In vivo diffusion measurements of hyperpolarized helium-3 in rat lungs at low field: time dependence with a fast sequence

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Introduction

Restricted diffusion causes a time dependence of the apparent diffusion coefficient (ADC) for a fluid inside porous medium[1]. *In vivo* observations with hyperpolarized gases in human lungs have already been reported at both short-time scale (ms)[2] and long-time scale (s)[3]. The time scale for which diffusion length gets longer than alveolar size (200 µm) is only about 200 µs, for ^{3}He diffusing in nitrogen. Diffusion measurements at longer times can thus potentially provide information about the lung airspaces interconnectivity[4]. In this work, the ADC time dependence was investigated in rat lungs at low magnetic field, taking advantage of long T_2* and T_2 with a CPMG sequence. This single-shot large flip angle sequence gave access to a fast and accurate measurement in the 100 ms time scale, thus corresponding to displacements over the acinus size. Global measurements were also compared to ADC maps obtained from standard FLASH acquisitions.

Materials and Methods

In vivo experiments were performed on five male Wistar rats (Janvier Laboratories, France, weight of 250 g). The animals were anaesthetized with intraperitoneal administration of thiopental (15 mg·kg^{-1}), then tracheotomized and placed supine in the scanner. Tracheal pressure was monitored using a Honeywell pressure transducer (DC001NGC4). MR acquisitions were performed immediately after forced inhalation of HP ^{3}He, polarized between 10 and 14% by metastable exchange optical pumping[5] with a 2 W laser (1083 nm) in a 50 cm glass cell. For each experiment, 5-7 mL of ^{3}He were transferred to the syringe, to be administered to the rat via a tracheal catheter. NMR experiments were performed on a 0.1 T scanner (Magnetech, France), controlled by an Apollo sequencer (Tecmag, Houston, TX, USA). A 40-cm saddle-shaped RF coil was used for transmission (Q=45), and a 10-cm diameter Helmholtz coil for reception (Q=340). Both coils were tuned at the ^{3}He NMR frequency (3.29 MHz). Global ADC measurements were made with a CPMG sequence (Fig. 1) consisting of a series of 10 echoes generated by 180°$_y$ hard pulses (249 µs) following an initial 90°$_x$ RF pulse, with an inter-echo time of 100 ms. The 5 first echoes were used to determine T_2. For the 5 last echoes, a bipolar gradient (ramp duration 2.2 ms, plateau duration 0.6 ms, gradient amplitude (G) 3.5 mT/m), was applied along the cranio-caudal direction before signal acquisition (observation time 6.656 ms). The time (t_diff) separating the two edges of the bipolar gradient and the delay t_var preceding the bipolar gradient were varied by steps of 10 ms, keeping their sum equal to 40 ms. The total acquisition time was 1 s. The signal magnitude for each echo was deduced by fitting the complex data to an exponential decay. After a nonlinear fit of the 5 first echo amplitudes to get T_2, diffusion-weighted signals were corrected from the T_2 decay to compute signal attenuation S due to the bipolar gradient alone. Taking S proportional to exp(-b·ADC), where b depends on each time profile of the bipolar gradient through the diffusion time Δ, the corresponding ADC(Δ) were found. Diffusion weighted images (Fig. 2) were obtained as coronal projections in 3 rats with a flip angle of 11°, FOV 8.25×8.25 cm^2, TR 32.8 ms, observation time 6.5536 ms, matrix 32×2×24, with 2 b-values (b=0 and b=11.98 s/cm^2) in an interleaved way. The diffusion bipolar gradient had the same shape as in the CPMG sequence with Δ=5 ms.

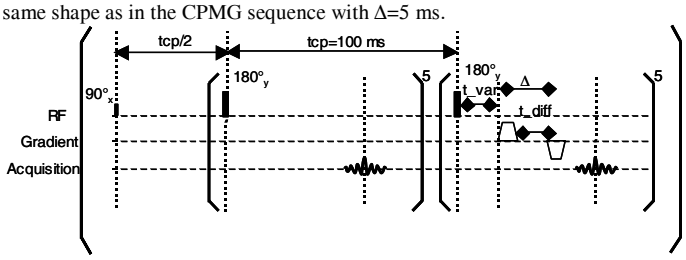

Fig. 1: CPMG sequence: 5 last echoes with a variable diffusion time Δ

Results

Table 1 : b and ADC values (mean ± standard deviation) for five rats and for the different diffusion times Δ

Δ (ms)	b (s/cm^2)	ADC_{CPMG} (cm^2/s)	ADC_{FLASH} (cm^2/s) (b=11.98 s/cm^2)
5	1.526	(7.4±1.31) 10^{-2}	(6.5±1.3) 10^{-2}
15	5.514	(4.69±0.43) 10^{-2}	
25	9.503	(3.41±0.36) 10^{-2}	
35	13.49	(2.94±0.56) 10^{-2}	
45	17.48	(2.17±0.27) 10^{-2}	

The measurements made *in vivo* on the rat lungs gave T_2* larger than 3 s, and T_2 of the same order at 100 ms echo time. The signal amplitude could be determined with an accuracy of 0.05%-0.5%. Fig. 3 shows the ADC values for the different rats plotted as a function of the diffusion time Δ. The tracheal pressure was in the range 15-30 mbar for all measurements. The mean values are reported in Table 1. The global ADC value decreased systematically when increasing the diffusion time Δ, by almost a factor of 4 on the investigated range, except for one animal, for which ADC at 35 ms was somewhat larger than that at 25 ms, but in agreement with the 10-20% reproducibility between different animals. These global ADC values were in good agreement with the ADC values found with the reference FLASH images at the same Δ.

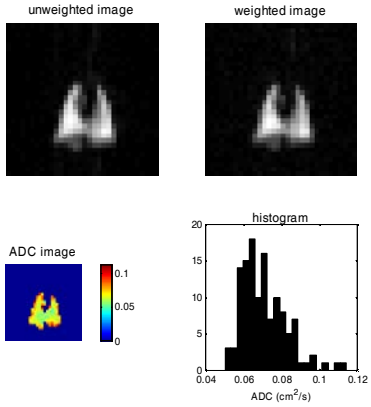

Fig. 2 : FLASH images (rat # 3), corresponding ADC map and histogram

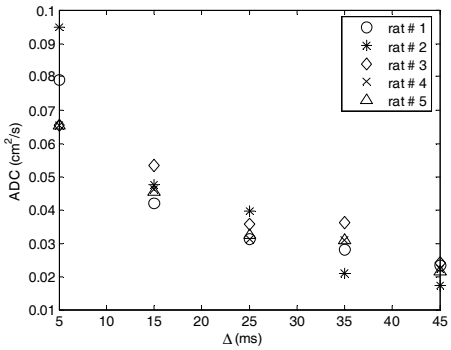

Fig. 3: Global ADC values as a function of Δ in each rat

Discussion and Conclusions

The long T_2* and T_2 values confirm previous measurements with animals and humans at low field[6], where susceptibility effects are weak. Such long values gave us the possibility to measure diffusion attenuation with a CPMG sequence with different diffusion times (5-45 ms) within 1 s, a short apnea duration for the rat. Our results show a 4-fold decrease of ADC over the 5-45 ms range, whereas Wang et al.[3] found a similar decrease in human healthy volunteers, but for longer time scales. Several reasons can be suggested for this time scale discrepancy: i) the rat acinus is somewhat smaller than the human one, ii) in our experiments pure ^{3}He volumes comparable to the rat inspiratory capacity were used, whereas in the global ADC measurements of Wang et al. on humans a small bolus of gas compared to the pulmonary capacity was used. Our preliminary results do not indicate a significant influence of tracheal pressure on the observed behavior. From the large flip angle of the CPMG sequence, the signal amplitude could be determined with an excellent sensitivity in small animals, but our measurements showed a relatively large variability (10%-20%), even during a given experiment, presumably due to physiological movement. In conclusion, fast multiecho sequences have been already used for *in vivo* MRI on humans with hyperpolarized gases at low field[7]; their high sensitivity from the large flip angle used make them also advantageous for fast measurements of the ADC time dependence. Pathological models will be investigated in future work.

References

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