Diffusion of hyperpolarized $^{129}$Xe in the lung: a simplified model of $^{129}$Xe septal uptake and experimental results

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Abstract. We used hyperpolarized $^{129}$Xe NMR to measure pulmonary alveolar surface area per unit gas volume $S_A/V_{\text{gas}}$, alveolar septal thickness $h$ and capillary transit time $\tau$, three critical determinants of the lung’s primary role as a gas exchange organ. An analytical solution for a simplified diffusion model is described, together with a modification of the xenon transfer contrast imaging technique utilizing $90^\circ$ radio-frequency pulses applied to the dissolved phase, rather than traditional $180^\circ$ pulses. With this approach, three-dimensional (3D) maps of $S_A/V_{\text{gas}}$ were obtained. We measured global $S_A/V_{\text{gas}}$, $h$ and $\tau$ in four normal subjects, two subjects with mild interstitial lung disease (ILD) and two subjects with mild chronic obstructive pulmonary disease (COPD). In normals, $S_A/V_{\text{gas}}$ decreased with increasing lung volume from $\sim320$ to $80\,\text{cm}^{-1}$; both $h \sim 13\,\mu\text{m}$ and $\tau \sim 1.5\,\text{s}$ were relatively constant. For the two ILD subjects, $h$ was, respectively, 36 and 97% larger than normal, quantifying an increased gas/blood tissue barrier; $S_A/V_{\text{gas}}$ and $\tau$ were normal. The two COPD subjects

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had $S_A/V_{gas}$ values $\sim 25\%$ that of normals, quantifying septal surface loss in emphysema; $h$ and $\tau$ were normal. These are the first noninvasive, non-radiation-based, quantitative measurements of $h$ and $\tau$ in patients with pulmonary disease.

1. Introduction

The lung is an exquisitely designed porous structure that supports efficient diffusion of oxygen from alveolar gas spaces to blood, and the reverse transport of carbon dioxide from blood to gas spaces [1]. This physiological transport, known as gas exchange, is essential for life. To enable efficient gas exchange, a healthy lung has approximately 300 million alveoli with diameter $\sim 200 \mu m$. Such a structure provides an alveolar surface area of $\sim 130 \text{ m}^2$ or three quarters the size of a tennis court. Gas exchange is further expedited because the tissue barrier separating alveolar gas spaces and blood is very thin ($< 1 \mu m$).

Derangements in pulmonary structure cause loss of function. For example, emphysema is characterized by loss of alveolar surface area, and interstitial fibrosis causes thickening of the tissue barrier between gas and blood. Both of these pathologies cause dyspnea and, if not treated, can progress and become debilitating. Current diagnostic methods are far from perfect. For example, pulmonary function tests (PFTs) lack disease specificity as they measure cooperative properties of the lung as a whole. Computed tomography (CT) adds some specificity by providing regional information but at the cost of exposure to ionizing radiation, which is problematic for frequent longitudinal assessment and for pediatric diagnosis. Further, rather than measuring function, CT measures tissue density. Thus, if both emphysema and interstitial fibrosis coexist, their effects on tissue density/CT negate each other. Novel, noninvasive methods for measuring regional pulmonary function are therefore needed.

Measurement of the diffusion of hyperpolarized $^{129}$Xe from alveolar gas spaces to septal tissue and blood as a function of time, commonly referred to as the xenon septal uptake curve, offers an opportunity to non-invasively obtain quantitative estimates of fundamental pulmonary parameters related to gas exchange. Measured parameters include quantities such as the alveolar
surface area per unit volume, the thickness of septal compartments and blood transit times. Regional maps of these parameters offer great promise of providing new methods that are (a) more sensitive to changes in pathology than existing methods and (b) have greater specificity in identifying the cause of any reduction in function.

Since the spectral peaks associated with $^{129}$Xe magnetization in different pulmonary compartments, i.e. gas and blood/tissue (the dissolved phase), are at different chemically shifted frequencies, it is relatively straightforward to monitor the kinetics of $^{129}$Xe magnetization diffusion from one compartment/phase to another. The basic method we have been investigating is called chemical shift saturation recovery (CSSR) [2]–[4]. In CSSR, a selective radio-frequency (RF) pulse is initially employed to destroy the $^{129}$Xe magnetization in tissue and blood. This creates a step function in the $^{129}$Xe magnetization at the alveolar gas–tissue boundary: zero magnetization in the dissolved phase and, due to the high gas diffusivity, relatively uniform magnetization in the gas phase. Recovery of the dissolved phase $^{129}$Xe magnetization is then observed as a function of time; this curve is known as the ‘xenon septal uptake curve’. The recovery is due to diffusion of $^{129}$Xe spins from alveolar gas spaces to septal tissue. In 2002, we demonstrated the ability to quantitatively measure surface area per unit volume in porous polyethylene phantoms by comparing our results with confocal microscopy measurements of the mean linear intercept $L_m$ [3]. We recently reported CSSR results in healthy humans where the early time behavior (before the septa saturate, i.e. for a diffusion time $t < \sim 100\,\text{ms}$) of the septal uptake curve was used to measure alveolar surface area per unit volume of gas, $S_A/V_{\text{gas}}$ [5, 6]. We showed that $S_A/V_{\text{gas}}$ can be measured with an average error bar of 13% in four healthy humans. Ignoring blood flow and assuming a one-dimensional (1D) model, xenon septal uptake can be modeled as equivalent to classical slab diffusion [4, 7]. The most sophisticated analytical form for xenon septal uptake, however, has been found by Mansson et al, who solved for a 1D diffusion model with three compartments including blood flow [8]. The compartments are alveolar gas, a capillary compartment containing plasma and red blood cells (RBC), and a tissue compartment that lies between the alveolar gas and capillary compartments. Whole lung spectra were obtained in rats and the time dependence of each spectral $^{129}$Xe component (tissue and plasma at $\sim 197\,\text{ppm}$ and RBCs at $\sim 212\,\text{ppm}$) was observed. Estimates for model parameters obtained from fits of the data to the analytical form showed good agreement with known values.

The total $^{129}$Xe magnetization in the dissolved phase signal is only $\sim 2\%$ that of the gas phase signal. This low signal arises from two factors: (a) the lung is mostly gas with only $\sim 20\%$ of the lung’s volume occupied by tissue and blood and (b) xenon has low solubility in tissue (Ostwald solubility coefficient $\lambda \sim 0.1$ [9]). Measuring two spectrally distinct dissolved phase signals, i.e. RBCs and parenchyma/plasma separately, reduces the signal further since it is now divided between two compartments. Although in principle one can solve this problem by signal averaging, such a solution is not practical for human subjects because of other considerations such as the cost of the hyperpolarized $^{129}$Xe, the cost of scanner time and patient tolerance.

In this work, we have not distinguished between the two dissolved state spectral peaks but rather lumped them together into a single dissolved phase signal. To that end, we describe here a simplified 1D analytical diffusion model for CSSR that includes blood flow. This simplifies the data collection and maximizes the signal-to-noise ratio (SNR) of the dissolved phase signal. Rather than restricting ourselves, as we did in our earlier work, to the early-time portion of the septal uptake curve and where we obtained estimates of alveolar surface area per unit volume ($S_A/V_{\text{gas}}$) only [3, 6], the new model fits data over a much longer time, allowing the estimation...
of two additional parameters: the total septal thickness \( h \) and the transit time of blood through the gas exchange region \( \tau \). Here, we reanalyze data from healthy subjects that were previously fitted only over the early-time portion of the septal uptake curve and present new data from two subjects with interstitial lung disease (ILD) and two subjects with chronic obstructive pulmonary disease (COPD). Note that there are two contributing factors to COPD, namely an emphysematous component and a bronchial airway component. Thus, relative to healthy subjects, we expect COPD subjects to demonstrate a reduction in \( S_A/V_{\text{gas}} \) due to emphysema, whereas the ILD subjects are expected to have an increase in \( h \).

For short interphase diffusion times, i.e. the ‘early-time’ region where CSSR is related to \( S_A/V_{\text{gas}} \), one can repeat these measurements at a rate that is roughly the inverse of the data readout time. Dynamic processes that are slow in comparison can then be studied. We provide an example of this by performing CSSR as a function of dynamically changing lung volume achieved by a subject slowly exhaling. Because of the limited SNR of the dissolved phase spectrum, our CSSR measurements have been carried out as whole lung spectroscopy experiments. It is important, however, to obtain regional measurements of pulmonary function. For example, to be sensitive to early disease, which can be highly local or have a specific spatial pattern (central versus peripheral, apex versus base), one must be able to detect these patterns. In addition, if the volume of pathologic tissue represents a small fraction of the measured volume, the measurement will be less sensitive to pathologic changes due to partial volume effects. For regional measurements of pulmonary function, we have used the xenon transfer contrast (XTC) method [7, 10, 11]. Compared to CSSR, which directly measures the dissolved phase xenon magnetization, the XTC method measures the reduction in the gas phase xenon magnetization after multiple opportunities for interphase diffusion. XTC is much more time efficient than CSSR because multiple repeats of the interphase diffusion are performed before a single readout. Despite its increased efficiency, however, XTC is fundamentally different from CSSR and does not necessarily produce identical results. It relies on the flux of \(^{129}\text{Xe}\) both from the gas phase to the tissue and vice versa. CSSR only relies on diffusion of \(^{129}\text{Xe}\) from gas to tissue. Here, we show that there is a special case for the flip angle used in XTC such that results identical to CSSR are obtained. We then describe initial 3D regional measurements of \( S_A/V_{\text{gas}} \) using this ‘special-case’ XTC method.

2. Model for xenon septal uptake

2.1. Static one-dimensional (1D) geometry

Here we describe the model used for \(^{129}\text{Xe}\) diffusion from alveolar gas spaces to septal tissue. We separate the problem into two parts. First, we review the solution to a simple static 1D geometry without blood flow. Then we describe the modification to the theory to account for blood flow. The static 1D problem is a classic periodic boundary value problem and is well known in the literature. This solution has also been described by both Ruppert et al [7] and Driehuys et al [4] for \(^{129}\text{Xe}\) septal diffusion. Figure 1 shows the sample geometry: a finite width septal tissue slab where the initial tissue phase \(^{129}\text{Xe}\) magnetization is zero and the magnetization in the alveolar gas spaces is uniform. A 90° selective RF pulse applied at the resonance frequencies of the dissolved phase \(^{129}\text{Xe}\) spins is used to initially destroy the tissue phase magnetization. Because the septal tissue, even when saturated, contains only \( \sim 2\% \) of the gas phase magnetization, the gas phase magnetization is relatively unchanged during the
(a) At \( t = 0 \), uniform gas phase magnetization = \( M_0 \), \( M_{\text{diss}} = 0 \).

(b) After time \( t \), \(^{129}\text{Xe}\) diffuses into septal tissue.

**Figure 1.** Schematic diagram of magnetization in the alveolar gas spaces and septal tissue. (a) Immediately after a selective RF pulse is applied to saturate the dissolved phase magnetization, an ideal step function magnetization is created, i.e. uniform magnetization in the gas phase and zero magnetization in the dissolved phase [3]. (b) Subsequently, magnetized \(^{129}\text{Xe}\) spins diffuse into the tissue.

CSSR experiment. Thus, in this model, we assume that the magnetization in the gas phase reservoir is constant and does not change. The solution of the 1D diffusion equation for the \(^{129}\text{Xe}\) magnetization density \( \rho(x, t) \) within the dissolved phase is obtained by assuming periodic boundary conditions at the septal–alveolar gas boundaries and a separation of spatial and temporal variables:

\[
\rho(x, t) = 1 - \sum_{n, \text{odd}} \left( \frac{4}{\pi n} \right) \sin \left( \frac{n \pi x}{h} \right) \exp \left( - \left[ \frac{n \pi}{h} \right]^2 D t \right),
\]

where \( D \) is the diffusivity of \(^{129}\text{Xe}\) in the dissolved phase. This solution is graphically illustrated in figure 2(a). Here, we have set the magnetization in the gas reservoir to one. The fraction of the septal slab that is filled with hyperpolarized \(^{129}\text{Xe}\) is given by (figure 2(b))

\[
f(t) = \frac{1}{h} \int_{x=0}^{h} \rho(x, t) \, dx = 1 - \sum_{n, \text{odd}} \frac{8}{\pi^2 n^2} \exp \left( - \left[ \frac{n \pi}{h} \right]^2 D t \right).
\]

To compare with experimental measurements, we calculate the fraction \( F \), which is the ratio of the magnetization in the dissolved phase at time \( t \), \( M_{\text{diss}}(t) \), to the gas phase magnetization at time \( t = 0 \), \( M_{\text{gas}}(t = 0) \).

\[
F(t) = \frac{M_{\text{diss}}(t \to \infty)}{M_{\text{gas}}(t = 0)} \frac{f(t)}{f(t)} = \frac{\lambda h}{2 V_{\text{gas}}} f(t).
\]
Figure 2. (a) Solution for the $^{129}$Xe magnetization density $\rho(x,t)$ in the tissue as a function of spatial position $x$ and time $t$ when blood flow is absent. (b) $f(t) = \frac{1}{h} \int_{x=0}^{h} \rho(x,t) \, dx$ gives the fraction of the slab that is saturated with $^{129}$Xe as a function of time. For this figure, we have assumed that the diffusivity of $^{129}$Xe in tissue is $3 \times 10^{-6}$ cm$^2$ s$^{-1}$ and the septal thickness $h = 10 \mu$m.

Here the volume of the dissolved phase or septal tissue is $V_{\text{diss}} = Ah = S_A h/2$, where $A$ is the surface area between alveolar gas and septal tissue (figure 1) along one boundary. The total alveolar surface area is $S_A = 2A$ since alveolar gas contacts the septal tissue on both sides of the finite width septum. Note that this model assumes a uniform septal thickness, which is certainly not true for a real lung.

2.2. Effect of blood flow

To incorporate blood flow into the formalism, we first make the approximation that blood flow and $^{129}$Xe diffusion are orthogonal and independent (figure 4). Thus, with respect to the alveolar gas–septal tissue boundary, the direction of $^{129}$Xe diffusion is perpendicular to this interface.
Figure 3. Position of three spatially distinct regions of blood flow, labeled 1, 2 and 3 at (a) time $t = 0$ and (b) time $t$. The distance the blood travels in time $t$ is $\Delta x = vt$. Blood in regions 1 and 3 experience gas exchange for only a fraction of the time $t$, whereas region 2 experiences gas exchange for the entire time $t$. Note that blood in region 1 in (a) and in region 3 in (b) correspond to blood in the pulmonary arterioles and venules and are therefore both located physically within the lung. Since we observe $^{129}$Xe within the lung, xenon diffusing into the blood within the gas exchange region and afterwards traveling downstream into the venules is observed as part of the xenon septal uptake data.

while blood flow is parallel. In addition, to further simplify the model, we ignore the very thin parenchymal tissue layer between alveolar gas and blood and treat the entire septal thickness as being composed of flowing blood. Finally, the blood flow is treated as simple plug flow. With these assumptions, we separate the blood that will be involved in gas exchange during the diffusion time $t$ into three spatial regions (see figure 3). Region 1 refers to blood that is completely upstream of the gas exchange region at $t = 0$ and travels into the gas exchange region during time $t$. Region 1 then refers to blood that spends a fraction of the time $t$ in the gas exchange region. Region 2 refers to blood that starts in the gas exchange region at $t = 0$ and remains in that region during the entire time $t$. Region 3 refers to blood that starts out within the gas exchange region and ends up downstream of that region while physically still in the lung. The longest diffusion time that it is valid in this model is one where the diffusion time is equal to the capillary transit time, which is where the length of region 2 along the blood flow direction goes to zero. Since the blood in region 2 remains in the gas exchange region during the entire time $t$, the fraction of the septal thickness for blood in region 2 that is occupied by magnetized $^{129}$Xe is simply $f(t)$. The fraction of the alveolar surface area associated with region 2 is $f_2 = (\tau - t)/\tau$ and thus the contribution to $F$ from region 2 is

$$F_2(t) = f_2 \cdot F(t) = \left(\frac{\tau - t}{\tau}\right) \frac{\lambda h}{2 V_{gas}} S_A f(t).$$

(4)
For regions 1 and 3, the time spent in the gas exchange region depends on the starting position. Therefore to find the average value of $f$, one must integrate over $f(t')$ where since we are considering blood with constant velocity, $t'$ varies linearly from 0 to the maximum time $t$. The mean value of $f$ for both regions 1 and 3 is thus given by

$$\bar{f}_1(t) = \bar{f}_3(t) = \frac{1}{t} \int_0^t f(t') \, dt'. \quad (5a)$$

$$\bar{f}_1(t) = \bar{f}_3(t) = 1 + \left( \frac{8h^2}{\pi^4 D} \right) \left( \frac{1}{t} \right) \sum_{n,\text{odd}} \left[ \frac{1}{n^4} \left\{ \exp \left( -\frac{n^2\pi^2 D t}{h^2} \right) - 1 \right\} \right]. \quad (5b)$$

The fraction of the alveolar surface area occupied by both regions 1 and 3 is $f_1 = f_3 = t/\tau$; therefore, the contribution to $F$ from regions 1 and 3 is

$$F_1(t) = f_1 \cdot F(t) = \frac{t}{\tau} \cdot \frac{\lambda h S_A}{2 V_{gas}} \bar{f}_1(t) \equiv F_3(t). \quad (6)$$

Thus for the case we have described with simple blood flow, $F_{\text{flow}}(t)$ is given by

$$F_{\text{flow}}(t) = F_1(t) + F_2(t) + F_3(t),$$

$$F_{\text{flow}}(t) = \frac{\lambda h}{2 V_{gas}} \left( \frac{\tau - t}{\tau} \right) f(Dt/h^2) + \lambda h \frac{S_A}{V_{gas}} \left[ \frac{t}{\tau} + \frac{8h^2}{D\pi^4} \frac{1}{\tau} g(Dt/h^2) \right]. \quad (7)$$
Here, $f$ and $g$ are functions of the dimensionless parameter $q = Dt/h^2$:

\[
f(q) = \left[ 1 - \sum_{n, \text{odd}} \frac{8}{\pi^2 n^2} \exp(-q\pi^2 n^2) \right],
\]

\[
g(q) = \left[ \sum_{n, \text{odd}} \frac{1}{n^8} \{ \exp(-q\pi^2 n^2) - 1 \} \right].
\] (8)

3. Human subjects protocol and the chemical shift saturation recovery (CSSR) method

Healthy subjects were studied with IRB- and FDA IND-approved protocols. The IRB protocol was through Brigham and Women’s Hospital (S Patz, PI) and the FDA IND one through the University of New Hampshire (UNH) (F W Hersman, PI). To polarize $^{129}$Xe, we used either a UNH polarizer [12] providing 30–50% polarization at 1 liter h$^{-1}$ or a Xemed prototype polarizer providing $\sim$30% polarization at 2 liters h$^{-1}$. Except for the two COPD subjects, all CSSR experiments were performed at a field strength of 0.2 T. Experimental details of these experiments have already been described in the work where the early-time septal uptake behavior only was analyzed to determine $S_A/V_{gas}$ [6]. CSSR methods at 3 T were similar to those at 0.2 T.

4. CSSR experimental results

Representative experimental spectra are shown in figure 5(a), and a typical $F(t)$ curve as a function of $\sqrt{t}$ from a healthy subject is shown in figure 5(b). The data are fitted to equation (7) with the addition of a dc offset term $F_0$:

\[
F(t) = F_0 + F_{\text{flow}}(t).
\] (9)

$F_0$ represents an offset associated with either an imperfect saturation of the dissolved phase and/or structures sufficiently thin that they saturate earlier than our measurement time window. The experimental data demonstrate the sequence of three regimes: (i) an initial boundary layer diffusion at short times ($0 < t < \sim 100$ ms); (ii) approaching saturation due to finite septal thickness; and (iii) the influence of blood flow. The protocol involves the inhalation of a specified volume of $^{129}$Xe and the acquisition of CSSR data during a 10 s breath-hold. Essentially identical values of $S_A/V_{gas}$ were found when fitting the early time data to the analytical form found previously, i.e. $F(t) = F_0 + \lambda(S_A/V_{gas})\sqrt{4Dt/\pi}$, which is valid for the early time regime only [3], or when fitting the entire time-dependent data to equation (9). After obtaining the fitted parameters $S_A/V_{gas}$, $h$, $\tau$ and $F_0$, a separate theoretical curve was generated by setting $\tau \rightarrow \infty$. This is shown in figure 5(b) as a red curve to demonstrate the behavior of $F$ in the absence of blood flow. Its asymptotic value amounts to a few per cent, consistent with a theoretical value of $\lambda \varphi/(1 - \varphi) \approx 0.02$, where $\varphi \sim 0.2$ is the lung’s tissue volume fraction at a lung volume near functional residual capacity (FRC). At long times, the actual time dependence of $F$ is dominated by the blood flow term, which in our model is simple constant velocity plug flow.

Using our analysis of the entire time range of the $F(t)$ curve, figure 6 reports results $S_A/V_{gas}$, $h$ and $\tau$ for four healthy subjects averaged over subjects and for two subjects with COPD and two subjects with ILD [13, 14]. Data were obtained at three different lung
DC offset = \( F_0 \)

Saturation capacity - ILD

Effect of blood flow

Volume = TLC

Figure 5. (a) Example of whole lung CSSR \(^{129}\)Xe spectra from a human subject at 0.2 T. The gas phase signal (0 Hz) has been normalized to a value of 1 for each diffusion time. The diffusion of \(^{129}\)Xe from alveolar gas spaces to septal tissue and blood (the dissolved phase signal) is shown as a function of diffusion time at +200 ppm (460 Hz). Diffusion times measured were 20, 29, 39, 69, 119, 219, 519 and 719 ms. The dissolved phase signal was interrogated with a selective 90° RF pulse centered on the dissolved phase frequency. At the gas phase frequency, this RF pulse provided a 0.7 flip angle. In the calculation of \( F \), the amplitude of the gas phase signal was scaled by \( 1/\sin(0.17°) \). (b) Example of \( F(t) \) data plotted versus \( \sqrt{t} \). The data here are for a healthy subject. Also shown is the fit to the theoretical expression (blue curve). Using the fitted parameters \( S_A/V_{\text{gas}} \) and \( h \) obtained for the blue curve, but setting \( \tau \to \infty \), a separate curve was plotted (red curve) that shows the behavior for no blood flow. Before the septa are saturated with \(^{129}\)Xe (early time regime), \( F(t) \sim (S_A/V_{\text{gas}})/\sqrt{t} \), and thus the early-time part of the curve is a straight line. After the septa are saturated, blood flow remains as the remaining 'sink' for \(^{129}\)Xe uptake. Thus at long times, \( F \sim t \). Note that the dissolved state data were corrected for \( T_1 \) decay [17] during the diffusion time \( t \).
Figure 6. Results of data analysis for (a) $S_A/V_{\text{gas}}$, (b) $h$ and (c) $\tau$ as a function of lung volume normalized to TLC. The results shown for four healthy subjects, two subjects with mild ILD and two subjects with COPD, one with mild and one with mild/moderate disease.

volumes for the healthy subjects [6] and at one lung volume for the patients with lung disease. For comparison between individuals with different lung capacities, lung volumes ($V_L$) are normalized to total lung capacity (TLC), $\bar{V} = V_L/\text{TLC}$. Figures 6(a), (b) and (c) show $S_A/V_{\text{gas}}$, $h$ and $\tau$ versus $\bar{V}$, respectively. There are several striking features. First, despite the use of a simple analytical model, the values for $S_A/V_{\text{gas}}$ and $h$ are remarkably similar to those measured with invasive, fixed lung histology [15]. In addition, the values obtained for $\tau$ are fairly constant.
as a function of lung volume and have a mean value of $\sim 1.5$ s, which is close to values found by Hogg et al [16] in human lungs (mean 1.6 s, median 1.2 s, but with a wide spread). This is also close to what one would expect assuming a typical cardiac output of $\sim 5$ liters min$^{-1}$ and a pulmonary blood volume of $\sim 200$ cc.

The two COPD subjects had mild or mild/moderate disease. Both subjects showed a large loss of pulmonary surface area per unit volume (figure 6(a)) by a factor of $\sim 4$ when compared to the healthy subjects. These patients were studied at a volume near FRC. Comparing normals and COPD subjects at FRC, figure 6(a) includes a bar graph that shows a significant decline in surface area despite the mild nature of the disease. For the two patients with mild ILD, experiments were performed at TLC. For these subjects note first that the $S_A/V_{\text{gas}}$ values fall within normal variation of the four healthy subjects, consistent with a lack of parenchymally destructive disease. Examination of figure 6(b), however, shows that the two ILD patients have septal thickness values that are 36 and 97% larger than the mean value of the normals at TLC, consistent with excess connective tissue and increased interstitial fluid in progressive fibrotic diseases. Regarding capillary transit times, subjects with disease did not show a significant difference compared to the normal subjects. The reason why the COPD subjects were studied at a smaller lung volume than the ILD subjects was because the time available to us on the scanner for the COPD subjects was limited, and that translated into having less time available for polarizing large quantities of gas.

It is of interest to compare these results to CT. Figure 7 shows CT images of (a) a normal lung, (b) one of our COPD subjects taken at relaxed exhalation, i.e. near FRC, and (c) one of our mild ILD subjects at full inflation. The white arrows in figures 7(b) and (c) identify regions of emphysematous destruction of the lung parenchyma and mild interstitial opacities, respectively. Remarkably, despite the very mild nature of the ILD depicted in figure 7(c), our CSSR results, which average the signal across the whole lung, detected an increase in septal thickness. This supports the sensitivity of $^{129}$Xe septal uptake measurements and the potential insensitivity of CT to mild changes in the pulmonary interstitium.

4.1. Technical details of CSSR

With respect to loss of $^{129}$Xe magnetization in the gas phase during a breath-hold experiment, there are three primary mechanisms. One is simple diffusion of $^{129}$Xe into the septa (which is the primary quantity of interest). The other two mechanisms are (i) depletion of the magnetization due to RF excitation (flip angles of only a few degrees) and (ii) relaxation due to the presence of oxygen ($T_1 \sim 10$ s). These are slow compared to the duration of each diffusion experiment and are compensated for by interrogating the gas phase magnetization at the beginning of each diffusion time measurement. Because $F(t)$ is an intensive quantity, depending only on the ratio of dissolved phase magnetization to gas phase magnetization, multiple measurements can be made during a single breath-hold as the overall magnetization decays [6].

Since the measurement of the gas-phase magnetization at $t = 0$ is performed at a different time from the measurement of the $^{129}$Xe magnetization in the dissolved phase, we must also consider $T_1$ relaxation of xenon in the blood during the diffusion time $t$. We corrected for this decay using the measured value of 6.4 s at 1.5 T [17]. The majority of the CSSR experiments were performed at 0.2 T; however, the two COPD subjects were studied at 3 T after our 0.2 T scanner was decommissioned. Since $T_1$ is known to have some field dependence, this is clearly a source of error. However, we arbitrarily corrected the data using both larger (8.4 s) and smaller
Figure 7. CT images of (a) a normal lung, (b) one of our COPD subjects taken at relaxed exhalation, i.e. near FRC, and (c) one of our mild ILD subjects at full inflation. The white arrows in (b) and (c) identify regions of emphysematous destruction of the lung parenchyma and mild interstitial opacities, respectively.

(4.4 s) values for the $T_1$ correction. There was a small change in the capillary transit time-fitted parameter but there were insignificant changes in the fitted parameters for septal thickness and $SA/V_{gas}$.

The data were fitted to the analytical form given by equation (9). Literature values were used for $\lambda$ ($\sim 0.1$) [9] and $D$ ($\sim 3 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$) [18]. A nonlinear least squares fitting routine was written using Matlab. The series expressions for $f(q)$ and $g(q)$ were truncated at $n = 7$, i.e. we used $n = 1, 3, 5$ and 7. The number of terms was chosen by ensuring that the fitting results were stable and did not change upon the addition of more terms. Another issue that arose was that for two data sets, negative values were found for $F_0$. Because this is physically impossible, for these two cases, the fit was redone with $F_0$ forced to 0 [6].

5. CSSR applied to healthy lung physiology

The CSSR experiments reported above were performed at fixed lung volumes during a breath-hold, with varying exchange times. We have also performed the complementary protocol, holding exchange time fixed and varying lung volume, measured by a specially constructed MRI-compatible spirometer. Here, the subject inhaled a Xe/O$_2$ bolus from residual volume (RV) to near FRC, followed by air to TLC. The subject then exhaled slowly ($\sim 8$ s) into the spirometer, during which measurements of $F$ at a fixed value of $t$ (either 20 or 323 ms) were
Figure 8. Examples of $F(t)$ versus variable $V_{gas}$ acquired at a fixed diffusion time. Data are from a healthy, male subject, 32 years old, who exhaled from $V_{gas} \approx TLC$ to close to RV. Two different diffusion times (20 and 323 ms) were measured. Power-law fits of the data to $F = F_0 + CV_{gas}^\alpha$ yield for $t = 20$ ms: $\alpha = -1.859$, $R^2 = 0.99$; and for $t = 323$ ms: $\alpha = -1.856$, $R^2 = 0.97$.

repeated every 618 ms. The sample data are shown in figure 8. Due to the offset $F_0$, it is not possible to convert these measurements into $S_A/V_{gas}$, which requires several time points for evaluating the slope of $F$ versus $\sqrt{t}$. Nevertheless, $F$ is dominated by $S_A/V_{gas}$. It has been well established morphometrically that $S_A/V_{gas}$ systematically decreases with increasing lung volume [19], and our results are fully consistent with this. The manner in which this occurs, particularly in the sense of a scaling law for surface area as a function of lung volume, remains open. We note that this technique is uniquely poised to answer such a question in live awake humans.

6. Xenon transfer contrast (XTC) images of alveolar surface area per unit volume

XTC [7, 10, 11] is a method that allows multiple opportunities for interphase diffusion before a readout sample is acquired. It is a much more efficient method to build up information about gas exchange than with multiple averages using CSSR, where each average requires a separate readout. The basic XTC pulse sequence consists of (gradient echo image 1 of the gas phase—the XTC sensitization sequence—gradient echo image 2 of the gas phase). The XTC sensitization sequence consists of $[\alpha_{diss} - t]^n$, i.e. there are $n$ repeats of a selective RF pulse of flip angle $\alpha_{diss}$ applied to the dissolved phase followed by a time $t$ for interphase diffusion. For each cycle, there is a depolarization per cycle $D_{XTC}(\alpha_{diss}, t)$ of the gas phase that occurs. It is calculated from $D_{XTC} = 1 - \sqrt{I_2/I_1}$, where $I_2/I_1$ is the ratio of signal intensities in image 2 to image 1.
Figure 9. $F(t)$ at (a) 44 ms and (b) 62 ms obtained from two separate acquisitions of 3D 90°-SB-XTC. Color bar range for $F = 0$–3%. (c) Calculated $S_A/V_{gas}$ in cm$^{-1}$. The measurements were carried out near FRC (~0.41 TLC). Four of 12 slices acquired are shown. $\langle F(44 \text{ ms}) \rangle = 0.75\%$, $\langle F(62 \text{ ms}) \rangle = 1.35\%$, $\langle S/V \rangle = 267 \pm 62 \text{ cm}^{-1}$.

The typical value used for $\alpha_{\text{diss}}$ is 180° (i.e. 180°-XTC). If for each cycle, ~1% of the gas phase magnetization diffuses into the dissolved phase, then for $\alpha_{\text{diss}} = 180°$ and for short values of $t$, an equal and opposite negatively signed $^{129}$Xe magnetization diffuses from the dissolved to gas phase. In such a scenario, the depolarization per pulse would be ~2%.

We do not use 180°-XTC, however, because it is not equivalent to CSSR. The reason why they are not equivalent can be seen by observing that 180°-XTC involves diffusion of $^{129}$Xe magnetization both from alveolar gas spaces to septal tissue and the reverse. However, the reverse diffusion from blood to alveolar gas spaces can only take place when the blood is in the gas exchange region. Therefore, there are two fundamentally different dependences determined by whether blood remains in the gas exchange region during the diffusion time or not. CSSR, however, only involves diffusion in one direction: from gas to tissue.

One can show by induction that if one uses 90° pulses for XTC (rather than the traditional 180° pulses), the ‘depolarization per pulse’ factor in XTC is identical to the $F(t)$ factor obtained with CSSR, i.e. $D_{\text{XTC}}(\alpha_{\text{diss}} = 90°, t) = F(t)$. Thus, using single breath XTC [5] with 90° pulses (90°-SB-XTC), we demonstrate here our first 3D regional measurements of $S_A/V_{gas}$. Note that original implementation of XTC required an additional breath-hold scan to control for other sources of gas phase $^{129}$Xe magnetization decay. SB-XTC is a modification we made to make both measurements in a single breath-hold.

For this initial demonstration, we acquired data at short times such that the septal uptake of $^{129}$Xe is diffusive and $F(t) \sim \sqrt{Dt}$. We examined two diffusion times that are within the $\sqrt{t}$ regime: 44 and 62 ms (see figure 5). Using the analytical form valid for the $\sqrt{t}$ regime [3], i.e. $F(t) = \lambda S_A/V \sqrt{4Dt/\pi}$, and the previously mentioned literature values for $\lambda$ and $D$, the experimentally determined slope $\Delta F/\Delta(\sqrt{t})$ for each image voxel was used to obtain regional...
values of $S_A/V_{gas}$. The results are shown in figure 9. The mean $S_A/V_{gas}$ from the 3D images was $267 \pm 62$ cm$^{-1}$ and agrees with those measured with CSSR on whole lungs obtained previously from normal healthy subjects at similar lung volumes.

Regarding regional variation in $S_A/V_{gas}$, the internal support of the lung against gravity is a classical origin for differences, as well as the nature of the lung’s filling during breathing, with gravitationally superior regions ventilating higher on their local pressure–volume relationship, and with commensurately lower compliance. Figure 9 shows a readily apparent gravitational dependence in $S_A/V_{gas}$ in the anterior posterior direction of the lung. Due to gravity, one expects the anterior sections to have the highest $S_A/V_{gas}$ because they support the weight of the dependent portion of the lung and are therefore stretched out to a greater degree than posterior portions. In addition to gravitationally based differences, we also note that pulmonary expansion has multiple degrees of freedom; the three most common are thoraco-abdominal, via descent of the diaphragm, and ‘pump handle’ and ‘bucket handle’ activation of inspiratory intercostal muscles. Pump handle refers to elevation of the sternum, an expansion of the rib cage in the anterior/posterior direction; bucket handle refers to elevation of the lateral sides of the rib cage. Depending on the interaction of these muscle groups, the lung does not expand in a uniform fashion. Heterogeneities thus introduced are in addition to those governed by gravitational effects. Departures from simple gravitational gradients are thus to be expected.

6.1. Technical details for 90°-SB-XTC imaging at 3 T

Each subject inhaled 600 ml of 86% enriched $^{129}$Xe with additional oxygen to make the mixture 21% oxygen. SB-XTC was implemented on a Siemens 3T Tim Trio. The RF coil was a 32 channel $^{129}$Xe coil provided by I M Dregely from UNH [20]. We used 90°-SB-XTC where three 3D gradient echo images are acquired during a several second breath-hold. The first two images are separated by the control XTC sequence [$\alpha_{diss}(-200 \text{ ppm}) - \tau]^n$, where $\alpha_{diss} = 90^\circ$, and is at a frequency of $-200$ ppm with respect to the gas phase (or $-400$ ppm from the dissolved phase resonances). The attenuation measured between the first pair of images provides a measurement of the sources of gas-phase attenuation that are not due to interphase diffusion (i.e. due to (a) RF depletion of the non-renewable hyperpolarized $^{129}$Xe magnetization and (b) $T_1$ decay). The second and third images are separated by the XTC sequence [$\alpha_{diss}(+200 \text{ ppm}) - \tau]^n$, where the selective RF pulse is applied to the dissolved phase peaks. Because $\alpha_{diss} = 90^\circ$, each RF pulse destroys xenon magnetization in tissue and blood. The spatial resolution, 2.2 cm, of the acquired data was isotropic $(16 \times 16 \times 8$ data matrix). The number of RF pulses used between image pairs was 90 (44) for the control (XTC) pulses. For the gradient echo images, $TE = 2.3$ ms and $TR = 5.1$ ms. The total 3D data acquisition was 10.1 (7.6) s for experiments using 44 ms (62 ms) diffusion times. The raw data were zero-filled by a factor of two in all three directions, resulting in 1.1 cm isotropic resolution. To account for possible non-uniform distribution of $B_1$, a separate experiment to measure the flip angle distribution was performed. The gradient echo images were corrected for flip angle differences on a pixel-by-pixel basis prior to the calculation of $F$. Before inhaling the xenon/oxygen gas mixture, the subject was asked to exhale as much as possible and to then inhale the prepared xenon/oxygen gas mixture. Assuming the subject exhaled to within 100 cc of RV, we estimate that all image sets were acquired at approximately the same lung volume, which in this case was at $\sim 40\%$ TLC, which is near FRC. Images from different data sets were registered manually and therefore could be a source of error, especially near the edges of the lung.

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7. Discussion and conclusions

To our knowledge, the measurements of \( h \) and \( \tau \) presented here are the first non-invasive, non-radiation-based, quantitative measurements of these gas exchange parameters in patients with pulmonary disease. Alveolar surface area per unit volume has also been measured with an apparent diffusion technique using hyperpolarized \(^3\)He [21]. We believe that the unique properties of \(^{129}\)Xe, together with advances in hyperpolarization technology, will provide a basis for measuring functionally important indices of the lung’s primary function as a gas exchange organ, heretofore inaccessible in both unfixed lungs and in intact animals and humans. Unlike diffusing capacity or ventilation/perfusion distributions obtained with the multiple inert gas elimination technique (MIGET), \(^{129}\)Xe MRI techniques provide regional information. Unlike CT, which measures tissue density and which is dependent on both surface area and septal thickness, our technique can separately measure each of these two important parameters, and does not expose subjects or patients to ionizing radiation. We specifically target (i) parenchymally destructive diseases such as emphysema, with its loss of functional gas exchange surface area, (ii) interstitial diseases involving septal thickening due to excess connective tissue in fibrotic disorders or fluid accumulation in edema secondary to pulmonary hypertension, and (iii) vascular diseases influencing capillary transit time distributions.

The data presented here raise as many questions as they answer, both in terms of new understanding of normal physiology in awake humans, as well as the potential for early diagnosis and management following therapeutic interventions. For example, an examination of the results [6] reveals that, as expected, \( S_A/V_{\text{gas}} \) decreases with lung volume [19]. However, on comparison of our \( S_A/V_{\text{gas}} \) estimates to literature values obtained from fixed lung histology [15], we found that our values are \( \sim 40\% \) lower. A possible explanation is that the lower bound on our diffusion time window was 17 ms. Thus, some of the thinner sections of the septal tissue between capillaries may already have been saturated by this time. For \( t = 17 \text{ ms} \), we estimate that the septal diffusion distance in tissue for \(^{129}\)Xe is \( \delta = \sqrt{2Dt} = 3.2 \mu\text{m} \), which is certainly large enough to saturate the thinner septal sections. This would also explain our observation of an exchange offset \( F_0 \).

Recently, Imai et al [22] measured \(^{129}\)Xe septal uptake in mice at 9.4 T using CSSR and fitted their data with our analytical formula (equation (9)), which we had presented at two previous conferences [13, 14]. Six controls and six elastase-treated animals were studied. As expected, a significant reduction in \( S_A/V_{\text{gas}} \) was seen in the elastase-treated animals, which was verified by histological measurements of the mean linear intercept \( L_{\text{m}} \). The absolute value of \( S_A/V_{\text{gas}} \) from \(^{129}\)Xe NMR and histology were in very good agreement, within 16\% of each other. No significant difference was seen between the controls and treated animals either for the mean septal thickness of \( \sim 6.2 \mu\text{m} \) or for \( \tau \), which was \( \sim 0.36 \text{ s} \). We believe that these data are very important as they (a) are an external validation of our method, (b) use both control animals and an elastase emphysema model, and (c) were performed at a different field strength from our original 0.2 T data.

In summary, the CSSR and XTC techniques described in this paper offer a unique window into direct measurements of parameters functionally important for gas exchange. The technique can be applied in spontaneously ventilating subjects, with no exposure to radiation. A particularly striking example of this is our measurements of septal surface area loss in patients with mild emphysema, and of septal thickening in patients with mild interstitial fibrosis. To our knowledge, these are the first such noninvasive measurements in humans with

\[ S_A/V_{\text{gas}} \]
interstitial fibrosis. In the absence of radiation, this technique is clearly poised to quantify disease progression, patient management and response to therapeutic interventions.

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References

[1] Weibel E R 2009 What makes a good lung? Swiss Med. Wkly 139 375–86
[2] Ruppert K et al 2000 NMR of hyperpolarized (129)Xe in the canine chest: spectral dynamics during a breath-hold NMR Biomed. 13 220–8
[3] Butler J P et al 2002 Measuring surface-area-to-volume ratios in soft porous materials using laser-polarized xenon interphase exchange nuclear magnetic resonance J. Phys.: Condens. Matter 14 L297–304
[4] Driehuys B et al 2006 Imaging alveolar-capillary gas transfer using hyperpolarized 129Xe MRI Proc. Natl Acad. Sci. USA 103 18278–83
[5] Patz S et al 2007 Hyperpolarized (129)Xe MRI: a viable functional lung imaging modality? Eur. J. Radiol. 64 335–44
[6] Patz S et al 2008 Human pulmonary imaging and spectroscopy with hyperpolarized 129Xe at 0.2 T Acad. Radiol. 15 713–27
[7] Ruppert K et al 2004 Exploring lung function with hyperpolarized (129)Xe nuclear magnetic resonance Magn. Reson. Med. 51 676–87
[8] Mansson S et al 2003 Characterization of diffusing capacity and perfusion of the rat lung in a lipopolysaccharide disease model using hyperpolarized 129Xe Magn. Reson. Med. 50 1170–9
[9] Eger E I and Larson C P J 1964 Anaesthetic solubility in blood and tissues: values and significance Br. J. Anaesth. 36 140–4
[10] Ruppert K et al 2004 Probing lung physiology with xenon polarization transfer contrast (XTC) Magn. Reson. Med. 44 349–57
[11] Ruppert K 2008 Measuring xenon gas-exchange time constants using XTC MRI Intl Summit: The Future of Quantitative and Functional Lung Imaging (Coralville, Iowa, 2–4 October 2008) Abstract 30
[12] Ruset I C, Ketel S and Hersman F W 2006 Optical pumping system design for large production of hyperpolarized Phys. Rev. Lett. 96 053002
[13] Patz S et al 2007 Human pulmonary physiology with hyperpolarized 129Xe RSNA (Chicago, IL, 25–30 November 2007) Abstract SSA21–06
[14] Patz S et al 2008 Detection of interstitial lung disease in humans with hyperpolarized 129Xe Proc. 16th Meeting, International Society of Magnetic Resonance in Medicine (Toronto, Canada, 3–9 May 2008) Abstract 2678
[15] Coxson H O et al 1999 A quantification of the lung surface area in emphysema using computed tomography Am. J. Respir. Crit. Care Med. 159 851–6
[16] Hogg J C et al 1994 Erythrocyte and polymorphonuclear cell transit time and concentration in human pulmonary capillaries J. Appl. Physiol. 77 1795–800

New Journal of Physics 13 (2011) 015009 (http://www.njp.org/)
[17] Wolber J et al 1999 Spin-lattice relaxation of laser-polarized xenon in human blood Proc. Natl Acad. Sci. USA 96 3664–9

[18] Maria N S and Eckmann D M 2003 Model predictions of gas embolism growth and reabsorption during xenon anesthesia Anesthesiology 99 638–45

[19] Gil J et al 1979 Alveolar volume–surface area relation in air- and saline-filled lungs fixed by vascular perfusion J. Appl. Physiol. 47 990–1001

[20] Dregely I M et al 2009 A 32 channel phased array lung coil for parallel imaging with hyperpolarized xenon 129 at 3 T Proc. Intl Soc. Mag. Reson. Med. 17 13 2203

[21] Yablonskiy D A et al 2009 Quantification of lung microstructure with hyperpolarized 3 He diffusion MRI J. Appl. Physiol. 107 1258–65

[22] Imai H et al 2010 Noninvasive detection of pulmonary tissue destruction in a mouse model of emphysema using hyperpolarized 129Xe MRS under spontaneous respiration Magn. Reson. Med. 64 929–38