ORIGINAL ARTICLE

On the role of abnormal DL_{CO} in ex-smokers without airflow limitation: symptoms, exercise capacity and hyperpolarised helium-3 MRI

Miranda Kirby,[1,2] Amir Owrangi,[1,3] Sarah Svenningsen,[1,2] Andrew Wheatley,[1] Harvey O Coxson,[4] Nigel A M Paterson,[5] David G McCormack,[5] Grace Parraga[1,2,3,6]

[1]Imaging Research Laboratories, Robarts Research Institute, London, Ontario, Canada
[2]Department of Medical Biophysics, University of Western Ontario, London, Ontario, Canada
[3]Graduate Program in Biomedical Engineering, University of Western Ontario, London, Ontario, Canada
[4]Department of Radiology and James Hogg Research Centre, University of British Columbia and Vancouver General Hospital, Vancouver, British Columbia, Canada
[5]Division of Respirology, Department of Medicine, University of Western Ontario, London, Ontario, Canada
[6]Department of Medical Imaging, University of Western Ontario, London, Ontario, Canada

Correspondence to
Dr G Parraga,
Imaging Research Laboratories, Robarts Research Institute, 100 Perth Drive, London, Canada N6A 5K8;
gparraga@robarts.ca

Received 7 December 2012
Revised 21 February 2013
Accepted 28 March 2013
Published Online First 19 April 2013

ABSTRACT

Background The functional effects of abnormal diffusing capacity for carbon monoxide (DL_{CO}) in ex-smokers without chronic obstructive pulmonary disease (COPD) are not well understood.

Objective We aimed to evaluate and compare well established clinical, physiological and emerging imaging measurements in ex-smokers with normal spirometry and abnormal DL_{CO} with a group of ex-smokers with normal spirometry and DL_{CO} and ex-smokers with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I COPD.

Methods We enrolled 38 ex-smokers and 15 subjects with stage I COPD who underwent spirometry, plethysmography, St George's Respiratory Questionnaire (SGRQ), 6 min Walk Test (6MWT), x-ray CT and hyperpolarised helium-3 (^{3}He) MRI. The 6MWT distance (6MWD), SGRQ scores, ^{3}He MRI apparent diffusion coefficients (ADC) and CT attenuation values below −950 HU (RA_{950}) were evaluated.

Results Of 38 ex-smokers without COPD, 19 subjects had abnormal DL_{CO} with significantly worse ADC (p=0.01), 6MWD (p=0.008) and SGRQ (p=0.01) but not RA_{950} (p=0.53) compared with 19 ex-smokers with normal DL_{CO}. Stage I COPD subjects showed significantly worse ADC (p=0.02), RA_{950} (p=0.0008) and 6MWD (p=0.005), but not SGRQ (p=0.59) compared with subjects with abnormal DL_{CO}. There was a significant correlation for ^{3}He ADC with SGRQ (r=0.34, p=0.02) and 6MWD (r=−0.51, p=0.0002).

Conclusions In ex-smokers with normal spirometry and CT but abnormal DL_{CO}, there were significantly worse symptoms, 6MWD and ^{3}He ADC compared with ex-smokers with normal DL_{CO}, providing evidence of the impact of mild or early stage emphysema and a better understanding of abnormal DL_{CO} and hyperpolarised ^{3}He MRI in ex-smokers without COPD.

Key messages

What is the key question?

- The functional effects of abnormal DL_{CO} in ex-smokers without airflow limitation are not well understood. To try to better understand the role of abnormal DL_{CO} in ex-smokers without COPD, we evaluated and compared clinical, physiological and emerging imaging measurements in ex-smokers with normal spirometry and DL_{CO}, ex-smokers with normal spirometry but abnormal DL_{CO} and those with GOLD stage I COPD.

What is the bottom line?

- We evaluated 53 ex-smokers including 15 subjects with stage I COPD and 38 subjects without airflow limitation. Of the 38 ex-smokers without airflow limitation, 19 had abnormal DL_{CO} and significantly worse symptoms, 6MWD and ^{3}He ADC compared with the 19 ex-smokers with normal DL_{CO} although CT derived measurements of emphysema were not significantly different.

Why read on?

- Abnormal DL_{CO} in ex-smokers without airflow limitation was related to worse symptoms, exercise capacity and ^{3}He ADC compared with ex-smokers with normal DL_{CO}, providing evidence of the impact of DL_{CO} abnormalities consistent with early or very mild emphysema and revealed by ^{3}He MRI but not CT. Abnormal DL_{CO} measurements in ex-smokers without COPD should be followed-up to evaluate potential progression of disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by chronic progressive expiratory flow limitation that develops as a result of the lung's inflammatory response to inhaled toxic gases and particles, primarily from tobacco smoke.[1] In COPD, airflow limitation is caused by both small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema)[1] but the relative contributions of these pathologies vary from person to person.

When COPD is suspected based on symptoms, such as dyspnoea, chronic cough or sputum production, and/or a history of exposure to risk factors,[1] airflow limitation is measured using spirometry and severity is determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[1] This approach, however, has been acknowledged to potentially result in an over diagnosis of COPD in the elderly,[2] as well as under diagnosis of mild or early stage COPD.[3]

To cite: Kirby M, Owrangi A, Svenningsen S, *et al*. *Thorax* 2013;**68**: 752–759.

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

The COPDGene study recently reported low forced expiratory volume in 1 s (FEV_1) and normal FEV_1/forced vital capacity (FVC) in ex-smokers with significant symptoms and decreased 6 min Walk Distance (6MWD), and defined these patients as GOLD unclassified (GOLD-U).[4] Until now, ex-smokers with GOLD-U or those with 'non-obstructive' or 'pure' emphysema without airflow limitation have been systematically excluded from COPD studies. With respect to non-obstructive emphysema, there have been a few case reports[5–7] and pilot studies[8] that described significant smoking history, severe symptoms and abnormal diffusing capacity for carbon monoxide (DL_{CO}) in patients concomitant with normal expiratory airflow. A recent study also reported that otherwise normal asymptomatic smokers with abnormal DL_{CO} showed evidence of endothelial microparticles in the circulation—a marker of early lung destruction associated with emphysema.[9] Although abnormal DL_{CO} in ex-smokers is a valuable marker of lung function impairment, even in the absence of airflow limitation, the relationship between DL_{CO} with other functional markers (ie, symptoms and exercise limitation) is not well understood. We hypothesised that subjects with abnormal DL_{CO} without airflow limitation would have imaging evidence of early or mild emphysema with measureable functional consequences.

Multidetector CT and hyperpolarised helium-3 (^{3}He) MRI have been used independently to measure emphysema and airways disease as distinct phenotypes in COPD.[10 11] In particular, hyperpolarised ^{3}He MRI apparent diffusion coefficients (ADC)[12 13] provide a way to sensitively measure regional lung tissue destruction—the hallmark of emphysema. Abnormally elevated ^{3}He ADC have previously been reported in asymptomatic smokers without COPD[14 15] although the relationship between ^{3}He MRI ADC in early disease with symptoms and other physiological measurements has never been reported and their functional impact is not known. To better understand the consequences of early or mild disease in ex-smokers, we have evaluated well established clinical, physiological as well as emerging imaging measurements in ex-smokers with normal spirometry but abnormal DL_{CO} as well as ex-smokers with GOLD stage I COPD and those with normal spirometry and DL_{CO}.

MATERIALS AND METHODS

Study subjects

All subjects provided written informed consent to the protocol approved by the local research ethics board and Health Canada, and the study was compliant with the Personal Information Protection and Electronic Documents Act (Canada) and the Health Insurance Portability and Accountability Act (USA). Ex-smokers were recruited from a local tertiary care centre and by advertisement. Thirty-eight subjects were enrolled who were ex-smokers without a diagnosis of COPD and 15 ex-smokers were enrolled with a previous diagnosis of GOLD stage I COPD,[1] all of whom were 60–85 years of age, with a smoking history ≥10 pack-years. Subjects without a diagnosis of COPD had no history of previous chronic or current respiratory disease and were classified according to American Thoracic Society/European Respiratory Society recommendations[16] on the approximate lower limits of normal for DL_{CO},[17] such that normal is defined as $DL_{CO} \geq 75\%_{pred}$ and abnormal $DL_{CO} < 75\%_{pred}$.

Spirometry, plethysmography and other tests

Spirometry was performed using an EasyOne spirometer (Medizintechnik AG, Zurich, Switzerland) according to the American Thoracic Society guidelines.[18] Lung volumes were measured using body plethysmography and DL_{CO} was assessed using the attached gas analyser (MedGraphics Corporation, St Paul, Minnesota, USA). The St Georges Respiratory Questionnaire (SGRQ) was administered[19 20] and a standard 6 min Walk Test (6MWT)[21] was performed.

Image acquisition

MRI was performed on a whole body 3.0 T Discovery 750MR (General Electric Health Care, Milwaukee, Wisconsin, USA) MRI system.[22] 3He gas was polarised to 30–40% (HeliSpin) and doses (5 ml/kg body weight) were administered in 1.0 l Tedlar bags diluted with medical grade nitrogen (N_2) (Linde, Ontario, Canada). ^{3}He MRI diffusion weighted images were acquired using a fast gradient recalled echo sequence immediately following inhalation of the $^3He/N_2$ gas mixture during breath hold conditions.[22] Two interleaved images were acquired (14 s total data acquisition, repetition time (TR)/echo time (TE)/flip angle=7.6 ms/3.7 ms/8°, field of view (FOV)=40×40 cm, matrix 128×128, seven slices, 30 mm slice thickness, 0 gap), with and without additional diffusion sensitisation with b=1.6 s/cm^2 (gradient amplitude (G)=1.94 G/cm, rise and fall time=0.5 ms, gradient duration=0.46 ms, diffusion time=1.46 ms).

CT was performed on a 64 slice Lightspeed VCT scanner (General Electric Health Care) (64×0.625 mm, 120 kVp, 100 effective mA, tube rotation time=500 ms, pitch=1.0). A single spiral acquisition was acquired in breath hold after inhalation of 1.0 l of N_2 from functional residual capacity. Reconstruction was performed (1.25 mm) using a standard convolution kernel.

To minimise the potential for differences in the levels of inspiration between ^{3}He MRI and CT, extensive coaching was performed prior to the imaging sessions to ensure subjects could completely inspire the contents of the 1.0 l bag. The order of ^{3}He MRI and CT acquisition was randomised for each subject.

Image analysis

Regions of signal void were quantified as the ^{3}He ventilation defect per cent (VDP).[23] ^{3}He ADC maps were also generated as previously described.[24] Regional differences in ADC were evaluated in the anterior–posterior (AP) direction.[25] The AP gradient (AP_G) was the slope of the line of best fit that described the change in ADC as a function of distance (in cm). Analysis of CT was performed using the Pulmonary Workstation 2.0 (VIDA Diagnostics Inc, Coralville, Iowa, USA). Wall area per cent (WA %) was measured for the segmental and subsegmental airways[10] and the relative area with attenuation values below −950 HU (RA_{950}) was generated.[26]

Statistical methods

A multivariate analysis of variance was performed using IBM SPSS Statistics V.20.0 (SPSS Inc, Chicago, Illinois, USA). Univariate comparisons were performed using an unpaired two tailed t test, and Welch's correction was used when the F test for equal variances was significant using GraphPad Prism V.4.00 (GraphPad Software Inc, San Diego, California, USA). A Fisher's exact test was performed for categorical variables. Linear regression (r^2) and Pearson correlation coefficients (r) were used to determine correlations using GraphPad Prism V.4.00. Results were considered significant when the probability of making a type I error was less than 5% ($p<0.05$).

RESULTS

We enrolled 53 ex-smokers, 38 subjects without a diagnosis of COPD and 15 subjects diagnosed with stage I COPD. Of the 38 ex-smokers without COPD, half had normal DL_{CO} without airflow obstruction (ND, n=19) and the other half had

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Table 1 Clinical, functional and radiographic measurements of asymptomatic ex-smokers with normal and abnormal diffusion capacity of the lung for carbon monoxide, compared with GOLD stage I chronic obstructive pulmonary disease

	ND (n=19)	AD (n=19)	Stage I COPD (n=15)	Significance of difference (p)	
				ND–AD	AD–COPD
Subject demographics					
Age (years)	71 (7)	74 (7)	77 (5)	0.09	0.30
No of women (n)	3	11	2	0.02	0.01
BMI (kg/m^2)	29.5 (3.4)	28.6 (4.0)	28.4 (4.0)	0.46	0.91
Pack-years	25 (12)	32 (23)	49 (36)	0.25	0.11
Time since quitting (years)	26 (9)	24 (14)	21 (14)	0.63	0.63
Pulmonary function tests					
FEV_1 $\%_{pred}$	107 (13)	99 (12)	95 (13)	0.07	0.34
FVC $\%_{pred}$	98 (12)	93 (12)	108 (14)	0.16	0.001
FEV_1/FVC	80 (6)	80 (7)	63 (5)	0.73	<0.0001
IC $\%_{pred}$	112 (17)	103 (22)	103 (17)	0.17	0.99
RV $\%_{pred}$	103 (17)	107 (25)	114 (29)	0.58	0.45
TLC $\%_{pred}$	101 (10)	101 (15)	109 (13)	0.96	0.12
RV/TLC $\%_{pred}$	101 (13)	104 (16)	103 (18)	0.49	0.77
DL_{CO} $\%_{pred}$	89 (9)	59 (13)	68 (19)	<0.0001	0.12
6MWT					
Pre 6MWT SpO_2%	97 (2)	95 (2)	95 (2)	0.06	0.57
Δ 6MWT SpO_2%	0 (2)*	0 (2)†	−1 (3)	0.55	0.25
Distance (m)	430 (99)	341 (95)	417 (41)	0.008	0.005
SGRQ					
Symptoms	18 (17)*	36 (30)*	36 (22)	0.04	0.99
Activity score	19 (21)†	41 (24)	36 (25)‡	0.006	0.54
Impact score	6 (11)†	17 (18)	15 (13)‡	0.04	0.68
Total score	12 (14)§	29 (21) *	25 (17)‡	0.01	0.59
CT measurements					
RA_{950}	1.36 (1.25)	1.60 (1.06)	5.50 (3.16)	0.53	0.0008
WA%	57 (4)	59 (2)	58 (2)	0.17	0.23
^{3}He MRI measurements					
ADC (cm^2/s)	0.27 (0.03)*	0.30 (0.03)§	0.36 (0.08)	0.01	0.02
VDP (%)	6 (3)*	7 (4)§	9 (5)‡	0.40	0.07

Values are mean (SD).
Missing values: SpO_2 not recorded post-6MWT (n=1, normal DL_{CO}; n=2, abnormal DL_{CO}); incomplete SGRQ questionnaire (n=3, normal DL_{CO}; n=1, abnormal DL_{CO}; n=1, COPD); and image acquisition failures (n=1, normal DL_{CO}; n=2, abnormal DL_{CO}; n=1, COPD).
*n=18, †n=17, ‡n=14, §n=16.
AD, abnormal DL_{CO}; ADC, apparent diffusion coefficient; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, force vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; 6MWT, 6 min Walk Test; ND, normal DL_{CO}; RA_{950}, relative area with attenuation values below −950 HU; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; SpO_2, peripheral oxygen saturation; TLC, total lung capacity; VDP, ventilation defect per cent; WA%, wall area per cent.

abnormal DL_{CO} without airflow obstruction (AD, n=19). Table 1 shows the subject demographics as well as pulmonary function, SGRQ, 6MWD, CT and ^{3}He MRI measurements for all subjects categorised according to their spirometry and DL_{CO} results.

Subjects with abnormal DL_{CO} without airflow obstruction (AD) were not significantly different from ex-smokers with normal DL_{CO} (ND) and stage I COPD subjects with respect to age, BMI, pack-years, years since smoking cessation, change in SpO_2 after the 6MWT, CT WA% and ^{3}He VDP. However, there were significantly more female AD subjects than ND (p=0.02) and stage I COPD (p=0.01) subjects.

Figure 1 shows the central coronal ^{3}He MRI static ventilation image and ^{3}He MRI ADC map for subjects with ND, AD and stage I COPD. As shown in table 1, AD subjects had a significantly worse ^{3}He ADC (0.30±0.03 cm^2/s; p=0.01), 6MWD (341±95 m; p=0.008) and SGRQ total score (29±21; p=0.01) compared with ND subjects, but there was no significant difference for RA_{950} (p=0.53). In comparison with stage I COPD, AD subjects had a significantly reduced 6MWD (341±95 m; p=0.005), FVC (93±12%$_{pred}$; p=0.001), RA_{950} (1.6±1.1; p=0.0008) and ADC (0.30±0.03 cm^2/s; p=0.02), and a significantly greater FEV_1/FVC (80±7%; p<0.0001) and no significant difference for SGRQ total score (p=0.59).

Figure 2A shows the mean ADC on a slice by slice basis in the anterior to posterior direction for ND, AD and stage I COPD subjects. For AD ex-smokers, the ADC gradient in the anterior–posterior direction (ADC AP_G) was significantly lower than for ND (p=0.02) and not significantly different from COPD subjects (p=0.20). Figure 2B shows the significant correlation between ADC AP_G and the 6MWD (r=−0.51, p=0.0002).

Figure 3 shows the correlations between ^{3}He ADC and CT RA_{950} with DL_{CO}, SGRQ and 6MWD. There was a significant correlation between ^{3}He ADC and DL_{CO} (r=−0.55, p<0.0001) and SGRQ (r=0.34, p=0.02) but not 6MWD (r=−0.17, p=0.24), and as shown in figure 2B, ADC AP_G was significantly correlated with 6MWD. RA_{950} was significantly correlated with DL_{CO} (r=−0.31, p=0.03) but not SGRQ (r=0.24, p=0.10) or 6MWD (r=0.0013, p=0.99).

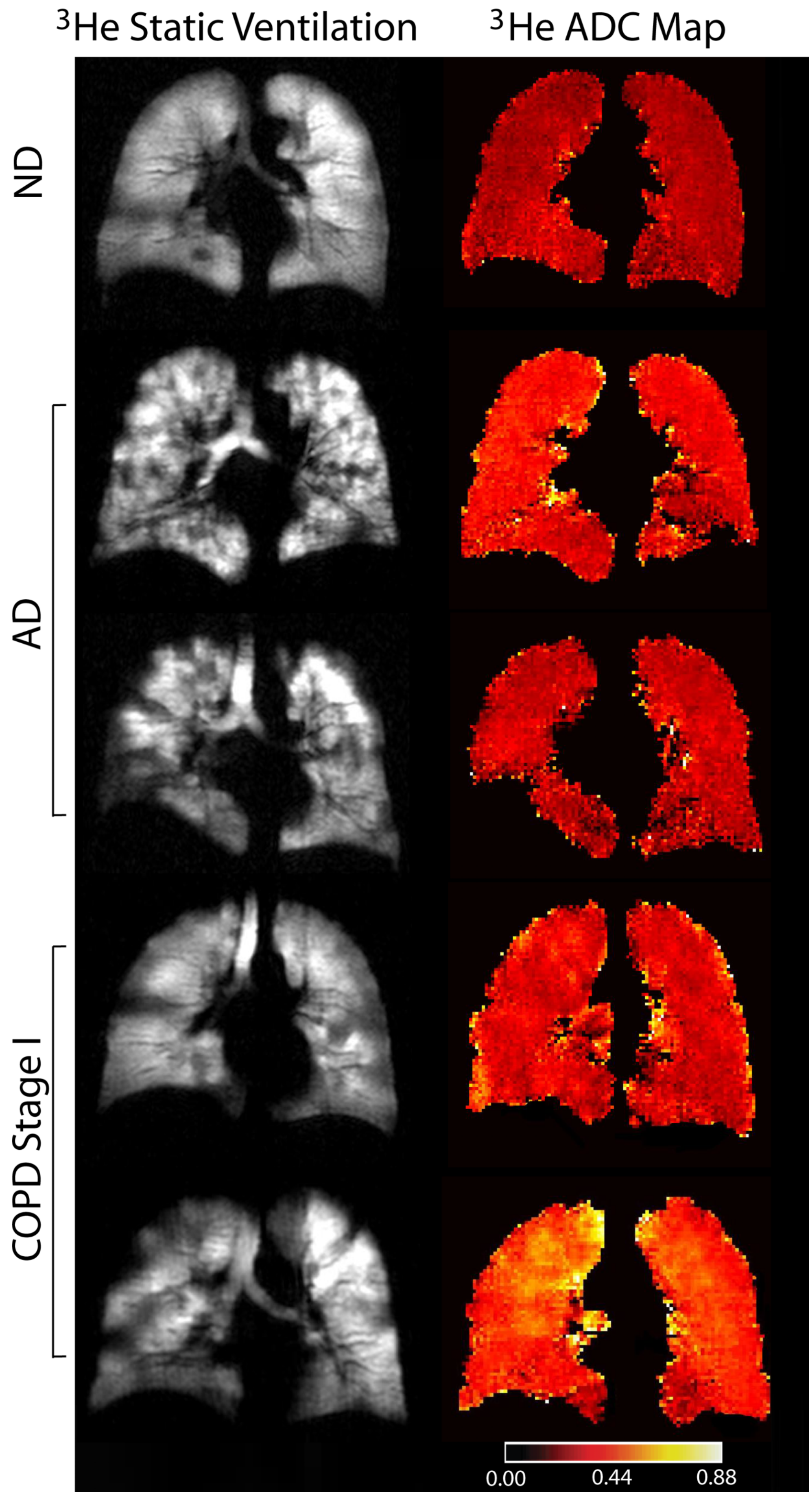

Figure 1 Helium-3 (^{3}He) MRI static ventilation images and ^{3}He apparent diffusion coefficient (ADC) maps for a representative ND and two representative AD and COPD stage I ex-smokers. ND subject is a 70-year-old man with FEV_1=101%$_{pred}$, FEV_1/FVC=0.75, DL_{CO}=113%$_{pred}$, ^{3}He ADC=0.26 cm^2/s and CT RA_{950}=1.25. AD subject No 1 is a 74-year-old man with FEV_1=89%$_{pred}$, FEV_1/FVC=0.77, DL_{CO}=41%$_{pred}$, ^{3}He ADC=0.31 cm^2/s and CT RA_{950}=1.52. AD subject No 2 is a 74-year-old man with FEV_1=95%$_{pred}$, FEV_1/FVC=0.85, DL_{CO}=63%$_{pred}$, ^{3}He ADC=0.29 cm^2/s and CT RA_{950}=0.52. GOLD stage I COPD subject No 1 is a 74-year-old man with FEV_1=86%$_{pred}$, FEV_1/FVC=0.59, DL_{CO}=45%$_{pred}$, ^{3}He ADC=0.37 cm^2/s and CT RA_{950}=6.14. GOLD stage I COPD subject No 2 is a 78-year-old man with FEV_1=118%$_{pred}$, FEV_1/FVC=0.62, DL_{CO}=71%$_{pred}$, ^{3}He ADC=0.38 cm^2/s and CT RA_{950}=5.52. AD, abnormal DL_{CO}; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, force vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ND, normal DL_{CO}; RA_{950}, relative area with attenuation values below −950 HU.

DISCUSSION

To better understand the relationship between lung structural markers, symptoms and physiological measurements in ex-smokers, we evaluated 53 ex-smokers, including 38 subjects who did not have a diagnosis of COPD and 15 subjects with stage I COPD, and observed the following. (1) Nineteen of 38 ex-smokers showed normal spirometry and CT but abnormal DL_{CO} and 19/38 ex-smokers showed normal spirometry, CT and DL_{CO}. (2) Subjects with abnormal DL_{CO} had significantly worse 6MWD compared with stage I COPD ex-smokers and significantly worse ^{3}He ADC, SGRQ and 6MWD compared with subjects with normal DL_{CO}. (3) Subjects with abnormal DL_{CO} had significantly smaller ^{3}He MRI ADC AP gradients compared with subjects with normal DL_{CO}.

We were surprised that half of the ex-smokers without COPD showed abnormal DL_{CO} and significantly worse ^{3}He ADC, but

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

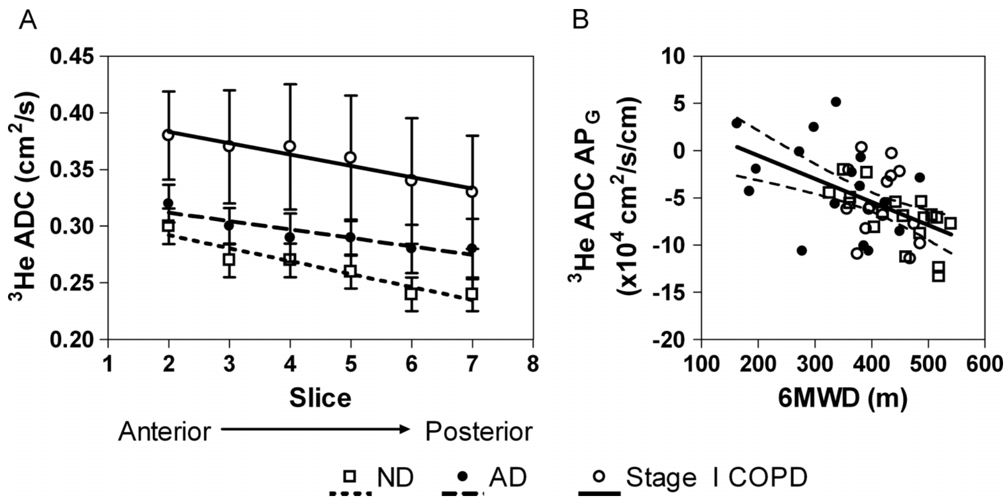

Figure 2 Regional helium-3 (^{3}He) MRI ADC anterior–posterior gradients (AP_G) for ND, AD and stage I COPD subjects, and correlation between ^{3}He ADC AP_G with 6MWD. (A) Mean AP_G was statistically significantly different for AD and ND subjects (AD: $AP_G=-3.55\times10^{-4}\pm4.85\times10^{-4}$ cm^2/s/cm; ND: $AP_G=-7.03\times10^{-4}\pm3.03\times10^{-4}$ cm^2/s/cm; p=0.02) but not between the AD and stage I COPD subjects (COPD: $AP_G=-5.58\times10^{-4}\pm 3.73\times10^{-4}$ cm^2/s/cm; p=0.20). Error bars represent the ADC SD for each image slice. (B) ^{3}He AP_G ADC was significantly correlated with 6MWD (r=−0.51, p=0.0002, r^2=0.26, p=0.0002, y=−0.02x+4.4). Dotted lines represent the 95% CIs of the regression. AD, abnormal DL_{CO}; ADC, apparent diffusion coefficient; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; 6MWT, 6 min Walk Test; ND, normal DL_{CO}.

with normal CT, which, based on previous studies,[14 15] was an unexpected result. Although we were not able to confirm significant disease other than emphysema that could account for these findings, we note that a previous evaluation[14] of 10 younger asymptomatic smokers (mean age=47 years, range=23–73) showed that three of five subjects aged 60 years or older also reported DL_{CO}<75%$_{pred}$. In ex-smokers, abnormal DL_{CO} is thought to reflect diminished lung surface area available for gas exchange although DL_{CO} also reflects the volume of blood in the pulmonary capillaries and thickness of the alveolar capillary membrane,[27] related to bronchiectasis and interstitial lung disease.[28] Abnormally low DL_{CO} is also consistent with pulmonary vascular disease,[29] and such patients exhibit normal spirometry, dyspnoea on exertion[30] and a decline in oxygen saturation with exertion.[31] In the current study, AD subjects did not show reduced oxygen saturation during the 6MWT nor did they report a history of pulmonary vascular disease, so there was no evidence to support the notion that pulmonary vascular disease was responsible for the abnormal exercise performance and dyspnoea observed here. Although DL_{CO} is a very sensitive marker of emphysema in smokers,[8] reproducibility can be low, and in some cases, low to moderate correlations have been reported between DL_{CO} and pathological assessments of emphysema.[32 33]

Previous work by Woods and Hogg[34] compared ^{3}He ADC with histology measurements of emphysema in explanted lungs and showed that ADC values could be used to distinguish normal from emphysematous lung tissue with greater precision than the mean linear intercept measurement from histology samples. Another previous study in COPD showed that while ^{3}He ADC correlated significantly with CT measurements (ie, RA_{950}), stronger correlations were observed for ^{3}He ADC and DL_{CO} than for RA_{950} and DL_{CO}.[35] In asymptomatic smokers, ^{3}He ADC was shown to correlate with DL_{CO}, but there was no significant correlation between DL_{CO} and CT RA_{950}.[14] Finally, abnormally elevated ^{3}He ADC values were previously observed in never smokers exposed to significant second hand-smoke[36] compared with never smokers with no such exposure. Taken together, these previous findings support the observation here that elevated ^{3}He ADC in ex-smokers with abnormal DL_{CO} may reflect mild emphysema not detected by CT. Our observations are also consistent with previous reports[5–8 37] and the identification of mild emphysema using histology that was not predicted using preoperative CT.[38 39] While we cannot rule out the presence of small airways disease in subjects with AD, there was no significant difference between the AD and ND subjects for ^{3}He VDP and CT WA%, both of which provide estimates of airways disease. Taken together, these results suggest that ^{3}He ADC is sensitive to very mild emphysema in subjects with abnormal DL_{CO} who have no CT evidence of airways disease or emphysema.

Concomitant with significantly elevated ^{3}He ADC, we observed significantly worse 6MWD in AD compared with COPD and ND ex-smokers. This is an important finding and the first to provide evidence of a relationship between ^{3}He MRI ADC reflective of early or mild emphysema and exercise capacity. It is also important to note that the ratio of female/male ex-smokers with AD was 11/8 (1.4), and for ND this ratio was 3/16 (0.2). Although the current study was not powered to evaluate sex differences, previous evidence suggests that female sex is significantly associated with early onset COPD.[40 41] However, previous studies have also shown that emphysema dominates in men compared with women,[42] whereas here the sex ratio was reversed. We note that imaging was performed at a fixed volume and because there were more women in the AD group (who potentially had smaller lungs), we investigated the relationship between lung size and ^{3}He ADC and observed no correlation for ^{3}He ADC with height (r=−0.36, p=0.18), total lung capacity (r=0.33, p=0.21) or thoracic cavity volume (r=−0.20, p=0.45). Therefore, the elevated ADC in the AD subjects observed here was not related to lung size and cannot explain the preponderance of female subjects in the AD subgroup. Consistent with our findings, the 6MWD in COPD was also previously shown to be lower for FEV_1 matched women versus men.[43]

We took advantage of the fact that ^{3}He MRI diffusion weighted images were acquired in the supine position and

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

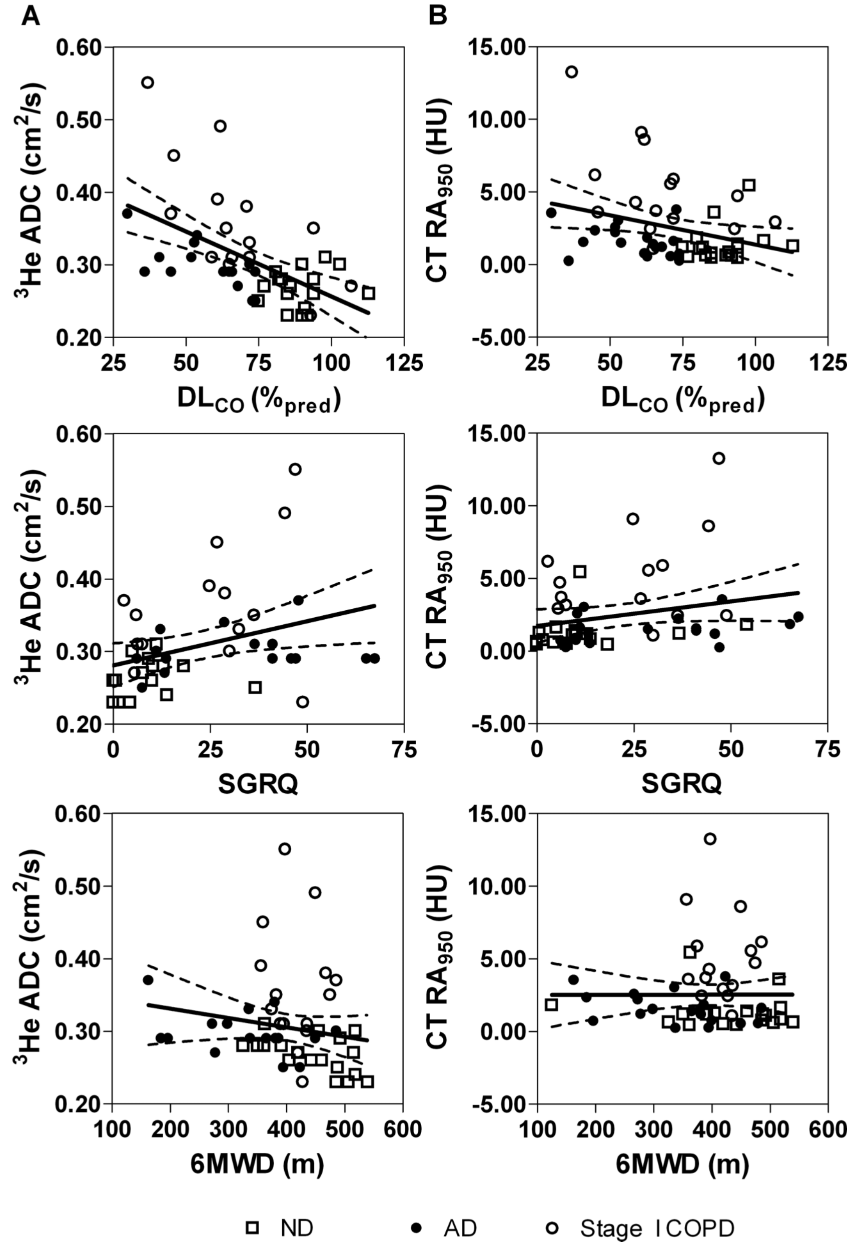

Figure 3 Correlation between helium-3 (^{3}He) ADC and CT RA_{950} with DL_{CO}, SGRQ and 6MWD for ND, AD and stage I COPD subjects. (A) ^{3}He ADC was significantly correlated with DL_{CO} (r=−0.55, p<0.0001, r^2=0.31, p<0.0001, y=−0.0018x+0.44) and SGRQ (r=0.34, p=0.02, r^2=0.12, p=0.02, y=0.0012x+0.28) but not with 6MWD (r=−0.17, p=0.24, r^2=0.03, p=0.24, y=−0.00013x+0.36). (B) CT RA_{950} was significantly correlated with DL_{CO} (r=−0.31, p=0.03, r^2=0.09, p=0.02, y=−0.040x+5.42) but not with SGRQ (r=0.24, p=0.10, r^2=0.06, p=0.10, y=−0.034x+1.71) or 6MWD (r=0.0013, p=0.99, r^2<0.0001, p=0.99, y=0.00003x+2.5). Dotted lines represent the 95% CIs of the regression. AD, abnormal DL_{CO}; ADC, apparent diffusion coefficient; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; 6MWT, 6 min Walk Test; ND, normal DL_{CO}; RA_{950}, relative area with attenuation values below −950 HU; SGRQ, St George's Respiratory Questionnaire.

measured compression of the dependent lung due to gravity. Several sites have reported smaller ^{3}He ADC in the dependent lung (or posterior slices) relative to the non-dependent lung,[25 44 45] likely due to gravitational compression of the parenchyma. In COPD subjects,[25 44] this anterior to posterior difference is significantly smaller and this is thought to be due to regional gas trapping that counteracts gravitational compression of the dependent regions. Here we observed that these gradients were significantly smaller in AD subjects compared with ND subjects, suggesting that regional gas trapping was greater in the AD subgroup.

Finally, we showed that ^{3}He ADC was significantly correlated with SGRQ and that ^{3}He ADC AP_Gs were significantly correlated with the 6MWD. The significant relationships between ^{3}He ADC with respiratory symptoms and exercise capacity suggest that in early emphysema, symptomatic changes can go unnoticed in older patients even when standardised tests report significant changes in health related quality of life and exercise capacity. While elevated ^{3}He ADC in asymptomatic ex-smokers was previously described,[14 15] the imaging to exercise capacity and imaging to symptoms correlations observed here in very early emphysema are novel findings. The unexpected finding of ^{3}He ADC AP gradient correlations with 6MWD also provides more evidence about the role of mild emphysema and regional gas trapping that may together lead to exercise limitation even in early disease. AD ex-smokers also reported a SGRQ that was not significantly different from the stage I COPD ex-smokers, and worse than ND subjects, which supports previous reports of compromised health related quality of life[46] and reduced work capacity in very early disease.[47]

This study was limited by the relatively small number of subjects evaluated, although we note that this is the single largest prospective study that directly compared CT, symptoms, exercise capacity and ^{3}He MRI in ex-smokers with and without airflow obstruction. We admit that we were surprised to find such a large proportion of asymptomatic ex-smokers without airflow limitation and abnormal DL_{CO} in this study. This finding raises the important question of whether this subgroup is

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

atypical or perhaps this is a unique finding because 'asymptomatic' ex-smokers are rarely administered the SGRQ or the 6MWT. Importantly, the selection criteria, manner and location for subject recruitment are those we have previously used for the recruitment of older ex-smokers, and typical of other studies. It is possible that in this unique subgroup, patients were less likely to recognise and report symptoms. Our results certainly raise many intriguing questions regarding whether these subjects are unusual or whether we have simply uncovered a group of older ex-smokers with both unrecognised mild emphysema and functional limitations.

In summary, we evaluated 38 ex-smokers without airflow limitation and 15 ex-smokers with COPD. In the absence of spirometry or CT abnormalities, half of the ex-smokers without COPD showed abnormal DL_{CO} and abnormally elevated ^{3}He ADC, consistent with early or mild emphysema. These subjects had significantly and markedly worse 6MWD and SGRQ compared with ex-smokers with normal ADC and DL_{CO}, and worse 6MWD than subjects with COPD. These findings provide a better understanding of abnormal DL_{CO} in ex-smokers without COPD.

Acknowledgements We thank S McKay and S Halko for clinical coordination and clinical database management, and T Szekeres for MRI of research volunteers.

Contributors MK was responsible for acquisition of the data, data analysis and interpretation, and drafting, final revisions and final approval of the manuscript. AO was responsible for acquisition of the data, and revision and final approval of the manuscript. SS was responsible for acquisition of the data, and revision and final approval of the manuscript. AW was responsible for acquisition of the data, and revision and final approval of the manuscript. HOC was responsible for conception and design, data interpretation, final revisions to the manuscript and final approval of the manuscript. NAMP was responsible for conception and design, data interpretation, final revisions to the manuscript and final approval of the manuscript. DGM was responsible for conception and design, data interpretation, final revisions to the manuscript and final approval of the manuscript. GP, the principal investigator, was responsible for conception and design, data acquisition and analysis plan and interpretation, drafting, final revisions and final approval of the manuscript, as well as guarantor of the integrity of the data. GP was also responsible for good clinical practice.

Funding MK and SS gratefully acknowledge scholarship support from the Natural Sciences and Engineering Research Council (NSERC, Canada) and GP gratefully acknowledges support from a Canadian Institutes of Health Research (CIHR) New Investigator Award. Ongoing research funding from the CIHR Team grant CIF# 97687 is gratefully acknowledged.

Competing interests None.

Ethics approval The study was approved by the local research ethics board and Health Canada, and the study was compliant with the Personal Information Protection and Electronic Documents Act (Canada) and the Health Insurance Portability and Accountability Act (USA).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Rabe KF, Hurd S, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532–55.

2 Hardie JA, Buist AS, Vollmer WM, *et al*. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002;20:1117–22.

3 Shahab L, Jarvis MJ, Britton J, *et al*. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax* 2006;61:1043–7.

4 Wan ES, Hokanson JE, Murphy JR, *et al*. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study. *Am J Respir Crit Care Med* 2011;184:57–63.

5 Reid J, Cockcroft D. Severe centrilobular emphysema in a patient without airflow obstruction. *Chest* 2002;121:307–8.

6 Chin NK, Lim TK. A 39-year-old smoker with effort dyspnea, normal spirometry results, and low diffusing capacity. *Chest* 1998;113:231–3.

7 Corsico A, Niniano R, Gatto E, *et al*. "Nonobstructive" emphysema of the lung. *Respir Med Extra 7* 2007;3:189–91.

8 Klein JS, Gamsu G, Webb WR, *et al*. High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest radiographs and isolated low diffusing capacity. *Radiology* 1992;182:817–21.

9 Gordon C, Gudi K, Krause A, *et al*. Circulating endothelial microparticles as a measure of early lung destruction in cigarette smokers. *Am J Respir Crit Care Med* 2011;184:224–32.

10 Nakano Y, Muro S, Sakai H, *et al*. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;162:1102–8.

11 Mathew L, Kirby M, Etemad-Rezai R, *et al*. Hyperpolarized (3)He magnetic resonance imaging: preliminary evaluation of phenotyping potential in chronic obstructive pulmonary disease. *Eur J Radiol* 2011;79:140–6.

12 Chen XJ, Moller HE, Chawla MS, *et al*. Spatially resolved measurements of hyperpolarized gas properties in the lung in vivo. Part I: diffusion coefficient. *Magn Reson Med* 1999;42:721–8.

13 Saam BT, Yablonskiy DA, Kodibagkar VD, *et al*. MR imaging of diffusion of (3)He gas in healthy and diseased lungs. *Magn Reson Med* 2000;44:174–9.

14 Fain SB, Panth SR, Evans MD, *et al*. Early emphysematous changes in asymptomatic smokers: detection with 3He MR imaging. *Radiology* 2006;239:875–83.

15 Swift AJ, Wild JM, Fichele S, *et al*. Emphysematous changes and normal variation in smokers and COPD patients using diffusion 3He MRI. *Eur J Radiol* 2005;54:352–8.

16 Pellegrino R, Viegi G, Brusasco V, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–68.

17 Irvin C. *Guide to the evaluation of pulmonary function. Physiologic basis of respiratory disease*. Hamilton: BC Decker Inc, 2005: 649–58.

18 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.

19 Jones PW, Quirk FH, Baveystock CM, *et al*. A self-complete measure of health status for chronic airflow limitation. The St George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–7.

20 Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. *Respir Med* 1991;85(Suppl B):25–31.

21 Enright PL. The six-minute walk test. *Respir Care* 2003;48:783–5.

22 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.

23 Kirby M, Heydarian M, Svenningsen S, *et al*. Hyperpolarized (3)He magnetic resonance functional imaging semiautomated segmentation. *Acad Radiol* 2012;19:141–52.

24 Kirby M, Heydarian M, Wheatley A, *et al*. Evaluating bronchodilator effects in chronic obstructive pulmonary disease using diffusion-weighted hyperpolarized helium-3 magnetic resonance imaging. *J Appl Physiol* 2012;112:651–7.

25 Evans A, McCormack D, Ouriadov A, *et al*. Anatomical distribution of 3He apparent diffusion coefficients in severe chronic obstructive pulmonary disease. *J Magn Reson Imaging* 2007;26:1537–47.

26 Gevenois PA, De Vuyst P, De Maertelaer V, *et al*. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;154:187–92.

27 George RB, Light RW, Matthay MA, *et al*. *Chest medicine: essentials of pulmonary and critical care medicine*, 5th edn. Philadelphia: Lippincott, Williams and Wilkins, 2005.

28 Plummer AL. The carbon monoxide diffusing capacity: clinical implications, coding, and documentation. *Chest* 2008;134:663–7.

29 Steenhuis LH, Groen HJ, Koeter GH, *et al*. Diffusion capacity and haemodynamics in primary and chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2000;16:276–81.

30 DePaso WJ, Winterbauer RH, Lusk JA, *et al*. Chronic dyspnea unexplained by history, physical examination, chest roentgenogram, and spirometry. Analysis of a seven-year experience. *Chest* 1991;100:1293–9.

31 Paciocco G, Martinez FJ, Bossone E, *et al*. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. *Eur Respir J* 2001;17:647–52.

32 Morrison NJ, Abboud RT, Ramadan F, *et al*. Comparison of single breath carbon monoxide diffusing capacity and pressure–volume curves in detecting emphysema. *Am Rev Respir Dis* 1989;139:1179–87.

33 West WW, Nagai A, Hodgkin JE, *et al*. The National Institutes of Health Intermittent Positive Pressure Breathing trial—pathology studies. III. The diagnosis of emphysema. *Am Rev Respir Dis* 1987;135:123–9.

34 Woods JC, Choong CK, Yablonskiy DA, *et al*. Hyperpolarized 3He diffusion MRI and histology in pulmonary emphysema. *Magn Reson Med* 2006;56:1293–300.

35 Diaz S, Casselbrant I, Piitulainen E, *et al*. Validity of apparent diffusion coefficient hyperpolarized 3He-MRI using MSCT and pulmonary function tests as references. *Eur J Radiol* 2009;71:257–63.

36 Wang C, Mugler JP, de Lange EE, *et al*. Healthy nonsmokers exposed regularly to secondhand smoke have evidence of lung injury detected by hyperpolarized-3 diffusion. *American Journal of Respiratory and Critical Care Medicine* 2010;181. doi:10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A5438

37 Hogg JC, Wright JL, Wiggs BR, *et al*. Lung structure and function in cigarette smokers. *Thorax* 1994;49:473–8.

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

38 Miller RR, Muller NL, Vedal S, *et al*. Limitations of computed tomography in the assessment of emphysema. *Am Rev Respir Dis* 1989;139:980–3.
39 Muller NL, Staples CA, Miller RR, *et al*. "Density mask". An objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782–7.
40 Sorheim IC, Johannessen A, Gulsvik A, *et al*. Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010;65:480–5.
41 Foreman MG, Zhang L, Murphy J, *et al*. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. *Am J Respir Crit Care Med* 2011;184:414–20.
42 Camp PG, Coxson HO, Levy RD, *et al*. Sex differences in emphysema and airway disease in smokers. *Chest* 2009;136:1480–8.
43 Marin JM, Carrizo SJ, Gascon M, *et al*. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1395–9.
44 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.
45 Fichele S, Woodhouse N, Swift AJ, *et al*. MRI of helium-3 gas in healthy lungs: posture related variations of alveolar size. *J Magn Reson Imaging* 2004;20:331–5.
46 Berry MJ, Rejeski WJ, Adair NE, *et al*. Exercise rehabilitation and chronic obstructive pulmonary disease stage. *Am J Respir Crit Care Med* 1999;160:1248–53.
47 Carter R, Nicotra B, Blevins W, *et al*. Altered exercise gas exchange and cardiac function in patients with mild chronic obstructive pulmonary disease. *Chest* 1993;103:745–50.

Thorax: first published as 10.1136/thoraxjnl-2012-203108 on 19 April 2013. Downloaded from http://thorax.bmj.com/ on April 20, 2024 by guest. Protected by copyright.