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MRI of the lung gas-space at very low-field using hyperpolarized noble gases

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Abstract

In hyperpolarized (HP) noble-gas magnetic resonance imaging, large nuclear spin polarizations, about 100,000 times that ordinarily obtainable at thermal equilibrium, are created in ^{3}He and ^{129}Xe. The enhanced signal that results can be employed in high-resolution MRI studies of void spaces such as in the lungs. In HP gas MRI the signal-to-noise ratio (SNR) depends only weakly on the static magnetic field (B_0), making very low-field (VLF) MRI possible; indeed, it is possible to contemplate portable MRI using light-weight solenoids or permanent magnets. This article reports the first in vivo VLF MR images of the lungs in humans and in rats, obtained at a field of only 15 millitesla (150 Gauss). © 2003 Elsevier Inc. All rights reserved.

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1. Introduction

The promise of using hyperpolarized (HP) noble-gas magnetic resonance imaging [1] for human subjects is gradually being realized [2–6]. HP gas MRI with ^{3}He is currently being tested diagnostically in patients with chronic obstructive pulmonary disease (COPD), to stage the progress of therapeutic approaches to cystic fibrosis and asthma, and to screen patients and assess the outcome of lung volume reduction surgery in patients with emphysema and in patients undergoing lung transplantation [2–6]. In HP gas MRI, spin- exchange optical pumping [7] creates large non-equilibrium nuclear spin polarizations in ^{3}He and ^{129}Xe, as much as 100,000 times greater than that obtainable at thermal equilibrium. The enhanced signal facilitates high-resolution MRI studies of void spaces such as in the lungs and sinuses. In addition, the solubility of ^{129}Xe makes it possible to image the blood vasculature, and tissues in the lung, heart and brain [1,8–12]. A special feature of HP gas MRI is that the signal-to-noise ratio (SNR) does not decrease appreciably when the static magnetic field (B_0) is lowered [13–16], obviating the need for the ubiquitous heavy and expensive superconducting magnets in conventional thermal-equilibrium MRI. Portable MRI would then become feasible, using far smaller and cheaper resistive solenoids or suitably configured permanent magnets. This paper reports the first *in vivo* very low-field (VLF) MR images of the lung gas-space in humans and in rats breathing hyperpolarized ^{3}He and ^{129}Xe, obtained at a field of 15 millitesla (150 Gauss).

Dispensing with expensive high-field superconducting magnets should drastically reduce the cost of implementing HP gas MRI as a diagnostic modality for the detection and staging of lung diseases. HP gas MRI at VLF could become

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portable, allowing the investigation of lung structure and function in a variety of settings, such as van-based imagers that could take this technique to patients unable to travel to a hospital, or even in the microgravity environments of spacecraft and space-stations.

2. Methods

Very low-field MRI system. Hyperpolarized ^{3}He and ^{129}Xe images were acquired on a 60 cm diameter prototype superconducting magnet with the magnetic field ramped down from 1.5 T to 15 mT (150 Gauss). Techron (Elkhart, IN, USA) 8604 gradient amplifiers were used to drive the x, y, and z gradients (maximum strength 0.8 Gauss/cm). The magnet and gradients were interfaced to a Resonance Instruments (Witney, UK) Maran Ultra imaging spectrometer. The Larmor resonance frequencies for ^{3}He and ^{129}Xe at 15 mT were 483.6 kHz and 175.6 kHz, respectively. To reduce electrostatic noise, a shield made from 0.1 mm thick copper sheet was installed within the magnet bore.

Noble gas polarization. ^{3}He or ^{129}Xe was polarized to about 5% via collisional spin-exchange with rubidium, optically pumped using an Optopower (Tucson, AZ, USA) 120 W fiber coupled laser-diode array.

Animal preparation. Sprague Dawley rats were anesthetized with a mixture of ketamine and xylaxine. A 14-gauge catheter was inserted into the trachea, and silk ligatures were tied around the endotracheal tube. The animal was placed supine in the RF coil. The endotracheal breathing tube was connected to the gas delivery system. A polarized-gas delivery system [27], designed for accurate delivery of hyperpolarized gas inside an MR imager, was used for the animal experiments. All animal procedures were approved by the Harvard Medical Area Standing Committee on Animals.

Animal imaging. Solenoid RF coils, tuned to 483.6 kHz and 175.6 kHz, the Larmor resonance frequencies of ^{3}He and ^{129}Xe at 15 mT, respectively, were used. To reduce electrostatic noise, the RF coils were housed in a box covered with a copper sheet (0.1 mm thick). Coronal images were acquired using a gradient-echo imaging pulse sequence, with 32 phase encodes, without slice- selection in a field-of-view of 8 cm for helium imaging and 20 cm for xenon imaging. Each phase encode step was acquired with either one breath (about 2 mL) of hyperpolarized ^{3}He using a 75° flip angle, or hyperpolarized ^{129}Xe using a 60° flip angle. MR data acquisition was synchronized to the breath-hold period of the ventilation cycle.

Human imaging. A dual-surface RF coil array of 10 inch diameter was tuned to ^{3}He. One coil was placed anterior and one placed posterior to the chest. About 500 mL of ^{3}He, polarized to ~5%, was expanded into an inert gas bag (Jensen Inert Products, Coral Springs, FL, USA) and handed to a healthy volunteer within the MRI magnet. Coronal images were acquired during a breath-hold of 10 s using a gradient-echo imaging pulse sequence, with 32 phase encodes and a flip angle of 25°. No slice-selection was employed and the field-of-view was 60 cm. The subject's left arm was positioned above the head for better accommodation within the bore of the MRI scanner. All imaging experiments were approved by the Human Research Committee at the Brigham and Women's Hospital.

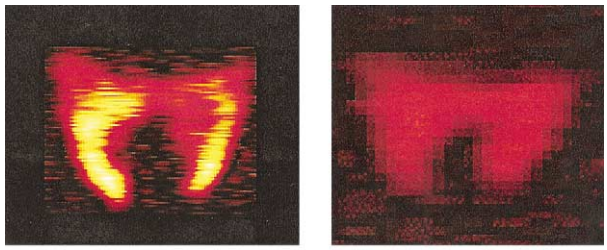

Fig. 1. Hyperpolarized (a) ^{3}He image and (b) ^{129}Xe image of the lungs in rats at very low magnetic field of B_0 = 15 mT.

3. Results

Fig. 1a depicts a gradient-echo hyperpolarized ^{3}He image of the lungs of a live rat shown in coronal view during a breath-hold. This is the first VLF hyperpolarized noble gas image of a living animal. The left and right lungs are clearly seen, the heart indicated by the expected signal void. Since there is no slice selection, the image intensity does not closely correspond to the gas density, but even so, the edges are rather well defined. These images were obtained by lowering the field of an obsolescent whole-body superconducting magnet from its normal value of 1.5 T, down to 15 mT while a resistive solenoid magnet of suitable field homogeneity is being built and tested. Fig. 1b displays a coronal view of the lungs from a rat breathing hyperpolarized ^{129}Xe. Although the image shows some lung structure and both lobes of the lung can clearly be seen, the signal-to-noise-ratio (SNR) is lower than in the ^{3}He image. In typical ^{129}Xe images the signal level is lower than in ^{3}He images, both because the gyromagnetic ratio of ^{129}Xe is 2.8 times smaller than that of ^{3}He, and because the attainable level of polarization is generally lower. The polarization levels of Fig. 1 were modest, about 5%, while levels of ~50% for ^{3}He and ~20% for ^{129}Xe are presently achievable. Finally, Fig. 2 shows the first human VLF hyperpolarized noble gas image, of the lungs of a healthy subject inhaling ^{3}He, demonstrating the potential of VLF HP gas MRI.

4. Discussion

In Fig. 2, while both lobes of the lung can be seen, the 10-inch diameter surface coil used for this image results in incomplete coverage of the lungs with an obvious lack of

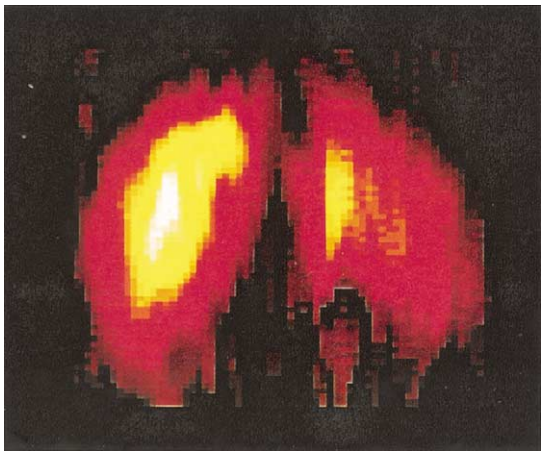

Fig. 2. Very low-field hyperpolarized ^{3}He image of the human lungs. The position of the subject, together with the presence of the heart, contributed to an asymmetric appearance of the lobes of the lung.

signal from the apex and base. This will be remedied by larger imaging coils in saddle and bird-cage geometries currently under construction. The mediocre SNR in Fig. 2 is a consequence of *i)* poorly shielded external noise and *ii)* the noise from the coil and front-end electronics. Shielding of low frequency electromagnetic interference is a major problem in VLF MR experiments [17]. The scanner used in these experiments has shielding and filters optimized to minimize interference at the 66 MHz resonance frequency of protons at 1.5 T—hence they are quite ineffective in the 100–500 kHz range in which the resonance frequencies of ^{129}Xe and ^{3}He lie at 15 mT. We have made first order corrections to improve shielding, by shifting the roll-off frequencies of the low-pass filters on the wires entering the room. The other major noise source is the RF pickup-coil and front end. This noise can be minimized, unlike the noise in high-field MRI, where the dominant source is the biologic sample, which cannot be significantly modified.

In conventional MR applications, the advantages in increasing the strength of the magnetic field, B_0, accrue from the consequent increase in equilibrium magnetization *and* the increase in the energy of the transition, resulting in the signal scaling as B_0^2. In MRI the two significant sources of noise are *i)* the biologic sample, and *ii)* the coil and associated circuitry. Coil noise *emf* goes as $\omega^{1/4}$ above ~1 MHz, due to the skin-depth effect, but this weak dependence can be ignored at our very low frequencies. The noise *emf* from the sample goes as ω (*i.e.*, as B_0) and dominates over the Johnson noise from the coil at high-field, especially for large, coil-filling samples [18]. Thus, in conventional MRI, in the sample- noise dominated high-field regime, the SNR goes as B_0, and in the coil-noise dominated low field regime, the SNR goes as B_0^2, ignoring the small skin-depth effect. This traditional analysis would indicate rather dismal prospects for conventional MRI at very low fields.

In HP gas MRI, however, the signal scales with B_0, and not B_0^2, since the polarization is determined by the hyperpolarization technique, and is therefore independent of the static magnetic field. Hence in combination with coil-noise, the SNR is independent of B_0 at high field, and scales simply with B_0 at low field. Since the SNR(*HP*)/SNR(*water*) ratio scales as $1/B_0$, HP gas MRI has a decisive advantage over conventional MRI at VLF. Wong *et al.* have argued that SNR(*HP*) can be four orders of magnitude greater than SNR(*water*) at 2 mT (20 G) [19]. Furthermore, since the source of noise at low field is the coil and associated electronics, cryogenic techniques can be used with profit. Superconducting coils with unloaded Q's of >50,000 [20] are an extravagance at high-field: especially with large coils and samples, the loading greatly reduces the Q, and, furthermore, the sample noise dominates. Sample noise and sample loading are almost negligible at VLF, especially with small coils. The use of high temperature superconducting (HTS) RF coils for small regions of interest can significantly improve the coil-noise limiting SNR. An increase in the SNR of MR images by a factor of 2 has been achieved at high-field (1.5 T), and by ~3.5 at low- and intermediate-field strengths (0.2 T and 0.5 T) [21]. At VLF, an improvement in the SNR by a factor >10 is not unreasonable, and can be used to improve speed and resolution. HTS material can nowadays be fashioned into coils operating at temperatures >77 K, cooled with liquid nitrogen or liquid helium evaporate. We are currently examining HTS coils for our next generation system.

HP ^{3}He MRI can visualize ventilation defects with a high sensitivity and is proving to be diagnostically useful in patients with various forms of pulmonary disease. ^{3}He MR spectroscopy, localized by means of surface RF coils or volume selective gradients, produces large signals at very low-field, making possible regional measurements of the ^{3}He longitudinal relaxation time, T_1, which can provide a local measure of the oxygen distribution in the lungs [22]. The solubility of ^{129}Xe in blood and tissue opens up the possibility of monitoring blood-flow and cardiac and brain function [1,12]. Thus both gases should find significant uses in VLF MRI.

MRI at VLF will have reduced imaging distortions and spectral line broadening caused by heterogeneous magnetic susceptibilities, which is particularly advantageous for MRI in heterogeneous samples such as the lung [23,24]. Another important benefit is the extended T_2*. We measured the T_2* to be ~100 ms for hyperpolarized gases in the lungs of living rats, similar to results reported in excised rat lungs [19]. Wong *et al.* and others have argued that the achievable imaging resolution for hyperpolarized gas imaging of the lung at VLF is limited by the diffusion of a gas, at both high and low-fields, to ~100 μm [19], adequate for most clinical studies. Finally, the relative field homogeneity requirements at VLF are less stringent because the image-encoding gradients (~1 Gauss/cm) are far greater in proportion to B_0 than they are at high-field. A high-field, high homogeneity magnet, together with its special site housing and shielding is expensive. Resistive wire-wound solenoid magnets can easily and inexpensively be built [19,25,26] to fields of

10–20 mT (100–200 Gauss), and sited near other equipment with little shielding.

5. Conclusions

We have presented the first *in vivo* VLF HP gas MRI images of the lung gas-space in humans and in rats breathing hyperpolarized ^{3}He and ^{129}Xe at a field of 150 Gauss (15 mT). While preliminary, the analysis of the SNR and techniques available provide a clear pathway to sufficient resolution and high SNR while maintaining the ease and portability of MR at very low static fields. We envision portable VLF HP gas MRI on van-based imagers, on space-based platforms, and at sufficiently low field, MRI may even be offered to patients with metallic prostheses or implanted electronic equipment (*e.g.*, pacemakers), who have hitherto been denied the benefits of this imaging modality.

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