Ventilation Study of the Human Lungs by $^{19}$F MRI at 0.5 Tesla

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Abstract
To show the feasibility of functional lung assessment by $^{19}$F MRI using low field (0.5 T) MRI scanner. One healthy volunteer participated in the studies. As a contrast for $^{19}$F pulmonary MRI, the gas mixture of 70% octafluorocyclobutane (OFCB) and 30% oxygen was used. $^{19}$F MR images of human lungs were obtained using 2D and 3D FSE methods. MRI data were used for volume reconstruction and for calculation of wash-in/-out and single-breath dynamics measurements. $^{19}$F 3D imaging provided information about gas distribution and lung volume assessment. The measured volume of the left and right parts of lungs were $\approx 1.7$L and $\approx 1.8$L, respectively. The wash-in/-out dynamics measurements determined that the effective time of gas washing in was $30 \pm 5$ s and washing out was $19 \pm 4$ s. Fractional ventilation was $29 \pm 3\%$ and $18 \pm 2\%$ for wash-in and wash-out processes, respectively. Dynamics of gas distribution during one breath cycle was analyzed. The calculated inspiration and expiration maps gave normalized effective times [rel. un.] for these stages $0.95 \pm 0.18$ and $0.84 \pm 0.15$, respectively. Different $^{19}$F pulmonary MRI methods were implemented: 3D imaging, wash-in/-out dynamics and single respiratory cycle imaging. The results are agreed with known data and demonstrates possibility of ventilation assessment of the lungs at 0.5 Tesla.
1 Introduction

Lung imaging is an important task for medical diagnostic, since respiratory diseases have one of the biggest impact for people disability worldwide [1]. The methods that are currently applied in clinic (X-ray, CT, PET, etc.) use harmful ionizing radiation, and are not preferable for frequent use (more than two times per a year) or for pediatric studies. MRI does not use any harmful ionizing radiation [2].

Multinuclear MRI approaches carrying out on specific contrast gases have possibilities for functional lung assessment—ventilation, perfusion and gas exchange studies. For this purpose, hyperpolarized noble gases (for example, xenon, krypton, and helium) or fluorinated gases (sulfur hexafluoride, perfluoropropane, etc.) [3, 4] can be used as inhalation contrast agents for MRI of the lungs. Fluorine-19 ($^{19}$F) has very closed to protons gyromagnetic relation and is almost as sensitive to NMR as hydrogen nuclei (~83% of $^1$H sensitivity [5]) and, hence, there is no need to hyperpolarize fluorinated gases. Noble gases are hyperpolarized by metastability exchange (ME) or spin exchange (SE) optical pumping techniques, which are complex, very expensive, and require skilled maintenance and operation [6]. Therefore, $^{19}$F MRI requires less equipment compared with hyperpolarized-gas MRI, and it is much easier to implement in clinical and preclinical practice than MRI of hyperpolarized noble gases. Moreover, some fluorinated gases are already used in clinical studies as ultrasound contrast agents [7, 8] and in eye surgery [9, 10].

$^{19}$F MRI of the lungs is usually performed in magnetic fields higher than 1.5 Tesla to increase the sensitivity [4]. However, the higher the field strength, the longer $T_1$ and shorter $T_2$. Moreover, magnetic susceptibility artifacts become more exaggerated. Wherein, because of SAR restrictions spin-echo-based pulse sequences are usually not applied in $^{19}$F MRI of the lungs [11]. All these complicate signal detection from lungs. However, such problems do not appear at low magnetic fields. In addition, low-field MRI scanners are significantly cheaper, they can work with permanent magnets, and can be installed in any hospital [12].

This work is dedicated to the development of $^{19}$F MRI approaches for functional lung assessment at low magnetic field—0.5 Tesla. As a contrast agent, we used octafluorocyclobutane gas ($C_4F_8$, OFCB). Although this gas is not commonly used for $^{19}$F MRI, it is prospective for lung imaging, since it has eight magnetically equivalent fluorine nuclei, which provide singlet NMR spectrum and strong fluorine signal. OFCB is an inert gas and often used as a refrigerant and heat-transfer medium, as a propellant for foods [13]. It is also applied in eye surgery [14]. Wherein, OFCB has the longest relaxation times ($T_1 \sim T_2 \sim 50$ ms [15]) among all fluorinated gases used in $^{19}$F MRI ($T_1 \sim T_2 \sim 1.8$ ms for sulfur hexafluoride, and $\sim 18$ ms for perfluoropropane [16]). Therefore, OFCB is suitable for conventional scanning pulse sequences with Cartesian k-space filling, there is no need to use radial pulse sequences providing short TE (such as UTE or ZTE) [17]. It is certainly an advantage, since not any MRI scanner can operate with such pulse sequences that require strong gradient systems. The use of OFCB as
inhaled contrast agent for $^{19}$F MRI was firstly proposed in 2010 and demonstrated pig lung imaging at 1.5 Tesla [18]. Recently we showed the effectiveness of this gas for $^{19}$F MRI for human lung imaging at 0.5 Tesla [15] and for small laboratory animal studies at 7 Tesla [19]. The comparison of this gas with perfluoropropane at 3 Tesla has been shown in the paper [20].

In our previous paper [15], we showed the possibility of using 2D and 3D fast spin-echo sequence (FSE) within SAR limitations for human lung imaging using OFCB as contrast agent at 0.5 T clinical scanner. The aim of this work was to use OFCB for functional lung assessment at the same MRI system. It is also interesting, since $^{19}$F MRI studies of lung functions have been carried out before only at fields higher than 1.5 Tesla.

### 2 Materials and Methods

#### 2.1 MRI System

$^{19}$F MRI studies were performed on a custom-modified clinical 0.5 T MR scanner Bruker Tomikon S50 (Bruker, Ettlingen, Germany). The system is equipped with a superconducting magnet (Magnex, Oxford, UK) with a bore diameter of 60 cm, 2 kW RF transmitter LPPA-2120 (Dressler, Stolberg, Germany), and gradient system S630 with 16.7mT/m power and 0.5 ms rise time. The scanner is driven by XwinNmr v.1.0 and ParaVision v.1.0—proprietary pieces of software by Bruker Corporation. For $^{19}$F MRI, we used the manufacturer’s receive-only body coil (Part No. T5968). For RF excitation of $^{19}$F nuclei, we used a propriate 60 cm diameter saddle coil build-in the bore of the magnet.

#### 2.2 Inhalation Contrast Agent

As a contrast for $^{19}$F pulmonary MRI the gas mixture of 70% OFCB (99.8% purity) with 30% $O_2$ (96–98% purity) was used.

#### 2.3 Subjects

One healthy volunteer (f. 28 y.o.) took participation in $^{19}$F MRI studies. In vivo studies were approved by the institutional review board, and written informed consent was obtained before the studies.

#### 2.4 $^{19}$F MRI Studies

We obtained $^{19}$F MR images by 3D and non-slice selective 2D scanning using FSE sequence. For 3D scan, the following parameters were used: TR/TE$_{\text{min}}$ = 42/8 ms, ETL = 4, BW = 7.8 kHz, FOV = 32×24×32 cm$^3$, Matrix size = 32×24×32, Voxel size = 1×1×1 cm$^3$. Total acquisition time with 4 averages was 33 s. For non-slice selective 2D scan, parameters were as
follow: TR/TE_{\text{min}} = 42/8 \text{ ms}, ETL = 4, BW = 7.8 \text{ kHz}, FOV = 32 \times 32 \text{ cm}^2, \text{Matrix size} = 32 \times 32. \text{Total acquisition time with 16 averages was 5 s.}

2.5 3D Imaging

Before $^{19}$F 3D scanning, a volunteer took two deep breathes: the first one—from air, and the second—from a plastic balloon (25 L) with gas mixture. On the third deep inhalation of the gas mixture, the volunteer held the breath, during which the scanning was carried out.

2.6 Wash-in/Wash-out Dynamics

The method for the fractional ventilation assessment based on monitoring the wash-in/-out dynamics [21] was carried out. For this method, a time series of images was obtained, showing the process of gas accumulation in lungs during breathing with fluorinated gas mixture (wash-in process) and its remove during breathing with air (wash-out process). A subject took a normal breath with gas mixture and held the breath for a short period of time (5 s) during the non-slice selective 2D scanning. The procedure repeated several times until the lungs saturated with fluorinated gas. Then, subject began to breathe air, and the fluorinated gas excretion from lungs was observed (wash-out process).

Fractional ventilation ($r$) is defined as the ratio of «new» gas ($V_{\text{new}}$) entering a voxel at each breath, divided by the total amount of gas in each voxel ($V_{\text{total}}$) [22]:

$$r = \frac{V_{\text{new}}}{V_{\text{total}}} \tag{1}$$

Wash-in process can be considered as replacing air in lungs with fluorinated gas mixture, otherwise wash-out process is observed. The value of $r$ for wash-in/ wash-out dynamics can be calculated as [21, 22]:

$$\begin{align*}
S_{n_{\text{wash-in}}} & = S_0 \left( 1 - (1 - r_{\text{wash-in}})^{n_{\text{wash-in}}} \right) \\
S_{n_{\text{wash-out}}} & = S_0 \left( 1 - r_{\text{wash-out}} \right)^{n_{\text{wash-out}}} \tag{2}
\end{align*}$$

where $S_{n_{\text{wash-in}}}/S_{n_{\text{wash-out}}}$ are signal intensities in MR images obtained on a certain breath hold, $n_{\text{wash-in}}/n_{\text{wash-out}}$—a number of a breath hold, $S_0$—the parameter of approximation corresponding to the maximal signal intensity in lungs saturated with fluorinated gas mixture.

The signal intensities in a time series of images can be approximated by the following functions [21]:

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where $t_{\text{wash-in/out}}$ —is an effective time of wash-in/wash-out dynamics. Time ($t$) can be calculated as $n_{\text{wash-in/out}} (aq + d)$, where $aq$—acquisition time of one MR image (5 s), and $d$—delay between scan shots for expiration and inspiration of a volunteer (3 s).

### 2.7 Single-Breath Dynamics

Another method for analyzing fluorinated gas accumulation in lungs and its subsequent removal from them based on monitoring gas distribution in lungs during one respiratory cycle was implemented. This study was conducted without holding the breath, but the subject took one deep breath and then exhalation of the fluorinated gas mixture slowly. During this breath cycle, a series of non-slice selective 2D images was obtained.

The whole process of gas dynamics during single breath can be divided into two separate stage—inspiration and expiration. The signal intensity through the time series of fluorine images can be approximated by functions:

\[
\begin{align*}
S_{\text{insp}} &= S_0 \left(1 - e^{-\frac{t}{t_{\text{insp}}}}\right) \\
S_{\text{exp}} &= S_0 e^{-\frac{t}{t_{\text{exp}}}}
\end{align*}
\]

where $S_{\text{insp}}$ and $S_{\text{exp}}$ are signal intensities in MR images during inspiration and expiration stages, respectively; $t_{\text{insp}}$ and $t_{\text{exp}}$—the effective times of inspiration and expiration stages.

In this study, we calculated time maps $t_{\text{insp}}$ and $t_{\text{exp}}$ normalized to the full time of inspiration ($T_{\text{insp}}$) and expiration ($T_{\text{exp}}$): $\tau_{\text{insp}} = t_{\text{insp}}/T_{\text{insp}}$ and $\tau_{\text{exp}} = t_{\text{exp}}/T_{\text{exp}}$. $\tau$-maps are measured in relative units.

### 2.8 Image Processing and Analysis

The raw data (k-space) were further processed using apodization to increase the SNR values:

\[
K_A(k_x, k_y, k_z) = K(k_x, k_y, k_z) \exp \left( -\frac{|k_x - k_{x0}|}{aN_x} \right) \exp \left( -\frac{|k_y - k_{y0}|}{aN_y} \right) \exp \left( -\frac{|k_z - k_{z0}|}{aN_z} \right)
\]

where $k_x, k_y, k_z$ — the coordinates of Cartesian k-space; $K_A(k_x, k_y, k_z)$ and $K(k_x, k_y, k_z)$ — k-space before and after apodization, respectively; $k_{x0} = N_x/2$, $k_{y0} = N_y/2$, $k_{z0} = N_z/2$; $N_x$, $N_y$, $N_z$—matrix sizes, $a$—apodization parameter. The Eq. (5) is shown in general form for 3D scanning.
The raw data processing was carried out using custom-written software (in C++). For 3D MRI data $a$ was 0.1, and for 2D MRI data $a$ was 0.2. Parametric maps were constructed using the program codes written in the Python v.3.8. 3D MRI data were used for volumetric reconstruction (3D rendering)—it was done using ImageJ v.1.58j software [23]. Lung volume was estimated from 3D FSE images using the Iterative Self-Organizing Data Analysis Technique algorithm [24] in ImageJ software based on an automatically determined intensity threshold.

### 3 Results

Figure 1 shows volumetric images (3D rendering) of the lungs. The images are presented at different azimuthal angles, where $0^\circ$ corresponds to the frontal view from the back. The volumes were measured for each lung, which were $\approx 1.8$ L and $\approx 1.7$ L for the right and left lungs, respectively.
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Figure 2A demonstrates the time series of images obtained during wash-in and wash-out dynamics. According to calculated functional maps the effective time of gas washing in was 30 ± 5 s and washing out was 19 ± 4 s—corresponding time maps are shown in Fig. 2B, C, respectively. Fractional ventilation maps are presented in Fig. 2D, E—$r_{\text{wash-in}}=29 ± 3\%$ and $r_{\text{wash-out}}=18 ± 2\%$.

Figure 3 shows images obtained during single breath. The experiment was performed twice—first, the images in coronal projection (A) were obtained, and then—in axial projection (B). Normalized maps of the effective times of inspiration and expiration are presented in Fig. 3C–F. $\tau_{\text{insp}}$ was 0.95 ± 0.18, $\tau_{\text{exp}}$—0.84 ± 0.15.

4 Discussion

In this work, different fluorine approaches of lung ventilation assessment were implemented on 0.5 T MRI scanner. They include 3D lung visualization, wash-in/wash-out dynamics, and gas distribution study during single respiratory cycle.

3D images reflects gas distribution in lungs and can be used for ventilation volume assessment. The measured volumes gave physiologically reasonable estimates: $\approx 1.8$ L for the right lung and $\approx 1.7$ L for the left lung in a female volunteer. However, considering relatively low SNR of 6–10 and a resolution of $1 \times 1 \times 1$ cm$^3$ in obtained images the error of such estimation reaches 40%.

2D non-slice selective $^{19}$F images of the lungs were obtained for 5 s to perform ventilation assessment during the wash-in/wash-out dynamics. As a result, fractional ventilation maps and time maps of gas washing in and out were calculated. The measured values of fractional ventilation and effective time of washing out process are agreed with the data obtained in the paper [25] for healthy volunteers. As far as we know, there is no data about wash-in process, wash-out dynamics is often monitored during MRI experiment [21, 25].

A method based on single-breath imaging was implemented. As a result, the effective time maps of the inspiration and expiration stages were calculated. An advantage of the experiment of single-breath dynamics is that the study is carried
out without breath hold, while the patient slowly takes a deep inhalation with a fluorinated gas mixture, and then a full exhalation. However, considering that the time during which a subject does a full breath cycle varies much from subject to subject, therefore we normalized these maps to the times during which the volunteer took inhalation and exhalation. Such normalized time maps (Fig. 3C–F) can be markers for ventilation lung assessment.

5 Conclusion

The use of OFCB gas as an inhalation contrast agent for $^{19}$F MRI gives acceptable results not only for imaging human lungs, but also for their functional assessment even at 0.5 Tesla.

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Data Availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Competing interests The authors declare no competing interests.

Conflict of Interest The authors have no competing interests, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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