Direct Gas Infusion of Hyperpolarized ^{129}Xe into Blood—A New Approach to Imaging Pulmonary Perfusion and Gas Exchange

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Introduction: Recently, a method for imaging pulmonary perfusion and gas exchange was demonstrated using venous injection of hyperpolarized (HP) ^{129}Xe dissolved in saline (1). Injected ^{129}Xe is cleared through the lungs where it can be imaged in the gas phase with relatively high resolution. Images can be quantified using adaptation of the Kety-Schmidt theory (2). However, because of the low ^{129}Xe solubility in saline, relatively large volumes of saline are required for this procedure, and this ultimately limits image resolution. In the present study, we circumvent this problem using elements of the well established, pulmonary bypass techniques (3) involving closed-looped, extracorporeal (EC) circulation of blood through a gas exchange membrane to continuously return to the animal, blood enriched with HP ^{129}Xe for imaging gas exchange processes in normal and disease models. By delivering ^{129}Xe signal continuously rather than by single injection, it becomes possible to improve image quality through signal averaging.

Methods: Five male Fischer rats (450-465g; Charles River, Raleigh, NC) were prepared according to a Duke-approved animal care protocol. Animals were anesthetized with IP injections of pentobarbital/butorphenol, perorally intubated, and ventilated on a HP-gas-compatible, constant-volume ventilator (60 breaths/min; 4 ml tidal volume). Rats were heparinized (420 UI/kg) to avoid clotting. To achieve maximal infusion of HP ^{129}Xe into blood, we used an EC method: blood was withdrawn from a left carotid artery catheter (3F) with aid of a peristaltic pump to maintain constant flow, then passed through a gas-exchange module and returned to the animal via a right jugular vein catheter (3F) (Fig. 1A). The gas-exchange MicroModule™ (Membrana, Charlotte, NC) had a volume of 2.7ml and contained polypropylene hollow-fiber membranes (CELGARD, surface area, $A \approx 100$ cm²). The EC circuit was primed with lactated Ringer's solution (about 5 ml). HP ^{129}Xe was produced in batches of 120 ml at $P \approx 10\%$ using a prototype commercial polarizer (MITI, Durham, NC). ^{129}Xe MR used a 23.6 MHz linear birdcage coil (L 8 cm, Ø 7cm) in a 2T, 15 cm clear-bore magnet (Oxford Instruments, Oxford, UK) with 400 mT/m shielded gradients and GE EXCITE console (GE Healthcare, Milwaukee, WI). MRS was performed with natural abundance Xe for parameter optimization. For perfusion MRI, HP ^{129}Xe was set to flow through the gas-exchange module at 7 ml/min, while blood was pumped at rates between 6 and 19 ml/min. Ventilation MRI was performed with real-time in vivo delivery of HP ^{129}Xe from the polarizer (4). Images were acquired using 83% enriched ^{129}Xe and a GRE sequence (α 30°, TR 250ms, bandwidth 4 kHz, matrix 64×64, FOV 7.5 cm, no slice selection). Excitation frequency was set to the ^{129}Xe gas resonance.

Results and Discussion: The rats tolerated EC circulation with pump rates $Q \leq 18.3$ ml/min (≈19% of the cardiac output) for up to 4 hrs. Fig. 1B shows the signal intensity, S, as a function of Q. The solid line is a computed time course using the relation $K = (Q/A)\ln[c^*/(c-c^*)] = 0.8\,(D/d_e)\,Re^{0.59}\,Sc^{0.33}$ for the mass-transfer coefficient, K (5) (c: outlet Xe conc.; c^*: equilibrium Xe conc.; Re: Reynolds no., Sc: Schmidt no., d_e: equiv. diameter, D: Xe diffusivity in blood) and $S = \varphi\, c\, \exp(-\tau/T_1)$ to consider relaxation inside the module (τ: residence time; T_1: relaxation time in blood; φ: scale factor). Slow pump rates improve Xe uptake ($c/c^* \approx 0.45$ and 0.33 @ 6.2 and 14.7 ml/min), but lead to substantial relaxation losses due to long residence times ($\exp(-\tau/T_1) \approx 0.13$ and 0.42 @ 6.2 and 14.7 ml/min). Figs. 1C & D show ventilation and perfusion images of the same rat with 1.2×1.2 mm² resolution. The ventilation image consumed 0.5 ml of ^{129}Xe (TA = 16 s); for the perfusion scan (TA = 768 s) ≈12.6ml of HP ^{129}Xe (estimated from the above model) were delivered to the lung capillaries by EC gas infusion.

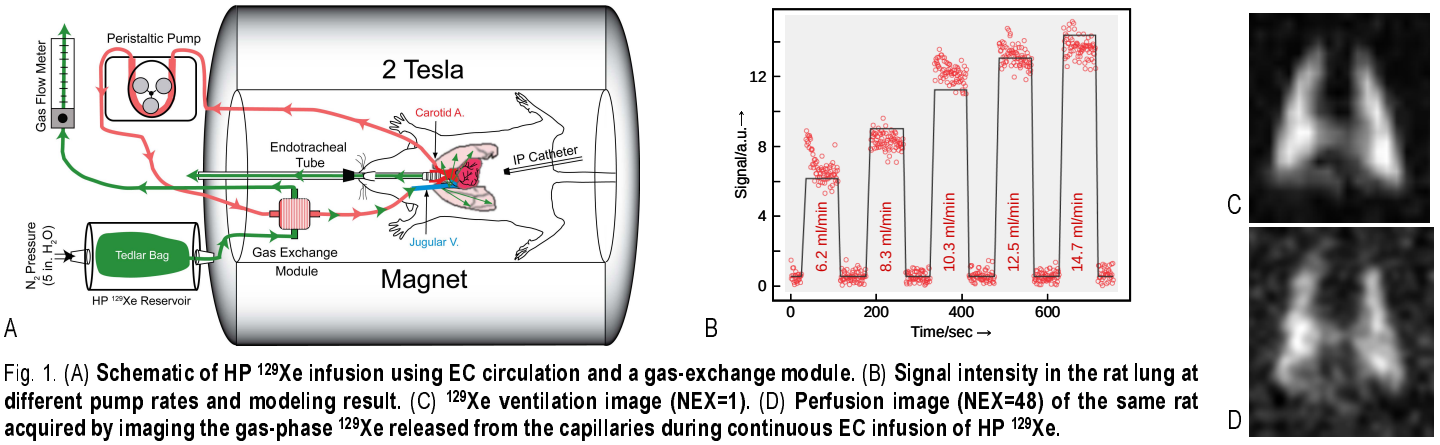

Fig. 1. (A) **Schematic of HP ^{129}Xe infusion using EC circulation and a gas-exchange module.** (B) **Signal intensity in the rat lung at different pump rates and modeling result.** (C) **^{129}Xe ventilation image (NEX=1).** (D) **Perfusion image (NEX=48) of the same rat acquired by imaging the gas-phase ^{129}Xe released from the capillaries during continuous EC infusion of HP ^{129}Xe.**

Conclusions: We have demonstrated the use of EC continuous infusion of HP ^{129}Xe into the blood to study the basic processes of gas exchange in the lung. This continuity of signal increases the available imaging time and should enable high-resolution MRI of perfusion. Such imaging is expected to be exquisitely sensitive to evaluate early stages of diseases that cause perfusion and gas-exchange anomalies in animal models. This novel infusion method may also serve as a means to deliver HP ^{129}Xe in high concentration to more distant organs such as the brain.

References: (1) B Driehuys, Radiology, in press. (2) HE Möller, Proc. ISMRM 2008; 16:1775. (3) FC Lewis in: P Mattei ed., Surgical Directives: Pediatric Surgery, Lippincott, 2003; p 83-91. (4) B Driehuys, MRM 2008; 60:14-20. (5) SR Wickramasinghe, AIChE J. 2005; 51:656-670.

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