Effect of Finite Gradient Width on Hyperpolarized 3He gas Lung Q-Space Diffusion Spectroscopy *in vivo*

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Introduction

Hyperpolarized ^{3}He gas based q-space diffusion measurements in lungs present an opportunity to non-invasively probe the morphology of lung airspaces. Q-space or for that matter any of the PFG based NMR diffusion techniques rely on the short gradient pulse (SGP) approximation **[1].** SGP assumes that the width of the diffusion sensitizing gradient is sufficiently narrow ($\delta << \Delta$) so that the motion of the molecules during the period of application of these gradients is negligible. However, given the finite rise times of the gradient systems, and due to hardware constraints, this approximation can never be realized on clinical scanners. Therefore when one is forced to use long δ on the clinical MRI scanners, it becomes necessary to understand the effect of this departure from SGP condition on the extracted ^{3}He displacement profiles using the q-space formalism **[2].** In this work, we present, with simulations and *in vivo* data, the effects of finite gradient width (FGW) on ^{3}He gas q-space diffusion parameters in the lungs.

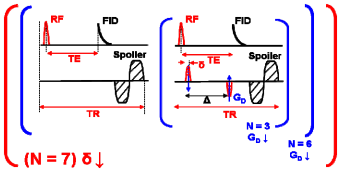

Figure 1. ^{3}He q-space DWS sequence for multiple δ times. The colors indicate the variation of DWS parameters in the loop

Methods and Materials

Simulations: FGW effects were simulated using the matrix formalism developed by Callaghan PT **[3].** The formalism decomposes the gradient pulses into discrete impulses and the phase evolution is for calculated for each of these times and then integrated (Fig 2). Given the complex geometry of the lung microstructure, simulations were performed with parallel plate geometries using ^{3}He gas as the probe. The gradient waveform was typically divided into 100 or more segments depending on the values of diffusion time (Δ) and finite gradient width (δ). The echo attenuation due to diffusion was obtained for diffusion coefficients of 0.88 cm^2/s (^{3}He diffusivity in air) and 2.0 cm^2/s (free diffusivity of ^{3}He) for δ varying from 0.1 s to 6.4 ms, The value of Δ was fixed at 6.8 ms and q_{max} fixed at 2 mm^{-1} (similar to q-space experimental parameters *in vivo*) with q values varying (by changing gradient amplitudes) from 0 mm^{-1} to q_{max} over 100 increments. The distance between the plates was varied from 100 µm to 700 µm, noting that the diameter of normal human alveoli is ~250 µm to predict the effect of FGW on varying geometry sizes. The q-curve was then Fourier transformed to provide the DPP. The root-mean-square value was calculated for the DPP. **Q-space Spectroscopy *in vivo*:** To validate the findings of analytical simulations for finite gradient width, data were collected from three healthy volunteers and one COPD patient. ^{3}He diffusion-weighted spectroscopy (DWS) datasets were obtained on a 1.5T Siemens Sonata MRI system using a ^{3}He flexible coil. The q-space sequence described in **[Ref 4]** was modified to accommodate variable width of diffusion gradient lobes (Figure 1). Data were collected for δ= 1.63 ms, 2.56 ms, 3.52 ms, 4.48 ms, 5.44 ms, 5.92 ms, 6.55 ms. For each δ, the sequence acquired 24 spectra (19 diffusion weighted spectra and non-diffusion weighted spectra which were interleaved throughout the diffusion weighted spectra), with the q_{max} and diffusion time Δ fixed at 2.008 mm^{-1} and 6.8ms respectively. Since the value of q_{max} was fixed, the diffusion gradient strengths were calculated such that for each δ, the q-space curve was sampled at same incremental q value of 0.106 mm^{-1}. The b value factor for each different δ was consequently different, ranging from 100 s/cm^2 for δ= 1.63 ms to 74 s/cm^2 for δ = 6.55 ms. For each different δ, the TE/TR changed accordingly, ranging from TE/TR =9.38/41.9 ms for δ= 1.63 ms to 14.3/46.8 ms for δ = 6.55 ms. Since the SNR decreases at longer TE due to T_2* effects at larger widths, the flip angles were varied accordingly from 5° to 14° to obtain adequate SNR (> 8) for later scans. The sequence thus collected 168 spectra, in a single breath hold of ~8 s. Flip angle and T_1 attenuation correction was performed separately for each set of TE/TR data. The *in vivo* data was processed and analyzed using the data analysis technique described in **[Ref 4]** and the DPP obtained. The DPP were resolved using a bi-Gaussian model. The weighted average rms displacement ($X_{rms,WA}$) **([4])** was used as single metric to describe the DPP and was correlated with the effects of increasing δ using the regression analysis tool provided in SigmaPlot (Version 7).

Results and Discussion

Simulations: Figure 3 indicates that as the δ increases, the echo attenuation decreases. In the conjugate Fourier domain, this implies that DPPs are narrower, resulting in smaller rms values (133 µm for δ = 0 ms to ~112 µm for δ = 6.4 ms). The decrease in the predicted rms displacement is also faster with the gas diffusing at rate of 2 cm^2/s compared to reduced diffusion coefficient of 0.88 cm^2/s, but becomes almost similar (CV < 0.22%) for $\delta \geq$ 4 ms(Figure 4). Moreover, as seen from Figure 5, the effects are more severe for larger geometrical dimensions (60% decrease for plates separated by 700 µm, compared to 3% for 100 µm plate separation).

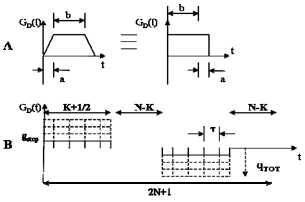

Figure 2. Setup for matrix simulation of q-space [2]

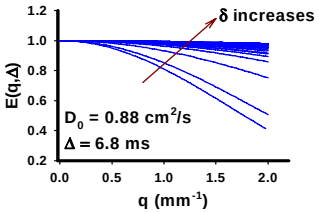

Figure 3. Echo attenuation decreases with increasing δ

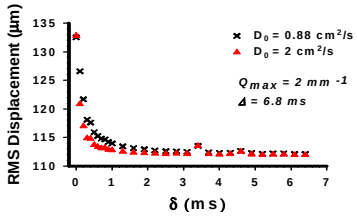

Figure 4. ↓ RMS displacements with ↑ δ, with the effects stronger with free diffusion

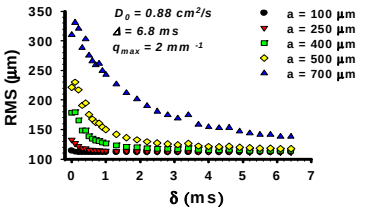

Figure 5. Effects of ↑ δ much more severe with larger geometrical sizes

Q-space Spectroscopy *in vivo*: As predicted by simulations, the diffusion attenuation decreased with increasing diffusion gradients width δ, consequently narrowing the DPP in healthy volunteers and COPD patient (Figures 4 and 5). The decrease in the measured rms displacements with increasing δ was found as predicted by simulations (Figure 6). In the all the volunteers, it was noticed that the weighted average rms displacements decreased by ~ 11-15% for a change in δ by 1 ms.

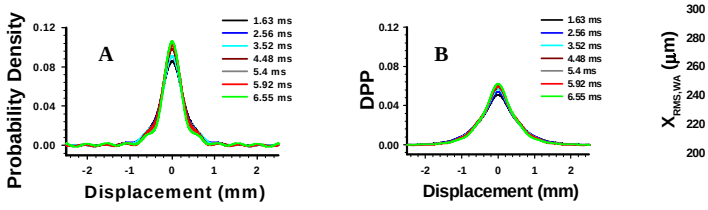

Figure 6 A: DPP in healthy volunteer. B DPP in COPD patient. C and D: Weighted average root mean square displacement↓ with ↑ gradient width

Conclusion The results suggest that in context of using q-space formalism for estimating alveolar dimensions on clinical scanners, the diffusion measurements inevitably underestimate the size of the alveoli within which the diffusion is taking place. This might be more relevant for enlarged alveolar dimensions, such as those expected in COPD. The result also strongly suggests that in order to compare results of diffusion experiments across groups, a standardized protocol must be adopted.

References: **[1]** J Chem Phys 1968;49(4):1768-1777 **[2]** NMR Biomed 2002;15(7-8):516-542 **[3]** J Magn Reson 1997;129(1):74**. [4].** *J Magn Reson Imaging.* 2006; 24: 84-94