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^{3}He diffusion MRI in human lungs

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ABSTRACT

Hyperpolarized ^{3}He gas allows the air spaces of the lungs to be imaged via MRI. Imaging of restricted diffusion is addressed here, which allows the microstructure of the lung to be characterized through the physical restrictions to gas diffusion presented by airway and alveolar walls in the lung. Measurements of the apparent diffusion coefficient (ADC) of ^{3}He at time scales of milliseconds and seconds are compared; measurement of acinar airway sizes by determination of the microscopic anisotropy of diffusion is discussed. This is where Dr. JJH Ackerman's influence was greatest in aiding the formation of the Washington University ^{3}He group, involving early a combination of physicists, radiologists, and surgeons, as the first applications of ^{3}He ADC were to COPD and its destruction/modification of lung microstructure via emphysema. The sensitivity of the method to early COPD is demonstrated, as is its validation by direct comparison to histology. More recently the method has been used broadly in adult and pediatric obstructive lung diseases, from severe asthma to cystic fibrosis to bronchopulmonary dysplasia, a result of premature birth. These applications of the technique are discussed briefly.

1. Introduction

The description of ^{3}He diffusion MRI presented here is narrowly focused on the developments at Washington University in St. Louis and at Cincinnati Children's Hospital, while trying to place these developments in the context of the larger work in the field. Of course, many researchers and many groups contributed (and continue today) to this exciting line of research, and this article is not intended to be a comprehensive review of the field, where many such reviews exist [1–7]. While the narrow focus of this manuscript is in part due to the fact that the authors know best this part of the ^{3}He MRI history, the more important reason for this focus is because the work in St. Louis was aided immensely by Prof. J.J.H. (Joe) Ackerman, in honor of whom this special issue of J. Magnetic Resonance is written.

Professor Ackerman was instrumental in creating the initial team of Dmitriy Yablonskiy, Brian Saam, and Mark Conradi. Joe went further, connecting the team of MR physicists to the medical team of Joel Cooper (lung surgeon) and Steve Lefrak (pulmonologist) and David Gierada (radiologist). This provided true multidisciplinarity, with a combination of skills and expertise that has been emulated by many groups and centers. Jason Woods quickly joined the effort, then as graduate student, and later as a postdoctoral fellow and professor, and now applies these techniques at a lung imaging center at Cincinnati Children's Hospital. This manuscript expresses our deep gratitude to Joe for helping to make this happen; his group was excellent at bridging the two cultures between medicine and basic science, and diffusion MRI was part of the daily regimen.

The early work of the multidisciplinary group at Washington University focused on chronic obstructive lung disease (COPD), because patients with COPD were expected to have much less restriction to gaseous diffusion as a result of tissue destruction in the lung, often known as emphysema [8,9]. After initial demonstration of larger ADC in COPD and of the large dynamic range of ^{3}He ADC in these patients [10,11], the interest in restricted diffusion significantly increased, as it seemed possible that imaging could be more sensitive to obstructive lung disease than any other research technique, and certainly more than any standard clinical exam like pulmonary function testing [12,13]. Importantly, this led our group and others to explore this sensitivity and potential for geometric modeling in great detail [14–18]. Twenty years later the collective body of work from the field includes demonstrations

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of exquisite sensitivity to early emphysematous changes in COPD [19–22], severity-related differences in childhood and adult asthma [23–25], a deeper understanding of alveolar recruitment in normal respiration [26], and geometric models of alveolar airspaces that match morphologic reality [16,27]. More recently, these same techniques are being applied to prematurely born infants, because of the underdeveloped and poorly-understood nature of their lung microstructure [28]. Older adults and premature infants, at opposite ends of life's spectrum, have lungs that are well probed by ^{3}He gas diffusion MRI.

2. Gas polarization, administration and imaging

2.1. Polarization of ^{3}He gas

A very practically-oriented discussion of polarizing ^{3}He by spin-exchange optical pumping of rubidium appeared early-on, with a "how to" slant [29]. The competing method involving optical pumping of helium atoms in the 2 s metastable state has not been as popular, in part because it must be performed at low pressures and requires a pump to reach useful pressures of a few bars; the pump must not de-polarize the gas [30,31].

Linearly polarized light at 794.7 nm at the level of ~50–100 W is obtained from a semiconductor diode laser array [32,33]. These remarkable devices have ~50% dc-to-light efficiencies and now significantly narrowed linewidths, due to wavelength-specific feedback [34]. The rather divergent light is collimated by cylindrical, converging lenses to approximately match the 4 cm diameter glass pumping cell. The light is converted to circular polarization by a quarter-wave plate and then reaches the cell.

The glass cell contains ~10 atm of ^{3}He with 1–2% of N_2 added as a buffer gas for collisional de-excitation of Rb [33]. A fraction of a gram of Rb metal is present in the cell; when heated to ~160 °C the vapor pressure of Rb is optimum at most laser powers. The 794.7 nm photons drive the Rb transition between the $5s_{1/2}$ ground state and the $5p_{1/2}$ first-excited state. In the presence of a weak (30 Gauss) field parallel to the optical axis, the Rb transitions obey selection rules of $\Delta m = +1$ or -1, depending on the right-vs-left hand circular polarization of the light [35].

For the $\Delta m = +1$ case, Rb atoms are driven out of the $m = -1/2$ sub-level of the ground-state. Half of these de-excite to the $m = +1/2$ sub-level, accomplishing *selective de-population*. The half that de-excite into the original $m = -1/2$ sub-level are simply returned to the excited state by subsequent resonant photons. The net result is that nearly all of the Rb atoms in the vapor are in their $m = +½$ sub-level of the ground state. Clearly, the electronic spins are far from thermal equilibrium.

The Rb atoms, even at the concentration of 10^{-6} (compared to ^{3}He atoms) *dominate* the ^{3}He relaxation. This is because monatomic ^{3}He has an extremely long T_1 in the absence of rubidium (almost always limited by wall relaxation with the walls of the glass cell), from 10 to 60 h [36]. Occasional Rb-^{3}He collisions result in spin exchange of the Rb electron spin and the ^{3}He nuclear spin. With typically a 6 h time constant, the ^{3}He nuclear spin polarization approaches its steady-state value of 30–55%. This is an example of the Overhauser effect, wherein electron spins far from equilibrium create a vastly enhanced nuclear spin polarization [37].

These large polarizations yield a ~10^5 increase in signal-to-noise ratio (S/N), compared with Boltzmann equilibrium in typical 1.5–3 T fields. This S/N increase more than compensates for the low density of a gas at atmospheric pressure, compared to the high density of proton spins in water in living subjects.

New developments in spin-exchange optical pumping include the use of line-narrowed diode laser arrays [38]. On their own, the diode laser arrays are "firehoses of infrared photons" (quote from Brian Saam) with spectra that are broad for a laser (~2–3 nm). With wavelength-selective feedback provided by an external grating or (better and more conveniently) a volumetric Bragg grating directly attached to the array, the laser runs with a much narrower optical spectrum (as small as 0.2 nm) [38]. The result is that a larger fraction of the photons are "on-resonance" with the Rb absorber atoms [34]. To say it differently, the typically 10 atm of ^{3}He gas does not provide adequate pressure broadening of the Rb absorption line, for the diode laser arrays without line-narrowing [33]; most of the photons pass through, unabsorbed. A second recent development is the use of double-alkali pumping [39]. One alkali metal atom absorbs the laser light and transfers its excitation to the other alkali, which eventually transfers the polarization to ^{3}He nuclear spins [40]. The idea is the first alkali is chosen for good optical absorption and the availability of lasers with the correct wavelength and the second alkali is selected for best transfer to the nuclear spins.

2.2. Delivery of gas to a typical patient

After sufficient polarization, the polarization cell is cooled to room temperature, where the Rb vapor condenses onto the glass cell walls. The 10 atm gas is released into a flexible bag (typically Tedlar material, for its polarization-friendly properties) and is walked to the patient [7]. After a tidal exhale, the patient inhales the ^{3}He and holds his or her breath and imaging commences. Sometimes the ^{3}He (typically 0.5 L STP) is used with added N_2 for a more comfortable breath hold [41]. Oxygen can be added, but this results in more rapid T_1 relaxation and destruction of the hyperpolarized ^{3}He magnetization. The relaxation rate from oxygen is approximately 0.5 s^{-1} per atmosphere of oxygen partial pressure [42]. Oxygen cannot be eliminated from patients' lungs of course (even after inert purge, O_2 passes back into the lungs from the blood); typically all MR imaging must be completed within about 20 s of introduction of ^{3}He into the lungs. On the other hand, when imaging explanted lungs, very long T_1 values can be had by excluding all oxygen [43–45].

2.3. Imaging with hyperpolarized ^{3}He

Imaging of the ^{3}He is often performed by FLASH (fast, low-angle shots), a gradient-recalled echo method [46–48]. For example, use of 10° rf pulses leaves 98.5% of the spin z-magnetization after each pulse. So, after 64 pulses (64 phase encode steps), 37% of M_z remains. Thus, most (but not all) of the M_z has been used to make the image. We note that small flip-angle sequences are generally not suitable for spin echo sequences, because of the cumulative effect on M_z of the large refocusing pulses. A side benefit of small-angle pulses is the small amount of rf energy deposited into the patient. A slightly more clever use of the nonrenewable (and progressively consumed) magnetization is by increasing flip angles as the polarization is consumed, thus allowing full use of the magnetization with closer to constant signal per rf pulse [49,50].

Others have used radial scanning of k-space, in two and three dimensions [51–53]. For example, the University of Virginia group showed excellent images obtained with spiral scanning of k-space acquired in such a way that sliding-window reconstructions (reconstructions of the dataset using only a few, new spirals in k-space for an updated image) provided exquisite apparent time resolution [54]. These non-Cartesian scans generally require careful adjustment, so the path through k-space matches that desired, but there clearly are benefits to the images in terms of time savings. As non-cartesian techniques gain popularity and are progressively more supported by the large MRI manufacturers, their full

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