Resolving the Conflict over the T_1 Values of ^{129}Xe in Blood

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Introduction

The viability of hyperpolarized ^{129}Xe MRI (HypX-MRI) of organs other than the lungs depends on whether the spin-lattice relaxation time, T_1, of ^{129}Xe, in blood, is sufficiently long [1]. Earlier, using hyperpolarized ^{129}Xe bubbled into blood, we found that the T_1 increased with oxygenation, from about 3 s in fresh venous blood, to about 10 s in samples at arterial levels of oxygenation [2]. Bifone *et al.*, using a saline injection technique, have measured the T_1 to be 5 s in deoxygenated blood [3].

Tseng *et al.* [4], however, reported extremely long T_1 values deduced from an *indirect* experiment in which hyperpolarized ^{129}Xe was used to create a "blood-foam". They found that oxygenation *decreased* T_1. Pivotal to their experiment is the continual and rapid exchange of hyperpolarized ^{129}Xe between the gas-phase (within blood-foam bubbles) and the dissolved-phase (in the skin of the bubbles); this necessitated a complicated analysis of the bi-exponential decay of polarization to extract the T_1 of ^{129}Xe dissolved in blood.

In the present study, our experimental design minimizes gas exchange after the initial bolus of hyperpolarized ^{129}Xe has been bubbled through the sample, and the effects of such exchange are shown to alter the T_1 values only to a small extent. In addition, to support our results from hyperpolarized ^{129}Xe studies, we have conducted T_1 measurements using thermally polarized ^{129}Xe in blood at 8°C that was kept mixed by constant gentle agitation; here the complications of hyperpolarized ^{129}Xe exchange dynamics are avoided entirely.

Methods

In both thermally polarized and hyperpolarized experiments, fresh venous blood was drawn from healthy volunteers and placed on ice. Some samples were diluted with saline to achieve concentrations ranging from 0% to 50% blood. Sample volumes of 50 mL were gently bubbled with nitrogen gas for deoxygenated blood, or with compressed air to obtain oxygenated blood. The pO_2 was measured to be 100 mm Hg for the oxygenated samples and 30 mm Hg for the deoxygenated samples before and after the experiments.

In hyperpolarized ^{129}Xe experiments, the gas was bubbled into the blood through a sintered glass frit inside a glass cylinder two-thirds filled with blood, fitted with an exhaust tube. Signal acquisition was started immediately before the bubbling. FID data sets were acquired with small flip-angle, 200 μs pulses at 2-10 s intervals that were centered on the ^{129}Xe blood resonances. In some experiments the signal from the gas phase was destroyed with a series of 2 ms sinc pulses to prevent further ^{129}Xe exchange. T_1 values were calculated from spectral peak areas. Only those measurements made well after the bolus was delivered were fitted to an exponential.

In thermally polarized ^{129}Xe experiments, blood aliquots and xenon at 3 atm were contained in cylindrical glass ampoules fitted with high pressure O-ring valves. A Look-Locker inversion recovery sequence was used for time-efficient sampling [5]. To inhibit the auto-oxidation of hemoglobin to paramagnetic methemoglobin, the temperature was maintained at 8˚C. All experiments were performed using a 4.7 T GE Omega spectrometer/imager employing a solenoid coil tuned to 55.5 MHz. In some experiments, the blood was treated with carbon monoxide instead of oxygen.

Results

With oxygenated whole blood, the hyperpolarized ^{129}Xe spectra shown in Figure 1, exhibits three peaks: at 0 ppm (gas), at 198 ppm (plasma), and at 224 ppm (RBC). In the low hematocrit samples (0-25% blood), only the plasma signal was detected. Spectra from samples at higher hematocrit showed both plasma and RBC ^{129}Xe peaks. The T_1 values of the plasma and RBC resonances were nearly identical, as expected from the exchange time of about 12 ms [3], which is fast on the relaxation time scale. The T_1 value for deoxygenated whole blood was extrapolated to be 4.2 s, from a plot of the T_1 values at various dilution. The extrapolated T_1 value for oxygenated blood was 12.4 s. The T_1 value directly measured from an oxygenated sample of 100% blood was 13.5 s. The close agreement between the extrapolated and measured value for 100% blood validates the extrapolation technique.

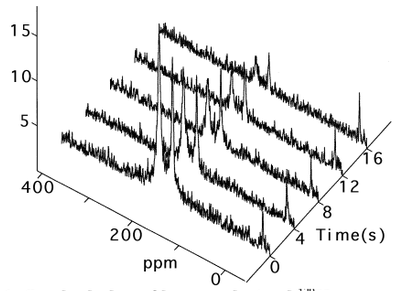

Figure 1. Stacked plot of hyperpolarized ^{129}Xe spectra obtained from oxygenated whole blood.

The thermally polarized ^{129}Xe T_1 value for deoxygenated whole blood samples was about 3 s, the T_1 for the oxygenated samples was about 8 s. Treatment with carbon monoxide increased T_1 even more than oxygenation, to about 11 s.

Discussion

The relaxation rate of ^{129}Xe depends strongly on the oxygenation state of the blood, with T_1 *increasing* from 4 s in venous blood to 13 s in blood oxygenated to the arterial level, at 4.7 T. Owing to careful experimental design minimizing gas exchange after the initial bolus of hyperpolarized ^{129}Xe, the effects of such exchange affect the T_1 values only to a small extent. This oxygenation trend is confirmed by our T_1 measurements using thermally polarized ^{129}Xe, at 8°C, in which we obtained T_1 values of 3 s in deoxygenated blood and 8 s in oxygenated blood. Our findings are also consistent with those of Bifone *et al.* [3]. The results of all of the above studies are at odds with those of Tseng *et al.* [4], who claim that the effect of oxygenation of the blood is to *decrease* the T_1 of dissolved ^{129}Xe, which they attribute to the paramagnetic effects of dissolved molecular oxygen.

It is clear from our studies, and from those of Bifone *et al.* [3] that RBCs, and hemoglobin in solution [6] are strong relaxation agents for ^{129}Xe, and that their relaxivity is markedly reduced on oxygenation. Treatment with carbon monoxide produces an even greater reduction in relaxivity, which is probably owing to the fact that on binding, CO produces nearly identical, but quantitatively greater structural changes in the hemoglobin molecule.

Inhaled xenon is transported from the lungs to other tissues via oxygenated arterial blood, the appropriate T_1 is probably the 13 s value. This should be long enough for HypX-MRI of the brain and other organs, since the transport time is only about 5 s in humans.

The observed oxygenation dependence of T_1 raises interesting prospects for hyperpolarized ^{129}Xe functional MRI (HypX-fMRI) studies. An increase in regional cerebral blood flow should increase the local hyperpolarized ^{129}Xe concentration, both directly and by lengthening T_1 by increased oxygenation; these mechanisms should cooperate to produce greater local signal enhancement in cerebral tissue.

References

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