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Abstract

Magnetic resonance imaging (MRI) may provide attractive biomarkers for assessment of pulmonary disease in clinical trials as it is free from ionizing radiation, minimally invasive and allows regional information. The aim of this study was to characterize lung MRI T_1 relaxation time as a biomarker of chronic obstructive pulmonary disease (COPD); and specifically its relationship to smoking history, computed tomography (CT), and pulmonary function test (PFT) measurements in comparison to healthy age-matched controls. Lung T_1 and inter-quartile range (IQR) of T_1 maps from 24 COPD subjects and 12 healthy age-matched non-smokers were retrospectively analyzed from an institutional review board approved study. The subjects underwent PFTs and two separate MR imaging sessions at 1.5 tesla to test T_1 repeatability. CT scans were performed on the COPD subjects. T_1 repeatability (intraclass correlation coefficient) was 0.72 for repeated scans acquired on two visits. The lung T_1 was significantly shorter ($p<0.0001$) and T_1 IQR was significantly larger ($p=0.0002$) for the COPD subjects compared to healthy controls. Lung T_1 significantly ($p=0.001$) correlated with lung density assessed with CT. Strong significant correlations ($p<0.0001$) between lung T_1 and all PFT measurements were observed. Cigarette exposure did not correlate with lung T_1 in COPD subjects. In conclusion, lung MRI T_1 mapping shows potential as a repeatable, radiation free, non-invasive imaging technique in the evaluation of COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease that is a major cause of morbidity and mortality. The Global Obstructive Lung Disease (GOLD) guidelines characterize COPD by limitation of airflow, tissue destruction and an abnormal inflammatory response, most often caused by cigarette smoking (1). Characterization of COPD relies on spirometry based pulmonary function test (PFT) measurements, such as forced expiratory volume in 1 s (FEV_1). PFTs are inexpensive, relatively easy to perform and therefore commonly used in clinical trials. However, these methods only measure global lung function, resulting in a loss of sensitivity in early/mild disease (2, 3). The discrepancy between spirometric measurements and COPD symptoms, as well as the nonspecific differentiation of lung disorders, is motivating the development of novel techniques to obtain regional lung function information and improved disease characterization (1, 4-6). Improved disease characterisation will allow the use of personalised medicine approaches to COPD treatment, an emerging field in which imaging biomarkers are likely to play an important role (7).

Regional biomarkers of emphysema in COPD lungs can be obtained from computed tomography (CT) (8) or single-photon emission computed tomography (SPECT) (9). The clinical benefits of CT and SPECT for diagnosis of COPD clearly outweigh the potential harmful effects due to ionizing radiation. However for clinical trials, particularly those including a placebo cohort, repeated exposure to ionizing radiation needs to be considered carefully given that there may be no clinical benefit of the examination to the patient. Magnetic resonance imaging (MRI) may provide attractive biomarkers for assessment of pulmonary disease in clinical trials as it is free from ionizing radiation, minimally invasive and allows regional information (10-12).

Lung MRI has well-known limitations because of the low density of the lung and the fast signal decay due to susceptibility differences between tissue and air in lung parenchyma. Nevertheless, several lung MRI applications have been developed and interest in MRI of the lungs has recently increased (10-12). One technique is oxygen-enhanced MRI, in which regional and global lung function can be assessed by measuring MR signal before and after a challenge with oxygen (13-17). The lung water proton longitudinal relaxation time (subsequently called T_1), a tissue specific MRI biomarker, is affected by interactions of water with macromolecules (18) and paramagnetic agents such as molecular oxygen (13). Moreover, T_1 measurements of the lung have been used to enable lung perfusion measurements using MRI contrast agents and to measure regional partial pressure of oxygen in the alveolar airspaces using hyperpolarised gases (10, 16, 19).

However, only a small number of studies have published data on changes in native T_1 in emphysema and fibrosis patients relative to healthy controls (20, 21). Little is known about lung T_1 for different GOLD stage defined COPD patients, especially in relation to well-established markers such as smoking history, CT and PFTs. In contrast to other studies of T_1 in the lungs (20, 21), we have enrolled subjects with both moderate and severe COPD, have age-matched controls, included smoking history, added CT lung density scans and complete PFT information.

The objective for our study, therefore, was to test T_1 repeatability and characterize the lung T_1 relationship to smoking history, CT density scans and systematically performed PFTs in moderate and severe GOLD stage defined COPD subjects and healthy age-matched controls.

Materials and methods

Subjects and study design

Lung T_1 measurements from 24 COPD subjects and 12 healthy age-matched non-smokers (Table 1) were retrospectively analyzed from an institutional review board approved single center lung MRI study conducted in Manchester, United Kingdom. All COPD subjects were current or former smokers; 12 subjects with moderate COPD, defined by FEV_1 > 50% predicted (GOLD stage 1-2) (22), and 12 with severe COPD, FEV_1 < 50% predicted (GOLD stage 3-4). A week prior to MRI scanning, all subjects underwent PFTs, whereas only the COPD subjects were scanned using CT, in order to not expose the healthy participants to ionizing radiation. Subsequently, a second lung MRI T_1 measurement was performed one week later to test T_1 repeatability.

Pulmonary function test

PFTs were performed to assess FEV_1, FEV_1/forced vital capacity (FVC) and the diffusing capacity of carbon monoxide divided by alveolar volume (DL_{CO}/VA). The measurements were carried out using a computerized spirometer system (V62J SensorMedics Plethysmograph, Viasys Healthcare, Carefusion, UK) by a trained test administrator according to ERS standards (23).

CT protocol

CT was carried out for the COPD subjects to allow quantification of global lung density using a LightSpeed Plus scanner (GE Medical Systems, Amersham, UK). Volumetric images of the lung were acquired at full inspiration with following parameters: 120 kVp, 40 mAs, matrix size 512^2 and 1.25 mm slice thickness. Images were reconstructed using the GE

standard algorithm and the data was measured using the VIDA software package (Vida Diagnostics, Inc., Coralville, IA). The 15th percentile density (PD_{15}) and relative lung area with attenuation values less than -950 Hounsfield units (HU), RA_{950}, were calculated as measures of lung density. PD_{15} is expressed as grams per litre (g/L) by adding 1000 to the HU values.

MRI protocol

MR imaging was performed on a 1.5 tesla Philips Achieva MR system (Philips Healthcare, Best, the Netherlands). Subjects were positioned supine and the body coil was used for radio frequency transmission and reception. Cardiac triggering, respiratory gating and respiratory manoeuvres were not employed, allowing normal tidal breathing. Localization scans were acquired to allow reproducible slice positioning at each visit, selecting a posterior two-dimensional coronal slice placed across the descending aorta to permit good lung coverage and avoid the heart.

Static T_1 mapping scans were performed during air breathing using a two-dimensional half Fourier acquired single shot turbo spin echo (HASTE) sequence preceded by an adiabatic non-selective inversion pulse. One week later the subjects were recalled and the repeatability of the T_1 measurements tested. The imaging parameters were: repetition time (TR)=5500 ms, echo time (TE)=3 ms, field of view (FOV)=450^2 mm^2, matrix size=128^2, 68 phase-encoding steps, coronal section with slice thickness=10 mm, flip angle (FA)=90°, with inversion times (TI) of 50, 300, 1100, 2000 and 5000 ms and 5 repeats acquired at each TI resulting in a 4 min T_1 mapping scan time. T_1 maps were calculated on a voxelwise basis from inversion recovery HASTE data by fitting the inversion recovery signal equation

$$SI = S_0(1 - 2fe^{\frac{TI}{T_1}} - (1 - 2f)e^{\frac{nTE-TR}{T_1}}), \quad (1)$$

where SI = signal intensity, S_0 = signal expected without the application of an inversion pulse, f = inversion efficiency set to 1, and n = echo train length set to 68 (24).

MR imaging analysis

All data analysis was performed using pulmolux:oe software (Bioxydyn Ltd, Manchester, United Kingdom). Image registration was used to correct for breathing-induced motion. The software uses a non-linear diffeomorphic registration algorithm with a neighbourhood cross correlation similarity metric to account for the large elastic deformations in the lung. Lung segmentation was performed using a semi-automatic method where an intensity threshold was defined in order to extract the lungs from the image. The intensity threshold was individual-specific to account for both physiological and technical variation between scans. The segmentation procedure also allowed the large pulmonary vessels to be excluded in the quantification. All segmentations were verified by a second observer to ensure the correct lung regions were defined for analysis. T_1 was calculated by fitting the inversion recovery signal equation pixel-by-pixel over each lung image and used to calculate the median and inter-quartile range (IQR) of each subject using RStudio (version 0.98.507). Average lung T_1 was compared between groups. Histograms and IQR of T_1 were assessed to reveal the inherent structure in the maps as median T_1 values are poorly suited to report image heterogeneity. Additionally, the signal to noise ratio (SNR), mean lung signal/standard deviation (SD) in background, was assessed for each TI image.

Statistical analysis

The T_1 repeatability was assessed by intraclass correlation coefficient (ICC) and coefficient of variation (SD/mean, CV) analysis. Mean T_1 from the two scanning visits was associated with pack-years (number of years or equivalent years in which 20 cigarettes a day was smoked, PY), CT density ($RA_{950,}$ PD_{15}) and PFTs (FEV_1, FEV_1/FVC, DL_{CO}/VA) by Pearson's correlation. Differences in demographic and lung T_1 variables between groups were tested using one-way ANOVA with Tukey's multiple comparison test. All p-values are nominal and 0.05 was used as a significance level throughout the study. If not stated otherwise, the reported values are given as the mean ± one SD. Analyses were performed using RStudio (version 0.98.507).

Results

The means ± SD of demographic, PFT, CT and lung T_1 biomarkers for all participants are shown in Table 1. There was no significant difference in age or body mass index across the three groups. The COPD smokers had smoking histories ranging from 12 to 102 PY; including 18 former and 6 current smokers (mean 49 ± 22 PY). One present healthy non-smoker had a past smoking history of 3.6 PY.

Representative lung T_1 maps from each of the three groups – healthy, moderate and severe COPD subjects– are shown in Figure 1. Heterogeneity of T_1 values is evident in the maps of those with COPD, whereas the T_1 map of a healthy subject appears relatively homogenous. Histograms of T_1 further reveal this heterogeneity with an asymmetric broadening of T_1 in the COPD subjects. Also, the mean T_1 for the COPD subjects appears to be shorter than seen in the healthy subject.

Repeated T_1 calculations in 27 participants were usable, 9 were excluded due to poor alignment, missing visits and data quality issues. The median lung T_1 of each subject was satisfactorily repeatable between visits (ICC=0.72). The mean T_1 difference and CV assessed from the median T_1 maps obtained from the two visits were 5 ms and 2.5%, respectively. Thus, T_1 values were averaged for each individual across the two scanning visits before testing for significant group differences and correlations. Typical mean SNRs in lung for TIs of 50, 300, 1100, 2000 and 5000 ms were 28, 17, 8, 28 and 56, respectively.

The lung T_1 (mean ± SD) was significantly shorter (10%, $p<0.0001$; 14%, $p<0.0001$) for the moderate COPD subjects (947 ± 56 ms) and severe COPD subjects (911 ± 64 ms) than in the

healthy controls (1053 ± 55 ms) (Figure 2a; Table 1). No statistically significant differences of T_1 were found between the subjects with different grades of COPD.

IQR of T_1 was significantly larger (57%, p<0.0001, 41%, p=0.0002) for the moderate COPD (324 ± 80 ms) and severe COPD subjects (291 ± 62 ms) than in the healthy controls (207 ± 45 ms) (Figure 2b; Table 1). No statistically significant differences in IQR of T_1 were found between the subjects with different grades of COPD.

Significant correlations between lung T_1 and CT density measurements; RA_{950} (r=-0.63, p=0.001) (Figure 3a) and PD_{15} (r=0.50, p=0.017) (Figure 3b) were found, showing that lung T_1 decreases with lower lung density. Moreover, strong significant correlations (p<0.0001) between lung T_1 and all PFT parameters; FEV_1 (r=0.74) (Figure 4a), FEV_1/ FVC (r=0.77) (Figure 4b) and DL_{CO}/VA (r=0.75) (Figure 4c) were observed, indicating that lung T_1 decreases with reduced lung function. There was no significant correlation between lung T_1 and PY in the COPD subjects (p=0.87).

Discussion

Data from this study demonstrates significantly shorter lung T_1 in moderate and severe COPD subjects than in healthy age-matched non-smoking controls. Additionally, IQR of T_1 significantly increased for the COPD subjects compared to healthy controls, indicating enhanced heterogeneity in the diseased groups. The T_1 protocol possessed good repeatability between the two visits in COPD and healthy subjects. Moreover, the significant T_1 correlations to CT density and PFT parameters indicate that lung T_1 is a potential biomarker for COPD staging. To the best of our knowledge, no other study has provided evidence of the lung T_1 relationship to PY, CT and PFTs in COPD subjects in conjunction with healthy age-matched controls.

There are a number of reasons why lung T_1 may be reduced in COPD subjects. It could be explained by the presence of tar or other substances which enhance dipolar relaxation in the extracellular tissue water and which accumulate in the lung as a direct consequence of smoking. However, we did not observe any T_1 correlation to PY in the COPD subjects, so therefore it is unlikely that smoke particles from the cigarette smoke is the cause of shorter T_1. Lung T_1 may also be changed due to reduced oxygen concentrations and increased inflammation with edema in the COPD subjects. However, these alterations would be expected to increase T_1 in the lung rather than reduce it as found in our study (13, 25). The observed finding with reduced T_1 in COPD patients, therefore, most likely reflects smoking-induced lung pathology, specifically emphysema which is supported by our PFT and CT measurements. Emphysema may reduce lung T_1 due to the elimination of long T_1 compartments such as water and blood (26, 27) and an increased fraction of fibrotic tissue (20). Fibrotic tissue is known to have short T_1 (28).

Stadler *et al*. found shorter lung T_1 values for 11 emphysema and 14 fibrosis patients (20) than 10 healthy volunteers (29). Dasenbrook *et al.* showed a lowered normalized T_1 for 10 cystic fibrosis patients than 5 healthy volunteers with unspecified age (21). Our observed T_1 changes for the COPD subjects are in the same order of magnitude as these studies. The results presented here extend the previous work (20, 21) by using larger study groups, different disease grades, age-matched healthy controls, smoking history information, CT lung density scans and systematically performed PFTs. Moreover, our MRI T_1 protocol allowed normal tidal breathing, while the studies mentioned above performed breath-hold protocols. A free-breathing MRI examination has a practical advantage in diseased subjects that might have difficulties in holding their breath. Moreover, capturing the lung during normal breathing is probably more likely to give representative information about lung function.

Additionally, a previous publication (30) analyzed the same individuals as in this study and retrieved proton density values from the T_1 mapping fitting routine (S_0, Equation 1). Normalized lung proton density strongly correlated with CT density scans (30). The addition of lung T_1 to proton density may provide extra information on the underlying biology. Thus, radiation-free lung MRI T_1 together with proton density quantification would be of considerable interest as an assessment of lung disease especially for longitudinal studies.

A limitation with this retrospective study was the two-dimensional MRI protocol that was restricted to one slice and did not cover the whole lung. A multi-slice or three-dimensional protocol would be preferred for improved regional analysis of the heterogeneous COPD disease. The present study showed good repeatability, however, reproducibility of lung T_1 across sites will need to be determined in a multi-center setting with carefully designed study protocols (31). No correlation between lung T_1 and cigarette exposure was seen in the COPD

subjects. However, we did not monitor interval between last cigarette smoked and the imaging sessions, so there may be some effect of smoke particles on lung T_1. To test this hypothesis a study in healthy smokers should be performed. Other limitations with this study were the small sample size, lack of mild COPD subjects and lack of baseline CT scans from the healthy controls.

The T_1 data was presented as the change of median T_1 and IQR, two quantities which describe the general change as well as the heterogeneity of T_1 in the COPD subjects. As indicated above, the relationship between T_1 and the underlying pathophysiology is not clearly outlined. In future studies it might be appropriate to compare other measures such as the 15th percentile of T_1 to CT PD_{15}, however first we need to increase our understanding of lung T_1. The mean lung density from CT was not used in the comparison with T_1, since it will represent a mixture of larger structures such as bronchi and vessels, emphysema and inflammation and will be of little value to increase the understanding of our findings (32, 33).

This was an exploratory study to investigate a potential new biomarker for COPD. The main application for the imaging biomarker would be in clinical trials where there are needs to perform multiple scans and ionizing radiation would be a limitation. The validation of MRI biomarkers is in some ways more challenging than for more familiar molecular biomarkers (31). For MRI measurements used as biomarkers, the quality and validity of the imaging measurement as a biomarker depends crucially on the use of a diagnostic imaging device, in the presence of the patient, in a manner for which the device was not primarily designed, and may be unfamiliar to the user in the trial site. It is essential to establish repeatability and variation before investigating response to therapy.

In conclusion, MRI T_1 mapping of the lung showed significant differences between COPD subjects and healthy controls, and lung T_1 correlated with CT density and PFTs, indicating the potential role of T_1 quantification in the evaluation of COPD and emphysema. The good repeatability, and the radiation-free and non-invasive nature of MRI, make T_1 mapping an attractive imaging biomarker of COPD for future longitudinal studies.

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Declaration of Interests Statement

The authors have no conflicts of interest to declare. The authors alone are responsible for the content and writing of the paper.

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Table 1

Demographic, pulmonary function, CT density and lung MRI T_1 data

	Healthy	Moderate COPD	Severe COPD
No. of subjects	12	12	12
No. of men	8	9	10
Age (years)	63 ± 12 (42-79)	66 ± 9 (49-80)	65 ± 6 (52-74)
Body mass index (kg/m^2)	25.3 ± 4.1 (18.1-32.1)	28.7 ± 4.3 (23.3-38.6)	25.6 ± 3.4 (20.6-32.9)
Smoking index (pack-years)	0.3 ± 1 (0-3.6)	52 ± 26 (17-102)	47 ± 19 (12-91)
Pulmonary function measurement			
FEV_1 (% predicted)	121 ± 14 (104-147)	69 ± 9 (51-82)	41 ± 6 (26-49)
FEV_1/FVC (% predicted)	78 ± 4 (72-85)	51 ± 8 (40-64)	33 ± 5 (25-44)
DL_{CO}/VA (% predicted)	88 ± 11 (71-109)	69 ±12 (51-90)	48 ±15 (26-77)
CT density scan			
PD_{15} (g/L)	ND	58 ± 23 (29-89)	30 ± 22 (2-77)
RA_{950} (%)	ND	14 ± 9 (4-30)	30 ± 15 (6-55)
Lung MRI measurement			
T_1 (ms)	1053 ± 55 (953-1167)	947 ± 56 (882-1029)†	911 ± 64 (811-991)†
IQR of T_1 (ms)	207 ± 45 (155-291)	324 ± 80 (231-460)†	291 ± 62 (182-385)†

Note.-Data are means ± standard deviations, with ranges in parentheses. ND=no data.

†Significant difference with healthy group, p<0.001.

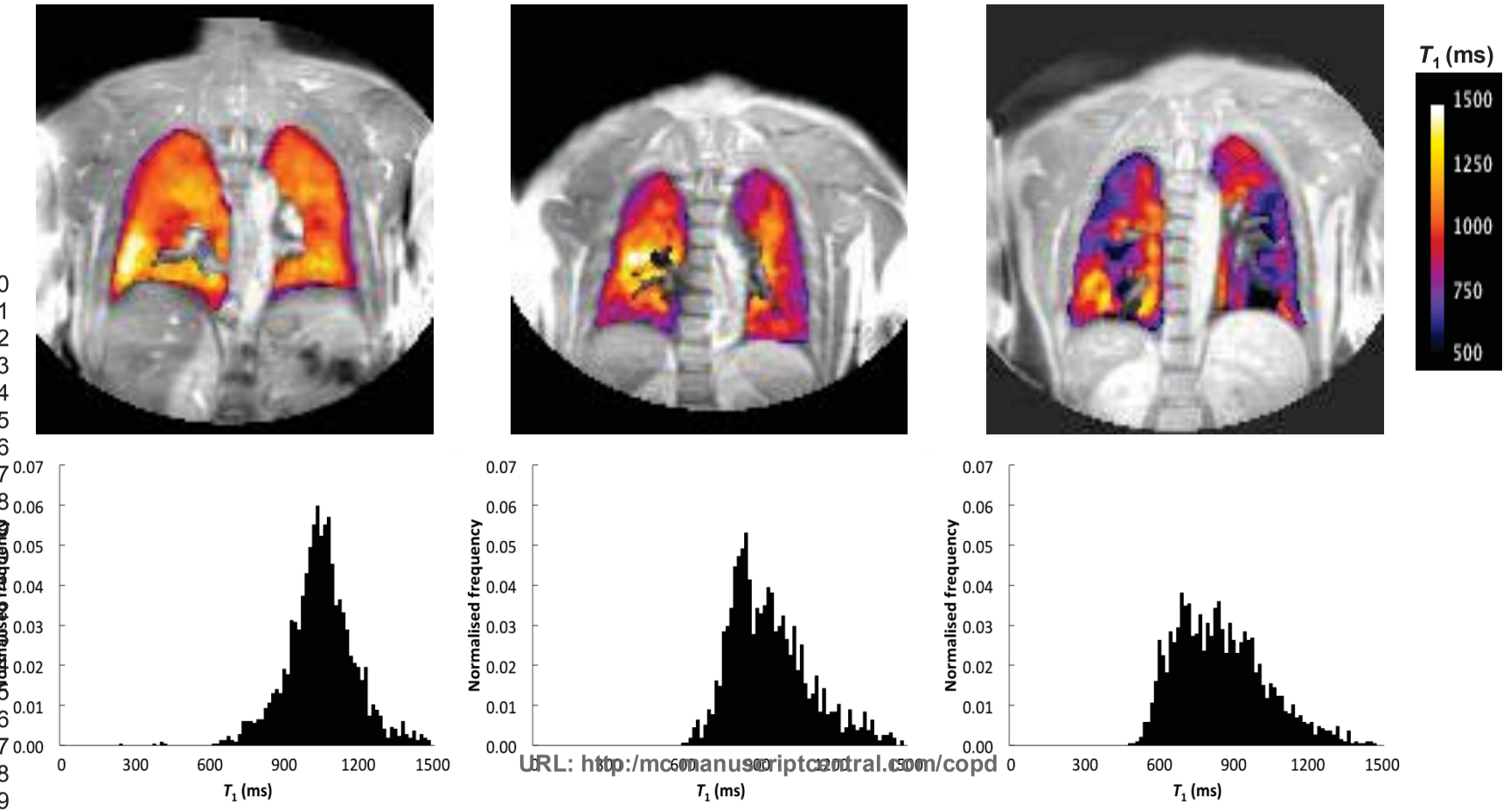
Figure captions

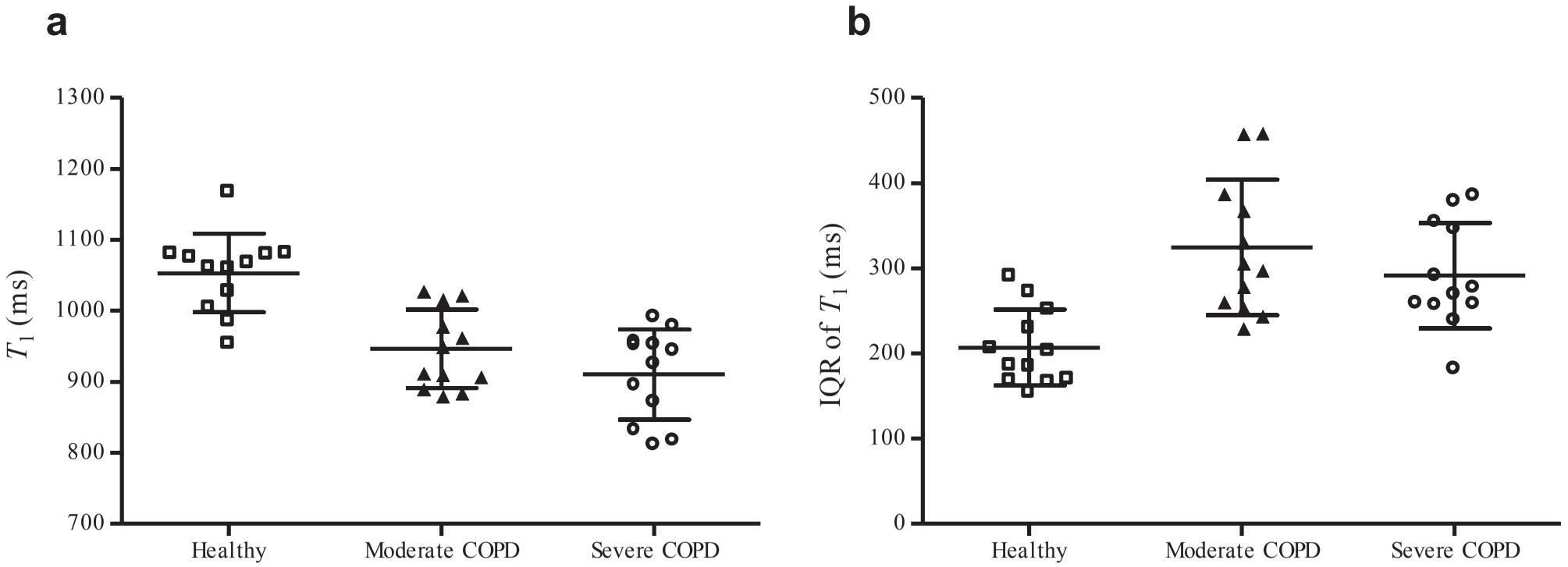
Figure 1. Representative coronal lung MRI T_1 maps overlaid on a signal intensity image with corresponding normalised T_1 histograms for healthy, moderate COPD and severe COPD subjects. Both T_1 maps and histograms reflected the severity of COPD by reduced T_1 and increased heterogeneity.

Figure 2. Global lung T_1 (a) and regional IQR of T_1 (b) for healthy (□), moderate COPD (▲) and severe COPD (○) subjects. T_1 was significantly shorter for the moderate COPD ($p<0.0001$) and severe COPD subjects ($p<0.0001$) than in the healthy controls. IQR of T_1 was significantly larger for the moderate COPD ($p<0.0001$) and severe COPD subjects ($p=0.0002$) than in the healthy controls. No statistically significant differences in T_1 and IQR of T_1 were found between the COPD subjects. The error bars indicate standard deviation of the mean.

Figure 3. Lung T_1 as a function of CT density measurements RA_{950} (a) and PD_{15} (b), for moderate COPD (▲) and severe COPD (○) subjects. Significant correlations between lung T_1 and RA_{950} ($r=-0.63$, $p=0.001$) and PD_{15} ($r=0.50$, $p=0.017$) were found.

Figure 4. Lung T_1 as a function of PFT parameters FEV_1 (a), FEV_1/ FVC (b) and DL_{CO}/VA (c), for healthy (□), moderate COPD (▲) and severe COPD (○) subjects. Strong significant correlations ($p<0.0001$) between lung T_1 and all PFT parameters; FEV_1 ($r=0.74$), FEV_1/ FVC ($r=0.77$) and DL_{CO}/VA ($r=0.75$) were observed.

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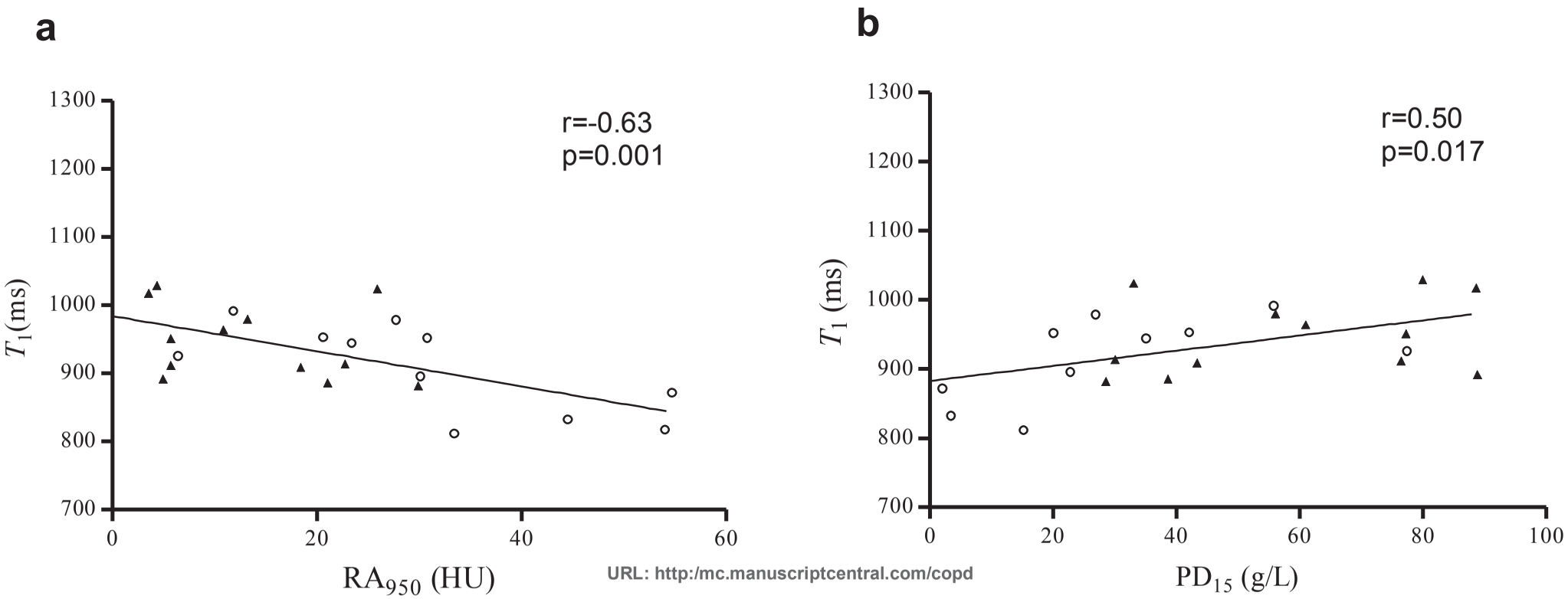
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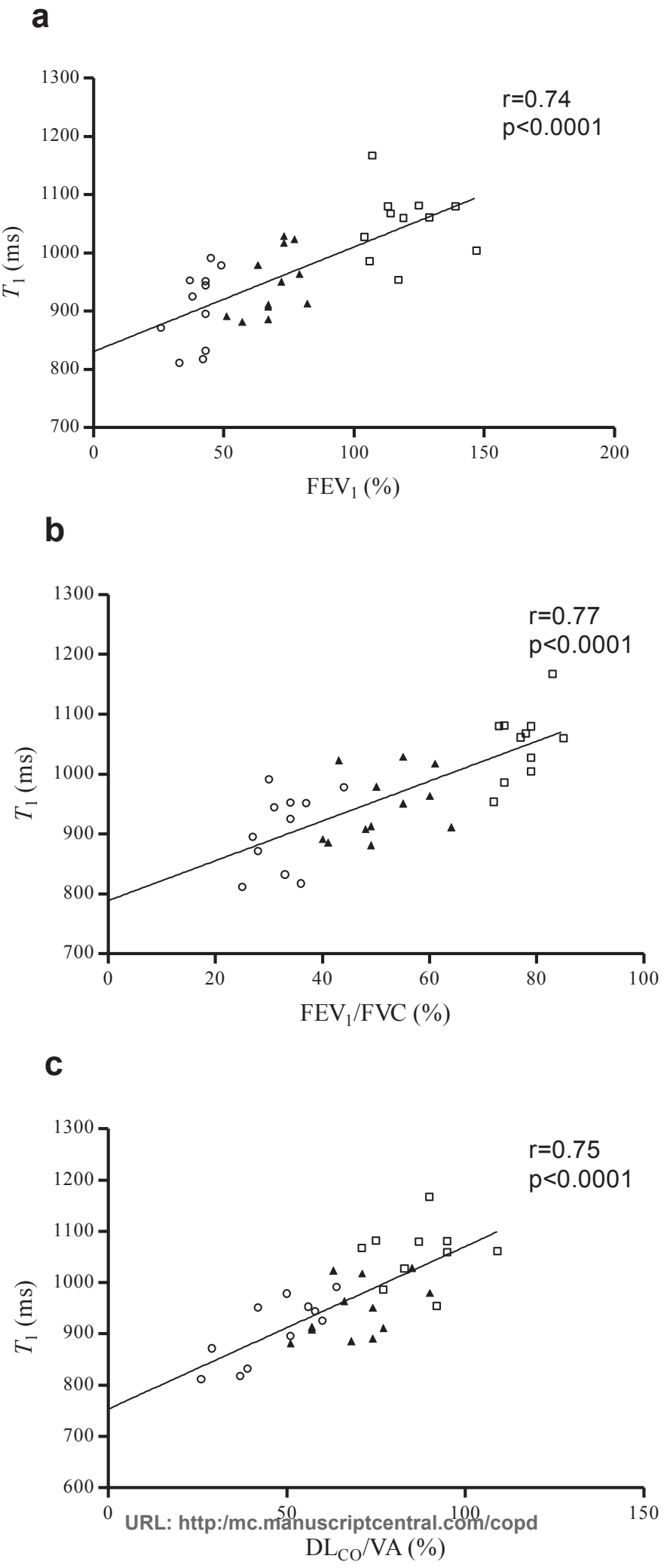
T_1 (ms)
PD_{15} (g/L)


a
r=0.74
p<0.0001
T_1 (ms)
FEV_1 (%)
b
r=0.77
p<0.0001
T_1 (ms)
FEV_1/FVC (%)
c
r=0.75
p<0.0001
T_1 (ms)
DL_{CO}/VA (%)