

Insights into pediatric asthma with hyperpolarized magnetic resonance imaging of the lung

Mario Castro, MD, MPH, and Jason Woods, PhD St Louis, Mo

Key words: Pediatric asthma, hyperpolarized magnetic resonance imaging, lung imaging

The application of sophisticated quantitative imaging techniques in the developing lung might provide insights into the underlying pathophysiology of respiratory disease beyond that we can obtain from physiologic testing alone. Hyperpolarized gas magnetic resonance imaging (MRI) can assess the functional alterations of airflow within the lung resulting from the structural changes occurring in the central and distal small airways and lung parenchyma of asthmatic patients. Hyperpolarized gases are used as inhaled contrast agents for MRI of the lung and provide images of the lung airspaces with high spatial resolution. $^3\text{Helium}$ (^3He) and $^{129}\text{xenon}$ are nonradioactive isotopes that can be polarized.¹⁻⁴ The excellent safety profile of hyperpolarized gases, the lack of ionizing radiation associated with MRI, and the rapid clearance of the gases from the lungs permits repeated evaluation of subjects, now including children, as demonstrated by Cadman et al.⁵

In a young healthy subject, inhaled ^3He gas distributes evenly throughout the airspaces, producing uniformly high signal throughout the lung on MRI, with expected gravitational dependence.^{6,7} When there is focal reduction in airflow, the airspaces distal to the area of obstruction do not fill with the gas and appear dark on the images, depicted as a so-called “ventilation defect.” Focal ventilation defects have been found in patients with a variety of obstructive lung diseases, such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis, and even healthy subjects.^{1,8-12} It is likely that multiple different factors, such as mucus plugging and airway narrowing or closure from a variety of causes, can cause ventilation defects on hyperpolarized gas MRI. ^3He MRI ventilation defects are common in asthmatic patients, and their size and extent are thought to reflect the regional severity of airway closure or narrowing.¹ However, there

is not a consistent correlation with lung function, as demonstrated in the study by Cadman et al.⁵

Cadman et al.⁵ present a novel approach using ^3He MRI in a cross-sectional study of children participating in the COAST study. The authors select 4 subgroups: high/lower quartiles of lung function and presence/absence of human rhinovirus–associated wheezing in the first 3 years of life. Interestingly, they found that the children with asthma had an increase in ventilation defects but also slightly lower ^3He diffusion length (smaller microstructure), surprisingly without correlation between the 2 measures. These novel results should be tempered by the fact this was a select subgroup of children from a larger prospective cohort, and therefore the hypothesis here was not prospectively tested.

A major limitation of quantitative lung imaging is the lack of objective validated measures. The current study uses a ventilation defect score based on a single blinded reader’s interpretation of the extent of lobar involvement, which was then summarized across the entire lung. Although this scoring system is simple and well suited to consensus evaluation in blinded studies,^{1,13} they typically condense the defect pattern into a single whole-lung metric that does not effectively capture regional information. Furthermore, additional work is needed to measure the interrater and intrarater reliability of this score in adults and children to understand its natural variability. An objective quantitative method that takes regional information into account would be superior.

The potential application of diffusion measurements in MRI as a measure of small-airways function is exciting yet needs further validation. Cadman et al.⁵ found that their asthmatic patients had lower whole-lung mean diffusion lengths compared with nonasthmatic subjects. Previous studies (not in asthma) have demonstrated that this measure reflects structural changes in alveolar spaces that are critically dependent on acinary airway geometry.^{14,15} Other studies in adults have demonstrated that the alveolar diffusion coefficient values in asthmatic patients are increased and spatially heterogeneous.^{16,17} These apparently discrepant results might reflect differences in small-airway dimensions and alveolar size across these populations or a real difference in children’s airways. Because alveolar development is still occurring in young children,¹⁶ interpretations of the changes in mean diffusion length are nontrivial.

In summary, quantitative imaging of the lungs is an evolving technology with exciting applications in understanding the pathophysiology of airway disease early in life and as a potential clinical end point for intervention. The use of polarized noble gases in combination with quantitative MRI might provide an imaging biomarker of lung remodeling that could be used safely early in life to understand the progressive loss of lung function that occurs in asthmatic patients.

REFERENCES

1. de Lange E, Altes T, Patrie J, Gaare J, Knake J, Mugler J III, et al. Evaluation of asthma with hyperpolarized helium-3 MRI: correlation with clinical severity and spirometry. *Chest* 2006;130:1055-62.

From the Division of Pulmonary and Critical Care Medicine, Departments of Medicine and Radiology, Washington University School of Medicine.

Disclosure of potential conflict of interest: M. Castro has received grants from the National Institutes of Health (NIH), the American Lung Association, Asthma/Boston Scientific, Amgen, Cepion/Cephalon, Genentech, Medimmune, Merck, Novartis, GlaxoSmithKline, and Sanofi-Aventis; has received travel support from the NIH; has consultant arrangements with Schering, Asthma/Boston Scientific, Genentech, IPS, Pulmagen, and Sanofi-Aventis; has received payment for lectures from Boehringer-Ingelheim, Pfizer, Merck, GlaxoSmithKline, Genentech, and Asthma/Boston Scientific; and has received royalties from Elsevier. J. Woods declares that he has no relevant conflicts of interest.

Received for publication December 10, 2012; accepted for publication December 12, 2012.

Corresponding author: Mario Castro, MD, MPH, Washington University School of Medicine, Campus Box 8052, 660 S Euclid, St Louis, MO 63110-1093. E-mail: castrom@wustl.edu.

J Allergy Clin Immunol 2013;131:377-8.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2012.12.669>

2. Fain S, Korosec F, Holmes J, O'Halloran R, Sorkness R, Grist T. Functional lung imaging using hyperpolarized gas MRI. *J Magn Reson Imaging* 2007;25:910-23.
3. Mugler J III, Altes T, Ruset I, Dregely I, Mata J, Miller G, et al. Simultaneous magnetic resonance imaging of ventilation distribution and gas uptake in the human lung using hyperpolarized xenon-129. *Proc Natl Acad Sci U S A* 2010;107:21707-12.
4. van Beek E, Dahmen A, Stavngaard T, Gast K, Heussel C, Krummenauer F, et al. Hyperpolarised 3-He MRI vs HRCT in COPD and normal volunteers-PHIL trial. *Eur Respir J* 2009;34:1311-21.
5. Cadman R, Lemanske J, Evans M, Jackson D, Gern J, Sorkness R, et al. Pulmonary ³He magnetic resonance imaging of childhood asthma. *J Allergy Clin Immunol* 2013;131:369-76.
6. Altes T, Powers P, Knight-Scott J, Rakes G, Platts-Mills T, Lange E, et al. Hyperpolarized ³He MR lung ventilation imaging in asthmatics: preliminary findings. *J Magn Reson Imaging* 2001;13:378-84.
7. Parraga G, Mathew L, Etemad-Rezai R, McCormack D, Santyr G. Hyperpolarized ³He magnetic resonance imaging of ventilation defects in healthy elderly volunteers: initial findings at 3.0 Tesla. *Acad Radiol* 2008;15:776-85.
8. de Lange E, Altes T, Patrie J, Parmer J, Brookeman J, Mugler J, et al. The variability of regional airflow obstruction within the lungs of patients with asthma: assessment with hyperpolarized helium-3 magnetic resonance imaging. *J Allergy Clin Immunol* 2007;119:1072-8.
9. Mentore K, Froh D, de Lange E, Brookeman J, Paget-Brown A, Altes T. Hyperpolarized He 3 MRI of the lung in cystic fibrosis: assessment at baseline and after bronchodilator and airway clearance treatment. *Acad Radiol* 2005;12:1423-9.
10. Saam B, Yablonsky D, Kodibagkar V, Leawoods J, Gierada G, Cooper J, et al. MR imaging of diffusion of 3He gas in healthy and diseased lungs. *Magn Reson Med* 2000;44:174-9.
11. van Beek E, Hill C, Woodhouse N, Fichelle S, Fleming S, Howe B, et al. Assessment of lung disease in children with cystic fibrosis using hyperpolarized 3-Helium MRI: comparison with Shwachman score, Chrispin-Norman score and spirometry. *Eur Radiol* 2007;17:1018-24.
12. Kauczor H, Ebert M, Kreitner K, Nilgens H, Surkau R, Heil W, et al. Imaging of the lungs using ³He MRI: preliminary clinical experience in 18 patients with and without lung disease. *J Magn Reson Imaging* 1997;7:538-43.
13. Gur D, Shabason L, Borovetz H, Herbert D, Reece G, Kennedy W, et al. Regional pulmonary ventilation measurements by xenon enhanced dynamic computed tomography: an update. *J Comput Assist Tomogr* 1981;5:678-83.
14. Woods J, Choong C, Yablonskiy D, Bentley J, Wong J, Pierce J, et al. Hyperpolarized ³He diffusion MRI and histology in pulmonary emphysema. *Magn Reson Med* 2006;56:1293-300.
15. Yablonskiy D, Sukstanskii A, Woods J, Gierada D, Quirk J, Hogg J, et al. Quantification of lung microstructure with hyperpolarized 3He diffusion MRI. *J Appl Physiol* 2009;107:1258-65.
16. Narayanan M, Owers-Bradley J, Beardsmore C, Mada M, Ball I, Garipov R, et al. Alveolarization continues during childhood and adolescence. New evidence from helium-3 magnetic resonance. *Am J Respir Crit Care Med* 2012;185:186-91.
17. Wang C, Altes T, Mugler J III, Miller G, Ruppert K, Malta J, et al. Assessment of the lung microstructure in patients with asthma using hyperpolarized ³He diffusion MRI at two time scales: comparison with healthy subjects and patients with COPD. *J Magn Reson Imaging* 2008;28:80-8.