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Reduced xenon diffusion for quantitative lung study—the role of SF_6

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ABSTRACT: The large diffusion coefficients of gases result in significant spin motion during the application of gradient pulses that typically last a few milliseconds in most NMR experiments. In restricted environments, such as the lung, this rapid gas diffusion can lead to violations of the narrow pulse approximation, a basic assumption of the standard Stejskal–Tanner NMR method of diffusion measurement. We therefore investigated the effect of a common, biologically inert buffer gas, sulfur hexafluoride (SF_6), on ^{129}Xe NMR and diffusion. We found that the contribution of SF_6 to ^{129}Xe T_1 relaxation in a 1:1 xenon/oxygen mixture is negligible up to 2 bar of SF_6 at standard temperature. We also measured the contribution of SF_6 gas to ^{129}Xe T_2 relaxation, and found it to scale inversely with pressure, with this contribution approximately equal to 1 s for 1 bar SF_6 pressure and standard temperature. Finally, we found the coefficient of ^{129}Xe diffusion through SF_6 to be approximately 4.6×10^{-6} $m^2 s^{-1}$ for 1 bar pressure of SF_6 and standard temperature, which is only 1.2 times smaller than the ^{129}Xe self diffusion coefficient for 1 bar ^{129}Xe pressure and standard temperature. From these measurements we conclude that SF_6 will not sufficiently reduce ^{129}Xe diffusion to allow accurate surface-area/volume ratio measurements in human alveoli using time-dependent gas diffusion NMR.

KEYWORDS: xenon; diffusion; sulfur hexafluoride; restricted diffusion; pulsed gradient spin echo, PGSE; gas-diffusion NMR

INTRODUCTION

Following the development of lung ventilation MRI using laser-polarized noble gases (^{129}Xe and ^{3}He),[1,2] attention has been given to NMR measures of noble gas diffusion as a new tool for studying lung structure and function.[3,4] In particular, we recently demonstrated that time-dependent noble gas diffusion NMR (i.e. observing variations in the diffusion coefficient as a function of diffusion time) can be used to determine the surface-area/volume ratio (*S/V*) and tortuosity of non-living porous media—packed beads and oil-reservoir rocks.[5,6] (Tortuosity is a measure of the long-range connectivity of a porous medium, and is related to the medium's fluid permeability.[7])

Gas diffusion NMR (GD-NMR) could have important clinical and scientific applications if successfully implemented in the lung:[8,9] e.g. determining regional variations in alveolar surface area and inter-alveolar connectivity. However, our recent work[6,10] also uncovered practical limitations to GD-NMR due to the rapid rate of gas diffusion. Diffusion coefficients for gases at standard temperature and pressure (STP) are typically on the order of 1×10^{-5} m^2 s^{-1}, which is 10^4–10^5 times greater than for liquids. Given the limited magnetic field gradients (about 0.01 T/m) that can be applied to humans, diffusion encoding for GD-NMR measurements typically requires 1–10 ms or more. During a 1 ms interval gas diffusion can be significant: approximately 75 μm for ^{129}Xe gas and 250 μm for ^{3}He gas at STP.

Theoretical studies have shown that when the distance diffused by a spin during the application of the gradient pulse is greater than about 14% of the diameter of the confining geometry (e.g. lung alveoli), then the narrow pulse approximation will be violated.[11] This approximation is a core feature of the standard Stejskal–Tanner

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Abbreviations used: GD-NMR, gas-diffusion NMR; *S/V*, surface area/volume ratio; STP, standard temperature and pressure.

NMR method for measuring diffusion,[12] and is the assumption that the movement of spins during the application of the diffusion encoding gradient pulse is negligible in comparison to any enclosing pores. Our work with time-dependent ^{129}Xe gas diffusion in small glass beads (2 mm diameter and less) has shown that the observed diffusion coefficient can change with variations in the gradient pulse time (δ).[10] In addition, the intended variation of diffusion coefficient with diffusion time (Δ) can lead to inaccurate measures of the *S/V*.[6,10] Such problems have rarely been important when studying water diffusion; however, with the advent of laser-polarized gas diffusion studies, these problems are now expected to occur more regularly. For ^{129}Xe gas at STP the limiting pore size that can yield accurate *S/V* data is $\sim$500 μm, assuming a 1 ms diffusion encoding pulse. Thus, a breakdown of the narrow pulse approximation may make GD-NMR ineffective for probing alveolar *S/V*, with current techniques.

We see two possible solutions to this inadequacy of GD-NMR: (i) new theoretical developments to show how to compensate for the breakdown of the narrow pulse approximation through advanced data analysis or pulse sequences;[13] and (ii) the use of a buffer gas to reduce noble gas diffusion such that the narrow pulse approximation is valid. In this paper we address the second of these possibilities. We report NMR measurements of reduced observed ^{129}Xe gas diffusion in the presence sulfur hexafluoride (SF_6), a biologically inert gas with large mass and an expected large scattering cross-section. As discussed below, we measured the coefficient of ^{129}Xe diffusion through SF_6 to be approximately 4.6×10^{-6} $m^2\,s^{-1}$ for 1 bar pressure of SF_6 pressure and standard temperature, only 1.2 times smaller than the ^{129}Xe self diffusion coefficient for 1 bar ^{129}Xe pressure and standard temperature. This ^{129}Xe-through-SF_6 diffusion coefficient is still much too large to prevent a breakdown of the narrow pulse approximation for ^{129}Xe GD-NMR applied to human alveoli. (The narrow pulse approximation will fail more severely for ^{3}He diffusion because the ^{3}He diffusion coefficient is an order of magnitude larger than that of ^{129}Xe for the same gas pressures and temperatures.)

EXPERIMENTAL METHODS

We performed thermally polarized xenon gas NMR measurements using glass sample cells filled with known pressures of gas at room temperature determined by a ratio method between the volume of a vacuum manifold and the sample cell. The sample cells had volumes of approximately 80 cm^3, and were fitted with valves to allow variation of gas pressure. Two bar pressure of isotopically enriched xenon (90% ^{129}Xe) was employed in all experiments. An additional 2 bar pressure of oxygen gas (O_2) was added to all sample cells to reduce the T_1 of ^{129}Xe from at least 1000 s to about 1 s and thus make signal averaging feasible. In total, three such cells were prepared. In addition to the xenon and oxygen mixture, the three cells were also filled with 0, 1 and 2 bar pressure of sulfur hexafluoride (SF_6) gas, respectively.

All NMR experiments were performed using a GE Omega/CSI spectrometer with a 4.7 T horizontal bore magnet. The spectrometer operated at 55.3 MHz for ^{129}Xe, using a home-built 5 cm inner diameter solenoid RF coil centered in the magnet, and aligned perpendicular to the B_0 axis. The 90° hard-pulse was 48 μs at maximum transmitter power, nominally 100 W. Gradients of up to 7 G/cm (0.07 T/m) were provided by a self-shielded Acustar S-200 gradient set supplied with the spectrometer; four term eddy current compensation and pre-emphasis was applied via the Techron gradient amplifiers. The system was controlled by a Sun 3/160 computer running SunOS 4.0.3 system software and release 6.0.3 Omega NMR software.

For all three sample cells, the basic ^{129}Xe NMR parameters of T_1 and T_2, along with the diffusion coefficient, were measured. ^{129}Xe T_1 was determined using the standard inversion recovery sequence.[14] A pre-delay of 5 s was used before the 180° pulse, and eight variable delays, of 0.001, 0.1, 0.5, 1, 2, 3, 5 and 8 s were used before the 90° pulse; eight scans were signal averaged. For all samples, a 5 Hz exponential line-broadening function was applied to the resulting FIDs before Fourier transformation. The integrals of the phased, real spectra were fitted to the standard T_1 equation,

$$S(\tau) = S(\infty)[1 - 2a\exp(-\tau/T_1)] \qquad (1)$$

to determine T_1, where a is a floating parameter reflecting the quality of inversion from the 180° pulse. The values of T_1 reported here have errors of less than 2% resulting from the non-linear least squares fit.

The ^{129}Xe T_2 was determined using the standard CPMG technique,[15,16] where an echo was acquired after every second 180° pulse. An acquisition time of 41 ms permitted an echo refocusing time of 45 ms, giving 90 ms between each acquired echo. A pre-delay of 10 s was used before the 90° pulse, and 16 scans were signal averaged. For all experiments, the resulting echoes were multiplied by a sine-squared function before Fourier transformation. The integral of the signal magnitude was fitted to the standard T_2 equation,

$$S(\tau) = S(0)\exp(-\tau/T_2) \qquad (2)$$

to determine T_2. The values of T_2 reported here have errors of less than 5% resulting from the nonlinear least squares fit.

The xenon diffusion coefficient was determined using the standard pulsed-gradient spin-echo (i.e. Stejskal–Tanner) technique.[12] The diffusion encoding gradient pulses were half-sine shaped, and in all experiments 12

gradient values were used, ranging from 0 to 0.06072 T/m in 0.00552 T/m steps. The duration of the diffusion encoding pulses, δ, was either 2.5 or 2.75 ms; the diffusion time between the pulses, Δ, was 50 ms; and an eddy current delay of 3 ms was inserted between gradient and subsequent RF pulses. A predelay of 10 s was used and 12 scans were signal averaged. For all samples, a 5 Hz exponential line-broadening function was applied to the resulting FIDs before Fourier transformation. The integrals of the phased, real spectra were used in a modified Stejskal–Tanner equation. A straight line fit to

$$\ln[S(g)/S(0)] = -\gamma^2 g^2 (\delta \times 2/\pi)^2 D(\Delta - \delta/4) \quad (3)$$

where γ is the xenon gyromagnetic ratio (7.41×10^7 rad T^{-1} s^{-1}) yielded the ^{129}Xe diffusion coefficient, D. The values of D reported here have errors of less than 3% resulting from the linear regression fit. Note that in eq. (3) the $2/\pi$ factor and the $\delta/4$ term (rather than $\delta/3$) accommodate the use of half-sine-shaped gradient pulses.[17]

All offline data processing was performed using the Prospa software package (Dr C. Eccles, Massey University, New Zealand) running on a Power Macinotsh 7200.

RESULTS

The use of enriched abundance ^{129}Xe in the large 80 cm^3 cells gave NMR signals of high signal-to-noise, close to 100:1 from a single pulse. As a result, both the exponential fits used in the relaxation time measurements, and the linear fits used in the diffusion coefficient measurements, were of high quality with uncertainties of no more than a few percent. An example data set, showing the variation of the xenon signal intensity with gradient strength, is shown in Fig. 1(a), and the corresponding Stejskal–Tanner semi-log plot that yields the diffusion coefficient is shown in Fig. 1(b). The relaxation times and diffusion coefficients measured in the three sample cells are listed in Table 1.

DISCUSSION

As can be seen in Table 1, the ^{129}Xe T_1 relaxation time did not change with SF_6 partial pressure (i.e. SF_6 is not paramagnetic). The O_2 partial pressure was constant throughout; and collisions with paramagnetic O_2 served as the prime source of ^{129}Xe longitudinal relaxation.[18] In contrast, we found that the increase in SF_6 partial pressure caused a considerable decrease in the ^{129}Xe T_2 relaxation time, close to a factor of two, although T_2 was still rather long (about 0.3 s) even for high SF_6 pressures. However, in a heterogenous system such as the lung, the ^{129}Xe T_2 will be one to two orders of magnitude lower due to surface effects and, at higher fields, diffusion through susceptibility-induced background gradients. Thus the practical effect of SF_6 on ^{129}Xe T_2 in the lung should be minimal, and SF_6 could be used as a benign buffer gas with laser-polarized xenon, in order to increase the pressure of a gas sample.

The observed xenon gas diffusion coefficients, D_{obs}, are also listed in Table 1. The xenon-in-SF_6 diffusion coefficient can be calculated for the two samples

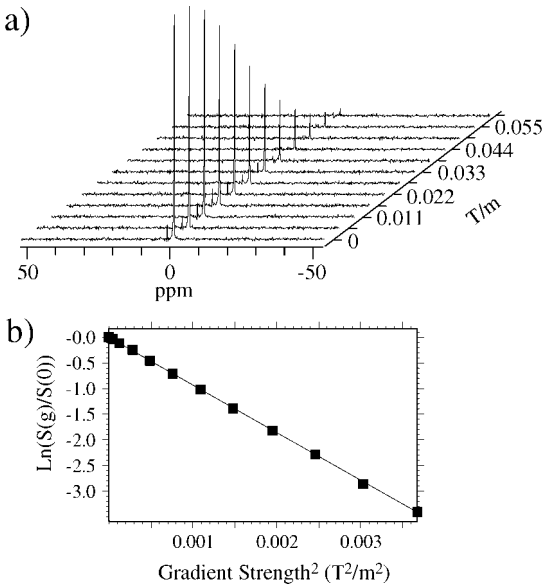

Figure 1. (a) Stack plot of ^{129}Xe spectra from a PGSE diffusion experiment, displayed as a function of diffusion-encoding gradient strength. The data is from the sample containing 2 bar pressure of both xenon and oxygen, and 1 bar pressure of SF_6. (b) Semi-log Stejskal–Tanner plot used to derive the observed ^{129}Xe gas diffusion coefficient from the above spectra.[12] The log of the integral of each spectral peak, normalized to the first (zero gradient) spectrum is plotted as a function of the square of the diffusion encoding gradient. The observed diffusion coefficient, derived from the slope of the fitted line is $1.38 \pm 0.03 \times 10^{-6}$ m^2 s^{-1}

Table 1. ^{129}Xe relaxation and diffusion parameters in the presence of SF_6

Gas mixture ($Xe/O_2/SF_6$)	T_1 (s)	T_2 (ms)	D_{obs} (m^2 s^{-1})	D(Xe–SF_6) (m^2 s^{-1})
2/2/0 bar pressure	1.40 ± 0.03	508 ± 25	$1.85 \pm 0.03 \times 10^{-6}$	—
2/2/1 bar pressure	1.45 ± 0.03	335 ± 17	$1.38 \pm 0.03 \times 10^{-6}$	$4.43 \pm 0.05 \times 10^{-6}$
2/2/2 bar pressure	1.41 ± 0.03	263 ± 13	$1.10 \pm 0.03 \times 10^{-6}$	$2.43 \pm 0.05 \times 10^{-6}$

containing SF_6 using the relation[19,20]

$$\frac{1}{D_{obs}} = \frac{1}{D(Xe–Xe)} + \frac{1}{D(Xe–O_2)} + \frac{1}{D(Xe–SF_6)} \quad (4)$$

where $D(Xe–Xe) = 2.86 \times 10^{-6}$ m^2 s^{-1} is the ^{129}Xe self diffusion coefficient at 2 bar pressure and standard temperature;[5] $D(Xe–O_2) = 6.75 \times 10^{-6}$ m^2 s^{-1} is the ^{129}Xe diffusion coefficient at infinite dilution in 2 bar of oxygen at standard temperature;[5] and $D(Xe–SF_6)$ is the ^{129}Xe-in-SF_6 diffusion coefficient, i.e. the ^{129}Xe diffusion coefficient at infinite dilution in SF_6 at standard temperature. One finds that $D(Xe–SF_6) = 4.43 \times 10^{-6}$ m^2 s^{-1} for the 1 bar SF_6 sample, and 2.43×10^{-6} m^2 s^{-1} for the 2 bar SF_6 sample, as given in Table 1.

Unfortunately, $D(Xe–SF_6)$ is not much smaller than $D(Xe–Xe)$ at the same xenon and SF_6 pressures. In instances where a constant pressure of the gas sample must be maintained (e.g. 1 bar pressure for lung inhalation), replacing ^{129}Xe with SF_6 will both lower the NMR signal and have minimal effect on D_{obs}, i.e. it will not ameliorate the breakdown of the narrow pulse approximation that occurs in gas diffusion NMR (GD-NMR) in porous or other restricted systems. Therefore, we see little useful application for the addition of SF_6 to laser-polarized xenon for human inhalation, except in the case where a benign buffer gas is required to increase the total sample pressure. Even in that case, adding SF_6 to a gas mixture will reduce the ^{129}Xe D_{obs}, however a similar reduction in diffusion can be obtained simply by adding more ^{129}Xe, with the side-benefit of increased NMR signal.

We conclude this section with a brief note on the use of SF_6 as a buffer gas for ^{3}He, another noble gas that can be laser-polarized and used in NMR studies of the lung.[2,3] The ^{3}He diffusion coefficient is an order of magnitude larger than that of ^{129}Xe for the same gas pressures and temperatures.[19] Being so much larger than ^{3}He in scattering cross-sectional area, SF_6 should greatly reduce the ^{3}He diffusion coefficient, but not below the ^{129}Xe gas diffusion coefficient for the same SF_6 partial pressure. Thus we expect that the narrow pulse approximation will also fail for ^{3}He diffusion in the lung, even in the presence of considerable SF_6.

CONCLUSION

Gas-diffusion NMR is a powerful new tool for obtaining structural information about porous media. However, fast gas diffusion can cause violations of the narrow pulse approximation in the standard Stejskal–Tanner NMR method of measuring diffusion, which can result in inaccurate determinations of the medium's surface-area/volume ratio, *S/V*.[6] This problem is likely to be severe in human lung studies, given prevailing instrumental and gas pressure limitations.

In an attempt to find a buffer gas that would suitably reduce the observed ^{129}Xe diffusion coefficient, and be appropriate for inhalation, we performed NMR measurements of ^{129}Xe gas diffusion through sulfur hexafluoride (SF_6). We found the coefficient of ^{129}Xe diffusion through SF_6 to be only 1.2 times smaller than the ^{129}Xe self diffusion coefficient at identical ^{129}Xe and SF_6 pressures and standard temperature. Hence SF_6 will not sufficiently reduce ^{129}Xe diffusion to allow accurate surface-area/volume ratio measurements in human alveoli using time-dependent gas diffusion NMR. We also found the contribution of SF_6 gas to ^{129}Xe T_2 to scale inversely with SF_6 pressure, with this contribution approximately equal to 1 s for 1 bar SF_6 pressure and standard temperature. In addition, we found a negligible contribution of SF_6 gas to ^{129}Xe T_1 relaxation in a 1:1 xenon/oxygen mixture for up to 2 bar of SF_6 at standard temperature.

A large reduction in ^{129}Xe (or ^{3}He) diffusion coefficient will require finding a gas with a much larger cross-sectional area than SF_6. Certain alkane compounds with carbon chains of 3–4 atoms in length may be suitable candidates, although whether such compounds are benign when breathed by humans remains to be seen. While time-dependent gas-diffusion NMR can provide a wealth of information on certain porous media, most notably the *S/V* and the pore connectivity, or tortuosity, it remains a challenge to apply this technique for *S/V* measurements *in vivo* in the lung because of rapid gas diffusion.

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