Development of a Hyperpolarized $^{129}$Xe System on 3T for the Rat Lungs

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MRI (magnetic resonance imaging) with $^{129}$Xe has gained much attention as a diagnostic methodology because of its affinity for lipids and possible polarization. The quantitative estimation of net detectability and stability of hyperpolarized $^{129}$Xe in the dissolved phase in vivo is valuable to the development of clinical applications. The goal of this study was to develop a stable hyperpolarized $^{129}$Xe experimental 3T system to statistically analyze the dissolved-phase $^{129}$Xe signal in the rat lungs.

The polarization of $^{129}$Xe with buffer gases at the optical pumping cell was measured under adiabatic fast passage against the temperature of an oven and laser absorption at the cell. The gases were insufflated into the lungs of Sprague-Dawley rats ($n = 15$, 400–550 g) through an endotracheal tube under spontaneous respiration. Frequency-selective spectroscopy was performed for the gas phase and dissolved phase. We analyzed the $^{129}$Xe signal in the dissolved phase to measure the chemical shift, $T_2^*$, delay and its ratio in a rat lungs on 3T.

The polarizer was able to produce polarized gas ($1.1 \pm 0.47\%$, 120 cm$^3$) hundreds of times with the laser absorption ratio (25%) kept constant at the cell. The optimal buffer gas ratio of 25–50% rendered the maximum signal in the dissolved phase. Two dominant peaks of $211.8 \pm 0.9$ and $201.1 \pm 0.6$ ppm were observed with a delay of $0.4 \pm 0.9$ and $0.9 \pm 1.0$ s from the gas phase spectra. The ratios of their average signal to that of the gas phase were $5.6 \pm 5.2\%$ and $4.4 \pm 4.7\%$, respectively. The $T_2^*$ of the air space in the lungs was $2.5 \pm 0.5$ ms, which was 3.8 times shorter than that in a syringe.

We developed a hyperpolarized $^{129}$Xe experimental system using a 3T MRI scanner that yields sufficient volume and polarization and quantitatively analyzed the dissolved-phase $^{129}$Xe signal in the rat lungs.

Keywords: xenon, hyperpolarized noble gas, high field MR

Introduction

MRI with $^{129}$Xe has been proposed$^1$ and has gained much attention as diagnostic methodology because of its possible polarization. Since the polarization and gyromagnetic ratio of $^3$He are greater than those of $^{129}$Xe, $^3$He has the potential to be used to depict lung functionality.$^2$–$^5$ On the other hand, the advantage of $^{129}$Xe is its affinity for lipids and lack of a need for isotopic condensation, which limits clinical use. Hyperpolarized $^{129}$Xe (HPXe) has a long $T_1$ even in blood (up to 10 s)$^6$–$^10$ and can be delivered to any organ by simple inhalation$^{11}$–$^{17}$ or by invasive injection$^{18}$–$^{21}$ to provide a high signal. HPXe diffuses freely and passes through the blood-brain barrier, unlike the conventional gadolinium chelate compound$^{22}$; therefore, it is expected to be adopted as a new exogenous NMR (nuclear magnetic resonance) tracer for cerebral perfu-
MRI with HPXe can be considered a noninvasive approach considering its non-radioactivity as compared with positron emission tomography examination\textsuperscript{20}; moreover, direct measurement of exogenous HPXe is tolerant of movement during scanning, unlike the arterial spin labeling technique,\textsuperscript{27} which requires subtraction from the control image. Furthermore, the large chemical shift of \textsuperscript{129}Xe\textsuperscript{6,11,12} may distinguish some organs such as gray and white matter.

An optical pumping technique with Rb vapor has been proposed\textsuperscript{28,29} with the goal of achieving the high polarization of \textsuperscript{129}Xe. The optimum distribution of Rb polarization in the cell has been measured as a function of temperature,\textsuperscript{30} but the laser heating effect dynamically changes its condition. Control of heating of the polarization cell remains unclear and optimizing this aspect is important from a practical perspective to ensure stable gas production. Polarization enhancement with buffer gases by non-radiative quenching and by spectral broadening has been reported quantitatively.\textsuperscript{29,31–33} Increasing the partial pressure of buffer gases lowers the density of xenon in the blood when mixed gases are inhaled. The xenon in the mixed gases can be condensed at low temperatures while maintaining its polarization\textsuperscript{31–33}; however, this requires a complex apparatus. It is important to measure the buffer gas effect in the dissolved phase \textit{in vivo}. Although the chemical shift\textsuperscript{12–14} and T\textsubscript{2}\textsuperscript{*14} of \textsuperscript{129}Xe have already been determined in the rat lung, measuring these factors quantitatively on 3T is still valuable. Further, quantitative estimation of net detectability and stability of HPXe in the dissolved phase \textit{in vivo} is valuable for the development of clinical applications.

The goal of this study was to develop a stable hyperpolarized \textsuperscript{129}Xe experimental system for statistical analysis of the dissolved-phase \textsuperscript{129}Xe signal to determine the chemical shift, T\textsubscript{2}*, delay and its ratio to the gas-phase in the rat lung under spontaneous respiration on 3T.

**Materials and Methods**

**Polarizer**

Optical pumping technology was adopted in the polarizer developed for the present study (Fig. 1). The outer shell electrons of Rb vapor molecules were excited with a circularly polarized diode array laser (Coherent, FAP system, 120W at 794.7 ± 3 nm) and their spins were pumped and polarized. To increase the Rb steam pressure, a Pyrex cell (300 cm\textsuperscript{3}) with Rb (up to 0.5 g) was heated to 80–160°C with a hot air blower and a glass oven.

Electron polarization was transferred to that of nuclear spin of \textsuperscript{129}Xe by collisional spin-exchange in a 10-mT magnetic field produced by a Helmholtz coil (60 cm). The MR signal of \textsuperscript{129}Xe was obtained by means of a small solenoid coil attached to the cell under adiabatic fast passage achieved by sweeping with a magnetic field (0.4 mT, 10 s), while constant RF irradiation was applied (117.76 kHz).\textsuperscript{33} The spectra were then fitted with a Lorentzian line shape model and were calibrated with the reference signal ratio of HPXe to the Boltzmann equilibrium state in the MR scanner. Finally, the polarization of \textsuperscript{129}Xe was measured against the temperature of the oven with a thermocouple, while the heating power of the air blower was varied. A standard laser power meter was used to calculate and monitor laser absorption at the cell with the laser power through the cell at high temperature subtracted from that at room temperature (25°C).

**Materials**

Naturally abundant xenon (99.995–99.999%), nitrogen (99.99999%), and helium (99.99998%) gases (Toyoko Kagaku) were used following purification (1 ppb for O\textsubscript{2}, 1 ppb for H\textsubscript{2}O).

The buffer gas ingredients were N\textsubscript{2} for non-radiative quenching and He for spectral broadening. The partial pressure ratio of N\textsubscript{2} to He was fixed at 0.5 in consideration of overall performance\textsuperscript{31} and simplification. The composition of the xenon gas was changed from 3% to 100% to measure buffer
Table 1. List of examinations for rat lungs

<table>
<thead>
<tr>
<th>Xe Gas Ratio (%)</th>
<th>Number of Rats</th>
<th>Xe Number of Insufflations** (Total)</th>
<th>Number of Insufflations** for Gas Phase</th>
<th>Number of Insufflations** for Dissolved Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>17</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
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<td>8</td>
<td>27</td>
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<td>50</td>
<td>12</td>
<td>43</td>
<td>12</td>
<td>31</td>
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<tr>
<td>75</td>
<td>10</td>
<td>36</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>90</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>100</td>
<td>12</td>
<td>38</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong>*</td>
<td><strong>189</strong></td>
<td><strong>44</strong></td>
<td><strong>145</strong></td>
</tr>
</tbody>
</table>

*The sum of each experiment exceeds the actual number of rats because each rat was repeatedly examined.

**A mixed (20 cm³, He:N₂ = 2:1) gas was used in each Xe insufflation under spontaneous respiration.

**In each Xe insufflation, 30–40 spectra were acquired.

gas enhancement. Table 1 summarizes the experiment.

MRI and MRS

A 35.34-MHz RF system for ¹²⁹Xe on a 3.0T MRI system with a 55-cm bore (GE Medical System, SIGNA) was developed for this study. A solenoid coil (5 cm, 2–3 turns) was placed on a rat’s breast and on a gas syringe after shimming and was placed in a magnet bore perpendicular to the orientation of the magnetic field. To test the developed experimental system, we performed gradient echo imaging on a rat lung under suspended inhalation of HPXe with centric k-space ordering, a 10-degree flip angle, 23-ms repetition time, 3.6-ms echo time, 2-kHz reception bandwidth, 64 × 32 matrix, non-slice selection, and 4-cm field of view. Free induction decay datasets were acquired for rat lungs with 512–1024 complex data points, a flip angle of 60 degrees, and a 1-s repetition time. Frequency-selective excitation with a 3.2-ms pulse was adopted to reduce the exchange effect between the gas and dissolved phase when the peak ratio was measured. The frequency was set to the gas phase (referenced to 0 ppm) and to the dissolved phase (206–208 ppm). Spectrum acquisition began three seconds before insufflation, and a total of 30–40 spectra were acquired in each insufflation (Table 1).

The time-domain data were filtered with an exponential weighting function (10 Hz) and were zero-filled to 2048 points before Fourier transformation. The area under each peak of the phase-corrected real part in the frequency domain was computed after least squares fitting to Lorentzian line shapes. Each area that exceeded the standard deviation of the noise dataset by 1.5 times was considered a significant signal and was compared by means of a one-way analysis of variance (ANOVA). P values < 0.01 were considered statistically significant. Values are presented as mean ± standard deviation.

Animal preparation and insufflation procedure

Figure 2 is a schematic illustration of the insufflation procedure. The gases were transferred from the polarizer with a disposable evacuated syringe (polypropylene, 60 × 2 cm³) provided with a copper-film RF shield and located far from the sensitive area of the coil. Each animal was anesthetized with an intraperitoneal injection of urethane (1 mg/
Fig. 3. Polarization factors measured against a) the ratio of xenon pressure, b) oven temperature, and d) laser absorption rate at the cell. a) The buffer gas ratio of N₂ to He was fixed at 0.5, and the xenon composition was changed from 3% to 100%. c) The optimal temperature for polarization at various laser irradiation powers.

g). The temperature was maintained at 37.0°C by means of a thermal pad placed under the abdomen. A total of 20 cm³ of gas was insufflated manually (1 cm³/s after rapid purging of 5 cm³) by means of spontaneous respiration through an endotracheal tube inserted by tracheotomy and purged with O₂. A total of 189 of gases was insufflated into male Sprague-Dawley rats (n = 15, 400–550 g; Table 1). This study was approved by the Ethics Committee of the Research Institute of the National Cardiovascular Center, and all operative procedures and animal care strictly conformed to the standards prescribed by the same.

Results

Polarizer

The polarizer had the capacity to produce polarized (1.1 ± 0.47%) gas hundreds of times through batch transfer (60–120 cm³) from a pressurized (0.2 MPa) cell to a evacuated syringe at minimum intervals of 5 min without degrading the Rb. The signal ratio of the polarized state to the Boltzmann equilibrium state of the same gas (60 cm³) was measured with a 3T MRI system without accumulation and was referenced to the calculation of polarization. The polarization of ¹²⁹Xe was measured directly in the cell under adiabatic fast passage without depolarization due to RF irradiation. The buffer gases enhanced the polarization factor by up to 8% (Xe rate: 6%), while pure xenon gas was polarized only 0.3% (Fig. 3a). Figure 3b shows the polarization of ¹²⁹Xe against the oven temperature. We found that the temperature that achieved the maximum polarization was proportional (R² = 0.99) to the irradiated laser power in this range (Fig. 3c). We also found the laser absorption ratio at the cell that achieved the maximum
polarization was constant (25%) at all laser irradiation powers (Fig. 3d). This indicated that the optimal heat control could be achieved by maintaining the ratio of laser absorption at 25%.

**In vivo experiment**

The centric order gradient echo image of the rat lungs on 3T depicted the air space (Fig. 4), and we confirmed that the experimental system had sufficient capacity to move on MRS study. Three peaks were observed in spectra of the rat lungs at 0, 201 and 212 ppm. Figure 5 shows the signal area under each peak normalized by that of 0 ppm against a mixture rate of xenon. The use of buffer gases (25–50%) made results in significant (p < 0.01) signal enhancement in both the dissolved and gas phases. Therefore, a Xe gas ratio of 50% was adopted for use in further studies. Figure 6 shows typical dynamic spectra of that, while Fig. 7 shows their statistical (n = 43 for 12 rats) averages and standard deviations. A prominent peak at 201.1 ± 0.6 ppm (Peak B) and a broader peak at 211.8 ± 0.9 ppm (Peak A) were observed in the dissolved phase spectra. Table 2 presents a statistical summary. T2* was calculated by the full-width half maximum of each peak [1/(π FWHM)]. The T2* of the gas space in the lungs (2.5 ms) was 3.8 times shorter than that in the syringe (9.5 ms). Dissolved phase peaks appeared with significant (p < 0.01) delay (0.4–0.9 s) from the gas peak (Table 2). The average signal area of peak A (B) was 5.6 ± 5.2% (4.4 ± 4.7%) of that of the gas peak (Table 2).

**Discussion**

We measured the Xe gas signal in the syringe (60 cm³) in the Boltzmann equilibrium state without accumulation on 3T. This signal could not be measured with a small-bore MR system even at 9.4T. This result can be attributable to the amount of gas (60 for up to 1 cm³) in a large-bore system, so the volume effect can be expected in future human studies. We did not require oxygen to shorten the T1 for accumulation and did not use the ratio of total spins in the polarized state to that in the Boltzmann state with oxygen in the calculation of the polarization. This monitoring system accounted for loss during transport and contributed to simple manipulation and quantitative measurement of the polarization. The optimal temperature of the cell is difficult to measure and control because the laser heats the gas and Rb continuously. Under this laser heating effect, optimal polarization was maintained by keeping a constant laser absorption ratio (25%) at the cell (Fig. 3d). This could be achieved by providing information-feedback of the laser power to the cell heater (Fig. 1). The spin density of Rb is proportional to the temperature power of 10 in our temperature range, and the required laser power should also be the same. Because our laser power was limited, the effective pass length of the laser at the cell was shortened while the temperature was rising. We assumed that the optimum temperature in Fig. 3c for each laser power was achieved when the effective laser pass length was the same as the cell length, when the chance of collisional exchange between Rb and 129Xe was at its highest.

Our results support previous findings that the buffer gas enhances the polarization of xenon (Fig. 3a) and extend to an in vivo study with statistical analysis of the dissolved phase spectra (Fig. 5). According to previous in vitro and in vivo studies, the peaks observed (Table 2) can be attributed to dissolved phase in red blood cells (RBC, peak A) and in pulmonary tissue (peak B). The 1–2 ppm difference probably results from a volume susceptibility effect in living animals or from imperfect shimming. A signal with a 191-ppm chemical shift, assuming superposition of both plasma and adipose, was not observed in the present study because of a narrower selective excitation pulse (1 kHz) and shorter insufflation. The T2*, measured in the previous study, of 5 ms...
Fig. 5. Normalized signal of a) gas, b) peak A and c) peak B against pressure ratio of xenon in rat lungs. The signal was calculated with the integral of the Lorentzian fitted model.

Fig. 6. Typical dynamic $^{129}$Xe spectra of a) gas phase and b) dissolved phase in rat lungs with 1024 complex data points, up to 60 degree flip angle, 3.2-ms frequency-selective pulses, and 1-s repetition time.

in the intrapulmonary air space of a rat under 2T was twice that of ours, which was 2.5 ms (Table 2). In our estimation, the small $T_2^*$ can be attributed to a higher magnetic field (3T against 2T) or to imperfect shimming. A delay of several hundred milliseconds in the dissolved phase peak (Table 2) is consistent with the rapid exchange among the hemoglobin in the RBC, pulmonary tissue, and gas through the lung's thin blood-gas barrier.\textsuperscript{12,35} The ratio of the RBC signal (5.6%) to the gas signal in selective excitation may reflect the blood gas partition coefficient, but it should be adjusted to
Table 2. Summary of spectral peaks of rat lungs

<table>
<thead>
<tr>
<th></th>
<th>Chemical Shift (ppm)</th>
<th>T2* (ms)</th>
<th>Arrival Time** (s)</th>
<th>Ratio of Dissolved Signal to Gas Signal*** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas</td>
<td>0</td>
<td>2.5 ± 0.5</td>
<td>1.3 ± 0.6</td>
<td>100</td>
</tr>
<tr>
<td>Peak A</td>
<td>211.8 ± 0.9</td>
<td>1.7 ± 0.7</td>
<td>1.7 ± 0.9</td>
<td>5.6 ± 5.2</td>
</tr>
<tr>
<td>Peak B</td>
<td>201.1 ± 0.6</td>
<td>2.9 ± 2.3</td>
<td>2.2 ± 1.0</td>
<td>4.4 ± 4.7</td>
</tr>
</tbody>
</table>

**Arrival Time: Time interval between gas supply and signal detection.
***A Xe gas ratio of 50% was used in this measurement (n = 43 for 12 rats; see Table 1).

compensate for T1 and the repetition time in the gas exchange model. While the SNR (signal-to-noise ratio) was, on average, sufficient to provide spectra and time-course curves for each peak, the variability between the experiments was relatively high (more than 100%). This variability can be attributed to several causes. The polarization in the cell, the relaxation time in the syringe and tube, depolarization by oxygen contamination, and manual insufflation are all possible determinants.

In conclusion, we have developed a hyperpolarized 129Xe experimental system incorporating a 3T MRI scanner capable of yielding a sufficient volume and adequate polarization and have measured the dissolved-phase 129Xe signal quantitatively in the rat lungs under spontaneous respiration. HPXe is expected to be a possible exogenous tracer for noninvasive measurement of cerebral blood.
perfusion and lung functionality. Further refinement of the HPXe MRI could expand the scope of its clinical application while satisfying the requirements for both accuracy and non-invasiveness.

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