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Human Pulmonary Imaging and Spectroscopy with Hyperpolarized ^{129}Xe at 0.2T

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Abstract

Rationale and Objectives—Using a novel ^{129}Xe polarizer with high throughput (1-2L/hr) and high polarization (~55%), our objective was to demonstrate and characterize human pulmonary applications at 0.2T. Specifically, we investigated the ability of ^{129}Xe to measure the alveolar surface area per unit volume of gas, S_A/V_{gas} .

Materials and Methods—Variable spin echo time (TE) gradient and radio frequency (RF) echoes were used to obtain estimates of the lung's contribution to both T_2^* and T_2 . Standard multi-slice ventilation images were obtained and signal to noise ratio (SNR) determined. Whole lung, time dependent measurements of ^{129}Xe diffusion from gas to septal tissue were obtained with a Chemical Shift Saturation Recovery (CSSR) method. Four healthy subjects were studied and the Butler et al CSSR formalism (*J Phys: Condensed Matter* **14**:L297–L304, 2002) was used to calculate S_A/V_{gas} . A Single Breath version of the Xenon Transfer Contrast (SB-XTC) method was implemented and used to image ^{129}Xe diffusion between alveolar gas and septal tissue. A direct comparison of CSSR and SB-XTC was performed.

Results— $T_2^*=135 \pm 29\text{ms}$ and $T_2 = 326.2 \pm 9.5\text{ms}$. Maximum SNR=36 for ventilation images from inhalation of 1L 86% ^{129}Xe and voxel volume=0.225cc. CSSR analysis showed S_A/V_{gas} decreased with increasing lung volume in a manner very similar to that observed from histology measurements, however the absolute value of S_A/V_{gas} is ~40% smaller than histology values. SB-XTC images in different postures demonstrate gravitationally dependent values. Initial comparison of CSSR with XTC showed fairly good agreement with expected ratios.

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Conclusion—Hyperpolarized ^{129}Xe human imaging and spectroscopy are very promising methods to provide functional information about the lung.

Keywords

hyperpolarized xenon; ^{129}Xe ; lung imaging; surface area per unit volume; S/V ; XTC; single breath XTC; SB-XTC; CSSR; T_2^* ; T_2 .

Introduction

To date, the vast majority of work in human hyperpolarized noble gas imaging has been with ^3He and not ^{129}Xe . Mugler et al [1] demonstrated the very first human ventilation images and spectra with ^{129}Xe in 1998 and later obtained the first human ADC images of the gas phase [2]. Kilian et al [3] demonstrated human time resolved ^{129}Xe spectra from both gray and white matter in 2004. A significant problem for ^{129}Xe in human studies has been the lack of a polarizer with sufficiently high polarization and throughput. High polarization is absolutely necessary because, compared to ^3He , ^{129}Xe suffers two significant disadvantages. First, the gyromagnetic ratio is less by a factor of ~ 3 and secondly, the isotopic abundance of ^{129}Xe is only 26% compared to 100% for ^3He . These two factors mean that ^{129}Xe suffers an inherent loss in signal of a factor of ~ 12 compared to ^3He . Despite these problems, there has been vigorous work studying both phantoms as well as animals using ^{129}Xe . This is because of the inherent advantage ^{129}Xe offers because of its solubility in tissue. This, together with the fact that there is a large ($\sim 200\text{ppm}$) chemical shift between the gas and dissolved spectral peaks of ^{129}Xe means that one can easily discern ^{129}Xe in the different chemical phases. Ruppert et al [4,5], Driehuys et al [6], and Mansson et al [7] have made very significant contributions towards demonstrating the ability to measure functional pulmonary physiology by observing the diffusion of ^{129}Xe from alveolar gas to dissolved phases. i.e. septal tissue. Our own work using a Chemical Shift Saturation Recovery (CSSR) method in porous phantoms [8] has demonstrated that the early time slope of the CSSR data is related to the alveolar surface area per unit of gas volume S_A/V_{gas} . Using this formalism, Cai et al. [9] demonstrated a high degree of correlation between the slope of the XTC depolarization curve and morphometric measurements of surface area per unit volume in a rabbit emphysema model. Here we report initial CSSR results in humans using a novel ^{129}Xe polarizer at 0.2T [10]. We also report human imaging with the XTC method and report an initial comparison with CSSR. Finally, we also report a measurement of the contribution to both T_2 and T_2^* from the lung at 0.2T as well as the signal to noise ratio (SNR) obtained with standard gradient echo imaging.

Materials and Methods

^{129}Xe Polarizer

A University of New Hampshire ^{129}Xe polarizer was installed at Brigham and Women's Hospital (BWH) and became operational in the second quarter of 2005. This polarizer is capable of delivering 1-2L/hr at $\sim 55\%$ polarization. This polarizer is the first UNH unit located outside of UNH and represents an early design from the UNH group. Nevertheless, this polarizer has proved exceptionally robust with only small periods of down time required for occasional maintenance. Polarized xenon is frozen to separate the buffer gases, then thawed into a Tedlar bag (Welch Fluorocarbon, Dover, NH) with $\sim 99\%$ polarization recovery. The volume of ^{129}Xe delivered to a subject varied from 0.5 – 2L depending on both the subject's Total Lung Capacity (TLC) as well as the fraction of TLC at which the experiment was being performed. There was some inefficiency in the polarizer in that it was necessary to prepare 0.3L more than the quantity delivered to the subject. This is because 0.3L is the volume of the spiral cell and connecting tubing to the tedlar bag. Although we were unable to use this gas for

human inhalation, we did measure the signal from the remaining gas in the spiral cell. By comparing this with that from a standard thermal cell, we were able to monitor the absolute polarization. The thermal cell consisted of a 2.91L spherical glass cell filled with 4.01atm of 86% enriched ^{129}Xe (thermal polarization) and 2.02atm O_2 . The oxygen was added to reduce T_1 , which was measured to be 0.89s. To account for any differences in field homogeneity due to different sizes of the thermal and hyperpolarized samples, the signal was measured by integration over the linewidth.

MRI Hardware

All experiments were performed on a GE Signa Profile IV MRI magnet operating at a static magnetic field (B_0) of 0.2T and interfaced with a broadband Tecmag Apollo (Houston, Texas) research console. The gradient power amplifiers (model Analogic AN 8290) and gradient coils from the GE Profile system were also utilized. To interface the analog gradient drive signals from the Apollo unit to the Analogic amplifiers, which normally accept a digital drive input, an op-amp buffer amplifier for each gradient channel was constructed and connected to an internal summing point identified by an Analogic engineer. Since the GE radio frequency (RF) system was narrowband and only for ^1H , it was completely bypassed. All ^{129}Xe lung studies were performed with a Mirtech, Inc (Brockton, MA) whole body transmit/receive coil, with an unloaded quality factor $Q=300$, operating at ^{129}Xe frequency (2.361MHz). The coil can be seen in Figure 1 and consists of 2 square planar loops arranged as a parallel circuit of impedance matched coils spaced 42.6cm apart. When loaded by a human subject the coil's Q would decrease by 4%. Since the scanner and RF room were originally designed for operation at 8.5MHz, it was necessary to add an RF-shielded enclosure inside the scanner itself to reduce stray interference at 2.36MHz. The thickness of the copper was minimal in order to minimize gradient eddy currents. Also, typical Ga-As preamps have poor noise figures at this frequency, and therefore a bipolar preamp (Miteq Model AU-1579-BNC) was used. The RF power amplifier was a CPC (Hauppauge, NY) Model 30LF1000 1KW (1–30MHz) unit and could be used at both ^{129}Xe and ^1H (8.35MHz) frequencies.

Human Protocols

All studies were conducted in accordance with IRB and FDA IND approved protocols. Informed consent was obtained as a prerequisite to participation in the study. The protocol requires all inhaled gas mixtures to contain at least 21% oxygen and no more than 70% xenon. In addition, the estimated alveolar xenon concentration is limited to no more than 35%. Standard spirometry was performed on each subject to obtain their residual volume RV and total lung capacity TLC. These values were used to calculate the volume of xenon, oxygen and air needed both to satisfy the above protocol as well as to obtain a lung volume that was specified as a fraction of the subject's TLC. Specifically, whatever volume of xenon was inhaled included an addition volume of oxygen so that the concentration of oxygen in the xenon/oxygen mixture was 21%. Any additional gas used to achieve a particular lung volume was air, which already contained 21% oxygen. Breath-hold times are limited to 40s for healthy subjects. Blood oxygen level (SpO_2), ECG, blood pressure, heart rate, and respiratory rate are measured before and after each experiment outside the scanner and SpO_2 and heart rate are also monitored while in the MRI scanner. Several practice sessions are performed outside the scanner, some with air and one with a volume of ^{129}Xe equal to the maximum that would be used for any of the experiments planned for that particular subject. The practice breaths familiarize the subject with the protocol, allow them to experience what breathing ^{129}Xe will be like, and allow us to make sure SpO_2 stays within allowed limits: no lower than an absolute value of 85% for healthy subjects. Four subjects involving 18 different breath-hold experiments were studied and there were no adverse events. Before breathing xenon, a subject is instructed to perform 2 cycles of a deep breath to TLC followed by exhalation to close to RV.

Diffusion of ^{129}Xe from Alveolar Gas Spaces to Septal Tissue

Several prior papers have described a Chemical Shift Saturation Recovery (CSSR) method in animals [4–7]. Figure 2 demonstrates the CSSR concept where one saturates the dissolved phase magnetization with a chemically selective RF pulse at $\sim +205\text{ppm}$ and then observes the recovery of the dissolved phase magnetization as hyperpolarized ^{129}Xe from the gas phase diffuses into the dissolved phase (parenchymal tissue and blood). In our earlier work on porous polyethylene phantoms [8], we demonstrated how the CSSR method could be used to measure the surface area per unit volume (S/V) in porous media. We showed that for a 1D, semi-infinite, 2 phase system, the fraction F of the gas phase signal at time $t=0$ that has diffused into the dissolved phase at time t is given by:

$$F(t) = \frac{\int s_{\text{diss}}(t, \omega) d\omega}{\int s_{\text{gas}}(t=0, \omega) d\omega} = \lambda \frac{S}{V_{\text{gas}}} \sqrt{\frac{4D_{\text{diss}}t}{\pi}}. \quad [1]$$

Here, λ is the Ostwald solubility coefficient, and D_{diss} is the diffusivity of ^{129}Xe in the dissolved phase. V_{gas} is the gas volume and S is the surface area between the two phases. For lungs, S is the alveolar surface area S_A . For an ideal infinite medium (Figure 2a), the dissolved state signal increases diffusively as $\sqrt{t}$ for all times t . However, the thickness of septal tissue is not infinite and thus saturates after some time (Figure 2b). Thus Eqn [1] is valid for short times before the septal tissue saturates. Note that solutions valid for all times have been given by Ruppert et. al [4.5], Driehuys [6], and Mansson et. al [7]. To measure the gas phase signal at $t=0$, a small flip angle (α) non-selective RF pulse is applied immediately before each diffusion measurement to interrogate the gas phase. The gas signal is then scaled by $1/\sin(\alpha)$ to obtain its amplitude as if it had been interrogated with a 90° pulse. A 10ms selective 90° RF pulse [11] is then applied first to destroy the dissolved phase magnetization and secondly to measure the dissolved phase after a specified time to allow for diffusion of ^{129}Xe from alveolar gas spaces to septal tissue. Eighteen different breath-hold experiments, each at a constant lung volume, were performed on four healthy subjects. In all but one subject, several different lung volumes were studied. Of the eighteen experiments, half were repeats to test reproducibility (see Table 2). For experiments performed at residual volume, RV, the subject first inhaled the xenon/oxygen/air mixture, waited a few seconds, then exhaled to RV, and then kept their lung volume constant during the experiment. In each breath-hold experiment, F was measured for a set of diffusion times. In the first 15 experiments, the set of diffusion times was: 20, 29, 39, 69, 119, 219, 519, and 719ms. For the last 3 experiments, additional time points were added and data was acquired at 13 time points: 17, 18, 22, 27, 37, 47, 57, 67, 77, 117, 267, 517, and 717ms. Since F is an intensive quantity, i.e. the ratio of the dissolved to gas phase signal, the fact that the gas phase magnetization decays during the breath-hold does not affect this ratio. Thus, during a single breath-hold experiment, each set of diffusion times was measured at least 3 separate times. The free induction decay (FID) from each diffusion time measurement was analyzed separately (Fourier transformed, phase corrected, spline baseline corrected and integrated over the spectral width corresponding to the linewidth of the dissolved (or gas) phase). The spectral data was discarded if the signal to noise ratio (SNR) of the dissolved phase went below ~ 5 . Data from identical time points was then signal averaged. Note that the dissolved state signal that we observe at 0.2T contains the signal from both blood and parenchyma as the chemical shift between these spectral peaks is not easily resolved at this field strength.

Results

Human multi-slice ventilation maps

Both normal isotopic abundance (26%) and enriched (86%) ^{129}Xe were used for ventilation 2D multi-slice gradient echo images. One liter of xenon gas was inhaled from a lung volume close to RV. Figure 3a and b show examples of the axial and coronal data obtained from 26%

and 86% ^{129}Xe respectively. Imaging parameters for axial data set were: FOV=300mm, voxel size: $4.7 \times 9.4 \times 15 \text{ mm}^3$, 20 slices acquired (16 shown), spin echo time (TE)=6.66ms, repetition time (TR)=23.47ms, readout bandwidth = 5.8kHz, matrix $64 \times 32 \times 20$, acquisition time = 15.02s. Typical SNR from high ventilation areas of the parenchyma = 16.7. For reconstruction, the data was zero filled to 128×128 . For the coronal data, imaging parameters were: FOV=300mm, voxel size: $3.26 \times 6.25 \times 12.5 \text{ mm}^3$, TE=6.45ms, TR=28.67ms, readout bandwidth = 5.8kHz, matrix $96 \times 48 \times 10$, acquisition time = 13.76s. Typical SNR from high ventilation areas of the parenchyma = 35.9. For reconstruction, data was zero filled to 128×128 and a mask was applied to allow display of voxels from 10–85% of the maximum intensity.

T_2^* and T_2 of gaseous ^{129}Xe in a healthy lung at 0.2T

A series of both gradient and spin echoes were acquired with variable TE on one healthy subject. For T_2^* , the first gradient echo was at 27.25ms with subsequent echoes spaced at a ΔTE of 27.25ms. For T_2 , the first echo was at 100ms with $\Delta\text{TE}=100\text{ms}$. At least twenty TE values were measured. No phase encoding or slice selection was used. Each echo was Fourier transformed, magnitude calculated, and integrated across the projection to obtain the observed signal S as a function of TE. The gradient echo data was fit to $S = S_0 \exp(-\text{TE}/T_2^*)$ and the spin echo data was fit to $S = S_0 \exp(-\text{TE}/T_2)$. The fitted values were: $T_2^* = 46.10(+4.15 / -3.51)$ ms with $R^2=0.992$ and $T_2 = 326.16(+9.86 / -9.20)$ ms with $R^2=0.998$. The error bars are the 95% confidence levels.

To interpret this further, we note that the gradient echo measured relation rate $1/T_{2,\text{meas}}^*$ has contributions from three terms [12,13]: the inherent transverse relaxation rate ($1/T_2$), the inhomogeneity of the static 0.2T magnetic field ($1/T_{2,\text{shim}}^*$), and the magnetic susceptibility differences in the lung between gas and tissue ($1/T_{2,\text{lung}}^*$).

$$\frac{1}{T_{2,\text{meas}}^*} = \frac{1}{T_2} + \frac{1}{T_{2,\text{shim}}^*} + \frac{1}{T_{2,\text{lung}}^*}. \quad [2]$$

For T_2 , we use the measured value reported above. To estimate $T_{2,\text{shim}}^*$, we measured the FWHM linewidth, $\Delta\nu_{\text{proton}}$, of a uniform proton sample (saline) that occupied a volume similar to the lung. This measurement was at the ^1H frequency ($f_{\text{proton}} = 8.536\text{MHz}$) and thus to obtain the equivalent linewidth at the ^{129}Xe frequency ($f_{\text{xenon}} = 2.361\text{MHz}$), one simply scales $\Delta\nu_{\text{proton}}$ by the frequency ratio. Further, using the relationship $\Delta\nu_{\text{FWHM}} = 1/(\pi T_2^*)$, one obtains:

$$\frac{1}{T_{2,\text{meas}}^*} = \frac{1}{T_2} + \pi \Delta\nu_{\text{proton}} \frac{f_{\text{xenon}}}{f_{\text{proton}}} + \frac{1}{T_{2,\text{lung}}^*}. \quad [3]$$

Typical values for the proton linewidth were $\Delta\nu_{\text{proton}} = 15 \pm 0.75\text{Hz}$; then $\Delta\nu_{\text{xenon}} = 4.15 \pm 0.21\text{Hz}$, which corresponds to a $\mathbf{B}_0$ inhomogeneity over the lung of 1.9 ppm or a $T_{2,\text{shim}}^* = 69.7 \pm 3.2\text{ms}$. This allows us to calculate $T_{2,\text{lung}}^* = 231 \pm 87\text{ms}$, where the error bar here is an estimate of one standard deviation. Note that since the error bars for T_2^* and T_2 were quoted with 95% confidence intervals, these values were halved to estimate one standard deviation for the error propagation calculation. The quantity we report for T_2^* is given by:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_{2,\text{lung}}^*} \equiv \frac{1}{T_{2,\text{meas}}^*} - \frac{1}{T_{2,\text{shim}}^*}, \quad [4]$$

and represents the T_2^* associated with a relaxation rate that would be measured in the absence of $\mathbf{B}_0$ inhomogeneities with a gradient echo sequence. Thus using Eqn. [4], we find that $T_2^* = 135 \pm 29\text{ms}$.

Note that the data acquired in this experiment was from hyperpolarized ^{129}Xe in both the gas and dissolved (or tissue) phases. The contribution from the dissolved phase, however, is minimal since at most it contributes a few percent to the observed signal. This is because the partition coefficient is ~ 0.1 [14] and because relative volumes of tissue and gas are in the ratio of $\sim 1:4$. Thus, one expects the dissolved phase signal relative to the gas phase signal to be $\sim (0.1)(0.25)=0.025$. Experimentally observed ratio was 0.022 and was measured by acquiring a whole lung spectrum after inhalation of 1L of ^{129}Xe from near RV and then waiting 2s before acquiring a FID with a nonselective RF pulse. Thus because the contribution of the dissolved phase signal is at most only a few percent, the values reported here can be considered as from the gas phase.

Chemical Shift Saturation Recovery (CSSR) Results

A typical data set from a healthy human subject is shown in Figure 4. The data is plotted both as a linear function of time (Fig. 4a) and as function of $\sqrt{t}$ (Fig. 4b). It is clear from Fig. 4b that there is a constant (DC) offset (see Discussion section for further explanation) in the fit to the data since the y-intercept is nonzero. Thus, for our analytical fits, we have added a DC offset term (F_0) to Eqn. [1]:

$$F(t)=F_0+\lambda\frac{S_A}{V_{\text{gas}}}\sqrt{\frac{4D_{\text{diss}}t}{\pi}}=F_0+K\sqrt{t}, \quad [5]$$

where the slope $K=\lambda\frac{S_A}{V_{\text{gas}}}\sqrt{4D_{\text{diss}}/\pi}$. Table 1 lists the age, gender, RV and TLC for each of the 4 subjects studied here. Table 2 lists the values for the least squares fit values for K and F_0 to Eqn. [5]. Using the fitted values of K , S_A/V_{gas} was also computed using a literature value for $\lambda = 0.1$ [13] and a literature estimate of $D_{\text{diss}} \sim 3 \times 10^{-6} \text{ cm}^2/\text{s}$ [15]. The data is fairly well fit by Eqn. [5] as the values for the coefficient of determination, R_2 , are all greater than 0.8 and the majority, 14 out of 18, have $R_2 \geq 0.9$. The average error bar for K is 13.8%. If λ and D_{diss} were known exactly, then the relative error for K and S_A/V_{gas} are identical. We must assume, however, that there may be some uncertainty in the literature values for λ and D_{diss} . Since there is no data near a diffusion time $t=0$, the percentage uncertainty in F_0 is significantly larger than that found for K . For two experiments, 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.

Figure 5a and b show a compilation of the measured values S_A/V_{gas} as a function of lung volume normalized to TLC, $V_{\text{lung}}/\text{TLC}$. Figure 5a shows each individual subject's data while Figure 5b shows the average S_A/V_{gas} at three values of $V_{\text{lung}}/\text{TLC}$ (0.24, 0.45 and 1.0). Note that except for the TLC measurements, the values of $V_{\text{lung}}/\text{TLC}$ for the individual subjects are not exactly equal to those reported in Figure 5b. Thus, there is a small error bar that is reported for the values of $V_{\text{lung}}/\text{TLC} = 0.24$ and 0.45. In addition to the above, this error bar also contains an estimate of the uncertainty for the lung volume at which the subject began the inhalation of the xenon gas mixture. The breathing protocol called for an exhalation to a volume as close as possible to RV before inhaling the xenon gas mixture. However, because this maneuver was not performed on a spirometer and because the subject was supine, the subject may not have achieved RV before inhalation. We estimated an uncertainty of 200cc for the subject with the largest lung volume and scaled this value proportionally with the measured TLC of the subject. Finally, while Figure 5a and Table 2 demonstrate that while some measurements reproduced extremely well, there was variation in other repeat measurements. For example, there were 7 data points that were repeated at least once; 6 measurements with 1 repeat and 1 measurement with 3 repeats. To obtain a numerical estimate of the reproducibility of a single measurement, the mean and standard deviation for each of the 7 data points with repeats was calculated. Then, the ratio of the standard deviation to the mean was calculated and averaged over the 7 data

points. Using this as an estimate for the reproducibility, one finds an average variability of $\pm 26\%$.

Imaging Xenon diffusion from Alveolar Gas spaces to Septal Tissue: Methods and Results

CSSR is an elegantly simple technique. However, since the maximum value of F_{CSSR} is $\sim 2\%$, the SNR is low. Therefore although this method works well for spectroscopy of the whole lung, it is not optimum for imaging where the available signal is distributed over an imaging matrix. Thus, rather than using CSSR, which measures the dissolved phase ^{129}Xe signal directly, for imaging we used the xenon transfer contrast (XTC) method developed by Ruppert et al [4,5]. XTC measures the diffusion into the dissolved phase indirectly by looking at the attenuation in the gas phase signal after multiple opportunities for interphase diffusion. Since we wish to utilize the CSSR formalism presented above to quantitatively measure S_A/V_{gas} with XTC, we need to understand the relationship between the two. Thus this section will first summarize a modification we have made to the original XTC method, present some basic imaging results, and then present experimental measurements showing the comparison between CSSR and XTC.

Ruppert et al's implementation of XTC involves two separate breath-hold experiments. One experiment, the control experiment, measures the voxel by voxel attenuation due to two "unwanted" sources of attenuation, i.e. T_1 decay due to the presence of oxygen and depletion of the ^{129}Xe magnetization reservoir due to the RF pulses used for imaging. A second XTC experiment measures the attenuation from the two "unwanted" sources as well as that due to interphase diffusion. The interphase diffusion part can then be solved for by using the results from the control experiment to remove the "unwanted" sources of attenuation in the XTC experiment. The XTC experiment acquires two images separated by $[180-\tau]^n$, where the 180 is a selective 180° pulse applied in the middle of the dissolved phase frequencies ($+205\text{ppm}$), τ is a time interval for diffusion, and n is the number of repeats. During each $(180-\tau)$ interval, alveolar gas diffuses into the septa and inverted dissolved phase spins diffuse into the alveolar gas spaces. Thus if a CSSR experiment is conducted and one measures $F_{\text{CSSR}}(\tau) = 2\%$, then for $n=1$, one would measure $F_{\text{XTC}}(\tau) = 2F_{\text{CSSR}}(\tau) = 4\%$. By repeating the $(180-\tau)$ sequence n times, the gas phase magnetization is reduced by the factor $1-[F_{\text{XTC}}(\tau)]^n$. However, for n repeats, it is not clear whether the attenuation per pulse in XTC remains equal to double that measured by CSSR, which is the rationale for comparing CSSR and XTC (see below). The XTC method also requires a separate control experiment where the selective 180° 's are applied off resonance (-205ppm). As stated above, the control experiment effectively measures the voxel by voxel attenuation of the gas phase magnetization due to (a) T_1 decay and (b) depletion of the gas phase magnetization reservoir due to the RF pulses. To obtain the attenuation due solely to interphase ^{129}Xe diffusion, one simply scales the XTC experiment determined attenuation up by that measured in the control experiment.

Ruppert et al were studying anesthetized animals and thus registration between successive breath-hold experiments was not a severe problem. However, because we were imaging live humans, this was an issue and thus we implemented a single-breath XTC (SB-XTC) protocol [11,16]. A schematic of this pulse sequence is shown in Figure 6. A typical example of data obtained with SB-XTC from a subject (HS6) in the supine position is shown in Figure 7. For comparison, Figure 8 shows results of a subject imaged while lying on their left side. Imaging parameters here are identical to those reported by Muradian et al [11] and were: matrix 64 (readout) $\times 32$ (phase encode), pixel size $4.69\text{mm} \times 9.38\text{mm}$, $\text{TE/TR} = 5.23/28.47\text{ms}$, $\text{FOV}=300\text{mm}$, readout bandwidth $= \pm 2893.5\text{Hz}$. The echo was asymmetric and was refocused 20% through the readout time. The diffusion time $\tau=62\text{ms}$ and was chosen to lie well within the early time regime, i.e. F linear with $\sqrt{t}$, that was measured with CSSR. For reconstruction,

the data was zero filled to 128×128 . After FT and magnitude calculation, signal below 10% of the maximum was masked.

Note that Figure 7f shows a small gradient in the mean of F_{XTC} , $\bar{F}_{XTC}$, in the superior/inferior direction despite the fact that the subject is supine. Here, $\bar{F}_{XTC}$ is computed by averaging in the right/left direction. In identical experiments acquired at a higher lung volume, this gradient disappears. This behavior is consistent for a number of subjects [11] and believed to be due to a residual memory effect of being in the vertical position for a substantial portion of our lives. Closer to TLC, the lung is expected to be more homogeneous, which supports this observation that any residual gradient disappears at higher lung volumes. Note that for a vertically oriented lung and at lung volumes less than TLC, one expects higher ventilation (lower S_A/V_{gas}) in the base of the lung compared to the apex West [17]. And in fact, Ruppert et al [5] have observed this with XTC in vertically oriented animal lungs. The observation of a superior/inferior gradient when the subject is supine, however, is unexpected. The gradient seen in Figure 7f accounts for a ~30% change in $\bar{F}_{XTC}$. In comparison, Figure 8f shows $\bar{F}_{XTC}$ (averaged in the superior/inferior direction) as a function of the gravitationally dependent direction (i.e. right/left) for a subject lying on their left side. Clearly the ventilation is much higher for the right lung and is believed to be the result of having less pressure on it compared to the left lung, which is being compressed by surrounding structures due to gravity. Most noticeable is that because of the much lower ventilation of the left lung, S_A/V_{gas} and F_{XTC} are much higher than in the right lung. In addition, in the right lung, we observe a substantial gradient in $\bar{F}_{XTC}$ in the gravitationally dependent direction. Although similar changes have been observed by performing separate SB-XTC breath-hold experiments at different lung volumes [11], these results are important because one lung serves as an internal control for the other during a single experiment. Also note that similar results (not shown), but reversed for right/left, are obtained with the subject lying on their right side. These results motivate our desire to compare SB-XTC to CSSR in order to gain insight in how to quantitatively convert F_{XTC} to S_A/V_{gas} .

Initial Comparison of CSSR with SB-XTC

Figure 9 shows whole lung spectroscopy data from both a CSSR and SB-XTC experiment. The subject was HS20 and $V_{lung}/TLC = 0.54$. Diffusion times used for the XTC experiment ranged from 12.1 – 112.1ms and for CSSR from 18 – 717ms. The two data sets were each fit to the analytical form in Eqn. [5] for diffusion times up to 57ms where the data was easily observed to be linear with $\sqrt{t}$. The results of the linear least squares fits for XTC are: $K_{XTC} = 0.0491 \pm 0.00230$, $F_{0,XTC} = 0.0030 \pm 0.0038$. For CSSR, $K_{CSSR} = 0.0195 \pm 0.00041$ while F_0 was forced to zero since when it was allowed to be a fit parameter, it was negative. The least squares fits are shown as solid lines in Figure 9. The ratio of the slopes $K_{XTC}/K_{CSSR} = 2.52 \pm 0.17$. Note that for $n > 1$ and for very large values of τ , Ruppert et al [4] argue that $F_{XTC}(\tau) = 2F_{CSSR}(\tau)$ holds. Hence this initial result is encouraging in that the ratio of the slopes is fairly close to the expected ratio for long diffusion times. However, it is also clear that much more extensive studies are needed to confirm the relationship between K_{XTC} and S_A/V_{gas} .

Discussion

The work presented here provides initial evidence that hyperpolarized ^{129}Xe MRI can provide a noninvasive direct measure of alveolar surface area through the quantity S_A/V_{gas} . Specifically, this can be accomplished by measuring the slope of the CSSR (or XTC) septal uptake curve at early diffusion times when the ^{129}Xe MRI signal increases as $\sqrt{t}$. Note that the “gold standard” measurement of emphysema is L_m , which is the mean distance between air and tissue interfaces seen on microscope slide samples obtained from fixed lungs. A measurement of S_A/V_{gas} is equivalent to measuring L_m since they are related through the relationship $L_m = 2/(S_A/V_{gas})$. Measurement of S_A/V_{gas} is important because pulmonary

diseases that are destructive of alveolar septa, such as emphysema, can compromise the surface area of the lung available for exchange to the extent that both O_2 and CO_2 transport are affected. The progressive nature of such diseases can result in systemic hypoxia, hypercapnea, and acidosis. There is significant morbidity and mortality associated with emphysema, often presenting with uncontrolled dyspnea.

Despite the fact that there is a clear clinical need for sensitive methods to detect early emphysematous disease, there are severe limitations with methods used in the clinic today according to a 2003 NIH workshop [18]. For example, CT is widely accepted as the imaging modality of choice in humans and the percent area of low attenuation area (%LAA) below a threshold Hounsfield Unit (HU), is a de facto standard for measuring severity of emphysematous disease. CT, however, exposes patients to ionizing radiation, with an associated increased risk of cancer [19]. Another routine test, carbon monoxide diffusing capacity (D_{LCO}) is routinely used as a surrogate index of the diffusing capacity of the lung for O_2 . D_{LCO} tests unquestionably reveal sharp decreases in lung surface area, especially in advanced diseases, where arterial hypoxia can be traced to an underlying emphysematous pathology. However, such measurements show significant deterioration only in advanced disease states. Moreover, neither D_{LCO} nor CT is free from ambiguities in interpretation in the early stages of septally destructive diseases. In particular, CT is fundamentally a measurement of tissue density, independent of how it is geometrically arranged; importantly, local S_A/V_{gas} is a degree of freedom independent of local tissue volume density.

Another aspect of this work is our report of T_2 and T_2^* in the human lung at 0.2T. For an ideal gas, $T_1 = T_2$, which would predict that T_2 should be $>10s$ [20]. Here, however, we report a much smaller value, i.e. that $T_2 = 326.16 (+9.86 / -9.20)ms$. We were concerned that diffusion of the ^{129}Xe gas molecules through the imaging gradients could be the cause of additional attenuation of the signal that might account for the low measured value of T_2 . To determine whether or not the imaging gradients were a significant factor, both for our measurement of T_2 and for T_2^* , we calculated an equivalent transverse magnetization time constant $T_{2,G}$ and $T_{2,G}^*$ for the spin echo and gradient echo experiments respectively due to the imaging gradients and their timing in each pulse sequence. We used the standard formalism for calculating the b factor of our pulse sequence together with a mean value of $0.02cm^2/s$ for the ^{129}Xe diffusivity in the lung parenchyma [21]. The results of these calculations are that $T_{2,G}$ and $T_{2,G}^*$ are 4.4s and 2.5s respectively. Both of these values are much larger than the measured values and hence we conclude that diffusion through the imaging gradients has a negligible effect on our reported values. Thus to explain the anomalously small value measured for T_2 , we hypothesize that there are interactions of the gas with the septal tissue that act to significantly increase the transverse magnetization relaxivity. For example, because of gas exchange, during a measurement time, gaseous ^{129}Xe can diffuse into the septal tissue and then return to the gas state. Such a mechanism argues that T_2 for ^{129}Xe is fundamentally different than for 3He since helium has negligible solubility in tissue. Finally, there is another decay mechanism associated with gas exchange that we argue is negligible. This component is due to blood that carries away ^{129}Xe and therefore also acts as a decay mechanism [7]. However, based on our measurements reported above that saturated septal tissue contains $\sim 2\%$ of the ^{129}Xe magnetization as in the gaseous phase, and the fact that the capillary transit time through the gas exchange region is $\sim 1s$, this decay mechanism is responsible for $\sim 2\%$ per second and is therefore negligible.

It is also of interest how T_2^* scales with field strength. To estimate this scaling, we compare our measurement at 0.2T to a literature measurement made at 2T in guinea pig lungs by Chen et al [12]; $T_2^* = 18.5 \pm 9.6ms$. Comparing our value of $T_{2,lung}^* = 231 \pm 87ms$ to that of Chen et. al, the ratio, $R_T = T_{2,lung}^*(0.2T)/T_2^*(2T) = 12.5 \pm 8$ whereas the field ratio is 10. Chen et. al state that

the B_0 field inhomogeneity contributions to their measurement were negligible. They also assume that T_2 is very long (tens of seconds), implying that their measurement of T_2^* (see Eqn [4]) is equivalent to a measurement of $T_{2,\text{lung}}^*$ at 2T. Based on our measurement of T_2 at 0.2T though, this may not be a valid assumption. If $1/T_2$ does in fact represent a more significant decay rate than Chen et. al assumed, then the component of T_2^* due to bulk magnetic susceptibility differences would be larger and the ratio R_T would be lower. Thus we can consider the value of $R_T = 12 \pm 11$ as a rough estimate of an upper bound of the ratio. One can then consider two contributions to T_2^* . One part scales linearly with the field and is due to static spin dephasing during the TE measurement time due to the field inhomogeneities created by the susceptibility mismatch between air and tissue. A second component scales quadratically with B_0 and is due to diffusion of the gas through these field inhomogeneities. Since the field ratio is 10, this argues that T_2^* scales approximately linearly with field strength. If T_2^* is primarily determined by diffusion through local field gradients, one would predict the T_2^* ratio to be 100. Further, we note that there may be a lung volume dependence for the T_2^* of ^{129}Xe . Our measurements were obtained at a single lung volume, $V_{\text{lung}}/\text{TLC} = 0.45$, which is very close to functional residual capacity, FRC. It is not clear if the Chen et al measurement of T_2^* in the guinea pig lung is at an equivalent normalized lung volume. Also of interest is that for ^3He , Chen et al observed a change of $\sim 50\%$ in T_2^* of the guinea pig lung as a function of lung volume. The stated reason for this dependence is that alveolar size, which changes with lung volume, will affect the local field inhomogeneities and therefore T_2^* . Although interesting, we have not explored this dependence here.

Of great interest to the hyperpolarized gas community is what field strength is optimal for hyperpolarized noble gases [22]. It is also well known that the theoretical SNR is independent of field strength when the RF coil losses are dominated by the sample. Since sample losses scale as the square of the field strength, this condition is more easily satisfied at higher field strength. Thus another comparison of interest is the SNR of our ventilation images at 0.2T to those obtained by others at 1.5T. For example, Mugler et. al [1] reported coronal ventilation images at 1.5T with SNR's from three xenon image sets. The highest SNR they reported was 32 and was from a centric encoded gradient echo method with voxel size of 1.8cm^3 , inhaled xenon gas volume between 300–500cc, using 71% enriched ^{129}Xe , and with polarization between 0.1–2.7%. Comparing this to our coronal ventilation images with a voxel size of 0.25cc (7.2 times smaller), we had a SNR of 36 (1.125 times higher). The volume of gas we inhaled was $\sim 1\text{L}$ (~ 2 times higher), we used 86% enriched gas (1.21 times higher), and our polarization was ~ 20 times higher. Based on these factors (and all other factors being equal), we estimate our SNR should be $\sim (1/7.2) \cdot (2) \cdot (1.21) \cdot (20) = 6.7$ times higher. However, it is also clear that our RF body coil is not optimal and improvements could be obtained by increasing the filling factor η of our coil. Specifically, although our coil has a $Q=300$ when loaded with a human body, the Q changes by only 4% when going from unloaded to loaded. To estimate how much better an optimal RF coil would perform, we performed tests with a different body coil with better filling factor that was constructed to eventually be incorporated into our system as a receive only coil. This receive-only coil is a solenoidal body coil with a $Q_{\text{unloaded}}=394$. We measured the relative sensitivity of the two body coils using a small broadband excitation source coil centered in the body coils and measured the received power (corrected for differences in the reflection coefficient) of the existing RF body coil and the receive-only solenoidal coil of smaller diameter. Based on these measurements, we estimate that an optimized RF coil would improve our SNR by $\sim 12\text{dB}$ (a factor of 4). This would hypothetically increase the SNR ratio to $1.125 \cdot 4 = 4.5$, which is not too far from the factor of 6.7 calculated above. An additional factor is that optimal SNR is obtained when sample losses dominate the coil losses and at 0.2T, we are not in this regime. Even though the body coil we used did not significantly load with a human body, we can estimate this factor because the receive-only solenoidal coil does show the effects of loading ($Q_{\text{loaded}} \sim 185$). This gives an additional factor

of $1/\sqrt{(1 - Q_{\text{loaded}}/Q_{\text{unloaded}})} = 1.37$. Taking this factor into account, this increases the SNR ratio from 4.5 to 6.2, which at this level of estimation, essentially shows that we can account for the SNR differences between 0.2T and 1.5T. Note that in this comparison, we have not taken into account any differences in readout bandwidth and TE. We conclude that at 0.2T, it is difficult to be in the regime where sample losses dominate the RF coil losses and that this factor indicates that a higher field strength may be optimal.

Regarding our CSSR experiments, there are several discussion points. First, we note that we have not corrected our dissolved state data for T_1 decay during the diffusion time. For example, at 1.5T, Wolber et al [23] found that T_1 of ^{129}Xe dissolved in arterial blood is $6.4 \pm 0.5\text{s}$. The magnitude of such a correction, even at the longest times used ($\sim 80\text{ms}$) for the $\sqrt{t}$ fits is very small, i.e. $\exp(-0.08/6.4) = 0.988$. A second issue for CSSR has to do with F_0 . When a nonzero, nonnegative value for F_0 is found in the least squares fits to Eqn. [5], we interpret this physically that there are thin portions of the septa that are completely saturated even at the shortest diffusion time measured. Thereafter, since these regions are saturated at the first time point, they will remain saturated at all later time points and appear as a DC offset. To obtain an estimate for how thin a septal section has to be in order to be saturated, we calculate the rms diffusion distance $\delta = \sqrt{2D_{\text{diss}}t} = 3.2\mu\text{m}$ for a 17ms diffusion time, the shortest diffusion time in our CSSR experiments. Such “thin” regions are consistent with the fact that between septal capillary blood vessels, there are thinner sections of connective/parenchymal tissue. Further, this implies that the S_A/V_{gas} values being measured here are from the thicker portions of the septa, i.e. the portion that contains capillaries. Thus we expect the S_A/V_{gas} values measured here to be less than those measured with histology from fixed human lungs. Further, since functional gas exchange takes place in those portions of the septa occupied by capillary blood vessels, the S_A/V_{gas} values reported here may represent functional rather than physical alveolar surface area. When we compare our values of S_A/V_{gas} to morphologically determined values in the literature [24], our values are $\sim 40\%$ smaller. Finally, another source of potential disagreement with the literature values is the uncertainty of λ and D_{diss} . To resolve these issues, future studies are planned in animals to directly compare CSSR with histology based morphometry.

It is also interesting to compare the CSSR determined lung volume dependence of S_A/V_{gas} to classic measurements by Gil et al [25] on fixed rabbit lungs. Using air-filled lungs, Gil et al found $S_A \sim (V_{\text{gas}})^{0.33}$. Dividing through by V_{gas} , the Gil et. al dependence becomes $S_A/V_{\text{gas}} \sim V^{2/3}$, which we have illustrated in Figure 5b by a solid blue line. We have also added a solid black line showing the scaling if one assumes S_A is constant with V_{gas} . These S_A/V_{gas} scaling relations start from the measured data point at a lung volume equal to TLC. The error bars on our measurements are too large to make a significant distinction between either of these scaling behaviors, however the data does favor a constant S_A as a function of lung volume. If this were true, a possible explanation is that as the lung expands, the major places in the septa where the surface area increases is in the thinner sections of the septa as they are more compliant than the thicker sections. And if this is the case and if our measurements of S_A/V_{gas} correspond to the thicker portions of the septal surface, one would expect our data to show a relatively constant alveolar surface area.

Regarding using SB-XTC imaging to determine S_A/V_{gas} , one needs to keep in mind that the imaging technique, at least as presently implemented, only measures F_{XTC} at a single time point. Because there is a DC offset, a single time point is insufficient to determine the slope K_{XTC} of the septal diffusion vs. time curve. Therefore, a minimum of two SB-XTC images at two separate time points, both within the early $\sqrt{t}$ regime would need to be measured to perform the S_A/V_{gas} analysis described here. We note, however, that relative values of F_{XTC} do correlate

with relative values of S_A/V_{gas} and thus SB-XTC may be very valuable for quantitative comparison of one lung region relative to another.

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Figure 1. View of a subject, ^{129}Xe RF coil and gas delivery apparatus in the 0.2T magnet. The RF coil is composed of two square planar loops in a near Helmholtz configuration separated by 42.6cm.

Figure 2. Schematic of Chemical Shift Saturation Recovery method. (a) Idealized 1D semi-infinite phases. (b) A more realistic model with a finite width septum. Net diffusion from gas to dissolved phase after time t_{diff} is shown in purple.

Figure 3.

Figure 3a. Typical 2D multi-slice gradient echo ventilation images after inhalation of 1L 26% hyperpolarized ^{129}Xe from a volume close to RV. Sixteen images from a 21 slice axial data set are shown. Imaging parameters are: FOV=300mm, voxel size: $4.7 \times 9.4 \times 15 \text{ mm}^3$, 20 slices acquired (17 shown), TE=6.66ms, TR=23.47ms, readout bandwidth = 5.8kHz, matrix $64 \times 32 \times 20$, acquisition time = 15.02s. Maximum SNR = 16.7. For reconstruction, data was zero filled to 128×128 .

Figure 3b. Typical coronal 2D multi-slice gradient echo ventilation images after inhalation of 1L 86% enriched hyperpolarized ^{129}Xe from a volume close to RV. Imaging parameters are: FOV=300mm, voxel size: $3.26 \times 6.25 \times 12.5 \text{ mm}^3$, TE=6.45ms, TR=28.67ms, readout bandwidth = 5.8kHz, matrix $96 \times 48 \times 10$, acquisition time = 13.76s. Maximum SNR = 35.9. For reconstruction, data was zero filled to 128×128 and a mask was applied to allow display of voxels from 10–85% of the maximum intensity.

Figure 4.

Experimentally measured $F(t)$ shown with blue dots as a function of (a) diffusion time t and (b) $\sqrt{t}$. Lung volume was fixed and in the example shown here, it is at total lung capacity (TLC). Also shown is a fit to the early time data using Eqn [5] (red line).

Figure 5.

Figure 5a. Alveolar surface area per unit volume of gas as a function of lung volume normalized to total lung capacity (TLC). Data was obtained from four normal, healthy adults. Note that HS stands for “Human Subject”. Also note that to convert from S_A/V_{gas} to K , a value of $S_A/V_{\text{gas}} = 100\text{cm}^{-1}$ corresponds to $K = 0.0195\text{s}^{-1/2}$.

Figure 5b. Average alveolar surface area per unit volume of gas as a function of normalized lung volume. Actual data values are $V_{\text{lung}}/\text{TLC} = \{0.24, 0.45, 1\}$, $S_A/V_{\text{gas}} = \{251.9, 124.2, 61.4\}$. Two theoretical estimates of the volume dependence of S_A/V_{gas} are also shown starting from the measured value at TLC. The black line shows how S_A/V_{gas} would scale if $S_A = \text{constant}$, i.e. $S_A/V_{\text{gas}} \sim 1/V_{\text{gas}}$. Note that the black line is not a fit to the data. The blue line shows the expected behavior if $S_A \sim (V_{\text{gas}})^{1/3}$, i.e. $S_A/V_{\text{gas}} \sim (V_{\text{gas}})^{-2/3}$.

Single Breath – Xenon Transfer Contrast (SB-XTC)

Figure 6.

Schematic of Single Breath XTC Method. The attenuation between the control images is due to (1) depletion of ^{129}Xe magnetization due to the RF pulses used for the imaging and (2) T_1 decay due to the presence of oxygen. The attenuation between the XTC images is due to the above two mechanisms plus (3) interphase diffusion. Note that the selective 180's between the XTC images are located in the center of the dissolved phase resonances (+205ppm) whereas the 180's between the control images are off resonance (−205ppm). The gas phase is at 0ppm.

Figure 7.

(a–c) Example of coronal projection images obtained with the SB-XTC method during a breath-hold at 47% of TLC. Image (c) has been scaled to remove the attenuation observed from (a) to (b) due to T_1 relaxation and RF pulses so that the observed attenuation from (b) to (c) is only due to ^{129}Xe diffusion between gas and tissue phases. The subject, HS6, is in the supine position. One liter of 86% enriched ^{129}Xe was inhaled. Also shown are (d) the resulting F_{XTC} map, (e) its histogram and (f) a plot of the $\bar{F}_{XTC}$ as a function of superior (apex)/inferior (base) position.

Figure 8.

(a–c) Example of coronal projection images obtained with the SB-XTC method during a breath-hold at 47% of TLC. Image (c) has been scaled to remove the attenuation observed from (a) to (b) due to T_1 relaxation and RF pulses so that the observed attenuation from (b) to (c) is only due to ^{129}Xe diffusion between gas and tissue phases. The subject, HS6, is lying on his left side. Also shown are (d) the resulting F_{XTC} map, (e) its histogram and (f) a plot of the $\bar{F}_{XTC}$ as a function of right/left (i.e. gravitationally dependent) position.

Figure 9. Comparison of $F(t)$ using CSSR and XTC methods. Both methods provide the same functional form for the short times. Data was obtained from human subject 20 (HS20) at a normalized lung volume $V_{\text{lung}}/\text{TLC} = 0.54$ and the ratio of the slopes $K_{\text{XTC}} / K_{\text{CSSR}} = 2.51$.

Table 1**Subject Data**

Subject	Age	Gender	RV(Liters)	TLC(Liters)
4	55	M	1.85	7.02
6	32	M	1.33	6.2
13	32	M	2.10	8.24
20	28	F	1.25	4.44

CSSR results

Fitting details for CSSR data for each breath-hold experiment. Reported are lung volume normalized to TLC, N = number of diffusion times points measured, R^2 =coefficient of determination, K = slope in Eqn [5], S_A/V_{gas} , F_0 , and the errors in their determination. Note that the error for K is given in percent while for F_0 , it is specified as an absolute number. Note that for two cases (denoted with an asterisk), F_0 has been forced to be zero. This was done because when a least squares fit was performed with F_0 as an adjustable parameter, negative values were found.

Table 2

Subject	$V_{\text{lung}}/\text{TLC}$	N	R^2	$K(\text{s}^{-1/2})$	$K(\% \text{ error})$	$S_A/V_{\text{gas}}(\text{cm}^{-1})$	F_0	$F_0 \pm \text{error}$
4	0.26	8	0.999	0.03902	1.42	199.7	0.00251	0.000131
4	0.26	8	0.866	0.02889	22.74	147.8	0.00614	0.001544
4	0.46	8	0.993	0.03255	4.27	176.4	0*	N/A
4	0.46	8	0.970	0.02654	10.17	158.7	0.00136	0.000634
4	0.59	8	0.939	0.02099	14.75	132.4	0.00132	0.000727
4	1.00	8	0.998	0.00719	2.76	36.8	0.00066	0.000047
4	1.00	8	0.900	0.00493	19.20	25.2	0.00133	0.000222
6	0.21	8	0.940	0.08469	17.86	433.3	0.00084	0.002996
6	0.21	8	0.806	0.03640	28.33	186.2	0.00772	0.002423
6	0.44	8	0.925	0.01242	16.42	63.5	0.00189	0.000479
6	1.00	8	0.922	0.00857	16.75	43.8	0.00024	0.000337
6	1.00	8	0.847	0.01187	24.57	60.7	0.00033	0.000685
13	0.25	8	0.968	0.05339	10.48	273.2	0.00902	0.001314
13	0.25	8	0.984	0.05298	7.43	271.1	0.00766	0.000925
13	1.00	8	0.888	0.00959	20.51	49.1	0.00158	0.000462
13	1.00	8	0.956	0.01383	12.32	70.8	0.00078	0.000400
13	1.00	13	0.935	0.02427	10.76	124.2	0.00173	0.000499
13	1.00	13	0.806	0.01569	18.51	80.3	0.00194	0.000602
20	0.42	13	0.990	0.01918	3.63	98.1	0*	N/A