Measurement of hyperpolarized gas diffusion at very short time scales

M. Carl[1], G. W. Miller[2], J. P. Mugler III[2], S. Rohrbaugh[1], W. A. Tobias[1], and G. D. Cates[1,2]

[1]Physics, University of Virginia, Charlottesville, VA, United States, [2]Radiology, University of Virginia, Charlottesville, VA, United States

Introduction/Purpose: Hyperpolarized ^{3}He diffusion MRI is a powerful tool to probe lung microstructure at a length scale inaccessible by conventional *k*-space MRI. For short diffusion times, Δ, time dependent diffusion measurements are sensitive to the surface to volume ratio (*S/V*) of the surrounding structure [1]. Because of the high gas diffusivity (D_{Xe}=0.14cm^2/s, D_{He}=0.88cm^2/s) and the small size of alveoli (~200μm)), measurement of *S/V* with the traditional single bipolar diffusion technique is challenging in the lung, since only small diffusion attenuation can be imparted within the short time scale regime (~200μs). Given the significance of short time scale diffusion in the assessment of lung microstructure, we developed a new technique that proves promising to enable such measurements.

Method: The basic idea behind our pulse sequence (Fig.1) is to concatenate many bipolar diffusion gradients ("unit cells") to increase the diffusion weighting ($b \rightarrow Nb$). It is this increase in diffusion attenuation that allows the measurement of *D* even at small diffusion times. One's first instinct might be to simply do so along only one axis, one after the other [2]. Preliminary simulations showed that although this method works for free diffusion, it fails for restricted diffusion. This breakdown appears to be due to the well known edge enhancement effect [3] that causes the signal near the edges of the structure to be higher then the signal away from the edge. If the next unit cell starts while there is still such a systematic signal variation across the sample, the spins are not weighted equally for the next iteration.

Our sequence employs two strategies to avoid such systematic deviations: 1) A wait time, T_{wait}, is inserted between each unit cell to allow the edge effect to diffuse away before application of the next unit cell. Given the restriction imposed by T_2* decay, this wait time should be kept as short as possible. 2) Temporally consecutive unit cells are applied along orthogonal axes. This allows the edge effect in the *x* direction to diffuse away, while imparting a diffusion weighting along the *y* and *z* axes. Therefore the effective wait time becomes three times the sum of the unit-cell duration and T_{wait}, which is denoted as $T_{equilib}$, allowing for a higher unit cell density. Finally, since by using a train of diffusion gradients, any gain in diffusion attenuation obtained by simply reading out the signal after the last unit cell is of course offset by the fact that the overall signal and therefore the SNR drops due to T_2* decay at the same time, we readout the signal during each T_{wait}.

The signal at the end of any n^{th} unit cell corresponds to:

$$S_1(n) = S_0 \cdot \exp\left(-n\left(bD + \frac{T_{cell}}{T_2^*}\right)\right) \qquad (1)$$

where $T_{cell} \equiv \Delta + T_{wait}$.

We also take reference runs with all gradients turned off:

$$S_2(n) = S_0 \cdot \exp\left(\frac{-nT_{cell}}{T_2^*}\right) \qquad (2)$$

Finally we compute their ratio:

$$R(n) \equiv \frac{S_1(n)}{S_2(n)} = \exp(-nbD) \qquad (3)$$

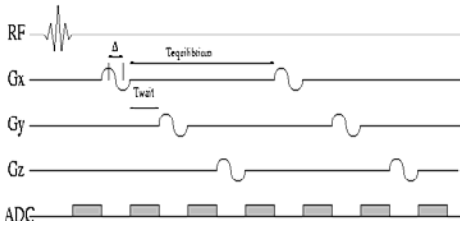

Fig.1: Pulse sequence timing diagram

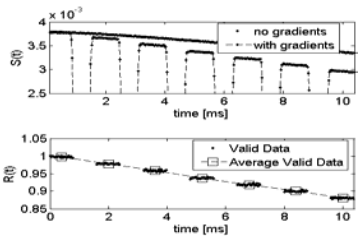

Fig.2: Experimental signal evolution

For every unit cell, we take the recorded ratio $R(t)$ during the following delay-time and assign its average value to $R(n)$, so that a fit to ln[$R(n)$] vs. n yields D.

We used simulations and phantom experiments to optimize and test our technique. Since the effectiveness of our method relies on imparting as many unit cells as possible within the limit imposed by T_2*, it was important to determine the minimum value for $T_{equilib}$. We studied this effect by simulating restricted diffusion for a given Δ in a 200μm sphere using bipolar gradients while varying the equilibrating time, $T_{equilib}$. To test the feasibility of our sequence in an experimental environment, we used a sphere of approximate diameter 1", containing 2.75 atm of hyperpolarized ^{3}He (D_0=0.65cm^2/s), to perform diffusion measurements from Δ=200μs to 3800μs and then calculated *S/V*. We also repeated the same measurements using the traditional method to highlight the advantages of our technique.

Results: A representative plot of experimental signal data is shown in Fig.2a. The continuous curve is the T_2* decay reference curve [Eq.(2)] and the dashed curve is the signal evolution during the gradient waveforms [Eq.(1)]. Fig.2b shows the corresponding ratio $R(t)$ [Eq.(3)]. The dashed line represents the exponential fit, which allows the calculation of *D*. We only display the results from six unit cells to facilitate comparison with the sequence shown in Fig.1.

Fig.3 shows the dependence of the simulated apparent diffusion constant for different Δ's as a function of $T_{equilib}/\Delta$. For each Δ, a horizontal dotted line represents the desired true $D(\Delta)$. As $T_{equilib}$ is increased, the diffusion constant asymptotically approaches the correct diffusivity. Note that for our sequence shown in Fig. 1, we are at $T_{equilib}/\Delta \geq 4$ even for $T_{wait} = 0$, for which all diffusion constants used in our experimental tests have settled to the correct asymptote.

Fig.4 shows experimentally measured diffusion constants plotted as a function of $\sqrt{\Delta}$. From the slope one can determine *S/V*. We found that the experimental *S/V* was 212±4 [m^{-1}]. Assuming that we know the radius of our sphere within 10%, this result is in agreement with the expected value of 236±24 [m^{-1}]. Finally, Fig.5 shows a comparison of the errors in determining *D* as a function of Δ for both our technique and the standard method. Note that our technique yields much lower error for diffusion times less than 400μs, which are relevant to the short-time-scale regime.

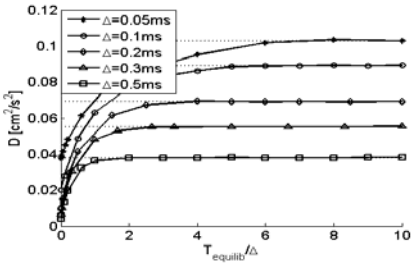

Fig3: Asymptotic approach to correct D

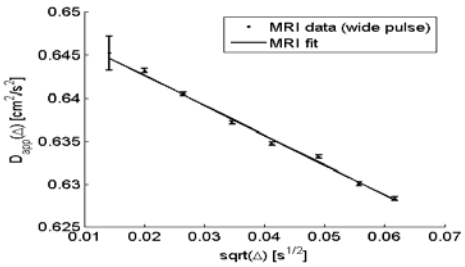

Fig4: Experimental diffusion data

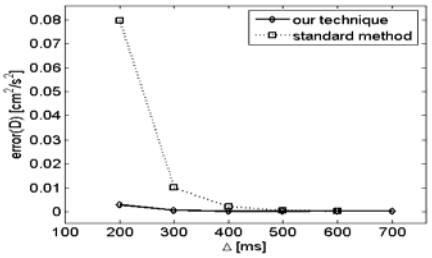

Fig5: Error (standard vs. our technique)

Conclusion/Outlook: We have developed and optimized a robust method for measuring diffusivities at very short diffusion times, which represents a crucial step toward enabling the extraction of *S/V* in the lung microstructure. Through simulations, we found that a naïve concatenation of bipolar gradients does not yield accurate diffusion measurements unless separated by a sufficient wait time. Experimental results demonstrate that in the short-time-scale regime, our sequence is capable of determining *D* much more precisely than the conventional method.

In future experiments, we will test our sequence on more elaborate phantoms such as glass bead packs and finally in vivo. We will concentrate our studies on the regime in which other groups have observed the breakdown of the standard diffusion sequence.

References: [1] P. P. Mitra et al, Phys. Rev. B47, No. 14, (1993) [2] Gross B. et al, Messtechnik **77**, 171-177 (1969) [3] A. L. Sukstanskii et al, J. Magn. Reson. **157**, 92-105 (2002)

Acknowledgments: Research supported by Siemens Medical Solutions.