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T_2*-weighted oxygen-enhanced pulmonary MRI in COPD is linked to resting and exertional functional measurements

Amany F Elbehairy ,[1,2] Josephine H Naish,[3,4] Hossein Baghertash,[1] Geoff J M Parker,[4,5] Christopher A Miller,[3,6] Jørgen Vestbo,[1] Alex R Horsley [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Alex R Horsley; alexander.horsley@manchester.ac.uk

ABSTRACT

Background T_2*-weighted oxygen-enhanced MRI (T_2*-OE-MRI) may directly assess pulmonary ventilation using oxygen as an inhaled tracer gas. It has shown promise in healthy volunteers (HVs) and cystic fibrosis but has yet to be demonstrated in patients with chronic obstructive pulmonary disease (COPD).

Research question To determine the feasibility and repeatability of T_2*-OE-MRI in patients with COPD. To assess correlations between T_2*-OE-MRI measurements of pulmonary ventilation, pulmonary function tests (PFTs) and measures of functional limitation.

Study design and methods 13 patients with mild-to-severe COPD and 13 HVs underwent PFTs, lung clearance index (LCI) measurement, incremental exercise test (patients only) and two lung MRI scans at 3 T. For T_2*-OE-MRI, participants were fitted with a non-rebreathing face mask and given 100% oxygen during image acquisition.

Results Patients (age: 63 (55–72) years, forced expiratory volume in 1 s (FEV_1): 63 (36–79) %predicted, median (IQR)) had evidence of pulmonary gas trapping, small airway disease (SAD) and ventilation heterogeneity. During T_2*-OE-MRI, the magnitude of the percentage difference between mean signal intensity at normoxia and hyperoxia (percent signal enhancement (PSE)) and the enhancing fraction (EF) were lower in patients versus HVs (2.77 (2.19–4.19) vs 5.34 (4.33–5.61) % and 0.74 (0.66–0.77) vs 0.89 (0.82–0.94), respectively, both $p<0.001$). Intraclass correlation coefficient values indicated moderate (0.74) and good (0.80) repeatability for PSE and EF, respectively. PSE and EF significantly correlated with FEV_1, LCI and SAD indices, and in COPD, they correlated with measures of exercise capacity, dynamic hyperinflation and dyspnoea intensity during exercise.

Interpretation In patients with COPD, T_2*-OE-MRI is feasible and repeatable and provides regional information on pulmonary ventilation that is linked with physiological measures of disease severity, functional limitation and exertional dyspnoea.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ T_1-weighted oxygen-enhanced MRI (OE-MRI) is an established technique that showed the potential for pulmonary functional assessment in patients with chronic obstructive pulmonary disease (COPD). However, T_2*-weighted OE-MRI (T_2*-OE-MRI) is believed to provide more specific information about pulmonary ventilation compared with the T_1 signal.

WHAT THIS STUDY ADDS

⇒ This is the first study to show that T_2*-OE-MRI, using oxygen as an inhaled tracer gas, provides a repeatable direct assessment of pulmonary ventilation in healthy individuals and patients with mild-to-severe COPD; its measurement correlated with exertional dyspnoea, forced expiratory volume in 1 s, physiological measures of small airway disease and ventilation heterogeneity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results set the stage for future studies to examine further potential clinical applications of T_2*-OE-MRI in patients with COPD and other patients with chronic respiratory diseases.

INTRODUCTION

Intrapulmonary gas distribution and mixing is an important functional property of the lungs and inhomogeneous ventilation reflects abnormalities at the level of the small airways and lung parenchyma.[1] In patients with chronic obstructive pulmonary disease (COPD), increased airway resistance due to small airway remodelling is a major cause of increased ventilation inhomogeneity.[2] In turn, increased overall ventilation heterogeneity is a hallmark feature of obstructive airway diseases, leading to pulmonary gas trapping, resting and dynamic hyperinflation, and is linked to important clinical outcomes even in early disease stages.[3–5] Over the past few years, MRI has emerged as an important instrument for functional ventilation imaging in COPD which can provide new parameters, different from conventional pulmonary function tests (PFTs).[6 7] Specifically, using

hyperpolarised noble gases with MRI can depict ventilation defects in patients with various respiratory diseases including those with COPD.[8] Though this technique provides detailed information about ventilation, it is technically demanding and requires specialised hardware and a supply of hyperpolarised gas. These are not readily available in many centres which support the need for a cheaper and more accessible method.

T_1-weighted oxygen-enhanced MRI (OE-MRI) is an established technique in which subjects breathe elevated concentrations of oxygen leading to an increased concentration of oxygen dissolved in blood and lung tissue.[9] This causes a shortening of the T_1 relaxation time which can be visualised on MRI as a signal increase on a T_1-weighted image.[10] A recent study showed that oxygen-enhanced change in pulmonary T_1 signal correlated with resting functional parameters and was able to identify disease severity among smokers with and without COPD.[11] Alternatively, oxygen-enhanced imaging of the human lung can be sensitised to T_2* contrast,[12 13] exploiting the change in magnetic susceptibility gradient that results from an increase in gaseous oxygen in the alveolar air space, which leads to a change in lung T_2*. This technique may provide a more direct assessment of pulmonary ventilation but has seen far less attention to date than the T_1-based approach. Furthermore, it has potential additional applications in understanding lung physiology and gas exchange, and in assessing response to pharmacological and interventional therapies in patients with COPD.

In this study, we used a recently described T_2*-weighted OE-MRI (T_2*-OE-MRI) free-breathing dynamic multislice protocol that allows both the change in signal and the rate of oxygen wash-in to be determined using MRI at 3 T.[13] We aimed to examine T_2*-OE-MRI-derived measurements of pulmonary ventilation (and their repeatability) in a cohort of patients with mild-to-severe COPD and healthy volunteers (HVs). We also aimed to assess the correlations between T_2*-OE-MRI measurements of pulmonary ventilation, resting PFTs and indices of functional limitation such as exercise intolerance and exertional dyspnoea.

STUDY DESIGN AND METHODS

Study participants

We included 26 participants (13 patients with mild-to-severe COPD and 13 HVs). Cases were required to have a physician diagnosis of COPD and a smoking history of ≥10 pack-years and to be clinically stable at study entry (defined as no worsening of respiratory symptoms requiring additional treatment within the preceding 2 weeks). HVs were non-smokers (≤2 smoking pack-years in total and none in the last 6 months). Exclusion criteria for both groups were having a contraindication for MRI (eg, metallic implants, claustrophobia, pacemakers, MR-incompatible prosthetic heart valves), known sensitivity to O_2, body mass index (BMI) <18 or ≥35 kg/m^2, and pregnant or lactating female participants.

For patients, we also excluded those with a resting partial pressure of carbon dioxide (PCO_2) of >6.5 kPa on air from ear lobe arterialised capillary blood gas and those with clinically significant comorbidities that might reduce exercise tolerance or contraindicate exercise testing (HVs did not undergo exercise testing or ear lobe blood gas measurements).

Study design

This was a cross-sectional study to assess feasibility, repeatability and relation to lung physiology of T_2*-OE-MRI parameters in a cohort of patients with mild-to-severe COPD versus HVs. The study was sponsored by the University of Manchester and ethically approved by the HRA and Health and Care Research Wales (REC reference: 22/NW/0114). After providing informed consent, participants completed two to three visits; online supplemental e-Figure 1 shows the study flow chart and details of study visits. Visits and procedures were conducted at Manchester University NHS Foundation Trust (Wythenshawe Hospital).

Study procedures

Symptom questionnaires included the modified Medical Research Council (mMRC) dyspnoea scale and COPD Assessment Test (CAT).[14 15] Spirometry, body plethysmography and the lung diffusing capacity for carbon monoxide were performed using the Vyntus-Vyaire system, and data were presented relative to the predicted normal values.[16–18] Multiple breath washout (MBW) testing was performed using the Innocor system as previously described,[19] according to guidelines.[20] Wash-in was conducted using a closed-circuit rebreathing protocol for HVs, but due to longer wash-in time, an open-circuit was used for patients with COPD using 0.2% sulfur hexafluoride (SF_6);[21] the primary outcome was the lung clearance index (LCI). An incremental cardiopulmonary exercise test (CPET) was performed, as previously described,[4] on an electronically braked cycle ergometer using a Quark-COSMED system. CPET protocol started with a 3 min rest, then a 1 min warm-up, followed by 20W/2 min increments until exhaustion. Measurements during CPET included breath-by-breath cardiorespiratory parameters; O_2 saturation (pulse oximetry) and dynamic lung volumes calculated from the inspiratory capacity (IC) with rest-to-peak decrease in IC reflected the degree of dynamic hyperinflation;[5] dyspnoea and leg discomfort intensity were measured by the modified 10-point Borg scale.[22]

OE-MRI protocol

Subjects were scanned twice in a supine position using a Siemens Vida 3 T MRI scanner (Siemens Healthcare, Erlangen, Germany). Before scanning, subjects were fitted with a non-rebreathing face mask (Intersurgical,

Berkshire, UK) to allow delivery of medical gases. The T_2*-OE-MRI protocol has been previously validated in healthy subjects[13] and consisted of a dynamic multi-slice RF-spoiled gradient echo sequence with 6×10 mm coronal slices, slice gap 5 mm, field of view 450 mm, in-plane resolution 4.7×4.7 mm, TR/TE=16/0.81 ms, flip angle=5°, temporal resolution=1.5 s and total number of dynamic acquisitions=360 (~9 min total scan time). For further standardisation, slice 5 was placed in line with the descending aorta. Medical air was delivered at a rate of 15 L/min for the first 60 dynamic acquisitions; this was switched to 100% oxygen for a further 150 acquisitions before being switched back to air for the remainder of the scan. Feasibility measures of T_2*-OE-MRI included the ability to depict signal changes in patients with COPD similar to HVs while ensuring the safety of breathing 100% oxygen in this patient cohort.

OE-MRI analysis

The first 10 images from the T_2*-OE-MRI dynamic series were discarded to ensure a steady state, and the remaining images were registered to the mean lung position using the Advanced Normalization Tools non-linear registration algorithm.[23] Breathing-related tissue density variation was corrected using the method described by Kim *et al*,[13] and the magnitude of the percent signal enhancement (PSE) was calculated as the voxel-wise mean difference in corrected signal intensity between air and 100% oxygen breathing. The enhancing fraction (EF) is the fraction of the lung showing a measurable signal change due to the presence of oxygen and is closely related to a ventilation fraction; EF was thus calculated as the percentage of lung voxels showing a negative (ie, due to a reduction in T_2*) enhancement. The mean percent signal change in the enhancing region (E-PSE) was also calculated. See online supplemental file 1 for further details.

Statistical analysis

This was an experimental study to examine new T_2*-OE-MRI measurements in patients with COPD, so formal power calculations were not possible without prior data. Between-group comparisons were performed using an appropriate test, after the normality check. Repeatability of MRI measurements was tested using Bland-Altman comparisons, and the two-way single-measure mixed-effect model intraclass correlation coefficient (ICC) with absolute agreement.[24] The ICC values were taken to indicate poor repeatability if <0.50, moderate repeatability if between 0.5 and 0.75, good repeatability if between 0.75 and 0.9 and excellent repeatability if >0.9.[25] Spearman's rank correlation coefficient test was used to assess relationships between T_2*-OE-MRI parameters, resting lung physiology and CPET parameters. Data analyses and graphing were completed using SPSS V.22.0 (IBM), GraphPad Prism V.10 and SigmaPlot V.11. Since these analyses were considered exploratory, significance was set at p<0.05, and no adjustment was made for multiple comparisons.

Patient and public involvement

Patients and members of the public were not involved in the study design or conduct.

RESULTS

Participants' characteristics, PFTs and CPET measurements

30 participants were screened, and 26 completed the study: 13 in each group (online supplemental e-Figure 1). Table 1 shows participants' characteristics. There were no between-group statistically significant differences in age, height or BMI. Patients had greater activity-related dyspnoea (mMRC dyspnoea scale) and higher CAT scores compared with HVs (both p<0.001). Patients had mild-to-severe airflow obstruction with FEV_1 (median (IQR)) of 63 (36–79) %predicted. They also had evidence of pulmonary gas trapping (residual volume/total lung capacity (RV/TLC): 45 (39–52) %) and small airway disease (SAD: lower mid-expiratory flow ($FEF_{25-75\%}$) and higher difference between slow and forced vital capacity (SVC-FVC) compared with HVs, both p<0.001) (table 1). LCI was greater in patients than in HVs (p=0.001).

Resting capillary PCO_2 and PO_2 were 4.98±0.47 and 9.92±1.54 kPa (mean±SD), respectively (table 2). Measurements during the incremental CPET are shown in table 2 and online supplemental e-Figure 2. Peak work rate (WR) and oxygen uptake ($\dot{V}O_2$) were 56±32 and 53±18 %predicted, respectively. The decrease in the IC from rest-to-peak exercise (ie, dynamic hyperinflation) was 0.27±0.58 L. Minute ventilation–CO_2 output ($\dot{V}_E$-$\dot{V}CO_2$) slope and $\dot{V}_E/\dot{V}CO_2$ nadir were 30.8±4.4 and 34.6±2.5, respectively.

T_2*-OE-MRI measurements

T_2*-OE-MRI measurements in COPD versus HVs

During T_2*-OE-MRI (first scan), PSE (magnitude) and EF were significantly lower in patients with COPD than in HVs: median (IQR) (2.77 (2.19–4.19) vs 5.34 (4.33–5.61) % and 0.74 (0.66–0.77) vs 0.89 (0.82–0.94), respectively, both p<0.001) (figure 1a, c). However, there was no between-group difference in E-PSE (5.79 (5.16–6.20) vs 6.00 (5.59–6.47), p=0.51) (figure 1e). Examples of scan-rescan PSE maps in a representative patient with COPD and a healthy individual are displayed in figure 2.

Repeatability of T_2*-OE-MRI measurements

12 participants in each group had a repeat scan within 7–28 days of the preceding visit (online supplemental e-Figure 1). Table 3 shows T_2*-OE-MRI repeat measurements in both groups. Bland-Altman analyses of repeat T_2*-OE-MRI measurements of the whole sample showed bias±95% limits of agreement of –0.18±2.1, 0.005±0.13 and –0.34±2.1 in PSE (magnitude), EF and E-PSE, respectively (figure 1b, d, f). Bland-Altman analyses of repeat

Table 1 Participants' characteristics and resting pulmonary function tests

Variable	Healthy volunteers (n=13)	Patients with COPD (n=13)	P value
Age, years (M:F)	58 (52–67) (6:7)	63 (55–72) (8:5)	0.18
Weight, kg	71.4 (67.7–84.4)	82.4 (70.5–108.8)	0.18
Height, cm	171 (163–177)	172 (164–176)	0.92
BMI, kg/m^2	26.8 (23.8–27.4)	29.1 (25.2–35.7)	0.18
Smoking status, n			
Current smoker	0	3	–
Ex-smoker	4	10	–
Never smoked	9	0	–
Smoking, pack-years	0.0 (0.0–1.25)	22.5 (21.5–40.5)*	<0.001
mMRC (0–4)	0.0 (0.0–0.0)	1.0 (1.0–3.0)*	<0.001
CAT score (0–40)	1.0 (0.0–4.0)	18.0 (8.0–23.5)*	<0.001
Resting pulmonary function tests			
FEV_1, L (%predicted)	3.15 (2.33–3.89) 106 (101–115)	1.61 (0.93–2.52)* 63 (36–79)*	0.003 <0.001
FVC, L (%predicted)	4.12 (3.13–4.97) 109 (102–117)	3.13 (1.90–3.55)* 79 (62–90)*	0.02 <0.001
FEV_1/FVC	0.77 (0.75–0.80)	0.60 (0.43–0.68)*	<0.001
SVC-FVC, L	0.12 (–0.06 to 0.26)	0.58 (0.51 to 0.83)*	<0.001
FEF_{25-75}, L/s (%predicted)	3.16 (1.87–3.50) 99 (86–111)	0.81 (0.44–1.81)* 35 (19–62)*	<0.001 <0.001
TLC, L (%predicted)	5.82 (5.59–7.07) 111 (94–113)	6.56 (5.82–7.51) 108 (97–123)	0.30 0.37
FRC, L (%predicted)	3.07 (2.58–3.64) 103 (90–118)	3.65 (2.95–4.42) 107 (93–148)	0.08 0.14
RV/TLC, %	31 (27–38)	45 (39–52)*	0.01
IC, L (%predicted)	2.93 (2.57–3.71) 104 (93–114)	3.03 (1.84–3.40) 95 (79–108)	0.39 0.22
V_A, L (%predicted)	5.25 (4.67–5.87) 103 (92–104)	5.20 (4.28–5.74) 93 (84–99)	0.83 0.17
V_A/TLC	0.85 (0.83–0.89)	0.79 (0.71–0.89)	0.27
DLCO, mmol/min/kPa (%predicted)	7.03 (5.95–9.43) 95 (89–98)	5.05 (4.27–7.03)* 73 (49–92)*	0.047 0.02
KCO, mmol/min/kPa/L (%predicted)	1.38 (1.22–1.48) 97 (86–103)	1.16 (0.82–1.45) 84 (57–99)	0.07 0.07
Multiple breath washout (n=12 each group)			
LCI	7.33 (6.79–8.48)	11.30 (8.76–14.37)*	0.001

Values are median and IQR.
*p<0.05, patients with COPD versus healthy volunteers.
BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; F, female; FEF_{25-75}, forced expiratory flow between 25 and 75% of the FVC; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; KCO, transfer factor; LCI, lung clearance index; M, male; mMRC, modified Medical Research Council; RV, residual volume; SVC, slow vital capacity; TLC, total lung capacity; V_A, alveolar volume.

T_2*-OE-MRI measurements within groups are shown in online supplemental e-Figure 3. In addition, the ICC values indicated moderate and good repeatability for PSE (magnitude) and EF, respectively (0.74 and 0.80), but poor repeatability was shown for E-PSE (ICC=0.40).

The link between OE-MRI measurements and resting/exertional physiological parameters

Figure 3 shows selected correlations between T_2*-OE-MRI measurements (first scan) and resting PFTs. In the whole sample, PSE (magnitude) and EF correlated well with

Table 2 Resting blood gases and measurements during the incremental CPET

Variable	Patients with COPD (n=13)
Resting blood gases	
pH	7.45±0.02
PO_2, kPa	9.92±1.54
PCO_2, kPa	4.98±0.47
HCO^3, mmol/L	26.4±1.6
Measurements at the peak of incremental CPET	
Work rate, watts (%predicted)	86±46 (56±32)
$\dot{V}O_2$, L/min (%predicted)	1.20±0.53 (53±18)
$\dot{V}CO_2$, L/min	1.22±0.63
RER	0.99±0.14
$\dot{V}_E$, L/min (%MVV)	43±20 (74±16)
V_T, L (%predicted VC)	1.48±0.60 (36±10)
Breathing frequency, per min	29±4
$\dot{V}_E/\dot{V}CO_2$	36.0±4.1
$PetCO_2$, mm Hg	36.3±4.3
SpO_2, %	91.9±5.2
HR, %predicted	76±6
O_2 pulse, mL/beat	9.8±3.4
Dyspnoea, Borg scale	5.2±2.4
Leg discomfort, Borg scale	5.5±2.4
Ventilatory efficiency during the incremental CPET	
$\dot{V}_E$-$\dot{V}CO_2$ slope	30.8±4.4
$\dot{V}_E$-$\dot{V}CO_2$ intercept	4.6±1.0
$\dot{V}_E/\dot{V}CO_2$ nadir	34.6±2.5
Exertional symptoms during the incremental CPET	
Dyspnoea/$\dot{V}O_2$ slope, Borg/L/min	7.54±4.72
Dyspnoea/WR slope, Borg/watts	0.08±0.07
Dyspnoea/$\dot{V}_E$ slope, Borg/L/min	0.24±0.21
Reason(s) for stopping exercise, n	
Breathing discomfort	3
Leg discomfort	1
Breathing and leg discomfort	7
Others	2

Values are mean±SD.
$\dot{V}CO_2$, carbon dioxide output; COPD, chronic obstructive pulmonary disease; $\dot{V}_E$, minute ventilation; HCO^3, bicarbonate; HR, heart rate; MVV, maximum voluntary ventilation; $\dot{V}O_2$, oxygen uptake; PCO_2, partial pressure of carbon dioxide; $PetCO_2$, end-tidal carbon dioxide; PO_2, partial pressure of oxygen; RER, respiratory exchange ratio; SpO_2, oxygen saturation by pulse oximetry; VC, vital capacity; V_T, tidal volume; WR, work rate.

FEV_1 (z-score) (r=0.62 and r=0.71, respectively, both p<0.001, figure 3a, e), RV/TLC (r=−0.58 and r=−0.69, both p<0.01, figure 3b, f), FEF_{25-75} (r=0.66 and r=0.77, both p<0.001, figure 3c, g) and SVC-FVC difference (r=−0.69 and r=−0.72, both p<0.001). Also, PSE (magnitude) and EF correlated with LCI (r=−0.75 and r=−0.81, both p<0.0001), respectively (figure 3d, h). Within the COPD group, both PSE (magnitude) and EF correlated with the change in IC from rest-to-peak exercise (r=0.58 and r=0.74, respectively, both p<0.05), dyspnoea/WR slope (r=−0.58 and r=−0.71, both p<0.05) and peak WR as %predicted (r=0.61 and r=0.59, both p<0.05) (online supplemental e-Figure 4). PSE (magnitude) and EF also correlated with $\dot{V}_E/\dot{V}CO_2$ nadir, a measure of ventilatory efficiency during CPET (r=−0.76, and r=−0.78, both p<0.01).

DISCUSSION

This is the first report of a new ventilation MRI technique allowing direct visualisation of ventilation distribution using oxygen as the tracer gas in patients with COPD. The study included a well-characterised group of symptomatic patients with a prior COPD diagnosis, mild-to-severe airflow obstruction, pulmonary gas trapping and evidence of SAD who were stable at the time of the study. We included HVs in whom detailed physiological testing and repeat OE-MRI were also conducted. The main findings were as follows: (1) T_2*-OE-MRI provides a repeatable direct assessment of pulmonary ventilation in healthy individuals and in patients with mild-to-severe COPD, (2) T_2*-OE-MRI showed significantly lower PSE and EF in patients with COPD compared with HVs with no between-group difference in E-PSE and (3) T_2*-OE-MRI indices of pulmonary ventilation correlate well with FEV_1, measures of SAD and ventilation heterogeneity, resting and dynamic hyperinflation, and exertional dyspnoea.

COPD is a heterogeneous disease that affects the large and small airways, the lung parenchyma and the pulmonary vascular bed.[2 26 27] The presence of lung parenchymal destruction and small airway obstruction hampers the even distribution of pulmonary ventilation, which ultimately affects pulmonary gas exchange, the main function of the lungs. Spirometry is the most widely used test to assess the severity of COPD (ie, the severity of airflow obstruction). Other physiological tests are helpful to specifically examine ventilation heterogeneity across the lungs in patients with COPD and smokers with normal spirometry, such as the MBW and poorly communicating fraction (PCF, ie, the ratio between alveolar volume (measured during single-breath diffusion test) and TLC).[4 28–31] In the current sample, 54% of patients with COPD had an abnormal V_A/TLC ratio (i.e., the PCF was <0.8), and they also showed significantly greater LCI compared with HVs, indicating inhomogeneous pulmonary ventilation related to small airway dysfunction.[28 31]

Current advances in MRI techniques and sequences, for example, the use of inhaled noble gases, and phase-resolved functional lung MRI (PREFUL-MRI), have expanded the utility of MRI in depicting abnormalities in pulmonary ventilation.[7 32] Davis *et al*[33] have previously shown a moderate correlation between ventilation

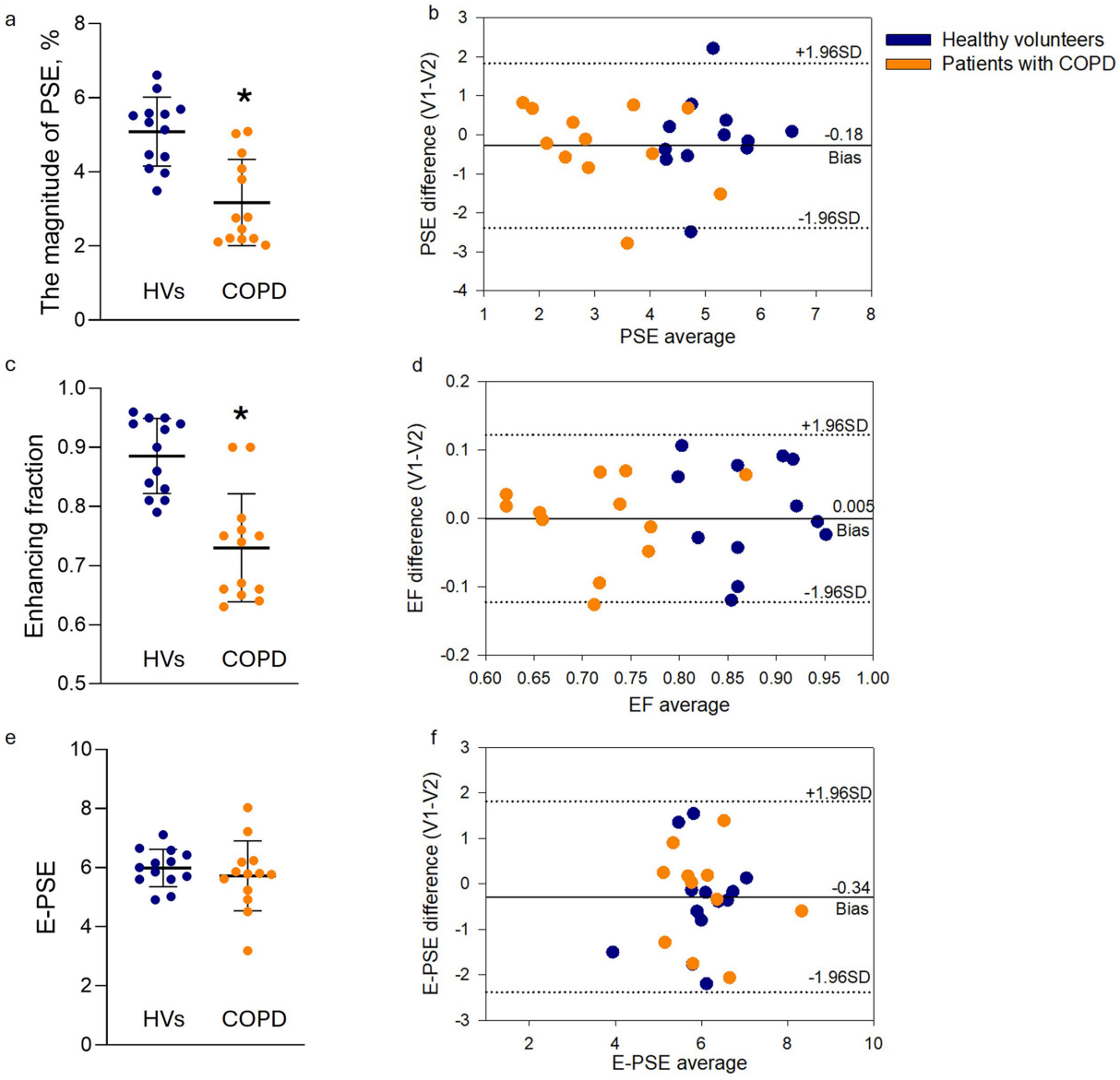

Figure 1 T_2*-OE-MRI measurements of ventilation in patients with COPD and healthy volunteers. Panels (a), (c) and (e) show individual data with the horizontal lines in each panel, representing the mean with SD. *p<0.05 patients with COPD versus HVs. Bland-Altman analyses of repeat T_2*-OE-MRI measurements (panels (b), (d) and (f)) showed bias±95% limits of agreement of –0.18±2.1, 0.005±0.13 and –0.34±2.1 in PSE (magnitude), EF and E-PSE, respectively. COPD, chronic obstructive pulmonary disease; EF, enhancing fraction; E-PSE, change in signal within the enhancing region; HVs, healthy volunteers; PSE (magnitude), the magnitude of the percentage difference between mean signal intensity at normoxia and hyperoxia; T_2*-OE-MRI, T_2*-weighted oxygen-enhanced MRI.

defects, as assessed by hyperpolarised ^{3}He MRI, and PCF in elderly never-smokers and ex-smokers with COPD. PREFUL-MRI was also shown to provide quantitative measures of dynamic ventilation, which can be used to assess treatment response in patients with COPD.[7 34] An advantage of OE-MRI is that it uses inhaled oxygen as a tracer, potentially providing a more direct link to ventilation than signal intensity changes during the breathing cycle. Conventional T_1-weighted OE-MRI uses the paramagnetic effect of oxygen, and the change in T_1 also shows the potential of pulmonary functional assessment using both 1.5 T and 3 T MRI in patients with COPD.[10 11 35] An advantage of the T_2*-related signal is that it is believed to provide more specific information about pulmonary ventilation compared with the T_1 signal, as it directly reflects the effect of changing concentrations of oxygen in the alveoli rather than measuring the dissolved oxygen signal.[12] In this regard, a recent study has refined a protocol to use T_2*-sensitised OE-MRI at 3 T in healthy subjects, and the method was found feasible and reproducible.[13] We expand on these results to progress them to clinical use and show for the first time that the magnitude of PSE and EF derived from T_2*-OE-MRI can differentiate patients with COPD from healthy individuals. The lower PSE and EF (a measure of the ventilated volume fraction) in patients with COPD compared with HVs in the

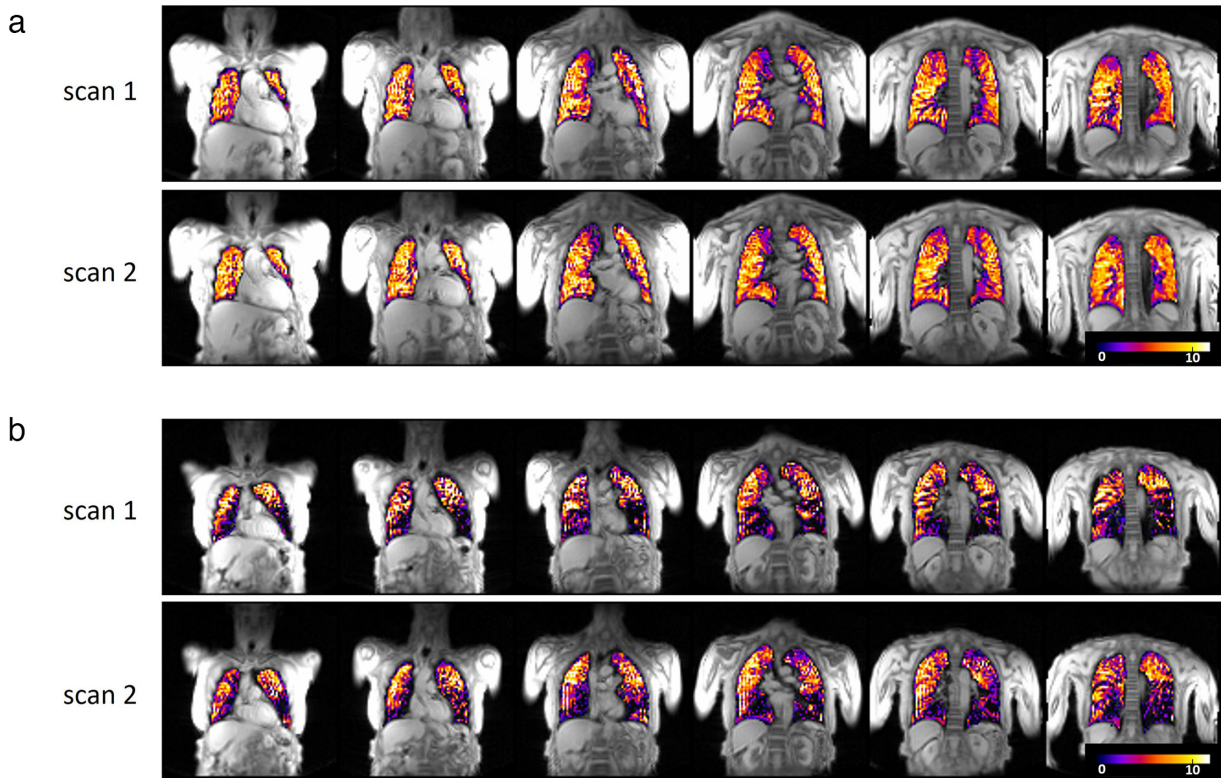

Figure 2 T_2*-OE-MRI percent signal intensity (PSE (magnitude)) maps for two female participants, age range 60–80 years: healthy subject (A) and patient with COPD (B). Compared with the healthy subject, the patient with COPD maps exhibit more patchy enhancement with ventilation defects in the lower lobes of both lungs. COPD, chronic obstructive pulmonary disease; PSE (magnitude), the magnitude of the percentage difference between mean signal intensity at normoxia and hyperoxia; T_2*-OE-MRI, T_2*-weighted oxygen-enhanced MRI.

absence of a difference in E-PSE (figure 1) suggest that PSE reflects the proportion of the lung that is ventilated. Bland-Altman and ICC analyses of repeated measures of T_2*-OE-MRI markers of ventilation distribution showed moderate-high interscan repeatability in both health and disease (figure 1 and online supplemental e-Figure 3).

Previous studies have shown that MRI-derived ventilation defect parameters using hyperpolarised gases were closely linked to COPD severity (ie, FEV_1) and might be more sensitive in assessing the small airway function.[36–38] Our results showed that T_2*-OE-MRI metrics of ventilation heterogeneity also correlate strongly with the severity of airflow obstruction (ie, FEV_1) and with resting physiological markers of SAD (eg, SVC-FVC and $FEF_{25-75\%}$) (figure 3). Furthermore, strong correlations were found between both PSE and EF and LCI, a finding suggesting that PSE and EF could be used as sensitive markers of uneven distribution of pulmonary ventilation in patients with COPD.

Previous studies on patients with COPD demonstrated that resting ventilatory heterogeneity (as assessed by single or multiple breath washout tests) and small airway dysfunction are the main predictors of dynamic hyperinflation, reduced exercise capacity and increased

Table 3 T_2*-OE-MRI repeat measurements in patients with COPD and healthy volunteers

	Healthy volunteers (n=12)		Patients with COPD (n=12)	
Variable	**Scan #1**	**Scan #2**	**Scan #1**	**Scan #2**
PSE (magnitude), %	5.24 (4.25–5.63)	5.07 (4.42–5.89)	2.61 (2.19–3.94)*	2.76 (2.11–3.81)*
EF	0.88 (0.82–0.94)	0.88 (0.83–0.91)	0.71 (0.65–0.76)*	0.72 (0.66–0.78)*
E-PSE	6.07 (5.59–6.51)	6.49 (6.02–6.80)	5.78 (5.08–6.22)	5.82 (5.29–6.61)

Values are median (IQR).
*p<0.05, patients with COPD vs healthy volunteers (differences between corresponding scans).
COPD, chronic obstructive pulmonary disease; EF, enhancing fraction; E-PSE, the percent signal change in the enhancing region; OE-MRI, oxygen-enhanced MRI; PSE (magnitude), the magnitude of the percentage difference between mean signal intensity at normoxia and hyperoxia.

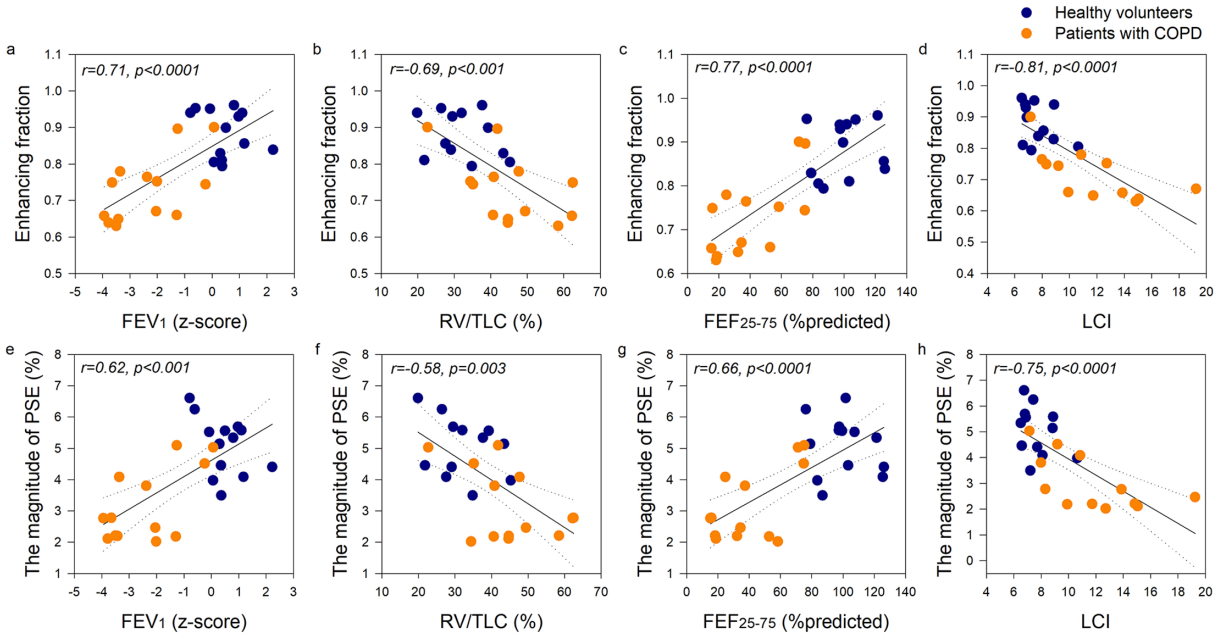

Figure 3 Correlations between T_2*-OE-MRI-derived measurements and selected resting pulmonary function test. The dotted line represents a 95% CI of the regression line. FEF_{25-75}, forced expiratory flow between 25 and 75% of the forced vital capacity; FEV_1, forced expiratory volume in 1 s; LCI, lung clearance index (plotted data are for 12 participants in each group); PSE (magnitude), the magnitude of the percentage difference between mean signal intensity at normoxia and hyperoxia; RV, residual volume; TLC, total lung capacity; T_2*-OE-MRI, T_2*-weighted oxygen-enhanced MRI.

exertional dyspnoea.[3 39–41] Several radiological studies have also shown a strong association between CT metrics of SAD and both reduced exercise capacity and increased dyspnoea intensity.[7 42–44] Furthermore, T_1-weighted OE-MRI showed a similar capability of pulmonary functional assessment, and its measurements were found linked to activity-related dyspnoea and exercise capacity (as assessed by 6 min walk distance) in one study.[11] In the current study, we show that T_2*-OE-MRI markers of pulmonary ventilation heterogeneity are closely related to measures of dynamic hyperinflation, reduced exercise capacity and exertional dyspnoea during incremental CPET in patients with mild-to-severe COPD.

OE-MRI is an emerging safe technique that is less demanding and could be readily available in most MR centres in comparison with hyperpolarised noble gases. This study provides the first evidence that the use of T_2*-OE-MRI at 3 T is feasible in patients with COPD and capable of depicting pulmonary ventilation abnormalities compared with healthy non-smoking individuals. The OE-MRI data represent summary measurements of ventilation at the whole-lung level, and additional sensitivity is provided from the 3D ventilation images. Our results show that the T_2*-OE-MRI-derived markers are representative of ventilation heterogeneity and small airway dysfunction (as assessed by conventional resting physiological tests) and are linked to important patient-centred outcomes such as exertional dyspnoea. Whether this method is more sensitive than conventional physiological tests in assessing longitudinal changes or responses to treatment is yet to be determined. These results, altogether, set the stage for future studies to examine further potential clinical applications of T_2*-OE-MRI in patients with COPD and other patients with chronic respiratory diseases. Finally, future comparative studies that examine pulmonary ventilation abnormalities assessed by T_2*-OE-MRI versus those measured by hyperpolarised gas MRI or phase-resolved MRI would provide a fair evaluation of T_2*-OE-MRI capability.

Strengths and limitations

To the best of our knowledge, this is the first study that examines the relationship between T_2*-OE-MRI-derived parameters at 3 T and detailed resting and exertional respiratory physiological measurements in healthy individuals and patients with COPD. OE-MRI can be challenging at a high magnetic field, but the current method enabled the dynamic measurement of PSE, which was repeatable in health and disease and was able to differentiate patients with COPD from healthy individuals. In contrast to Kim *et al*,[13] we were unable to reliably quantify T_2* in the current study due to scanner limitations on the minimum echo time, so we report only signal changes (ie, the magnitude of PSE) rather than changes in T_2*. We acknowledge that in the current study, the OE-MRI method was not validated against other functional imaging modalities, such as ^{129}Xe MRI. The study is a proof of principle; hence, a power calculation was not possible. For the same reason, the analyses were exploratory, statistical significance was uncorrected for multiple comparisons, the sample size might be limited, and therefore, the

results should be interpreted cautiously. There were no statistically significant differences between groups in age and BMI; this should be cautiously interpreted due to the possibility of insufficient power to detect real differences. Though exposure to high oxygen concentration was for a few minutes, this still might have carried a risk of 'absorption atelectasis', leading to decreased lung volume and impaired gas exchange and potentially affecting the PSE measurement. HVs did not undergo CPET, as comparing exercise responses was beyond the aim of the current study.

INTERPRETATION

This is the first study to examine T_2*-weighted OE-MRI dynamic signal enhancement behaviour and repeatability at 3 T in patients with COPD. T_2*-OE-MRI could provide useful information on pulmonary ventilation; it enables dynamic measurements of signal enhancement that are repeatable and can differentiate patients with COPD from healthy individuals. Our results also show that T_2*-OE-MRI-derived measures are closely linked with resting lung function parameters of airflow limitation, pulmonary gas trapping, small airway disease and ventilation heterogeneity. In addition, T_2*-OE-MRI-derived markers correlated with measurements of exertional dyspnoea, reduced exercise capacity and dynamic hyperinflation in patients with mild-to-severe COPD. The study is a proof of principle, and further validation studies are required, yet our results set the stage for future studies to assess potential additional clinical applications for T_2*-OE-MRI in different patient cohorts and in evaluating response to therapy in patients with chronic obstructive diseases.

Author affiliations
[1]Division of Infection, Immunity, and Respiratory Medicine, The University of Manchester, and Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK
[2]Department of Chest Diseases, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[3]BHF Manchester Centre for Heart and Lung Magnetic Resonance Research, Manchester University NHS Foundation Trust, Manchester, UK
[4]Bioxydyn Limited, Manchester, UK
[5]Department of Medical Physics and Biomedical Engineering, Centre for Medical Image Computing (CMIC), University College London, London, UK
[6]Division of Cardiovascular Sciences, The University of Manchester, and Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK

X Amany F Elbehairy @AmanyElbehairy and Alex R Horsley @alexrhorsley

Contributors All authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. All authors played a role in the content and writing of the manuscript. In addition, ARH provided the original idea for the study; AFE, JHN and ARH contributed to the study concept and the study design. AFE, HB and JHN collected the data. AFE and JHN performed data analysis and prepared it for presentation. AFE and JHN are the data guarantors. AFE wrote the first draft of the manuscript. JHN, GJMP, CM, JV and ARH contributed to data interpretation, manuscript writing and editing. All authors have read and approved the manuscript.

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Competing interests AFE and HB have nothing to disclose. JHN has a part-time appointment with Bioxdyn Ltd. GJMP receives a salary from, holds shares in, and is a director of Bioxydyn Limited, a company with an interest in imaging biomarkers. GJMP also holds shares in and is a director of Queen Square Analytics Limited, a company with an interest in imaging biomarkers. GJMP also holds shares in and is a director of Quantitative Imaging Limited, a company with an interest in imaging biomarkers. CM, Advanced Fellowship, NIHR301338 is funded by the National Institute for Health and Care Research (NIHR). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care. CM acknowledges support from the University of Manchester British Heart Foundation Accelerator Award (AA/18/4/34221) and the NIHR Manchester Biomedical Research Centre (NIHR203308). CM has participated on advisory boards/consulted for AstraZeneca, Boehringer Ingelheim and Lilly Alliance, Novartis, and PureTech Health, serves as an advisor for HAYA Therapeutics, has received speaker fees from AstraZeneca, Boehringer Ingelheim and Novo Nordisk, conference attendance support from AstraZeneca, and research support from Amicus Therapeutics, AstraZeneca, Guerbet Laboratories Limited, Roche and Univar Solutions B.V. JV reports personal fees from ALK-Abello, AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, and Teva, outside the submitted work. ARH reports personal fees from Vertex Pharmaceutical; and grants from CF Trust, Cystic Fibrosis Foundation, NIHR, and JP Moulton Charity outside the submitted work. ARH and JV are supported by the NIHR Manchester Biomedical Research Centre.

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ORCID iDs
Amany F Elbehairy http://orcid.org/0000-0001-5180-519X
Alex R Horsley http://orcid.org/0000-0003-1828-0058

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