**In vivo NMR and MRI using injection delivery of laser-polarized xenon**  
(xenon injection/optical pumping)


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**ABSTRACT** Because xenon NMR is highly sensitive to the local environment, laser-polarized xenon could be a unique probe of living tissues. Realization of clinical and medical science applications beyond lung airspace imaging requires methods of efficient delivery of laser-polarized xenon to tissues, because of the short spin-lattice relaxation times and relatively low concentrations of xenon attainable in the body. Preliminary results from the application of a polarized xenon injection technique for *in vivo* 129Xe NMR/MRI are extrapolated along with a simple model of xenon transit to show that the peak local concentration of polarized xenon delivered to tissues by injection may exceed that delivered by respiration by severalfold.

In certain systems, the angular momentum of circularly polarized light can be transferred to nuclear spins by optical pumping (OP) (1–3), thus increasing the NMR sensitivity by four to five orders of magnitude. This potential for enormous signal enhancement has been the driving force behind the study of "polarized" noble gases for possible clinical and biomedical applications. MRI of polarized 129Xe and 3He in the gas phase has already been utilized to image the void spaces in lungs (4–13), the oral cavity (14), and materials (15). The sensitivity enhancement obtained through OP well outweighs the loss in signal suffered from imaging low-density gas-phase media.

Because of the sensitivity of the NMR parameters of 129Xe to its environment (16) and its safety for medical applications (17), it is hoped that dissolved polarized xenon could serve as a probe of tissues and blood flow in living organisms. Recent *in vivo* work in this direction includes imaging of xenon in the brain (5) and xenon NMR of blood and other tissues following respiration of polarized xenon by laboratory animals (9) and humans (13).

One of the major challenges for the application of dissolved polarized xenon for *in vivo* studies is its efficient delivery to the blood and tissues while maintaining its large nonequilibrium spin polarization. With current respiration methods (4–13), the dissolved xenon is diluted throughout the body via blood flow from the lungs; furthermore, because the spin-lattice relaxation time (T1) of xenon in tissues is generally short (18) [e.g., ~5 s in blood (19)], loss of xenon polarization can occur in transit before a significant concentration can accumulate in tissues. In previous work (19), a polarized xenon injection technique was developed and used to perform *in vitro* magnetic resonance (MR) studies. In this paper, the feasibility of using polarized xenon injection for *in vivo* studies is demonstrated. 129Xe NMR and MRI were performed following direct intramuscular or intravenous injection of biologically compatible solvents saturated with polarized xenon. Additionally, the advantages and limitations of this method are described in light of a one-compartment xenon uptake/washout model.

**BACKGROUND**

To date, tissue delivery of polarized xenon has been performed using xenon respiration (9, 13, 5). Respiration is ideally suited as a means of introducing polarized gases into the body for pulmonary studies, but it may be less efficient for certain studies involving remote organs, such as blood flow in the brain or muscular tissue. Recent simulations considering various physiological and experimental parameters have investigated the feasibility of using xenon respiration for such experiments by predicting the time-dependent concentration of polarized xenon in a chosen tissue (20, 21**).

One possible alternative to respiration delivery of polarized xenon is the localized injection of nontoxic solutions containing dissolved polarized xenon. Injection has been used as a means of delivering radioactive xenon isotopes (e.g., 133Xe) to tissues for studies of muscular blood flow (22, 23). In circumstances where the invasiveness of injection is acceptable, polarized xenon injection would be advantageous when higher local concentrations of polarized xenon could be delivered to tissues relative to the concentration attainable by respiration. In the following, we adapt a simple, illustrative model to estimate the effective concentration of polarized xenon†† that could be delivered to tissues by direct injection.

Consider a one-compartment uptake/washout model using a bolus injection of an inert, freely diffusible tracer (polarized xenon) (see, for example, ref. 24). Such an injection could in principle be performed intravenously, intraarterially, or directly into the target organ. One can use the following relation...
for the effective concentration \( C \) of polarized xenon in the targeted tissue following injection:

\[
C(t) = \begin{cases} 
0, & t \leq T_0, \\
\frac{k_1 A}{k_2} \cdot e^{-T_d/\tau_{1Xe}} \cdot [1 - e^{-u-T_2\lambda k_2}], & T_d < t \leq T_p, \\
\frac{k_1}{\lambda} \cdot e^{-T_1/\tau_{1Xe}}, & T_p < t,
\end{cases}
\]

where \( k_1 \) is the specific volume flow in the tissue, \( k_2 \) is the effective washout rate defined by

\[
k_2 = \left( \frac{k_1}{\lambda} + \frac{1}{T_1^{\ast Xe}} \right); \tag{2}
\]

(\( \lambda \) is the tissue/blood partition coefficient), \( T_1^{\ast Xe} \) is the spin-lattice relaxation time of xenon in the solvent/blood environment, the peak time \( T_p = T_d + T_\nu \), and \( C_{T_\nu} \) is the effective concentration of polarized xenon in the tissue at \( T_p \). This model will be used to estimate expected NMR signal intensities after xenon injection.

**MATERIALS AND METHODS**

Detailed descriptions of both the polarized xenon injection technique (19) and the OP apparatus (25, 26) can be found elsewhere. Approximately \( 5 \times 10^{-4} \) mol of isotopically enriched \( ^{129}\text{Xe} \) (80% \( ^{129}\text{Xe} \); EG & G Mound, Miamisburg, OH) was placed in a glass cell with a small quantity of rubidium and was optically pumped with a 1.3-W Titan Ti:sapphire laser (continuous wave, 794.7 nm) for \( \approx 30 \) min. The OP apparatus typically produces xenon samples with 5–10% nuclear polarization.

The remainder of the experimental procedure is shown schematically in Fig. 1. After OP, the xenon was frozen into the sidearm of the shaker in the presence of a magnetic field (50 mT) provided by a small permanent magnet. A delay of approximately 20 min between polarization and injection was necessary to transport the polarized xenon to the location of the imaging apparatus; however, the \( T_1 \) of solid xenon at the described magnetic field strength and temperature is on the order of hours (27). The xenon was sublimated and admitted to the degassed solvent [3 ml of 20% Intralipid emulsion (Pharmacia) or 3 ml of partially deuterated saline water, 0.9% by weight] under approximately 5 atm (1 atm = 101.3 kPa) of initial xenon pressure. In each experiment, 1 ml of the saturated xenon solution was withdrawn into a syringe through the rubber septum of the shaker prior to injection. NMR signal acquisition began at the start of the injection.

Male rats weighing 200–250 g were anesthetized intramuscularly with ketamine/xylazine/acepromazine (30/3/0.6 mg/kg), with supplemental doses administered as needed. For the spectroscopy experiment a venous catheter was placed into a tail vein, and the receiver–transmitter surface coil had a diameter of 3.5 cm. For the imaging experiment, axial images were acquired perpendicular to the coil by using the FLASH pulse sequence (28) shown in Fig. 2.

Before each experiment the rat was placed in lateral recumbency into the magnet. Afterward the catheter was removed and the rat was returned to its cage to recover from anesthesia.

The \( ^{129}\text{Xe} \) magnetic resonance (MR) images and spectra were obtained on a home-built NMR spectrometer interfaced with a 2.35-T magnet (xenon frequency, 27.68 MHz; bore diameter, 25 cm). The receiver–transmitter surface coil had a diameter of 3.5 cm. For the spectroscopy experiment, spectra were obtained every second (pulse angle = 20°). For the imaging experiment, axial images were acquired perpendicular to the coil by using the FLASH pulse sequence (28) shown in Fig. 2.

**RESULTS AND DISCUSSION**

**Preliminary in Vivo Xenon Injection Experiments.** In the spectroscopy experiment, a series of xenon NMR spectra were taken from the start of the intravenous injection of the xenon/intralipid solution, with the detection coil placed over the heart/liver region. A sum of the spectra of the 7th through 12th scans is shown in Fig. 3; the time dependence of the individual spectra is shown in the Inset. The single resonance signal at about 190 ppm (downfield from a high-pressure xenon gas reference signal; see Fig. 3 legend) is consistent with xenon in the Intralipid (19). It was anticipated that the Intralipid would initially accumulate in the liver; it is likely that the initial rise in signal amplitude reflects this accumulation, while the subsequent decay is due to wash-out, relaxation, and magnetization loss from the application of the rf observation pulses.

In the imaging experiment, 10 two-dimensional \( ^{129}\text{Xe} \) MR images were taken at intervals of 6–7 s (with the exception of an 18-s delay between the fifth and sixth images) from the start of the injection of the xenon/saline solution. Six of these images are shown in Fig. 4, which depicts the signal intensity of the polarized xenon in the upper part of the rat’s hind leg in near-axial cross section. The central region of lower xenon signal intensity (most visible in the second image) corresponds to the position of the rat’s femur. From the six images, one may observe that the signal intensity first rises, reaching a maximum at the second image, and then decays. The initial rise in
the long xenon

100 g (29).
in muscle at rest is low, approximately equal to 2.12 ml
and wash-out causing the secondary losses; the blood flow rate
approximately 5° tipping angle for each image), with relaxation
primarily due to the application of the rf pulses (48 pulses of
solution from the injection, while the subsequent decay is
following experimental parameters were used: tipping angle, 5°;
pulse repetition time, 100 ms; slice thickness, 10 mm; field of view, 256
× 256 mm²; acquisition matrix, 48 × 256.

intensity is due to the accumulation of the xenon/saline solution
from the injection, while the subsequent decay is primarily due to the application of the rf pulses (48 pulses of
approximately 5° tipping angle for each image), with relaxation
and wash-out causing the secondary losses; the blood flow rate
in muscle at rest is low, approximately equal to 2.12 ml/min per
100 g (29).

The major advantage of using saline water as the solvent is
the long xenon T₁, which causes negligible loss of polarization
over the injection time. However, the solubility of xenon in
saline water is low, with an Ostwald coefficient of only 0.0926

(30).

Higher xenon concentrations can be obtained with alternative
xenon solvents [e.g., Intralipid and Fluosol (19, 31)], albeit at the
expense of somewhat faster relaxation. For example, the T₁
of xenon in the Intralipid emulsion is about 40 s, whereas the
T₁ of xenon in partially deuterated saline water is several
hundred seconds (19). Furthermore, the xenon partitioning
properties of such solvents in biological tissues may allow
particular in vivo applications. Previous in vitro studies dem-

onstrated that such solvents can bring about a 3-fold increase in
the effective spin-lattice relaxation time of xenon in blood
(19).

One clear disadvantage of using polarized xenon for tissue
studies in general is the nonrenewable nature of the xenon
polarization. Each acquisition destroys some of the polariza-
tion; the application of a pulse with tipping angle θ reduces the
remaining longitudinal polarization by a factor of cos θ, and
the spent polarization can be restored only by delivering fresh
polarized xenon to the region being studied. This problem
creates an additional difficulty for the imaging of polarized
xenon, as the polarization loss incurred during the application
of the rf pulses needed for multidimensional imaging can cause
image blurring. It has been suggested that this problem can be
avoided by using pulse sequences that use variable tip-angle
pulses to maintain signal amplitude during image acquisition
(32, 33).

The loss of polarization after each acquisition during blood-
flow studies may also make accurate measurement of perfu-
sion rates difficult, a problem that can be appreciated by
examining the signal decay in Fig. 4. If the signal loss from
image to image due to rf pulse application is significant with
respect to that due to wash-out, highly accurate pulse calibra-
tion would be critical to extracting the intrinsic wash-out rate
from the observed rate of signal loss. Two possible methods
that may be applicable in such circumstances for calibrating the
tipping angle of an arbitrary pulse are discussed in ref. 33.
However, signal loss due to pulsing would not likely affect
chemical-shift studies.

Predictions of the Model. Previous models of polarized
xenon respiration were designed for brain studies, motivated by
a variety of possible biomedical applications [e.g., brain blood
flow and demyelination studies (20, 21)]. To compare the
injection method with xenon respiration, one can use the
model described by Eq. 1 to estimate the peak effective
polarized xenon concentration in the brain after an intraca-
rotid injection of a polarized xenon/Intralipid solution. Using
Eq. 1 and the parameter values summarized in Table 1, one can
estimate a peak polarized xenon concentration of about 7 ×
10⁻² mM at T₁ = 5 s. This concentration could be increased
with better initial xenon polarization, the injection of more
solution, greater xenon overpressure in the shaker, or by using
a biologically compatible solvent with a greater xenon solu-
bility. However, this calculation does not consider certain
complicating physiological issues, such as the differing perfu-
sion rates, xenon solubilities, and xenon relaxation times of
different brain tissues. As k₂ is approximately 0.043 s⁻¹, the
xenon concentration will decay with a time constant of about
23 s after T₁ = 5 s. Thus, even when the targeted organ has a
relatively high rate of blood flow, the contribution from
rf-induced polarization loss to the observed signal decay rate
would likely be significant in a perfusion imaging experiment.

In comparison to the estimated peak polarized xenon con-
centration of 7 × 10⁻² mM for an intracarotid injection, models of respiration tissue delivery of polarized xenon predict
peak concentrations that are severalfold less. For example,
using the interactive model of Martin (21), one can obtain a
peak polarized xenon concentration in the brain of 8.2 × 10⁻³
mM after a single held breath composed of 80% xenon with
the same polarization. (This value was calculated using the
same

![Figure 2](https://example.com/fig2.png)

**Fig. 2.** The radiofrequency (RF) and gradient (G) pulse sequences for the FLASH (Fast Low-Angle SHot) imaging experiment. The following experimental parameters were used: tipping angle, 5°; pulse repetition time, 100 ms; slice thickness, 10 mm; field of view, 256 × 256 mm²; acquisition matrix, 48 × 256.

![Figure 3](https://example.com/fig3.png)

**Fig. 3.** ¹²⁹Xe spectrum obtained by summing the 7th through 12th scans of an injected xenon/Intralipid solution. The xenon/Intralipid solution was injected intravenously in the tail, and signal was acquired with a surface coil localized over the liver region. The chemical shift range is referenced to a polarized xenon gas sample (pressure = 5 atm) scanned prior to experiment; the chemical shift is consistent with xenon residing in Intralipid once the reference pressure has been considered (19). (Inset) Time dependence of the integrated xenon signal in the liver region.
experimental and physiological parameter values as those used in our estimate, excepting those related exclusively to respiration, for which the model’s default values were used.) Continuous breathing of a 35% xenon mixture [whose xenon concentration would be low enough to prevent anesthetic effects (36)] would yield a peak polarized xenon concentration of $3.3 \times 10^{-3}$ mM. The increase in peak polarized xenon concentration estimated for injection delivery from that predicted for respiration is primarily due to rapid and localized delivery, high initial concentration (i.e., xenon solubility in Intralipid), and extended $\textit{in vivo}$ xenon relaxation time. However, it must be mentioned that the polarized xenon concentrations predicted by both our simple estimate and the respiration models depend greatly upon the values of experimental and physiological parameters, some of which are not known with a high degree of accuracy for all physiological conditions.

The respiration techniques are well suited for cardiopulmonary applications, and they have the advantage of being noninvasive. However, they require preparation of large amounts of polarized xenon gas. On the other hand, the injection technique is by its nature invasive, but it requires a far smaller amount of polarized xenon, which may be an important consideration in light of the cost and local availability of laser-polarized isotopically enriched $^{129}$Xe. Furthermore, in some circumstances it may be required to reduce the amount of xenon in the breathing mixture used in the respiration method to avoid unwanted anesthetic effects, as the concentration of relaxed xenon in the brain during such experiments would be significantly higher than the effective polarized xenon concentration (21). However, because of the invasive nature of intraarterial injection, the arterial route is not appropriate for routine clinical applications.

Even when circumstances present an advantage of using xenon injection over respiration (i.e., when the local perfusion rate is low, the transit time of blood from the lungs to the target region is long, and the danger from invasive injections is relatively low, such as for studies involving muscular tissue) the observable signal intensity from the polarized xenon will still be generally inferior to that of tissue protons. Consider a best-case scenario in which the xenon has been polarized to 50%. When the previous example of injection delivery of xenon to the brain is used, a peak polarized xenon concentration of about $0.3$ mM would be obtained, yielding $\approx 30\%$ of the NMR signal-to-noise from protons in a 1-T magnet (recall that the concentration of protons in the body is $\approx 80$ M, their

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Table 1. Parameter values used for xenon injection model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_i$</td>
<td>5 ml</td>
</tr>
<tr>
<td>$T_i$</td>
<td>3 s</td>
</tr>
<tr>
<td>$I$</td>
<td>8.7 mM*</td>
</tr>
<tr>
<td>$k_1$</td>
<td>$[0.00917 \text{ s}^{-1}]^\dagger$</td>
</tr>
<tr>
<td>$P$</td>
<td>4.9 ml/s‡</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>1§</td>
</tr>
<tr>
<td>$T_{1 Xe}$</td>
<td>16 s¶</td>
</tr>
<tr>
<td>$T_{1}$</td>
<td>30 s‖</td>
</tr>
<tr>
<td>$T_d$</td>
<td>2 s</td>
</tr>
</tbody>
</table>

*Estimated from the relative solubility of xenon in the Intralipid emulsion (19), and assuming a 5-atm equilibrium xenon overpressure, an initial xenon polarization of 0.1, and 100% isotopic labeling.
†From a brain blood flow rate of 52.9 ml/min per 100 g (ref. 29), a brain mass of 1,400 g, and a specific gravity of 1.04 (ref. 34).
‡Estimated as the total volume of blood per second supplied by one carotid artery, given the value for $k_1$.
§Effective value estimated from those of white and gray matter given in ref. 35 ($\textit{in vitro}$ data from dogs).
¶From ref. 19.
‖From † footnotes in text, in rat brain.
polarization in a 1-T field is \(3.2 \times 10^{-6}\), and the relationship between the proton and \(^{129}\text{Xe}\) magnetogyric ratios is \(\gamma_{\text{H}} = 3.61\gamma_{\text{Xe}}\).

The promise of polarized xenon lies primarily in its large chemical-shift range \([\sim 200 \text{ ppm when dissolved in various solutions (37)}]\), derived from xenon’s high polarizability. It is hoped that xenon’s sensitivity to its local magnetic environment will enable novel \textit{in vivo} localized NMR spectroscopy and chemical-shift imaging experiments. Additionally, high local concentrations of polarized xenon may permit the differential measurement of polarization transfer to other nuclear spins (38) in the body, providing a novel means of contrast on both the macroscopic and molecular level. These effects have been shown to be larger and site-selective in molecules that hydrophobically interact with xenon (39).

**CONCLUSION**

This report contains MR images and spectra taken of polarized xenon injected directly into the tissues of living organisms. While it is believed that in general polarized xenon may be useful for a number of biomedical applications such as MRI angiography and perfusion imaging, the injection of polarized xenon solutions is particularly promising for \textit{in vivo} localized NMR spectroscopy and chemical-shift imaging. By using injection, one can administer polarized xenon rapidly, locally, and efficiently, especially if the experimental situation has an indication for intraarterial or intramuscular injections. Specifically, under conditions where unique information regarding disease mechanisms can be revealed by NMR spectroscopy, injections of polarized xenon may have substantial medical science benefits in human studies regarding the nature of healthy and pathological tissues.

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34. Snyder, W. S., chair of Task Group Reference Man (1975) \textit{Ann. ICRP} \textbf{23}, 121.


