Editorial

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Hyperpolarized Helium 3 Diffusion Imaging of the Lung[1]

Asthma and chronic obstructive pulmonary disease (COPD) constitute the two largest categories of airway disease, which generate an enormous burden of morbidity and mortality. There is strong evidence that the worldwide occurrence of asthma is increasing (1,2). In a recent review of global illness, COPD ranked 12th as a cause of lost quantity and quality of life and was projected to rank fifth by the year 2020 (3). Currently, COPD affects 4%–6% of adult Europeans (4) and results in approximately 90,000 deaths per year in the United States (5). The obstructive airway diseases cause nonspecific symptoms (cough, shortness of breath) and may be difficult to diagnose clinically. There are no reliable signs at physical examination. Thoracic imaging is often used to help determine the diagnosis and assess the effect of therapy. Although the obstruction of expiratory airflow is the hallmark signature of these diseases, this particular pathophysiologic abnormality results from both a loss of lung elastic recoil (emphysema) and airway narrowing secondary to inflammatory thickening, scarring, and mucous plugging. Computed tomography (CT) and, more recently, thin-section CT have become the imaging modalities of choice in the assessment of the extent and pattern of emphysema (6). Two approaches are possible to examine the airway component of these diseases: *(a)* direct imaging of the airway wall structure, which is best accomplished with thin-section CT (7), and *(b)* a functional estimate of airway narrowing assessed on the basis of the distribution of ventilation, which is currently studied with nuclear medicine techniques (8,9).

CT provides excellent anatomic imaging of central, segmental, and proximal subsegmental airways, which allows estimation of airway diameter and wall thickness (7). Unfortunately, the spatial resolution limitations of current CT scanners make direct visualization of more peripheral airways impossible. CT attenuation measurements permit the calculation of the air-to–soft-tissue ratio within peripheral lung tissue (10), which in turn provides indirect evidence of lung disease. As well, the addition of respiratory maneuvers (inspiratory or expiratory imaging) to CT acquisition protocols was shown to improve the detection of air trapping caused by airway disease (11). However, CT techniques that rely on the assessment of regional differences in lung attenuation as an indirect measure of airway disease have limited sensitivity to depict changes associated with mild COPD and may be inaccurate in the presence of pulmonary vascular disease (12).

Nuclear medicine images of regional ventilation can be produced with either radioactive noble gases (xenon 133, ^{127}Xe, or krypton 81) or technetium 99m–labeled aerosols (13). When these images are acquired by using controlled conditions, they can be used to help quantify regional lung ventilation. Nuclear medicine techniques provide a physiologic, rapid, relatively noninvasive assessment of regional ventilation, but the spatial resolution that can be achieved is limited.

Although minimally invasive, both CT and nuclear medicine techniques expose the patient to ionizing radiation, which limits their application in longitudinal studies. Long-term studies would be very useful in the assessment of the effect of new drug therapies designed to cure or reduce the progression of COPD. Laboratory pulmonary function testing is noninvasive, but it cannot help detection of localized ventilation abnormalities that are associated with early, potentially reversible COPD. For these reasons, there is great interest in the development and validation of techniques with no associated ionizing radiation exposure that are sensitive to regional changes in the structure and morphology of distal airways and alveoli.

Salerno et al, in this issue of *Radiology* (14), report a magnetic resonance (MR) imaging technique that is sensitive to changes in peripheral lung structure associated with emphysema. The ventilation imaging technique makes use of a chemically inert, nonradioactive, gaseous MR contrast agent: hyperpolarized helium 3 (^{3}He). This contrast agent has been used on an experimental basis for a number of years to provide both static and dynamic ventilation maps of inhaled gases in animals and humans (15–20).

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Unlike many previous applications of the technique, which were primarily sensitive to the density of the inhaled gas within the lung, the current study probes the ease with which ^{3}He gas was able to move about within the gas spaces of the lung during a breath hold. This was accomplished by adding additional magnetic field gradients (bipolar, pulsed) to the MR imaging sequence. These gradients sensitize the image to the apparent diffusion coefficient (ADC) of the ^{3}He atoms, which in turn reflects the geometry of the structures that compartmentalize the gas within the lung. Regions in which the diffusive motion of the gas is relatively unimpeded (eg, trachea, emphysematous bulla) during the measurement are characterized by a large ADC, whereas regions in which the motion of ^{3}He atoms is severely restricted by physical barriers (eg, alveolar ducts) are characterized by a smaller ADC. This type of measurement provides a unique noninvasive method to probe small lung structures. It is hoped that this type of measurement might be more sensitive than CT to airspace changes caused by COPD. In this editorial, we briefly describe the diffusion-imaging technique with hyperpolarized ^{3}He MR and discuss its potential application to airway and emphysema imaging.

Conventional MR images are derived from hydrogen atoms associated with water molecules in body tissues. An equilibrium polarization of the nuclei of these hydrogen atoms is established in vivo by applying a large, static external magnetic field. In general, the larger the external magnetic field, the greater the induced polarization and the better the signal-to-noise ratio of the detected MR signals. Conventional MR imagers with field strengths of a few Tesla typically give rise to thermal equilibrium nuclear polarizations that are on the order of a few parts per million. The improvement in signal-to-noise ratio with increased field strength leads to an enhancement of image quality in all parts of the body except air-inflated lung tissue. This exception is a consequence of the heterogeneous nature of the air–soft-tissue matrix in inflated lungs.

The relative difference between the magnetic susceptibility of the alveolar wall and that of the gas within the alveolar space is large (21). The effective magnetic field gradients that result from the spatial variation of the magnetic susceptibility can be enormous compared with typical applied imaging gradients: At 1.5 T, they can approach 1 T/m near the alveolar wall. These susceptibility-induced gradients markedly degrade the quality of MR images in air-inflated lungs. Since the magnitude of these gradients scales linearly with the applied magnetic field, some improvement in the quality of air-inflated lung images can be achieved by using lower magnetic field strengths.

In the presence of diffusion and perfusion, susceptibility-induced gradients cause a nonrecoverable dephasing of the signal from water molecules. This nonrecoverable dephasing is the origin of the very short T2* and T2 that are observed in the soft tissue of air-inflated lungs. Additionally, the density of water vapor within ventilating lung gases is very low; thus, negligible conventional hydrogen MR signal is obtained from gas spaces. In experimental animal studies, investigators have administered a nebulized mixture of mannitol, surface-active detergent, and gadolinium chelates to increase the signal intensity from the airspace (22). This ventilation mixture has been shown to produce a detectable signal within the alveolar airspace. However, this line of investigation has not been extended to studies in human subjects.

A radically different approach to ventilation imaging with MR was developed during the past 7 years by using the spin-½ noble gases ^{3}He and ^{129}Xe as MR contrast agents (15,19,23). These gases are inhaled as a bolus and imaged with conventional MR imagers tuned to the appropriate resonance (Larmor) frequency. The critical distinction between this technique and conventional MR techniques lies in the manner in which the nuclear polarization of the gaseous contrast agent is established. A laser is used to induce an extremely large nonequilibrium nuclear polarization in the noble gas atoms before they are administered to the subject. This hyperpolarized state can be maintained for hours when the gas is stored appropriately. The level of nuclear polarization that can be achieved with this nonequilibrium technique is more than 100,000 times the typical level of polarization that is produced with conventional equilibrium techniques. The resulting increase in signal strength is more than enough to compensate for the low density of the gas and allows direct visualization of the gas and its distribution in the lung (ventilation) by using MR techniques (24).

The nonequilibrium nature of hyperpolarized MR contrast agents imposes a unique set of constraints on the imaging environment. In particular, since the gases must be polarized ex vivo, there is a finite (ie, nonrenewable) nuclear magnetization associated with each bolus of gas that is introduced. Every MR tipping pulse consumes a fraction of this magnetization. At the same time, T1 relaxation processes (induced primarily by interactions with oxygen, which is a strongly paramagnetic molecule [25]) lead to a further depletion of the magnetization. Gradient-echo images are usually acquired by using low–flip-angle tipping pulses that make judicious use of the available magnetization. This produces serial images of regional ventilation with millimeter spatial resolution. Dynamic ventilation images of hyperpolarized ^{3}He gas have been produced in animals (26) and human subjects (15,16,18,27). By modifying the MR pulse sequence used to acquire the ^{3}He signal, however, additional unique and potentially clinically relevant parameters can be measured. Two such parameters that have recently received considerable attention are the ADC of the polarized gas within the lungs and the residual alveolar oxygen distribution.

The individual atoms or molecules of which a liquid or gas is composed are in constant random (ie, thermally excited) motion. Over time, it becomes less and less likely that a given atom or molecule will be found close to the location in space that it occupied at the start of any observation period. Conversely, the longer the observation period, the further the average distance traveled by the atom or molecule. This process of random displacement is known as translational diffusion and is characterized by a parameter referred to as a diffusion coefficient. The diffusion coefficient of a liquid or a gas can be measured with MR techniques by adding a pulsed field gradient to the MR pulse sequence. This procedure adds a "magnetic label" to each atom or molecule that effectively identifies its initial position in space. Later, during the readout phase of the MR sequence, the extent to which the atoms or molecules have moved influences the detected signal (28–30).

In a restricted geometry where the diffusive motion of atoms or molecules is impeded by physical boundaries (eg, alveolar and airway walls), the measured effective or apparent diffusion coefficient is suppressed relative to the free diffusion coefficient. The magnitude of the ADC that is measured depends on the time interval during which the molecules are allowed to diffuse (31). Detailed studies of time-dependent gas diffusion coefficients have been used to probe the microstructural properties of nonbiologic

porous media, including random packs of glass beads and oil reservoir rocks (32). In model systems, these studies can yield information ranging from surface area-to-volume ratios to quantitative measures of the long-distance heterogeneity (pore connectivity) of the medium (33). The study of Salerno et al (14) is one of a number of recent attempts to apply these sophisticated MR techniques to the study of human lungs (34,35).

Diffusion-weighted or sensitized MR sequences of varying degrees of complexity have been developed (36,37). Generally, these sequences can be broken down into three distinct components. Initially, a combination of pulsed field gradients and radio-frequency pulses is used to encode the nuclei with a spatially dependent phase. The nuclear spins are then allowed to evolve freely in their local environment for the duration of a storage interval. Finally, a decoding or read sequence of pulsed field gradients and radio-frequency pulses is used to generate and detect a spin echo. Translational diffusion of the spins during the storage period results in an incomplete refocusing of the spins or attenuation of the signal that is measured during the read phase. This attenuation depends exponentially on the product of the ADC and a gradient factor (often referred to as a *b* value) that depends in a nontrivial manner on the details of the particular imaging sequence. By adjusting the gradient strength, one can measure the signal intensity as a function of the gradient factor and extract a direct measurement of the ADC. More elaborate pulse sequences can be used to mitigate the effects of unwanted signal attenuation such as that caused by the diffusion of spins in susceptibility-induced field gradients (38) or to account for the nonrenewable magnetization characteristic of hyperpolarized gas applications (38,39).

Diffusion-weighted imaging was previously applied to conventional MR imaging sequences in the brain where it was shown to outline areas of acute ischemic injury in exquisite detail (40). The change in membrane permeability that accompanies acute brain ischemia can be probed by using MR sequences sensitive to water diffusion. In a similar fashion, Salerno et al (14) measured the ADC of hyperpolarized ^{3}He gas in the gas spaces of the lungs in healthy volunteers and patients with emphysema. In their study, they produced coronal ADC images in the lung by adding diffusion-encoding gradients in the readout superior-inferior direction of a fast low-angle shot, or FLASH, MR pulse sequence. Each ADC image was derived from two or more base images that were generated by using different gradient factors and were acquired during one breath hold. Four different gradient factors were used for 12 subjects, whereas two gradient factors (the minimum required) were used for the remaining 17 subjects, to permit greater anatomic coverage during the (limited) breath hold.

Salerno et al (14) observed that the mean ADC was significantly larger ($P < .002$) in patients with emphysema than in healthy volunteers, which is consistent with the enlargement of peripheral airspaces in these patients. Likewise, the SD of the ADCs was significantly larger ($P < .002$) in emphysema patients than in the volunteers, which suggests a greater regional variation of airspace sizes associated with the underlying disease. Patients with suspected centrilobular emphysema had significantly larger ($P < .002$) ADCs in the upper lung zone than in the lower lung zone. In contrast, the one patient in their study who had emphysema related to α-1–antitrypsin deficiency showed increased ADCs in the lower lung relative to those in the upper lung. The authors found good inverse correlation between the ADCs for all subjects and the corresponding indexes of pulmonary function, including both the percentage predicted forced expiratory volume in 1 second, or FEV_1, ($r = -0.797$, $P < .001$) and the ratio of forced expiratory volume in 1 second to forced vital capacity, or FEV_1/FVC, ($r = -0.930$, $P < .001$).

These data are encouraging in that they suggest that ADC measurements reflect the extent of airspace enlargement and wall destruction by emphysema. Moreover, the distribution of ADCs in the lung appears to be consistent with well-known patterns characteristic of the regional variation in emphysema: The extent of structural changes is greater in the upper lung zones.

Ultimately, there will be limitations on the information that can be derived from ADC measurements in human lungs. A full characterization of lung morphology based solely on gas diffusion data requires that the ADC is measured during a broad range of diffusion length scales. Constraints imposed by the maximum field gradients and gas pressures that can be safely applied in humans, as well as the limited duration of any breath-hold maneuver, will necessarily restrict the range of parameters that can be explored in vivo. Further complications are introduced by the simple fact that the rate at which gases diffuse within the lung is so rapid that individual atoms can move distances equivalent to several alveolar diameters even during the time interval when one MR gradient pulse is applied (33,41). It is clear that a broad range of research and validation efforts (35,42,43) are needed before quantitative interpretations of ADC data in terms of the underlying geometric structure of the human lung are possible.

ADC measurements such as those described by Salerno et al (14) represent only one of several emerging technologies with polarized noble gases that promise to yield important clinical information. For example, it was noted earlier that interactions between ^{3}He atoms and oxygen molecules represent an important mechanism for the destruction of the polarization of the ^{3}He gas (25). In fact, it is possible to correlate measurements of the rate at which the polarization of the gas is destroyed (T1 relaxation) with regional in vivo oxygen concentrations (44). This effect was exploited to provide noninvasive measurements of the intrapulmonary oxygen concentration in experimental animals (45,46) and humans (47). Ultimately, the measurement of other parameters of hyperpolarized noble gas, such as T2*, may yield additional probes of lung disease (48,49).

In summary, the use of hyperpolarized ^{3}He as an MR contrast agent shows promise for the quantification of at least three aspects of lung ventilation that cannot be assessed with conventional techniques. First, it provides a means of visualizing bulk ventilation in the lungs, which may be useful in the assessment of COPD. Second, on the basis of the ADC of polarized gases within the lung, it appears to be sensitive to changes in peripheral lung morphology. This enables noninvasive measurement of parameters that were previously unobtainable in vivo and may prove useful in the assessment of early emphysema. An additional advantage of this new technique over CT is the lack of exposure to ionizing radiation. In turn, this makes it possible to pursue longitudinal follow-up studies in patients. This may provide improved assessment of new therapies for COPD. Finally, on the basis of the relaxation rate (1/T1) of polarized gases within the lung, this technology can provide a measure of local alveolar oxygen concentrations. In conjunction with local perfusion information, these types of measurements may yield important information relative to the local ventilation perfusion relation-

ships within the lung. We believe that these and related techniques offer great potential to further our understanding of the structure and dynamic function of the lung.

References

1. Habbick BF, Pizzichini MM, Taylor B, Rennie D, Senthilselvan A, Sears MR. Prevalence of asthma, rhinitis and eczema among children in 2 Canadian cities: the International Study of Asthma and Allergies in Childhood. CMAJ 1999; 160:1824–1828.
2. Burney PGJ. Epidemiologic trends. In: Barnes P, Grunstein M, Leff A, Woolcock A, eds. Asthma. Philadelphia, Pa: Lippincott-Raven, 1997; 35–47.
3. Murray CJL, Lopez AD. Evidence-based health policy: lessons from the Global Burden of Disease Study. Science 1996; 274:740–743.
4. Gulsvik A. Mortality in a prevalence of chronic obstructive pulmonary disease in different parts of Europe. Monaldi Arch Chest Dis 1999; 54:160–162.
5. Wise RA. Changing smoking patterns and mortality from chronic obstructive pulmonary disease. Prev Med 1997; 26:418–421.
6. Cleverley JR, Müller NL. Advances in radiologic assessment of chronic obstructive pulmonary disease. Clin Chest Med 2000; 21:653–663.
7. King GG, Müller NL, Paré PD. Evaluation of airways in obstructive pulmonary disease using high-resolution computed tomography. Am J Respir Crit Care Med 1999; 159:992–1004.
8. King GG, Eberl S, Salome CM, Young IH, Woolcock AJ. Differences in airway closure between normal and asthmatic subjects measured with single-photon emission computed tomography and technegas. Am J Respir Crit Care Med 1998; 158:1900–1906.
9. King GG, Eberl S, Salome CM, Meikle SR, Woolcock AJ. Airway closure measured by a technegas bolus and SPECT. Am J Respir Crit Care Med 1997; 155:682–688.
10. Coxson HO, Hogg JC, Mayo JR, et al. Measurement of lung structure in idiopathic pulmonary fibrosis using computed tomography and quantitative histology. Am J Respir Crit Care Med 1997; 155:1649–1656.
11. Stern EJ, Swensen SJ, Hartman TE, Frank MS. CT mosaic pattern of lung attenuation: distinguishing different causes. AJR Am J Roentgenol 1995; 165:813–816.
12. Worthy SA, Müller NL, Hartman TE, Swensen SJ, Padley SP, Hansell DM. Mosaic attenuation pattern on thin-section CT scans of the lung: differentiation among infiltrative lung, airway, and vascular diseases as a cause. Radiology 1997; 205:465–470.
13. Parker JA, Coleman RE, Siegel BA, Sostman HD, McKusick KA, Royal HD. Procedure guideline for lung scintigraphy. J Nucl Med 1996; 37:1906–1910.
14. Salerno M, de Lange EE, Altes TA, Truwit JD, Brookeman JR, Mugler JP III. Emphysema: hyperpolarized helium 3 diffusion MR imaging of the lungs compared with spirometric indexes—initial experience. Radiology 2001; 22:252–260.
15. Kauczor HU, Hofmann D, Kreitner KF, et al. Normal and abnormal pulmonary ventilation: visualization at hyperpolarized He-3 MR imaging. Radiology 1996; 201:564–568.
16. MacFall JR, Charles HC, Black RD, et al. Human lung airspaces: potential for MR imaging with hyperpolarized He-3. Radiology 1996; 200:553–558.
17. Kauczor HU, Ebert M, Kreitner KF, et al. Imaging of the lungs using helium-3 MRI: preliminary clinical experience in 18 patients with and without lung disease. Magn Reson Imaging 1997; 7:538–543.
18. McAdams HP, Palmer SM, Donnelly LF, Charles HC, Tapson VF, MacFall J. Hyperpolarized 3He-enhanced MR imaging of lung transplant recipients: preliminary results. AJR Am J Roentgenol 1999; 173: 955–959.
19. Kauczor HU, Chen XJ, van Beek EJR, Schreiber WG. Pulmonary ventilation imaged by magnetic resonance: at the doorstep of clinical application. Eur Respir J 2001; 17:1008–1023.
20. Altes TA, Powers PL, Knight-Scott J, et al. Hyperpolarized 3He MR lung ventilation in asthmatics: preliminary findings. Magn Reson Imaging 2001; 13:378–384.
21. Mayo J. MR imaging of pulmonary parenchyma. Magn Reson Imaging Clin N Am 2000; 8:105–123.
22. Berthezene Y, Vexler V, Clement O, Muhler A, Moseley ME, Brasch RC. Contrast-enhanced MR imaging of the lung: assessments of ventilation and perfusion. Radiology 1992; 183:667–672.
23. Albert MS, Cates GD, Driehuys B, et al. Biological magnetic resonance imaging using laser-polarized 129Xe. Nature 1994; 370:199–201.
24. Swanson S, Rosen M, Coulter K, Welsh R, Chupp T. Distribution and dynamics of laser-polarized 129Xe magnetization in vivo. Magn Reson Med 1999; 42:1137–1145.
25. Saam B, Happer W, Middleton H. Nuclear relaxation of 3He in the presence of oxygen. Phys Rev A 1995; 52:852–865.
26. Black RD, Middleton HL, Cates GD, et al. In vivo He-3 MR images of guinea pig lungs. Radiology 1996; 199:867–870.
27. Girerada DS, Saam B, Yablonskiy DA, Cooper JD, LeFrak S, Conradi MS. Dynamic EPI of lung ventilation with hyperpolarized helium-3 in normal subjects and patients with severe emphysema. NMR Biomed 2000; 13:176–181.
28. Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. Phys Rev 1954; 94:630–638.
29. Stejskal EO, Tanner JE. Spin diffusion measurements: spin-echoes in the presence of a time-dependent field gradient. J Chem Phys 1965; 42:288–292.
30. Callaghan PT. Principles of nuclear magnetic resonance microscopy. Oxford, England: Oxford University Press, 1991.
31. Woessner E. NMR spin-echo self-diffusion measurements on fluids undergoing restricted diffusion. J Phys Chem 1963; 67:1365–1367.
32. Mair RW, Wong GP, Hoffmann D, et al. Probing porous media with gas diffusion NMR. Phys Rev Lett 1999; 83:3324–3327.
33. Mair RW, Hürlimann MD, Sen PN, Schwartz LM, Patz S, Walsworth RL. Tortuosity measurement and the effects of finite pulse widths on xenon gas diffusion NMR studies of porous media. Magn Reson Imaging 2001; 19:345–351.
34. Saam BT, Yablonskiy DA, Kodibagkar VD, et al. MR imaging of diffusion of He-3 gas in healthy and diseased lungs. Magn Reson Med 2000; 44:174–179.
35. Durand E, Guillot G, Darrasse L, et al. CPMG measurements and ultrafast imaging in human lungs with hyperpolarized helium-3 at low field (0.1 T). Magn Reson Med (in press).
36. Latour LL, Li L, Sotak CH. Improved PFG stimulated-echo method for the measurement of diffusion in inhomogeneous fields. J Magn Reson 1993; 101:72–77.
37. Cotts RM, Hoch MJR, Sun T, Markert JT. Pulsed field gradient stimulated echo methods for improved NMR diffusion measurements in heterogeneous systems. J Magn Reson 1989; 83:252–266.
38. Mair RW, Cory DG, Peled S, Tseng CH, Patz S, Walsworth RL. Pulsed-field-gradient measurements of time-dependent gas diffusion. J Magn Reson 1998; 135:478–486.
39. Patyal BR, Gao JH, Williams RF, et al. Longitudinal relaxation and diffusion measurements using magnetic resonance signals from laser-hyperpolarized 129Xe nuclei. J Magn Reson 1997; 126:58–65.
40. Le Bihan D. Diffusion and perfusion magnetic resonance imaging: applications to functional MRI. New York, NY: Raven, 1995.
41. Mair RW, Hoffmann D, Sheth SA, et al. Reduced xenon diffusion for quantitative lung study: the role of SF6. NMR Biomed 2000; 13:229–233.
42. Chen XJ, Möller HE, Chawla MS, Driehuys B, Hedlund LW, Johnson GA. Spatially resolved measurements of hyperpolarized gas properties in the lung in vivo. I. Diffusion coefficient. Magn Reson Med 1999; 42:721–728.
43. Chen XJ, Hedlund LW, Moller HE, Chawla MS, Maronpot RR, Johnson GA. Detection of emphysema in rat lungs by using magnetic resonance measurements of 3He diffusion. Proc Natl Acad Sci U S A 2000; 97:11478–11481.
44. Eberle B, Weiler N, Markstaller K, et al. Analysis of intrapulmonary O2 concentration by MR imaging of inhaled hyperpolarized helium-3. J Appl Physiol 1999; 87:2043–2052.
45. Eberle B, Weiler N, Markstaller K, et al. Analysis of regional intrapulmonary O2-concentrations by magnetic resonance imaging of inhaled hyperpolarized helium-3. J Appl Physiol 1999; 87:2043–2052.
46. Deninger A, Eberle B, Ebert M, et al. Quantification of regional intrapulmonary oxygen partial pressure evolution during apnea by 3He-MRI. J Magn Reson 1999; 141:207–216.
47. Deninger AJ, Eberle B, Ebert M, et al. 3He-MRI-based measurements of intrapulmonary pO2 and its time course during apnea in healthy volunteers: first results, reproducibility, and technical limitations. NMR Biomed 2000; 13:194–201.
48. Chen XJ, Möller HE, Chawla MS, et al. Spatially resolved measurements of hyperpolarized gas properties in the lung in vivo. II. T2*. Magn Reson Med 1999; 42:729–737.
49. Darrasse L, Guillot G, Nacher PJ, Tastevin G. Low-field 3He nuclear magnetic resonance in human lungs. C R Acad Sci Paris 1997; 324(IIb):691–700.