Dissolved Phase MR Imaging of Continuously Infused Hyperpolarized ^{129}Xe Using Hydrophobic Gas Exchange Membranes

Z. I. Cleveland[1], H. E. Möller[1,2], L. W. Hedlund[1], G. P. Cofer[1], B. Fubara[1], and B. Driehuys[1]

[1]Center for In vivo Microscopy, Duke University Medical Center, Durham, NC, United States, [2]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Introduction: Hyperpolarized (HP) noble gases enable a wide range of novel MR applications including non-invasive, regional visualization of pulmonary function [1]. HP ^{129}Xe is of particular interest because it is soluble in tissues and its large (~300 ppm) chemical shift range provides detailed information about the local chemical environment including physiologically important parameters such as blood oxygenation [2]. Further, HP ^{129}Xe in conjunction with cryptophane biosensors holds great potential as a molecular imaging contrast agent [3]. However, to make use of these properties in vivo, efficient delivery of HP to the blood is crucial. HP ^{129}Xe is most commonly delivered by inhalation and dissolution of the Xe through the lung, but this approach is time consuming and inefficient [4]. Alternately, dissolved HP ^{129}Xe can be injected directly into the blood where it is transported throughout the body and can be used, for instance, to probe pulmonary perfusion and gas exchange [5]. Unfortunately, this approach is constrained by the tolerable injection volume, and the HP ^{129}Xe signal is thus available for only a short duration. Ideally, Xe would be delivered continuously allowing signal averaging and permitting the study of biological processes over an extended time period. It was previously shown with NMR spectroscopy at 7 T with static liquid samples that high HP ^{129}Xe signals can be obtained by directly infusing Xe into solution using microporous, hydrophobic membranes [6]. Here, we extend membrane infusion of HP ^{129}Xe to flowing liquids including blood and demonstrate the feasibility of continuous, dissolved-phase imaging.

Methods: ^{129}Xe was hyperpolarized to P ≈ 10% and cryogenically accumulated in 200 mL batches using a prototype commercial polarizer (model 9800, MITI, Durham, NC). HP ^{129}Xe was dissolved using a gas-exchange MicroModule™ (Membrana, Charlotte, NC) comprising a series of microporous polypropylene hollow-fiber membranes with a total gas exchange surface area of ≈100 cm² and a liquid volume of 2.7 mL. Dissolved-phase imaging was performed with isotopically enriched Xe (83% ^{129}Xe; Spectra Gases, Alpha, NJ) using a 23.6 MHz linear birdcage coil (L = 8 cm, ϕ = 7 cm) in a 2 T, horizontal, 15 cm clear-bore magnet (Oxford Instruments, Oxford, UK) equipped with 400 mT/m shielded gradients and operated with a GE EXCITE console (GE Healthcare, Milwaukee, WI). Images were acquired using a non-slice-selective gradient-echo sequence and a 30° flip angle (TR = 500 ms, bandwidth = 4 kHz, matrix = 64×64, FOV = 4.0 cm, NEX = 16). MR spectroscopy was performed in either distilled water or rat blood using a solenoid probe (L = 6.6 cm, ϕ = 3.3 cm) and 90° RF pulses with natural abundance Xe (26.4% ^{129}Xe). Blood was taken from a 645 g Sprague-Dawley rat (Charles River, Raleigh, NC) following an approved Duke animal care protocol. The rat was anesthetized by IP injection of pentobarbitol/butorphanol, heparinized (420 UI/kg), and blood was withdrawn from the carotid artery.

Results and Discussion: At all liquid (4-55 mL/min) and Xe gas (2-25 mL/min) flows rates studied, steady-state MR signals were observed from dissolved HP ^{129}Xe within one minute. The signal intensity depended strongly upon liquid flow and represents a trade-off between two competing processes. Slower flow rates favor efficient Xe exchange and thus improved mass transport [7]. However, in fluids that produce rapid ^{129}Xe spin-lattice relaxation, such as blood, more rapid flows improve signal intensities by reducing depolarization in solution. Additionally, rapid flow rates allow the system to return to the steady-state quickly following an RF pulse allowing faster signal averaging. Consistent with theory [7], the HP ^{129}Xe signal depends only weakly upon the Xe flow rate, and high signal intensities were observed from Xe flow rates as low and 2 mL/min. Thus, signal averaging can be performed for well over an hour with 200 mL of Xe gas. Optimizing the flow characteristics and pulse parameters allows dissolved-phase HP ^{129}Xe imaging with sub-millimeter resolution in less than 9 minutes.

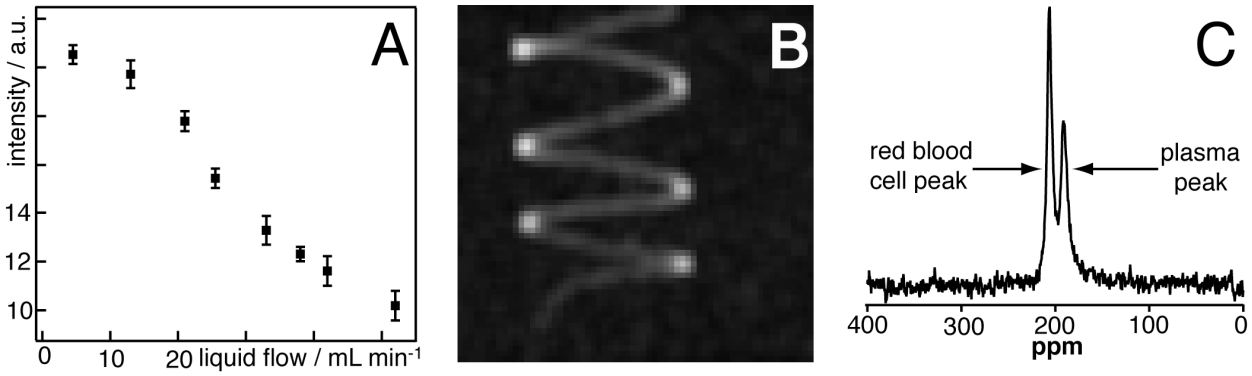

Fig. (A) Representative aqueous HP ^{129}Xe signal intensity data. **(B)** Image of aqueous HP ^{129}Xe in a spiral-shaped phantom (625×625 μm² resolution). **(C)** HP ^{129}Xe spectrum from rat blood referenced to gas-phase Xe at zero ppm (NEX = 128).

Conclusions: We have demonstrated the feasibility of continuously infusing HP ^{129}Xe into flowing solutions for MR applications. The hydrophobic membranes are compatible with a variety of liquids, including whole blood, and provided signal intensities high enough for sub-millimeter MR imaging. When adapted for in vivo use, this technique may find applications in the study of pulmonary function, ^{129}Xe MR angiography, and Xe biosensors-based molecular imaging. Directly infused HP ^{129}Xe could be applied to essentially any organ system and may be useful in studies of the brain.

References: [1] B Driehuys *et al.*, Proc Nat Acad Sci USA **103**, 18278, 2006, . [2] J Wolber *et al.*, Magn Reson Med **43**, 491, 2000. [3] L Schroder *et al.*, Science **314**, 446, 2006. [4] C Lavini *et al.*, NMR Biomed **13**, 238, 2000. [5] B Driehuys *et al.*, Radiology, in press. [6] D Baumer *et al.*, Angew Chem Int Ed **45**, 7282, 2006. [7] SR Wickramasinghe *et al.*, Aiche J **51**, 656, 2005.