Pulmonary capillary blood volume response to exercise is diminished in mild chronic obstructive pulmonary disease

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\textbf{ABSTRACT}

\textbf{Background:} Previous work suggests that mild chronic obstructive pulmonary disease (COPD) patients have greater lung dysfunction than previously appreciated from spirometry alone. There is evidence of pulmonary microvascular dysfunction in mild COPD, which may reduce diffusing capacity (DLCO) and increase ventilatory inefficiency during exercise. The purpose of this study was to determine if DLCO, pulmonary capillary blood volume (Vc), and membrane diffusing capacity (Dm) are diminished during exercise in mild COPD, and whether this is related to ventilatory inefficiency and dyspnea.

\textbf{Methods:} Seventeen mild COPD patients (FEV\textsubscript{1}/FVC: 64 ± 4\%, FEV\textsubscript{1}=94 ± 11\%pred) and 17 age- and sex-matched controls were recruited. Ten moderate COPD patients were also tested for comparison (FEV\textsubscript{1}=66 ± 7\%pred). DLCO, Vc, and Dm were determined using the multiple-fraction of inspired oxygen (FIO\textsubscript{2}) DLCO method at baseline and during steady-state cycle exercise at 40W, 50\%, and 80\% of VO\textsubscript{2peak}. Using expired gas data, ventilatory inefficiency was assessed by V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}}.

\textbf{Results:} Compared to controls, mild COPD had lower DLCO at baseline and during exercise secondary to diminished Vc (P < 0.05). No difference in Dm was observed between controls and mild COPD at rest or during exercise. Patients with high V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} (i.e. ≥34) had lower Vc and greater dyspnea ratings compared to control at 40W. Moderate COPD patients were unable to increase Vc with increasing exercise intensity, suggesting further pulmonary vascular impairment with increased obstruction severity.

\textbf{Conclusion:} Despite relatively minor airflow obstruction, mild COPD patients exhibit a diminished DLCO and capillary blood volume response to exercise, which appears to contribute to ventilatory inefficiency and greater dyspnea.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive partially reversible airway obstruction and exertional dyspnea [1], which impairs a patient's ability to complete day-to-day tasks and reduces quality of life [2]. Evolving work in mild COPD (GOLD stage 1, forced expiratory volume in 1s (FEV\textsubscript{1})/forced vital capacity (FVC) < 70\%, FEV\textsubscript{1} ≥ 80\% predicted) have demonstrated greater functional impairment than previously appreciated [3,4], suggesting that the physiological impact of the disease is worse than indicated by spirometry alone. Despite their relatively minor airway impairment, during exercise, mild COPD patients demonstrate increased ventilatory inefficiency (V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}}), increased dyspnea, and reduced VO\textsubscript{2peak} compared to control [3,5]. Importantly, increased ventilatory inefficiency (i.e. a nadir V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} during exercise ≥34) is predictive of mortality in COPD [6]. Some have suggested the increased V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} during exercise in mild COPD is due to greater deadspace [5], as a result of pulmonary vascular dysfunction [7–9]. Pulmonary vascular dysfunction reduces pulmonary microvascular perfusion [8], decreases surface area for gas exchange, increases deadspace ventilation, and thus requires greater minute ventilation to maintain alveolar ventilation (i.e. greater V\textsubscript{E}/V\textsubscript{CO\textsubscript{2}} during exercise).

During exercise, diffusing capacity must increase in order to augment gas exchange [10]. The main components of diffusing capacity are the membrane diffusing capacity (Dm), which reflects the surface area
available for gas exchange and alveolar membrane thickness, and pulmonary capillary blood volume (Vc) [11]. During exercise, there is typically recruitment and distention of pulmonary capillaries, which act to increase Vc and Dm, as well as blunt the rise in pulmonary artery pressure with exercise [12]. Capillary recruitment would reduce deadspace ventilation, and therefore reduce V̇E/VCO₂ during exercise. Compared to age-matched controls, resting diffusing capacity (DLCO) is reduced by 20% in mild COPD [3], and lower resting DLCO is correlated with lower V̇O₂peak and a greater exercise V̇E/VCO₂ nadir in mild COPD [13]. However, it is unclear how DLCO, and its components Vc and Dm, respond to exercise in mild COPD. We hypothesized that mild COPD would have a blunted DLCO and Vc response to exercise, suggesting pulmonary vascular dysfunction which would contribute to deadspace ventilation (i.e. V̇E/VCO₂) and dyspnea. With an increase in the severity of COPD, there may be further changes to the pulmonary vascular response to exercise. Therefore, 10 moderate COPD patients were also studied to describe the continuum of responses to increasing obstruction severity.

2. Material and methods

2.1. Ethical approval

This study was approved by the Human Research Ethics Board of the University of Alberta (protocol #54658). All subjects gave written, informed consent to participate in the study.

2.2. Subjects

Seventeen patients with mild COPD (post-bronchodilator FEV₁/FVC < lower limit of normal (LLN) and FEV₁ ≥ 80% predicted) and 17 age-, sex-, and height-matched control subjects, as well as 10 moderate COPD patients (FEV₁ 50–80% predicted) were recruited for this study. Four mild and six moderate COPD patients were current smokers, and were instructed to withhold from smoking 24 h prior to testing day.

The sample size was derived from a similar study that demonstrated a 12% difference in pulmonary capillary blood volume between old and young male subjects during exercise [14], and a priori power calculation to determine that a sample size of n = 15 was appropriate to detect a between-group difference (α = 0.05, β = 0.8).

2.3. Study overview

In total, subjects completed three visits to the laboratory. In visit one, subjects completed full pulmonary function testing followed by an incremental cardiopulmonary exercise test to determine V̇O₂peak on a cycle ergometer. At least 48 h later, subjects returned to the laboratory for the exercise DLCO sessions. Subjects performed multiple-FIO₂ DLCO maneuvers [11] at rest and during steady state exercise [15–17]. Participants returned at least one week later for the echocardiography session to estimate cardiac output and pulmonary artery systolic pressure at rest and during exercise.

2.4. Pulmonary function testing

Participants completed a full pulmonary function test, including pre- and post-bronchodilator spirometry (400μg Salbutamol), determination of lung volumes by plethysmography, and resting DLCO (V62J Body Plethysmograph, SensorMedics, Yorba Linda, CA) in accordance with clinical practice guidelines [18].

2.5. Cardiopulmonary exercise test

Subjects then performed an incremental cycle test (Ergoselect II 1200 Ergoline, Blitz, Germany) to determine V̇O₂peak [19]. Inspiratory capacity (IC) measurements were performed at rest and every 2 min during the exercise test [20]. Participants rated the intensity of their “breathing discomfort” and “leg discomfort” at rest and every 2 min during exercise using the modified 10-point Borg Scale [21]. The nadir V̇E/VCO₂ was determined as the lowest 30-s value achieved during the incremental exercise test.

2.6. Exercise diffusing capacity

DLCO was determined using the single-breath breath-hold technique [18] at baseline and during exercise. The relative exercise intensities of 50% and 80% of V̇O₂peak were determined by linear regression of work rate and VO₂ obtained during the incremental exercise test on the preliminary day, similar to our previous work [15]. Prior to data collection, subjects were coached to avoid Müller or Valsalva maneuvers during the breath hold maneuver. To ensure alveolar PO₂ was stable, each subject was given five breaths of gas at the respective FIO₂ for each DLCO test gas [15,16]. Diffusing capacity was adjusted for hemoglobin concentration [22] (HemoCue 201+, HemoCue AB, Angelholm, Sweden) as well as CO [23], which was estimated in real-time using non-invasive CO-oximetry (Radical 7, Masimo, Irvine, CA, USA), for each exercise workload.

To assess Vc and Dm, multiple-FIO₂ DLCO breath holds were performed with three different FIO₂ values (0.21, 0.40, 0.60) during steady state exercise at 40 W, 50% and 80% of V̇O₂peak similar to our previous work [15,16]. Steady state was determined by exercising for a minimum of 3 min at the previously determined intensity, with a change in heart rate ≤ 3 bpm in 1 min. Vc and Dm were calculated from the equation [11]

\[
\frac{1}{\text{DLCO}} = \frac{1}{\text{Dm}} + \frac{1}{\text{CO} \times \text{Vc}},
\]

and theta was calculated using the equation

\[
\frac{\theta}{\text{DLCO}} = \alpha \times P_aO_2 + \beta,
\]

with the values α = 0.0058 and β = 0.73, based on moderate red cell permeability [15,16,24]. For each workload, the relationship between 1/DLCO and 1/θ for the three FIO₂ values were plotted, and a regression equation was then calculated, determining the values of 1/Vc as the slope and 1/Dm as the y-intercept of the resulting linear equation. The minimum acceptable r² was 0.95, and DLCO maneuvers were repeated when r² fell below this value, or if quality assurance standards as discussed below were not met.

2.7. Quality assurance of breath hold maneuvers

Recognizing the challenge of a 6-s breath hold during exercise in COPD patients, we spent considerable time and effort in training subjects to the proper breath holding technique and timing to adhere to our quality standards. Mouth pressure measured at the mass flow sensor was monitored throughout the breath hold to be within ± 20 mmHg to ensure no Valsalva or Müller maneuvers and an open glottis. Acceptable breath hold time during trials was 6.0 ± 0.3 s. Exhaled methane was monitored to ensure a horizontal tracing throughout the exhalation, which suggests adequate mixing of test gas in resident alveolar air. The breath hold was repeated if measured Vₐ was not within 5% of the previous trial, or if any of the quality standards described above were not met.

2.8. Echocardiography

At least one week after the exercise DLCO, participants returned for an exercise echocardiogram. All echocardiograms were performed by
2.9. Statistical analysis

Pulmonary function variables presented as percent predicted are based on normative data [26]. Spirometric data are also presented as z-scores using the Global Lungs Initiative 2012 equations [27]. For all inferential analyses, the probability of a type I error was set at 0.05. Values are expressed as means ± standard error of the mean unless otherwise indicated. Unpaired Student’s T-test were used to compare subject characteristics (age, height, weight, etc.) between groups. Statistical analysis was performed using two-way repeated measures ANOVA (SigmaPlot, v.13, Systat Software, San Jose, CA, USA) and were later interpreted by a cardiologist blind to experimental conditions. Where appropriate, the main effect of disease state was found, a Holm-Sidak post-hoc test was performed to locate differences between groups and exercise intensities. The moderate COPD response was compared to control at 3 levels: baseline, 40W and 80% of VO2peak using two-way repeated measures ANOVA. The 50% of VO2peak exercise workload was removed from the moderate COPD analysis because the workload was nearly identical to that of 40W in these patients.

To further examine the COPD response, the mild COPD group was subdivided by the nadir V̇E/V̇CO2 observed during the incremental exercise test, as defined as V̇E/V̇CO2 < 34 vs. ≥ 34 [6], as well as whether dynamic hyperinflation developed with exercise, as defined by a decrease in their IC from baseline to peak exercise [28,29]. One-way ANOVA was used to determine differences between these subgroups at an identical workload of 40W, at which the metabolic demand would be similar. An additional comparison was made at the relative workload of 50% of VO2peak as it was the closest data point to the observed nadir V̇E/V̇CO2 (60 ± 10% of VO2peak).

3. Results

Descriptive characteristics of the study sample are provided in Table 1. As expected, mild COPD patients had lower FEV1 (P = 0.017) and greater functional residual capacity %pred compared to control (P = 0.010), but there was no significant difference in total lung capacity (P = 0.410, Table 1).

3.1. Cardiopulmonary response to exercise in mild COPD

Cardiopulmonary responses to steady state exercise at 40W, 50%, and 80% of VO2peak are given in Table 2. Absolute VO2 was not different between mild COPD and controls at rest (P = 0.645) or at 40W (P = 0.294), but was lower in the mild COPD group at 50% (P = 0.001) and 80% of VO2peak (P < 0.001, Table 2). Similarly, HR was lower in mild COPD at 50% (P = 0.006) and 80% of VO2peak compared to control (P = 0.016). PASP and Q were not significantly different between groups at rest or during exercise, although there were fewer comparisons of PASP due to a lack of subjects with sufficient quality of tricuspid regurgitant jet Doppler envelope during exercise (control n = 11, mild COPD n = 9). Dyspnea was not different between groups at rest. During exercise, dyspnea was greater in the mild COPD group as compared to controls at 40W (P = 0.002, Table 3).

3.2. Exercise diffusing capacity

At baseline, DLCO was lower in the mild COPD group compared to control (P = 0.049). With incremental exercise, both mild COPD and controls increased DLCO with increasing oxygen consumption (P < 0.001). However, DLCO was higher in control subjects at all exercise intensities (Fig. 1A).

3.3. Pulmonary capillary blood volume

At baseline, Vc was lower in the mild COPD group compared to control (P = 0.033, Fig. 1B). With incremental exercise, both mild COPD and control groups increased Vc with increasing oxygen...
consumption \((P < 0.001)\). During exercise, the mild COPD group had significantly lower \(V_c\) at 40W \((P = 0.033)\), 50\% \((P = 0.029)\), and 80\% of \(\dot{V}O_2\text{peak}\) \((P = 0.010)\) compared to control.

### 3.4. Membrane diffusing capacity

At baseline, \(D_m\) was not different between mild COPD and controls \((P = 0.643)\). With incremental exercise, both groups increased \(D_m\) with increasing \(\dot{V}O_2\) \((P < 0.001)\), but \(D_m\) was not significantly different between groups during exercise at any intensity \((P = 0.269, \text{Fig. 1C})\).

### 3.5. Grouping the mild COPD response by ventilatory inefficiency

\(\dot{V}E/\dot{V}CO_2\) was greater in mild COPD at rest and during all exercise intensities \((P < 0.001)\). Furthermore, the mean nadir \(\dot{V}E/\dot{V}CO_2\) was significantly higher in mild COPD compared to control \((P = 0.01)\).

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### Table 2
Cardiopulmonary response to exercise in mild COPD.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>40W</th>
<th>50%</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PO_2) (W)</td>
<td>Control</td>
<td>0</td>
<td>40 ± 0</td>
<td>75 ± 0</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>0</td>
<td>40 ± 0</td>
<td>46 ± 20</td>
</tr>
<tr>
<td>(P)</td>
<td>NA</td>
<td>NA</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>(\dot{V}O_2) (\frac{L}{min})</td>
<td>Control</td>
<td>0.34 ± 0.09</td>
<td>0.94 ± 0.21</td>
<td>1.27 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>0.29 ± 0.06</td>
<td>0.83 ± 0.20</td>
<td>0.91 ± 0.30</td>
</tr>
<tr>
<td>(P)</td>
<td>0.645</td>
<td>0.294</td>
<td>0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>(\dot{V}CO_2) (\frac{L}{min})</td>
<td>Control</td>
<td>0.31 ± 0.07</td>
<td>0.82 ± 0.20</td>
<td>1.16 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>0.25 ± 0.05</td>
<td>0.70 ± 0.20</td>
<td>0.76 ± 0.28</td>
</tr>
<tr>
<td>(P)</td>
<td>0.573</td>
<td>0.236</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>(P_{\text{ETO}_2}) (\text{mmHg})</td>
<td>Control</td>
<td>96.4 ± 17.9</td>
<td>91.4 ± 15.4</td>
<td>91.4 ± 15.5</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>101.8 ± 4.0</td>
<td>97.0 ± 3.5</td>
<td>96.7 ± 3.9</td>
</tr>
<tr>
<td>(P)</td>
<td>0.101</td>
<td>0.091</td>
<td>0.014*</td>
<td>0.844</td>
</tr>
<tr>
<td>(P_{\text{ETCO}_2}) (\text{mmHg})</td>
<td>Control</td>
<td>32.4 ± 3.6</td>
<td>35.2 ± 3.2</td>
<td>37.4 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>30.0 ± 1.7</td>
<td>33.4 ± 2.6</td>
<td>34.2 ± 3.2</td>
</tr>
<tr>
<td>(P)</td>
<td>0.056</td>
<td>0.161</td>
<td>0.001*</td>
<td>0.344</td>
</tr>
<tr>
<td>(\dot{V}E) (\frac{L}{min})</td>
<td>Control</td>
<td>13.3 ± 2.7</td>
<td>26.4 ± 6.7</td>
<td>35.3 ± 9.4</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>12.1 ± 2.1</td>
<td>25.9 ± 6.4</td>
<td>27.8 ± 8.5</td>
</tr>
<tr>
<td>(P)</td>
<td>0.723</td>
<td>0.876</td>
<td>0.040*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>(\dot{V}E/\dot{V}CO_2)</td>
<td>Control</td>
<td>44 ± 5</td>
<td>35 ± 3</td>
<td>31 ± 3</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>51 ± 9</td>
<td>38 ± 5</td>
<td>37 ± 5</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt; 0.001*</td>
<td>0.005*</td>
<td>0.001*</td>
<td>0.009*</td>
</tr>
<tr>
<td>(S_{\text{PO}_2}) (%)</td>
<td>Control</td>
<td>98.1 ± 1.1</td>
<td>97.2 ± 1.7</td>
<td>97.0 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>96.4 ± 2.7</td>
<td>96.1 ± 2.6</td>
<td>96.0 ± 2.9</td>
</tr>
<tr>
<td>(P)</td>
<td>0.075</td>
<td>0.244</td>
<td>0.271</td>
<td>0.220</td>
</tr>
<tr>
<td>(Q) (\frac{L}{min})</td>
<td>Control</td>
<td>3.47 ± 0.73</td>
<td>5.50 ± 1.24</td>
<td>7.23 ± 1.88</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>3.69 ± 1.23</td>
<td>5.69 ± 1.33</td>
<td>5.96 ± 0.94</td>
</tr>
<tr>
<td>(P)</td>
<td>0.651</td>
<td>0.800</td>
<td>0.053</td>
<td>0.440</td>
</tr>
<tr>
<td>(HR) (\text{bpm})</td>
<td>Control</td>
<td>77 ± 10</td>
<td>99 ± 14</td>
<td>112 ± 15</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>76 ± 0</td>
<td>96 ± 11</td>
<td>100 ± 10</td>
</tr>
<tr>
<td>(P)</td>
<td>0.684</td>
<td>0.558</td>
<td>0.006*</td>
<td>0.001*</td>
</tr>
<tr>
<td>(SV) (\text{mL})</td>
<td>Control</td>
<td>48 ± 9</td>
<td>58 ± 13</td>
<td>66 ± 16</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>48 ± 15</td>
<td>62 ± 14</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>(P)</td>
<td>0.949</td>
<td>0.492</td>
<td>0.543</td>
<td>0.577</td>
</tr>
<tr>
<td>(\text{PASP}) (\text{mmHg})</td>
<td>Control</td>
<td>22.8 ± 10.4</td>
<td>34.4 ± 15.7</td>
<td>42.4 ± 18.5</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>23.8 ± 7.5</td>
<td>32.4 ± 12.3</td>
<td>34.1 ± 13.0</td>
</tr>
<tr>
<td>(P)</td>
<td>0.807</td>
<td>0.770</td>
<td>0.362</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Values mean ± SD. \(PO_2\), power output; \(\dot{V}O_2\), oxygen consumption; \(\dot{V}CO_2\), carbon dioxide production; \(P_{\text{ETO}_2}\), partial pressure of end tidal \(O_2\); \(P_{\text{ETCO}_2}\), partial pressure of end tidal \(CO_2\); \(\dot{V}E\), minute ventilation; \(\dot{V}E/\dot{V}CO_2\), ventilatory equivalent for carbon dioxide; \(S_{\text{PO}_2}\), oxygen pulse saturation; \(Q\), cardiac output; \(HR\), heart rate; \(SV\), stroke volume; \(\text{PASP}\), pulmonary artery systolic pressure. *Significantly different than control.
Table 3
Lung volumes during exercise in mild COPD.

<table>
<thead>
<tr>
<th>Lung Volume</th>
<th>Control</th>
<th>Mild COPD</th>
<th>50%</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vₐ, L</td>
<td>5.49 ± 1.37</td>
<td>4.76 ± 1.04</td>
<td>5.56 ± 1.41</td>
<td>4.90 ± 1.03</td>
</tr>
<tr>
<td>P</td>
<td>0.090</td>
<td>0.134</td>
<td>0.090</td>
<td>0.090</td>
</tr>
<tr>
<td>Vₐ, L</td>
<td>0.79 ± 0.18</td>
<td>0.68 ± 0.16</td>
<td>1.21 ± 0.26</td>
<td>1.21 ± 0.37</td>
</tr>
<tr>
<td>P</td>
<td>0.352</td>
<td>0.992</td>
<td>0.234</td>
<td>0.003*</td>
</tr>
<tr>
<td>IC, L</td>
<td>2.65 ± 0.67</td>
<td>2.48 ± 0.75</td>
<td>2.58 ± 0.73</td>
<td>2.55 ± 0.72</td>
</tr>
<tr>
<td>P</td>
<td>0.502</td>
<td>0.349</td>
<td>0.118</td>
<td>0.050*</td>
</tr>
<tr>
<td>IC/TLC, %</td>
<td>43 ± 7</td>
<td>44 ± 13</td>
<td>46 ± 7</td>
<td>45 ± 11</td>
</tr>
<tr>
<td>P</td>
<td>0.737</td>
<td>0.994</td>
<td>0.397</td>
<td>0.104</td>
</tr>
<tr>
<td>IRV, L</td>
<td>1.86 ± 0.68</td>
<td>1.80 ± 0.67</td>
<td>1.60 ± 0.77</td>
<td>1.36 ± 0.76</td>
</tr>
<tr>
<td>P</td>
<td>0.797</td>
<td>0.267</td>
<td>0.232</td>
<td>0.654</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.0 ± 0.0</td>
<td>0.2 ± 0.6</td>
<td>1.6 ± 0.6</td>
<td>2.5 ± 0.9*</td>
</tr>
<tr>
<td>P</td>
<td>0.374</td>
<td>0.002*</td>
<td>0.655</td>
<td>1.000</td>
</tr>
</tbody>
</table>

VA, alveolar volume; Vₐ, tidal volume; IC, inspiratory capacity; IC/TLC, inspiratory capacity as a percent of total lung capacity; IRV, inspiratory reserve volume; Dyspnea, Borg Scale of Breathlessness (1-10). *Significantly different than control, P < 0.05.

3.6. Grouping the mild COPD response by hyperinflation

Dynamic hyperinflation with exercise was observed in 11 mild COPD patients (ΔIC from rest = −0.35 ± 0.25L), while six did not hyperinflate with exercise (ΔIC = 0.35 ± 0.18L). When mild COPD patients were grouped by level of dynamic hyperinflation, there were no between-group differences in IC from rest (P = 0.101) or ΔIC (P = 0.898) during exercise at 40W, and no differences in Vc (P = 0.596) or ΔIC (P = 0.998) during exercise at 50% of VO₂peak.

3.7. Moderate COPD

Additional information for the moderate COPD group can be found in the online supplement. Mean FEV₁ in the moderate COPD group was 69 ± 8% predicted, and moderate patients had greater percent predicted functional residual capacity (%pred) (P = 0.006) and residual volume (P = 0.003) compared to control. At baseline, the moderate COPD group had lower DLCO (Supplement Fig. 1A, P = 0.023) compared to controls. Compared to rest, exercise intensity increased DLCO (P < 0.001), secondary to increased Dm (Supplement Fig. 1C, P = 0.003). Moderate COPD patients failed to demonstrate an increase in Vc with exercise (Supplement Fig. 1B, P = 0.222).

4. Discussion

The present study examined the diffusing capacity, pulmonary capillary blood volume, and membrane diffusing capacity responses to exercise in mild COPD patients and age-, sex-, and height-matched controls. DLCO was lower in mild COPD at rest and during exercise compared to controls as a result of lower Vc. A reduced Vc, and thus lower surface area for gas exchange would increase deadspace ventilation and lead to increased ventilatory demand (i.e. greater V/VA). To maintain adequate alveolar ventilation. In keeping with this idea, the current study found that in addition to the reduced exercise Vc, the mild COPD group had both greater V̇E/V̇CO₂ and dyspnea during exercise at 40W compared to controls. As an additional comparison, moderate COPD patients were also studied, and these patients failed to increase Vc with exercise, suggesting further pulmonary vascular impairment with greater COPD severity. These data suggest that despite the relatively mild perturbation in airflow obstruction (i.e. FEV₁), mild COPD patients exhibit early pulmonary vascular impairment that contributes to an exaggerated ventilatory and dyspnea response to exercise.

4.1. The pulmonary vasculature in mild COPD

In both controls and mild COPD patients, DLCO rises during exercise to meet the increased metabolic demand in part through an increase in Vc, which reflects recruitment and distension of pulmonary capillaries. The slope of Vc response from rest to 40W appears similar between mild COPD and controls, suggesting that COPD patients started at a lower Vc. The comparison during exercise at 40W allows us to evaluate the Vc and Δm response between groups at the same metabolic demand, where the O₂ diffusion requirement would be the same in both mild COPD and controls groups. Given that cardiac output and V̇O₂ were not different between groups, it can be concluded that the lower Vc observed in mild COPD at 40W is independent of global pulmonary blood flow or O₂ requirement. The lower Vc in mild COPD could be a result of
diminished blood flow proximal to the capillaries, secondary to vascular dysfunction. Previous research has demonstrated thickening of smooth muscles in the pulmonary arteries and arterioles of mild COPD patients [30], which would increase vascular resistance and thus reduce perfusion of the pulmonary capillaries. More recent work using contrast-enhanced magnetic resonance imaging has shown a 30% reduction in resting blood flow to the pulmonary microvasculature in mild COPD [8]. Pulmonary vascular dysfunction in COPD patients would reduce capillary perfusion and result in more zone 1 conditions [31]. This would disrupt $V_{A}/Q$ (ventilation-perfusion) matching, thereby increasing deadspace ventilation and thus augmenting ventilatory inefficiency [7]. Taken together, despite the increase in Vc from rest to exercise, these data suggest that mild COPD patients likely have pulmonary vascular dysfunction or destruction which prevents the appropriate DLCO response to exercise.

The reduction in Vc could also be a consequence of emphysema, which would diminish gas exchange surface area and increase deadspace ventilation [32,33]. Our finding of reduced Vc with a high $V_{E}/V_{CO_2}$ is consistent with previous research showing that COPD patients with greater emphysema severity have reduced resting diffusing capacity and greater ventilatory inefficiency during exercise [32]. Interestingly, pulmonary capillary blood flow has also found to be reduced in non-emphysematous areas of the lung, suggesting microvascular impairment within an intact vascular network in mild COPD [8]. However, the current study was not able to distinguish vascular impairment from vascular destruction (i.e. emphysema). Taken together, these data suggest that mild COPD patients likely have impairment or destruction of their pulmonary vasculature which attenuates the increase in diffusing capacity needed for exercise. Future research should assess pulmonary capillary blood volume in targeted cohorts of COPD with known emphysema to further identify if pulmonary microvascular blood flow is reduced independent of, or concurrent to emphysema.

It is unlikely that the low capillary blood volume in COPD is an adaptive response to poor regional ventilation, given that $V_{A}/Q$ matching is typically worse in COPD compared to healthy individuals. In the current study, $V_{E}/V_{CO_2}$ was greater in the mild COPD group as compared to control at rest and at every exercise intensity (Table 2), which parallels previous work in mild COPD [5,32,34]. When the mild COPD group was subdivided based on a nadir $V_{E}/V_{CO_2}$ above or below 34, the group with a nadir $V_{E}/V_{CO_2}$ ≥ 34 had significantly lower exercise Vc. This is consistent with the concept that high $V_{A}/Q$ areas and deadspace (and thus ventilation inefficiency), are secondary to reduced capillary blood volume in COPD [7].

4.2. Implications for exertional dyspnea

Previous research in mild COPD has demonstrated that exertional dyspnea is the result of an exaggerated ventilatory response to exercise (i.e. increased minute ventilation relative to carbon dioxide production, $V_{E}/V_{CO_2}$) and airflow limitation (i.e. expiratory flow limitation and resulting dynamic hyperinflation) [5,6,28,35,36]. In addition to the lower Vc and increased $V_{E}/V_{CO_2}$, mild COPD patients in the current study also reported greater dyspnea at 40W. Further, when mild COPD patients were subdivided by ventilatory inefficiency, the high $V_{E}/V_{CO_2}$ patients had worse dyspnea (Fig. 2C) compared to controls, while dyspnea in the low $V_{E}/V_{CO_2}$ COPD group was not significantly different from controls. These findings suggest that impairments in the pulmonary vasculature may be linked to dyspnea in mild COPD. Specifically, the diminished exercise Vc in mild COPD reduces surface area for gas exchange, which increases deadspace ventilation. This increased deadspace necessitates greater minute ventilation (i.e. greater $V_{E}/V_{CO_2}$) in order to maintain alveolar ventilation, which translates to greater perceived dyspnea in these patients.

The lower Vc in mild COPD may result in greater pulmonary vascular resistance, which would thus require greater pulmonary artery pressure for a given cardiac output. However, in the current study, pulmonary artery systolic pressure was not found to be significantly elevated in mild COPD compared to control. It is likely that the parallel nature of the pulmonary microvasculature provides redundancy such that a significant reduction in capillary perfusion does not result in a larger increase in pulmonary vascular resistance. Unfortunately, high quality Doppler signals of the tricuspid regurgitant jet could only be obtained in 9 mild COPD patients and 11 controls during exercise, and thus the current study may have been underpowered to detect a significant between-group difference in pulmonary artery systolic pressure.

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**Fig. 1.** A. Diffusion capacity response to exercise. B. Pulmonary Vc response to exercise. C. Membrane diffusing capacity response to exercise. *Mild COPD had significantly lower DLCO and Vc compared to control $P < 0.05.$
4.3. Hyperinflation in mild COPD

The increased FRC observed in mild COPD in the current study provides some evidence of static lung hyperinflation (Table 1). During exercise, dynamic hyperinflation could mechanically collapse or reduce the transverse surface of pulmonary capillaries, thereby decreasing capillary blood volume [30,37]. In the current study, exercise Vc was not different between hyperinflators compared to non-hyperinflators, which suggests that the lower Vc in mild COPD is unlikely to result from differences in operating lung volume. This finding is consistent with previous work demonstrating no change in Vc/VCO₂ when dynamic hyperinflation is reduced with either heliox and/or short-acting β-agonist administration during exercise in COPD [38–40]. Taken together, these data appear to support the concept that pulmonary vascular dysfunction worsens with COPD disease severity, consequently reducing the diffusing capacity during exercise. However, it is unclear if the lack of increase in Vc during exercise in moderate COPD is predominantly due to emphysema or vascular impairment.

4.4. Moderate COPD

The moderate COPD group demonstrated no increase in Vc with increasing exercise intensity, which may indicate further impairment of the pulmonary vasculature with advancing COPD (Supplement Figure 1). There is previous evidence that pulmonary microvascular perfusion is reduced in moderate COPD at rest compared to mild COPD [8], and previous work using the multiple inert gas elimination technique has found increased ventilation-perfusion mismatch at rest in moderate COPD, secondary to areas of high Vₐ/Q ratio [7], consistent with increased deadspace and ventilatory inefficiency. Taken together, these data appear to support the concept that pulmonary vascular dysfunction worsens with COPD disease severity, consequently reducing the diffusing capacity during exercise. However, it is unclear if the lack of increase in Vc during exercise in moderate COPD is predominantly due to emphysema or vascular impairment.
difference in calculated Vc between mild COPD and controls. The multiple-FIO2 DLCO method assumes that alveolar PO2 does not affect Dm or Vc in a significant way [11,24,42]. Despite the brief exposure to 40% and 60% O2, there is potential concern that hyperoxia might disengage hypoxic pulmonary vasoconstriction in COPD. If this were the case in the current study, an increase of blood flowing to the capillaries would result in an overestimation of Vc on room air, and thus the difference in Vc between healthy controls and COPD during exercise would be greater than we observed. Therefore, it is extremely unlikely that the finding of blunted pulmonary capillary blood volume in COPD is the result of the transient exposure to hyperoxia.

Another potential methodological limitation is the challenge of the breath-hold maneuver. Exhalation to residual volume could be impeded with airway obstruction, and thus gas trapping may decrease the available surface area for diffusion. However, alveolar volume did not change with increasing exercise intensity in either group, suggesting that all subjects were able to reach residual volume prior to each breath hold maneuver.

This study was designed to compare Vc and Dm during exercise both at an absolute workload (40 W) and at exercise workloads relative to each individual’s VO2peak. The 40 W comparison allows us to compare the physiological responses between groups at an identical metabolic demand, whereas the relative intensity comparison at 50% and 80% of VO2peak allows for a better understanding of the diffusing capacity response to increased oxygen requirement, at similar percentages of VO2peak. We would suggest that the inclusion of both absolute and relative intensity comparisons is a strength of the study.

Lastly, the control group had significantly higher VO2peak compared to COPD. Our previous investigation showed that Vc was not different between aerobic trained and untrained individuals for a given work rate [15]. However, the current study observed lower Vc in COPD compared to controls at the same absolute work rate of 40W, suggesting that the difference in VO2peak between groups is unlikely to explain the differences in DLCO and Vc during submaximal exercise.

5. Conclusion

Patients with mild COPD demonstrated a lower diffusing capacity response to exercise compared to control subjects due to reduced pulmonary capillary blood volume. The lower Vc during exercise appeared to be associated with increased Vd/VCO2, suggesting pulmonary vascular impairment leading to ventilatory inefficiency and dyspnea in mild COPD. Moderate COPD patients showed further impairment with an inability to increase Vc during exercise. Despite their relatively minor airway obstruction, mild COPD patients appear to have adverse changes to their pulmonary vascular response that affects their ability to perfuse pulmonary capillaries and increase diffusion appropriately during exercise.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2018.10.015.

References


