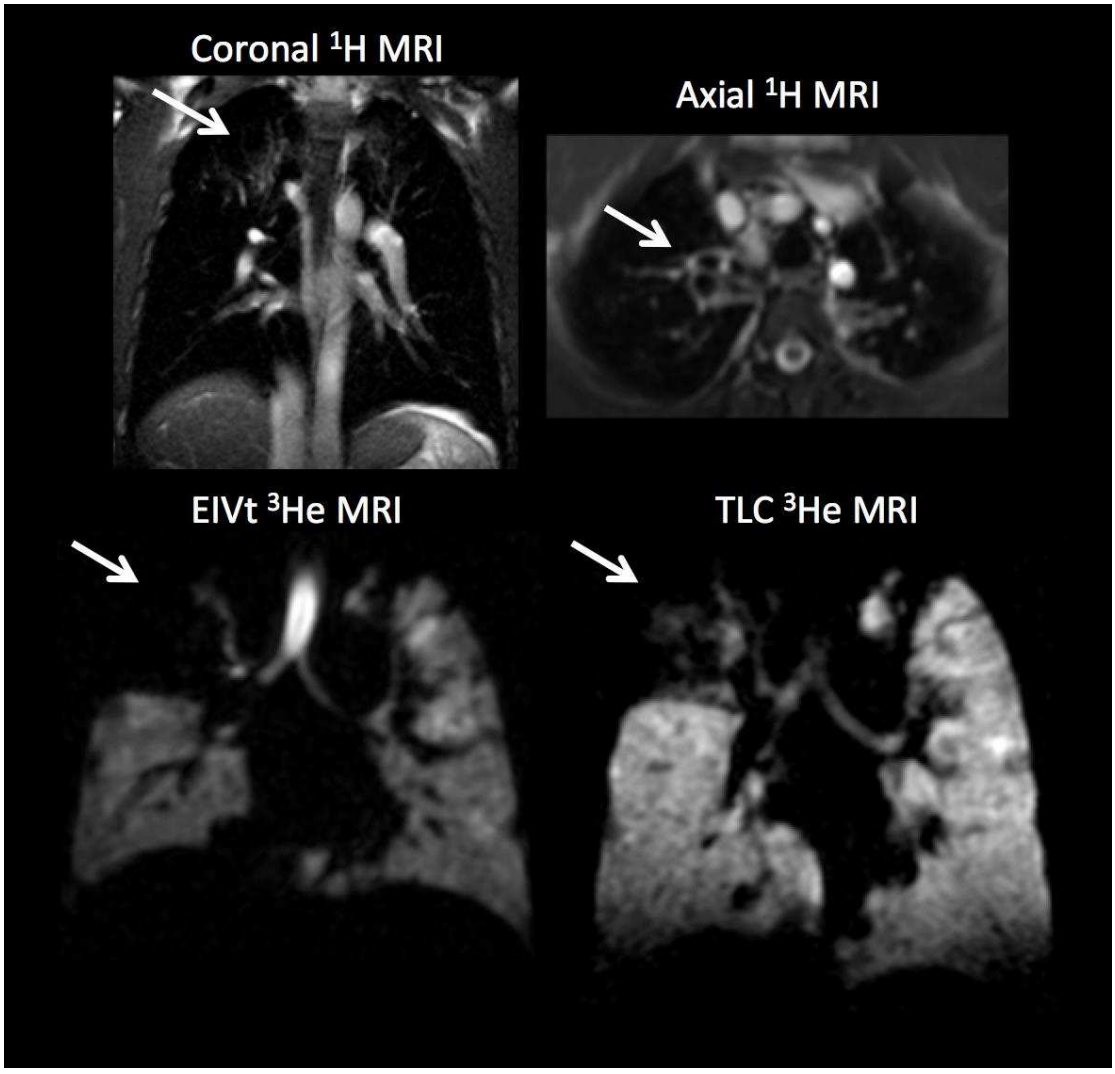
	LCI	**S_{cond}**	**S_{acin}**
VDP (%)	0.83*	-0.003	0.8*
VH_I (%)	0.80*	0.17	0.75*
Largest defect (%TCV)	0.80*	-0.02	0.75*
$N_{defects}$	-0.66*	0.14	-0.65*
Reversible-volume index	0.78*	-0.15	0.76*
ΔVH_I	0.22	0.28	0.35



E-Figure 5: *Scatterplots of S_{acin} (open circles, right Y axis) and S_{cond} (closed circles, left Y axis) against; LCI (dashed line indicates the upper limit of normal), VDP and VH_I. S_{cond} consistently demonstrates a plateau effect with increased levels of disease severity, without evidence of statistical correlation. S_{acin} however demonstrates significant correlations with LCI (r=0.86), VDP (r=0.84) and VH_I (r=0.82).*



E-Figure 6: *Spearman correlation of LCI and VDP at both EIVt and TLC, against the reversible-volume index. The data has been segregated to visualise two groups, those with an* $FEV_1 \leq -1.64$ *(closed circles) and those with an* $FEV_1 > -1.64$ *(open circles). Dashed line represents the LCI upper limit of normal. There is a strong correlation between the reversible-volume index and both LCI (r=0.82) and VDP at both lung volumes (r=0.85 at EIVt and r=0.75 at TLC) (p<0.001). The data points highlighted by a red circle represent a patient with a low reversible-volume index, but relatively large values for VDP. Images for this patient are shown in E-Figure 7.*



E-Figure 7: *EIVt and TLC* ^{3}*He comparison for a patient with CF and representative* ^{1}*H anatomical MR imaging demonstrating bronchiectasis. At EIVt this patient has a*

large ventilation defect in the right upper lobe (defect size = 10 %TCV, total VDP = 16.6%), which is in the same area as the anatomical abnormalities. At TLC, this ventilation defect only achieves a small amount of ventilation and reduces in volume by 103ml (defect size = 5.7 %TCV, total VDP = 9.5%). As a result this subject has a low reversible-volume index of 1.1. This patient however has an arguably lower than anticipated LCI of 8.3, when compared to the FEV_1 z-score of -3.1. These data suggest that the low LCI is due to this large defect being almost completely obstructed and therefore not contributing to ventilation during MBW.

References

1. Horn, F.C., B.A. Tahir, N.J. Stewart, G.J. Collier, G. Norquay, G. Leung, R.H. Ireland, J. Parra-Robles, H. Marshall, and J.M. Wild, *Lung ventilation volumetry with same-breath acquisition of hyperpolarized gas and proton MRI.* NMR Biomed, 2014. **27**(12): p. 1461-7.
2. Rosenthal, M., D. Cramer, S.H. Bain, D. Denison, A. Bush, and J.O. Warner, *Lung function in white children aged 4 to 19 years: II--Single breath analysis and plethysmography.* Thorax, 1993. **48**(8): p. 803-8.
3. Hughes, P.J.C., F.C. Horn, G.J. Collier, A. Biancardi, H. Marshall, and J.M. Wild, *Spatial fuzzy c-means thresholding for semiautomated calculation of percentage lung ventilated volume from hyperpolarized gas and (1) H MRI.* J Magn Reson Imaging, 2018. **47**(3): p. 640-646.
4. Tzeng, Y.S., K. Lutchen, and M. Albert, *The difference in ventilation heterogeneity between asthmatic and healthy subjects quantified using hyperpolarized 3He MRI.* J Appl Physiol (1985), 2009. **106**(3): p. 813-22.
5. Smith, L.J., K.A. Macleod, G.J. Collier, F.C. Horn, H. Sheridan, I. Aldag, C.J. Taylor, S. Cunningham, J.M. Wild, and A. Horsley, *Supine posture changes lung volumes and increases ventilation heterogeneity in cystic fibrosis.* PLoS One, 2017. **12**(11): p. e0188275.