Evaluation of Global Surface-to-Volume Ratio of Rabbit Lung Using Hyperpolarized 129Xe Uptake Spectroscopy at 1.5T

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Introduction Xe129 dissolves into tissue and binds hemoglobin in the lung (dissolved phase or DP) [1,2]. Study of the dynamics of DP Xe129 is enabled by its large chemical shift at about 200 ppm from the gas-phase signal as well as hyperpolarization [3,4]. The DP Xe129 signal can be further split into a peak of Xe dissolved into tissue and blood plasma (TP Xe) at approximately 197 ppm and another peak of Xe binding hemoglobin (B Xe) at 203--225 ppm (species dependent) [5,6]. The uptake dynamics of these two compartments of DP Xe contain valuable information about lung structure and function [7,8]. It is widely acknowledged that the short-time uptake behavior of the DP Xe surveys the local surface-to-volume ratio (SVR) [9-11] which is a key physiological parameter characterizing lung function and some lung diseases [12]. Since a tissue barrier is always present between the alveolar gas space and the capillary blood vessels [8], i.e., only tissue is in direct contact with the gas space in the lung, we hypothesize that the initial uptake of TP Xe alone can be used for SVR calculation. In this work we investigate the feasibility of measuring global SVR in the rabbit lung using a simple uptake model of the TP Xe at short delay times.

Theory Let V denote the volume of total alveolar gas space in the lung. Let S_g be the amplitude of gas signal, then $S_g = \alpha V$, where α is a ratio constant. For a short time t_d, the average depth of the tissue a Xe molecule travels into is $(2D_{Xe(t)}t_d)^{1/2}$, where $D_{Xe(t)}$ is the diffusivity of Xe in the lung tissue. If A is the total lung surface area, then the total amount of Xe in the tissue would be $\lambda A(2D_{Xe(t)}t_d)^{1/2}$, where λ is the Ostwald solubility of Xe in the lung tissue, and thus the tissue Xe signal S_t would be $S_t = \alpha\lambda A(2D_{Xe(t)}t_d)^{1/2}$. Thus, $S_t/S_g = (A/V)\lambda(2D_{Xe(t)}t_d)^{1/2}$ is linear with $t_d^{1/2}$, and the slope k is proportional to A/V or SVR via the relation $k = (A/V)\lambda(2D_{Xe(t)})^{1/2}$ (1).

Methods The pulse sequence starts with three 900-μs Gaussian RF pulses at 200 ppm, separated by gradient spoilers, to ensure a complete saturation of the DP Xe. At a delay time td after the saturation a 90˚ RF at 200 ppm following a 1˚ RF at 0 ppm is applied and FID is collected 100 μs after the end of the RF pulse (32.55 Hz bandwidth/pixel, 1024 data points). 32 different values from 2 to 900 ms are used. Experiments were performed on a 1.5-T commercial whole-body imager (Avanto, Siemens Medical Solutions, Malvern, PA) using a custom-made transmit-receive birdcage RF coil (IGC Medical Advances, Milwaukee, WI). Two New Zealand rabbits (approximately 4 kg) were anesthetized with a mixture of Xylazine 5 mg/kg and Ketamine 50 mg/kg. The animals were then intubated and placed in the xenon RF coil. The rabbits were ventilated with 30 cc of isotopically enriched (85% Xe129) xenon gas, polarized to approximately 10-15% via spin exchange with an optically pumped rubidium vapor (Model IGI 9600Xe Xenon Polarizer, MITI, Durham, NC). The protocol was approved by our Institutional Animal Care and Use Committee. Details of data analysis can be found in [6]. In brief, a function consisting of the sum of two Lorentzians is used to fit the Fourier transformed data at 900-ms delay, where both TP and B Xe are evident in the DP spectrum, to obtain their heights, peak positions and line widths (full width at half maximum, or FWHM). Then the rest of the 31 spectra are fitted using the same function except with the peak positions fixed (~ 6 ppm apart). The signal amplitude of each compartment is calculated by integrating the associated Lorentzian. The fitting to the 900-ms delay DP spectrum is illustrated in Fig. 1. In order to compensate for signal loss before ADC, T_2^* of each signal source is estimated using the relation $T_2^* = 1/(\pi\,\text{FWHM})$. Signal amplitude is compensated by multiplying $\exp(t'/T_2^*)$ with its associated T_2^* and delay t' between center of RF and the beginning of ADC. All DP (TP + B) Xe signal amplitudes are divided by the corresponding gas amplitudes corrected for the 1˚ RF and are thus converted into the percentage of total gas in the lung. Because the time constant of B Xe is fairly long [6] and we are most interested in the short time behavior of uptake in this study, the B Xe is ignored and the TP Xe signals at short-delay times are fitted linearly with $t_d^{1/2}$. From the slope we can extract SVR using Eq. (1).

rabbit	position (ppm)		FWHM (ppm)			T_2^* (ms)		
	tissue	blood	tissue	blood	gas	tissue	blood	gas
1	197.57	203.89	6.63	6.24	1.4	2.73	2.9	12.9
2	197.6	203.09	7.36	4.93	0.76	2.46	3.67	23.9

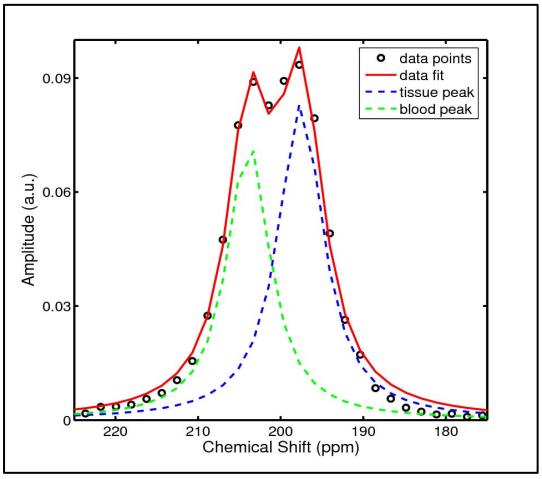

Fig. 1 Fitting of a 900-ms delay DP Xe spectrum to the sum of two Lorentzian shapes to separate the blood and tissue peaks and to determine their peak positions.

Result The basic spectral information of the DP Xe is listed in the Table. TP signals of short-time delays from rabbit #1 are plotted against $t_d^{1/2}$ in Fig. 2. A straight line going through the origin is used to fit data at delays less than 25 ms ($\sqrt{t_d}$ < 0.16 $\sqrt{s}$), where data from both rabbits displayed good linearity. Using a previously estimated diffusion coefficient of dissolved Xe in tissue, $D_{Xe(t)} = 3.3\times10^{-6}$ cm^2/s [5], and $\lambda = 0.078$ at 37 C [13], we get SVR = 363 ± 24 cm^{-1}.

Discussion The result is in good agreement with histology studies [14]. However, the calculation of SVR relies heavily on the diffusion coefficient of Xe in the tissue $D_{Xe(t)}$, which is tricky to measure and was only roughly estimated previously [5]. A more careful study of $D_{Xe(t)}$ will improve the accuracy of SVR calculation. Another source of error comes from the small off-resonance excitation of the gas Xe from the exciting RF of DP Xe, which would slightly reduce the calculated SVR. Comparing with a similar work previously published [15], where the depolarization of the gas phase is plotted against $t_d^{1/2}$ and slopes are compared with the histology studies, the current work excludes the exchange contribution from the B Xe at short delays and is able to calculate SVR directly from MR signals. Using only TP Xe signals prevented the calculation from being contaminated by B Xe signals that occur at early stage (likely due to thin tissue barrier). This approach can be potentially used to obtain SVR map of the lung when combined with imaging of the dissolved phase [8].

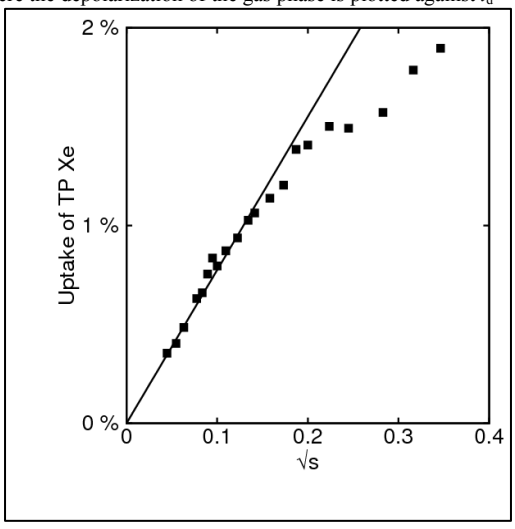

Fig. 2 Signals of TP Xe uptake at delays shorter than 25 ms display good linearity with square root of delay time. The slope of the fitted straight line is proportional to SVR.

Conclusion In this work we demonstrated the feasibility of measuring global lung SVR using the uptake spectroscopy of only the tissue/plasma compartment of the dissolved-phase Xe, which may lead to accurate calculation of local SVR in the lung when imaging techniques are involved.

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