ON THE ESTIMATION OF THE ALVEOLAR SIZE IN THE HUMAN LUNG USING PROTON MRI

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Purpose: The alveolar size is a parameter of paramount importance in the lung, since it could help to develop a better understanding of respiratory dynamics and to detect microstructural injuries [1,2]. In this work a novel approach based on proton MRI is proposed, which allows for the quantification of the alveolar size *in vivo*, by exploiting the transverse relaxation enhancement due to water diffusion through the internal magnetic field gradients of the lung.

Methods: Susceptibility differences between air and tissue in the lung generate microscopic magnetic field gradients at the alveolar length scale. Diffusion of spins through these internal gradients affects the magnetization by enhancing its transverse relaxation (R_2), such that: $R_2 = R_{2,0} + \Delta R_2$, where $R_{2,0}$ is the spin-spin relaxation and ΔR_2 is the enhancement due to diffusion [3]. The lung tissue can be modeled as a densely packed array of spheres (the alveoli) generating dipolar fields in the surrounding lung tissue [4], where the water molecules diffuse. ΔR_2 can thus be described by [5]:

$$\Delta R_2 \propto \frac{\eta}{r}\sqrt{\frac{4\pi}{3}\,\Delta\chi\, B_0\, D} \qquad (1)$$

where r=sphere radius, η=volume fraction occupied by the spheres, Δχ=susceptibility difference, D=diffusion coefficient. The basic idea of the presented technique is to quantify the alveolar size by exploiting the dependence of ΔR_2 on r.

A fast technique, based on a HASTE sequence with Hahn-echo preparation, is proposed for the quantification of ΔR_2. The Hahn-prepared HASTE sequence, as shown in Fig.1, was implemented on a 1.5T MR-scanner. In this sequence, the signal decay due to $R_{2,0}$ and ΔR_2 is dictated by different time variables: the echo time ($TE = \Delta TE_1 + n\cdot\Delta TE_2$) and the effective echo time ($TE_{eff}^3 = \Delta TE_1^3 + n\cdot\Delta TE_2^3$), respectively [6]. Hence, the overall signal decay due to transverse relaxation is:

$$S(\mathrm{TE}, \mathrm{TE}_{\mathrm{eff}}) \propto \exp\left(-R_{2,0}\,\mathrm{TE} - \Delta R_2\,\mathrm{TE}_{\mathrm{eff}}\right) \qquad (2)$$

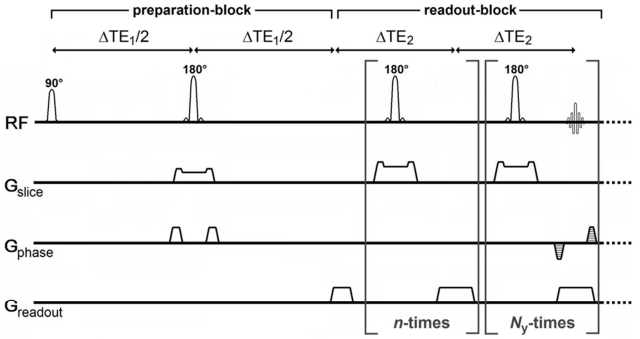

Fig. 1 Pulse diagram of the Hahn-prepared HASTE sequence used to image ΔR_2. Main parameters: inter-pulse time of the preparation-block ($\Delta TE_1/2$), inter-pulse time of the readout-block (ΔTE_2), number n of refocusing pulses in the readout-block which can be applied before actual image acquisition, number of phase-encoding steps N_y for repeated signal acquisition.

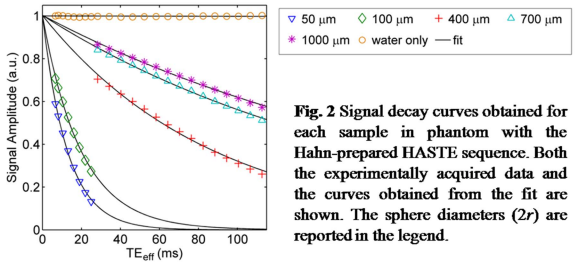

Fig. 2 Signal decay curves obtained for each sample in phantom with the Hahn-prepared HASTE sequence. Both the experimentally acquired data and the curves obtained from the fit are shown. The sphere diameters ($2r$) are reported in the legend.

Direct quantification of ΔR_2 can be performed, without knowledge of $R_{2,0}$, by acquiring several images with different values of TE_{eff}, but identical TE, and fitting them using Eq. 2. This can be achieved by properly regulating ΔTE_1 and n in the sequence (with ΔTE_2 fixed).

In a first step, phantom experiments were performed, as a prove-of-principle, to verify the ability of the sequence to discriminate signals with different ΔR_2. Six samples containing a mixture of water and glass microspheres of known diameters were used (see Fig.2). All samples had the same $R_{2,0}$ but different ΔR_2, according to Eq. 1.

In a second step, *in vivo* experiments were performed on healthy volunteers. Two images, both with TE=27ms and ΔTE_2=2.4ms, were acquired in one breath-hold of about 10s duration: one image with TE_{eff}=5.5ms (n=10 and ΔTE_1=3ms); the other image with TE_{eff}=27ms (n=0 and ΔTE_1=27ms). ΔR_2 was calculated on a voxel-by-voxel basis from Eq. 2.

Coronal slice imaging, with ECG triggering in the diastolic phase, was performed at different breathing states: functional residual capacity (end expiration) and total lung capacity (end inspiration). Imaging parameters: FOV=500x500mm^2, matrix=128×128, slice thickness=15mm, partial Fourier factor=5/8, TR=6000ms.

Maps of the alveolar diameter ($2r$) were calculated from the ΔR_2 maps, using Eq. 1. To account for variations of η with inflation, a proton density image was additionally acquired using a proton density-weighted UTE sequence (TR=2.5ms, flip-angle=2°); η maps were calibrated by assuming that large vessels consist of 100% water and then used for a voxel-by-voxel correction. So far, other parameters in Eq. 1 were assumed to be constant within the lung ($4\pi\cdot\Delta\chi\approx$10ppm [7], $D\approx 2.3\cdot10^{-3}$mm^2/s: diffusion coefficient of water).

Results: In the phantom study, a high discrimination of signals with different ΔR_2 was observed (Fig.2). The expected diameter-dependent relaxation, which monotonically decreases with the sphere radius, was obtained. The signal decay in the pure water sample is negligible ($1/\Delta R_2$>50000 ms), demonstrating the insensitivity of the method to $R_{2,0}$. *In vivo* results are shown in Fig.3. The ΔR_2 maps show a much higher relaxation in the lung compared to other tissues, with a rather homogeneous distribution within the lung parenchyma. In addition, a slight dependence on lung inflation was found. Mean values in the lung parenchyma for the maps of Fig.3: $1/\Delta R_2$=28.2ms (expiration) and 26.1ms (inspiration). The η maps exhibit an air fraction within the lung of about 80%, which increases with inflation. The calculated maps of the alveolar diameter ($2r$) show quite similar values in expiration and inspiration, with a mean value within the lung of about 230µm. This is in good agreement with previous reports [2,8], as well as with the alveolar recruitment theory [1,2].

Conclusion: The presented method can be potentially used to quantify the alveolar size of the human lung in-vivo. To this end, maps of the transverse relaxation enhancement, due to diffusion within internal gradients, are acquired. An additional proton density image is used to correct for variations of the air fraction. Since diffusion and susceptibility heterogeneities within the lung are affecting the quantification (see Eq.1) and perfusion effects could also have a significant influence [9], additional corrections are required in the future. Finally, the ΔR_2 maps themselves could be used to assess alterations or mismatches, which can be eventually induced by lung pathologies, between microstructural and tissue-specific properties (as stated by Eq.1).

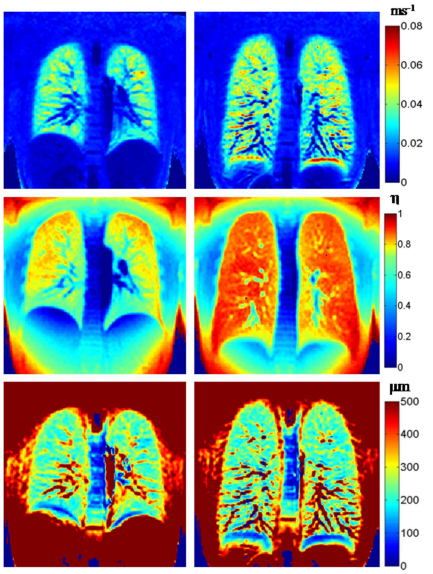

Fig. 3 Top: Maps of ΔR_2 acquired with the Hahn-HASTE sequence. Center: Maps of the air volume fraction η obtained with the UTE sequence. Bottom: Maps of the alveolar diameter ($2r$), calculated from a combination of the two above. A comparison between the results obtained at end expiration (left) and end inspiration (right) is shown.

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