Background: Noninvasive monitoring of early abnormalities and therapeutic intervention in cystic fibrosis (CF) lung disease using MRI is important. Lung T1 mapping has shown potential for local functional imaging without contrast material. Recently, it was discovered that observed lung T1 depends on the measurement echo time (TE).

Purpose: To examine TE-dependence of observed T1 in patients with CF and its correlation with clinical metrics.

Study Type: Prospective.

Population: In all, 75 pediatric patients with CF (8.6 ± 6.1 years, range 0.1–23 years), with 32 reexamined after 1 year.

Field Strength/Sequence: Patients were examined at 1.5T using an established MRI protocol and a multiecho inversion recovery 2D ultrashort echo time (UTE) sequence for T1(TE) mapping at five TEs including TE1 = 70 μs.

Assessment: Morphological and perfusion MRI were assessed by a radiologist (M.W.) with 11 years of experience using an established CF-MRI scoring system. T1(TE) was quantified automatically. Clinical data including spirometry (FEV1pred%) and lung clearance index (LCI) were collected.

Statistical Tests: T1(TE) was correlated with the CF-MRI score, clinical data, and LCI.

Results: T1(TE) showed a different curvature in CF than in healthy adults: T1 at TE1 was shorter in CF (1157 ms ± 73 ms vs. 1047 ms ± 70 ms, P < 0.001), but longer at TE3 (1214 ms ± 72 ms vs. 1314 ms ± 68 ms, P < 0.001) and later TEs. The correlations of T1(TE) with patient age (ρTE1-TE5 = −0.55, −0.44, −0.24, −0.30, −0.22), and LCI (ρTE1-TE5 = −0.43, −0.42, −0.33, 0.27, −0.22) were moderate at ultra-short to short TE (P < 0.001) but decreased for longer TE. Moderate but similar correlations at all TE were found with MRI perfusion score (ρTE1-TE5 = −0.43, −0.51, −0.47, −0.46, −0.44) and FEV1pred% (ρTE1-TE5 = +0.44, +0.44, +0.43, +0.40, +0.39) (P < 0.05).

Data Conclusion: TE should be considered when measuring lung T1, since observed differences between CF and healthy subjects strongly depend on TE. The different variation of correlation coefficients with TE for structural vs. functional metrics implies that TE-dependence holds additional information which may help to discern effects of tissue structural abnormalities and abnormal perfusion.

Level of Evidence: 2
Technical Efficacy Stage: 1
CHRONIC PROGRESSIVE LUNG DISEASE dominates morbidity and mortality in patients with cystic fibrosis (CF). Early diagnosis together with recent improvements in therapy and preventive therapy strategies require the development of novel sensitive endpoints in order to monitor disease activity, even when spirometry shows normal lung function. Cross-sectional imaging using computed tomography (CT) and magnetic resonance imaging (MRI) has demonstrated that CF lung disease manifests early after birth, with detectable structural and functional lung impairment, even in the absence of clinical symptoms including individuals identified by new-born screening. Perfusion MRI is often part of MRI protocols, as perfusion abnormalities linked to airway obstruction by hypoxic pulmonary vasoconstriction may be detected in parts of the lung even without morphologically detectable disease. Other non-contrast functional proton MRI methods have been explored recently, which rely on exploiting the intrinsic properties of MRI signal related to tissue composition and perfusion, including Fourier decomposition MRI and T1 mapping. Such quantitative methods have the advantage of deriving measures of tissue properties that are independent of scanner type and observer. Lung T1 relaxation specifically is determined by the local environment of protons in tissue and capillary blood, which may be present in varying fractions inside a given imaging voxel. Previously, shortened T1 was observed in adults with chronic obstructive pulmonary disease (COPD) and adults with CF when measured at conventional echo times (TEs). T1 was also found to correlate with the Global initiative for chronic Obstructive Lung Disease (GOLD) stage and lung perfusion abnormalities in COPD, and with spirometry and perfusion abnormalities in adults with CF. Based on these studies, improvements in sequence technique were recently introduced which allow for lung T1 mapping at ultrashort echo times (UTEs) during free breathing and at multiple TEs. Using this method, observed lung T1, or T1(TE), was shown to depend on the measurement of TE in healthy volunteers. It was hypothesized that this effect may hold the potential to differentiate the influence of tissue composition from blood volume fraction on T1 inside each imaging voxel on a scale smaller than the MRI resolution itself. The aim of the present study was to determine if this TE dependence on lung T1 contains information beyond base T1 at a single TE. This was investigated in CF patients across the pediatric age range (infant to adult), who would particularly profit from free-breathing, contrast agent-free methods, using a previously established morphofunctional MRI protocol and CF-MRI scoring system as well as lung function testing with spirometry and multiple breath washout as references for disease severity.

Materials and Methods

Subjects

This prospective cross-sectional study (clinicaltrials.gov identifier NCT00760071 & NCT02270476) was approved by the institutional Ethics Committee, and informed written consent was obtained from all subjects or their parents or legal guardians. Infants, preschool, and school-age children, adolescents, and adults with CF were recruited between 2015 and 2016 during annual routine examinations including surveillance MRI in stable clinical condition. Patients who were reexamined approximately 1 year later were included. Diagnosis of CF was confirmed by increased sweat Cl− concentrations (≥60 mmol/L), CF transmembrane conductance regulator (CFTR) mutation analysis (Table 1), and in pancreatic sufficient patients with borderline sweat test results (sweat Cl− between

| TABLE 1. Demographics of Cystic Fibrosis Patients |
|-----------------------------------------------|
| n    | 75 |
| Sex  | 36 f, 40 m |
| Age mean ± SD (range) [years] | 8.6 ± 6.1 (0.1–23.2) |
| Weight mean ± SD (range) [kg] | 30 ± 19 (3–80) |
| Weight mean SDS ± SD (range) | −0.49 ± 0.91 (−3.0 to 1.7) |
| Height mean ± SD (range) [cm] | 125 ± 36 (53–195) |
| Height mean SDS ± SD (range) | −0.4 ± 1.4 (−2.8 to 3.5) |
| BMI mean ± SD (range) [kg²/cm²] | 16.8 ± 2.7 (11.8–24.6) |
| BMI mean SDS ± SD (range) | −0.4 ± 1.0 (−4.0 to 1.7) |
| Pseudomonas aeruginosa-positive | 9 (12%) |

SDS = standard deviation scores for anthropomorphic data in relation to the average German population; BMI = body mass index; Pseudomonas-positive is defined as chronic colonization with Pseudomonas aeruginosa with positive antibody status.
30 and 60 mmol/L) by assessment of CFTR function in rectal biopsies according to established diagnostic criteria.20

**Lung Function Testing**

Spirometry was performed routinely in cooperative patients able to perform reproducible tests to derive forced expiratory volume in 1 second in % predicted (FEV1pred%), as well as the functional residual capacity (FRC).21 Multiple breath washout (MBW) measurements were performed in an age-dependent manner to determine the lung clearance index (LCI).8,22 Depending on age and necessity of sedation, LCI was measured using SF6 as the tracer gas or N2 without or with sedation. To compensate for this, LCI values were converted to z-scores by comparing them to an institutional reference cohort.23 Further details are provided in the online data supplement.

**Chest MRI**

T1-weighted sequences before and after intravenous contrast, T2-weighted sequences and first-pass 4D perfusion imaging were acquired using a clinical 1.5T MR scanner (Magnetom Avanto, Siemens, Erlangen, Germany).7,9,12 The imaging parameters used for patients aged up to 6 years of age and for those older are given in Tables S4 and S5 in the supplement, respectively. 4D perfusion imaging was performed using time-resolved angiography with stochastic trajectories (TWIST) with contrast injection of 0.1 mmol/kg body weight Gd-DOTA (Dotarem, Guerbet, Villepinte, France) using a power injector at a rate of 2 mL/s, followed by a 30-mL 0.9% NaCl chaser. In total, 35 3D volumes were acquired at a time resolution of 0.8 seconds.

For T1(TE) mapping, an inversion recovery multiecho 2D UTE sequence was employed (Fig. 1): In 2D UTE, each radial spoke is measured twice using identical half-sinc pulses and slice select gradients with opposite signs to allow for signal acquisition immediately after the excitation pulse.24 Only the downramp of the slice select gradient needs to be phased. By then starting the acquisition on the ramp of the frequency encoding gradient, echo times as short as TE = 70 μs are possible. Since this requires sampling during gradient ramps, which in this case differ from their theoretical shape, the actual gradient shapes (the k-space trajectory) were measured beforehand and used for the reconstruction of all 2D UTE images in this work. However, this 2D UTE approach also limits the acquisition to one slice at a time. Accordingly, one slice concurrent with the descending aorta to maximize parenchymal area was measured per patient.

T1 quantification was based on the Look–Locker sequence: After a global adiabatic inversion pulse, 300 radial spokes at repetition time (TR) = 5 ms were acquired, followed by a delay of 3 seconds to allow for free T1 relaxation before the next inversion. Twenty inversions in total were acquired during each measurement. Each radial spoke was acquired as a monopolar gradient echo: At each TE, the signal was read out starting with the ramp of the frequency encoding gradient and then phased using maximum gradient strength before acquiring the next echo. The radial spokes were encoded such that after sorting by inversion time, the angular increment was 222.5°, the golden angle.26 After sorting, images were reconstructed using a sliding window and a nonuniform Fourier transform implemented in MatLab (MathWorks, Natick, MA).27 For each image, 120 projections were used, reconstructing images 60

**FIGURE 1:** (a) Pulse program for the 2D UTE sequence. For each spoke, slice select gradients were run with opposite signs. Due to the RF half-pulse, only the falling ramp (hatched area) required rephasing. Spokes were acquired with identical k-space sampling for each echo with rephasers for each readout gradient. (b) For T1 quantification, a series of inversion blocks consisting of an inversion pulse, n radial projections, and delay τ were applied. Each spoke shown corresponds to two applications of a half-pulse with opposing slice select gradients. Adapted from Ref. 19.
projections apart, corresponding to a time resolution of 32 ms and 99 images in total. To achieve a higher temporal resolution for TE, each patient was examined in the same slice using two separate measurements as described above with interleaved echoes: The first covered TE1 = 70 μs, TE3 = 1200 μs, and TE5 = 2300 μs, and the second TE2 = 500 μs and TE4 = 1650 μs. These were reconstructed individually and then combined to provide T1(TE1-5). This results in a total acquisition time of 4 minutes for the 2D UTE, amounting to a total of 30 minutes examination time including the routine morphofunctional protocol. From these image series, M0 (the undisturbed magnetization), M0* (the equilibrium magnetization), and T1* (the effective longitudinal relaxation time) maps were generated using an exponential fit of M(TI) = M0*(M0 + M0*)e−TI/T1*. From this, T1 maps were calculated by T1 = M0/M0*.T1* for each voxel and each TE.28 Compensation for respiratory motion was performed as described previously, using the reconstruction parameters given before,19 gating to use the 50% of acquired data that was assigned to expiration.

Children younger than 6 years were routinely sedated with oral or rectal chloral hydrate (100 mg/kg body weight, maximum dose of 2 g) and monitored by MRI-compatible pulse oximetry.7,8,22 Since no age-matched controls were available, 15 adult healthy volunteers (age range 23–33 years) scanned with the same T1(TE) sequence and on an identical scanner served as a previously published standard of reference.17

Image Assessment
A senior chest radiologist (M.W.) with 11 years of experience evaluated all routine sequences employing the well-evaluated morphofunctional CF MRI score,7,9 blinded to the results of T1(TE) mapping and lung function testing: Abnormalities in each lobe were rated as 0, 1 (<50% of the lobe), or 2 (≥50%) for a maximum perfusion score of 12 and morphology score of 60. The radiologist had previously acted as the single observer in multiple published studies8,12,22,29,30 as well as in studies together with other observers,7,9,31,32 including testing of the interobserver reliability of the CF MRI score.

For the quantification of T1(TE), lung segmentation masks were obtained on 2D UTE slices using threshold-based region-growing (see the online supplement for details). Median T1 values at each TE and the median absolute differences (MAD) to that average were determined using these segmentation masks. These values are given in the tables and all tests were performed on these values. As a measure of the TE-dependence of T1, the mean curvature κ = T1(TE)*/(1 + T1(TE)^2)^3/2 was calculated from the first (T1*) and second (T1***) numerical derivative for all measurements. T1(TE) maps were also automatically scored for relative defect area (defect %) by comparing local values to a linear regression with age, weight, size, and gender as detailed in the online data supplement.

Statistical Analysis
Data were analyzed using SciPy.33 The difference in T1 between TE1,5 was examined using Wilcoxon signed-rank tests. Spearman’s ρ and corresponding P-values for the correlation between T1(TE) and clinical metrics were calculated. Lung T1(TE) values measured in 15 healthy adult volunteers taken from an institutional database as published previously were used for comparison.17 Three levels of statistical significance were considered: P < 0.05 was considered significant, with P < 0.01 and P < 0.001 as levels of higher significance. Further details are provided in the online data supplement.

Results

Patient Recruitment
In all, 75 patients were included (Table 1, Table S1 in the supplement), with 32 reexamined after 379 ± 104 days. In 56 patients, the diagnosis of CF was based on clinical symptoms and 19 patients were identified by new-born screening.34 LCI was measured using SF6 as the tracer gas in n = 13 patients, using N2 without sedation in n = 45, and using N2 with sedation in n = 16.

Representative T1(TE) maps for two patients are shown in Fig. 2, displaying shorter T1 in areas with reduced perfusion and increased mucus deposition. The corresponding defect maps from automated scoring in Fig. 3 demonstrate the delineation of these areas.

FIGURE 2: Representative proton density (M0) and T1 maps as well as 4D perfusion images of corresponding slices of two cystic fibrosis patients aged 9 (upper row) and 14 years (lower row). Note the matching inhomogeneities seen both in the T1 maps and the abnormalities in the accompanying perfusion images. Overall, lung areas with reduced or delayed perfusion (white arrows) or visible mucus tend to show shorter T1 times at all TEs.
T1(TE) in CF patients examined here was found to increase with longer TE (Fig. 4a). The increase in T1 from TE1 to TE2 was not significant (P = 0.53), but from TE1 to TE3, TE4 and to TE5 all were significant (P < 0.001). This was a different dependency than what was observed in healthy volunteers previously (Fig. 4b): The median T1 for patients measured at ultrashort TE1 was significantly higher compared to healthy adult volunteers (P < 0.001) (Fig. 4c). However, at intermediate TE, T1(TE2-4) was shorter in patients (P < 0.01–0.001). Finally, at TE5 there was no significant difference (P = 0.15). While T1 varied substantially among

**FIGURE 3:** Automated scoring of regions with abnormal T1(TE). Automatically determined defects based on thresholds for abnormal T1(TE) are displayed using a green lookup table, normal lung using red. Patients are the same as shown in Fig. 2. The defects visible on T1(TE) maps and perfusion MRI images in Fig. 2 are clearly delineated.

**FIGURE 4:** Propagation of T1 with increasing echo time in CF and healthy volunteers. (a,b) Median T1(TE) in the lungs of CF patients and healthy volunteers, the latter taken from Ref. 17. (c) The same data as in a,b, shown as a boxplot showing medians and the 1st and 3rd quartiles, whiskers indicating 2nd and 98th percentile for CF as well as the means in each group. (d) Histogram of the curvature κ of T1(TE) in CF patients. The mean curvature found in the data from c is indicated by vertical lines.
individual subjects, the dependency of $T_1$ on TE appears to be fairly similar. Mean values and the standard deviation indicating interpatient variance along with the MAD reflecting intrapatient variance are given in Table 2.

$T_1$ in adult volunteers$^{17}$ exhibited a downward curve approaching a maximum towards longer TEs, with a mean curvature of $\kappa = -2.25 \times 10^{-5}$. In contrast, in CF $T_1(TE)$ showed an upward curve with an increasing slope towards longer TE and a significantly different $\kappa = 9.92 \times 10^{-5}$ ($P < 0.001$) (Fig. 4d).

**Correlation of $T_1$(TE) With Clinical Metrics**

The strongest overall correlation was found between $T_1$ at TE$_1$ and patient age ($\rho = -0.55$). This correlation decreased towards TE$_X$ ($\rho = -0.22$, Table 3, Fig. 5a). A similar decrease was also observed with FRC ($\rho = -0.54$ to $\rho = -0.10$), and, to a lesser degree, with LCI ($\rho = -0.43$ to $\rho = -0.22$). In contrast, the correlation of $T_1$ with FEV1pred% was found to be moderate but of similar strength at all TEs (between $\rho = +0.44$ and $\rho = +0.39$). When using automated scoring, defect% did not show a correlation with age or FRC at any TE, indicating that defect% is effectively corrected for age (Table 4, Fig. 5b), since it is determined by comparison to a linear regression. However, a correlation between defect% and LCI remained and still showed a slight decrease with TE. For FEV1pred%, correlation with defect% was slightly weaker than with $T_1$, and remained TE-independent.

Finally, the correlation of $T_1$ with LCI decreased only slightly with TE and remained correlated when using defect%. Other metrics are not shown here since they displayed similar behavior, but are given in the online supplement, along with explicit $P$-values (Supplemental Table S2).

**TABLE 2. $T_1$(TE), CF MRI Score, as Well as FEV1pred% and LCI in Cystic Fibrosis (CF) Patients**

|                | All patients | Repeat study | MRI1 | MRI2 | MRI1 vs. MRI2 |
|----------------|--------------|--------------|------|------|--------------|
|                |              |              | Relative change (%) | $P$  |
| $T_1$(70 $\mu$s) |              |              |                  |      |
| $n$            | 75           | 32           | 32               |      |
| Mean $\pm$ SD [ms] | 1157 $\pm$ 73 | 1170 $\pm$ 77 | 1156 $\pm$ 64 | -1.2 | 0.09         |
| Defect% $\pm$ SD | 32 $\pm$ 22  | 30 $\pm$ 22  | 31 $\pm$ 20     | +5.6 | 0.37         |
| $T_1$(500 $\mu$s) |              |              |                  |      |
| Mean $\pm$ SD [ms] | 1157 $\pm$ 68 | 1166 $\pm$ 74 | 1164 $\pm$ 66 | -0.1 | 0.82         |
| Defect% $\pm$ SD | 35 $\pm$ 19  | 35 $\pm$ 19  | 31 $\pm$ 21     | -11  | 0.27         |
| $T_1$(1200 $\mu$s) |             |              |                  |      |
| Mean $\pm$ SD [ms] | 1210 $\pm$ 72 | 1210 $\pm$ 76 | 1227 $\pm$ 55 | +1.4 | 0.26         |
| Defect% $\pm$ SD | 38 $\pm$ 21  | 39 $\pm$ 24  | 32 $\pm$ 18     | -20  | 0.12         |
| $T_1$(1650 $\mu$s) |             |              |                  |      |
| Mean $\pm$ SD [ms] | 1242 $\pm$ 71 | 1242 $\pm$ 78 | 1254 $\pm$ 65 | +1.0 | 0.43         |
| Defect% $\pm$ SD | 39 $\pm$ 18  | 41 $\pm$ 21  | 33 $\pm$ 18     | -19  | 0.06         |
| $T_1$(2300 $\mu$s) |             |              |                  |      |
| Mean $\pm$ SD [ms] | 1344 $\pm$ 83 | 1335 $\pm$ 93 | 1358 $\pm$ 63 | +1.7 | 0.14         |
| Defect% $\pm$ SD | 41 $\pm$ 18  | 43 $\pm$ 21  | 37 $\pm$ 14     | -15  | 0.11         |
| Morphology      |              |              |                  |      |
| Mean score $\pm$ SD | 9.1 $\pm$ 5.7 | 8.8 $\pm$ 5.2 | 10.5 $\pm$ 6.1 | +18.7| 0.01         |
| Perfusion       |              |              |                  |      |
| Prevalence $n$ (%) | 63(84)       | 25(78)       | 26(81)           | +4.0 | 0.32         |
| Mean score $\pm$ SD | 4.7 $\pm$ 2.8 | 4.8 $\pm$ 2.7 | 5.0 $\pm$ 2.8   | +4.7 | 0.58         |
| Global          |              |              |                  |      |
| Mean score $\pm$ SD | 13.4 $\pm$ 8.4 | 12.9 $\pm$ 8.0 | 15.0 $\pm$ 8.8 | +16.3| 0.03         |
| FEV1 pred%      |              |              |                  |      |
| $n$            | 57           | 18           | 18               |      |
| Mean $\pm$ SD   | 85.0 $\pm$ 21.3 | 81.3 $\pm$ 25.0 | 78.9 $\pm$ 22.2 | -2.9 | 0.59         |
| LCI             |              |              |                  |      |
| $n$            | 67           | 26           | 26               |      |
| Mean $\pm$ SD   | 5.3 $\pm$ 5.7 | 5.5 $\pm$ 6.8 | 3.9 $\pm$ 3.9   | -28.9| 0.38         |

Mean values are given for 75 CF patients, and further, for a subset of 32 patients examined twice within approximately 1 year. For $T_1$(TE), the mean of the median absolute differences (MAD) to median $T_1$ is given as a measure of intrapatient variability. The relative differences between these longitudinal measurements and applicable $P$-values are indicated. Note that FEV1pred% and LCI were not available for all patients.
Correlation of T1(TE) With the CF-MRI Score

Confi

rming the major contribution of lung perfusion to T1(TE), the strongest correlations were found between T1(TE) and the MRI perfusion score (between $\rho = -0.51$ and $\rho = -0.43$), with weaker correlations with the global and weakest with the morphology score, respectively (Table 3). These correlations were strongest at intermediate TE (TE2 and TE3), but while the correlation to the perfusion score was similar at all TEs, the correlation to the other scores decreased with longer TE (Fig. 4). Analogous inverse correlations were found for defect% (Table 4, Fig. 5b).

While the correlations of T1 with age, MRI score, FRC, and LCI were inverse, FEV1pred% was positively correlated with T1(TE). This is consistent with all observed correlations with defect% having the opposite orientation.

Longitudinal T1(TE) Mapping in Patients With CF

Thirty-two patients with CF were measured twice adjunct to their annual surveillance MRI in order to compare variability of T1(TE) with the variability in lung function and CF MRI score (Table 2). No statistically significant differences in T1(TE) were found. The mean difference found in T1(TE) was on average 17 $\pm$ 59 ms ($P = 0.052$) at TE1, whereas it was negative at longer TEs, for example $-20 \pm 85$ ms at TE5 ($P = 0.20$). Lung function testing did not reveal differences within this timespan, whereas the MRI morphology and the MRI global score increased significantly from 8.8 $\pm$ 5.2 to

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**TABLE 3. Correlation of T1(TE) at Different Echo Times With CF MRI Score and Lung Function Testing**

| T1(TE) | n | 70 $\mu$s | 500 $\mu$s | 1200 $\mu$s | 1650 $\mu$s | 2300 $\mu$s |
|--------|---|---------|---------|----------|----------|----------|
| Age    | 75 | $-0.55^\dagger$ | $-0.44^\dagger$ | $-0.24^*$ | $-0.30^\dagger$ | $-0.22$ |
| FEV1pred% | 57 | $+0.44^\dagger$ | $+0.44^\dagger$ | $+0.43^\dagger$ | $+0.40^\dagger$ | $+0.39^\dagger$ |
| FRC    | 67 | $-0.54^\dagger$ | $-0.41^\dagger$ | $-0.17$ | $-0.20$ | $-0.10$ |
| LCI    | 67 | $-0.43^\dagger$ | $-0.42^\dagger$ | $-0.33^\dagger$ | $-0.27^*$ | $-0.22$ |
| MRI morphology score | 75 | $-0.31^\dagger$ | $-0.38^\dagger$ | $-0.25^*$ | $-0.22$ | $-0.21$ |
| MRI perfusion score | 70 | $-0.43^\dagger$ | $-0.51^\dagger$ | $-0.47^\dagger$ | $-0.46^\dagger$ | $-0.44^\dagger$ |
| MRI global score | 70 | $-0.43^\dagger$ | $-0.51^\dagger$ | $-0.41^\dagger$ | $-0.39^\dagger$ | $-0.33^\dagger$ |

Spearman’s correlation coefficient $\rho$ for the correlation of T1 at different echo times with patient age, MRI morphology, MRI perfusion, and MRI global score, forced expiratory volume in 1 sec percent predicted (FEV1pred%) and lung clearance index (LCI). Note that FEV1pred% and LCI are not available for every patient.

* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.  

FIGURE 5: Correlations of T1(TE) and defect% with clinical metrics, dependent on TE. Inverse correlations are shown as dashed lines and positive correlations are shown using solid lines.
10.5 ± 6.1, and from 12.9 ± 8.0 to 15.0 ± 8.8, respectively (P < 0.05–0.01). The MRI perfusion score was relatively stable, with 4.8 ± 2.7 vs. 5.0 ± 2.8 (P = 0.58).

Discussion

A decrease in lung $T_1$ was described in adults with CF or emphysema due to COPD examined at single TEs around 1 ms,\textsuperscript{13,18,35} as well as a correlation of $T_1$ inhomogeneities with perfusion abnormalities.\textsuperscript{15} The development of UTE-based multiecho lung $T_1$ mapping revealed that observed $T_1(TE)$ depends on the measurement TE. This was shown first in healthy adults.\textsuperscript{17} In the infant to adult CF patients examined in this study, $T_1(TE)$ increased with TE as well. $T_1$ is determined by the vicinity of protons, which can be assumed to belong to either of two tissue compartments in every lung voxel: The first are intravascular protons in blood vessels, especially capillaries, with the long $T_1$ of blood\textsuperscript{36,37} and short $T_2^*$ due to the local magnet field inhomogeneities caused by air–tissue boundaries. The second are extravascular protons in the remaining tissue, which contribute a shorter $T_1$ and even shorter $T_2^*$, possibly due to being closer to these inhomogeneities. When observing $T_1$ at increasing TE, this difference in $T_2^*$ causes a variable weighting of influence from these compartments: At UTE, both contribute equally to $T_1(TE)$, but as TE increases the contribution of intravascular protons gradually predominates $T_1(TE)$, which thus approaches $T_1$ of pure blood.\textsuperscript{16,17,38}

Here we have shown that the different curvatures of $T_1(TE)$ revealed a difference in the dependence of $T_1$ on TE in infant to adult patients with CF compared to adult healthy volunteers. This may be both due to the difference in age and the influence of CF lung disease, since a changing ratio of protons in the compartments during lung development is likely to affect $T_1(TE)$.

Correlation analysis revealed two categories of parameters: The first correlate moderately well with $T_1$ at UTE, with the largest contribution of the extravascular protons to $T_1$, and show a correlation that grows weaker with increasing TE, for example, age, FRC, and the MRI morphology score (ie, metrics of structure).

In the second category, the correlation is highest at medium (compared to UTE) TE and otherwise fairly constant. This second category includes the chest MRI perfusion score and FEV1pred%, as well as LCI (ie, metrics of function). This supports our hypothesis that $T_1(TE)$ reflects local structural and functional aspects, and $T_1$ dependence on TE may thus help to differentiate between these contributors. Notably, while this implies $T_1(TE)$ includes perfusion information, measuring it does not require a contrast agent. This may be advantageous both in patients where contrast agent injection is inadvisable and for repeat measurements, which may also be distorted by residual contrast agent at short time intervals.\textsuperscript{39}

$T_1(TE)$ at UTE showed a moderate inverse correlation with age, which decreases toward the longest TE. During growth, alveolar size increases, whereas the increase in numbers of alveoli slows down during early childhood, which results in a subsequent relative increase of air per lung voxel.\textsuperscript{40,41}

TABLE 4. Correlation of Automated Scoring for Defect% in $T_1$ at Different Echo Times With CF MRI Score and Lung Function Testing

| Defect % (TE)     | n   | 70 µs  | 500 µs | 1200 µs | 1650 µs | 2300 µs |
|-------------------|-----|--------|--------|---------|---------|---------|
| Age               | 75  | +0.13  | +0.04  | +0.05   | +0.05   | +0.12   |
| FEV1pred%         | 57  | −0.35† | −0.31* | −0.39†  | −0.37†  | −0.36†  |
| FRC               | 67  | +0.13  | +0.01  | −0.01   | −0.03   | +0.06   |
| LCI               | 67  | +0.35† | +0.29* | +0.26*  | +0.19   | +0.19   |
| MRI morphology score | 75  | +0.21  | +0.29* | +0.24*  | +0.16   | +0.20   |
| MRI perfusion score | 70  | +0.32† | +0.41† | +0.46‡  | +0.41‡  | +0.43‡  |
| MRI global score  | 70  | +0.34† | +0.41† | +0.41‡  | +0.35‡  | +0.31†  |

Spearman’s correlation coefficient $\rho$ for the correlation of $T_1$ at different echo times with patient age, MRI morphology, MRI perfusion, and MRI global score, forced expiratory volume in 1 sec percent predicted (FEV1pred%) and lung clearance index (LCI). Note that FEV1pred% and LCI are not available for every patient. These values are complementary to Table 3.

\* $P < 0.05$.
\† $P < 0.01$.
\‡ $P < 0.001$. 

TABLE 4. Correlation of Automated Scoring for Defect% in $T_1$ at Different Echo Times With CF MRI Score and Lung Function Testing

| Defect % (TE)     | n | 70 µs  | 500 µs | 1200 µs | 1650 µs | 2300 µs |
|-------------------|---|--------|--------|---------|---------|---------|
| Age               | 75 | +0.13  | +0.04  | +0.05   | +0.05   | +0.12   |
| FEV1pred%         | 57 | −0.35† | −0.31* | −0.39†  | −0.37†  | −0.36†  |
| FRC               | 67 | +0.13  | +0.01  | −0.01   | −0.03   | +0.06   |
| LCI               | 67 | +0.35† | +0.29* | +0.26*  | +0.19   | +0.19   |
| MRI morphology score | 75 | +0.21  | +0.29* | +0.24*  | +0.16   | +0.20   |
| MRI perfusion score | 70 | +0.32† | +0.41† | +0.46‡  | +0.41‡  | +0.43‡  |
| MRI global score  | 70 | +0.34† | +0.41† | +0.41‡  | +0.35‡  | +0.31†  |

Spearman’s correlation coefficient $\rho$ for the correlation of $T_1$ at different echo times with patient age, MRI morphology, MRI perfusion, and MRI global score, forced expiratory volume in 1 sec percent predicted (FEV1pred%) and lung clearance index (LCI). Note that FEV1pred% and LCI are not available for every patient. These values are complementary to Table 3.

\* $P < 0.05$.
\† $P < 0.01$.
\‡ $P < 0.001$. 

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Increasing disease severity in CF goes along with an increase of inflammation and mucus load in the lungs of patients, and thus increased proton density.7,11,22 We assume that this could affect T1 in the extravascular compartment, leading to an overall shortened T1. It may be possible to discern this disease-related change from effects due to natural growth by exploiting the TE-dependency demonstrated in this work. Furthermore, the difference in T1 between healthy adults and CF patients strongly depends on TE: The choice of TE determines whether the difference is positive, negative, or negligible.

Thus, as stated previously,17 T1 measurements in the lungs should always be discussed in the context of their acquisition TE. In an attempt to compensate for the age-dependence of T1(TE), we also categorized lung areas as defects based on a linear regression with age, weight, size, and sex. This corresponded well with the irregularities seen. Apart from FRC, which itself depends strongly on patient size, defect% still correlated with the clinical parameters of disease severity, but showed somewhat weaker correlations, since the comparison reference was derived from measurements within the patient group.

**Limitations**

One essential limitation of T1(TE) is that it only provides parameter maps on individual slices, which reduces the comparability with both global lung measures and the chest MRI scores derived from 3D images. Since there may be inconsistencies between the slice positions, this may also reduce the accuracy of the repeated measurements. Lung T1 mapping using Look-Locker has been demonstrated in 3D,42 but only at a single conventional TE. Hence, a 3D UTE implementation is desirable in the future, especially for comparability to 4D perfusion MRI.

The T1(TE) values measured in this study were compared to values previously measured in healthy adults. Since age-matched controls would require MRI measurements in healthy infants, most likely requiring sedation, they would be very difficult to acquire.

The method discussed here was applied on a 1.5T clinical scanner and could be transferred to other current scanners. Due to the large fields of view involved in lung imaging, short or wide bore geometries would be additionally detrimental to the quality of parameter maps. In principle, the approach could also be transferred to 3T, but since higher fields also lead to much shorter T2*, this would require further splitting the acquisition into multiple measurements and thus significantly longer total measurement times.

**Conclusion**

This study demonstrates that whether lung T1 in infants to adult CF patients was found shorter or longer than in healthy adults at T1(TE) mapping, using UTE MRI depended on measurement TE. Further, T1(TE) shows correlations with lung function tests and the CF-MRI score dependent on TE. This suggests that T1(TE) may provide additional information beyond perfusion measurements. This method may be developed further into an endpoint for quantification of structural and functional disease severity requiring neither injectable contrast materials nor visual reader evaluation.

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