8-1-2014

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Citation of this paper:

Sheikh, Khadija; Paulin, Gregory A; Svenningsen, Sarah; Kirby, Miranda; Paterson, Nigel A M; McCormack, David G; and Parraga, Grace, "Pulmonary ventilation defects in older never-smokers" (2014). *Medical Biophysics Publications*. 113.

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Pulmonary ventilation defects in older never-smokers

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

Submitted 22 January 2014; accepted in final form 29 May 2014

Sheikh K, Paulin GA, Svenningsen S, Kirby M, Paterson NA, McCormack DG, Parraga G. Pulmonary ventilation defects in older never-smokers. *J Appl Physiol* 117: 297–306, 2014. First published June 5, 2014; doi:10.1152/jappphysiol.00046.2014.—Hyperpolarized ³He MRI previously revealed spatially persistent ventilation defects in healthy, older compared with healthy, younger never-smokers. To understand better the physiological consequences and potential relevance of ³He MRI ventilation defects, we evaluated ³He-MRI ventilation-defect percent (VDP) and the effect of deep inspiration (DI) and salbutamol on VDP in older never-smokers. To identify the potential determinants of ventilation defects in these subjects, we evaluated dyspnea, pulmonary function, and cardiopulmonary exercise test (CPET) measurements, as well as occupational and second-hand smoke exposure. Fifty-two never-smokers (71 ± 6 yr) with no history of chronic respiratory disease were evaluated. During a single visit, pulmonary function tests, CPET, and ³He MRI were performed and the Burden of Obstructive Lung Disease questionnaire administered. For eight of 52 subjects, there was spirometry evidence of airflow limitation (Global Initiative for Chronic Obstructive Lung Disease–Unclassified, I, and II), and occupational exposure was reported in 13 of 52 subjects. In 13 of 52 (25%) subjects, there were no ventilation defects and in 39 of 52 (75%) subjects, ventilation defects were observed. For those subjects with ventilation defects, six of 39 showed a VDP response to DI/salbutamol. Ventilation heterogeneity and VDP were significantly greater, and forced expiratory volume in 1 s (FEV₁)/forced vital capacity was significantly lower ($P < 0.05$) for subjects with ventilation defects with a response to DI/salbutamol than subjects with ventilation defects without a response to DI/salbutamol and subjects without ventilation defects. In a step-wise, forward multivariate model, FEV₁, inspiratory capacity, and airway resistance significantly predicted VDP ($R^2 = 0.45$, $P < 0.001$). In conclusion, most never-smokers had normal spirometry and peripheral ventilation defects not reversed by DI/salbutamol; such ventilation defects were likely related to irreversible airway narrowing/collapse but not to dyspnea and decreased exercise capacity.

bronchodilation; cardiopulmonary exercise testing; deep inspiration; pulmonary aging; ³He MRI

PULMONARY AGING IS CONCOMITANT with changes in elastic recoil (10, 42, 43), chest-wall compliance (10, 43), and respiratory muscle strength (8, 21). In concert with these physiological changes, functional residual capacity (FRC), residual volume (RV), and airway resistance (Raw) also increase (21), whereas the forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) (9), and inspiratory capacity (IC) decrease (35).

Healthy, older adults may experience breathlessness during everyday activities (1, 17, 19, 30, 41), and this is related to mortality risk (1, 19, 41). In addition, in older adults, cardio-

pulmonary exercise test (CPET) measurements (3) correlate more strongly with overall health status than do measurements of resting lung function (3a, 12, 33). Moreover, CPET measurements show that in “normal,” healthy aging, there is lower exercise-related oxygen uptake (VO₂), as well as greater minute ventilation (V_E) and increased respiratory exchange ratio (RER) (16, 23, 24). Recent studies have also shown that during exercise, significant ventilatory impairment is possible without increased dyspnea or premature exercise limitation (13).

The role of occupational and second-hand tobacco smoke exposure is important to acknowledge and understand in both normal and accelerated lung aging. In this context, the Burden of Obstructive Lung Disease (BOLD) study (5) showed that in never-smokers, the prevalence of airflow limitation consistent with chronic obstructive pulmonary disease (COPD) was as high as 30%. The BOLD study also revealed the critical relationships in never-smokers among airflow limitation and age, history of occupational exposure, and childhood respiratory disease (28).

³He ventilation MRI provides high-resolution, noninvasive measurements of lung function (27, 37) and identifies those regions of the lung that participate in ventilation and those that do not (27, 36). In healthy, young subjects, a single inhalation of hyperpolarized ³He gas results in homogeneous lung filling, but in older never-smokers, characteristic “focal” ventilation defects are observed, corresponding to poorly ventilated lung regions (36, 37). In older never-smokers, ventilation defects are commonly observed on the lung periphery and the dependent lung regions, and this is in contrast with COPD and asthma, where numerous and large defects are heterogeneously distributed throughout the lung (6, 27, 37).

The finding of spatially and temporally persistent ³He MRI ventilation defects in older never-smokers with normal spirometry (36, 37) raises questions about the physiological meaning of ventilation defects in all subjects. For example, as shown previously, ³He MRI ventilation abnormalities induced by methacholine challenge in young, healthy volunteers were reversed by deep inspiration (DI) (44). In young asthmatics, salbutamol inhalation reduced ventilation defects observed with ³He MRI after methacholine challenge (40), but the effect of DI was not investigated. Raw measurements determined that asthmatic subjects cannot maximally dilate their airways and that the dilation that does occur after DI constricts back to baseline much faster than in healthy subjects (22). This suggested that in asthma, ventilation defects were related to salbutamol-responsive airway abnormalities, whereas in healthy volunteers, ventilation defects may reflect normal airway smooth muscle behavior that is reversible using DI.

We hypothesized that in older never-smokers, narrowed or collapsed airways were responsible for the persistent ventila-

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tion defects observed, and these would be responsive to and improve following DI. To test this hypothesis, we evaluated the effect of both DI and salbutamol on ^3He ventilation defects in a relatively large group of older never-smokers with no history of respiratory disease. We also evaluated the relationship of ventilation defects with occupational exposures, pulmonary function, and CPET measurements.

MATERIALS AND METHODS

Study subjects and logistics. All subjects provided written, informed consent to a study protocol approved by a Local Research Ethics Board and Health Canada. Subjects were enrolled between the ages of 60 and 90 yr with a smoking history of <0.5 pack-years and no history of chronic respiratory or cardiovascular disease. After providing consent, all subjects made a single, 2- to 3-h visit and underwent the following evaluations in the same order: 1) BOLD occupational questionnaire (5), 2) spirometry, 3) plethysmography and the diffusing capacity of carbon monoxide (DL_{CO}), 4) CPET, including dyspnea score, and 5) MRI. Pulmonary function tests were completed in ~ 45 min, followed by CPET, which was completed in 10–15 min. MRI was performed following CPET, and for subjects who did not have ventilation defects and those with defects that responded to DI, MRI was completed within 10–15 min. For subjects who were administered salbutamol, MRI was performed 25–30 min post-salbutamol inhalation.

Questionnaire. All subjects completed the BOLD occupational questionnaire (5) with exposures defined as described previously (28), including: 1) organic dust (farming; flour, feed, or grain milling; and cotton or jute processing), 2) inorganic dust (working with asbestos; hard-rock mining; coal mining; sandblasting; and foundry or steel milling), and 3) irritant gases (welding; firefighting; and chemical or plastics manufacturing). We also queried subjects directly about spousal and/or life-partner smoking history and recorded potential household second-hand smoke exposure.

Pulmonary function and CPETs. Spirometry was performed using an EasyOne spirometer (ndd Medizintechnik, Zurich, Switzerland), according to American Thoracic Society (ATS) guidelines (31). Body plethysmography was performed for the measurement of lung volumes, and DL_{CO} was measured using the gas analyzer (MedGraphics, St. Paul, MN). IC, defined as the volume change recorded at the mouth when taking a slow, full inspiration from a position of passive end-expiration, was measured using body plethysmography (31), as was Raw, defined as the pressure difference/unit flow. Post-DI pulmonary function tests were not performed, but for subjects administered salbutamol, FEV₁ and FVC were recorded, 35–40 min postinhalation and upon completion of MRI.

After completion of pulmonary function tests, all subjects performed CPET using a cycle ergometer (Ultima PFX; MedGraphics), according to ATS guidelines (3a), with a 2-min warm-up with no resistance, followed by a 20-W incremental increase in work rate. Subjects were required to pedal at a frequency of 60 rpm with increasing work rate until the ventilatory anaerobic threshold was reached. Ventilatory anaerobic threshold was defined as the time when CO_2 production increased disproportionately in relation to VO_2 . The ventilatory anaerobic threshold was determined by onboard software for the CPET unit, which used an iterative regression and analysis of slope. Subjects continued exercise until fatigue was reported. VO_2 , RER, work rate (i.e., power), as well as V_E were measured at rest, at the ventilatory anaerobic threshold, and when maximum pulmonary VO_2 ($\text{VO}_{2\text{max}}$) was reached. The time taken to reach $\text{VO}_{2\text{max}}$ was also recorded. CPET measurements, including VO_2 , power, and V_E , were adjusted for age, sex, and height using percent-predicted values reported previously (11, 16, 24). Borg dyspnea and leg discomfort scales were used before and after exercise.

Image acquisition. MRI was performed after completion of all pulmonary function and CPETs on a 3.0 Tesla MR750 (GE Healthcare, Milwaukee, WI) system, as described previously (37), using a whole-body gradient set with a maximum gradient amplitude of 1.94 G/cm and a single-channel, rigid elliptical transmit/receive chest coil (Rapid Biomedical GmbH, Rimpf, Germany). For both ^1H and ^3He MRI, subjects were instructed to inhale a gas mixture from a 1-liter Tedlar bag (Jensen Inert Products, Coral Springs, FL) from FRC, and image acquisition was performed during a 16-s breath-hold. Coronal (anatomical) ^1H MRI was performed using the whole-body radiofrequency coil and ^1H fast-spoiled, gradient-recalled echo sequence using a partial echo [16 s total data acquisition; repetition time (TR)/echo time (TE)/flip angle = 4.7 ms/1.2 ms/30°, field of view (FOV) = 40 × 40 cm, bandwidth = 24.4 kHz, matrix = 128 × 80, 15–17 slices, 15 mm slice thickness, zero gap], as described previously (37). ^3He MRI static ventilation images were acquired using a fast-gradient echo method using a partial echo (14 s total data acquisition; TR/TE/flip angle = 4.3 ms/1.4 ms/7°, FOV = 40 × 40 cm, bandwidth = 48.8 kHz, matrix = 128 × 80, 15–17 slices, 15 mm slice thickness, zero gap).

Immediately after image acquisition at the scanner, while the subject was still in position, ^3He static ventilation images were qualitatively evaluated for ventilation abnormalities by a single, trained observer. If ^3He gas were homogeneously distributed throughout the lung, and there were no visible ventilation defects, then the subjects were classified as belonging to the no-defect group, and the session was deemed complete. In contrast, if ^3He gas were heterogeneously distributed throughout the lung and/or there were visually obvious ventilation defects, then the subject was classified as having ventilation defect(s). Upon qualitative inspection, subjects with visually obvious ventilation defects were instructed to perform DI. They were instructed to sit up while remaining on the scanner bed and to take four deep breaths in through their nose and out through their mouth. Imaging was performed immediately following DI. If defects persisted following DI, then the subject inhaled four puffs (400 μg) of salbutamol while seated upright, and 25 min later, imaging was performed on a final occasion.

Image analysis. Based on visual inspection at the scanner, subjects were classified as: 1) no defects—those subjects without visually obvious ventilation defects, 2) subjects with ventilation defects that responded to DI or salbutamol, and 3) subjects with ventilation defects that did not respond to DI or salbutamol. ^3He MRI semiautomated segmentation was performed, as described previously (25), to generate ventilation-defect percent (VDP)—the ventilation defect volume (VDV) normalized to ^1H MRI thoracic cavity volume. Briefly, ^3He static ventilation images were segmented using a k-means approach that classified voxel-intensity values into five clusters, ranging from signal void [cluster 1 (C1) or VDV] and hypointense [cluster 2 (C2)] to hyperintense signal [cluster 5 (C5)], therefore generating a gas distribution cluster map. For delineation of the ventilation-defect boundaries, a seeded, region-growing algorithm was used to segment the ^1H MRI thoracic cavity for registration to the cluster map, as described previously (25).

Ventilation heterogeneity was estimated, according to a previously described method (44), using the coefficient of variation (COV). A local COV, rather than a global COV, was generated (44) to ensure that local ventilation heterogeneity was not ignored. Briefly, for each voxel in a region of interest (ROI), a local ventilation heterogeneity value was calculated by computing the COV of the signal intensity in a 5 × 5 voxel neighborhood, which corresponded to a 244-mm² area centered on that voxel. To ensure that the 5 × 5 voxel neighborhood did not include voxels that were outside of the lungs, a signal-to-noise threshold of five was established. For example, any voxels that were in a neighborhood with an overall signal-to-noise ratio (SNR) of less than five were excluded from the COV computation. COV of the lung was calculated for each subject as in Eq. 1

$$COV = \frac{\sqrt{\frac{\sum_{i=1}^N \sigma_i^2}{N}}}{\frac{\sum_{i=1}^N \mu_i}{N}}$$

where σ_i is the SD of the signal intensity of the 5×5 voxel neighborhood, μ_i is the mean signal intensity of the 5×5 voxel neighborhood, and N is the number of ventilation ROIs in the lung. The ventilated lung ROI was defined as gas distribution cluster map C2–C5.

We also measured regional differences in VDP for the center nine, 15-mm-thick slices using several different measurements, as shown in Fig. 1. The VDP gradient in the posterior-anterior (PA) direction was defined as the slope of the line that described the change in VDP from the most posterior slice in centimeters over the nine central slices (with a slice thickness of 15 mm each). The center nine slices were used to ensure that the static ventilation slices across subjects had adequate SNRs (i.e., $SNR > 10$) for VDP calculations, as well as to maintain an equal number of slices among all subjects. To calculate the gradient in the superior-inferior (SI) direction, the center nine coronal slices were reformatted into 15-mm axial slices. The VDP SI gradient was defined as the slope of the line that described the change in VDP over the axial SI slices. In addition, the VDP difference between the most posterior and anterior slices (VDP Δ PA) was calculated, as was the VDP difference between the most superior and inferior slices (VDP Δ SI) of the central nine slices. The VDP located on the peripheral boundary of the lung (relative peripheral VDP) was estimated as the ratio of the VDV for the outermost 10 voxels of each slice (not including boundary voxels, defined as $SNR < 2$) to the 1H MRI thoracic-cavity volume. The proportion of ventilation defects located on the peripheral boundary was quantified as the ratio of peripheral lung VDV to whole-lung VDV (i.e., VDV_{Per}/VDV_{WL}).

Statistical analysis. ANOVA, multivariate regression, and post hoc analysis, using the Holm Bonferroni correction (45), were performed using SPSS 20.0 software (IBM, Armonk, NY). Paired sample *t*-tests were performed to determine the differences in VDP Δ PA and VDP Δ SI using SPSS 20.0. We used the National Health and Nutrition Examination Survey III reference standards (14) for percent-predicted values. Univariate relationships were determined using regression (r^2) and Pearson correlation coefficients (r) for all subjects with GraphPad Prism V.6.00 (GraphPad Software, La Jolla, CA). Step-wise, multivariate regression was used to identify the predictors of VDP. The variables considered for modeling were chosen based on statistically significant, univariate relationships with VDP. Results were considered statistically significant when the probability of making a type I error was $<5\%$ ($P < 0.05$).

Fig. 1. Schematic for regional evaluation of 3He MRI ventilation-defect percent (VDP). The central coronal static ventilation image slices (9×15 mm) were evaluated. The lung was also divided into 15-mm slices in the axial direction. The VDP Δ SI was defined as the difference between the most superior slice and the most inferior slice. The VDP Δ PA was defined as the difference between the most posterior slice and the most anterior slice.

RESULTS

Subject data. As summarized in Table 1 (and a detailed subject listing in Table 2), 52 never-smokers (71 ± 6 yr) completed all measurements during a single visit. In total, there were 13 of 52 (25%) subjects without 3He MRI ventilation defects and 39 of 52 (75%) with ventilation defects. Of those subjects with ventilation defects, six (of 39, 15%) showed a VDP response (i.e., visually obvious and quantitative decrease in VDP) to DI ($n = 4$) or salbutamol ($n = 2$).

Figure 2 shows 3He MRI coronal slices at baseline, post-DI, and post-salbutamol for four representative subjects. For the subject shown without ventilation defects, there was homogeneous signal intensity over the entire lung with no obvious ventilation defects in the center MR slice or any of the anterior-to-posterior slices. For two representative subjects that showed an imaging response to DI or salbutamol, there were ventilation defects peripherally located in the central and posterior slices that resolved in response to DI or bronchodilation. For the representative subject with ventilation defects that did not appear to respond to DI or salbutamol, a number of small peripheral ventilation defects remained spatially persistent post-DI and 25 min after salbutamol inhalation.

For the three comparator groups (Table 1), there was no significant difference for age, sex, or body mass index. However, there was a significant difference for FEV_1/FVC ($P = 0.004$), VDP, 3He COV, VDP Δ PA, and PA gradient ($P < 0.001$), as well as relative peripheral VDP ($P = 0.001$). There was no significant difference for any CPET or other pulmonary function measurements for the three subgroups. Post hoc analysis showed that the imaging responder group had significantly lower FEV_1/FVC and significantly higher VDP, 3He COV, PA Δ VDP, PA VDP gradient, and relative peripheral VDP than the no-defect and no-imaging-response groups. Figure 3 shows scatter plots for VDP, relative peripheral VDP, VDP Δ PA, VDP Δ SI, PA VDP gradient, SI VDP gradient, and 3He COV.

Table 2 shows that 13 subjects reported significant exposure, 10 of whom (77%) had ventilation defects. Of those 10 subjects, three showed an imaging response to DI or salbutamol. Table 2 also shows that eight never-smokers had spirometry evidence of airway obstruction (47) [Global Initiative for Chronic Obstructive Lung Disease (GOLD)–Unclassified ($n = 2$), GOLD I ($n = 4$), GOLD II ($n = 2$)]. Five of these eight subjects reported second-hand smoke or occupational exposures, and two subjects responded to salbutamol. In addition, 10 never-smokers had $0.70 \leq FEV_1/FVC \leq 0.73$, where the 0.73 threshold was used to compensate for the variability in FEV_1 and FVC (20, 29). The eight never-smokers with spirometry evidence of COPD had significantly greater VDP ($5.5 \pm 3.1\%$, $P < 0.001$) than the never-smokers with (VDP = $2.5 \pm 1.2\%$) or without (VDP = $1.6 \pm 0.7\%$) ventilation defects. When the subjects with spirometry evidence of COPD ($n = 8$) were removed in a sub-analysis, only VDP remained significantly different across all three subgroups ($P = 0.03$). Post hoc analysis showed that the no-imaging-response group had greater baseline VDP than the no-defect group but was not significantly different from the imaging-response group.

Pre- and post-DI/salbutamol analysis. Table 3 shows a subject listing for pre- and post-salbutamol FEV_1 , VDP, and 3He COV for all subjects administered salbutamol ($n = 35$). Three subgroups were identified for those subjects adminis-

Table 1. Baseline subject demographic and other measurements

	No Defects (n = 13)	Ventilation Defects (n = 39)		Significance of Difference
		Imaging Response (n = 6)	No Imaging Response (n = 33)	(P value)* ND-IR-NIR
<i>Demographics</i>				
Age, yr (±SD)	71 (8)	72 (4)	71 (6)	0.90
Men, n	6	3	12	
BMI, kg/m ² ([plusmn]SD)	26 (4)	27 (3)	26 (3)	0.90
<i>Occupational exposures</i>				
Organic dust, n	3	1	4	
Inorganic dust, n	0	2	2	
Irritant gases, n	0	0	1	
<i>Pulmonary function</i>				
FEV ₁ % _{pred} (±SD)	113 (11)	93 (29)	106 (20)	0.09
FVC% _{pred} (±SD)	107 (15)	96 (26)	103 (17)	0.40
FEV ₁ /FVC, % (±SD)	80 (5)	71 (4)†	77 (5)	0.004
FRC% _{pred} (±SD)	105 (24)	114 (15)	107 (17)	0.60
IC% _{pred} (±SD)	112 (20)	94 (26)	106 (19)	0.20
RV/TLC, % (±SD)	41 (7)	43 (15)	41 (7)	0.50
DL _{CO} % _{pred} (±SD)	96 (7)	75 (13)	92 (19)	0.07
Raw% _{pred} (±SD)	71 (25)	100 (82)	72 (31)	0.20
<i>CPET</i>				
VO ₂ max% _{pred} (±SD)	83 (18)	86 (11)	87 (19)	0.80
RER (±SD)	1.17 (0.15)	1.19 (0.11)	1.21 (0.12)	0.90
Power% _{pred} (±SD)	126 (38)	118 (9)	121 (31)	0.70
V _E max% _{pred} (±SD)	50 (17)	54 (19)	51 (16)	0.90
Postexercise dyspnea (±SD)	2.1 (1.4)	2.0 (1.0)	2.3 (1.6)	0.80
Postexercise leg discomfort (±SD)	11.5 (2.4)	11.0 (3.7)	10.9 (3.3)	0.90
Time to VO ₂ max, s (±SD)	478 (89)	532 (111)	494 (82)	0.50
<i>MRI</i>				
VDP, % (±SD)	1.6 (0.7)	5.8 (3.8)†	2.6 (1.2)	<0.001
³ He COV (±SD)	0.19 (0.01)	0.24 (0.04)†	0.21 (0.02)	0.001
VDP ΔPA, % (±SD)	0.7 (2.7)	11.2 (13.5)†	1.5 (4.0)	0.001
PA VDP gradient, %/cm (±SD)	−0.02 (0.17)	−0.69 (0.93)†	−0.05 (0.21)	<0.001
VDP ΔSI, % (±SD)	−1.9 (1.3)	−3.4 (9.6)	−2.8 (2.3)	0.67
SI VDP gradient, %/cm (±SD)	0.14 (0.1)	0.26 (0.72)	0.21 (0.17)	0.67
Relative peripheral VDP, % (±SD)	1.3 (0.6)	3.3 (1.8)†	1.9 (0.8)	0.001
VDV _{Per} /VDV _{WL} , % (±SD)	80 (10)	68 (13)	78 (10)	0.05

Imaging Response refers to subjects with change in ventilation-defect percent (VDP) after deep inspiration (DI) or salbutamol. No Imaging Response refers to subjects with no VDP change after salbutamol. ND, nonresponders; IR, imaging response; NIR, imaging nonresponders; BMI, body mass index; FEV₁, forced expiratory in 1 s; %_{pred}, percent predicted; FVC, forced vital capacity; FRC, functional residual capacity; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; DL_{CO}, diffusing capacity of carbon monoxide; Raw, airways resistance; CPET, cardiopulmonary exercise test; VO₂max, maximal oxygen capacity; RER, respiratory exchange ratio at VO₂max; Power, work rate; V_Emax, minute ventilation at VO₂max; Time to VO₂max, time taken to reach VO₂max during CPET; ³He COV, ventilation coefficient of variation; VDP Δ PA, change in posterior and anterior VDP; VDP Δ SI, change in superior and inferior VDP; VDV_{Per}, ventilation defect volume in the periphery of the lung; VDV_{WL}, VDV in the whole lung. *Significance of difference ($P < 0.05$) determined using multivariate ANOVA; †post hoc analysis conducted using Holm-Bonferroni, demonstrating significant difference between groups.

tered salbutamol: imaging responders, FEV₁ responders, and nonresponders. Twenty-eight of 35 subjects did not show an imaging response or a FEV₁ response to salbutamol. There were five subjects who responded to salbutamol (Δ FEV₁ > 200 ml) but did not have an imaging (VDP or C1) response to salbutamol. In addition, for these five subjects, there was no significant change in any of ventilation C2–C5 or any combination of ventilation clusters (i.e., C1 + C2) post-salbutamol. It is worth noting that one of the five FEV₁ responders reported 30 yr of occupational exposure working in the steel mill industry (S63), whereas two were lifelong farmers (S25 and S59). Finally, for those subjects administered salbutamol, there were no relationships for the change in FEV₁ post-salbutamol with change in VDP ($r^2 = 0.04$, $P = 0.50$) or change in ³He COV ($r^2 = 0.08$, $P = 0.10$).

Table 4 shows VDP and ³He COV measurements for all three time points for imaging responders (DI or salbutamol responders). There were no statistically significant differences

in ³He COV or VDP across time points for the imaging responders.

Relationships between imaging and other measurements. Table 5 shows the results of a forward, step-wise multivariate regression model using ³He VDP as the dependent variable and all significant pulmonary function test measurements (obtained from the univariate analysis) as the independent variables. FEV₁%_{pred}, IC%_{pred}, and Raw%_{pred} were shown to predict 45% of the variability in VDP ($P = 0.001$), with FEV₁%_{pred} making the greatest contribution. The univariate relationships are shown in Fig. 4, including FEV₁%_{pred} ($r^2 = 0.29$, $P < 0.0001$), Raw%_{pred} ($r^2 = 0.29$, $P < 0.0001$), and IC%_{pred} ($r^2 = 0.17$, $P = 0.003$). There were no statistically significant relationships for VDP with CPET, dyspnea, or occupational-exposure measurements. It is important to note that three subjects had VDP ≥ 3 SD of the mean, and when these data were removed from the regression analysis, FEV₁%_{pred} ($r^2 = 0.13$, $P = 0.009$) and IC%_{pred} ($r^2 = 0.17$, $P = 0.003$)

Table 2. Subject listing of demographics, pulmonary function tests, cardiopulmonary exercise testing, and imaging measurements

Subject	Age, yr	BMI, kg/m ²	FEV ₁ /FVC, %	FVC% _{pred}	FEV ₁ % _{pred}	FRC% _{pred}	IC% _{pred}	TLC% _{pred}	RV% _{pred}	RV/TLC, %	DLCO% _{pred}	Raw% _{pred}	VOmax% _{pred}	RER	Power% _{pred}	V _E % _{pred}	Postdyspnea	Postexertion	VDP, %	³ He COV	Occupational Exposure
001	74	F	22	89	91	73	92	112	95	43	99	130	103	1.22	159	64	3	11	1.37	0.200	
002	68	F	27	101	97	79	102	125	112	47	79	81	86	1.39	123	56	4	12	2.39	0.206	
003*	76	F	27	70	78	67	127	92	112	62	52	181	66	1.14	109	38	2	11	9.17	0.274	
004	69	M	25	94	84	83	86	111	98	38	116	84	87	1.27	96	56	3	13	4.70	0.238	
005	77	M	24	133	128	74	135	83	110	37	153	62	113	1.25	136	83	0.5	7	1.34	0.200	Construction
006	66	M	23	88	94	70	90	92	91	33	90	99	67	1.25	85	43	2	11	2.96	0.227	
007	65	F	31	86	76	86	81	90	85	43	78	52	72	1.11	97	34	0.5	7	1.45	0.201	
012	71	M	29	84	83	75	134	72	105	131	80	80	100	1.68	49	108	3	11	3.91	0.230	
013	83	M	27	151	141	75	92	125	107	64	62	58	122	1.24	148	87	0.5	7	2.05	0.203	
015	65	F	20	91	86	81	136	76	110	45	81	56	82	1.17	110	45	7	12	2.69	0.195	
016	67	F	30	120	116	77	123	124	123	37	114	39	49	1.29	105	28	0.5	12	2.22	0.205	
017*	69	F	27	59	65	68	107	81	96	61	68	216	84	1.07	129	34	1	14	10.6	0.294	
018	61	F	22	111	107	80	102	112	106	83	95	62	98	1.27	128	46	3	13	5.55	0.223	
019	67	M	26	131	129	75	118	138	128	33	84	44	86	1.36	107	83	2	13	1.08	0.199	Organic dust
020†	78	M	23	101	105	68	133	60	99	100	78	30	99	1.22	121	63	2	6	7.49	0.235	Inorganic
021	74	M	34	82	85	70	102	90	96	42	97	189	95	1.38	124	68	2	15	5.99	0.260	Welding
022	81	F	20	123	116	78	122	143	131	50	75	69	83	1.14	129	41	0.5	13	3.01	0.221	
023	68	F	30	93	90	79	92	99	95	43	90	102	115	1.18	116	55	3	9	1.60	0.215	
024	62	F	21	109	105	86	108	97	103	78	77	45	94	1.20	102	48	2	9	1.17	0.195	
025	66	M	24	95	98	72	139	88	115	46	114	29	92	1.16	102	54	2	11	3.10	0.234	Farming
029	84	M	24	102	80	87	79	114	67	35	92	65	53	1.03	64	36	5	14	2.74	0.229	
030	77	M	32	98	91	77	87	104	95	38	89	73	80	1.00	109	42	0	7	2.70	0.221	
031†	71	M	30	103	109	69	107	90	99	80	77	45	94	1.20	56	71	0.5	12	2.22	0.216	Fire fighting
032	69	F	29	106	103	78	91	130	108	99	81	39	107	1.17	169	49	2	13	1.83	0.215	
033†	80	M	26	89	94	68	93	93	93	40	74	82	82	1.11	113	40	3	12	4.63	0.222	
034	69	M	28	122	120	75	113	103	108	92	78	28	93	1.26	118	63	4	15	2.46	0.196	
035	74	F	31	107	103	77	152	137	145	56	76	107	96	1.06	179	44	3	13	1.67	0.187	
036†	78	M	24	106	109	69	124	77	103	39	75	51	92	1.30	122	67	1	8	2.73	0.206	Farming
038	79	F	29	108	111	71	116	102	110	96	73	106	81	1.00	145	52	2	11	1.25	0.196	Farming
039	71	F	32	122	115	80	86	153	115	101	89	102	96	1.25	161	56	3	14	0.65	0.210	
041	71	F	31	89	87	78	110	116	112	51	101	99	99	1.18	184	56	3	13	3.62	0.216	
042	61	F	26	98	94	81	123	103	114	47	87	64	89	1.07	117	39	3	15	1.38	0.200	
044	65	F	28	95	88	82	92	109	99	44	81	61	68	1.15	110	30	4	13	1.82	0.194	
045	77	F	31	116	109	80	98	135	113	45	90	82	100	1.25	140	65	4	13	1.49	0.194	
046	73	F	27	102	90	85	92	93	92	40	81	73	100	1.00	80	100	0	6	2.29	0.218	Farming
047	63	F	23	114	109	80	111	120	115	37	99	78	69	1.14	94	37	1	8	2.68	0.203	
049	63	F	23	126	137	71	88	71	123	29	96	92	71	1.48	114	47	0.5	11	0.85	0.183	
050	66	F	22	123	117	80	132	105	121	2	91	48	68	1.29	101	39	0.5	7	0.72	0.188	
052	68	F	30	122	110	84	108	128	117	43	119	63	120	1.12	177	59	3	9	1.83	0.197	
053	75	F	33	111	107	78	73	128	96	78	86	41	103	1.14	181	51	1	9	1.58	0.243	Farming
054	65	F	27	102	111	70	98	121	108	86	119	44	68	1.07	98	34	3	13	2.30	0.192	
055	66	M	24	114	96	88	92	121	106	41	90	34	55	1.11	66	35	0.5	13	2.08	0.190	
056	61	F	25	108	102	81	105	127	115	41	72	58	76	1.20	105	41	6	18	2.10	0.206	
057	78	F	29	114	117	72	84	134	105	98	84	79	82	1.07	159	40	3	15	1.60	0.205	
059	79	M	26	116	98	83	78	91	84	41	74	85	62	1.06	93	40	0	9	2.83	0.221	Farming
060	77	F	24	120	112	80	104	107	105	47	91	89	84	1.14	135	47	2	14	1.27	0.195	
061‡	74	F	24	72	71	77	126	83	108	64	90	34	65	1.03	92	30	3	7	3.26	0.231	
062	82	M	26	164	135	84	127	101	115	39	91	51	101	1.20	125	74	3	9	3.48	0.209	
063‡	77	M	31	72	77	70	90	87	88	93	89	100	90	1.10	125	41	1	7	4.17	0.232	Foundry and steel milling
064	69	M	25	130	123	78	134	111	123	37	90	50	96	1.30	120	61	2	10	1.79	0.193	Farming
065	69	F	26	109	113	73	127	99	115	41	80	68	59	1.24	79	37	2	13	1.59	0.193	
066	73	M	28	110	104	76	101	112	106	99	82	55	111	1.34	156	99	3	12	2.10	0.207	

*Stage II chronic obstructive pulmonary disease (COPD); †Stage I COPD; ‡Global Initiative for Chronic Obstructive Lung Disease—Unclassified.

Fig. 2. ^3He MRI for 4 representative subjects. ^3He MRI ventilation (in blue) coregistered with anatomical ^1H MRI (gray-scale) of the center coronal slice. Subject 64 (S64) is a 69-yr-old man [forced expiratory volume in 1 s (FEV_1) = 130%, $\text{FEV}_1/\text{forced vital capacity (FVC)}$ = 78%, slice number shown: 7]. S19 is a 67-yr-old man (FEV_1 = 131%, FEV_1/FVC = 75%, slice number shown: 8). S20 is a 78-yr-old man (FEV_1 = 101%, FEV_1/FVC = 68%, slice number shown: 9). S15 is a 65-yr-old woman (FEV_1 = 91%, FEV_1/FVC = 81%, slice number shown: 8). Yellow arrows identify the position of ventilation defects. DI, deep inspiration.

were significantly related to VDP, and $\text{Raw}\%_{\text{pred}}$ was not.

DISCUSSION

To understand better the determinants and physiological consequences of ventilation defects in older never-smokers, we evaluated pulmonary function and CPET measurements, as well as occupational/second-hand smoke exposure in 52 older adults. We made a number of key observations, including: 1) three-quarters of older never-smokers had ventilation defects, the majority of whom showed no VDP response to either DI or salbutamol; 2) ventilation heterogeneity and VDP were significantly greater, and FEV_1/FVC was significantly lower ($P < 0.05$) for subjects with ventilation defects responsive to DI/salbutamol compared with subjects without ventilation defects and subjects with ventilation defects with no response to DI/salbutamol; and 3) in a multivariate model, FEV_1 , IC, and Raw explained nearly 50% of the variability in ^3He VDP in these older never-smokers.

Ventilation abnormalities in older never-smokers. In the 39 subjects with visually obvious ventilation defects, VDP was modest and lower than previously reported in COPD and asthma subjects; furthermore, only four subjects showed a change in VDP in response to DI. This is consistent with previous findings that showed that the bronchodilatory effects

of DI decrease with age (39), which may explain the low number of DI responders in this study. Similar to previous observations in COPD (26) and asthma (6, 40), two subjects showed an imaging response to salbutamol, and this supports previous findings that reversible airflow limitation may be underappreciated in the elderly. Unexpectedly, the majority of older never-smokers with visually obvious ventilation defects ($n = 33$ of 39, 85%) did not respond to DI or salbutamol. This is consistent with the notion that in older never-smokers, small ventilation defects are related to irreversible airway narrowing or collapse, loss of elastic recoil, and/or small peripheral regions that are slow filling.

The majority of defects was observed along the periphery of the lung, suggesting that terminal airway closure or narrowing may be a normal, age-related pulmonary finding. Relative peripheral VDP, ^3He COV, VDP ΔPA , and VDP PA gradient were significantly greater in the imaging responders compared with the nonresponder and no-defect groups. Together, these findings suggest that subjects who responded to DI or salbutamol also had greater ventilation heterogeneity (or patchiness) and greater posterior/peripheral ventilation defects. The difference in ventilation heterogeneity among groups may reflect differences in lung-filling related to airway lumen morphology, but this is yet to be determined. Other potential mechanisms for ventilation heterogeneity have been suggested, including the

Fig. 3. Scatter plots of MRI metrics. Plots showing all MRI metrics for 3 subgroups (nonimaging responders, imaging responders, and no defects). A: VDP and relative peripheral VDP, (B) VDP Δ PA and VDP Δ SI, (C) PA and SI gradients, and (D) 3 He coefficient of variation (COV). Error bars are the SD of the mean.

loss of parenchymal tethering forces due to alveolar collapse that alters airway diameters, differences in regional lung expansion due to diaphragm and ribcage motions, or gravity-dependent differences in lung expansion contributing to airway constriction in the gravity-dependent regions (46). Nevertheless, in these older never-smokers, there appears to be a small, yet irreversible, VDP component. Finally, as might be expected based on the BOLD study (28), eight subjects showed spirometry evidence of COPD, and another 10 subjects exhibited $0.70 \leq \text{FEV}_1/\text{FVC} \leq 0.73$ [0.73 accounts for FEV_1 and FVC variability of 2–3% (20, 29)]. Therefore, here, the proportion of subjects with undiagnosed airflow limitation was 35%, which is in agreement with the results of the BOLD study (28). It is interesting to note that when the eight subjects with spirometry evidence of COPD were removed from the analysis, FEV_1/FVC was no longer different across the three subgroups; however, VDP remained different. For five subjects with a FEV_1 response to salbutamol ≥ 200 ml, there were no significant changes in VDP, ^3He COV, or any of the ventilation clusters (C2–C5) post-salbutamol. The discrepancy between the FEV_1 response and ^3He MRI response may have been due to the effort-dependence of spirometry. It is also important to note that all ventilation defects were peripherally located near the distal airways, and this may also explain why salbutamol did not influence the size or magnitude of these ventilation defects.

Relationships: ventilation defects with exercise capacity and dyspnea. In this study, the range of dyspnea scores and magnitude of ventilation defects observed were small compared

with recent findings in COPD and asthmatic subjects (6, 26, 27, 40). For these reasons, we were not surprised that there were no differences in CPET or dyspnea measurements between subjects with and without ventilation defects. Further supporting this finding, O'Donnell and colleagues (13) have shown that it is possible to have substantial ventilatory impairment during exercise without a corresponding effect on dyspnea. This is consistent with the notion that in healthy subjects, cardiovascular, and not respiratory factors provide the dominant contributions to exercise limitation (7, 15). Furthermore, unlike previous work (35), there were no relationships between dyspnea and other pulmonary function or CPET measurements that could be due to the limited range of dyspnea scores reported. Subjects with ventilation defects had normal lung function and exercise-capacity measurements for their age (4, 9, 35).

Relationships: ventilation defects with pulmonary function and volumes. There were significant but weak univariate relationships for VDP with $\text{FEV}_1\%_{\text{pred}}$, $\text{IC}\%_{\text{pred}}$, and $\text{Raw}\%_{\text{pred}}$, although the relationship between VDP and $\text{Raw}\%_{\text{pred}}$ was dominated by three subjects with relatively large VDP values (S3, S17, and S21). S21 had occupational and environmental exposures, and both S3 and S17 had spirometry evidence of GOLD II COPD. In a multivariate regression model, $\text{IC}\%_{\text{pred}}$, $\text{Raw}\%_{\text{pred}}$, and $\text{FEV}_1\%_{\text{pred}}$ all provided significant contributions to VDP, with $\text{FEV}_1\%_{\text{pred}}$ as the strongest predictor. The negative correlation of $\text{IC}\%_{\text{pred}}$ with VDP is concordant with previous results in COPD ex-smokers, who showed that ab-

Table 3. Subject listing for FEV₁, VDP, and ³He COV for all subjects administered salbutamol, n = 35

Subject	Pre-Salbutamol						Post-Salbutamol					
	Age, yr	FEV ₁ , liter	FEV ₁ % _{pred}	VDP, %	³ He COV	FEV ₁ , liter	FEV ₁ % _{pred}	VDP, %	³ He COV	ΔFEV ₁ , liter	ΔFEV ₁ % _{pred}	ΔVDP, %
001	74	1.68	89	1.35	0.20	1.70	91	0.84	0.20	0.02	2	-0.51
002*	68	2.52	101	2.34	0.21	2.72	109	1.65	0.20	0.20	8	-0.69
003	76	1.30	70	9.17	0.27	1.34	72	8.15	0.28	0.04	2	-1.02
004	69	3.33	94	4.49	0.24	3.31	94	4.02	0.24	-0.02	0	-0.47
005	77	3.36	133	1.32	0.20	3.06	122	1.55	0.21	-0.30	-11	0.23
006	66	3.30	88	2.87	0.23	3.29	88	2.73	0.22	-0.01	0	-0.14
007	65	2.01	86	1.43	0.20	2.08	89	2.11	0.22	0.07	3	0.68
012	71	2.78	84	3.76	0.23	2.66	81	2.87	0.23	-0.12	-3	-0.90
015	65	2.38	91	2.61	0.20	2.52	96	2.29	0.21	0.14	5	-0.33
016	67	3.80	120	2.22	0.21	3.88	123	1.65	0.22	0.08	3	-0.57
017†	69	1.24	59	10.6	0.29	1.35	64	7.91	0.27	0.11	5	-2.70
018	61	3.06	111	5.26	0.22	3.14	114	5.62	0.24	0.08	3	0.36
020†	78	2.76	101	7.49	0.24	3.02	110	3.47	0.24	0.26	9	-4.02
021	74	2.32	82	5.65	0.26	2.41	85	3.25	0.25	0.09	3	-2.40
022*	81	2.18	123	2.92	0.22	2.43	137	5.37	0.23	0.25	14	2.45
023	68	1.96	93	1.57	0.22	2.09	99	1.25	0.21	0.13	6	-0.32
025*	66	3.54	95	3.01	0.23	3.78	102	2.33	0.22	0.24	7	-0.68
031	71	3.14	103	2.17	0.22	3.15	103	1.93	0.22	0.01	0	-0.24
032	69	2.75	106	1.79	0.22	2.82	109	1.56	0.21	0.07	3	-0.24
033	80	2.86	89	4.42	0.22	2.76	86	6.13	0.23	-0.10	-3	1.71
036	78	2.88	106	2.73	0.21	3.06	112	1.92	0.20	0.18	6	-0.81
041	71	2.19	89	3.49	0.22	2.31	94	3.38	0.22	0.12	5	-0.11
044	65	2.24	95	1.79	0.19	2.14	90	1.84	0.22	-0.10	-5	0.05
045	77	2.44	116	1.46	0.19	2.31	109	2.02	0.21	-0.13	-7	0.55
046	73	2.06	102	2.35	0.22	1.90	94	2.14	0.22	-0.16	-8	-0.21
047	63	2.52	114	2.61	0.20	2.53	116	3.09	0.20	0.01	2	0.48
052	68	2.55	122	1.83	0.20	2.63	125	1.58	0.19	0.08	3	-0.25
054	65	2.42	102	2.24	0.19	2.49	105	3.33	0.20	0.07	3	1.08
056	61	3.12	108	2.10	0.21	3.19	110	1.90	0.21	0.07	2	-0.20
057	78	2.23	114	1.58	0.21	2.27	116	1.29	0.21	0.04	2	-0.28
059*	79	2.53	116	2.83	0.22	2.73	125	2.90	0.22	0.20	9	0.07
060	77	2.36	120	1.26	0.20	2.37	121	1.55	0.20	0.01	1	0.29
061	74	1.53	72	3.15	0.23	1.59	75	5.21	0.24	0.06	3	2.03
063*	67	2.46	72	4.00	0.23	2.94	86	3.72	0.22	0.48	14	-0.28
065	69	2.57	109	1.59	0.19	2.70	114	1.79	0.20	0.13	5	0.20
Imaging responders†	74	2.0	80	9.0	0.27	2.2	87	5.7	0.26	0.2	7.0	-3.4
Mean (SD), n = 2	(6)	(1.1)	(30)	(2.2)	(0.04)	(1.2)	(33)	(3.0)	(0.02)	(0.1)	(2.8)	(0.9)
FEV ₁ responders*	74	2.7	102	3.1	0.22	3.0	112	3.3	0.22	0.3	10.0	0.2
Mean (SD), n = 5	(7)	(0.5)	(20)	(0.5)	(0.01)	(0.5)	(20)	(1.3)	(0.01)	(0.1)	(3.8)	(1.3)
Nonresponders	71	2.5	100	2.8	0.21	2.5	101	2.7	0.22	0.00	1.0	-0.04
Mean (SD) n = 28	(5)	(0.6)	(16)	(1.7)	(0.02)	(0.6)	(15)	(1.7)	(0.02)	(0.1)	(4.4)	(0.8)

normal IC is a marker of expiratory flow limitation and a predictor of dynamic hyperinflation during exercise (31). An increase in dynamic hyperinflation results in an increased elastic load on the inspiratory muscles, thus increasing the work and cost of breathing. This mechanical constraint can predispose individuals to fatigue, and it has been shown that dynamic hyperinflation contributes to perceived exertional dyspnea in subjects with COPD (31, 32, 34). It is also interesting to note that resting IC can predict the peak, symptom-limited VO₂ in patients with expiratory flow limitation at rest (34).

Table 4. VDP and ³He COV measurements for imaging responders

	Baseline	Post-DI	Post-Salbutamol
Imaging responders, n = 6			
VDP, % (±SD)	5.8 (3.8)	4.7 (2.6)	5.7 (3.1)
³ He COV (±SD)	0.24 (0.04)	0.24 (0.04)	0.25 (0.02)
DI responders, n = 4			
VDP, % (±SD)	4.2 (3.5)	3.5 (2.3)	
³ He COV (±SD)	0.23 (0.04)	0.23 (0.04)	
Salbutamol responders, n = 2			
VDP, % (±SD)	9.0 (2.2)	7.0 (1.0)	5.7 (3.1)
³ He COV (±SD)	0.26 (0.04)	0.25 (0.03)	0.25 (0.02)

Limitations. We recognize a number of limitations that restrict the general applicability of our results. First, subjects were classified by viewing the gray-scale images, while the patients were still in the scanner. Offline, once the ventilation images were coregistered to the anatomical ¹H images, in two cases, previously classified ventilation defects could be directly related to anatomical bony structures and were unlikely to be ventilation abnormalities. As a result, two subjects, who were classified at the scanner as having ventilation defects, did not appear to have these once a full analysis was completed, although both completed DI and salbutamol inhalation. One

Table 5. Univariate and multivariate relationships for ³He MRI VDP with pulmonary function measurements

Parameters	Univariate Relationship VDP	Multivariate Model VDP
	r ² (P value)	β, r ² , Δr ² (P value)
FEV ₁ % _{pred}	0.29 (<0.001)	-0.541, 0.292, 0.292 (<0.001)
Raw% _{pred}	0.29 (<0.001)	0.359, 0.391, 0.099 (<0.001)
IC% _{pred}	0.17 (0.003)	-0.265, 0.449, 0.058 (<0.001)
FEV ₁ /FVC, %	0.17 (0.002)	-0.147, 0.449, 0 (0.23)
FVC% _{pred}	0.24 (<0.002)	0.114, 0.449, 0 (0.68)
RV/TLC, %	0.15 (0.005)	0.105, 0.449, 0 (0.44)

Fig. 4. Univariate correlations for VDP with: (A) predicted FEV_1 percent ($FEV_1\%_{pred}$) for all subjects ($r^2 = 0.29$, $r = -0.54$, $P < 0.0001$); (B) airway resistance ($Raw\%_{pred}$) for all subjects ($r^2 = 0.29$, $r = 0.54$, $P < 0.0001$); and (C) inspiratory capacity ($IC\%_{pred}$) for all subjects ($r^2 = 0.17$, $r = -0.41$, $P = 0.003$). The black regression lines are the result of when all subjects were included in the analysis. Gray circles show the subjects with $VDP > 3$ SD of the mean. The gray regression lines show the alternate regression, resulting when these subjects were excluded.

subject had ventilation defects that responded to DI (but not salbutamol), whereas the other subject had no ventilation defects and did not respond to DI or salbutamol. We did not remove these subjects from the analysis, and their inclusion did not alter the final overall results. It should also be noted that since all subjects were imaged ~ 30 min after completion of CPET, ventilation defects and ventilation heterogeneity may have been influenced by exercise. Previous studies have shown that during exercise, athletes experience ventilation-perfusion mismatch and diffusion limitation (18). Other studies have evaluated the progression of ventilation-perfusion mismatch after exercise and showed that some subjects do not recover fully from ventilation-perfusion mismatch until 20 min postexercise (38). Because of the time delay between imaging and CPET and the fact that in this study, VDP did not correlate with any CPET measurements, it is unlikely that prior exercise influenced the presence or absence of 3He MRI ventilation defects.

Conclusions. In summary, we evaluated hyperpolarized 3He MRI ventilation defects—a surrogate measurement of airway function—in the first large imaging study of healthy, older

never-smokers with no history of chronic heart or lung disease. Whereas a minority of subjects reported occupational exposures, most subjects had visually obvious ventilation defects that did not change after DI or salbutamol administration, suggesting that terminal airway closure or narrowing may be a normal, age-related lung finding. Whereas there were no differences in CPET or conventional pulmonary function measurements between subjects with and without ventilation defects, $FEV_1\%_{pred}$, in combination with $IC\%_{pred}$ and $Raw\%_{pred}$, predicted VDP in a multivariate regression model. Taken together, these findings provide a better understanding of the nature of ventilation defects in healthy, older never-smokers.

ACKNOWLEDGMENTS

We thank S. Blamires and D. Buchanan for clinical coordination and clinical database management, A. Wheatley for gas-contrast dispensing and administration, and T. Szekeres for MRI of research volunteers.

GRANTS

Support is gratefully acknowledged from G. Parraga for a Canadian Institutes of Health Research (CIHR) New Investigator Award and ongoing research funding from CIHR Operating Grant MOP 106437.

DISCLOSURES

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Author contributions: G.P. conception and design of research; K.S. and S.S. performed experiments; K.S., G.A.P., and G.P. analyzed data; K.S., G.A.P., S.S., M.K., and G.P. interpreted results of experiments; K.S. prepared figures; K.S., G.A.P., and G.P. drafted manuscript; K.S., G.A.P., S.S., M.K., N.A.M.P., D.G.M., and G.P. edited and revised manuscript; K.S., G.A.P., S.S., M.K., N.A.M.P., D.G.M., and G.P. approved final version of manuscript.

REFERENCES

- Ahmed T, Steward JA, O'Mahony MS. Dyspnoea and mortality in older people in the community: a 10-year follow-up. *Age Ageing* 41: 545–549, 2012.
- Albouni K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Postgrad Med J* 83: 675–682, 2007.
- American Thoracic Society; American College of Chest Physicians. Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 167: 211–277, 2003.
- Astrand I, Astrand PO, Hallback I, Kilbom A. Reduction in maximal oxygen uptake with age. *J Appl Physiol* 35: 649–654, 1973.
- Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, Crapo RO, Jensen RL, Burney PG. The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. *COPD* 2: 277–283, 2005.
- Costella S, Kirby M, Maksym GN, McCormack DG, Paterson NA, Parraga G. Regional pulmonary response to a methacholine challenge using hyperpolarized (3He) magnetic resonance imaging. *Respirology* 17: 1237–1246, 2012.
- Dempsey JA, Hanson PG, Henderson KS. Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J Physiol* 355: 161–175, 1984.
- Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *Am J Respir Crit Care Med* 149: 430–438, 1994.
- Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1: 1645–1648, 1977.
- Frank NR, Mead J, Ferris BG Jr. The mechanical behavior of the lungs in healthy elderly persons. *J Clin Invest* 36: 1680–1687, 1957.
- Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 126: 2261–2274, 2012.

12. Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm Med* 2013; 956081, 2013.
13. Guenette JA, Diane Loughheed M, Webb KA, O'Donnell DE. Can an 86-year-old woman with advanced lung disease be a world class athlete? *Respir Physiol Neurobiol* 181: 162–166, 2012.
14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 159: 179–187, 1999.
15. Harms CA, Wetter TJ, St Croix CM, Pegelow DF, Dempsey JA. Effects of respiratory muscle work on exercise performance. *J Appl Physiol* (1985) 89: 131–138, 2000.
16. Heath GW, Hagberg JM, Ehsani AA, Holloszy JO. A physiological comparison of young and older endurance athletes. *J Appl Physiol Respir Environ Exerc Physiol* 51: 634–640, 1981.
17. Ho SF, O'Mahony MS, Steward JA, Breay P, Buchalter M, Burr ML. Dyspnoea and quality of life in older people at home. *Age Ageing* 30: 155–159, 2001.
18. Hopkins SR, McKenzie DC, Schoene RB, Glenny RW, Robertson HT. Pulmonary gas exchange during exercise in athletes. I. Ventilation-perfusion mismatch and diffusion limitation. *J Appl Physiol* (1985) 77: 912–917, 1994.
19. Huijnen B, van der Horst F, van Amelsvoort L, Wesseling G, Lansbergen M, Aarts P, Nicolson N, Knottnerus A. Dyspnea in elderly family practice patients. Occurrence, severity, quality of life and mortality over an 8-year period. *Fam Pract* 23: 34–39, 2006.
20. Humerfelt S, Eide GE, Kvale G, Gulsvik A. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) variability in asymptomatic never-smoking men. *Clin Physiol* 18: 387–396, 1998.
21. Janssens JP, Pache JC, Nicod LP. Physiological changes in respiratory function associated with ageing. *Eur Respir J* 13: 197–205, 1999.
22. Jensen A, Atileh H, Suki B, Ingenito EP, Lutchen KR. Selected contribution: airway caliber in healthy and asthmatic subjects: effects of bronchial challenge and deep inspirations. *J Appl Physiol* (1985) 91: 506–515; discussion 504–505, 2001.
23. Jensen D, Ofir D, O'Donnell DE. Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. *Respir Physiol Neurobiol* 167: 87–100, 2009.
24. Kasch FW, Boyer JL, Van Camp S, Netti F, Verity LS, Wallace JP. Cardiovascular changes with age and exercise. A 28-year longitudinal study. *Scand J Med Sci Sports* 5: 147–151, 1995.
25. Kirby M, Heydarian M, Svenningsen S, Wheatley A, McCormack DG, Etemad-Rezai R, Parraga G. Hyperpolarized 3He magnetic resonance functional imaging semiautomated segmentation. *Acad Radiol* 19: 141–152, 2012.
26. Kirby M, Mathew L, Heydarian M, Etemad-Rezai R, McCormack DG, Parraga G. Chronic obstructive pulmonary disease: quantification of bronchodilator effects by using hyperpolarized (3)He MR imaging. *Radiology* 261: 283–292, 2011.
27. Kirby M, Mathew L, Wheatley A, Santyr GE, McCormack DG, Parraga G. Chronic obstructive pulmonary disease: longitudinal hyperpolarized (3)He MR imaging. *Radiology* 256: 280–289, 2010.
28. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, Studnicka M, Bateman E, Anto JM, Burney P, Mannino DM, Buist SA. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 139: 752–763, 2011.
29. Margaret R, Becklake SP. *Evaluation of Tests of Lung Function for Screening for Early Detection of Chronic Obstructive Lung Disease*. New York: Marcel Dekker, 1979, p. 345–388.
30. Nejari C, Tessier JF, Dartigues JF, Barberger-Gateau P, Letenneur L, Salamon R. The relationship between dyspnoea and main lifetime occupation in the elderly. *Int J Epidemiol* 22: 848–854, 1993.
31. O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 155: 109–115, 1997.
32. O'Donnell DE, Laveneziana P. Dyspnea and activity limitation in COPD: mechanical factors. *COPD* 4: 225–236, 2007.
33. O'Donnell DE, O'Donnell CD, Webb KA, Guenette JA. Respiratory consequences of mild-to-moderate obesity: impact on exercise performance in health and in chronic obstructive pulmonary disease. *Pulm Med* 2012: 818925, 2012.
34. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 164: 770–777, 2001.
35. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J Appl Physiol* (1985) 104: 1583–1593, 2008.
36. Parraga G, Mathew L, Etemad-Rezai R, McCormack DG, Santyr GE. Hyperpolarized 3He magnetic resonance imaging of ventilation defects in healthy elderly volunteers: initial findings at 3.0 Tesla. *Acad Radiol* 15: 776–785, 2008.
37. Parraga G, Ouriadov A, Evans A, McKay S, Lam WW, Fenster A, Etemad-Rezai R, McCormack D, Santyr G. Hyperpolarized 3He ventilation defects and apparent diffusion coefficients in chronic obstructive pulmonary disease: preliminary results at 3.0 Tesla. *Invest Radiol* 42: 384–391, 2007.
38. Schaffartzik W, Poole DC, Derion T, Tsukimoto K, Hogan MC, Arcos JP, Bebout DE, Wagner PD. VA/Q distribution during heavy exercise and recovery in humans: implications for pulmonary edema. *J Appl Physiol* (1985) 72: 1657–1667, 1992.
39. Scichilone N, Marchese R, Catalano F, Toggias A, Vignola AM, Bellia V. The bronchodilatory effect of deep inspiration diminishes with aging. *Respir Med* 98: 838–843, 2004.
40. Svenningsen S, Kirby M, Starr D, Leary D, Wheatley A, Maksym GN, McCormack DG, Parraga G. Hyperpolarized He and Xe MRI: differences in asthma before bronchodilation. *J Magn Reson Imaging* 38: 1521–1530, 2013.
41. Tessier JF, Nejari C, Letenneur L, Filleul L, Marty ML, Barberger Gateau P, Dartigues JF. Dyspnea and 8-year mortality among elderly men and women: the PAQUID cohort study. *Eur J Epidemiol* 17: 223–229, 2001.
42. Thurlbeck WM. Internal surface area and other measurements in emphysema. *Thorax* 22: 483–496, 1967.
43. Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. *J Appl Physiol* (1985) 25: 664–671, 1968.
44. Tzeng YS, Lutchen K, Albert M. The difference in ventilation heterogeneity between asthmatic and healthy subjects quantified using hyperpolarized 3He MRI. *J Appl Physiol* (1985) 106: 813–822, 2009.
45. VanBell GFL, Heagerty P, Lumley T. Multiple comparisons. In: *Biostatistics: A Methodology for the Health Sciences*. Seattle, WA: Wiley-Interscience, 2004.
46. Venegas JG, Winkler T, Musch G, Vidal Melo MF, Layfield D, Tgavalekos N, Fischman AJ, Callahan RJ, Bellani G, Harris RS. Self-organized patchiness in asthma as a prelude to catastrophic shifts. *Nature* 434: 777–782, 2005.
47. Wan ES, Hokanson JE, Murphy JR, Regan EA, Make BJ, Lynch DA, Crapo JD, Silverman EK. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGen study. *Am J Respir Crit Care Med* 184: 57–63, 2011.