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MR Imaging of Mouse Lung Using Hyperpolarized ^3He : Image Acquisition and T_1 Estimation under Spontaneous Respiration

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Purpose: The purpose of this study was to acquire a hyperpolarized (HP) ^3He image of the mouse lung and to estimate ^3He T_1 in the lung from wash-out curve analysis under spontaneous respiration.

Materials and Methods: We first tested the K-Rb hybrid method for the spin-exchange optical pumping (SEOP) of ^3He using a home-built noble gas polarizer operated at atmospheric pressure and then applied it to MR imaging and spectroscopy of the mouse lung. The longitudinal relaxation time (T_1) of ^3He in the mouse lung was estimated under spontaneous respiration by exploiting a novel method in which SF_6 gas at thermal equilibrium was utilized in combination with the HP ^3He gas in the quantitative wash-out curve analysis. This method utilizes the difference in the profile of the wash-out curve of HP ^3He and SF_6 at thermal equilibrium. That is, the slope of the ^3He wash-out curve in the semi-logarithmic plots is affected by 3 factors, including RF pulse angle, respiration, and T_1 , whereas the slope of the SF_6 wash-out curve is only the function of respiratory term.

Results: A ^3He lung image was obtained successfully, and we were able to estimate successfully ^3He T_1 in the mouse lung under spontaneous respiration using a novel method; the estimated T_1 value was 68 ± 25 s, which was reasonable compared with the value calculated from the literature data measured during breath-hold.

Conclusion: We succeeded in acquiring the first ^3He image of mouse lung *in vivo* in this country, and our proposed method of estimating ^3He T_1 in the lung under spontaneous respiration is noninvasive and readily applied to animals and would be useful to evaluate the alveolar gas exchange function as well as oxygen partial pressure (p_{O_2}) in lungs of animals.

Keywords: hyperpolarized ^3He , lung image, wash-out, longitudinal relaxation time, SF_6

Introduction

The sensitivity in NMR experiments of noble gas isotopes, such as ^3He and ^{129}Xe , can be increased by several orders of magnitude through optical pumping techniques.¹ Hyperpolarized (HP) gases can be used to visualize directly the void spaces in the lungs and are expected to provide a new modality for analyzing lung function. That is, HP gases have been applied to magnetic resonance spectroscopy (MRS) and imaging (MRI) of the lung to gain information about function as well as morpholo-

gy.² For example, dynamic imaging³ and measurements of the apparent diffusion coefficient (ADC)⁴ following the inhalation of HP ^3He gas, which yield information about ventilatory function and porous structure, respectively, have been demonstrated in healthy and diseased lungs.

The longitudinal relaxation time (T_1) of ^3He is strongly dependent on oxygen partial pressure (p_{O_2}) in the gas mixture.⁵ Hitherto, several works exploiting this characteristic have appeared, wherein ^3He T_1 in the lung was investigated in live guinea pigs in relation to intrapulmonary p_{O_2} .⁶ Also, regional intrapulmonary p_{O_2} and its depletion rate during breath-hold have been measured for humans and animals.^{7–9}

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Fig. 1. Experimental setup of the hybrid spin-exchange optical pumping (SEOP) and the gas flow system for supplying hyperpolarized (HP) ^3He gas to the mouse.

Several groups have reported *in vivo* dynamics of HP ^{129}Xe in the lung and brain. Peled and associates¹⁰ have established a ^{129}Xe uptake model in tissue under constant inhalation of HP ^{129}Xe gas on the basis of Kety's model.¹¹ Martin's group¹² extended and refined Peled's model by including terms for the transport of HP ^{129}Xe gas from the reservoir, through the mouth and throat, and into the lungs. Kilian and collaborators¹³ modified Peled's model, including the destruction of polarization by repetitive RF excitations in the breath-hold technique. Möller's group¹⁴ developed a model for signal dynamics of HP ^{129}Xe and ^3He in the lung measured during inspiration and breath-hold periods based on Bloch equations, and they analyzed the dynamics measured in guinea pig lung under ventilation control mode. Swanson and associates¹⁵ demonstrated the uptake and wash-out dynamics of HP ^{129}Xe magnetization in the rat lung under ventilation control mode. Sakai's group¹⁶ reported wash-in and wash-out dynamics of HP ^{129}Xe signals in the rat lung under spontaneous respiration. In these reports, the spontaneous respiration mode was only adopted by the Sakai group, but their method was invasive, using a catheter inserted into the trachea, and no quantitative analysis was made. Thus, no detailed analysis has been reported under spontaneous respiration.

In the present study, a handy home-built ^{129}Xe polarizer operated at atmospheric pressure and

previously reported by the authors¹⁷ was applied to ^3He polarization adopting the hybrid method.^{18,19} HP ^3He gas was then applied to MR imaging and spectroscopy of the mouse lung to estimate ^3He T_1 in the lung from quantitative wash-out curve analysis under spontaneous respiration.

Materials and Methods

Materials

High-purity ^3He gas (^3He , over 99.95%; ^4He , under 0.05%; Cambridge Isotope Laboratories, Inc.), and standard gases of N_2 and O_2 (Japan Air Gases Co., Ltd.), and of SF_6 (Kanto Denka Kogyo Co., Ltd.) were used. Sodium (Reagent Grade, over 99%), potassium (EP Grade, 98%), and rubidium (EP Grade, over 99.5%) metals (Nacalai Tesque Co., Ltd.) were used without further purification.

Polarizer

The nuclear spins of ^3He were polarized by the K-Rb hybrid SEOP with a home-built noble gas polarizing system (Fig. 1). A cylindrical Pyrex® glass cell of 60-mm diameter and 100-mm length equipped with an optically polished window was used as an optical pumping (OP) cell and placed in a fringe field of 12 mT of a super-conducting magnet used for NMR measurements. A droplet of K and Rb metals mixed with the volume ratio of $V_{\text{K}}/V_{\text{Rb}} \sim 7$ was deposited into the OP cell. The

temperature of the cell was set at 473 K in an oven equipped with a heated air-blower (Leister CH-6056; Kägiswil, Switzerland). The vapor density ratio was estimated as $[\text{K}]/[\text{Rb}] \sim 1.5$ from Raoult's law and saturated vapor curves.^{19–21} The ^3He and N_2 gases were mixed in plastic syringes and transferred to the OP cell at atmospheric pressure through a predrying vessel containing K-Na alloy. Three diode laser arrays (Coherent Japan, DUO-FAP system, 795 nm) were used for polarizing the Rb electron spins; the output power of each was 30 W.

Animal preparation and gas supply

Male ddY mice aged 6 to 14 weeks, weighing 30 to 42 g, and purchased from Japan SLC, Inc. were used. All experimental procedures and animal care conformed to our university's guidelines. The mice were anesthetized with an intraperitoneal injection of pentobarbital sodium (50 mg/kg; Dainippon Pharmaceutical Inc.), and a mouth mask was attached from which gases such as ^3He , SF_6 , N_2 , or O_2 were supplied. Each mouse was held in an acrylic tube (i.d. 26 mm) and fixed in the imaging probe so that the entire lungs were covered by the NMR RF coil.

The ^3He gas was first transferred to storage syringes, which were then pressed by an air compressor to a constant pressure to supply to the OP cell. The HP ^3He gas was delivered to the mouth mask through a polyethylene tube (Fig. 1). The mouse inhaled the gas mixture spontaneously through the mask to which the O_2 gas was applied.

Measurement of ^3He polarization

The polarization of the HP ^3He atoms was estimated from the comparison of the signal-to-noise ratio (SNR) of the HP gas with that of the thermal equilibrium ^3He signals at ambient temperature. Using a standard sample of ^3He gas that included 100% ^3He gas at 1 atm, the thermally polarized ^3He signals were detected by applying the same flip-angle pulse after accumulation of 2048 free induction decays (FIDs) with repetition time (TR) of 4 s. Use of a small flip angle and the effect of diffusion of ^3He atoms in the long cylindrical glass tube enabled us to accumulate signals with a short TR.

MR imaging and dynamic spectroscopy measurement

All MR measurements were performed with a Varian Unity INOVA 400WB high-resolution NMR spectrometer equipped with a 9.4T vertical magnet with a bore width of 89 mm. ^3He SNR was measured at 304.414 MHz with a 5ϕ NMR probe using a single RF pulse with flip angle of 12° .

MR imaging was performed with Litz volume RF coils tunable to ^3He , ^{129}Xe , ^1H , and ^{19}F with a

32-mm inner diameter (Doty Scientific, Inc.). ^1H images were obtained using a gradient echo sequence with TR = 100 ms; echo time (TE) = 2 ms; number of accumulation = 2; field of view (FOV) = $50 \times 50 \text{ mm}^2$; matrix = 128×128 ; and slice thickness = 2 mm. The RF pulse used was a sinc pulse with PW = 2 ms, corresponding to a flip angle of 70° . The ^3He imaging was performed using a gradient echo sequence with TR = 100 ms, TE = 1.2 ms, number of accumulation = 16, FOV = $50 \times 50 \text{ mm}^2$, matrix = 32×32 (zero-filled to 256×256), and slice thickness = 50 mm, with a centric ordering in k-space sampling using a 37° hard pulse. Here, TE was set as short as possible to prevent signal loss from fast diffusion of ^3He atoms.

Dynamic spectroscopy measurement was made by applying RF pulses repetitively to obtain wash-in as well as wash-out curves from the chest of each mouse. The pulse width was 200 or 400 μs , and repetition time was 0.7 or 1.4 s, respectively. In the wash-in process, HP ^3He and O_2 gases flowed into the mask at the rate of 200 to 300 mL/min and 15 mL/min, respectively. After reaching a steady state, the polarized gas was depolarized by its passage through a depolarizing tube packed with steel wire (Fig. 1), and the wash-out process was monitored. The signal dynamics of ^{19}F in SF_6 gas were also observed in a similar way. The ^{19}F signal was measured at 376.026 MHz by the RF pulse with PW = 200 μs , corresponding to the flip angle of 90° , and 6 FIDs were accumulated with TR = 0.12 s. The wash-out curve of SF_6 gas was obtained by switching the SF_6 gas to N_2 gas under the same flow rate while maintaining the supply of O_2 gas at a constant rate of 15 mL/min.

Calculations

Integrals were taken for ^3He signals in the dynamic study and analyzed by a least-squares fitting of Eq. [a-4] described in the Appendix using Origin (Lightstone Corp.) to obtain the value of the slope given in Eq. [1] or [3].

Results

^3He polarization

The polarization of ^3He was observed to change with polarizing time as shown in Fig. 2a for a mixture of 80% ^3He plus 20% N_2 . The polarization of ^3He increased until it reached a plateau at about 70 min. The polarization was also dependent on the percentage of ^3He composition in the mixed gas (Fig. 2b). The maximum SNR was obtained at a mixed gas composition of 80% ^3He plus 20% N_2 . Therefore, the following imaging and spectroscopic studies were performed using 80% ^3He plus 20% N_2

Fig. 2. Plots of the polarization of ^3He against polarizing time and gas composition
a: Dependence of the ^3He polarization on the polarizing time. **b:** Dependence of the ^3He polarization (■) and SNR (●) on the percentage of ^3He in the mixture of ^3He plus N_2 . The dashed line represents the guide for eyes.

The signal-to-noise ratio (SNR) of the signal for the mixed gas shows a maximum at 80% ^3He and 20% N_2 , whereas polarization of ^3He itself increases with dilution by N_2 gas.

Fig. 3. Images of the live mouse chest
a: coronal ^1H image (scout image). **b:** coronal ^3He image, **c:** axial ^3He image.

gas polarized over 90 min.

MRI of mouse chest

^1H and the ^3He images of the mouse chest were obtained (Fig. 3). The ^1H images showed motion artifacts, and the lung was not clearly visible. On the other hand, the ^3He images, both coronal and axial, showed distribution of ^3He gas in the lung void space.

^3He dynamic spectroscopy of mouse lung

The time evolution of the ^3He spectrum in the mouse lung was obtained under spontaneous

Fig. 4. ^3He dynamic spectroscopy of the mouse lung to estimate ^3He T_1 in the lung under spontaneous respiration

respiration (Fig. 4). The wash-in process continued for about 7 s (Fig. 5); integral intensities of the ^3He spectra were plotted. The wash-in process was followed by a steady state, wherein the signal intensity oscillated reflecting the inhalation-exhalation cycle of the HP gas. This steady state continued from 7 s to 22 s in evolution time. When the HP gas was depolarized, signal intensity decreased, reflecting the replacement in the lung of HP gas by the depolarized gas. This wash-out process continued from 22 s to 29 s.

Application of the dual flip-angle method

Fig. 6. shows the semi-logarithmic plots of the signal intensities of ^3He MR spectra during the wash-out process measured by pulses with flip angles of α and 2α . The slopes of these wash-out curves were -0.367 for the α pulse and -0.491 for the 2α pulse. The difference in these 2 slopes was

Fig. 5. Plots of integral intensities of the ^3He spectra as a function of time during wash-in (0–7 s), steady-state (7–22 s), and wash-out (22–29 s) processes

Fig. 6. Semi-logarithmic plots of the ^3He signal intensity in the wash-out process measured by the pulses with flip angle of α (●) and 2α (○). The solid lines show results from the least-squares fitting by Eq. [a-4]. The flip angle α can be determined from the difference in these 2 slopes as given in Eq. [2].

determined to be -0.125 , and hence, a flip angle of $\alpha = 13.5^\circ$ was obtained from the relationship expressed in Eq. [2], $\{\ln(\cos 2\alpha) - \ln(\cos \alpha)\} / \text{TR} = -0.125$.

Discussion

^1H lung imaging is usually difficult to perform because ^1H concentration is low in lungs, and T_2 and T_2^* are short as a result of inhomogeneous distribution of magnetic susceptibility within the many air-tissue interfaces of the alveoli and bron-

chioles. In addition, artifacts from cardiac and respiratory motion disturb the image. This difficulty can be overcome by using much shorter TE with much higher gradient field in echo acquisition and by synchronizing the pulse sequence with respiration and heartbeat. However, in the present study, the ^1H image was used as a reference image, and no elaboration of the experimental condition was attempted. In the coronal image of ^3He (Fig. 3b), variations in signal intensity across the lung may reflect actual lung structures as described in references 2 and 22. In the axial image of ^3He (Fig. 3c), 2 lobes are clearly recognized, with the central dark portion for the heart and a bright portion visible separately in the right lobe region. This bright portion is thought to come from ^3He gas outside of the lung, e.g., the trachea or mouth mask, because we set the slice thickness as large as 50 mm to increase the signal intensity. Although the image obtained here required spatial and contrast enhancement, ^3He image of the lung obtained after increasing the polarization by future improvement in polarizing conditions could be useful for quantitative analysis of function as well as morphology.

MR spectroscopic study has given a dynamic profile for the wash-in, steady-state, and wash-out processes in the lung (Fig. 5). At steady state, the signal intensity was observed to oscillate, which undoubtedly reflects the volume change in the lungs on respiration. This effect of respiration is also seen in the wash-in process, although the effect is weaker. On the other hand, the signal decrease at the wash-out process was smooth and followed by an exponential decay predicted from Eq. [a-4]. In the wash-out process, the mouse inhales the normal gas (not the HP gas), and hence, the residual HP gas in the lung is replaced by the normal gas, giving rise to a smooth decay curve (Fig. 5). That is, the difference in the effect of the volume change in respiration in the wash-in and wash-out curves is that the inhaled HP gas directly affects the observed intensity in the wash-in process; however, the inhaled normal gas does not affect the signal intensity in the wash-out process. This changes the volume of the lungs, thus making the wash-out curve smoother than the wash-in curve. This situation is similar to the ^{129}Xe inhalation experiment.²³

Calculations for the wash-out process

The wash-out curve of the lungs can be analyzed on the basis of the equations derived in reference 10, although inclusion of pulse depolarization effect is necessary for the wash-out process. The expression for the slope of the ^3He wash-out curve under spontaneous respiration is given in Eq. [a-5] in the Appendix:

$$\text{slope}({}^3\text{He}) = \frac{\ln(\cos \alpha)}{TR} - \frac{R_F}{V_A} - \frac{1}{T_1}, \quad [1]$$

where α is the flip angle, R_F is the ventilation volume per second, V_A is the total volume of alveoli, and T_1 is the longitudinal relaxation time of ${}^3\text{He}$ atoms in the lung void space. We used the dual flip-angle method²⁴ to determine the flip angle α that should change depending on the experimental conditions, such as the volume of the mouse, its position in the RF coil, or RF tuning. With this method, we can exactly determine the flip angle α from the difference in the 2 slopes of the wash-out curve measured with α and 2α pulses:

$$\text{slope}({}^3\text{He}_{2\alpha}) - \text{slope}({}^3\text{He}_{\alpha}) = \frac{1}{TR} \ln \frac{\cos 2\alpha}{\cos \alpha}. \quad [2]$$

Although the first term in the right-hand side of Eq. [1] can be estimated from this experiment, the second and third terms remain unresolved. This problem is usually overcome by using a held-breath mode, wherein the second term ($-R_F/V_A$) vanishes. In the present study, we utilized ${}^{19}\text{F}$ MR spectroscopy to resolve this difficulty. Here, spontaneous respiration without surgical operation is intended as a noninvasive diagnostic applicable to small animals. The slope of the ${}^{19}\text{F}$ wash-out curve of SF_6 gas is only a function of the respiratory term ($-R_F/V_A$) because the SF_6 gas is insoluble in blood and tissue, like He gas (partition coefficient for SF_6 between blood and gas: $\lambda \sim 0.0075$)²⁵, and because the relaxation term of $1/T_1$ and the effect of pulse angle α in Eq. [1] disappear for SF_6 when measured at thermal equilibrium. Because the ${}^{19}\text{F}$ relaxation time is very short in SF_6 gas ($T_1 \sim 2.2$ ms in mouse chest at 9.4T), a thermal condition is rather easy to achieve for this gas. Therefore, the slope of the wash-out curve of SF_6 gas is given by:

$$\text{slope}({}^{19}\text{F}) = -\frac{R_F}{V_A}. \quad [3]$$

By using this relationship, the respiratory term can be separated out from the relaxation term in Eq. [1].

Figure 7 shows the semi-logarithmic plots of the

signal intensities of ${}^{19}\text{F}$ MR spectra during the wash-out process. The slope of the wash-out curve of ${}^{19}\text{F}$ was -0.315 after averaging several repeated measurements, which represent directly the ventilation-volume ratio ($-R_F/V_A$) according to Eq. [3]. Substituting the values of ${}^3\text{He}$ and ${}^{19}\text{F}$ slopes and flip angle α for the parameters in Eq. [1], we obtained the value of ${}^3\text{He}$ T_1 for 2 mice (Table).

The T_1 value is known to reflect p_{O_2} in the lung. In our conditions, gas flow rates of mixed gas of ${}^3\text{He}$ and N_2 , and O_2 gas in the inhalation experiments were 200 to 300 mL/min and 15 mL/min, respectively. p_{O_2} in the gas mixture calculated from these gas flow rates was 48–71 hPa. Using p_{O_2} in the inhaled gas mixture, T_1 values in the lung calculated from literature data measured postmortem and *in vivo* for guinea pig⁶ during breath-hold were 37 to 54 s and 261 s, respectively. The value of 261 s is an intrapulmonary wall relaxation time measured for a postmortem pig.⁷ In cases with low p_{O_2} conditions, the relaxation rate of ${}^3\text{He}$ atoms caused by collision with the intrapulmonary wall was larger than the relaxation rate from the interaction with paramagnetic oxygen. The longer T_1 value meas-

Fig. 7. Semi-logarithmic plots of the ${}^{19}\text{F}$ signal intensity in the wash-out process. The solid line is obtained from the least-squares fitting. The value of the ventilation-volume ratio ($-R_F/V_A$) can be obtained from this slope as given in Eq. [3].

Table. Derivation of ${}^3\text{He}$ T_1 in mouse lung

Mouse	Slope α [s^{-1}]*	Slope 2α [s^{-1}]*	TR [s]	α [$^\circ$]	Slope (${}^{19}\text{F}$) [s^{-1}]*	T_1 [s]
1	-0.367	-0.491	0.7	13.5	-0.315	86
2	-0.356	-0.423	1.4	13.9	-0.315	50
Average						68 ± 25

*Standard deviations are ± 0.029 , ± 0.015 , and ± 0.067 for slope α , slope 2α , and slope (${}^{19}\text{F}$), respectively.

ured *in vivo* compared with the value measured postmortem results from pulmonary gas exchange; that is, the alveolar p_{O_2} is reduced during breath-hold. The T_1 value of 68 ± 25 s estimated in the present study was within these ranges. The difference in T_1 values for 2 mice is caused by the difference in p_{O_2} in the inhaled gas mixture because gas flow rates of HP gas and O_2 varied from mouse to mouse.

The ^3He polarization was low compared with the polarization achieved by the hybrid method already reported.¹⁹ This may result from inhomogeneity in the fringe field of the super-conducting magnet, which is used for the polarizing field. Inhomogeneity in the polarizing field increases the relaxation rate of ^3He ,^{26,27} reducing the attainable polarization. Also, this inhomogeneity is increased in the transversal plane in the large cell. And the diffusion constant of the ^3He is increased to give increased relaxation rate in the low pressure condition.^{26,27} Therefore, large cell under reduced pressure used in the present study is also responsible to the lower polarization achieved here. The cell temperature should also be mentioned. The alkali metal vapor density is reduced when 2 metals are mixed to form K-Rb alloy. Therefore, an increase in the cell temperature would also be useful to realize higher polarization. However, these modifications would require remodeling our polarizing system and, thus, were not attempted.

By using HP ^3He gas with a much higher polarization, which would be achievable with further optimization of polarizing conditions, the T_1 value could be determined in a regional mode. Such a study would be useful for the estimation of regional p_{O_2} , which offers information about gas exchange efficiency in the void space of lungs.

Conclusion

We tested the K-Rb hybrid method for polarizing ^3He spins on a polarizing system operating under atmospheric pressure, and ^3He polarizations of 6% to 8% were achieved after the polarization for 90 min. ^3He image of the mouse lung was obtained successfully under this polarization, and wash-out curve was analyzed under spontaneous respiration to estimate ^3He T_1 in the lung with the aid of the same analysis using SF_6 at thermal equilibrium. The estimated T_1 in mouse lung was 68 ± 25 s. This novel method will be applied to animals noninvasively and readily, which will be useful for repeated animal study in long-term testing.

Appendix

We modified the ^{129}Xe uptake model described by Peled and associates¹⁰ to include the pulse depolarizing effect and enable its application to the analysis of ^3He wash-out curve. Considering the insolubility of the He gas in blood and tissue, unlike Xe gas (partition coefficient for He between blood and gas: $\lambda \sim 0.0085$),²⁵ the change with time of the total amount of HP ^3He in the alveoli is given by:

$$V_A \frac{dC_A}{dt} = C_I R_F - C_A \left(R_F + \frac{V_A}{T_1} \right), \quad [\text{a-1}]$$

where V_A is the total volume of the alveoli; C_A and C_I are the concentration of HP ^3He atoms in the alveoli and of the inhaled gas, respectively; R_F is the ventilation volume per second; and T_1 is the longitudinal relaxation time of ^3He atoms in the lung void space. In the case of the wash-out process, the time-dependent concentration, $C_A(t)$, is given by solving Eq. [a-1] on the condition of $C_I = 0$:

$$C_A(t) = C_{A0} \exp \left(- \left(\frac{R_F}{V_A} + \frac{1}{T_1} \right) t \right) \quad \text{for } 0 \leq t, \quad [\text{a-2}]$$

where t is the wash-out time and C_{A0} is the concentration of HP ^3He atoms in the alveoli at the beginning of the wash-out process.

In the case of the HP gas experiment, we need to consider the decay of polarization by applied RF pulses. When the polarized magnetization is applied at an RF pulse with flip angle α , its longitudinal magnetization is reduced to a component of $\cos \alpha$, providing the component of $\sin \alpha$ in the transverse direction. Because the HP longitudinal magnetization does not recover, unlike the magnetization at thermal equilibrium, the signal intensity of HP ^3He at the n th excitation is given by:

$$S_n = S_0 C_A ((n-1)TR) \cos^{n-1} \alpha \sin \alpha \quad \text{for } 1 \leq n, \quad [\text{a-3}]$$

where $\cos^{n-1} \alpha$ is the factor of longitudinal magnetization reduction by preceding $(n-1)$ pulses and $(n-1)TR$ is the wash-out time when the n th pulse is applied. Here, S_0 is the standardized signal intensity that would be obtained with the 90° pulse for the HP ^3He at a unit concentration. By substituting Eq. [a-2] into Eq. [a-3], we can obtain the signal intensity of HP ^3He at the n th excitation in the wash-out process as shown below:

$$S_n = S_1 \exp \left(\left(\frac{\ln(\cos \alpha)}{TR} - \frac{R_F}{V_A} - \frac{1}{T_1} \right) (n-1)TR \right). \quad [\text{a-4}]$$

The logarithmic form of Eq. [a-4] is as follows:

$$\ln(S_n) = \left(\frac{\ln(\cos \alpha)}{TR} - \frac{R_F}{V_A} - \frac{1}{T_1} \right) (n-1)TR + \ln(S_1). \quad [\text{a-5}]$$

This equation indicates that the plots of $\ln(S_n)$ against $(n-1)TR$ will give a straight line.

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