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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 ^{3}He magnetic resonance imaging for evaluation of lung function pre- and post-AB. ^{3}He 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 ^{3}He 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 ^{3}He magnetic resonance imaging*

L'imagerie par résonance magnétique fonctionnelle par ^{3}He 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 ^{3}He hyperpolarisé pour évaluer la fonction pulmonaire avant et après la DVR. Il avait subi une IRM par ^{3}He 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 ^{3}He 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.

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 ^{3}He 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 ^{3}He 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 ^{3}He mixed with nitrogen gas from functional residual capacity. Proton MRI of the thorax was also acquired as previously described (4) within 3 min of ^{3}He 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, ^{3}He MRI performed at 32 months pre-AB (top left panel), shows heterogeneous distribution of gas with large ventilation defects and regionally heterogeneous ^{3}He MR signal intensity characteristic of COPD. On returning for follow-up imaging 24 months later (eight months pre-AB [Figure 1, top right panel]), ^{3}He 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 ≥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 ^{3}He 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 ^{3}He MRI gas distribution that generally correspond to stent placement were observed throughout the right lung

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TABLE 1
Pulmonary function and ^{3}He 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; FEV_1 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

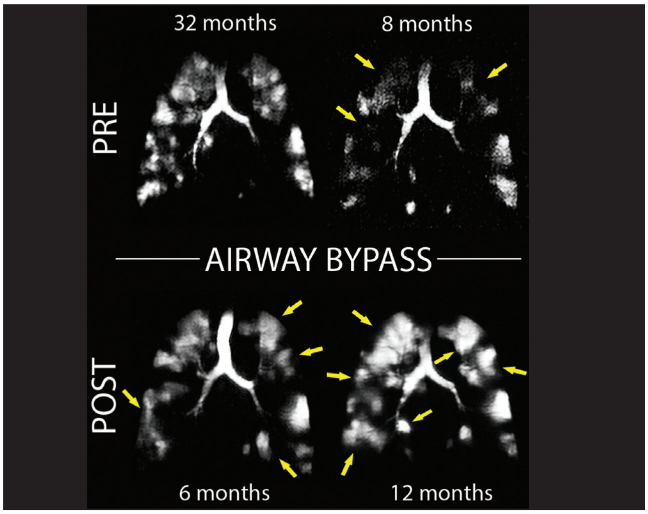

Figure 1) *^{3}He magnetic resonance (MR) ventilation image of a Global initiative for chronic Obstructive Lung Disease (GOLD) stage III chronic obstructive pulmonary disease exsmoker 32 months before airway bypass (AB) (top left panel): forced expiratory volume in 1 s (FEV_1) = 32% predicted, forced vital capacity (FVC) = 66% predicted, and eight months before AB (top right panel), FEV_1 = 23% predicted, FVC = 49% predicted. Heterogeneous ^{3}He signal intensity and large ventilation defects are visualized in both scans, with ^{3}He 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 ^{3}He MRI acquired six months post-AB (lower left panel): FEV_1 = 33% predicted, FVC = 76% predicted; and 12 months post-AB (lower right panel), FEV_1 = 35% predicted, FVC = 81% predicted. Improved gas distribution post-AB is suggested with new regions of ^{3}He ventilation and increased ^{3}He 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 ^{3}He 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 FEV_1 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 ^{3}He MRI in a single case of COPD in an exsmoker who underwent AB. Results of pulmonary function tests and ^{3}He 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 ^{3}He MRI (5) based on a reproducibility study in COPD. Although ^{3}He 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 ^{3}He gas distribution, DLCO and quality of life measures that endured 12 months post-AB in the only EASE trial subject for whom ^{3}He 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 ^{3}He 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 ^{129}Xe MRI (17,18) or conventional ^{1}H 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.

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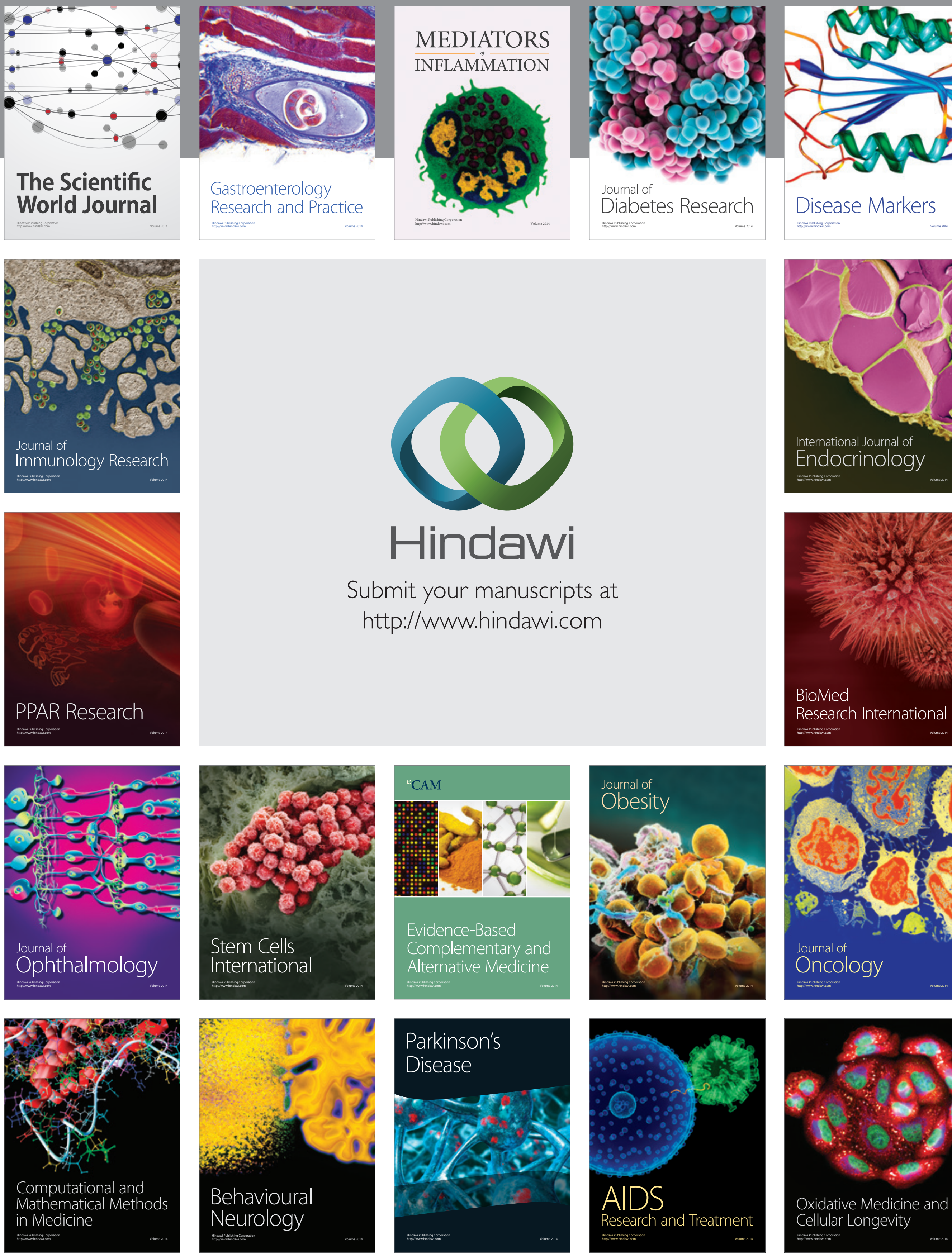
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