Development of Novel Parameter that reflects Xe Transfer Rate in Mouse Lung from Hyperpolarized ^{129}Xe Dynamic Study under Spontaneous Respiration: Definition and Application to Murine Tumor B16BL6 Melanoma

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Introduction: Intrapulmonary gas exchange is important in lung function analysis and quantitative method that enables a precise and exact estimation of this process is now eagerly awaited although advanced technique of hyperpolarized ^{129}Xe is believed to offer promising methodology to this end[1,2]. In the present study, a novel parameter k_1k_2, product of rate constant for the Xe transfer from gas-phase to dissolved-phase (k_1) and that from dissolved-phase to gas-phase (k_2), is shown to be derived successfully from a wash-out curve analysis in the hyperpolarized (HP) ^{129}Xe dynamic MR spectroscopic study under selective pre-saturation condition. Comparative study using healthy and melanoma model mice proved enhancement of this parameter in the pathological model which was twice as large as that in healthy mice. Possibility is also discussed for this parameter as an indicator of progress in the pathological state.

Model: A two-compartment model is set up for the wash-out curve analysis of the lung under spontaneous respiration (Fig. 1) so that Xe exchange between the gas- and dissolved-phases can be discussed in detail in the lung. Xe can move back and forth between the two compartments before it is transferred to the whole body through blood circulating system. The hyperpolarized Xe concentration is depicted by C_g and C_d in the gas- and dissolved-phase, respectively, and the hyperpolarized magnetization is assumed to be negligibly small when returning to the lung from the circulation of the whole body. When wash-out curve is measured for the gas-signal after pre-saturation of the dissolved-phase signal, $S_{DPS\text{-}WO}$, and for the dissolved-phase signal after pre-saturation of the gas-signal, $S_{GPS\text{-}WO}$, calculations based basically on the Kety model have given following exponential decays and slopes:

$$\ln(S_{DPS\text{-}WO}) = \{\ln(\cos\alpha)/TR\text{-}R_f/V_g\text{-}1/T_{1g}\text{-}k_1\}(n\text{-}1)TR+\ln(S_1) \qquad slope(S_{DPS\text{-}WO}) = \{\ln(\cos\alpha)/TR\text{-}R_f/V_g\text{-}1/T_{1g}\text{-}k_1\}, \quad [1]$$

$$\ln(S_{GPS\text{-}WO}) = \{\ln(\cos\beta)/TR\text{-}1/T_{1d}\text{-}k_2\text{-}k_3\}(n\text{-}1)TR+\ln(S_1) \qquad slope(S_{GPS\text{-}WO}) = \{\ln(\cos\beta)/TR\text{-}1/T_{1d}\text{-}k_2\text{-}k_3\}, \quad [2]$$

where α and β are flip angles for the gas-phase and dissolved-phase signals, respectively, T_{1g} and T_{1d} are ^{129}Xe T_1 relaxation times for the gas- and dissolved-phase, respectively, R_f, V_g, n, and TR are ventilation volume per second, total volume of gas-phase in the lung, excitation number of observing pulse, and repetition time, respectively, and k_1, k_2, and k_3 are rate constants as assigned in Fig.1. Also in the steady state the signal intensity $S_{DPS\text{-}SS}$ in DPS mode divided by the intensity $S_{S\text{-}SS}$ in the standard mode is given by:

$$S_{DPS\text{-}SS}/S_{S\text{-}SS} = 1\text{-}k_1k_2/\{slope(S_{DPS\text{-}WO})\text{-}\ln(\cos\alpha)/TR\}/\{slope(S_{GPS\text{-}WO})\text{-}\ln(\cos\beta)/TR\}. \quad [3]$$

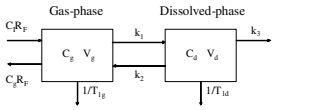

Fig.1: 2-compartment model in the lung.

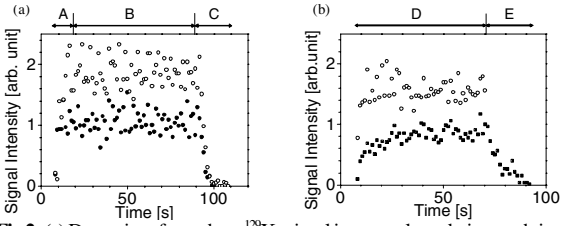

Fig.2: (a) Dynamics of gas-phase ^{129}Xe signal in mouse lung during wash-in (A), steady state (B), and wash-out (C) processes in the standard mode (○) and dissolved-phase saturation mode (●). The oscillation of the signal intensity in the steady state reflects inhalation-exhalation cycle of the HP gas. (b) Dynamics of gas-phase (○) and dissolved-phase (■) ^{129}Xe signals observed under the standard mode in D and gas-phase saturation mode in E.

Materials and Methods: Female C57BL/6 mice were inoculated via the tail-vein with B16BL6 melanoma cells, and MR dynamic study was performed 16 days after tumor inoculation. The HP ^{129}Xe gas produced in a homebuilt polarizing system [3] was supplied continuously to an anesthetized mouse under spontaneous respiration after mixing with oxygen in a mask. MR spectroscopic measurements were performed on a Varian INOVA 400WB NMR spectrometer equipped with a 9.4T vertical magnet. ^{129}Xe spectra were monitored by applying a series of pre-saturation pulse with the duration of 0.8 s and observe pulse in every 1.2s.

Results and Discussion: The signal intensity in the steady-state in the DPS mode was decreased from that in the standard mode in the gas-phase (Fig.2(a)). This decrease indicates in-flow of the pre-saturated dissolved-phase signal. The time evolution of the ^{129}Xe dissolved-phase signal in the GPS mode was measured by additional application of the gas-phase pre-saturation pulse after the gas- and dissolved-phase signals reached a plateau in the standard observation (Fig.2(b)). Table 1 lists the parameters obtained from these measurements and analysis using Eqs.[1] and [2]. The product of the transfer rate constants (k_1k_2) was obtained by substituting these values of the signal intensity ratio and slopes into Eq.[3] after the correction for the RF pulses. The resulting k_1k_2 values are compared in Fig.3 for the healthy and pathological model mice, which supports clear increase in the product in case of the pathological model mice. This increase may be interpreted to come from an increase in blood flow caused by the tumor progress. Our method contrasts well with the XTC method which is applied under held-breath mode [1].

Mouse number	$S_{DPS\text{-}SS}/S_{S\text{-}SS}$	slope($S_{DPS\text{-}WO}$) (s^{-1})	slope($S_{GPS\text{-}WO}$) (s^{-1})
Healthy			
1	0.654±0.025	-0.392±0.019	-0.080±0.006
2	0.690±0.027	-0.345±0.025	-0.082±0.007
3	0.468±0.025	-0.334±0.018	-0.089±0.011
Melanoma model			
m1	0.623±0.024	-0.413±0.069	-0.122±0.009
m2	0.664±0.025	-0.488±0.018	-0.138±0.012
m3	0.550±0.020	-0.391±0.024	-0.116±0.009

Mean± Standard error

Table 1: Obtained parameters for estimating k_1k_2 values.

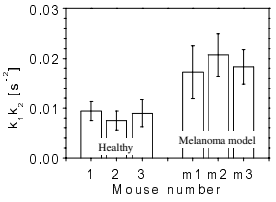

Fig.3: k_1k_2 values for healthy and melanoma model mice.

Conclusion: ^{129}Xe k_1k_2 value in mouse lung was successfully measured from HP ^{129}Xe dynamic MR spectroscopic study under spontaneous respiration. Clear difference was observed in the k_1k_2 value between the healthy and melanoma model mice. Thus, the value is shown to have a potential use as the indicator of the lung tumor detection. Our method is also considered to be useful as a noninvasive method for repeated as well as long-term testing of progress and treatment of different lung tumors.

References: [1] Ruppert K, et al., Magn Reson Med 2004;51:676. [2] Narazaki M, et al, Magn Reson Med Sci 2006; 5: 119. [3] Fukutomi J, et al, J Magn Reson 2003;160:26.