

Hyperpolarized ^3He functional magnetic resonance imaging of bronchoscopic airway bypass in chronic obstructive pulmonary disease

Lindsay Mathew PhD^{1,2}, Miranda Kirby BSc^{1,2}, Donald Farquhar MD³, Christopher Liciskai MD³, Giles Santyr PhD^{1,2}, Roya Etemad-Rezai MD⁴, Grace Parraga PhD^{1,2,4}, David G McCormack MD³

L Mathew, M Kirby, D Farquhar, et al. Hyperpolarized ^3He functional magnetic resonance imaging of bronchoscopic airway bypass in chronic obstructive pulmonary disease. *Can Respir J* 2012;19(1):41-43.

A 73-year-old exsmoker with Global initiative for chronic Obstructive Lung Disease stage III chronic obstructive pulmonary disease underwent airway bypass (AB) as part of the Exhale Airway Stents for Emphysema (EASE) trial, and was the only EASE subject to undergo hyperpolarized ^3He magnetic resonance imaging for evaluation of lung function pre- and post-AB. ^3He magnetic resonance imaging was acquired twice previously (32 and eight months pre-AB) and twice post-AB (six and 12 months post-AB). Six months post-AB, his increase in forced vital capacity was <12% predicted, and he was classified as an AB nonresponder. However, post-AB, he also demonstrated improvements in quality of life scores, 6 min walk distance and improvements in ^3He gas distribution in the regions of stent placement. Given the complex relationship between well-established pulmonary function and quality of life measurements, the present case provides evidence of the value-added information functional imaging may provide in chronic obstructive pulmonary disease interventional studies.

Key Words: Airway bypass; Chronic obstructive pulmonary disease; Hyperpolarized ^3He magnetic resonance imaging

CASE PRESENTATION

A 73-year-old male exsmoker with Global initiative for chronic Obstructive Lung Disease (GOLD) stage III chronic obstructive pulmonary disease (COPD) underwent airway bypass (AB) in February 2009 as part of the Exhale Airway Stents for Emphysema (EASE) trial. Thirty-two months before AB (June 2006), he reported a 70 pack-year smoking history, having ceased smoking approximately 13 years earlier, and was enrolled in a longitudinal hyperpolarized ^3He magnetic resonance imaging (MRI) study. At the initial study visit 32 months pre-AB, his measured forced expiratory volume in 1 s (FEV_1) was 1.2 L (32% predicted); all other measured parameters are presented in Table 1. Hyperpolarized ^3He MRI was performed at 3.0 Tesla using a fast-gradient recalled echo-pulse sequence for static ventilation imaging as previously described (1-3). Images were acquired with the subject in breath-hold, after inspiration of 1.0 L of 5 mL/kg ^3He mixed with nitrogen gas from functional residual capacity. Proton MRI of the thorax was also acquired as previously described (4) within 3 min of ^3He MRI, with the same breath-hold volume to obtain a structural image of the thorax that enabled clear delineation of the thoracic cavity. This MRI approach has been previously used in acute COPD therapy (5) and longitudinal studies (6). MRI reproducibility in COPD was also previously evaluated at the Imaging Research Laboratories, Robarts Research Institute (London, Ontario) (1) and elsewhere (7,8), and was high, supporting its use in serial studies. In Figure 1, ^3He MRI performed at 32 months pre-AB (top left panel), shows heterogeneous distribution of gas with large ventilation defects

L'imagerie par résonance magnétique fonctionnelle par ^3He hyperpolarisé de la dérivation des voies respiratoires par bronchoscopie en cas de maladie pulmonaire obstructive chronique

Un ex-fumeur de 73 ans atteint d'une maladie pulmonaire obstructive chronique de phase III d'après la *Global Initiative for Chronic Obstructive Lung Disease* a subi une dérivation des voies respiratoires (DVR) dans le cadre de l'essai EASE sur les endoprothèses des voies respiratoires par expiration et était le seul sujet de l'essai EASE à subir une imagerie par résonance magnétique (IRM) par ^3He hyperpolarisé pour évaluer la fonction pulmonaire avant et après la DVR. Il avait subi une IRM par ^3He deux fois auparavant (32 mois et huit mois avant la DVR) et deux fois après la DVR (six et 12 mois après). Six mois après la DVR, l'augmentation de sa capacité vitale forcée était de 12 % inférieure aux valeurs prévues, et il avait été classé comme ne répondant pas à la DVR. Cependant, après la DVR, il a également présenté des améliorations aux indices de qualité de vie, au test de marche de 6 minutes et des améliorations de la distribution de gaz par ^3He dans les foyers d'installation des endoprothèses. Étant donné le lien complexe entre la fonction pulmonaire bien établie et les mesures de qualité de vie, ce cas démontre l'information à valeur ajoutée que peut fournir l'imagerie fonctionnelle dans le cadre d'études d'intervention sur les maladies pulmonaires obstructives chroniques.

and regionally heterogeneous ^3He MR signal intensity characteristic of COPD. On returning for follow-up imaging 24 months later (eight months pre-AB [Figure 1, top right panel]), ^3He MRI showed a decrease in ventilation of the right upper and lower, and left upper lung regions as well as a decreased signal-to-noise ratio. Quantitative analysis (9) revealed a ventilation volume (VV) decrease of 3.8 L over the two-year period, and a corresponding decrease in per cent ventilated volume (PVV) from 73% to 26%. The functional imaging changes observed were coincident with a large decrease in forced vital capacity (FVC), and small decreases in FEV_1 and inspiratory capacity (Table 1). There were no exacerbations or hospitalizations reported during this 24-month period.

At this time, the subject was enrolled in a randomized double-blind study evaluating the safety and efficacy of AB in subjects with homogeneous emphysema and severe hyperinflation. Clinical trial primary end points consisted of the change in the modified Medical Research Council scale (ΔmMRC) ≥ 1 and ΔFVC $\geq 12\%$ predicted. As part of the EASE protocol, he underwent six weeks of pulmonary rehabilitation before AB. In February 2009, four stents were placed: two in the right lower and two in the left upper lung. EASE trial follow-up occurred one, three, six and 12 months poststenting, with ^3He MRI at the six- and 12-month post-AB time points. At six months post-AB, his FVC increased by 8% predicted; he was, therefore, categorized as an AB nonresponder. In contrast, at six months post-AB, visually obvious changes in the ^3He MRI gas distribution that generally correspond to stent placement were observed throughout the right lung

¹Imaging Research Laboratories, Robarts Research Institute; ²Department of Medical Biophysics; ³Division of Respirology, Department of Medicine, ⁴Department of Medical Imaging, University of Western Ontario, London, Ontario

Correspondence and reprints: Dr Grace Parraga, Imaging Research Laboratories, Robarts Research Institute, PO Box 5015, 100 Perth Drive, London, Ontario N6A 5K8. Telephone 519-913-5265, fax 519-913-5260, e-mail gep@imaging.robarts.ca

TABLE 1
Pulmonary function and ³He magnetic resonance imaging measurements pre- and post-airway bypass

	Months							
	Pre-airway bypass				Post-airway bypass			
	32	8	2	0.1	1	3	6	12
FEV ₁ , L	1.2	0.8	0.9	1.1	1.2	1.2	1.1	1.2
FEV ₁ , % predicted	32	23	27	32	34	35	33	35
FVC, L	3.2	2.3	2.6	3.2	3.6	3.6	3.5	3.8
FVC, % predicted	66	49	57	68	77	78	76	81
FEV ₁ /FVC, %	37	34	35	35	32	33	32	31
RV, L	5.2	5.2	5.6	4.4	5.0	4.5	4.7	5.0
RV, % predicted	193	200	213	169	190	169	169	189
TLC, L	8.4	8.0	8.6	7.8	8.2	8.2	8.3	8.5
TLC, % predicted	111	107	115	104	114	110	108	114
RV/TLC	0.62	0.65	0.65	0.57	0.60	0.55	0.56	0.58
IC, L	1.8	1.6	1.6	2.1	2.3	2.3	1.8	2.8
DLCO, mL/min/mmHg	–	–	9.2	9.9	14.6	16.9	14.6	18.7
DLCO, % predicted	–	–	26	28	42	48	42	53
mMRC	–	–	–	2	1	0	1	1
6MWD, m	–	–	–	288	315	330	366	330
SGRQ	–	–	–	65	27	27	27	31
CE, s	–	–	–	750	–	–	1084	–
WL TCV, L	7.3	6.3	–	–	–	–	8.5	8.1
WL VV, L	5.4	1.6	–	–	–	–	4.8	5.8
WL PVV, %	73	26	–	–	–	–	57	72
WL VDV, L	2.0	4.7	–	–	–	–	3.6	2.4
WL VDP, %	27	74	–	–	–	–	43	28

6MWD 6 min walk distance; CE Cycle ergometry; DLCO Carbon monoxide diffusion capacity of the lung; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; IC Inspiratory capacity; mMRC Modified Medical Research Council; PVV Per cent ventilated volume; RV Residual volume; SGRQ St George's Research Questionnaire; TCV Thoracic cavity volume; TLC Total lung capacity; VDP Ventilation defect per cent; VDV Ventilation defect volume; VV Ventilated volume; WL Whole lung

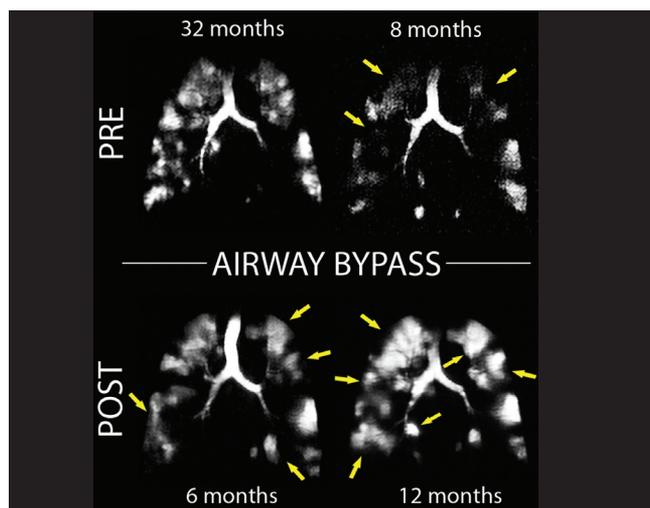


Figure 1) ³He magnetic resonance (MR) ventilation image of a Global initiative for chronic Obstructive Lung Disease (GOLD) stage III chronic obstructive pulmonary disease exsmoker 32 months before airway bypass (AB) (top left panel): forced expiratory volume in 1 s (FEV₁) = 32% predicted, forced vital capacity (FVC) = 66% predicted, and eight months before AB (top right panel), FEV₁ = 23% predicted, FVC = 49% predicted. Heterogeneous ³He signal intensity and large ventilation defects are visualized in both scans, with ³He MR ventilated volume decreased by 3.8 L during this two-year time period. In February 2009, two stents were inserted into the left upper lung and two into the right lower lung, with ³He MRI acquired six months post-AB (lower left panel): FEV₁ = 33% predicted, FVC = 76% predicted; and 12 months post-AB (lower right panel), FEV₁ = 35% predicted, FVC = 81% predicted. Improved gas distribution post-AB is suggested with new regions of ³He ventilation and increased ³He signal intensity, and ventilated volume at both time points post-AB.

and in the left upper lobe (Figure 1, lower left panel) with further improvements, specifically in the right lower lung observed 12 months post-AB (Figure 1, lower right panel). The visually apparent ventilation improvements in the right lower and left upper lobes were in the same regions where stents were originally placed. There were also other areas of regionally improved gas distribution (arrows), and all of these visually apparent changes in gas distribution corresponded to ³He MRI VV increases of 3.2 L at six months and 4.2 L at 12 months post-AB. At the same time, other surrogate measures of functional capacity including 6 min walk distance (6MWD), the St George's Respiratory Questionnaire (SGRQ) score and cycle ergometry time showed improvements six months post-AB (6MWD increased by 78 m, SGRQ score decreased by 38 and cycle ergometry time improved by 334 s). Along with improvements in quality of life measures, the diffusing capacity of carbon monoxide (DLCO) nearly doubled between the pre-AB and 12-month post-AB time points (Table 1).

DISCUSSION

AB is an investigational procedure that involves the creation of extra-anatomical passages reinforced by a drug-eluting stent in the airway wall, with stents delivered using Doppler-guidance to avoid pulmonary vasculature in airway regions where the stents are inserted. The aim of AB is to artificially connect the segmental airways to adjacent lung tissue, thereby allowing trapped gas to be exhaled. Bronchoscopic lung volume reduction methods, such as AB, provide a minimally invasive alternative to lung volume reduction surgery with the goal of improving COPD quality of life, pulmonary function and survival (10-12). Unfortunately, for many of these approaches, significant improvements in intermediate end points such as FEV₁ and residual volume/total lung capacity have not been realized postintervention (13-15) and, occasionally, these results are discordant with symptomatic or other functional improvements.

We highlighted hyperpolarized ³He MRI in a single case of COPD in an exsmoker who underwent AB. Results of pulmonary function tests and ³He MRI suggest a decline in lung function over the pre-AB, two-year time period. Post-AB however, significant improvements in gas distribution were visually and quantitatively apparent after six months and 12 months, including increases in VV and PVV. Regional changes in ventilation were visualized throughout the lung, even in regions not associated with stent placement, perhaps due to redistribution of ventilation following the release of trapped gas. It is worth noting that the most visually prominent changes occurred in the right lower and left upper lobes – the same regions where stents were originally placed. The resultant changes in VV and PVV were much greater than the smallest detectable difference previously estimated for ³He MRI (5) based on a reproducibility study in COPD. Although ³He MRI was not available immediately preceding AB, which would have enabled identification of ventilation improvements that were due to stent placement alone, the imaging results obtained provided functional information that was in agreement with 6MWD, SGRQ and mMRC, as well as DLCO, but not with spirometry and plethysmography measurements. Perhaps unexpectedly, both DLCO and PVV continued to increase post-AB, evidenced by large changes between six- and 12-month post-AB time points. These relatively late changes post-AB suggest continued improvements in gas distribution post-AB that coincided with improved gas transfer. The intriguing coincidence of improved ³He gas distribution, DLCO and quality of life measures that endured 12 months post-AB in the only EASE trial subject for whom ³He MRI was performed certainly generates new hypotheses to test – especially with respect to the use of imaging to guide stent placement and track regional changes in lung function.

The high cost and limited availability of ³He MRI prohibits its prospective routine use in clinical research and its translation to clinical practice (16). However, its high short-term reproducibility (1) and

sensitivity (5,6), coupled with the intriguing findings in longitudinal (6) and other acute COPD therapy studies (5), suggest that hyperpolarized noble gas imaging may be an ideal tool for visualization and quantitative evaluation of functional differences in COPD post-therapeutic intervention. The results of the present case study highlight the advantage of including functional MRI techniques such as hyperpolarized ¹²⁹Xe MRI (17,18) or conventional ¹H MRI (19) in COPD interventional studies, and suggest the application of these types of imaging in interventional studies may offer new insights into regional physiological changes in COPD following treatment.

ACKNOWLEDGEMENTS: The authors gratefully acknowledge the late Peter T Macklem MD FRCPC OC, for his guidance and feedback on this study and case report. They also thank S Halko and S McKay for clinical coordination, and T Szekeres for MRI and A Wheatley for gas dispensing and administration.

FUNDING/SUPPORT: This work was supported by the Canadian Institutes of Health Research (CIHR) Operating Grant MOP # 97748 and Team Grant FRN #97687. Dr Parraga also acknowledges salary support from a CIHR New Investigator Award.

FINANCIAL/NONFINANCIAL DISCLOSURES: No potential conflicts of interest exist with any companies/organizations whose products or services are discussed in this article. Three of the authors (McCormack, Farquhar and Licskai) participated as investigators in the EASE trial and were reimbursed by Broncus for study-specific subject costs related to the AB procedures; MRI, however, was performed under a separate investigator-sponsored protocol for longitudinal ³He MRI (Parraga and McCormack) and there was no Broncus involvement or funding for the MRI performed for this case.

REFERENCES

- Mathew L, Evans A, Ouriadov A, et al. Hyperpolarized (3)He magnetic resonance imaging of chronic obstructive pulmonary disease reproducibility at 3.0 tesla. *Acad Radiol* 2008;15:1298-311.
- Parraga G, Ouriadov A, Evans A, et al. Hyperpolarized 3He ventilation defects and apparent diffusion coefficients in chronic obstructive pulmonary disease: Preliminary results at 3.0 Tesla. *Invest Radiol* 2007;42:384-91.
- Parraga G, Mathew L, Etemad-Rezai R, et al. Hyperpolarized 3He magnetic resonance imaging of ventilation defects in healthy elderly volunteers: Initial findings at 3.0 Tesla. *Acad Radiol* 2008;15:776-85.
- Mathew L, Gaede S, Wheatley A, et al. Detection of longitudinal lung structural and functional changes after diagnosis of radiation-induced lung injury using hyperpolarized 3He magnetic resonance imaging. *Med Phys* 2010;37:22-31.
- Kirby M, Mathew L, Heydarian M, Etemad-Rezai R, McCormack DG, Parraga G. Chronic obstructive pulmonary disease: Quantification of bronchodilator effects by using hyperpolarized ³He MR imaging. *Radiology* 2011;261:283-92.
- Kirby M, Mathew L, Wheatley A, et al. Chronic obstructive pulmonary disease: Longitudinal hyperpolarized (3)He MR imaging. *Radiology* 2010;256:280-9.
- Diaz S, Casselbrant I, Piitulainen E, et al. Hyperpolarized 3He apparent diffusion coefficient MRI of the lung: Reproducibility and volume dependency in healthy volunteers and patients with emphysema. *J Magn Reson Imaging* 2008;27:763-70.
- Morbach AE, Gast KK, Schmiedeskamp J, et al. Diffusion-weighted MRI of the lung with hyperpolarized helium-3: A study of reproducibility. *J Magn Reson Imaging* 2005;21:765-74.
- Kirby M, Svenningsen S, Ahmed H, et al. Quantitative evaluation of hyperpolarized helium-3 magnetic resonance imaging of lung function variability in cystic fibrosis. *Acad Radiol* 2011;18:1006-13 (doi:10.1016/j.acra.2011.03.005).
- Yim APC, Hwang TMT, Lee TW, et al. Early results of endoscopic lung volume reduction for emphysema. *J Thorac Cardiovasc Surg* 2004;127:1564-73.
- Wood DE, McKenna J, Yusef RD, et al. A multicenter trial of an intrabronchial valve for treatment of severe emphysema. *J Thorac Cardiovasc Surg* 2007;133:65-73.
- Choong CK, Macklem PT, Pierce JA, et al. Airway bypass improves the mechanical properties of explanted emphysematous lungs. *Am J Respir Crit Care Med* 2008;178:902-5.
- Broncus Technologies Inc. Broncus Reports Early EASE Trial Results for Airway Bypass With Exhale(R) Drug-Eluting Stents <<http://www.broncus.com/PDFS/Early%20EASE%20Trial%20results.pdf>> 11-17-2009 (Accessed on September 30, 2010).
- Sterman DH, Mehta AC, Wood DE, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration* 2010;79:222-33.
- Berger RL, Decamp MM, Criner GJ, et al. Lung volume reduction therapies for advanced emphysema: An update. *Chest* 2010;138:407-17.
- Fain S, Schiebler ML, McCormack DG, et al. Imaging of lung function using hyperpolarized helium-3 magnetic resonance imaging: Review of current and emerging translational methods and applications. *J Magn Reson Imaging* 2010;32:1398-408.
- Mugler JP, III, Altes TA, Ruset IC, et al. Simultaneous magnetic resonance imaging of ventilation distribution and gas uptake in the human lung using hyperpolarized xenon-129. *Proc Natl Acad Sci USA* 2010;107:707-12.
- Cleveland ZI, Cofer GP, Metz G, et al. Hyperpolarized Xe MR imaging of alveolar gas uptake in humans. *PLoS One* 2010;5:e12192.
- Bauman G, Puderbach M, Deimling M, et al. Non-contrast-enhanced perfusion and ventilation assessment of the human lung by means of fourier decomposition in proton MRI. *Magn Reson Med* 2009;62:656-64.



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

