T1 relaxation time constants, influence of oxygen, and the oxygen transfer function of the human lung at 1.5 Tesla – a meta-analysis

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Abstract

Purpose: To pool and summarize published data from magnetic resonance longitudinal relaxation measurements of the human lung at 1.5 Tesla to provide a reliable basis of T_1 relaxation time constants of healthy lung tissue both under respiration of room air and of pure oxygen. In particular, the oxygen-induced shortening of T_1 was evaluated.

Materials and Methods: The PubMed database was comprehensively searched up to June 2016 for original publications in English containing quantitative T_1 data (at least mean values and standard deviations) of the lung parenchyma of healthy subjects (minimum subject number: 3) at 1.5 Tesla. From all included publications, T_1 values of the lung of healthy subjects were extracted (inhaling room air and, if available, inhaling pure oxygen). Weighted mean values and standard deviations of all extracted data and the oxygen transfer function (OTF) were calculated.

Results: 22 publications were included with a total number of 188 examined healthy subjects. 103 of these subjects (from 13 studies) were examined while breathing pure oxygen and room air; 85 subjects were examined only under room-air conditions. The weighted mean value (weighted sample standard deviation) of the room-air T_1 values over all 22 studies was 1196 ms (152 ms). Based on studies with room-air and oxygen results, the mean T_1 value at room-air conditions was 1172 ms

(161 ms); breathing pure oxygen, the mean T_1 value was reduced to 1054 ms (138 ms). This corresponds to a mean T_1 reduction by 118 ms (35 ms) or 10.0 % (2.3 %) and to a mean OTF value of 1.22 (0.32) × 10^{-3} s^{-1}/(%O$_2$).

Conclusion: This meta-analysis with data from 188 subjects indicates that the average T_1 relaxation time constant of healthy lung tissue at 1.5 Tesla is distributed around 1200 ms with a standard deviation of about 150 ms; breathing pure oxygen reduces this value significantly by 10 % to about 1050 ms.

Keywords

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Introduction

The relaxation time constant of the longitudinal magnetization (T_1) is an important physical magnetic resonance parameter [1], which is frequently used for the characterization and differentiation of tissues and of pathological changes. Important applications of T_1 measurements include MR relaxometry of the brain [2, 3], the heart [4, 5], or of abdominal organs [6, 7]. Based on a physical and quantitative parameter, T_1 relaxometry is generally expected to provide more objective and reproducible results than conventional MR acquisitions such as T_1-weighted MRI [8].

T_1 mapping of the human lung has the particular advantage that the lung parenchyma is depicted much better on T_1 parameter maps than in conventional proton-density-weighted or T_1-weighted MR acquisitions. In the latter, the lung tissue has very low signal intensity because of the low proton density and the very short reversible transverse relaxation time constants (T_2^*) of the lung [9-11]. In contrast, T_1 mapping allows the direct visualization of the lung tissue and also the quantitative assessment of pathological changes [12] such as T_1 shortening in patients with COPD [13].

In addition, T_1 of the lung tissue can be modulated by inhaling molecular oxygen (O_2) [14]. Oxygen is a paramagnetic gas (with a molar magnetic susceptibility of about 43×10^{-9} m³/mol at standard conditions [15]) that shortens the T_1 relaxation time constant of the lung tissue. This property has been employed for oxygen-enhanced MRI of the lung: difference images of T_1-weighted acquisitions of a subject breathing either room air or pure oxygen are interpreted as reflecting the lung function, i. e., a combination of ventilation, perfusion, and oxygen diffusion properties of the lung [14, 16, 17]. A disadvantage of the analysis of T_1-*weighted* oxygen-enhanced lung acquisitions is that the observed T_1-weighted signal modulation depends on the acquisition details of the applied pulse sequence such as the inversion time. A more quantitative approach is based on the absolute value of the T_1 relaxation time constant instead of the T_1-weighted MRI signal. Difference images of T_1 maps can be used to depict regional ventilation properties [18]; the quantitative effect of the administered oxygen concentration on the lung T_1 value can be described by the oxygen transfer function (OTF) [19].

The purpose of this meta-analysis was to pool and summarize published data from magnetic resonance longitudinal relaxation measurements of the human lung at 1.5 Tesla to provide a reliable basis of T_1 relaxation time constants of healthy lung tissue both under respiration of room air and of pure oxygen. In addition, the oxygen-induced shortening of T_1 and the oxygen transfer function were evaluated based on the collected data.

Methods

Data source, literature research, study selection

The present study is a meta-analysis of previously published results, and no approval by the local institutional review board was required. The PubMed database was searched on 30 June 2016 for publications containing quantitative T_1 results with two sets of keywords focusing (a) on oxygen-enhanced [1]H-MRI of the lungs

> **("magnetic resonance" OR MRI)**
> **oxygen-enhanced**
> **(pulmonary OR lung OR ventilation)**

and (b) on T_1 quantification of the lung parenchyma

> **("magnetic resonance" OR MRI)**
> **(pulmonary OR lung)**
> **("T1 mapping" OR "T(1) mapping"**
> **OR "T1 maps" OR "T(1) maps"**
> **OR "T(1) map" OR "T1 map"**
> **OR "T1 relaxation time"**
> > **OR "T(1) relaxation time"**
> **OR "T1 relaxation times"**
> > **OR "T(1) relaxation times"**
> **OR "T1 quantification"**
> > **OR "T(1) quantification"**
> **OR "T1 relaxometry" OR "T(1) relaxometry"**
> **OR "longitudinal relaxation")**
> **NOT myocardial NOT hyperpolarized .**

The lists of publications resulting from these searches were screened for inclusion into this meta-analysis in two steps: first, based on the title and abstract information and, second, if required by in-depth inspection of the full text of these publications. Publications were excluded if one of the following exclusion criteria applied:

- publication not in English
- review publication without original data
- non-proton MRI studies (e. g., of hyperpolarized noble gases or fluorine-19 MRI)
- studies at magnetic field strengths other than 1.5 Tesla
- phantom or in vitro studies without human subjects
- studies of animal models without human subjects
- studies without or with fewer than 3 healthy control subjects
- studies without quantitative T_1 relaxation time constants or without statistics (minimum requirement: subject number, mean value, and standard deviation).

If included studies referred to publications not contained in our search results, these were also screened for possible inclusion.

Data extraction

The following data were extracted from each selected study: (1) the T_1 relaxation time constant of lung tissue of healthy volunteers when breathing room air (or medical air) and (2) the T_1 relaxation time constant of lung tissue of healthy volunteers when breathing pure (100 %) oxygen. If relaxation time constants were provided for different lung regions (e. g., for more than one slice or for several region within a slice) or for different respiratory phases, these values were combined into one representative value. If several experiments or experimental setups were described which provided data of different quality (e. g., with different inversion preparations, different oxygen masks, or different oxygen flow rates), the results with the best data quality (following the conclusions of the study authors) were selected.

When available, the mean age of the examined subjects was extracted; if T_1 measurements were performed only in a subgroup of all included subjects (without explicitly defined mean age), then the mean age of the larger sample was taken as estimate for the subgroup as well. If no individual ages or mean age, but only the age range was reported, the mean age was estimated to be the arithmetic mean of minimum and maximum age. The fraction of female subjects (i. e., the number of female subjects divided by

the total number of subjects) was extracted, if the number of male and female subjects was given.

If T_1 values for individual subjects were provided, these were also collected for subsequent statistical analysis. If no individual T_1 values were provided, (collective) mean values, standard deviations, and subject number as provided in the publications were extracted. If the mean value, sample size n, and a 95% confidence interval $[a; b]$ were provided, then the standard deviation s was estimated as

$$s = \frac{b-a}{2} \frac{\sqrt{n}}{1.96}.$$

If the median M as well as the 1st and 3rd quartiles (Q_1, Q_3) were provided, the mean value m and standard deviation s were estimated as described by Wan et al. [20] as

$$m = (Q_1 + M + Q_3)/3, \quad s = (Q_3 - Q_1)/1.35.$$

If T_1 values for breathing room air, $T_{1,\text{air}}$, and OTF values were provided, we calculated T_1 values for breathing pure oxygen, $T_{1,\text{O2}}$, as

$$T_{1,\text{O2}} = \left(\frac{1}{T_{1,\text{air}}} + 79\% \times \text{OTF} \right)^{-1},$$

which is based on the oxygen concentration difference of 79 % between room air (21 % O_2) and pure oxygen (100 % O_2) and the original definition of the OTF as given by Jakob et al. [19]. If extrapolated T_1 values for an oxygen concentration of 0 %, $T_1(0)$, and OTF values were provided, we calculated T_1 values for breathing room air and pure oxygen as [19]

$$T_{1,\text{air}} = \left(\frac{1}{T_1(0)} + 21\% \times \text{OTF} \right)^{-1};$$

$$T_{1,\text{O2}} = \left(\frac{1}{T_1(0)} + 100\% \times \text{OTF} \right)^{-1}.$$

Standard deviations of the calculated parameters ($T_{1,\text{air}}$, $T_{1,\text{O2}}$) for each study were estimated using error propagation based on the standard deviations of the input quantities.

If room air and oxygen T_1 relaxation time constants were available, OTF values were determined as

$$\text{OTF} = \left(\frac{1}{T_{1,\text{O2}}} - \frac{1}{T_{1,\text{air}}} \right)/79\%.$$

The OTF was determined as mean value of the examined volunteer group for each study and also on a per-subject basis, if individual data were provided.

Following the approach by Morgan et al. [21] and Zhang et al. [22], we estimated the partial pressure ΔPO_2 of oxygen dissolved in the tissue water and

plasma of the lung as

$$\Delta PO_2 = \frac{1/T_{1,O_2} - 1/T_{1,\text{air}}}{r_1} = \frac{79\% \times \text{OTF}}{r_1}$$

with an estimated relaxivity, r_1, of oxygen in the lung of $r_1 = 2.49 \times 10^{-4}\ \text{s}^{-1}\ \text{mmHg}^{-1}$ [23].

Statistical analysis

T_1 values for lung tissue from all included studies were listed; the weighted mean value and the weighted (corrected, "n–1") sample standard deviation were determined separately for all room air results as well as comparing room air and oxygen results. All OTF values were listed and the weighted mean value as well as the weighted standard deviation were calculated. The weighted mean value of each parameter was calculated from the study mean values m_k standard deviations s_k, and the number of subjects n_k as

$$m = \sum_k n_k m_k / \sum_k n_k;$$

and the weighted standard deviation was calculated as

$$s = \sqrt{\frac{\sum_k (n_k-1)s_k{}^2 + \sum_k n_k m_k^2 - m^2 \sum_k n_k}{\sum_k n_k - 1}}.$$

The individual values ($T_{1,\text{air}}$, T_{1,O_2}, OTF), as far as these were available, were post-processed by pooling each parameter and calculating the mean value (averaged over all subjects) as well as the (corrected, "n–1") sample standard deviation over all subjects.

$T_{1,\text{air}}$ relaxation time constants were also evaluated separately for the three basic pulse sequence types (single-shot fast-spin-echo techniques, snapshot gradient-echo techniques, and ultra-short-echo-time techniques) and pairwise statistically compared with a t-test. In addition, possible correlations of relaxation times and the mean age or the fraction of female subjects were analyzed using the Pearson product-moment correlation coefficient. Finally, the weighted mean values of T_1 relaxtion times of room-air and oxygen measurements were compared with a t-test. All p-values were adjusted using the Benjamini-Hochstein correction [24] to account for multiple testing; adjusted p-values lower than 0.05 were considered to indicate statistical significance. All statistical tests were performed with "R: A Language and Environment for Statistical Computing" (version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Literature research, study selection

The search for keywords set #1 (focusing on oxygen-enhanced MRI of the lungs) returned 75 publications with publication dates between 1996 and 2016. Of these, 3 were not published in English, 9 were review papers, 1 was not proton-MRI-based (but fluorine-19), 6 reported only animal model results, 2 only results in subjects with pathologies, and 37 publications did not contain quantitative T_1 relaxation time constants (but, e. g., oxygen-induced relative signal enhancement ratios or specific ventilation maps). One publication contained quantitative T_1 results only of arterial blood in the aorta (but not of lung tissue) and one publication contained only T_1 mean values without any statistics. After exclusion of these 60 publications, 15 publications (from publication dates between 1996 and 2015) with quantitative T_1 results in the lung of healthy subjects measured at 1.5 Tesla remained.

The search for keywords set #2 (focusing on quantitative T_1 results) returned 58 publications with publication dates between 1983 and 2016. Of these, 3 were not published in English, 5 were review papers, 8 were not proton-MRI-based, 14 reported only in vitro or animal model results, 3 reported only results in subjects with pathologies, 3 only results in tissues other than lung parenchyma, 2 were performed at 3 Tesla instead of 1.5 Tesla, and 8 studies did not contain either quantitative T_1 results or a statistical analysis of T_1 results. After exclusion of these 46 publications, 12 publications (publication dates between 1999 and 2016) with quantitative T_1 results in the lung of healthy subjects measured at 1.5 Tesla remained.

6 publications of the selected 15 and 12 publications appeared in both selections such that in total 21 publications were identified (publication dates between 1996 and 2016). Two further publications with quantitative T_1 results by Mai et al. [25] and Jakob et al.[19], which were referenced by Arnold et al. [26], were added to this selection. An article by Hatabu et al. [27] provides more details about the same volunteer group that was also described by Edelman et al. [14]; these two publications were merged in all subsequent analyses. The remaining 22 publications are

summarized in Table 1 with details about the volunteers and data acquisition. All included studies performed image acquisition in coronal orientation; if

only a single slice was acquired, slice positioning was most commonly in a dorsal to central positioning within the lung.

Table 1: Summary of 22 included studies[1]

Publication	Subjects		O₂ administration	Individual data	Evaluated regions, breathing/breath-hold strategy	Pulse sequence
	number	sex/age				
Edelman et al. 1996 [14], Hatabu et al. 2001 [27]	6	2m, 4f, 20–29 y	yes	yes	right/left lung, quiet breathing	IR-HASTE 10 TIs: 200..2500 ms TE=25 ms, ES=4.2 ms, BW=488 Hz/px
Chen et al. 1998 [28]	5	(n. a.), (n. a.)	yes	yes	upper region in right lung, quiet breathing	IR-RARE 8..12 TIs: 100..4000 ms TE=4.2 ms, ES=4.2 ms, BW=650 Hz/px
Stock et al. 1999 [29]	8	3m, 5f, 30–48 y	yes	no	right/left and upper/lower lobe, breath-hold (deep inspiration)	IR-RARE 12 TIs: 150..2000 ms TE=4.2 ms, ES=4.2 ms, BW=650 Hz/px
Mai et al. 1999 [30]	3 of 5	4m, 1f, 25–42 y	no	no	right/left lung, 35s breath-hold	IR-HASTE 5 TIs: 100..3000 ms TE=38 ms, ES=4.2 ms
Mai et al. 2000 [25]	5 of 10	(n. a.) 25–42 y	no	no	4 averaged ROIs (no large vessels), end-expiration/end-inspiration	IR-HASTE 5 TIs: 100..3000 ms TE=38 ms, ES=4.2 ms
Löffler et al. 2000 [16]	5 of 9	7m, 2f, 28±1 y	yes	no	10 ROIs, breath-hold (deep inspiration)	IR-RARE 16 TIs 10..5000 ms TE=4.2 ms, ES=4.2 ms, BW=651 Hz/px
Nakagawa et al. 2001 [31]	8	(n. a.) 24–38 y	yes	yes	6 averaged ROIs (no large vessels), breath-hold	IR-HASTE 11 TIs: 200..1400 ms TE=28.8 ms, ES=4.8 ms, BW=±31.2 kHz
Jakob et al. 2001 [32]	6	4m, 2f, 19–38 y	yes	yes	right/left lung, breath-hold (end-expiration)	SnpFLASH 16 TIs: 112..3472 ms TE=1.0 ms, TR=3.5 ms, FA=7
Mai et al. 2002a [33]	6	3m, 3f, 25–48 y	yes	no	upper left lung(?), quiet breathing	IR-HASTE 5 TIs: 100..3000 ms TE=21 ms, ES=3.6 ms, BW=250 kHz
Mai et al. 2002b [34]	5 of 10	(n. a.) 25-48 y	no	yes	4 averaged ROIs, (n. a.)	IR-HASTE 5 TIs: 100..3000 ms TE=20 ms, ES=3.6 ms, BW=250 kHz
Jakob et al. 2002 [35]	3	1m, 2f, 24–27 y	no	yes	upper right lung, breath-hold (end-expiration)	SnpFLASH 16 TIs: 112..3472 ms TE=1.0 ms, TR=3.5 ms, FA=7°
Jakob et al. 2004 [19]	5	3m, 2f, 22–35 y	yes	yes	right lung, breath-hold (end-expiration)	SnpFLASH 16 TIs: 112..3472 ms TE=1.0 ms, TR=3.5 ms, FA=7°
Arnold et al. 2004 [26]	3	(n. a.) (n. a.)	no	yes	4 ROIs, breath-hold (end-exp./-inspiration)	SnpFLASH 16 TIs: 112..3472 ms TE=1.4 ms, TR=3.5 ms, FA=7°
Stadler et al. 2005 [36]	10	8m, 2f, 23–36 y	no	yes	entire lung (histogram analysis), inspiration and expiration	SnpFLASH 16 TIs: 112..3472 ms TE=1.4 ms, TR=3.5 ms, FA=7°
Arnold et al. 2007 [37]	10	(n. a.), (n. a.)	yes[2]	yes	averaged right/left lung, breath-hold	SnpFLASH 16 TIs: 112..3472 ms TE=1.4 ms, TR=3.5 ms, FA=7°
Molinari et al. 2008 [38]	23	15m, 8f, 20–35 y	yes	no	right/left lung, breath-hold	SnpFLASH 40 TIs: 50..3700 ms TE=0.5 ms, TR=1.6 ms, FA=5°, BW=1 kHz/px
Renne et al. 2015a [39]	12	7m, 5f, 28.5±7.3 y	yes	no	8 regions, breath-hold	SnpFLASH 32 TIs: 96..6000 ms TE=0.8 ms, TR=3.0 ms, FA=8°
Renne et al. 2015b [40]	4	4m, 0f, 36–50 y	yes	no	entire lung, breath-hold (end of normal insp.)	SnpFLASH 32 TIs: 96..6000 ms TE=0.8 ms, TR=3.0 ms, FA=8°
Triphan et al. 2015a [18]	7	(n. a.), (n. a.)	yes	yes	entire lung, inspiration/expiration	IR-UTE 4 TIs: 660..2640 ms TE=70..2300 μs, TR=5.5 ms
Triphan et al. 2015b [41]	12	(n. a.), 23–33 y	no	yes	entire lung, free breathing, gated to expiration	IR-UTE 4 TIs: 660..2640 ms TE=70..2300 μs, TR=5.5 ms
Kindvall et al. 2016 [42]	30	16m, 14f, 22–62 y	no	no	entire lung (histogram analysis), tidal end-inspiration breath-hold	SnpFLASH 16 TIs: 96..3000 ms TE=0.7 ms, TR=3.0 ms, FA=7°
Alamadi et al. 2016 [13]	12	8m, 4f, 42–79 y	no	no	entire lung, normal tidal breathing	IR-HASTE 5 TIs: 50..5000 ms TE=3 ms, TR=5500 ms

[1] abbreviations: m: male, f: female, y: years, n. a.: not available, ROI: region of interest, IR: inversion recovery, HASTE: half-Fourier-acquired single-shot turbo-spin-echo sequence, RARE: rapid acquisition with relaxation enhancement, SnpFLASH: snap-shot-FLASH sequence, UTE: Ultrashort-TE sequence, TI: inversion time, TE: echo time, TR: repetition time, ES: echo spacing, BW: (receiver) bandwidth, FA: flip angle
[2] carbogen (95% O_2, 5% CO_2) was administered

Table 2: Summary of T_1 relaxation time constants of the lung tissue of healthy subjects breathing room air[1]

Publication	n	$T_{1,air}$ (ms) mean (SD)	Mean age (y)	Fraction of females	Comments
Edelman et al. 1996 [14, 27]	6	912.5 (44.9)	24.5	4/6	right and left lung T_1 individually averaged
Chen et al. 1998 [28]	5	1351.8 (39.9)	(n. a.)	(n. a.)	–
Stock et al. 1999 [29]	8	904.0 (99.0)	37.0	5/8	–
Mai et al. 1999 [30]	3	1390.0 (176.3)	33.5	(n. a.)	right and left lung T_1 statistically combined
Mai et al. 2000 [25]	5	1290.0 (96.5)	33.5	(n. a.)	inspiration and expiration T_1 statistically combined
Löffler et al. 2000 [16]	5	1219.0 (176.0)	28.0	(n. a.)	only breath-hold data included
Nakagawa et al. 2001 [31]	8	1146.6 (79.8)	31.0	(n. a.)	–
Jakob et al. 2001 [32]	6	1249.2 (75.2)	28.5	2/6	right and left lung T_1 individually averaged
Mai et al. 2002a [33]	6	1399.0 (130.0)	33.7	3/6	–
Mai et al. 2002b [34]	5	1359.8 (116.4)	36.5	(n. a.)	only non-selective inversion data included
Jakob et al. 2002 [35]	3	1372.7 (81.6)	25.0	2/3	–
Jakob et al. 2004 [19]	5	1297.6 (79.0)	27.0	2/5	$T_{1,air}$ calculated individually from $T_1(0)$ and OTF
Arnold et al. 2004 [26]	3	1243.3 (58.6)	(n. a.)	(n. a.)	inspiration and expiration T_1 of subject #1 averaged
Stadler et al. 2005 [36]	10	1265.5 (132.8)	29.7	2/10	inspiration and expiration T_1 individually averaged
Arnold et al. 2007 [37]	10	1259.8 (63.9)	(n. a.)	(n. a.)	–
Molinari et al. 2008 [38]	23	1129.3 (68.5)	25.0	8/23	right and left lung T_1 and data from both masks statistically combined
Renne et al. 2015a [39]	12	1247.1 (52.4)	28.5	5/12	8 separate regions statistically combined
Renne et al. 2015b [40]	4	1306.3 (150.4)	43.5	0/4	–
Triphan et al. 2015a [18]	7	1022.1 (23.3)	(n. a.)	(n. a.)	inspiration and expiration T_1 individually averaged
Triphan et al. 2015b [41]	12	1267.6 (58.4)	28.0	(n. a.)	T_1 individually averaged over all echo times
Kindvall et al. 2016 [42]	30	1199.5 (125.8)	30.0	0.5	male and female T_1 (calculated for age of 30 y) statistically combined
Alamidi et al. 2016 [13]	12	1053.0 (55.0)	63.0	4/12	–
Pooled	**188**	**1195.7 (151.6)**	**32.2 (9.6)**	**0.41 (0.14)**	

[1] abbreviations: n: number of included subjects, SD: standard deviation, n. a.: no data available
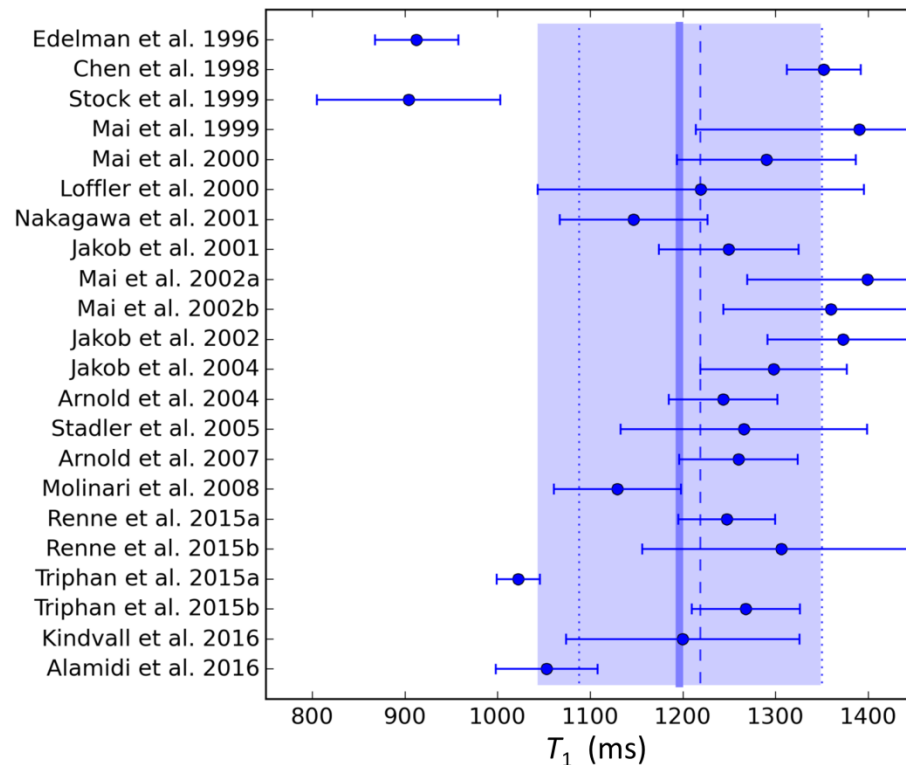

Fig. 1: T_1 relaxation time constants of normal lung parenchyma from 22 articles. Displayed are the sample mean value and sample standard deviation from each study as well as the weighted sample mean value (1196 ms) and pooled sample standard deviation (152 ms) over all studies (thick blue line and blue shaded area); dashed (dotted) is the pooled sample mean (standard deviation) of 1219 ms (131 ms) without the two studies with markedly smaller T_1 values from 1996 and 1999.
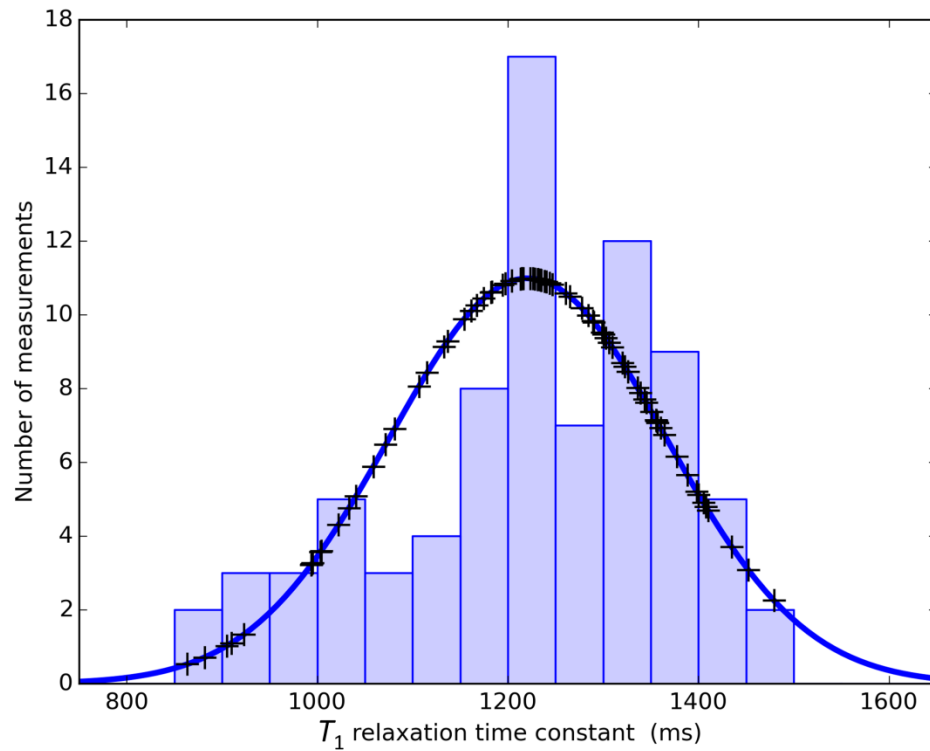
Fig. 2: T_1 relaxation time constants of the lung parenchyma from 80 healthy subjects reported in 12 articles. Displayed is the histogram of all individual T_1 values (bin size 50 ms), the normal distribution based on the mean value (1221 ms) and standard deviation (145 ms) of all values, as well as each individual value (crosses on distribution curve).

Table 3: T_1 relaxation time constants and influence of inhaled oxygen[1]

Publication	n	$T_{1,O2}$ (ms) mean (SD)		$T_{1,air}$ (ms) mean (SD)		ΔT_1 (ms)	$\Delta T_1/T_{1,air}$ (%)	OTF 10^{-3} s^{-1}/(%O$_2$)
Edelman et al. 1996 [14, 27]	6	836.8	(54.6)	912.5	(44.9)	75.7	8.3	1.25
Chen et al. 1998 [28]	5	1183.4	(69.8)	1351.8	(39.9)	168.4	12.5	1.33
Stock et al. 1999 [29]	8	790.0	(114.0)	904.0	(99.0)	114.0	12.6	2.02
Löffler et al. 2000 [16]	5	1074.0	(92.0)	1219.0	(176.0)	145.0	11.9	1.40
Nakagawa et al. 2001 [31]	8	1069.6	(77.1)	1146.6	(79.8)	77.0	6.7	0.79
Jakob et al. 2001 [31] [2]	4	1151.8	(50.0)	1289.9	(52.8)	138.1	10.7	1.18
Mai et al. 2002a [33] [2]	6	1207.0	(42.0)	1399.0	(130.0)	192.0	13.7	1.44
Jakob et al. 2004 [19]	5	1159.6	(65.3)	1297.6	(79.0)	138.1	10.6	1.16
Arnold et al. 2007 [37] [3]	10	1137.5	(60.3)	1259.8	(63.9)	122.3	9.7	1.08
Molinari et al. 2008 [38]	23	1045.4	(84.7)	1129.3	(68.5)	83.9	7.4	0.90
Renne et al. 2015a [39] [4]	12	1091.6	(37.7)	1247.1	(52.4)	155.5	12.5	1.45
Renne et al. 2015b [40] [5]	4	1178.7	(133.3)	1306.3	(150.4)	127.7	9.8	1.05
Triphan et al. 2015a [18]	7	922.8	(25.7)	1022.1	(23.3)	99.4	9.7	1.33
Pooled	**103**	**1053.6**	**(137.6)**	**1171.8**	**(160.5)**	**118.1 (34.8)**	**10.0 (2.3)**	**1.22 (0.32)**

[1] abbreviations: n: number of included subjects, SD: standard deviation, OTF: oxygen transfer function
[2] only 25 L/min O$_2$ data included,
[3] $T_{1,O2}$ individually calculated from $T_{1,air}$ and relative change,
[4] only data from tight mask group included,
[5] $T_{1,O2}$ calculated from $T_{1,air}$ and (averaged) OTF

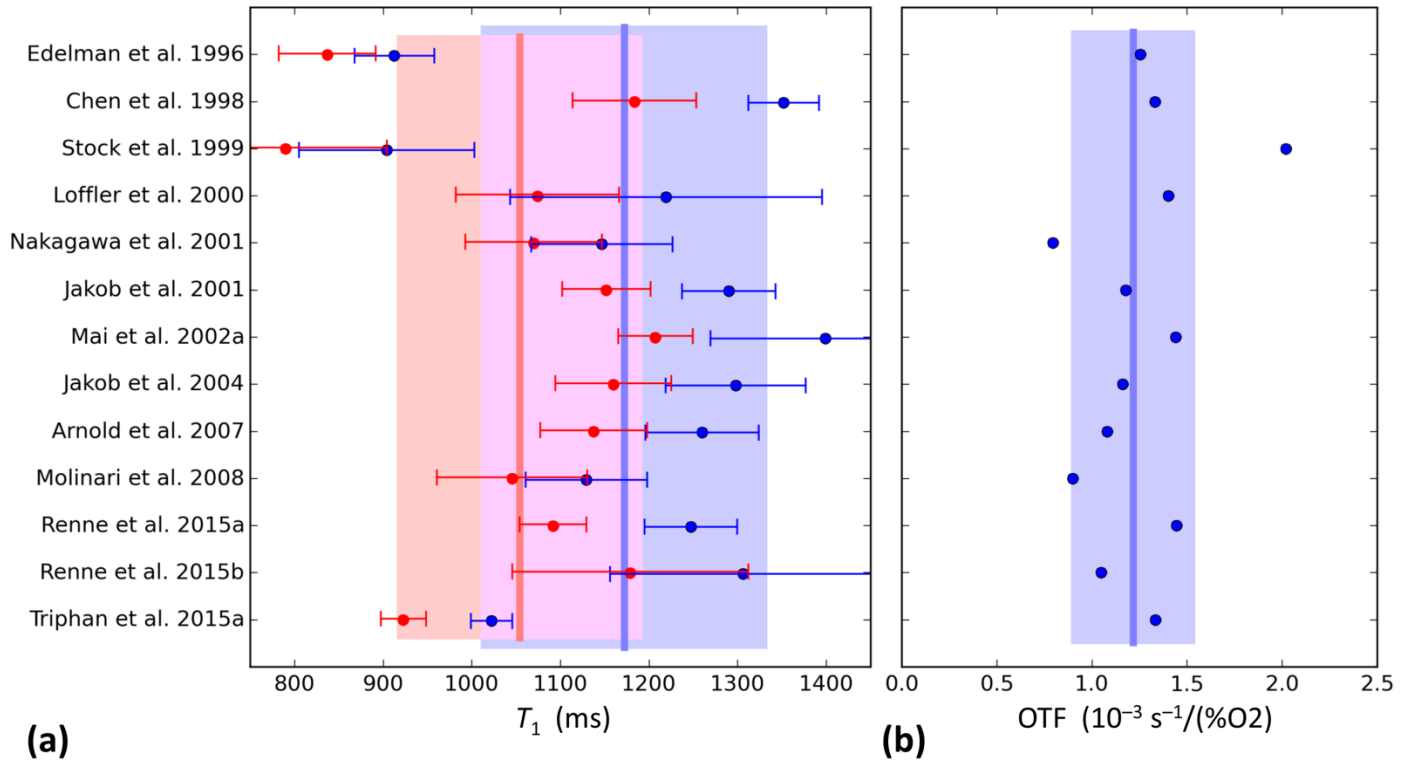**(a)**   **(b)**

Fig. 3: Influence of inhaled oxygen on the T_1 relaxation of lung tissue. (a) T_1 relaxation time constants of lung tissue of subjects breathing room air (blue) and pure oxygen (red) from 13 publications. Displayed are the sample mean values and sample standard deviations from each study as well as the weighted mean values (1054 ms and 1172 ms) and pooled standard deviations (138 ms and 161 ms) over all studies (thick vertical red and blue lines and overlapping red and blue shaded areas). (b) Oxygen transfer function values from all studies calculated from the mean values shown in (a); the weighted sample mean value (standard deviation) is 1.22 (0.32) $\times 10^{-3}$ s^{-1}/(%O$_2$) (thick blue line and blue shaded area).

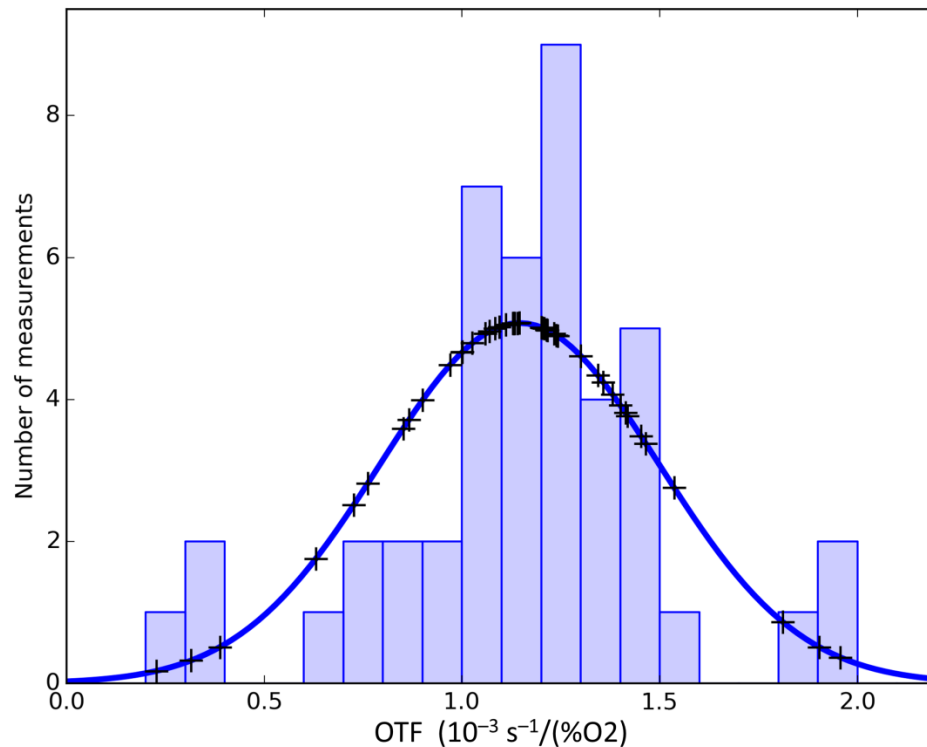**Fig. 4:** OTF values from 45 healthy volunteers. Displayed is the histogram of all individual OTF values (bin size 0.1 $\times 10^{-3}$ s^{-1}/(%O$_2$)), the normal distribution based on the mean value (1.15 $\times 10^{-3}$ s^{-1}/(%O$_2$)) and standard deviation (0.35 $\times 10^{-3}$ s^{-1}/(%O$_2$)) of all values, as well as each individual value (crosses on distribution curve).

Data extraction

The total number of examined subjects (summed over all 22 included studies) was 188; 103 of these subjects were examined while breathing pure oxygen and room air, and 85 subjects were examined only under room-air conditions. In terms of publications, 13 articles reported pulmonary T_1 values of volunteers breathing both pure oxygen (or, in one case, carbogen [37]) and room air, while 9 studies contained only T_1 values acquired during inhalation of room air.

Individual data (of each included volunteer) were available in 12 studies (7 of which included oxygen measurements), resulting in data from 45 subjects with lung T_1 values for both oxygen and room air inhalation, and 35 additional subjects with lung T_1 values only under room air conditions. The remaining 10 studies provided statistical data (typically the sample mean value and standard deviation) for all examined subjects.

T_1 relaxation time constants at room air

The reported T_1 relaxation time constants of the lung parenchyma of healthy subjects are summarized in Table 2 and Fig. 1. The weighted mean value (weighted sample standard deviation) over all studies is 1196 ms (152 ms). Two early studies [14, 29] reported markedly lower T_1 values than all later ones; if one excludes these two studies from the statistical evaluation, the weighted mean value is 1219 ms (131 ms). Based on individual (per-subject) T_1 values, the sample mean value is 1221 ms (145 ms); the distribution of individual T_1 values (from those studies that made these data available) is shown in Fig. 2.

Separate evaluation for the three basic pulse sequence types yielded weighted mean values of $T_{1,air} = 1162$ ms (203 ms) for data acquired with single-shot fast-spin-echo techniques (total number of subjects $n = 63$), $T_{1,air} = 1219$ ms (112 ms) for data acquired with snapshot gradient-echo techniques ($n = 106$), and $T_{1,air} = 1177$ ms (131 ms) for data acquired with ultra-short-echo-time techniques ($n = 19$). Pairwise comparison between these mean values resulted in p-values between 0.12 and 0.70. In an evaluation over all acquisition techniques, we did not find any statistically significant correlations between the reported (mean) T_1 values on the one hand

and the mean subject age ($p = 0.66$) or the fraction of female subjects ($p = 0.41$) on the other hand.

Influence of oxygen on T_1 relaxation time constants

The T_1-shortening effect of inhaled oxygen was quantitatively demonstrated in 13 included studies and is summarized in Table 3 and in Fig. 3a. In these studies, the (weighted) mean T_1 value at room air conditions was 1172 ms (161 ms); breathing pure oxygen, the mean T_1 value was reduced to 1054 ms (138 ms). This corresponds to a weighted mean T_1 reduction by 118 ms (35 ms) or 10.0 % (2.3 %) and to a mean OTF value of 1.22 (0.32) $\times 10^{-3}$ s^{-1}/(%O$_2$); cf. Fig. 3b. The OTF value can be transformed to a change of oxygen partial pressure of $\Delta PO_2 = 386$ (102) mm Hg (when switching from room air to pure oxygen inhalation). The relative T_1 shortening ranges between 6.7 % and 13.7 % over all studies; the OTF ranges from 0.79 to 2.02 $\times 10^{-3}$ s^{-1}/(%O$_2$). The weighted mean T_1 value at room-air conditions was significantly longer than at oxygen conditions ($p = 3 \times 10^{-7}$).

Individual T_1 data for each examined subject were available in 7 of these 13 studies for a total number of 45 subjects. We determined individual OTF values from these T_1 data; the result is shown in Fig. 4. Based on these data, the mean OTF is 1.15 $\times 10^{-3}$ s^{-1}/(%O$_2$) with a standard deviation of 0.35 $\times 10^{-3}$ s^{-1}/(%O$_2$).

Discussion

In this meta-analysis of 22 studies, we pooled and summarized values of the longitudinal (T_1) relaxation time constant of lung tissue at 1.5 Tesla of (in total) 188 healthy subjects breathing room air and of 103 subjects breathing also pure oxygen. To describe the influence of the inhaled oxygen on the T_1 relaxation, we determined the induced absolute and relative T_1 shortening as well as the oxygen transfer function; thus, providing for the first time average OTF values based on more than 100 subjects. The weighted sample mean value (standard deviation) over all studies was $T_{1,air} = 1196$ ms (152 ms). In the sub-group, for which oxygen-enhanced MRI was performed, the weighted sample mean values were $T_{1,O2} = 1054$ ms (138 ms) and $T_{1,air} = 1172$ ms (161 ms), which corresponds to an average oxygen-induced T_1 shortening by 10.0 % (2.3 %) and an OTF value of

1.22 (0.32) $\times 10^{-3}$ s^{-1}/(%O$_2$). These results now provide an appropriate and reliable basis for T_1-quantifying MRI studies (with or without oxygen as T_1-shortening contrast agent) in patients with lung pathologies, enabling, e. g., the differentiation or detection of T_1-changing processes without the need to include a group of healthy subjects.

The reported values exhibit relatively large variances, particularly when considering all results together as in Figs. 1 to 4. Four major factors that contribute to these variances are: (1) "real" parameter variations across the samples, (2) measurement-related parameter variations due to different data acquisition techniques in different studies, (3) statistical parameter variations caused by the influence of signal noise on the determined parameters, and (4) parameter errors due to inappropriate or erroneous post-processing strategies. Only the first of these factors results in a parameter variance that we would actually like to measure, while items (2) to (4) can be regarded as confounding effects that should ideally be minimized or – if possible – corrected.

Measurement-related variations may depend on the pulse sequence type and acquisition parameters. Examples are the influence of different inversion pulses (in particular, of non-selective vs. slice-selective inversion [34]), or of different echo times in gradient-echo acquisitions, that have been demonstrated to result in different weightings of the signal of blood relative to other lung tissues and, thus, in shorter T_1 relaxation times at ultra-short TEs of 70 μs [41].

*Intra*individual T_1 variations of each subject depend, e. g., on the respiratory phase with about 7 % [25, 26] to 10 % [36] lower T_1 values in inspiration than in expiration. Other factors potentially influencing the pulmonary T_1 are imaging during breath-hold vs. free breathing [16] or the positioning of the subject (prone vs. supine [41]). The latter is related to the spatial variation of T_1 in each lung caused by gravitational effects [43]; hence, slice positioning and selection of one or several regions of interest within the lung (as well as the degree of exclusion or inclusion of large vessels) influences the obtained T_1 results.

Significant *inter*individual T_1 variations of the lung tissue were observed by Kindvall et al. in different

subjects depending on the sex and age [42]: While male subjects showed almost no age-dependence, the lung T_1 values in healthy female subjects decreased approximately linearly with age from about 1280 ms at 25 years to 1140 ms at 60 years (the calculated slope was −4.1 ms/y).

The observed distribution of T_1 values included in the present meta-analysis is certainly a result of several of these factors, which cannot be easily separated. We did, however, not find any statistical correlations between the reported mean subject age or sex distribution on the one hand and the T_1 values one the other hand (both p-values > 0.3). This may be explained by the predominance of systematic T_1 deviations between different studies that mask any (smaller) age or sex dependencies. We did not find any significant differences depending on the pulse-sequence type either. However, a tendency to lower T_1 values with fast-spin-echo-based acquisitions compared to gradient-echo-based techniques was observed, which is compatible with a T_1-increasing influence of the blood signal at longer gradient-echo TEs [41] (since the T_2^*-weighting effect of spin-echo measurements is practically zero).

With respect to the relatively large appearing standard deviation of T_1 values of about 150 ms found as a result of this meta-analysis, it is worth noting that several earlier studies found similarly large standard deviations between 130 ms [33, 36] and 175 ms [16, 30] (cf. Table 2), although much more homogeneous methods were used within each of these studies (i. e., each study applied only a single pulse sequence type with fixed acquisition parameters; slice positioning and region placement were also not varied within the individual studies). This may indicate that the standard deviation found in this meta-analysis is indeed dominated by actual interindividual parameter variations.

A similar variation of T_1 values as discussed above for measurements during breathing room air was also found for oxygen-enhanced MRI measurements. An additional factor influencing these results is the efficiency of the oxygen administration that has been demonstrated to vary depending on the oxygen flow rate [32, 33] or the used face mask [39]. The majority of included studies do not provide detailed infor-

mation about the oxygen administration system and do not describe if oxygen saturation was measured to verify sufficient oxygen respiration. The oxygen-induced T_1 shortening ranged from 7 % to 14 % with a mean value of 10.0 % (2.3 %). Since these latter results were generally obtained from intraindividually paired examinations, they may be expected to show fewer undesirable experimental influences, but to reflect the true parameter variance in healthy subjects.

This meta-analysis has the following limitations: We included only MRI results obtained at a field strength of 1.5 Tesla, since the vast majority of all published results were measured at this field strength. Few results at other field strengths include substantially lower T_1 values of 632 ms (54 ms) [29] and 686 ms (61 ms) [44] at 0.2 T. At 3 Tesla, Nichols et al. reported a relatively high T_1 value of 1374 ms (226 ms) from a study in 16 healthy subjects [45], in contrast to Mirsadraee et al. who found lower T_1 values of 1011 ms (172 ms) in 7 healthy volunteers [46]. A second limitation is the diversity of used T_1 quantification techniques (with different pulse sequences or acquisition parameters such as the echo time or range of inversion times) over all included studies, which can be expected to result in certain systematic T_1 variations. However, no statistically significant differences between different pulse sequence types were observed; thus, all studies with quantitative T_1 data were included independent of the used acquisition technique to avoid any selection bias.

In conclusion, this meta-analysis of data from (in total) 188 healthy subjects indicates that the average T_1 relaxation time constant of healthy lung tissue at 1.5 Tesla is distributed around 1200 ms with a standard deviation of about 150 ms; breathing pure oxygen reduces this value significantly by 10 % to about 1050 ms. This decrease of T_1 of lung tissue corresponds to an average OTF value of 1.2 (0.3) $\times 10^{-3}$ s^{-1}/(%O$_2$).

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