

Technical Note

Development of ^1H - ^{31}P Animal RF Coil for pH Measurement Using a Clinical MR Scanner

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Purpose : To establish a pH measurement system for a mouse tumor study using a clinical scanner, to develop the ^1H and ^{31}P radio frequency (RF) coil system and to test pH accuracy with phantoms.

Materials and Methods: The ^1H and the ^{31}P surface coils were designed to acquire signals from mouse tumors. Two coils were positioned orthogonally for geometric decoupling. The pH values of various pH phantoms were calculated using the ^1H decoupled ^{31}P MR spectrum with the Henderson-Hasselbalch equation. The calculated pH value was compared to that of a pH meter.

Results: The mutual coil coupling was shown in a standard S_{12} . Coil coupling (S_{12}) were -73.0 and -62.3 dB respectively. The signal-to-noise ratio (SNR) obtained from the homogeneous phantom ^1H image was greater than 300. The high resolution *in vivo* mice images were acquired using a ^{31}P -decoupled ^1H coil. The pH values calculated from the ^1H -decoupled ^{31}P spectrum correlated well with the values measured by pH meter ($R^2=0.97$).

Conclusion: Accurate pH values can be acquired using a ^1H -decoupled ^{31}P RF coil with a clinical scanner. This two-surface coil system could be applied to other nuclear MRS or MRI.

Index words : pH · ^1H - ^{31}P MR coil · mouse · clinical MR

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INTRODUCTION

Many tumor studies have been performed with high magnetic field animal magnetic resonance (MR) scanners using magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS) of ^1H and other nuclei such as ^{31}P , ^{13}C , and ^{19}F (1-6). These MRI/MRS provide some information on tumor microenvironment. MRS is especially useful in studying metabolism but can also be utilized to characterize tumor metabolism, pH, hypoxia, drug delivery, treatment efficacy, and apoptosis (1).

Alterations in tissue pH underlie many pathological processes. The capability to image tissue pH in a clinic

could offer new ways of detecting disease and response to treatment (7). A change in tumor microenvironment pH compared to that in normal tissue is a well-recognized phenomenon. The slightly acidic pH in tumor microenvironments has become an important aspect in designing anti-tumor therapy (4, 8). Moreover, pH can have a major impact on successful metastasis, which involves several pH-sensitive steps (9, 10).

Several methods have been proposed for measuring tissue pH including MRS and MRI. Some of these methods exploit endogenous MR resonance, while others require the administration of exogenous agents (7). In human cancers, ^{31}P MRS has been used to endogenously measure pH (11). We propose small animal RF coils to be used in a tumor study with both ^1H MRI and ^{31}P MRS. And this ^1H - ^{31}P coil system for the clinical MR scanner, which is a more popular and convenient than the animal MR scanner.

Technically, proton-decoupling is a necessary requirement to improve low sensitivity ^{31}P MRS (9). The accuracy of the pH values could be increased by the proton-decoupled ^{31}P spectrum. Some reports have suggested arranging coil fields in an orthogonal fashion (12, 13) in order to avoid substantial coil-flux coupling. Bottomley et al. (12) used figure-8 type geometry ('butterfly design') for the ^1H decoupling coil, where the proton field was orthogonal to the ^{13}C field. Merkele et al. (13) described a similar design, which was known as a co-planar dual-loop surface coil, consisting of a center-fed loop producing counter-rotating currents in half-loops, thus creating a magnetic field orthogonal to the ^{13}C plane. Although these designs provided good decoupling between the ^1H coil and ^{13}C or ^{31}P coil, the proton coil produced a

parallel magnetic field intensity that decreased very quickly with distance from the coil plane; therefore, if the region of interest were located at a greater distance from the coil, this design would not provide sufficient proton performance. A newly designed half-volume coil using a lower-frequency coil a significant distance from the protons had been reported to experience blocking field problems (14). This half-volume coil provided -20 dB isolation between the ^{13}C coil and ^1H coils (14). Recently, a birdcage-type coil with two independent, separated RF channels was reported by Jeon et al. for ^{19}F imaging (15).

In this study, we sought to confirm properties of the ^1H - ^{31}P coil system by measuring and comparing pH values using a ^{31}P MRS and a pH meter.

MATERIALS AND METHODS

Magnetic resonance is widely used for tumor

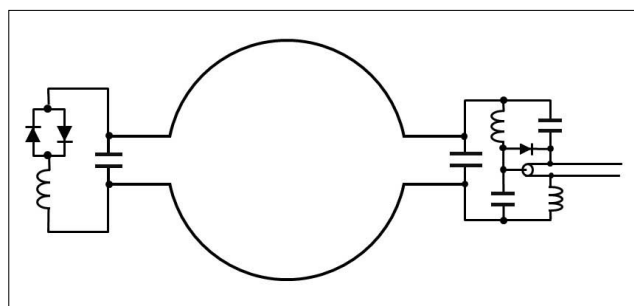


Fig. 2. The ^1H receive-only coil scheme. Active decoupling consists of a PIN diode switching design and passive decoupling with crossed high-speed switching diodes and a detuning inductor.

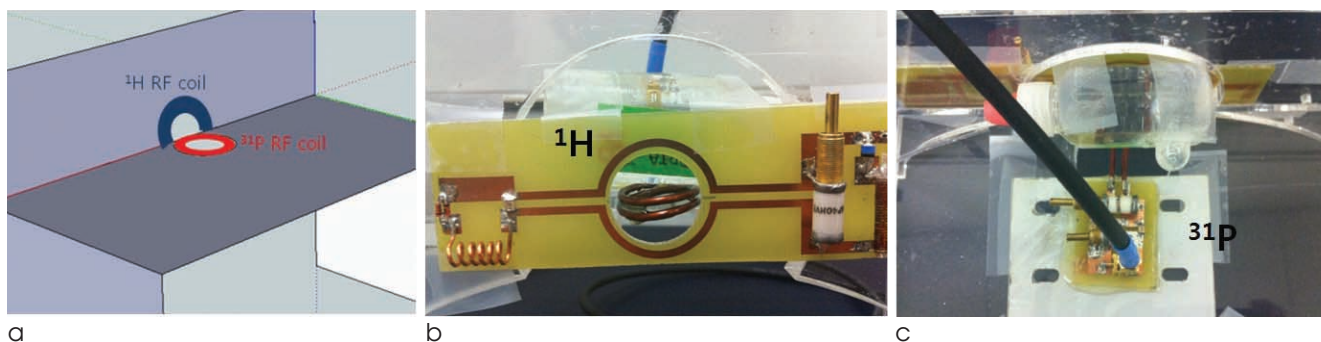


Fig. 1. The set-up of ^1H and ^{31}P RF coils. The two RF coil planes were located orthogonally for geometric decoupling (a). Photo of a ^1H receive-only coil (b) and a ^{31}P transmit-and-receive coil (c).

imaging and spectroscopy. Proton MR imaging was acquired using receive-only coils, whereas the phosphorus MR spectrum was acquired using transmit-and-receive coils.

The proton MR images and phosphorus spectrum were acquired using a 3.0 T GE Discovery MR750 scanner (General Electric Company, Milwaukee, USA).

Proton - Phosphorus coil coupling

The ^1H and ^{31}P RF coil planes were located orthogonally for geometric decoupling (Fig. 1). The two coils were tuned at 127.74 for protons and 51.75 MHz for phosphorus, matched to 50 Ω , and decoupled from each other. Electromagnetic coupling between two coils was measured using a network analyzer HP8753D (Hewlett Packard, USA).

Proton Receive-Only Coil & MR Imaging

For the receive-only proton coil, a single 25-mm loop coil etched on a copper PCB (Printed Circuit Board) was used. A non-magnetic PIN diode (MA4P4001, M/A-COM Technology Solution, Lowell, MA, USA) (16) was used to control decoupling. Passive decoupling through the use of a pair of crossed high-speed switching diodes was included as a safety precaution (Fig. 2).

The SNR was determined by the ratio of mean signal intensity to the standard deviation of background noise on phantom image.

The Fast Recovery Fast Spin Echo pulse sequence parameters for proton *in vivo* mouse images were TR/TE = 3500/89.3 or 88.4 ms, image matrix = 256 \times 256, 2 NEX, FOV 12 \times 12, slice thickness 4.0 mm. The animal experiment was conducted with the approval of the Association for Assessment and Accreditation of Laboratory Animal Care International.

Phosphorus Transmit-and-Receive Coil & MR Spectroscopy

The 25-mm, two-turn ^{31}P RF coil loops were formed from copper wire, functioning as a transmit-and-receive coil. Impedance matching to 50 ohm was achieved using the balanced capacitive matching method (17).

The single voxel phosphorus spectrum was acquired using an FID CSI (chemical Shift imaging) MNS (Multi-

Nuclear Spectroscopy) pulse sequence (TR = 1500 ms, number of points 2048, total number of scans 128 or 256 (*in vivo*)). The spectrum analysis was performed with SAGE 7 (Spectroscopy Analysis, GE Healthcare) on an MR750 system.

Intracellular pH was calculated from resonance positioning of Pi with respect to phosphocreatine (PCr) using the following modification of the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_a + \log \frac{\delta - \delta_{\text{HA}}}{\delta_{\text{A}} - \delta} \quad \text{Eq. [1]}$$

The observed Pi position relative to PCr at 0 ppm is represented by δ , and δ_{A} and δ_{HA} are the respective chemical shifts of the protonated and unprotonated forms of Pi (at 5.7 and 3.23 ppm). The pK_a (6.77) is the logarithm of the equilibrium constant for the acid-base equilibrium between protonated and unprotonated forms of Pi (18, 19).

The ^1H images and ^{31}P MR spectrum were acquired from a nude mouse (about 23 g) *in vivo*.

The phosphorus phantom for pH measurement was filled with 100 mM Pi (Na_2HPO_4), 40 mM phosphocreatine (PCr), and 0.05 mM ethylenediaminetetraacetic acid (EDTA). The volume of each phantom was less than 5 ml. The pH values of the phantoms ranged from 6.4 to 7.6.

RESULTS

^1H - ^{31}P coil coupling and SNR

The mutual coil coupling between ^1H - ^{31}P coil was shown in a standard S_{12} analyzer measurement, transmitting into the ^{31}P coil and receiving with the ^1H coil and vice versa. The resulting coupling between the ^{31}P coil and ^1H coil is shown in Table 1.

Table 1. Measurements of Mutual Coil Coupling

	Coil Coupling (S_{12})	
	^{31}P coil	^1H coil
^{31}P coil	–	–73.0 dB ^a
^1H coil	–62.3 dB ^b	–

Note.— ^a measured at 127.74 MHz, ^b measured at 51.75 MHz

Proton Receive-Only Coil & MR Imaging

The spin-echo images of a homogeneous phantom are shown in Fig. 3. The SNR of axial images (Fig. 3a) was 300, and that of coronal images (Fig. 3c) was 460.

The high resolution *in vivo* images acquired with ^1H receive-only coils are shown in Fig. 4. The single-voxel ^{31}P MR spectrum was acquired with a calculated pH value of 7.24.

Phosphorus Transmit-and-Receive Coil & MR Spectroscopy

We acquired pH values from MR spectra with various pH phosphorus phantoms. Some of ^{31}P MR spectra are shown in Fig. 5a. The position of the Pi peak relative to that of PCr at 0 ppm shifted depending on pH. With increased pH values, the Pi peak was more distant from the PCr peak at 0 ppm. The pH values were calculated using the Henderson-

Hasselbalch equation (Eq. [1]).

The pH values of the same phantom were measured by pH meter (pH 2700, Eutech Instruments). These pH values are plotted in Fig. 5b, where the x-axis represents pH value by pH meter, and the y-axis values represents those calculated from ^{31}P MRS. These values had about 97% correlation.

DISCUSSION

The tumor microenvironment is significantly different from that of normal tissue and is known for its acidic properties. Tumor acidity has important consequences for therapy and cancer progression (10). MRI/MRS has been used as a common noninvasive modality for studying tumor microenvironments. Most animal tumor studies were performed with high

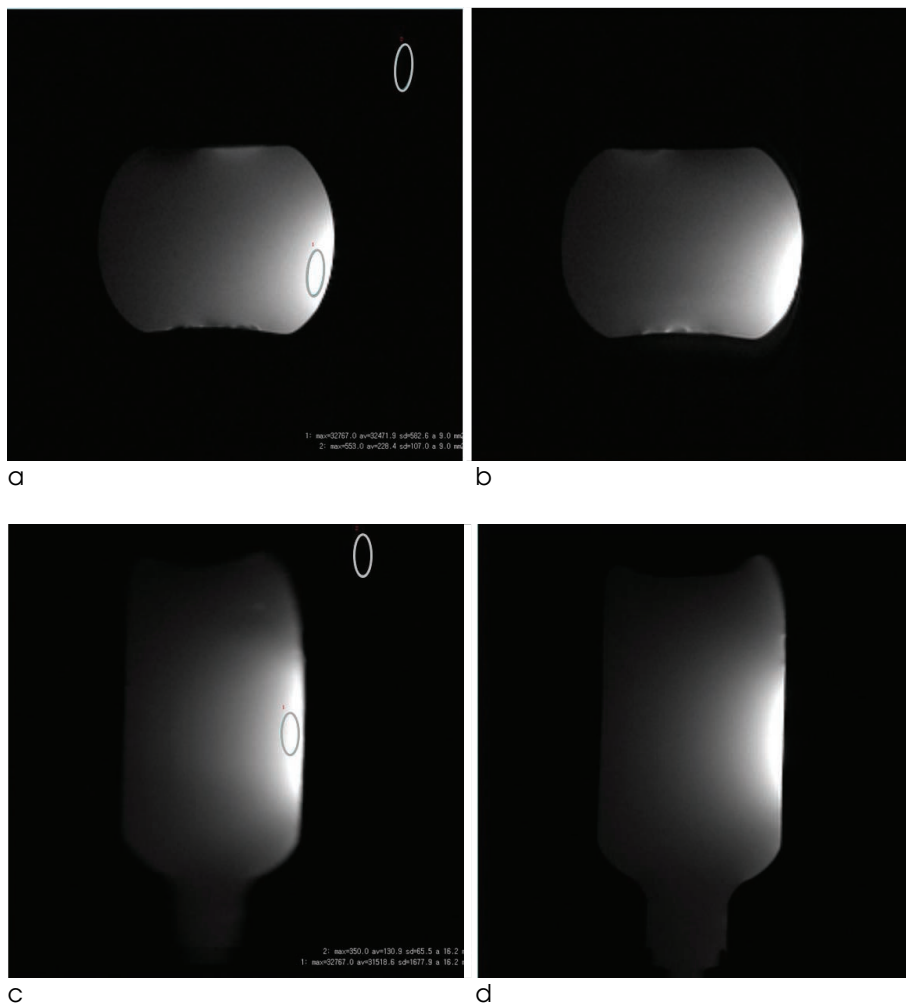


Fig. 3. The ^1H spin-echo images of a homogeneous phantom: (a, b) axial images (TR/TE = 167/15 ms, FOV $6 \times 6 \text{ cm}^2$, 256×256), (c, d) coronal images (TR/TE = 150/15 ms, FOV $8 \times 8 \text{ cm}^2$, 256×256). The SNR was measured at ROI (gray ellipse) in (a) and (c).

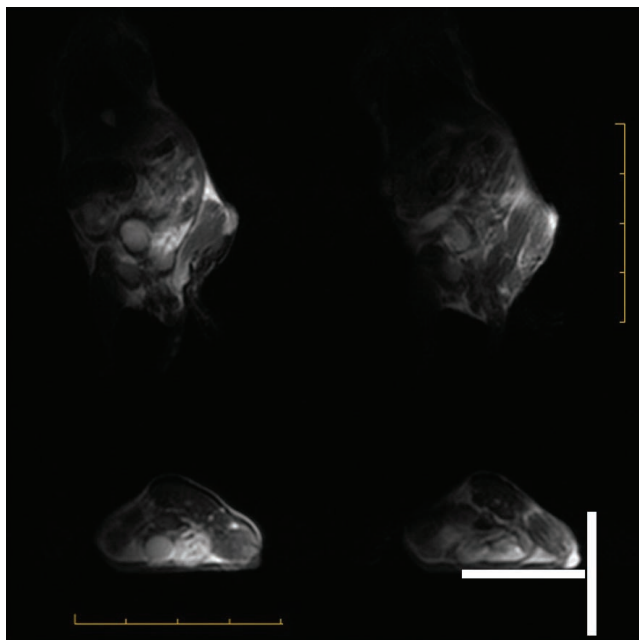


Fig. 4. The T_2 weighted *in vivo* mouse images acquired from a ^1H receive-only coil with a Fast Recovery Fast Spin-Echo pulse sequence. The parameters of these images were $\text{TR}=3500$ ms, $\text{TE}=89.3$ (coronal)/ 88.4 (axial) ms, thickness 4 mm, FOV 12×12 cm 2 , matrix 256×256 (coronal), 256×224 (axial) 2 NEX. One segment of the scale bar denotes 10 mm. The two white bars show the positions of the ^1H and ^{31}P RF coils.

magnetic field MR scanners. But the clinical MR scanner was more familiar and convenient than the animal scanner.

In this study, we attempted to establish a scanning system to measure pH using clinical MR scanner. To distinguish differences in tumor microenvironment, ^{31}P MRS was used. The ^1H images and ^{31}P spectrum were acquired using an existing pulse sequence installed on clinical scanner.

For the animal study with a clinical MR scanner, a small RF coil was required to acquire the MR signal with appropriate SNR. Additionally, the proton-decoupled magnetic resonance spectroscopy (MRS) of ^{31}P posed an issue for acquiring the appropriate ^{31}P spectrum. We were able to solve this problem by using a geometric decoupling method. S.I. Babic et al. calculated the mutual inductance between two filamentary circular coils whose centers were not on the same axis (20, 21). If the angle between the two coil planes was 90° , the calculated mutual inductance was 0.

We developed a ^1H receive-only coil and a ^{31}P transmit-and-receive coil for an animal study using a

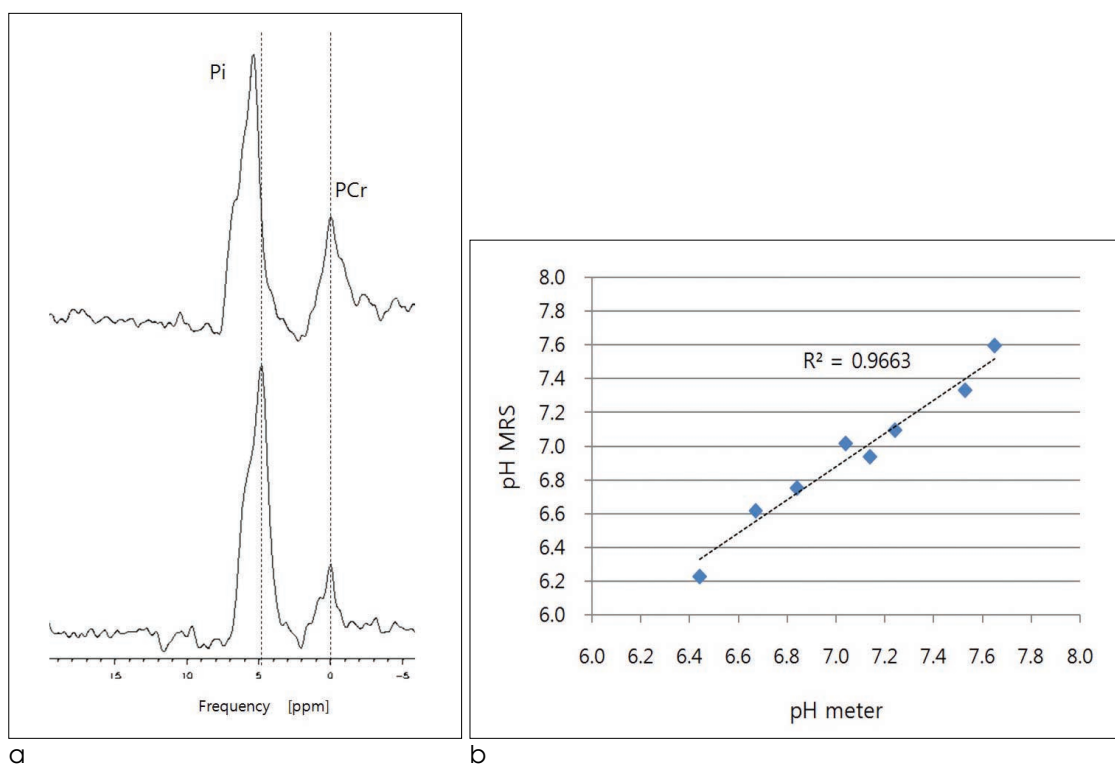


Fig. 5. (a) ^{31}P MR spectra of the phosphorus phantom. The pH determined by ^{31}P MRS was 7.6 for the upper spectrum and 7.03 for the lower spectrum. (b) Comparison of pH values determined by ^{31}P MRS and pH meter.

clinical scanner. The coil planes were orthogonal to one another, allowing for -60 to -70 dB isolation between ^{31}P coil and ^1H coils (Table 1).

^1H MR images were acquired with appropriate SNR (greater than 300). High-resolution images and ^{31}P spectrum were obtained with ^1H coils and ^{31}P coils, respectively.

To test the ^{31}P MR coil, we compared pH values calculated from the ^{31}P MR spectrum and those directly measured by pH meter. The pH values measured using these two methods had a good correlation (about 97%) (Fig. 4b).

In this study, we developed an animal study system using a clinical scanner and measured pH using this system. If another nuclear surface coil could be used instead of the ^{31}P coil, other metabolic information could be acquired. MRS of other nuclei, such as ^{31}Na , could be acquired by using this simple two-surface coil system.

CONCLUSION

We developed a ^1H and ^{31}P surface coil system for an animal study using a clinical MR scanner. These two coil planes were orthogonally placed, allowing for sufficient decoupling of both coils. Accurate pH values were measured using this ^1H -decoupled ^{31}P MRS. This simple two-coil system is an alternative to other nuclear RF coils.

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임상용 MR에서 pH 측정을 위한 동물 실험용 ^1H - ^{31}P RF 코일 개발

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목적: 임상용 MRI에서 마우스 종양의 pH 측정을 위한 ^1H - ^{31}P RF 코일 시스템을 개발하고 팬텀을 이용하여 pH 값의 정확도를 시험하고자 한다.

대상과 방법: 마우스 종양 연구를 위한 표면형 ^1H 및 ^{31}P radio frequency (RF) 코일을 개발하였다. 두 코일을 서로 수직이 되도록 설치하여 두 코일간의 상호인덕턴스를 0으로 하였다. 다양한 pH 값을 가진 팬텀으로부터 ^{31}P MR 스펙트럼을 얻어 Henderson-Hasselbalch equation을 이용하여 pH를 구하였다. ^{31}P 스펙트럼으로부터 얻은 pH값은 pH meter를 사용하여 직접 구한 pH값과 비교한다.

결과: ^1H - ^{31}P RF 코일 상호간 coil coupling (S12)은 각각 -73.0, -62.3 dB로 충분히 분리 되었다. 균일한 팬텀으로부터 얻은 ^1H 영상의 signal-to-noise ratio (SNR)는 약 300 이상이며, *in vivo* 고해상도 마우스 영상을 얻을 수 있었다. ^1H 신호가 분리된 ^{31}P MR 스펙트럼으로부터 얻은 pH값은 pH meter로 직접 측정하여 얻은 값과 약 97% 상관관계를 가졌다.

결론: 본 연구에서 개발한 임상 MRI 장비용 ^1H - ^{31}P RF 코일 시스템으로부터 정확한 pH를 구할 수 있었다. 본 코일 시스템은 ^{31}P 이외의 다른 핵 MRS 혹은 MRI에 적용 가능할 것으로 기대된다.

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