Echo Time-Dependent Observed Lung \( T_1 \) in Patients With Chronic Obstructive Pulmonary Disease in Correlation With Quantitative Imaging and Clinical Indices

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Abstract

Background: There is a clinical need for imaging-derived biomarkers for the management of chronic obstructive pulmonary disease (COPD). Observed pulmonary \( T_1(TE) \) depends on the echo-time (TE) and reflects regional pulmonary function.

Purpose: To investigate the potential diagnostic value of \( T_1(TE) \) for the assessment of lung disease in COPD patients by determining correlations with clinical parameters and quantitative CT.

Study Type: Prospective non-randomized diagnostic study.

Population: Thirty COPD patients (67.7 ± 6.6 years). Data from a previous study (15 healthy volunteers [26.2 ± 3.9 years]) were used as reference.

Field Strength/Sequence: Study participants were examined at 1.5 T using dynamic contrast-enhanced three-dimensional gradient echo keyhole perfusion sequence and a multi-echo inversion recovery two-dimensional UTE (ultra-short TE) sequence for \( T_1(TE) \) mapping at \( TE_{1-5} = 70 \mu \text{sec}, 500 \mu \text{sec}, 1200 \mu \text{sec}, 1650 \mu \text{sec}, \) and \( 2300 \mu \text{sec} \).

Assessment: Perfusion images were scored by three radiologists. \( T_1(TE) \) was automatically quantified. Computed tomography (CT) images were quantified in software (qCT). Clinical parameters including pulmonary function testing were also acquired.

Statistical Tests: Spearman rank correlation coefficients (\( \rho \)) were calculated between \( T_1(TE) \) and perfusion scores, clinical parameters and qCT. A \( P \)-value <0.05 was considered statistically significant.

Results: Median values were \( T_1(TE_{1-5}) = 644 ± 78 \mu \text{sec}, 835 ± 92 \mu \text{sec}, 835 ± 87 \mu \text{sec}, 831 ± 131 \mu \text{sec}, 893 ± 220 \mu \text{sec} \), all significantly shorter than previously reported in healthy subjects. A significant increase of \( T_1 \) was observed from \( TE_1 \) to \( TE_2 \), with no changes from \( TE_2 \) to \( TE_3 \) (\( P = 0.48 \)), \( TE_3 \) to \( TE_4 \) (\( P = 0.94 \)) or \( TE_4 \) to \( TE_5 \) (\( P = 0.02 \)) which demonstrates an increase at shorter TEs than in healthy subjects. Moderate to strong Spearman’s correlations between \( T_1 \) and parameters including the predicted diffusing capacity for carbon monoxide (DLCO, \( \rho < 0.70 \)), mean lung density (MLD, \( \rho < 0.72 \)) and the perfusion score (\( \rho > 0.69 \)) were found. Overall, correlations were strongest at \( TE_2 \), weaker at \( TE_1 \) and rarely significant at \( TE_4 \) to \( TE_5 \).

Received Mar 2, 2021, Accepted for publication May 12, 2021.

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Data Conclusion: In COPD patients, the increase of $T_1(TE)$ with TE occurred at shorter TEs than previously found in healthy subjects. Together with the lack of correlation between $T_1$ and clinical parameters of disease at longer TEs, this suggests that $T_1(TE)$ quantification in COPD patients requires shorter TEs. The TE-dependence of correlations implies that $T_1(TE)$ mapping might be developed further to provide diagnostic information beyond $T_1$ at a single TE.

Level of Evidence: 2
Technical Efficacy: Stage 1

The clinical assessment of chronic obstructive pulmonary disease (COPD) is traditionally based on clinical history, physical disability, and pulmonary function testing (PFT).\(^1\) X-ray imaging has primarily been used to rule out differential diagnosis, for example, heart failure, infectious complications (pneumonia, bronchopneumonia), and malignancy, but has only limited value for the further classification of COPD.\(^2\) Increasingly, computed tomography (CT) is used for the regional assessment of the extent and distribution of structural and functional lung alterations, such as emphysema, gas trapping, and airway remodeling.\(^3\)–\(^5\) Regarding the heterogeneity of disease manifestation with differentiated options for treatment in patients with different phenotypes of the disease, quantitative imaging-based biomarkers appear to play an increasingly important role for the assessment and monitoring of the disease beyond visual reading and descriptive radiologic reporting.\(^6\) MRI can provide both regional morphologic and functional assessment of the lungs without radiation exposure.\(^7\)–\(^9\) In current practice, dynamic contrast-enhanced (DCE) perfusion imaging is considered the most robust MR technology for assessing obstructive airway disease, reflecting the effect of hypoxic pulmonary vasoconstriction as a surrogate for lung ventilation.\(^10\)–\(^12\) In COPD it has been shown to correlate with the degree of emphysematous destruction as quantified with CT.\(^13\) However, DCE MRI visualizes lung pathology only indirectly and may fail to differentiate between perfusion deficits due to airway obstruction or emphysematous tissue loss.\(^7\) Furthermore, due to potential adverse events and the possibility of cerebral gadolinium deposition, a method without the need of intravenous contrast material is desirable. $T_1$ relaxation time maps may serve as an interesting alternative for this purpose. $T_1$ is a physical parameter that directly correlates with composition and state of lung tissue, including the blood volume fraction.\(^14\)–\(^15\) Shorter $T_1$ values have been observed in the lungs of patients with COPD compared to healthy volunteers.\(^15\)–\(^18\) This has led to further developments in $T_1$ mapping methods, including the inversion recovery radial multi-echo two-dimensional (2D) UTE (ultra-short TE) sequence used in this work.\(^19\) In a small sample of COPD patients, it has been shown that visual abnormalities on $T_1$ maps correlated well with perfusion deficits in DCE MRI.\(^15\) The study concluded that $T_1$ reflects the regional pulmonary blood pool and may contribute to the further differentiation of perfusion deficits demonstrated with DCE MRI. A further study revealed that the observed $T_1$ in the lungs depends on the echo time it is measured at.\(^20\) This is assumed to be due to the presence of essentially two separate compartments of protons in each voxel: firstly, intravascular protons in blood vessels, which exhibit a long $T_1$ and a very short $T_2^*$, due to the field inhomogeneities caused by lung structure, and secondly, extravascular protons in the tissue outside the blood vessels, such as alveolar walls, which have a shorter $T_1$ and an even shorter $T_2^*$. Accordingly, when measuring $T_1$ at ultra-short TE, both compartments contribute to the observed $T_1$ by their volume fraction, but as TE increases, $T_2^*$ weighting results in a signal loss of the extravascular components and a relative predominance of the signal from the intravascular compartment, that is, blood. Being physical parameters, $T_1$ and $T_1(TE)$ might provide objective quantitative biomarkers for the local characteristics of pulmonary disease independent of scanner type or observer.\(^21\) As such, it may have potential to provide an outcome measure for patient stratification and therapy monitoring in clinical trials, without the need for ionizing radiation and intravenous contrast materials.

Thus the aim of this study was to examine the TE-dependence of the correlations between $T_1(TE)$ and quantitative CT (qCT), DCE MRI and clinical indices in patients with COPD.

Materials and Methods

Patient Characteristics

A total of 30 participants of the German multicenter COPD cohort study COSYCONET (“COPD and SYstemic consequences-COmorbidities NETwork”, ClinicalTrials.gov Identifier: NCT01245933) were included\(^22\) by selecting those patients assigned to a specific study center. The overarching COSYCONET study as well as the part of the imaging-based sub-study (“Image-based structural and functional phenotyping of the COSYCONET cohort using MRI and CT [MR-COPD]”, ClinicalTrials.gov Identifier: NCT02629432) described here were approved by the responsible ethics committees of the coordinating centers (Institutional Review Board of the Medical Faculty of the University of University of Marburg [200/09] and of the University of Heidelberg [S-656/2012, Germany]). The participants of the present sub-study gave written informed consent to undergo extensive clinical assessment including lung function testing, noncontrast CT, and morpho-functional MRI. The patient characteristics are summarized in Table 1.
Clinical Assessment and Pulmonary Function Testing

Body plethysmography was conducted with the subject in a seated position (MasterScreen Body, E. Jaeger, Hoechberg, Germany) according to the guidelines of the European Respiratory Society and the standards of the American Thoracic Society (ATS), and the European Coal and Steel Community (ECSC) predicted values served as the standard of reference.\textsuperscript{23,24} PFT data collected included the predicted Forced Expiratory Volume in 1 second (FEV1pred%), forced vital capacity (FVC), the Tiffeneau index (FEV1/FVC), and diffusing capacity for carbon monoxide (DLCO pred%). Global initiative for chronic Obstructive Lung Disease stage (GOLD) and the smoking history (number of pack-years) were also noted. A full list of the examined parameters is given in Table S1 in the Supplemental Material.

Quantitative Chest Computed Tomography

Paired non-enhanced low-dose chest CT was acquired using a 64-detector row scanner (Somatom Definition AS64, Siemens Healthineers, Erlangen, Germany) in a standardized fashion in inspiratory and end-expiratory breath-hold with slice collimation 0.6 mm, pitch 0.75, tube voltage 120 kVp, tube current time product 35 mAs, and a total effective dose <3.5 mSv. Axial volumetric image reconstructions were performed using a smooth B30f convolution kernel at a slice thickness of 1.0 mm and a reconstruction interval of 0.5 mm. Dose modulation and iterative reconstruction were not applied. Inspiratory and expiratory CT images were analyzed automatically using YACTA (yet another CT analyzer).\textsuperscript{25-28} The qCT parameters mean lung density (MLD), emphysema index (EI %), lung volume (LV), and vessel volume (VV) were determined on the inspiratory CTs. MLD was the mean attenuation of all segmented lung voxels in Hounsfield units (HU) and EI% referred to the fraction of voxels in the lung where that attenuation was below ~950 HU.\textsuperscript{29} LV was the volume of the entire lung as segmented by YACTA, while VV was the volume of only the segmented intrapulmonary blood vessels. Furthermore, parametric response mapping (PRM)\textsuperscript{30} was performed, which allowed for the linkage of inspiratory and expiratory CT after deformable CT volume registration. Three PRM measures were derived as previously described: healthy tissue (PRM\textsuperscript{Horm}), functional small airways disease (PRM\textsuperscript{SAD}), and emphysema (PRM\textsuperscript{Emph}). YACTA also provided multiple measures of airways disease, of which the wall percentage, that is, the fraction of the airway cross section occupied by the walls was considered here. This value was averaged over the 5th to 8th generation of the segmented airways.

Chest Magnetic Resonance Imaging

Morpho-functional MRI was performed with a standardized protocol to the demands of the COPD study employing commercially available T\textsubscript{1}-weighted sequences before and after intravenous gadolinium-based contrast administration, T\textsubscript{2}-weighted sequences, and first-pass DCE perfusion imaging using a 1.5 T MR scanner (Magnetom Aera, Siemens Healthineers, Erlangen, Germany).\textsuperscript{9,11,12,31} DCE perfusion imaging at a time resolution of 1.7 seconds was obtained using 20 acquisitions of a three-dimensional (3D) gradient echo keyhole sequence with echo sharing (Time-resolved angiography With Stochastic Trajectories [TWIST]; Siemens Erlangen) and intravenous contrast injection of 2 mL gadobutrol 1.0 mmol/mL (Gadovist, Bayer, Leverkusen, Germany) using a power injector at a rate of 4 mL/second, followed by a 30 mL 0.9% NaCl chaser. Perfusion images were acquired in between 40 and 56 5 mm thick slices with 208 \times 256 matrix size over 365.63 \times 450 mm\textsuperscript{2} field of view. For this, TE = 0.76 msec and a flip angle of 20° were used.

For T\textsubscript{1}(TE) mapping, before contrast injection an inversion recovery multi-echo 2D ultra-short TE sequence was employed with five echo times TE\textsubscript{1-5} = 70 μsec, 500 μsec, 1200 μsec, 1650 μsec, and 2300 μsec as previously described (19,20), with TE\textsubscript{1} considered to be ultra-short. In 27 of 30 patients, two coronal 15 mm slices at a 128 \times 128 matrix in a 50 \times 50 cm\textsuperscript{2} field of view were acquired, while in the remaining patients, only one slice was acquired. The total acquisitions times were 8 min (2 slices) and 4 min (1 slice). The acquisition was based on golden angle-distributed radial spokes,\textsuperscript{32} which were reconstructed using a non-uniform Fourier transform implemented in MATLAB (Mathworks, Natick, USA)\textsuperscript{33}: A total of 6000 spokes were acquired during each measurement and then assigned to images through a sliding window 120 spokes wide and a step-width of 60 spokes. This resulted in 99 images per measurement and with TR = 5 msec, a time resolution of 32 msec over the inversion recovery. For the excitation, half-since pulses at a flip angle of 6° were used. T\textsubscript{1} maps were calculated from these images at each TE.\textsuperscript{34} Each measurement was acquired during free breathing and images were reconstructed from 50% of data assigned to expiration, as described previously, using the reconstruction parameters given by Triphan et al.\textsuperscript{19} Previously published data from 15 adult healthy volunteers (age range 23–35 years) scanned with an implementation of the same sequence acquired on a different 1.5 T scanner served as a standard of reference.\textsuperscript{20}

MR Image Assessment

MRI, including DCE perfusion MRI, was assessed independently by two readers (HM and CM, 5 years and 4 years of experience, respectively) using the chest MRI score as described previously,\textsuperscript{11,16,31,35,36} with conflicts between the readers being resolved by a third reader.

\begin{table}[h]
\centering
\caption{Patient Characteristics}
\begin{tabular}{|l|c|}
\hline
Sex distribution & 15 female, 15 male \\
Total no. of patients & 30 \\
Age (years) & 67.7 ± 6.6 (51.0–79.0) \\
Weight (kg) & 74.9 ± 14.7 (49.0–115.0) \\
Height (cm) & 169.2 ± 7.0 (154.0–181.0) \\
BMI (kg²/cm) & 26.6 ± 4.7 (19.7–39.1) \\
GOLD stage & 1.9 ± 1.3 (0–4) \\
FEV1 predicted % & 58% ± 19% (27%–110%) \\
\hline
\end{tabular}
\end{table}

Values are given as mean ± standard deviation with the range in brackets.
For $T_1(TE)$ quantification, lung segmentation masks were calculated automatically (for details, see the Supplemental Material) and used to determine median $T_1$ values at $TE_{1-5}$ and the median absolute differences (MAD) from that average. In patients where two slices were acquired, median values of the included volume were calculated. As a measure of the TE-dependence of $T_1$, the mean curvature $\kappa$ of $T_1(TE)$ was calculated from the first and second numerical derivative for all measurements.14

Defective lung areas were detected by comparing local $T_1(TE)$ to the overall median value found at the same TE. Voxels where $T_1(TE)$ was lower than the median minus half the standard deviation of $T_1$ at $TE_2$ (39 msec) were categorized as defects. Further, defect% was used to refer to the fraction of voxels relative to the entire segmented area that were considered defects.

Statistical Analysis
Data analysis was implemented in Python using SciPy.37 Paired Wilcoxon signed-rank tests were used to determine the significance of the differences in $T_1$ between echo times. The Bonferroni-Holm method was applied to compensate for the comparison at multiple echo times.

Correlations between $T_1$ at each TE with clinical metrics were examined by calculating Spearman’s $\rho$. Lung $T_1(TE)$ values published previously for 15 healthy adult volunteers were used as a reference.20 Three levels of statistical significance were considered: A $P$-value $<0.05$ was considered significant.

Results

**TE-Dependence of $T_1$ and Comparison to Healthy Volunteers**

The median values of $T_1$ were $T_1(TE_{1,5}) = 644 \pm 78$ msec, $835 \pm 92$ msec, $835 \pm 87$ msec, $831 \pm 131$ msec, and $893 \pm 220$ msec. These were all significantly shorter than the previously published median $T_1$ times at every TE in healthy volunteers previously published.20 $T_1$ significantly increased from the first echo at $TE_1 = 70 \mu$sec to all following echoes ($P < 0.05$), but did not differ significantly from $TE_2$ to $TE_5$ ($P = 0.48$), $TE_3$ to $TE_4$ ($P = 0.94$), or $TE_4$ to $TE_5$ ($P = 0.02$) (Fig. 1a–c). Compared to the previously reported healthy volunteers, observed $T_1$ increased with TE much more sharply at shorter TEs in the COPD patients. However, when considering the curvature $\kappa$ of $T_1(TE)$, the mean in COPD patients ($\kappa = -2.6 \times 10^{-5} \pm 2.6 \times 10^{-5}$) was not significantly different ($P = 0.51$) from that in healthy volunteers ($\kappa = -2.2 \times 10^{-5}$) (Fig. 1d). Upon visual assessment, several patients showed an inhomogeneous distribution of $T_1$ within the lung.

Overall, signal at the longest TE, that is, $TE_4$ and $TE_5$, was extremely low and thus local $T_1$ was severely distorted. A typical example is given in Fig. 2 showing representative $T_1(TE)$ maps with corresponding $M_0$ (proton density) maps from two COPD patients. Corresponding defect% maps are shown in Fig. 3, along with CT images with the segmented vessels and detected emphysema marked. Additional examples taken from patients with varying severity of disease are included in Fig. S2 in the Supplemental Material.

**Correlation Between $T_1(TE)$ and Clinical Indices**

**NON-IMAGING PARAMETERS.** Almost all correlations were strongest at $TE_2$ (Fig. 4), with few exceptions such as the moderate inverse correlation with the reported number of pack years, which showed minimal dependency on TE. Accordingly, example values of $\rho$ at $TE_2$ ($\rho_2$) are given here with the full results in Table 2. Median lung $T_1(TE)$ correlated moderately with FEV1 pred% ($\rho_2 = 0.49$, $P < 0.05$) and with FEV1/FVC ($\rho_2 = 0.51$, $P < 0.05$). Among the global, nonimaging parameters, DLCO pred% showed the strongest correlation ($\rho_2 = 0.70$, $P < 0.05$). In the Supplemental Material, correlations with all available parameters are given in Table S1 in the Supplemental Material as well as plots of $T1(TE)$ against several parameters in Fig. S1 in the Supplemental Material.

**Quantitative CT**
Overall, $T_1(TE)$ correlated moderately to strongly with the quantitative CT measures MLD ($\rho_2 = 0.72$, $P < 0.05$), PRM$^{Normal}$ ($\rho_2 = 0.69$, $P < 0.05$), EI% ($\rho_2 = -0.69$, $P < 0.05$), and VV/LV ($\rho_2 = 0.58$, $P < 0.05$). Notably, $T_1(TE)$ showed moderate inverse correlations with LV ($\rho_2 = -0.48$, $P < 0.05$), no significant correlations with absolute VV ($\rho_2 = 0.22$, $P = 0.25$) and the highest correlations with VV normalized to LV ($\rho_2 = -0.58$, $P < 0.05$). Correlations with PRM$^{SAD}$ ($\rho_2 = -0.58$, $P < 0.05$) and PRM$^{Emp}$ ($\rho_2 = -0.62$, $P < 0.05$) were weaker than with PRM$^{Normal}$ ($\rho_2 = -0.69$, $P < 0.05$). The airway measures including the wall percentage were not found to correlate with $T_1(TE)$ ($P = 0.38$). Finally, these correlations showed a similar dependence on TE as $T_1$ and were weaker at $TE_1$ than at longer TEs.

**DCE Perfusion Scores**
A strong inverse correlation was found between $T_1(TE)$ and the perfusion score ($\rho_2 = -0.69$, $P < 0.05$), which was similar at all TE. Finally, at $TE_1$ a weak correlation ($\rho_1 = -0.44$, $P = 0.016$) implying short $T_1$ at UTE coincides with the predominance of emphysema as determined by readers was found. However, this was not significant ($P_{2.5} = 0.065$, 0.065, 0.12, 0.18) at longer TEs.
Correlation of Defect% With Clinical/Image Indices

An overview of Spearman’s correlations between defect% derived from local T1 at each TE and several clinical indices is given in Table 3. Correlations with all tested parameters are given in Table S2 in the Supplemental Material.

Overall, defect% correlations were mostly similar to T1(TE) correlations, except for showing the opposite sign. However, they were generally slightly stronger, especially at UTE, thus reducing but not erasing the TE-dependency of the correlation. Notably, the correlation with VV/LV did not increase. In the correlation with the perfusion score, this led to a higher correlation at TE1 than at TE2.

Discussion

Compared to values previously reported in healthy volunteers,20 lung T1 values at all TEs in patients with COPD were shorter, as has been previously reported at a single, conventional TE(750 μsec) for COPD patients alone15 and in comparison to an age-matched control group.18 Similar to observations in healthy volunteers, T1(TE) was found to increase with TE in COPD patients, but this increase occurred only at the shortest echo times, from TE1 = 70 μsec to TE2 = 500 μsec. The TEs employed in this study had been successfully applied in healthy subjects and patients with cystic fibrosis.14,20 However, our results
suggest that the ideal set of TEs for sampling the dynamic range which contains relevant T1 changes should be chosen depending on the presence of suspected pathologies.

The T1 maps, as well as the disappearance of correlations at TE4 and TE5, demonstrated that it was no longer practical to quantify T1(TE) at TEs that were still feasible in healthy volunteers, most likely due to low signal-to-noise ratio. This might be due to the presence of emphysema causing a reduction of proton density or affecting local T2*.

A TE-dependence was visible in most of the investigated correlations with clinical and imaging biomarkers, to varying degrees: correlations of T1 with almost all parameters were weaker at TE1 than at TE2 with the strongest effect in the correlation of T1 with DLCO pred%. In contrast to this, the weak correlation of T1 with the predominance of emphysema was only significant at the shortest TE. Together, this implies that T1(TE) may contain additional diagnostic information beyond T1 quantified at a single TE.

Inverse correlations of T1(TE) with perfusion scores and EI% were found, while the correlations with FEV1/FVC, DLCO pred%, PRM\textsuperscript{Normal}, and VV/LV were positive. This is consistent with correlations between defect% and these indicators having the opposite sign. The moderate correlation between T1(TE) and LV was also negative, and likely reflects the tendency of lungs to overinflate in more severe disease.

As several of the indicators used for comparison describe a fraction of the lung volume, most notably EI%, the PRM parameters, and the perfusion scores, we used T1(TE) to calculate defect% as a means of automatic scoring in order to produce a measure that would be more directly comparable. Correlations of defect% with the other indicators notably showed a less pronounced TE-dependency than those of T1(TE), and were overall slightly stronger. For instance, MLD, which describes a local tissue attribute like T1(TE), showed overall roughly similar correlations to T1(TE) and defect%, while VV/LV, an estimate of the total blood volume fraction (including air), correlated better with T1(TE) than with defect%. It should be noted that the median T1(TE) that was used here to determine local defects was taken from the patient collective itself and is much lower than
The TE-dependence of $T_1(TE)$ is observed in this group at very short TEs, the TEs used here cannot sample this dynamic well. Measurements with a higher time-resolution at short TEs may be necessary to yield sufficient precision for the determination of curvature.

Finally, while strong correlations of $T_1(TE)$ with quantitative CT measures of emphysema and air-trapping as well as MR perfusion scores were found, no correlations were found with the biomarkers applied to larger airways (up to the eighth generation). This is consistent with the assumption that $T_1$ primarily reflects changes in the composition and perfusion of the lung parenchyma: the strongest correlations were those with qCT markers describing emphysema and vessels, perfusion MRI scores and DLCO. Due to hypoxic vasoconstriction, these are directly linked, while changes in larger airways would only affect very few voxels in $T_1(TE)$ maps.

| TE      | 70 μsec | 500 μsec | 1200 μsec | 1650 μsec | 2300 μsec |
|---------|---------|----------|-----------|-----------|-----------|
| Median $T_1$ | 644 ± 78 msec | 835 ± 92 msec | 835 ± 87 msec | 831 ± 131 msec | 893 ± 220 msec |
| MAD $T_1$  | 240 ± 147 msec | 203 ± 86 msec | 220 ± 70 msec | 282 ± 85 msec | 505 ± 134 msec |
| $\rho_1$ | $P_1$ | $\rho_2$ | $P_2$ | $\rho_3$ | $P_3$ | $\rho_4$ | $P_4$ | $\rho_5$ | $P_5$ |
| FEV1pred% | +0.35 | 0.054 | +0.49 | 0.006 | +0.40 | 0.030 | +0.24 | 0.208 | +0.15 | 0.444 |
| FEV1/FVC  | +0.46 | 0.010 | +0.53 | 0.002 | +0.49 | 0.007 | +0.35 | 0.061 | +0.25 | 0.190 |
| Pack years | −0.44 | 0.018 | −0.45 | 0.015 | −0.43 | 0.020 | −0.46 | 0.012 | −0.23 | 0.229 |
| DLCO pred% | +0.49 | 0.006 | +0.70 | <0.001 | +0.68 | <0.001 | +0.50 | 0.005 | +0.24 | 0.194 |
| MLD (Exp) | +0.57 | <0.001 | +0.72 | <0.001 | +0.65 | <0.001 | +0.59 | <0.001 | +0.28 | 0.141 |
| PRMNormal | +0.54 | 0.002 | +0.69 | <0.001 | +0.63 | <0.001 | +0.56 | 0.001 | +0.20 | 0.287 |
| PRMfSAD  | −0.45 | 0.012 | −0.58 | <0.001 | −0.49 | 0.006 | −0.52 | 0.003 | −0.22 | 0.241 |
| PRMEmph | −0.44 | 0.015 | −0.62 | <0.001 | −0.59 | <0.001 | −0.51 | 0.004 | −0.14 | 0.471 |
| EI%     | −0.54 | 0.002 | −0.69 | <0.001 | −0.66 | <0.001 | −0.56 | 0.001 | −0.22 | 0.235 |
| LV      | −0.38 | 0.037 | −0.48 | 0.007 | −0.38 | 0.039 | −0.40 | 0.028 | −0.25 | 0.179 |
| VV      | +0.11 | 0.562 | +0.22 | 0.248 | +0.23 | 0.212 | +0.28 | 0.136 | +0.18 | 0.336 |
| VV/LV   | +0.45 | 0.012 | +0.58 | <0.001 | +0.58 | <0.001 | +0.57 | 0.001 | +0.43 | 0.017 |
| Wall percent | −0.18 | 0.377 | −0.04 | 0.835 | −0.11 | 0.596 | +0.01 | 0.971 | −0.19 | 0.348 |
| MR Perfusion | −0.54 | 0.002 | −0.69 | <0.001 | −0.58 | <0.001 | −0.57 | 0.001 | −0.30 | 0.111 |
| Predominance | −0.44 | 0.016 | −0.30 | 0.112 | −0.34 | 0.064 | −0.24 | 0.196 | −0.21 | 0.261 |

Shown parameters are: median absolute difference (MAD), predicted forced expiratory volume in 1 second (FEV1pred%), Tiffeneau Index (FEV1/FVC), Global initiative for chronic Obstructive Lung Disease stage (GOLD), number of pack-years, Diffusing capacity of the Lung for Carbon monOxide (DLCO), Mean Lung Density (MLD), Parametric Response Map Normal tissue (PRMNormal), PRM function Small Airways Disease (PRMfSAD), PRM Emphysema (PRMEmph), Emphysema Index (EI%), Lung Volume (LV), Vessel Volume (VV), percentage fraction of airway walls to total cross section (wall percent), MR Perfusion Score and predominance of emphysema phenotype as determined by readers from MRI.
directly. In general, $T_1$ measurements appear to be a useful biomarker of pulmonary disease reflecting both persistent lung destruction (emphysema) as well as functional impairment due to airway disease, covering a similar spectrum of pathologies compared to DCE MRI measurements. Due to ambiguity, it might be worthwhile to develop a simplified model which could compensate for this and separate diagnostically useful information, while still describing the underlying physiology.

**Limitations**

An essential limitation of the $T_1(TE)$ measurements discussed here is that the acquisitions cover only two (and in three patients, only one) central slices of the lungs. Since the CT and DCE MRI measurements cover the entire lungs, more comprehensive local comparisons could be made using $T_1(TE)$ maps with full lung coverage. Notably, COPD also affects the lungs in an inhomogenous matter and thus itself likely leads to inhomogenous distribution of $T_1(TE)$ as well as the undisturbed (M0) and equilib-rium magnetization (M0*) in each. Since this model has eight parameters it is not well suited to produce parameter maps due to ambiguity. It might be worthwhile to develop a simplified model which could compensate for this and separate diagnostically useful information, while still describing the underlying physiology.

**Table 3. Spearman’s $\rho$ and $P$ values Between Defect% at Each TE and Clinical Parameters**

| TE     | 70 μsec | 500 μsec | 1200 μsec | 1650 μsec | 2300 μsec |
|--------|---------|----------|-----------|-----------|-----------|
| Defect%| 36%     | ±26%     | 37%       | ±20%      | 37%       | ±16%      | 40%       | ±17%      | 45%       | ±13%      |

|        | $\rho_1$ | $P_1$ | $\rho_2$ | $P_2$ | $\rho_3$ | $P_3$ | $\rho_4$ | $P_4$ | $\rho_5$ | $P_5$ |
|--------|----------|-------|----------|-------|----------|-------|----------|-------|----------|-------|
| FEV1pred%| -0.40   | 0.028 | -0.41   | 0.023 | -0.46   | 0.011 | -0.31    | 0.101 | -0.17    | 0.376 |
| FEV1/FVC| -0.50   | 0.005 | -0.52   | 0.003 | -0.55   | 0.002 | -0.40    | 0.027 | -0.29    | 0.120 |
| Pack years| +0.42   | 0.022 | +0.44   | 0.016 | +0.40   | 0.030 | +0.44    | 0.017 | +0.27    | 0.152 |
| DLCO pred%| -0.51   | 0.004 | -0.69   | <0.001| -0.72   | <0.001| -0.59    | <0.001| -0.27    | 0.142 |
| MLD (Exp)| -0.60   | <0.001| -0.71   | <0.001| -0.67   | <0.001| -0.64    | <0.001| -0.31    | 0.093 |
| PRMNormal| -0.58   | <0.001| -0.69   | <0.001| -0.67   | <0.001| -0.63    | <0.001| -0.24    | 0.200 |
| PRM(SAD)| +0.47   | 0.010 | +0.53   | 0.003 | +0.53   | 0.003 | +0.53    | 0.002 | +0.29    | 0.125 |
| PRM(Emph)| +0.49   | 0.006 | +0.66   | <0.001| +0.62   | <0.001| +0.58    | <0.001| +0.13    | 0.490 |
| EI%     | +0.59   | <0.001| +0.71   | <0.001| +0.68   | <0.001| +0.64    | <0.001| +0.23    | 0.230 |
| LV      | +0.46   | 0.010 | +0.50   | 0.004 | +0.39   | 0.034 | +0.42    | 0.020 | +0.23    | 0.217 |
| VV      | -0.06   | 0.737 | -0.16   | 0.389 | -0.20   | 0.295 | -0.22    | 0.234 | -0.21    | 0.274 |
| VV/LV   | -0.45   | 0.012 | -0.54   | 0.002 | -0.53   | 0.003 | -0.56    | 0.001 | -0.44    | 0.014 |
| Wall percent| +0.13  | 0.518 | -0.04   | 0.854 | +0.09   | 0.672 | +0.04    | 0.830 | +0.14    | 0.471 |
| MR perfusion| +0.60  | <0.001| +0.65   | <0.001| +0.61   | <0.001| +0.61    | <0.001| +0.32    | 0.084 |
| MR Pred/Emph| +0.46 | 0.011 | +0.34   | 0.064 | +0.34   | 0.064 | +0.29    | 0.122 | +0.25    | 0.182 |

Shown parameters are: predicted forced expiratory volume in 1 second (FEV1pred%), Tiffeneau Index (FEV1/FVC), Global initiative for chronic Obstructive Lung Disease stage (GOLD), number of pack-years, diffusing capacity of the lung for carbon monoxide (DLCO), mean lung density (MLD), parametric response map normal tissue (PRM(normal)), PRM function small airways disease (PRM(SAD)), PRM emphysema (PRM(Emph)), Emphysema Index (EI%), lung volume (LV), vessel volume (VV), percentage fraction of airway walls to total cross section (wall percent), MR perfusion score and predominance of emphysema phenotype as determined by readers from MRI.
improvements on the measurement technique before applying it in a larger cohort. This should then also include investigating $T_1$ at multiple TEs in an age-matched control group, noting that $T_1$ has been shown to depend on age and sex. However, this showed that this primarily showed longer $T_1$ in younger women with the disparity due to sex decreasing with age and no notable age dependency in males.

**Clinical Perspective**

The evaluation of the presented method is at a very early stage. However, in the context of COPD, methods for the regional analysis of lung function deficits are sought for, with the perspective of more precise diagnosis and follow-up of disease activity and related lung damage for research and individualized therapy. In particular standard, global lung function tests fail to cover regional changes, which defines the need for appropriate functional imaging. Although the underlying mechanisms of the echo-time dependence of observed $T_1$ due to the influence of tissue compartments are still subject to discussion, the current work supports the hypothesis that this effect is a possible candidate as a diagnostic tool for multi-parametric, compartment-selective imaging of regional lung function. As the detected defects correlate well with results from DCE MRI, $T_1$ alone might at least serve as a non-contrast enhanced tool for the analysis of lung perfusion, while also providing the possibility of platform- and observer-independent quantitative evaluation. This encourages further research to analyze the diagnostic scope of this approach, with the perspective that TE dynamics might differentiate lung parenchyma even beyond the scope of an alternative to DCE MRI. In a way this potential can be seen analogous to PRM providing a refinement to the emphysema detection (i.e. EI%) in qCT by further differentiating voxels into a permanent component from emphysematous destruction and a variable, reversible component of air trapping from obstructive bronchiolitis.

**Conclusion**

Compared to healthy volunteers, $T_1$(TE) in the lungs of COPD patients was shorter at all TE with an increase of $T_1$ occurring only at very short TEs. Moderate to strong correlations of $T_1$(TE) and defect% derived from $T_1$(TE) with clinical indices, especially qCT and perfusion MR scores, were found and showed similar TE-dependences. These correlations disappeared at the longest examined TEs, suggesting that the ideal set of TEs for $T_1$(TE) quantification in patients may depend on the presence of pathologies in the parenchyma. Slightly stronger correlations and weaker TE-dependencies of defect% with clinical indicators suggest that it is at least possible to extract additional, potentially useful parameters from $T_1$(TE) measurements. Further research on this topic may eventually lead to the development of methods that provide diagnostic information beyond $T_1$ at single TEs, while also providing quantitative functional information without the need for contrast agents or evaluation by radiologist readers.

**Acknowledgments**

This study was supported by the Competence Network on Asthma/COPD (ASCONET) through a grant from the Federal Ministry of Education and Research (Bundesministerium för Bildung und Forschung, BMBF) of the Federal Government of Germany (01GI0884, http://www.gesundheitsforschung-bmbf.de/en/4214.php). Contrast medium for MRI was sponsored by Bayer Vital GmbH, Leverkusen, Germany. The funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Open Access funding enabled and organized by Projekt DEAL.

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