# Hyperpolarized ³He MR Imaging:
## Physiologic Monitoring Observations and Safety Considerations in 100 Consecutive Subjects[1]

Barbara A. Lutey, MD
Stephen S. Lefrak, MD
Jason C. Woods, PhD
Tariq Tanoli, MD
James D. Quirk, PhD
Adil Bashir, PhD
Dmitriy A. Yablonskiy, PhD
Mark S. Conradi, PhD
Seth T. Bartel, MS
Thomas K. Pilgram, PhD
Joel D. Cooper, MD
David S. Gierada, MD

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**Purpose:** To evaluate the safety of hyperpolarized helium 3 (³He) magnetic resonance (MR) imaging.

**Materials and Methods:** Local institutional review board approval and informed consent were obtained. Physiologic monitoring data were obtained before, during, and after hyperpolarized ³He MR imaging in 100 consecutive subjects (57 men, 43 women; mean age, 52 years ± 14 [standard deviation]). The subjects inhaled 1–3 L of a gas mixture containing 300–500 mL ³He and 0–2700 mL $N_2$ and held their breath for up to 15 seconds during MR imaging. Heart rate and rhythm and oxygen saturation of hemoglobin as measured by pulse oximetry ($SpO_2$) were monitored continuously throughout each study. The effects of ³He MR imaging on vital signs and $SpO_2$ and the relationship between pulmonary function, number of doses, and clinical classification (healthy volunteers, patients with asthma, heavy smokers, patients undergoing lung volume reduction surgery for severe emphysema, and patients with lung cancer) and the lowest observed $SpO_2$ were assessed. Any subjective symptoms were noted.

**Results:** Except for a small postimaging decrease in mean heart rate (from 78 beats per minute ± 13 to 73 beats per minute ± 11, $P < .001$), there was no effect on vital signs. A mean transient decrease in $SpO_2$ of 4% ± 3 was observed during the first minute after gas inhalation ($P < .001$) in 77 subjects who inhaled a dose of 1 L for 10 seconds or less, reaching a nadir of less than 90% at least once in 20 subjects and of less than 85% in four subjects. There was no correlation between the lowest $SpO_2$ and pulmonary function parameters other than baseline $SpO_2$ ($r = 0.36$, $P = .001$). The lowest mean $SpO_2$ varied by 1% between the first and second and second and third doses ($P < .001$) and was unrelated to clinical classification ($P = .40$). Minor subjective symptoms were noted by 10 subjects. No serious adverse events occurred.

**Conclusion:** Hyperpolarized ³He MR imaging can be safely performed in healthy subjects, heavy smokers, and those with severe obstructive airflow limitation, although unpredictable transient desaturation suggests that potential subjects should be carefully screened for comorbidities.

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Magnetic resonance (MR) imaging of hyperpolarized helium 3 (³He) gas in the lungs can be used to evaluate the spatial and temporal distribution of ventilation, quantitatively assess air space size, and determine regional oxygen partial pressure in the lungs (1). Investigational and potential clinical uses of ³He MR imaging have included the characterization of lung microstructure (2,3), assessment of age-related changes in air space size (4–6), early detection and quantification of emphysema (7–11), evaluation of ventilation abnormalities in patients with asthma (12,13) and cystic fibrosis (14,15), and noninvasive early detection of chronic rejection in lung transplant recipients (16,17). Although inhalation of hyperpolarized ³He gas is generally considered to be safe, it is classified as an investigational contrast agent by the U.S. Food and Drug Administration and is not approved for clinical use. Despite this factor, potential safety concerns have received limited attention (18–20). Thus, our purpose in this study was to evaluate the safety of investigational ³He MR imaging by retrospectively analyzing the monitoring data collected in all subjects who underwent the procedure at our institution during the period of 2000–2006.

## Materials and Methods

### Subjects

³He MR imaging was performed under an Investigational New Drug exemption from the U.S. Food and Drug Administration (Investigational New Drug authorization no. 59, 269). Local institutional review board approval was obtained for all ³He MR imaging studies, and written informed consent specific to ³He MR imaging was obtained from all subjects. Health Insurance Portability and Accountability Act guidelines were followed. A commercial polarizer, loaned by GE Healthcare (Princeton, NJ), was used to prepare gas for some of the studies. The authors had control of the data and the information submitted for publication.

Safety monitoring data for the 100 consecutive individuals who had undergone investigational ³He MR imaging during the period 2000–2006 were retrospectively reviewed. The subjects comprised six distinct groups (Table 1): Healthy subjects were primarily members and contacts of the research team with no reported history of or symptoms of lung disease. Subjects with asthma were recruited for investigational ³He MR studies from the outpatient clinics of our institution by physicians specializing in asthma. Heavy smokers were participants in the National Lung Screening Trial (21) (*http://www.cancer.gov/NLST*), in which mortality rates of participants screened for lung cancer with either low-radiation-dose chest computed tomography (CT) or chest radiography are compared. The heavy smokers in our study had expressed interest in volunteering for a ³He MR imaging investigation un-

related to the National Lung Screening Trial at the time of their last of three annual screening CT examinations and had no coronary artery calcifications or CT findings requiring further evaluation. Requirements for National Lung Screening Trial enrollment included a smoking history of at least 30 pack-years and age of 55–74 years. Lung volume reduction surgery (LVRS) patients underwent investigational ³He MR imaging during their evaluation for LVRS for advanced emphysema. Some LVRS subjects also returned for ³He MR imaging at the time of their 6- or 12-month postoperative clinical evaluation. One patient with lung cancer underwent investigational ³He MR imaging before undergoing upper lobectomy of the right lung.

Most subjects had normal pulmonary function test results, but approximately one-third (the LVRS subjects) had advanced obstructive lung disease (Table 1). Twelve subjects, all belonging to the LVRS group, were receiving ambulatory supplemental oxygen. Because of the potential for transient hypoxia from inhalation of anoxic gases, exclusion criteria included persons who were clinically known to have or who were suspected of having cardiac or cerebrovascular disease and anemia and those

### Advances in Knowledge

- There were no clinically important effects of ³He MR imaging on vital signs.
- A mean transient oxyhemoglobin desaturation of 4% occurred when 1-L doses were inhaled for 10 seconds or less, with a nadir of less than 90% saturation after at least one dose in 26% of subjects and a nadir of 81%–84% after at least one dose in 5% of subjects.
- Baseline oxyhemoglobin saturation, pulmonary function tests, clinical status, or number of doses administered do not appear to be of practical value in predicting individual desaturation.

### Implications for Patient Care

- Potential subjects for ³He MR imaging should be carefully screened for conditions in which even transient oxyhemoglobin desaturation would be inadvisable.
- Oxygen saturation of hemoglobin as measured by pulse oximetry should be monitored during ³He MR imaging.

who were known to be or who were suspected of being pregnant.

## Hyperpolarized $^3$He MR Imaging Procedures

The $^3$He (Spectra Gases, Branchburg, NJ) was hyperpolarized with spin-exchange optical pumping (22) by using a custom-built laser apparatus or the commercial polarizer. MR imaging was conducted with the patient in the supine position by using a 1.5-T unit (Magnetom Vision or Sonata; Siemens, Erlangen, Germany) with custom-built radiofrequency coils positioned against the anterior and posterior chest wall. Conventional proton T1-weighted gradient-echo scout MR images were obtained first, while subjects held their breath with room air for the same period as or longer than the subsequent $^3$He MR imaging. For $^3$He imaging, a mouthpiece attached to a flexible ventilator tube (length, 30.5 cm; inner diameter, 2.54 cm; approximate volume, 150 mL) was inserted into the subject's mouth. Nose clips were applied to prevent mixing of room air oxygen with the hyperpolarized $^3$He gas, which would reduce the polarization and decrease image quality, during inhalation (23).

Before inhaling each dose, subjects exhaled to approximate functional residual capacity. A sealed polyethylene bag containing approximately 300–500 mL $^3$He at 20%–40% polarization and 0–2700 mL $N_2$ was then connected to the flexible tube through which the subject inhaled. The 23 subjects studied through July 2001 inhaled to approximate total lung capacity and were administered up to 3 L of gas. For the next 77 subjects, studied from August 2001 through the end of 2006, a standard inhaled dose of 1 L (300–500 mL $^3$He) was adopted. Imaging commenced with the start of the breath hold, which was limited to 15 seconds or less. Subjects who required supplemental oxygen at rest breathed room air immediately before inhaling the $^3$He-$N_2$ mixture, and supplemental $O_2$ delivery was resumed after the $^3$He-$N_2$ mixture was exhaled.

## Subject Monitoring

The physiologic parameters measured and monitored were selected to help characterize baseline lung function, identify any effects of the overall $^3$He MR imaging procedure on basic cardiopulmonary vital signs, and assess the risks specific to inhalation of the anoxic gas mixture. Because helium is an inert simple asphyxiant with negligible solubility in water (24) and fat (25) and is used as a diluent for oxygen in deep sea diving and in the treatment of selected patients with upper airway obstruction and severe pulmonary disease (26), biochemical effects on blood chemistry and urinalysis were not expected or assessed.

## Pre- and Postimaging Assessment

Pulmonary function test data were obtained before imaging in all subjects except those from the healthy group. As a surrogate functional assessment, the healthy subjects underwent a 6-minute walk test (27) before imaging to identify anyone with relatively advanced but undiagnosed lung disease who may have been unknowingly susceptible to desaturation. None were identified. Before placing the subject in the MR unit, the monitoring physician measured the subject's heart rate, blood pressure, respiratory rate,

**Clinical Data in Subjects**

| Data | Healthy Subjects | Subjects with Asthma | Heavy Smokers | Subjects with Lung Cancer | Subjects Before LVRS | Subjects After LVRS | All Subjects |
|---|---|---|---|---|---|---|---|
| No. of subjects | 20 | 7 | 35 | 1 | 27 | 10 | 100 |
| No. of men | 11 | 3 | 17 | 0 | 18 | 8 | 57 |
| No. of women | 9 | 4 | 18 | 1 | 9 | 2 | 43 |
| Age (y) | 32 ± 9 | 45 ± 12 | 61 ± 3 | 60 | 59 ± 9 | 58 ± 8 | 52 ± 14 |
| &lt;40 | 16 | 3 | 0 | 0 | 1 | 1 | 21 |
| 40–59 | 4 | 3 | 14 | 0 | 15 | 4 | 40 |
| ≥60 | 0 | 1 | 21 | 1 | 11 | 5 | 39 |
| Pack-years of smoking | 7 ± 11 | 0 | 47 ± 21 | 16 | 56 ± 29 | 57 ± 29 | |
| Smoking status | | | | | | | |
| Never smoked | 9 | 7 | 0 | 0 | 0 | 0 | 16 |
| Former smoker | 11 | 0 | 23 | 0 | 27 | 10 | 71 |
| Current smoker | 0 | 0 | 12 | 1 | 0 | 0 | 13 |
| $FEV_1$ (percent predicted) | NR | 78 ± 20 | 91 ± 14 | 109 | 31 ± 12 | 46 ± 10 | ... |
| $FEV_1$/FVC ratio (percent predicted) | NR | 72 ± 13 | 90 ± 9 | 100 | 44 ± 13 | 50 ± 11 | ... |
| RV (percent predicted) | NR | 113 ± 27 | 120 ± 31 | 156 | 284 ± 61 | 202 ± 58 | ... |
| TLC (percent predicted) | NR | 91 ± 6 | 109 ± 13 | 146 | 142 ± 22 | 126 ± 24 | ... |
| $D_{LCO}$ uncorrected for hemoglobin (percent predicted) | NR | NR | 76 ± 16 | 52 | 38 ± 14 | 46 ± 13 | ... |

Note.—Values for nominal variables are frequencies; values for continuous variables are given as the mean ± standard deviation. $D_{LCO}$ = diffusing capacity of the lung for carbon monoxide, $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, NR = not recorded, RV = residual volume, TLC = total lung capacity.

and oxygen saturation of hemoglobin as measured by pulse oximetry (SpO$_2$) and reviewed a lead II electrocardiographic rhythm strip. These parameters were reassessed immediately after the imaging session was completed, and any symptoms were addressed. All subjects were contacted by telephone the following day (no later than 24 hours later) and asked to report any unusual symptoms or adverse events.

### Subject Monitoring during Imaging

While the subject was in the imaging unit, a monitoring device (3150 MRI Physiologic Monitor; Invivo Research, Orlando, Fla) continuously displayed the subject's heart rate, lead II electrocardiographic rhythm strip, and SpO$_2$ for the physician monitoring the study. When the patient inhaled each dose of the $^3$He-N$_2$ mixture, the monitoring physician recorded the

nadir SpO$_2$ and the elapsed time after the commencement of the breath hold at which the nadir occurred (desaturation time). The elapsed time from the commencement of the breath hold until the return of the SpO$_2$ back to baseline (recovery time) also was recorded.

### Statistical Analysis

Values are presented as the mean ± standard deviation. Pre- and postimaging physiologic parameters were compared by using two-tailed paired $t$ tests. The relationship between the lowest SpO$_2$ observed after each subject's first dose to multiple physiologic parameters including baseline SpO$_2$, spirometry, lung volumes, and diffusing capacity of lung for carbon monoxide was evaluated with the Pearson product moment correlation. Differences in lowest SpO$_2$ for the first in-

haled dose among the six investigational groups were tested for significance with analysis of variance. The effect of the first three doses was tested with repeated-measures analysis of variance. Differences with a $P$ value of less than .05 were considered significant.

### Results

No change in SpO$_2$ was seen from breath holding with room air during proton MR scout imaging. When data from all 100 subjects were combined, a mean decrease in heart rate of 5 beats per minute was found at the postimaging assessment compared with the preimaging assessment ($P < .001$) (Table 2). No change in heart rate, however, was seen in the healthy subject group. There was no change in mean blood pressure, respiratory rate, electrocardiographic rhythm, or SpO$_2$ in any of the groups at the postimaging assessment.

All subjects but one received more than one dose of the $^3$He-N$_2$ mixture (mean, 2.92 doses per subject ± 0.69; range, 1–6 doses). Of the 292 total doses, 216 (73.9%) were administered at a volume of 1 L for a breath-hold time of 10 seconds or less (range, 5–10 seconds), 31 (10.6%) were administered at a volume of more than 1 L (maximum, 3 L) for 10 seconds or less (range, 7–10 seconds), seven (2.4%) were administered at a volume of 1 L or less (minimum, 0.4 L) for more than 10 seconds (range, 11–15 seconds), and seven (2.4%) were administered at a volume of more than 1 L (maximum, 3 L) for more than 10 seconds (range, 11–15 seconds). For the remaining 11 doses (3.8%), imaging was performed continuously during inhalation and exhalation, without breath holding. Dose data were incomplete for 20 (6.9%) doses in 16 subjects.

A total of 77 subjects inhaled the 216 doses of 1 L for 10 seconds or less. The nadir SpO$_2$ remained at least 90% for 84% of these 216 doses (Table 3) and for all doses in 57 (74%) of these 77 subjects. In the other 20 subjects (26%), the nadir SpO$_2$ decreased to less than 90% for at least one dose. The

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**Vital Signs and Values from Pulse Oximetry at Baseline and after Imaging in 100 Subjects**

| Parameter | Baseline | After Imaging | Change |
|---|---|---|---|
| Systolic blood pressure (mm Hg) ($n = 90$) | 125 ± 15 (90–174) | 126 ± 15 (101–163) | 1 ± 12 (−51 to 47) |
| Diastolic blood pressure (mm Hg) ($n = 89$) | 78 ± 9 (50–99) | 77 ± 11 (48–105) | 0 ± 9 (−27 to 28) |
| Heart rate (beats/min) ($n = 99$) | 78 ± 13 (48–110) | 73 ± 11 (48–102)* | −5 ± 9 (−33 to 19) |
| Respiratory rate (breaths/min) ($n = 97$) | 15 ± 5 (8–36) | 15 ± 5 (8–54) | 0 ± 4 (−10 to 18) |
| SpO$_2$ (%) ($n = 99$) | 97 ± 2 (93–99) | 97 ± 2 (92–99) | 0 ± 2 (−4 to 6) |

Note.—Data are the mean ± standard deviation. Numbers in parentheses are the ranges. Measurements of some parameters were not obtained in some subjects; those in whom both baseline and postimaging measurements were obtained are shown.

* $P < .001$ compared with baseline (two-tailed paired $t$ test).

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**Frequency of Desaturation Levels with 216 Doses of Inhaled Gas Volume of 1 L and a Breath Hold of 10 Seconds or Less in 77 Subjects**

| Minimum SpO$_2$ (%) | Healthy Subjects | Subjects with Asthma | Heavy Smokers | Subjects with Lung Cancer | Subjects Before LVRS | Subjects After LVRS | All Subjects |
|---|---|---|---|---|---|---|---|
| ≥95 | 8/27 (30) | 0/13 (0) | 36/109 (33) | 0/3 (0) | 12/45 (27) | 5/19 (26) | 61/216 (28) |
| 90–94 | 12/27 (44) | 6/13 (46) | 61/109 (56) | 3/3 (100) | 28/45 (62) | 10/19 (53) | 120/216 (56) |
| 85–89 | 6/27 (22) | 6/13 (46) | 11/109 (10) | 0/3 (0) | 5/45 (11) | 3/19 (16) | 31/216 (14) |
| 81–85 | 1/27 (4) | 1/13 (8) | 1/109 (1) | 0/3 (0) | 0/45 (0) | 1/19 (5) | 4/216 (2) |

Note.—Values are fraction of doses associated with each minimum SpO$_2$ range. Numbers in parentheses are percentages.

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**Baseline and Nadir Sp$o_2$ for Inhaled Gas Volume of 1 L and Breath Hold of 10 Seconds or Less**

| Group | Baseline Sp$o_2$ (%) | Nadir Sp$o_2$ (%) | Desaturation Time (sec)* | Change from Baseline | Recovery Sp$o_2$ (%) | Recovery Time (sec)[†] |
|---|---|---|---|---|---|---|
| Normal; 10 subjects, 27 doses | 97 ± 2 | 92 ± 4[‡] | 46 ± 11 (23 doses) | −5 ± 4 | 97 ± 2 (18 doses) | 65 ± 17 (15 doses) |
| Asthma; 4 subjects, 13 doses | 95 ± 1 | 89 ± 3[‡] | 39 ± 6 (12 doses) | −6 ± 3 | 95 ± 1 (11 doses) | 57 ± 4 (4 doses) |
| Heavy smokers; 35 subjects, 109 doses | 96 ± 2 | 93 ± 3[§] | 32 ± 8 | −3 ± 3 | 97 ± 2 | 48 ± 8 |
| Cancer; 1 subject, 3 doses | 98 ± 0 | 92 ± 1 | 27 ± 2 | −6 ± 1 | 96 ± 1 | 45 ± 4 |
| Before LVRS; 18 subjects, 45 doses | 97 ± 2 | 93 ± 3[‡] | 44 ± 18 (33 doses) | −4 ± 3 | 96 ± 2 (31 doses) | 66 ± 22 (25 doses) |
| After LVRS; 9 subjects, 19 doses | 96 ± 2 | 92 ± 4[‡] | 41 ± 19 (17 doses) | −4 ± 4 | 96 ± 2 (11 doses) | 59 ± 10 (9 doses) |
| All subjects; 77 subjects, 216 doses | 96 ± 2 | 93 ± 3[‡] | 37 ± 13 (196 doses) | −4 ± 3 | 96 ± 2 (183 doses) | 53 ± 15 (165 doses) |

Note.—Values are the mean ± standard deviation. Where complete data were not available for each dose, the number of doses is shown in parentheses.

* Desaturation time was the time elapsed from the start of imaging to the nadir Sp$o_2$.

[†] Recovery time was the time elapsed from the start of imaging until the return of Sp$o_2$ to the baseline level.

[‡] $P < .001$, compared with baseline Sp$o_2$ (two-tailed paired $t$ test).

[§] $P < .05$, compared with baseline Sp$o_2$ (two-tailed paired $t$ test).

nadir was less than 85% in four (5%) of the 77 subjects and was as low as 81% in one subject, 83% in two subjects, and 84% in one subject and was less than 90% for all doses in four subjects.

For the 77 subjects who inhaled a 1-L dose for 10 seconds or less, the nadir Sp$o_2$ after the first dose correlated only weakly with the baseline Sp$o_2$ ($r = 0.36$, $P = .001$). For 67 of these subjects who underwent pulmonary function testing (four with asthma, 35 heavy smokers, 18 before LVRS, nine after LVRS, and one with lung cancer), the correlations with the first-dose nadir Sp$o_2$ were low ($r = -0.21$ to $0.15$, $P = .1–.91$) for all parameters tested, which included the percent predicted values for forced expiratory volume in one second, forced vital capacity, ratio of forced expiratory volume in 1 second to forced vital capacity, residual volume, total lung capacity, ratio of residual volume to total lung capacity, diffusing capacity of the lung for carbon monoxide, alveolar volume, and diffusing capacity of the lung for carbon monoxide corrected for alveolar volume. No significant difference in the first-dose nadir Sp$o_2$ of the six different investigational groups was seen ($P = .4$, analysis of variance).

Transient desaturation from baseline by an absolute amount of 3% or greater during the 1st minute after $^3$He-$N_2$ inhalation was observed in 130 (60%) of 216 1-L doses administered for a breath hold

**Summary of Symptoms That Occurred during or after $^3$He MR Imaging**

| Symptom | Healthy Subjects | Subjects with Asthma | Subjects before LVRS | Subjects after LVRS | Total |
|---|---|---|---|---|---|
| Lightheadedness | 2 | 2 | 1 | 0 | 5 |
| Mild headache | 2 | 0 | 0 | 0 | 2 |
| Cough | 0 | 0 | 1 | 0 | 1 |
| Mild dyspnea | 0 | 1 | 0 | 0 | 1 |
| Chest tightness | 0 | 1 | 0 | 0 | 1 |
| Chest heaviness | 0 | 0 | 0 | 1 | 1 |
| Nausea | 0 | 0 | 1 | 0 | 1 |
| Sore shoulders | 0 | 0 | 1 | 0 | 1 |
| Sweaty palms | 0 | 0 | 1 | 0 | 1 |
| Epigastric discomfort* | 0 | 0 | 1 | 0 | 1 |

Note.—Symptoms were reported by 10 subjects; three subjects reported more than one symptom.

* Reported at telephone follow-up on the following day.

of 10 seconds or less, with a mean transient decrease in Sp$o_2$ of 4% ($P < .001$) (Table 4). A significant difference ($P < .001$) in nadir Sp$o_2$ was found for the different doses (first dose vs second dose vs third dose), but the differences between the mean nadir Sp$o_2$ for each dose were minimal (93% vs 92% vs 93%, respectively). The changes in Sp$o_2$ were similar with the other combinations of dose and breath-hold time. For example, the mean nadir for the seven subjects (four healthy subjects and three before LVRS) who inhaled more than 1 L for more than 10 seconds was 95% (range, 87%–98%); one of these subjects had desaturation to 87%, whereas the level in

the remaining six subjects remained at more than 92%.

When transient desaturation occurred, a consistent temporal pattern was seen. The decrease in Sp$o_2$ began approximately 20–30 seconds after initiation of the breath hold, after the subjects had resumed breathing room air (or their supplemental $O_2$). The Sp$o_2$ decrease continued for approximately 10–15 seconds until it reached its nadir, where it remained for no more than 10 seconds. The Sp$o_2$ then returned to the preinhalation baseline values after about 10–15 more seconds.

Transient subjective symptoms were reported by 10 (10%) subjects (Table 5),

nine before discharge and one during telephone follow-up. All symptoms resolved during or immediately after the imaging sessions. No medical intervention was required, although resolution of mild dyspnea, chest tightness, and lightheadedness that developed after the first ³He dose in a subject with asthma followed inhalation of albuterol by means of a metered-dose inhaler, administered as part of a protocol in which pre- and postbronchodilator imaging was performed; asthma symptoms in this subject were known to be induced by stress, cold, and allergens.

## Discussion

Since initial reports in 1996 (28,29), hyperpolarized ³He MR imaging has been performed in more than 1000 human subjects (30). Although subject characteristics and study protocols varied, the inhaled gas compositions, volumes, and breath-hold times used have been similar. To our knowledge, the only serious adverse event reported was an uncontrolled cough necessitating treatment in a patient with atypical asthma characterized by severe, chronic cough (18). However, objective and ongoing evaluation of the theoretic and known risks is important, not only to protect the safety of subjects but also to guide investigators and institutional review boards in assessing the safety of research protocols involving ³He inhalation.

Both normal subjects and subjects with severe obstructive airflow limitation tolerated ³He MR imaging, with no clinically important effects on the parameters monitored. It is unlikely that the small decrease in mean heart rate (5 beats per minute) observed after the imaging session is attributable to inhalation of the ³He-$N_2$ mixture. The factors most likely to account for this postimaging decrease are the effects of lying for nearly 1 hour at rest in the imaging unit and, possibly, relief of apprehension about imaging. The latter possibility is supported by the observation that the subjects in the healthy group, who were most familiar with the study personnel and procedures, did not have a decrease in heart rate.

Our analysis documents the frequency and degree of transient hypoxemia with ³He MR imaging in both healthy subjects and those with obstructive airflow limitation. The nadir $SpO_2$ was only weakly correlated to the baseline $SpO_2$ and did not correlate significantly with pulmonary function parameters. These findings indicate that the results of pulmonary function tests cannot help predict the degree of transient desaturation or whether the $SpO_2$ will decrease with subsequent doses or in other subjects with similar clinical characteristics. It is possible that physiologic factors such as differences in the basal metabolic rate, unventilated dead space, or ventilation-perfusion mismatch contributed to some of the variability in the degree of desaturation. Regardless of the mechanism, the observation that $SpO_2$ may decrease to as low as 80%–85% with relatively small inhaled volumes and short breath-hold times emphasizes that transient hypoxemia is a risk that investigators should be aware of and attempt to minimize. Thus, monitoring of $SpO_2$ during ³He MR studies seems prudent.

Temporal changes in $SpO_2$ during ³He MR imaging similar to the changes in our study have been reported in a study of five subjects who had undergone single-lung transplantation for pulmonary fibrosis (31) and in a study of 18 children with cystic fibrosis (32). Other studies (8–20 subjects in each) have reported observing a decrease in $SpO_2$ of 5% or less (33, 34), a decrease no greater than 10% (12), and a nadir less than 90% for no more than 10 seconds (7), without specifying details. Reasons for any differences from our experience are uncertain but may be due to differences in protocols and subject populations studied. We note that other studies have shown that breath holding with smaller lung volumes or lower initial alveolar $Po_2$ results in a faster decrease in alveolar $Po_2$ (35,36). Thus, we expect that larger inhaled volumes of anoxic gas, smaller lung volumes during the breath hold, and longer breath-hold periods would result in greater desaturation. The number of observations with the nonstandard inhaled volumes and breath-hold

periods used in our cohort, however, was too small to determine these effects.

Transitory and mild adverse events were noted by 10% of our subjects, and this finding was similar to the experience of other investigators (18,37). Some of these symptoms, such as sweaty palms, shoulder soreness, and epigastric discomfort, were probably unrelated to ³He-$N_2$ inhalation. Other symptoms conceivably could have been induced by the ³He-$N_2$ inhalation or by anxiety from participating in a research study. Although no serious adverse events requiring physician intervention were encountered, it is possible that albuterol administration would have been needed to relieve the symptoms of mild dyspnea, chest tightness, and lightheadedness that occurred in the subject with asthma had it not been administered for postbronchodilator imaging as planned.

Several limitations of this study should be recognized. Because subjects were excluded from ³He MR imaging for conditions in which even transient desaturation may be medically inadvisable, safety in those with known cardiovascular or cerebrovascular disease or anemia could not be evaluated. Because only those physiologic parameters considered clinically relevant were monitored and analyzed, there could be risks of which we are unaware or of such low frequency that exposure of much larger numbers of subjects would be required for their identification. Finally, the effects of the procedure on subjects with other pulmonary diseases, such as interstitial lung disease in which gas exchange is impaired, were not evaluated and may be different.

In summary, our data support the safety of hyperpolarized ³He MR imaging. Healthy subjects, heavy smokers, and subjects with severe obstructive airflow limitation tolerated ³He MR imaging, with no clinically significant effects on the parameters monitored. However, desaturation to the 80%–90% range may briefly occur in a minority of both healthy subjects and subjects with disease with use of typical inhalation and imaging protocols. Because most subjects develop transient

decreases in SpO$_2$ after inhalation of the $^3$He-N$_2$ mixture, screening for relevant medical comorbidities, minimizing the breath-hold time and inhaled gas volume, and monitoring SpO$_2$ levels are advisable. Methods with inhalation of room air after that of pure $^3$He gas have been reported to provide an acceptable signal-to-noise ratio (2) and may attenuate oxyhemoglobin desaturation (20), but the full effect of this factor on SpO$_2$ levels, $^3$He gas distribution, and diffusivity measurements remains to be determined.

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