Emphysema on Thoracic CT and Exercise Ventilatory Inefficiency in Mild-to-Moderate COPD

Joshua H. Jones, Joel T. Zelt, Daniel M. Hirai, Camilla V. Diniz, Aida Zaza, Denis E. O'Donnell & J. Alberto Neder

To cite this article: Joshua H. Jones, Joel T. Zelt, Daniel M. Hirai, Camilla V. Diniz, Aida Zaza, Denis E. O'Donnell & J. Alberto Neder (2016): Emphysema on Thoracic CT and Exercise Ventilatory Inefficiency in Mild-to-Moderate COPD, COPD: Journal of Chronic Obstructive Pulmonary Disease, DOI: 10.1080/15412555.2016.1253670

To link to this article: http://dx.doi.org/10.1080/15412555.2016.1253670
Emphysema on Thoracic CT and Exercise Ventilatory Inefficiency in Mild-to-Moderate COPD

Joshua H. Jones a, Joel T. Zelt a, Daniel M. Hirai a, Camilla V. Diniz a, Aida Zaza a, Denis E. O’Donnell b, and J. Alberto Neder a

Abstract

There is growing evidence that emphysema on thoracic computed tomography (CT) is associated with poor exercise tolerance in COPD patients with only mild-to-moderate airflow obstruction. We hypothesized that an excessive ventilatory response to exercise (ventilatory inefficiency) would underlie these abnormalities. In a prospective study, 19 patients (FEV1 = 82 ± 13%, 12 Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1) and 26 controls underwent an incremental exercise test. Ventilatory inefficiency was assessed by the ventilation (VE)/CO2 output (VCO2) nadir. Pulmonary blood flow (PBF) in a submaximal test was calculated by inert gas rebreathing. Emphysema was quantified as % of attenuation areas below 950 HU. Patients typically presented with centrilobular emphysema (76.8 ± 10.1% of total emphysema) in the upper lobes (upper/total lung ratio = 0.82 ± 0.04). They had lower peak oxygen uptake (VO2), higher VE/VCO2 nadir, and greater dyspnea scores than controls (p < 0.05). Lower peak VO2 and worse dyspnea were found in patients with higher VE/VCO2 nadirs (≥30). Patients had blunted increases in PBF from rest to iso-VO2 exercise (p < 0.05). Higher VE/VCO2 nadir in COPD was associated with emphysema severity (r = 0.53) which, in turn, was related to reduced lung diffusing capacity (r = −0.72) and blunted changes in PBF from rest to exercise (r = −0.69) (p < 0.01). Ventilation “wasted” in emphysematous areas is associated with impaired exercise ventilatory efficiency in mild-to-moderate COPD. Exercise ventilatory inefficiency links structure (emphysema) and function (D2/CO) to a key clinical outcome (poor exercise tolerance) in COPD patients with only modest spirometric abnormalities.

Introduction

There is mounting evidence that COPD patients with largely preserved FEV1 may present with substantial burden of emphysema on thoracic computed tomography (CT) (1–5). These abnormalities have been associated with meaningful patient-centered outcomes, including breathlessness (1,3) and poor exercise tolerance (1,3,6–8). Elucidation of the mechanisms underlying these associations might provide novel insights into the function–structure relationship prior to the development of the severe mechanical constraints that characterize patients with advanced COPD (9).

In this context, it is noteworthy that both exertional breathlessness and exercise intolerance have been consistently associated with an excessive ventilatory response to exercise in COPD patients (or even healthy smokers) with largely preserved FEV1 (10–15). The physiological bases of the so-called “ventilatory inefficiency” stem from an enlarged physiological dead space, i.e., a high dead space (V D)/tidal volume (VT) ratio reflecting increased “wasted” ventilation (15). Of note, (Enghoff’s) V D/VT is sensitive to any pathophysiological mechanism leading to increased arterial–alveolar CO2 difference, including alveolar ventilation/perfusion (VA/Q) heterogeneity (16). Emphysema, in particular, is associated with enlarged airspaces, loss of alveolar attachments to small airways, and disturbed microvascular perfusion (17,18), which jointly induce marked VA/Q mismatching, i.e., either low or high VA/Q ratios (16,19–22). It is therefore conceivable that under the magnifying effects of increased ventilation and cardiac output (exercise), patients with greater burden of emphysema and more disturbed pulmonary hemodynamics would present with particularly poor ventilatory efficiency. Confirmation of these premises would support the notion that early emphysema provides the structural bases for the increased “wasted” ventilation previously found in patients at the beginning of the spectrum of COPD severity (10–15).

The present study, therefore, aimed to determine the structural correlates of exercise ventilatory inefficiency in COPD patients with mild-to-moderate airflow obstruction. We specifically hypothesized that CT measurements of emphysema would be associated with blunted increases in PBF from rest to exercise, worse ventilatory inefficiency, greater activity-related dyspnea and lower exercise tolerance.
Methods

Subjects
Clinical and physiological data from 54 patients with mild-to-moderate COPD (smoking history of at least 10 pack-years, post-bronchodilator FEV₁/FVC < 0.7 and FEV₁ ≥ 60% predicted) were reviewed for potential study inclusion. All patients had established clinical diagnosis of COPD, being followed by respirologists. Disease severity was classified according to the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD)’s recommendation (23). Twenty-six sedentary volunteers were recruited by advertisement from our hospital workforce. They were free from pulmonary, cardiac, or metabolic conditions as established by their medical records that could contribute to dyspnea or exercise limitation. All participants had preserved left ventricular ejection fraction (> 40%) as assessed by echocardiography, and they were considered “physically inactive” according to the Baecke’s questionnaire (24). Co-morbidity burden was determined by the combined 19-disease Charlson index (25). Dyspnea was assessed by the modified Medical Research Council (mMRC) questionnaire. All participants signed an informed consent, which had been previously approved by the Queen’s University and Affiliated Teaching Hospitals Research Ethics Board (DMED-1701–14).

Measurements

Lung function
Spirometry, lung diffusing capacity for carbon monoxide (DLCO), and static lung volumes were evaluated according to current guidelines (1085 ELITE D™, Medical Graphics). Controls performed only spirometry.

CT imaging
Thoracic CT scans were acquired only in the patient group, i.e., for ethical reasons, controls did not undergo imaging assessment. Scans were obtained at suspended inspiration without intravenous contrast and reconstructed using a spatial contrast algorithm with 1.25-mm slice thickness. Study scans were acquired on Siemens and GE 64-slice scanners (GE Healthcare, Waukesha, Wisconsin) using a single spiral acquisition from apex to base (64 × 0.625 mm collimation, 120 kVp, 100 mA). Quantitative measures of emphysema and airway wall thickness were generated with VIDA software (VIDA Diagnostics, Iowa City, IA). Threshold-based measures of % low attenuation areas (LAA)-950 were calculated for each lung CT scan by quantifying the percentage of the overall lung density histogram below the −950 Hounsfield unit threshold (emphysema index, %) (26). The radiologist used an electronic score sheet to record the extent of each emphysema subtype assessed visually on CT according to the following definitions (27): a) centrilobular emphysema: focal regions of low attenuation, surrounded by normal lung attenuation, located within the central portion of secondary pulmonary lobules; b) panlobular emphysema: diffuse regions of low attenuation involving entire secondary pulmonary lobules; and c) paraseptal emphysema: regions of low attenuation adjacent to visceral pleura (including fissures). Upper lobe (including right middle)/total lung ratio was calculated for each lung and averaged for reporting. Airway wall thickness of airways with an internal perimeter of 10 mm (Pi10) were also obtained (26).

Incremental cardiopulmonary exercise tests
Patients performed a symptom-limited incremental cardiopulmonary exercise test (CPET) on an electronically braked cycle ergometer using the Vmax229d System (SensorMedics). The rate of work rate (WR) increment was individually selected according to reported exercise tolerance (typically 10–15 W). Oxygen uptake (VO₂, L/min), carbon dioxide output (VCO₂, L/min), respiratory exchange ratio (RER, VCO₂/VO₂), minute ventilation (VE, L/min), end-tidal partial pressure for carbon dioxide (PETCO₂, mmHg), tidal volume (VT, L), and breathing frequency (f, cycles/min) were averaged at 20-second intervals. Peak VE was also expressed relative to the estimated maximal voluntary ventilation (MVV (L/min) = FEV₁ × 35). VE/VCO₂ nadir was the lowest test data point. Slope and intercept of the linear VE-VCO₂ relationship were determined by linear regression (9). Gas exchange threshold (GET) was estimated by the gas exchange method (V-slope). Arterial oxygen saturation was measured non-invasively by pulse oximetry (SpO₂, %). Breathlessness and leg effort scores were rated according to the 10-point Borg category-ratio scale.

Constant work rate exercise tests
On a different day (at least 48 hours apart), subjects performed 5-minute 25 and 50 W exercise bouts separated by 5-minute resting periods. At rest and after 3 minutes of exercise, patients were switched to breathe from a rebreathing bag filled with a gas mixture consisting of 5% blood soluble nitrous oxide (N₂O), 1% blood insoluble hexafluoride (SF₆), and 94% O₂ (InnocoTM, Innovision, Odense/Denmark). The bag volume and rebreathing frequency were adjusted in accordance with the subjects’ VT and f at each WR. Assuming that pulmonary uptake of a blood soluble gas is proportional to PBF (L/min) (28), pulmonary N₂O uptake was assessed as the decrease in N₂O over three expiration after a stable SF₆ concentration was established (29–31). Only measurements in which the SF₆ curve indicated complete mixing of gases were included in the analysis. In order to assess the method’s limits of agreement (LoA) between test and retest, 12 patients and 21 controls repeated 25 and 50 W bouts, respectively. This analysis revealed LoA values for PBF in the range of ±1 L/min at both 20 and 50 W for patients and controls (~±15% of mean value). Test–retest variability did not change as a function of the measured value, i.e., there was no significant data heteroscedasticity (Figure 1).

Statistical analysis
Values are reported as means ± standard deviation unless otherwise specified (IBM® SPPS® Statistics version 22.0.0.0). Based on previous studies that contrasted ventilatory efficiency in COPD patients with similar disease severity versus controls (9–15), we estimated that a sample size of 20 subjects in each group would be required. According to variable distribution (Kolmogorov–Smirnov), controls and COPD patients were contrasted by non-paired t or Mann–Whitney’s test. A chi-square
test assessed differences in proportions. Pearson’s $r$ assessed linear association between continuous variables. The accepted risk for a type I error was less than 5% ($p < 0.05$).

**Results**

**Subject characteristics**

Twenty patients were excluded due to major co-morbidity, which could potentially interfere with patients’ response to exercise (neoplasms = 4, heart failure = 4, active coronary disease = 3, recent myocardial infarction = 3, advanced liver disease = 2, orthopedic limitation = 2, morbid obesity = 2). Fifteen patients either recused participation or failed to attend the initial screening visit. All but 5 of the 19 enrolled patients were receiving short-acting bronchodilators as needed, and 10 were under long-acting bronchodilator treatment (7 of them with associated inhaled steroids).

Patients and controls were well matched by key demographic and anthropometric variables. Moreover, there were no between-group differences in the regular physical activity scores or co-morbidity burden as indicated by the Charlson index (Table 1). As expected, patients presented with higher mMRC dyspnea scores and greater impairment on resting lung function compared to controls (Table 1). Most patients presented with COPD GOLD stage 1. Most noticeable abnormalities on lung volumes included mild absolute and relative air trapping, increased airway resistance, and mild decrements in $D_L$CO and KCO (Table 1).

Evidence of emphysema was found in all patients with 14/19 (73.7%) presenting with more than 5% LAA (26). As shown in Table 1, there was a predominance of centrilobular over panlobular (18.4 ± 6.3%) and paraseptal (6.5 ± 3.1%) emphysema involving the upper lobes. In contrast, evidence of airway disease was less extensive compared to emphysematous changes.

**Symptom-limited incremental CPET**

Patients with COPD presented with significantly lower symptom-limited peak exercise capacity than healthy controls ($p < 0.05$; Table 2). There were no significant between-group differences in cardiovascular and arterial oxygenation variables. Variables typically related to deconditioning (e.g., low $\dot{\text{V}}_\text{O}_2$GET and low peak $\text{O}_2$ pulse) did not differ between patients and controls ($p > 0.05$). However, a greater symptom burden (both in relation to dyspnea and leg discomfort scores) was found in the patient group (Table 2).

As shown in Figure 2, significantly steeper $\dot{\text{V}}_\text{E}/\dot{\text{V}}\text{CO}_2$ slope and, marginally, higher $\dot{\text{V}}_\text{E}/\dot{\text{V}}\text{CO}_2$ intercept led to greater $\dot{\text{V}}_\text{E}/\dot{\text{V}}\text{CO}_2$ nadir in patients compared to controls, i.e., poorer ventilatory efficiency (9). Particularly low peak $\text{O}_2$ and high dyspnea scores were found in a subgroup of patients with $\dot{\text{V}}_\text{E}/\dot{\text{V}}\text{CO}_2$ nadir $\geq 30$ (N = 12) compared to their counterparts with lower nadirs (peak $\dot{\text{V}}_\text{O}_2 = 76 \pm 16\%$ pred vs. $97 \pm 12\%$ pred).
measurements were obtained in 14 (25 W) and 12 (50 W) patients and 26 controls. Technically acceptable PBF
fraction
Smoking, pack-years
Resting lung function
Subjects.

Table 1. Subject characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>COPD (n = 19)</th>
<th>Controls (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic/anthropometric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, female, n</td>
<td>9/10</td>
<td>14/12</td>
</tr>
<tr>
<td>Age, years</td>
<td>62 ± 6.65 ± 11</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 ± 10</td>
<td>167 ± 10</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>77.5 ± 17.1</td>
<td>75.1 ± 13.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 ± 5.2</td>
<td>26.8 ± 4.1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>68.7 ± 7.4</td>
<td>—</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>40.4 ± 17.9*</td>
<td>5.6 ± 11.6</td>
</tr>
<tr>
<td>Smoking status, n:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>GOLD stages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2BI</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Modified MRC dyspnea score ≥1</td>
<td>14*</td>
<td>2</td>
</tr>
<tr>
<td>Baæcke physical activity score</td>
<td>7.1 ± 1.9</td>
<td>7.6 ± 1.9</td>
</tr>
<tr>
<td>Charlson co-morbidity Index</td>
<td>2.4 ± 1.6</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Resting lung function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( FEV_1 ) (%) pred</td>
<td>2.31 ± 0.68* (82 ± 13*)</td>
<td>2.92 ± 0.62 (104 ± 12)</td>
</tr>
<tr>
<td>( FVC ) (%) pred</td>
<td>3.80 ± 1.03 (97 ± 14)</td>
<td>3.76 ± 0.88 (99 ± 15)</td>
</tr>
<tr>
<td>( FEV_1/FVC ) (%pred)</td>
<td>62.3 ± 6.3* (68 ± 11*)</td>
<td>73.1 ± 5.8 (102 ± 10)</td>
</tr>
<tr>
<td>( FEV_1/VC_{TLC} ) L/s (%pred)</td>
<td>1.10 ± 0.42* (42 ± 28*)</td>
<td>2.66 ± 0.93 (96 ± 22)</td>
</tr>
<tr>
<td>( IC_{L} ) (%) pred</td>
<td>2.88 ± 0.64 (102 ± 21)</td>
<td>2.95 ± 0.73 (108 ± 14)</td>
</tr>
<tr>
<td>( FRC ) (%) pred</td>
<td>3.38 ± 0.62 (106 ± 19)</td>
<td>—</td>
</tr>
<tr>
<td>( TLC ) (%) pred</td>
<td>6.13 ± 1.11 (104 ± 10)</td>
<td>—</td>
</tr>
<tr>
<td>( RV ) (%) pred</td>
<td>2.44 ± 0.92 (117 ± 29)</td>
<td>—</td>
</tr>
<tr>
<td>( RV/TLC )</td>
<td>36 ± 9 (115 ± 18)</td>
<td>—</td>
</tr>
<tr>
<td>( D_1 ) CO, ml/min/mmHg (% pred)</td>
<td>15.9 ± 6.1 (80 ± 17)</td>
<td>—</td>
</tr>
<tr>
<td>( KCO ), ml/min/mmHg/L (% pred)</td>
<td>3.2 ± 0.66 (86 ± 15)</td>
<td>—</td>
</tr>
<tr>
<td>sRAW, cmH₂O/S (% pred)</td>
<td>9.6 ± 4.1 (231 ± 84)</td>
<td>—</td>
</tr>
<tr>
<td>Thoracic CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema index (LAA,cm²)</td>
<td>11.1 ± 8.0</td>
<td>—</td>
</tr>
<tr>
<td>Upper lobes/basal lobes ratio</td>
<td>0.82 ± 0.04</td>
<td>—</td>
</tr>
<tr>
<td>Centrilobular emphysema (%) total</td>
<td>76.8 ± 10.1</td>
<td>—</td>
</tr>
<tr>
<td>Emphysema thickness (P100, mm)</td>
<td>4.8 ± 0.5</td>
<td>—</td>
</tr>
<tr>
<td>Emphysema predominant over airway disease (Number of patients)</td>
<td>15</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± SD.
* \( p < 0.05 \). GOLD: Global Initiative for Obstructive Lung Disease; MRC: Medical Research Council; \( FEV_1 \): forced expired volume in 1 second; \( FVC \): forced vital capacity; \( FEV_1-25-75 \% \): forced expiratory flow between 25% and 75% of forced vital capacity; \( IC \): inspiratory capacity; \( FEF_{25-75} \): functional residual capacity; \( TLC \): total lung capacity; \( RV \): residual volume; \( D_1 \) CO: diffusing capacity of the lung for carbon monoxide; \( KCO \): \( D_1 \) CO relative to alveolar volume (transfer coefficient); \( sRAW \): specific airway resistance; \( FEV_1/FVC \): ratio between \( FEV_1 \) and \( FVC \); \( FRC \): functional residual capacity; \( RV \): residual volume; \( sRAW \): specific airway resistance; LAA: lower attenuation areas; P100: Airway wall thickness of airways with an internal perimeter of 10 mm.

pred and dyspnea = 6.1 ± 1.6 vs. 4.4 ± 1.9, respectively; \( p < 0.05 \).

**Constant work rate exercise tests**

Constant WR tests were performed by 16 (25 W) and 13 (50 W) patients and 26 controls. Technically acceptable PBF measurements were obtained in 14 (25 W) and 12 (50 W) patients and 21 controls, respectively. As expected from similar WRs in subjects with comparable body dimensions (Table 1), metabolic demand (expressed as \( VO_2 \) ) (Figure 3A) was equivalent between patients and controls. We found that despite similar resting values, patients presented with lower PBF at both exercise intensities (Figure 3B). Thus, PBF increased to a lesser extent from rest to exercise in patients compared to controls.

![Figure 2. Parameters of the ventilation (\( V_{1} \))–carbon dioxide output (\( V_{CO2} \)) relationship obtained in the symptom-limited incremental CPET in patients with mild-to-moderate COPD (N = 19) and controls (N = 26). Values are mean ± SD.](image-url)
Figure 3. (A) Absolute metabolic (oxygen uptake, VO₂) and (B) pulmonary hemodynamic responses (pulmonary blood flow, PBF) to two constant work rate exercise tests in patients with mild-to-moderate COPD and controls. Exercise-induced changes in PBF either in absolute or VO₂-corrected values are depicted in (C) and (D), respectively. Values are mean ± SD. ∗p < 0.05 for patients vs. controls at a given testing condition.

(p < 0.05) (Figure 3B and C). However, there were no between-group differences in PBF changes from 25 to 50 W (p > 0.05). As expected from similar metabolic demands, VO₂-corrected PBF values closely followed this pattern of abnormalities (Figure 3D).

**Structural and functional correlates of ventilatory inefficiency**

Patients with low peak VO₂ presented with greater ventilatory inefficiency (Figure 4A). Emphysema severity was positively related to V̇E/VTCO₂ nadir (Figure 4B); in contrast, we did not find a significant correlation between airway wall thickness (Pi10) with V̇E/VTCO₂ nadir or any of the resting physiological variables (p > 0.05). Low DlCO (but not low FEV₁ or high RV; p > 0.05) was associated with higher V̇E/VTCO₂ nadir (Figure 4C) and more impaired PBF from rest to 25 W (r = −0.69, p < 0.01) and higher V̇E/VTCO₂ nadir (Figure 4D). Moreover, V̇E/VTCO₂ nadir was marginally related to changes in PBF from rest to 50 W (r = 0.44; p = 0.07). An integrative overview of the key inter-measurement correlations is shown in Figure 5.

**Discussion**

This study investigated the structural (emphysema and airway wall thickness by thoracic CT) and resting functional correlates of exercise ventilatory inefficiency in COPD patients with mild-to-moderate airflow obstruction. Our main results indicate that, compared to controls, patients with COPD presented with impaired lung diffusing capacity (DlCO), lower maximal exercise capacity (peak VO₂), greater ventilatory inefficiency (V̇E/VTCO₂), and blunted changes in PBF from rest to exercise. Emphysema severity (but not airway disease) was associated with DlCO and PBF impairments and greater ventilatory inefficiency. These data provide evidence that ventilation “wasted” in emphysematous areas has an important role in disturbing pulmonary gas exchange at rest and ventilation and lung hemodynamics during exercise in COPD patients with only modest spirometric abnormalities. Considering its association with meaningful patient-centered outcomes (poor exercise tolerance and exertional dyspnea), emphysema on thoracic CT should be clinically valued in COPD patients with largely preserved FEV₁.

Our population of patients with mild-to-moderate COPD was typically younger than that evaluated in most studies with more advanced COPD, a finding expected by the natural history of COPD (32). Most patients were overweight or had only
mild obesity; thus, we avoided the complex effects of obesity on exercise responses in patients with COPD (33). We excluded patients with major cardiovascular co-morbidities and impaired left ventricular systolic function. Moreover, patients and controls were well matched by regular physical activity and the burden of co-morbidities as assessed by the Charlson index (25). Thus, we avoided major confounding factors regarding the determinants of peak exercise capacity and ventilatory efficiency in COPD, e.g., heart failure (34) and coronary artery disease (35). The patient population presented with a pattern of resting physiological abnormalities which closely resembles that found in previous studies involving mild-to-moderate COPD (11,14,15).

The key novel finding of the present study was the significant cross-correlations between emphysema severity, $D_l$CO impairment, and worse ventilatory inefficiency (Figure 5). These data therefore provide compelling evidence that increased alveolar dead space due to emphysema was a relevant mediator of impaired ventilatory efficiency in our patients. Increased “wasted” ventilation represents a major challenge for the lungs as an efficient gas exchanger (16). Enghoff’s physiological dead space is strongly influenced by VA/Q mismatching (16). Structure–function correlation studies in patients with mild-to-moderate COPD have shown that centrilobular emphysema results in a wide spectrum of VA/Q heterogeneity, including: a) areas of low VA/Q ratio, due to reduced ventilation secondary to airway narrowing and distortion (36); and b) areas of high VA/Q ratio due to more extensive microvascular destruction than loss of alveolar units (37) and mechanical compression by over-distended air spaces in the distal acinus (38–40). Thus, emphysema may have not only contributed to decreased
D_{13}CO but also impaired exercise ventilatory efficiency. Considering that ventilation delivered to non-perfused alveolar spaces has an even greater impact on alveolar dead space, microvascular destruction in non-emphysematous areas may have also contributed to poor ventilatory efficiency (37). Thus, inflammatory/hyperoxidative processes involving the genesis of emphysema may also have damaged the lung microvasculature in adjacent non-emphysematous areas, thereby contributing to further increase in "wasted" ventilation (37).

In line with our main premises, we found poorer ventilatory efficiency in the patient group. Thus, higher nadirs in patients were consequence of steeper slopes and, secondarily, higher intercepts (Figure 2). These data corroborate the notion that all parameters of the V_{2}-VCO_{2} relationship are able to reflect the presence of ventilatory inefficiency in mild-to-moderate COPD (9). Considering, however, that the nadir represents the combined effects of increases in slope and intercept (9), the nadir might constitute a more sensitive index of ventilatory inefficiency in these patients. Greater dyspnea scores were found in patients with higher nadirs. This finding largely stems from the combined effects of higher neural drive and greater erosion of the mechanical reserves induced by an excessive ventilatory response to exertion (9–15).

Our study confirms previous findings that despite the presence of only modest spirometric abnormalities, emphysema on CT and low D_{13}CO carries with poor tolerance to exertion (1–5). Of note, most of our patients presented with > 5% LAA on chest CT scan, a widely used threshold to suggest “clinically-significant” emphysema (26). There is evidence that patients with mild-to-moderate COPD presenting with an emphysema-dominant phenotype—as in the present study—had increased lung volumes and greater impairment of gas exchange in comparison with an airways disease-dominant phenotype (41). In the MESA study, smokers with centrilobular emphysema had greater dyspnea, reduced walk distance, greater hyperinflation, and low D_{13}CO than their counterparts without emphysema (42). Lung volume reduction surgery, targeting areas with more extensive emphysema, has been associated with improved dead space ventilation (43) and better ventilatory efficiency (44). Collectively, these data (and ours) indicate that emphysema is more likely to be associated with negative physiological outcomes pertinent to exercise tolerance than airway disease in patients with mild-to-moderate disease.

It is also noteworthy that we found a predominance of centrilobular emphysema involving the upper lobes. Similarly, Pike et al. (2) found that patients with milder COPD present with a higher probability to develop centrilobular emphysema in the upper lobes compared to that in the lower lobes in patients with equivalent degrees of airflow obstruction. Of note, Wang and co-workers also found that D_{13}CO and air trapping were primarily affected by the % LAA of the upper lobes (45). The upper lobes characteristically present with areas of high V/Q ratios, including during exercise (46). Thus, it is conceivable that areas of centrilobular emphysema in the upper lobes are more prone to "waste" ventilation upon exertion than better perfused areas of the lower lobes.

We found a downward displacement of the PBF-VO_{2} relationship in patients with COPD (Figure 3). Thus, reduced absolute PBF in patients is unlikely to reflect lower cardiac output due to diminished metabolic demands. Our patients did not present with major cardiovascular co-morbidities, and, considering the presence of only mild resting air trapping, had a low probability of negative cardiopulmonary interactions (32). In other words, it is also improbable that they had lower cardiac output/VO_{2} ratios than controls. The exact mechanism behind low exercise PBF in our patients, however, remains elusive. However, it is noteworthy that emphysema severity was associated with lower PBF/VO_{2} (Figure 4D). On one hand, this might reflect, at least partially, the inherent limitations of inert gas rebreathing in patients with ventilation distribution abnormalities (as discussed in the next paragraph) (31). On the other hand, there is a morphological background to support the notion that emphysema-related vascular destruction/obliteration (36) may have compromised PBF under the stress of exercise, i.e., when distension and recruitment of a healthy vasculature are particularly important (47). Indirect compressive effects on lung microvasculature due to over-distension of expanded air spaces and less tethering effects due to loss of alveolar attachments may also have played a role (36). Whether PBF was also impaired due to microvascular abnormalities beyond that induced by emphysema per se should be further investigated using advanced vascular imaging during exercise (18).

As a small clinical physiology study, our investigation has some limitations. Functional assessment restricted to the conventional lung function tests and more sophisticated tests of small airways function and ventilation distribution abnormalities were not performed (14). We were also unable to separate the membrane and vascular components of gas transfer, which precluded us to further advance on the seeds of a low D_{13}CO in patients (47). Technologically more advanced and accurate imaging techniques reflecting ventilation distribution abnormalities (such as hyperpolarized H_{2}He magnetic resonance imaging) might have uncovered important abnormalities with a potential to increase "wasted" ventilation (2,3). We did not measure operating lung volumes or arterial blood gases as the seeds and consequences of mechanical-ventilatory, and pulmonary gas exchange abnormalities have already been extensively investigated in patients with mild COPD (10–15). At least in patients with moderate-to-severe COPD, inadequate gas mixing and gas exchange disturbances might lead to an underestimation of PBF (31). Thus, we acknowledge that the observed association between emphysema extent and low exercise PBF likely represents the combined effects of poor lung perfusion in emphysematous areas with the undesired consequences of higher alveolar dead space on inert gas rebreathing measurements.

We conclude that centrilobular emphysema in the upper lobes is an important structural correlate of low D_{13}CO and exercise ventilatory inefficiency in COPD patients with largely preserved FEV_{1}. Low D_{13}CO and ventilatory inefficiency, in turn, are associated with activity-related dyspnea and exercise intolerance. The present study shed new light on the mechanisms behind the previously reported correlations between emphysema extent and low D_{13}CO with poor exercise capacity in the early stages of COPD (1,3,6,8). Ventilatory inefficiency, therefore, is an important exercise-based biomarker that links structural abnormalities (emphysema) and resting physiological...
impairment (D_{1}CO) to a key clinical outcome (exercise intolerance) in COPD patients with only modest spirometric abnormalities.

**Acknowledgments**

The authors would like to thank Kathy Webb, Kristin MacLeod, and Casey Ciavaglia for dedicating their valuable time in performing pulmonary function tests. They also thank Dr. Amany Elbehairy for patients’ referral and Mrs. Ingrid Raaffety and Luiza Castanhas for their technical assistance. They are also grateful to Prof. John T Fisher (Department of Biomedical and Molecular Sciences, Queen’s University) for his intellectual support. They are particularly indebted to patients and volunteers for their time and commitment to the study.

**Funding**

JH Jones was partially supported by the McLaughlin Fellowship during his MSc in Experimental Medicine at Queen’s University. J A Neder was supported by the Southeastern Academic Medical Association (SEAMO)’s New Clinician Scientist Program. His laboratory was established owing to the Canadian Foundation for Innovation’s Leader Operating Fund.

**Declaration of interest**

Each of the authors declare no conflict of interest regarding to this manuscript.

**References**


