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Measurement of ^{129}Xe T1 in Blood to Explore the Feasibility of Hyperpolarized ^{129}Xe MRI

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Objective: The major obstacle to the use of 129-xenon (I = 1/2) as a new source of contrast in magnetic resonance is its low sensitivity. The hyperpolarized ^{129}Xe-MRI technique using laser optical pumping of rubidium promises to resolve this problem. The potential of xenon-based MRI for the body tissues other than the lung air spaces depends on the ^{129}Xe polarization lifetime (T1) in the blood at a magnetic field of commonly available clinical MRI systems.

Materials and Methods: Xenon with natural abundance of ^{129}Xe (26%) was dissolved in human blood and studied at 36°C in a 2.35 T 40 cm bore MRI spectrometer (27.6 MHz). Zeeman relaxation (T1) of six blood samples was measured by the progressive saturation method for periods of 4–8 h each.

Results: NMR spectra revealed two peaks at 216.0 ppm (A) and 194.0 ppm (B) relative to the xenon gas above the blood volume. Assignment and ^{129}Xe T1 values were 4.5 ± 1 s for red blood cells (A), 9.6 ± 2 s for plasma (B) and 11.9 ± 1.6 s for xenon gas at atmospheric oxygen pressure. Xenon dissolved in distilled water appears at 189.8 ppm and has T1 = 26.3 ± 1.4 s.

Conclusion: These relaxation times, though shorter than expected, are comparable to the transport time of blood, and are long enough to encourage use of hyperpolarized xenon for MRI studies in tissues, in addition to lung.

Index Terms: Xenon—NMR relaxation—MRI.

Xenon is a known anesthetic gas and can be directly observed in living systems. It is highly soluble in lipids and after inhalation is readily absorbed and concentrates in tissues. As a tracer of perfusion, radioactive xenon (^{127}Xe, ^{133}Xe) has been used to study brain blood flow, brain functional activation, and muscle perfusion. Nonradioactive ^{129}Xe (I = ½, natural abundance 26%), being markedly affected by the environment, may provide additional information using the MR technique.

The major obstacle to the use of xenon as a new source of contrast is the low sensitivity (0.02 that of proton) and low concentrations (~10 m*M*) achievable in tissue. The hyperpolarized ^{129}Xe MRI technique, using laser optical pumping of rubidium, overcomes this by increasing the sensitivity of ^{129}Xe detection nearly 1×10^5 times (1–4). Recently, the use of hyperpolarized ^{129}Xe to image the air space of the mouse lungs was demonstrated (5). This new technique differs from conventional MRI in that the polarization is not achieved in the body, but is produced in the xenon externally and then the polarized xenon is introduced into the body by inhalation.

The only hyperpolarized noble gas images acquired thus far are of the lung gas space using ^{129}Xe (5) and more recently ^{3}He (11). The usefulness of laser-polarized ^{129}Xe imaging is, however, not restricted to the gas phase. Inhaled xenon is rapidly transferred from lungs to blood and thence to other tissues where it diffuses in and washes out in proportion to the local partition coefficients. A major question in the development and applications of this new technique is whether the polarization decay time T1 is long enough in the lungs and blood to reach the tissue of interest.

In a previously reported study (5), a T1 value of 28 s was reported for gaseous ^{129}Xe in excised mouse lungs that were previously flushed with N_2 gas. Such a T1 value would apply to a deep breath of ^{129}Xe into a lung, from which most of the oxygen had been expired. For the steady state, a person

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breathing 40–70% xenon and 30% oxygen [70% of xenon produces an anesthetic effect (16–18)], one can apply the data of Jameson et al. (6) to the O_2 relaxivity in a normally breathing subject to predict T1 values of ~15 s in the lung (5). Thus, the feasibility for NMR imaging of the lung gas space appears excellent.

To establish whether the ^{129}Xe polarization can survive long enough to be observable in the body, there have been considerable efforts to measure the range for xenon T1 (7–9). At 9.4 T, T1 is 130 s in water, 80 s in octanol (a standard cell membrane model), and 5 ms in 10% Fe(III) metmyoglobin (7). At the oxygen pressure of alveolar air, the T1 in fully oxygenated cell membranes was estimated to be 15–20 s (5). Under physiological conditions the large T1 of ^{129}Xe and the small concentration of xenon in tissue entailing a long accumulation time make T1 a difficult parameter to measure at thermal equilibrium.

The importance of xenon-based MRI for the vascular system and body tissues other than the lung cannot be estimated without an accurate knowledge of the lifetime of ^{129}Xe polarization in the blood. In the present study, we have measured the T1 of ^{129}Xe gas dissolved in human blood at a magnetic field approximately that of commonly available human MRI systems.

METHODS

Sample Preparation

Natural abundance xenon gas (26% ^{129}Xe) with research-grade purity of 99.995% was used as received (UN2036; Air Products and Chemicals). Fifty milliliter samples of blood were drawn from an antecubital vein of healthy volunteers into a syringe containing 10 units of heparin/ml. Each blood sample was placed into a 200 ml round-bottom flask fitted with a gas-tight septum. Xenon gas was added through a needle by exchanging the gas above the blood three to five times. Samples were continuously swirled for 20–30 min to ensure enrichment by xenon. Rapid absorption of xenon in blood can be expected if adequate surface area for exchange is provided; thus, we used long mixing times. The resulting blood samples were transferred to 50 ml round-bottom flasks that contained ~10 ml of gas space above the blood.

Additionally, two samples were prepared by adding xenon to distilled water and to commercial vegetable oil both at atmospheric oxygen pressure, using a similar dissolving procedure. The vegetable oil was a mixture by weight of sunflower (23.8%), corn (28.6%), soybean (33.3%), and canola (14.3%) oils.

NMR Measurements

^{129}Xe spectra were obtained at 27.68 MHz on a home-built imaging spectrometer with a Bruker 2.35 T magnet that has a 40 cm horizontal clear bore and a 25 cm working bore. The spectrometer is interfaced with a Sun SPARC-10 computer and uses Mystic NMR software (15). The receiver/transmitter coil was 6 cm in diameter, and the 90° pulse was 35 μs. NMR free induction decay was sampled using 4,096 points, a spectral width of 20 kHz, and a 5 kHz filter. All NMR spectra are given as magnitude values after Fourier transform. T1 values were measured using a progressive saturation pulse sequence (. . . $-90\text{-}t_n-90$-. . .). Time delays were chosen according to $t_n = t_0^*(K)^n$, where t_0 is the starting period and $K = (1.3 \div 2)$. Typically, five to seven time points were measured in a delay range from 2 to 30 s with 550 acquisitions in ~10 h. The relaxation data were fitted by a nonlinear regression method to the function $y = M_0^* [1 - \exp(-t/T1)]$. The spectrometer was not field frequency locked during the spectral acquisitions. Instability of resonance conditions was monitored by the ^{129}Xe resonance in the gas phase and was less than 3 Hz/10 h. All NMR measurements were performed close to the normal physiological temperature at 36 ± 1°C.

RESULTS

The NMR spectra obtained from whole human blood are shown in Fig. 1. The blood exhibits three

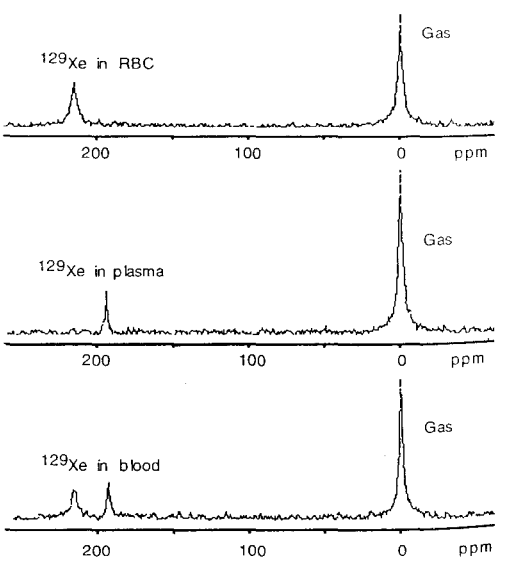

FIG. 1. Natural abundance ^{129}Xe (27.68 MHz) absorbed in whole human blood **(bottom)**, plasma **(middle)**, and red blood cells **(top)** at 36°C and normal pressure. Chemical shifts are given relative to xenon gas resonance. Each sample was placed in a 50 ml spherical bulb, where ~10 ml was occupied by xenon gas. NMR spectral width was 10 kHz and recycle delay 30 s, and 794 acquisitions were collected with 90° pulse.

peaks at 216.0, 194.0, and 0 ppm. Measurement of a sphere filled only with xenon gas confirmed the assignment of peak at 0 ppm to ^{129}Xe in a gas phase. Assignments of other spectral peaks were achieved by separate NMR measurements of the plasma and red blood cell (RBC) components isolated by centrifugation (2,900 *g*, 20 min). Chemical shifts of the lines are given relative to that of the xenon gas resonance.

For comparison, NMR spectra of ^{129}Xe dissolved in vegetable oil and in water are shown in Fig. 2. Chemical shifts are 191.6 and 189.8 ppm for oil and water, respectively. The high solubility of xenon in oil relative to that of water is evident from comparison of the ^{129}Xe signals shown in the spectra.

Spin lattice relaxation in human blood was measured for six samples. The plasma and RBC T1 average values were 9.6 ± 2 s and 4.6 ± 1 s, respectively. Xenon gas above the blood had T1 = 11.9 ± 1.6 s. The level of oxygenation of the blood was checked for one sample at the commencement of the measurement and at the end of the experiment. It was found to be unchanged at ~20%.

The T1 value of ^{129}Xe in oil at 36°C and atmospheric oxygen pressure was 10.0 ± 0.6 s, which is remarkably close to the T1 value of ^{129}Xe in the plasma.

The T1 for xenon in distilled water was 26.3 ± 1.4 s. Eleven time points were used, ranging from 3 to 41 s, with 1,000 acquisitions per each point.

DISCUSSION

The results reveal two peaks in the whole-blood spectrum. The peaks suggest the existence of two absorption sites and are to our knowledge the first report of multiple ^{129}Xe resonance from blood.

Inspection of the separate blood components after centrifugation showed no evidence of hemolysis, but we note that our blood samples were still subject to oxidation and cell sedimentation over the long time period required to measure ^{129}Xe NMR signal.

Our measurements of average T1 = 9.6 s in the plasma and 4.5 s in the RBC components of intact human blood are much shorter than originally expected; however, these data are comparable with the transport time of blood, e.g., from the lungs (or heart) to the brain (12–14). The 11.9 s value for T1 of ^{129}Xe in the gas phase over the blood is comparable with the estimated value of 15 s for the lung of a normally breathing person (5). Thus, significant magnetization should be carried from the lungs to the tissues of interest such as the brain, supporting the proposal that hyperpolarized xenon MRI could be of great benefit for brain imaging, distribution of perfusion, and partitioning of xenon of normal and disease states.

Hyperpolarized xenon MRI also has potential to supplant nuclear medicine lung ventilation and perfusion techniques. The high signal of polarized xenon obtained after inhalation together with its reasonably long T1 in the blood argue for its applicability to the study of the cardiovascular system. In addition, hyperpolarized ^{129}Xe dynamic imaging allows xenon-specific differential diffusion studies of physiological problems.

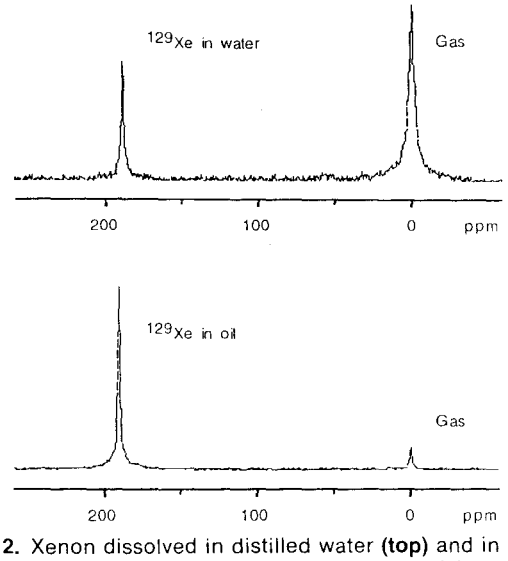

FIG. 2. Xenon dissolved in distilled water **(top)** and in vegetable oil **(bottom).** NMR spectra were measured for natural abundance ^{129}Xe at 27.68 MHz, 36°C, and normal pressure. Sample volume was 50 ml including 10 ml of xenon gas space above the liquid. Number of acquisitions and relaxation delay were correspondingly 1,000 and 10 s for water and 512 and 20 s for vegetable oil.

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