Hyperpolarised ^{129}Xe MRI to monitor treatment response in children with cystic fibrosis:
Online Data Supplement

Methods

MRI Protocols

During a breath-hold of up to 14 seconds, 129Xe gradient recalled echo (GRE) images were acquired with the following settings: TR = 11 ms, TE = 2.7 ms, flip angle = 7°, FOV = 480 x 480 mm^2, matrix = 128 x 128, 9 – 12 slices, thickness = 18 mm, BW = 100 Hz/pixel. For conventional proton MRI, the participant inhaled a 1L bag of UHP N_2 using the same procedures as described above, and a GRE dataset was acquired in a 10 second breath-hold with following settings: TR = 2.87 ms, TE = 1.0 ms, flip angle = 6°, FOV = 480 x 480 mm^2, matrix = 256 x 256, 22 – 28 slices, thickness = 8 mm, BW = 500 Hz/pixel.

Gas dosing and administration

Xe was dosed to 10% of TLC (measured by body plethysmograph). For each administration, the Xe was mixed with ultra high purity N_2 to a total gas dose of 1L. For proton MRI images, the entire 1L dose consisted of N_2. The 1 L gas dose was inhaled from a tedlar bag from end expiration following 2-3 tidal breaths (judged by the gas administrator NM, NK or JHR). Therefore, all images were acquired at a lung volume approximating FRC + 1L.

Results

Xe dosing and lung volumes

The total dose of gas administered was 1L, regardless of participant size. Therefore, the fraction of TLC at which the XeMRI images were obtained differed between participants, but overall was between 80% and 85% on the two testing occasions (Table S1).

Healthy Controls and VDP Threshold Calculation

The healthy normalised voxel intensity distribution was calculated from the mean distribution of 10 healthy children (median age 11, IQR 9.5-12.5). The mean normalised signal intensity was 0.973 units (SD 0.429) (Figure S1). For the linear binning technique, the VDP threshold was derived from this healthy distribution to be 2SD below the mean. Therefore, regions with a normalised signal intensity less than 0.115 units were considered ventilation defects using this analytic technique.

An example of raw XeMRI images from a participant with significant, patchy ventilation defects, along with ventilation defect maps determined using k-means and linear binning techniques, are shown in Figure 2A-D. An example of an intensity histogram of the same participant is shown in Figure 2E, with the healthy distribution overlaid.

Impact of using the highest SNR

Two analyzable image datasets acquired on 23/30 test occasions (76.7%). We assessed the impact of analysing one or more XeMRI images by comparing VDP results generated from the highest SNR image from each test occasion to those generated by averaging all images from each test occasion. This analysis

showed no significant difference in the primary outcome between these approaches (Table S1). The mean SNR of the 30 analyzed images was 45.1 (range 11.7, 82.2) and the mean SNR of the excluded 23 images was 36.3 (range 15.6, 80.3). In order to minimize the potential impact of low SNR on VDP calculation (1), the primary analysis was performed on the single image (highest SNR) dataset.

MBW Postural Dependence

MBW testing was performed in both the seated and supine postures on both test occasions for all participants. Overall, LCI_{supine} was significantly higher than $LCI_{sitting}$ (mean difference 0.7 units; 95%CI 0.2, 1.2; p=0.008) but this difference was driven by data from post-treatment tests, with significant postural changes in LCI only seen after treatment (Table S2). Within subjects, the average postural LCI change was greater on the post-treatment test occasion than on the pre-treatment test occasion (mean difference 0.9 units; 95%CI 0.2, 1.7; p=0.01). In other words, LCI increased more when transitioning from the seated to the supine position after treatment than it did before treatment.

The posture-dependence of the components of LCI (LCI=cumulative expired volume [CEV]/functional residual capacity [FRC]) were inspected individually. FRC_{supine} was significantly lower than $FRC_{sitting}$ both before and after treatment (Table S2). Within-subjects, this postural dependence was enhanced after antibiotic treatment, with FRC dropping 0.12L further (95%CI -0.24, -0.01; p=0.003) with a shift to the supine position on post-treatment test occasions compared to pre-treatment test occasions. No such relationship was seen with CEV, suggesting that the postural change in LCI was driven mostly by a change in the FRC.

MRI-physiology correlation

Significant correlations were observed between VDP (k-means and histogram techniques) and LCI, FEV_1 and RV:TLC (Table S3). Correlation of k-means and linear binning VDP values with seated LCI (R^2=0.38 and 0.36 respectively) was higher than with supine LCI (R^2=0.21 and 0.18 respectively). Correlation of FEV_1 and RV:TLC with K-means VDP (R^2=0.30 and 0.34 respectively) was higher than with the linear binning VDP (R^2=0.17 and 0.15 respectively).

Table S1 – Median (IQR) plethysmographic lung volumes of patients measured at the pre- and post-treatment scans. The fractional imaging volume represents the percent of total lung capacity (TLC) at which the imaging was performed.

	Pre-treatment	**Post-treatment**
TLC (L)	3.78 (3.52, 5.25)	4.00 (3.75, 4.8)
FRC_{pleth} (L)	2.41 (2.00, 3.06)	2.20 (2.01, 2.75)
^{129}Xe dose (mL)	380 (350, 530)	400 (380, 480)
Imaging volume (L)	3.41 (3.00, 4.06)	3.20 (3.01, 3.75)
Fractional imaging volume (%)[1]	84.6 (79.0, 88.5)	79.5 (75.1, 83.7)

[1](FRC+1)/TLC x 100%

Table S2 – Sensitivity analysis of using the highest SNR image or the average of all interpretable images. *denotes statistical significance p<0.05.

	Pre-treatment; mean (SD)	**Post-treatment; mean (SD)**	**Within subject absolute change; mean (95%CI)**	**Within-subject relative change (%); mean (95%CI)**
Highest bag only				
VDP (%; LB)	6.4 (3.8)	3.4 (2.9)	-3.0 (-5.0, -1.0)*	-44.2 (-60.2, -28.3)*
VDP (%: k-means)	10.4 (4.5)	6.7 (4.1)	-3.8 (-5.9, -1.7)*	-34.6 (-49.3, -19.9)*
Mean of all bags				
VDP (%; LB)	6.6 (3.9)	3.7 (2.7)	-2.8 (-4.1, -1.5)*	-38.3 (-49.4, -27.1)*
VDP (%; k-means)	10.6 (4.6)	6.9 (4.5)	-2.6 (-3.9, -1.2)*	-33.3 (-44.9, -21.8)*

Table S3 – Postural dependence of MBW outcomes, stratified by pre- and post-treatment test occasions. Difference between supine and seated MBW outcomes are shown from all visits as well as isolated to pre- and post-treatment visits. The within-subject mean change of the supine-sitting difference is shown in the last column. Data are displayed as mean difference (95%CI). *denotes that the mean difference is significantly different from 0 ($p<0.05$).

	Supine – seated postural difference, by test occasion			**Within-subject change in postural difference after treatment**
	Overall	**Pre-treatment only**	**Post-treatment only**	
LCI2.5	0.7 (0.2, 1.2)*	0.2 (-0.5, 0.9)	1.2 (0.5, 1.8)*	0.9 (0.2, 1.7)*
FRC (L)	-0.25 (-0.31, -0.17)*	-0.18 (-0.28, -0.08)*	-0.30 (-0.40, -0.20)*	-0.12 (-0.24, -0.01)*
CEV (L to achieve the 2.5% threshold)	-2.1 (-4.0, -0.1)*	-2.5 (-5.2, 0.2)	-1.6 (-4.6, 1.3)	0.9 (-1.5, 3.2)

Table S4 – MRI-physiology correlation. Results of linear regression of XeMRI outcome measures (k-means VDP, Histogram VDP) with MBW, spirometry and plethysmography outcomes. Data are shown as R^2 and p-value for significance of association. *denotes a significant correlation ($p<0.05$).

	LCI (seated)	**LCI (supine)**	**FEV1 (%)**	**RV/TLC**
K-means	0.38*	0.21*	0.30*	0.34*
Linear binning	0.36*	0.18*	0.17*	0.15*

Supplemental Figures

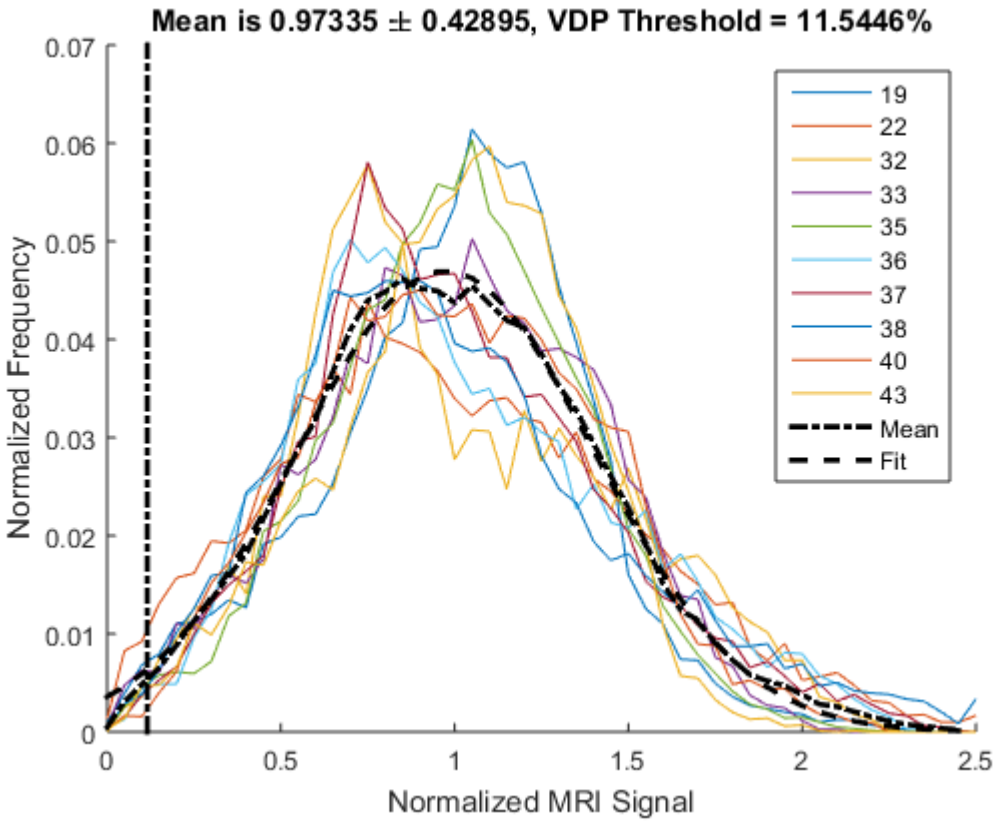

Figure S1 – Normalised voxel signal intensity histograms for all healthy subjects. The voxel intensity distribution for all healthy subjects with an overlaid mean (dot/hash line) and fit (dash line) curves is shown. The vertical line represents the VDP threshold that was established from this distribution.

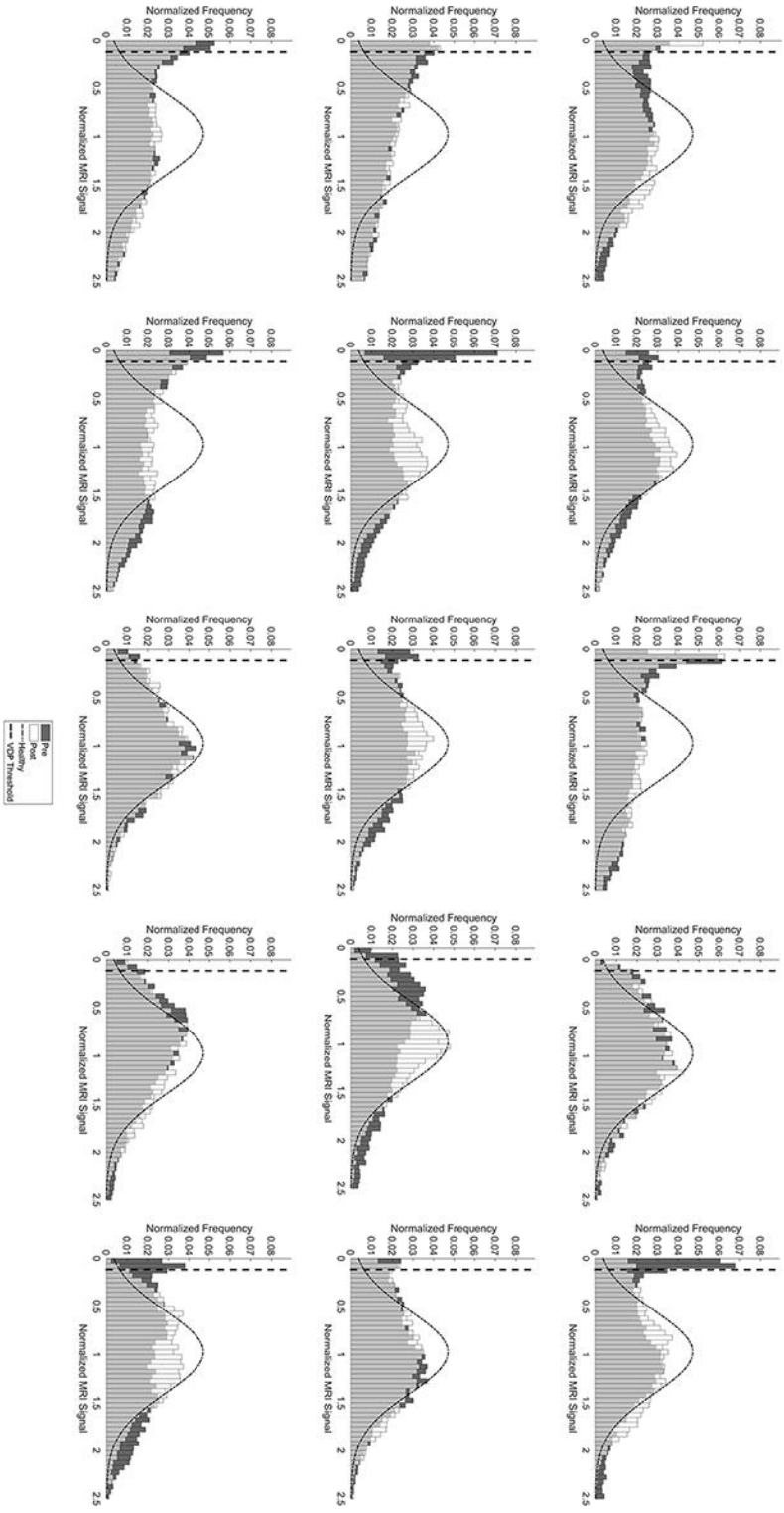

Figure S2 – Normalized voxel signal intensity histograms for all CF subjects before and after therapy. Pre-treatment distribution is shown in dark grey and post-treatment distribution is shown in white. Healthy distributions are overlaid in a hashed black curve and the ventilation defect threshold is identified with a dashed vertical line.

References

1. He M, Tan F, Rankine L, Fain S, Driehuys B. The Effect of Signal to Noise Ratio on Linear-binning and Adaptive k-means Quantification of Hyperpolarized Xe Ventilation MRI. ISMRM. Paris, FRA; 2018.