The supine position improves but does not normalize the blunted pulmonary capillary blood volume response to exercise in mild COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by progressive partially reversible airway obstruction, exertional dyspnea, and exercise intolerance (7). Patients with mild COPD, defined spirometrically by a ratio of the forced expiratory volume in 1 s to forced vital capacity (FEV₁/FVC) below the lower limit of normal (LLN) and FEV₁ ≥80% predicted (7), demonstrate disproportionally high dyspnea and reduced exercise tolerance in relation to their minor airflow obstruction (5, 31). Previous studies have established that the potentiated exertional dyspnea in mild COPD is the result of increased work of breathing during exercise (9) that is second-order to: 1) an exaggerated ventilatory response to exercise [i.e., increased minute ventilation relative to carbon dioxide production (Ve/VCO₂)] and 2) airflow limitation (i.e., dynamic hyperinflation; see Refs. 5, 11, 24, 29, 30). While a large body of work has focused on improving airflow limitation in COPD, very little research has focused on better understanding the exaggerated ventilatory response to exercise in COPD. The increased Ve/VCO₂ during exercise in mild COPD can be explained in part by increased deadspace ventilation (i.e., ventilation with no perfusion; see Ref. 5). Although COPD is pathologically associated with obliteration of the alveolar-capillary interface (characteristic of emphysema; see Ref. 27), emerging work has demonstrated that patients with mild COPD also have reduced pulmonary blood flow in nonemphysematous lung regions, suggesting pulmonary microvascular dysfunction in addition to vascular destruction (18).

During exercise, the diffusing capacity of the lung must increase to meet the increased metabolic demand (36). The primary 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). With exercise, there is an increase in pulmonary diffusing capacity (DLCO), VC, and DM in healthy individuals (39); however, recent work has demonstrated that the DLCO and VC responses to exercise are blunted in mild COPD (41). It has been speculated that this reduced DLCO and VC response to exercise in mild COPD may be the result of early pulmonary vascular dysfunction and hypoperfusion of the pulmonary capillaries. This reduction in perfusion appears important, since a blunted VC response to exercise V̇E/V̇CO₂ during exercise in COPD can be explained in part by increased deadspace ventilation (i.e., ventilation with no perfusion; see Ref. 5). Although COPD is pathologically associated with obliteration of the alveolar-capillary interface (characteristic of emphysema; see Ref. 27), emerging work has demonstrated that patients with mild COPD also have reduced pulmonary blood flow in nonemphysematous lung regions, suggesting pulmonary microvascular dysfunction in addition to vascular destruction (18).

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exercise was associated with increased exercise $\dot{V}_{E}/\dot{V}_{CO2}$ and dyspnea in these patients (41).

The transition from the upright position to the supine position is a simple and effective maneuver to translocate blood centrally, increase pulmonary perfusion pressure (42), and improve DLCO (36). In young healthy individuals, the combination of supine positioning and exercise improves DLCO beyond what is observed with exercise alone up until near-maximal exercise (38). This response to supine positioning has been previously found to be attenuated but still present with healthy aging (4). By shifting blood centrally, and increasing perfusion pressure, it is possible that supine positioning may overcome microvascular dysfunction in an otherwise intact alveolar-capillary interface. Thus, the supine position may reverse the blunted DLCO and $V_C$ responses to exercise typically observed in mild COPD. Accordingly, the purpose of the present study was to determine whether the supine position improves diffusing capacity (DLCO) and pulmonary capillary blood volume ($V_C$) responses to exercise in mild COPD. We speculated that the reduction in DLCO and $V_C$ observed in mild COPD is primarily because of vascular dysfunction. In this regard, we hypothesized that the supine position would normalize the capillary blood volume and diffusing capacity responses to exercise in mild COPD.

**METHODS**

**Ethical approval.** This study was approved by the Human Research Ethics Board of the University of Alberta (protocol no. 00054658), and all participants provided written informed consent.

**Subjects.** Sixteen patients with mild COPD and 13 age-, sex-, and height-matched control subjects were recruited for this study. Mild COPD was defined by a postbronchodilator FEV1/FVC < LLN, an FEV1 of >80% predicted, and a smoking history of ≥10 pack-years (2, 7). Control participants all had less than a five pack-year smoking history and normal pulmonary function. Participants were excluded if they were on supplemental oxygen therapy, had a BMI greater than 32, were under the age of 40, were currently prescribed oral corticosteroids, or had cardiac rhythm abnormalities that would preclude exercise. All participants were asked to withhold from smoking 24 h before each testing day.

**Study design overview.** All participants completed three sessions over a 4-wk period. On day 1, participants completed a full pulmonary function test followed by a cardiopulmonary exercise test on a cycle ergometer (1, 39). At least 48 h later, subjects returned to the laboratory for exercise DLCO trials. Subjects completed multiple $F_{IO2}$-DLCO maneuvers in either the upright (day 2) or supine (day 3) position, with the order of days 2 and 3 randomized. Data were collected at baseline, 40 W, and 60 W during upright exercise and at baseline, 35 W, and 55 W during supine exercise. The target power output was based on pilot work, which demonstrated lower ergometer efficiency in the supine position, whereby a 5 W reduction in power output in the supine position was found to match the oxygen consumption for the corresponding upright position. During each of these trials, steady state was achieved at each intensity.Expired gases, operating lung volumes, and cardiac output (by noninvasive impedance cardiography) data were collected immediately before participants performed the DLCO maneuvers at each intensity.

**Preliminary screening.** Participants completed a full pulmonary function test, including pre- and postbronchodilator spirometry (400μg Salbutamol), determination of lung volumes by plethysmography, and resting DLCO (V62J Body Plethysmograph; SensorMedics, Yorba Linda, CA) in accordance with guidelines (8, 28, 43). Subjects then performed an incremental cardiopulmonary exercise test on a cycle ergometer (Ergoselect II 1200 Ergoline, Blitzz, Germany) as previously described (15, 41). All exercise tests were performed using a cardiorespiratory metabolic measurement system (Encore229 Vmax; SensorMedics, Yorba Linda, CA). Exercise tests consisted of a 5-min steady-state resting period followed by 2 min of unloaded pedaling and then a 20-W increase in work rate every 2 min to symptom limitation. Inspiratory capacity (IC) measurements were taken at baseline, every 2 min during the exercise test, and at symptom limitation (10).

**Exercise diffusing capacity, pulmonary capillary blood volume, and membrane diffusing capacity.** During visits 2 and 3, hemoglobin-corrected DLCO was determined using the multiple-$F_{IO2}$ single-breath hold technique (8) at baseline and during exercise (Encore229 Vmax; SensorMedics). Hemoglobin concentration ([Hb]) was measured during steady state at each intensity (HemoCue 201+; HemoCue AB, Angelholm, Sweden), and DLCO was adjusted using the following equation (26):

$$DLCO_{adj.\text{Hb}} = DLCO \times \left(10.22 + [\text{Hb}]\right)/1.7 \times [\text{Hb}]$$

To determine $V_C$ and $D_M$, multiple-$F_{IO2}$ DLCO breath holds were performed with three different $F_{IO2}$ values (0.21, 0.40, 0.60) during steady-state exercise, with a standardized washout period between trials (4 min at rest, 2 min during exercise; see Refs. 1, 39, 47). Each subject was given five breaths of gas at each respective $F_{IO2}$ for each DLCO test gas using a Douglas bag (1, 40, 41). The order of $F_{IO2}$ trials at each workload was randomized at every visit.

Breath holding during exercise can be challenging in patients with mild COPD; therefore, participants were first familiarized on how to perform a proper breath hold. Participants were instructed on appropriate timing in coordination with the tester and performed “practice” maneuvers until they were comfortable with the technique. Subjects were informed not to perform Valsalva or Müllerian maneuvers during breath holds, so as not to influence DLCO and $V_C$ measurements. As reported previously (46), DLCO was not adjusted for carbon monoxide (CO), which was measured in real time using noninvasive CO-oximetry (Radical 7; Masimo, Irvine, CA). Carboxyhemoglobin (CO-Hb) has been shown to not affect $V_C$ or $D_M$ when levels are below 6% (46).

With the use of a second cardiorespiratory metabolic system (Encore229 Vmax; SensorMedics, Yorba Linda, CA), steady-state expired gases and IC measurements were collected immediately before the multiple-$F_{IO2}$ DLCO measurements at each intensity. Steady state was achieved by exercising for a minimum of 3 min at each intensity and was confirmed by a change in heart rate of ≥3 beats/min in 1 min. Cardiac output was also estimated by noninvasive impedance cardiography (Physioflow; Manatec, Paris, France).

Consistent with previous work (41), mouth pressure was monitored throughout breath holds to confirm no Valsalva or Müller maneuvers and was always within ±20 mmHg. Acceptable breath-hold time during trials was 6.0 ± 0.3 s. Methane (0.3%) was used in each gas mixture to measure alveolar volume ($V_A$). Exhaled methane was monitored to ensure a horizontal tracing throughout the exhale for adequate gas equilibration. The breath hold was repeated if measured $V_A$ was ·5% of other breath holds at a given intensity.

$V_C$ and $D_M$ were calculated from the equation (34):

$$I/D_{LCO} = 1/D_M + 1/(\theta_{CO} \times V_C)$$

Consistent with our previous work in health and COPD, theta (θ) was calculated using the equation $\theta_{CO} = \alpha \times PAO2 + \beta$, with the values $\alpha = 0.0058$ and $\beta = 0.73$ based on moderate red cell permeability (1, 3, 40, 41). Alveolar $P_{O2}$ ($PAO2$) was calculated with the standard alveolar air equation $PAO2 = FIO2 \times (PAin - 47) - PAco2 \times [1 - FIO2/\text{RER}]/(\text{RER})$ (44), with measured barometric pressure ($PAin$) and respiratory exchange ratio (RER) at each workload. Arterial $P_{CO2}$ ($PAco2$) was estimated from end-tidal $CO2$ values (21) collected during steady-state exercise before the breath-hold maneuver. For each work-
load, the relationship between 1/DLCO and 1/θ for the three $Fl_O_2$ values were plotted, and a regression equation was then calculated to determine the values of 1/$V_a$ (i.e., the slope) and 1/DLCO (i.e., the y-intercept) of the resulting linear equation as described previously (34, 40). DLCO maneuvers were repeated if the $r^2$ for the three maneuvers plotted fell below 0.95 within a given workload.

Because of the effects of the supine position reducing alveolar volume (4) and thereby reducing absolute DLCO, $V_C$, and $D_M$, parameters are reported as unadjusted and adjusted for alveolar volume. The adjustment for $V_a$ was performed with the equation as per guideline recommendations (19, 25):

$$DLCO_{Adj} = 0.58 + 0.42V_A/V_{Alc}$$

where $V_{Alc}$ is the $V_A$ obtained at rest in the upright position. $V_C_{Adj}$ and $D_M_{Adj}$ were then calculated based on the DLCOAdj values obtained from the three $Fl_O_2$ DLCO maneuvers.

**Statistical analysis.** Pulmonary function data are reported as a percentage predicted of reference values (12). Spirometric data are also reported as Z-scores, based on the Global Lung Function Initiative 2012 equations (33). Values are expressed as means ± SE unless otherwise indicated. Unpaired Student’s t tests were used to compare subject characteristics between groups. A two-way repeated-measures ANOVA was used to evaluate the effect of disease state (mild COPD group vs. control group) on the diffusing capacity responses (dependent variables: DLCO, $V_C$, and $D_M$ and their adjusted values, DLCOAdj, $V_C_{Adj}$, and $D_M_{Adj}$) to exercise (3 workloads: baseline, 35 W/40 W, and 55 W/60 W) and to position (upright and supine). Ultimately, less than one-half of mild COPD subjects were able to complete the 55 W/60 W workload in both positions. Therefore, a two-way repeated-measures ANOVA was performed to assess the diffusing capacity responses (dependent variables: DLCO, $V_C$, and $D_M$ and their adjusted values, DLCOAdj, $V_C_{Adj}$, and $D_M_{Adj}$) to exercise (3 workloads: baseline, 35 W/40 W, and 55 W/60 W) and to position (upright and supine). Where a main effect was found, a Bonferroni post hoc test was performed to locate differences between groups, workloads, and body position. The effect of disease state and position at the 55 W/60 W workload was assessed separately by univariate two-way ANOVA in those participants who completed this higher workload. All statistical analysis was performed using SPSS Statistics version 24.0 (IBM, Armonk, NY). Figures 1–3 were generated using SigmaPlot Software version 13.0 (Systat Software, San Jose, CA). For all inferential analyses, the probability of a type I error was set at 0.05.

**RESULTS**

**Descriptive characteristics.** Demographic pulmonary function and baseline CPET data are presented in Table 1. As expected, the mild COPD group had a larger pack-year smoking history and a lower $FEV_1$, $FEV_1$-to-FVC ratio, resting DLCO, $V_A$, and DLCO adjusted for $V_A$ compared with controls. Five patients with mild COPD were current smokers. Patients with mild COPD had a lower $V_O_{2peak}$ compared with healthy controls.

**Physiological responses during upright and supine exercise.** The metabolic and pulmonary mechanical responses to exercise and subject completion rates are listed in Table 2. At rest and during exercise at 35/40 W, the supine position decreased $V_e/N_{CO_2}$ ($P = 0.044$) and increased $PET_{CO_2}$ ($P = 0.036$) compared with the upright position. The supine position also decreased $V_A$ ($P < 0.001$). There was no main effect observed between positions for IC ($P = 0.067$, $S_{PO_2}$ ($P = 0.955$), or $V_{CO_2}$ ($P = 0.558$). Importantly, there was also no main effect observed between positions for oxygen consumption ($P = 0.261$) or cardiac output ($P = 0.344$), indicating that the upright vs. supine workloads were appropriately matched for metabolic rate. Similarly, during exercise at 55/60 W oxygen consumption ($P = 0.915$) and cardiac output ($P = 0.453$) were unaffected by position.

**Positional diffusing capacity at rest and during exercise.** The supine position did not result in an increase in DLCO in either group (control upright = 17.8, control supine = 18.2, COPD upright = 12.1, COPD supine = 11.5 mL·min⁻¹·mmHg⁻¹; main effect $P = 0.918$, Fig. 1). Compared with rest, exercise at 35 W/40 W did increase DLCO in both groups (control upright = 21.8, control supine = 21.8, COPD upright = 14.6, COPD supine = 14.8 mL·min⁻¹·mmHg⁻¹; $P < 0.001$). There was no disease-by-position interaction ($P = 0.526$), workload-by-position interaction ($P = 0.773$), or disease-by-workload interaction ($P = 0.09$). Evaluating the 55 W/60 W data, there was no effect of supine position on DLCO ($P = 0.704$), with no disease-by-position interaction ($P = 0.907$). These results indicate that supine position did not increase DLCO in either group at rest or during exercise.

At baseline, DLCOAdj was lower in the mild COPD group compared with the control group ($P < 0.001$). The supine position did not increase DLCOAdj (control upright = 17.8, control supine = 18.8, COPD upright = 12.1, COPD supine = 11.8 mL·min⁻¹·mmHg⁻¹; main effect $P = 0.002$), whereas exercise at 35 W/40 W did increase DLCOAdj (control upright = 21.5, control supine = 22.4, COPD upright = 14.3, COPD supine = 14.9 mL·min⁻¹·mmHg⁻¹; $P < 0.001$). There

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### Table 1. Descriptive characteristics, pulmonary function, and baseline exercise testing

<table>
<thead>
<tr>
<th>n</th>
<th>Control</th>
<th>Mild COPD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
<td>16</td>
<td></td>
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<tr>
<td>Sex</td>
<td>Male/female</td>
<td>9/4</td>
<td>10/6</td>
</tr>
<tr>
<td>Age, yr</td>
<td>64 ± 6</td>
<td>66 ± 9</td>
<td>0.407</td>
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<tr>
<td>Height, m</td>
<td>1.72 ± 0.09</td>
<td>1.69 ± 0.11</td>
<td>0.376</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>83.8 ± 14.5</td>
<td>73.4 ± 13.5</td>
<td>0.057</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2 ± 3.9</td>
<td>25.6 ± 3.3</td>
<td>0.058</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>4 ± 7</td>
<td>29 ± 11</td>
<td>&lt;0.001*</td>
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<tr>
<td>$FEV_1$, liters</td>
<td>3.35 ± 0.82</td>
<td>2.34 ± 0.54</td>
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<tr>
<td>$FEV_1$, %</td>
<td>110 ± 15</td>
<td>85 ± 9</td>
<td>&lt;0.001*</td>
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<tr>
<td>$FEV_1$, Z-score</td>
<td>0.55 ± 0.92</td>
<td>-1.14 ± 0.61</td>
<td>0.001*</td>
</tr>
<tr>
<td>$FVC$, liters</td>
<td>4.55 ± 1.18</td>
<td>3.87 ± 0.80</td>
<td>0.075</td>
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<tr>
<td>$FVC$, %</td>
<td>109 ± 16</td>
<td>104 ± 11</td>
<td>0.340</td>
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<tr>
<td>$FVC$, Z-score</td>
<td>0.88 ± 1.00</td>
<td>0.36 ± 0.59</td>
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<tr>
<td>$FEV_1$/FVC, %</td>
<td>74 ± 5</td>
<td>61 ± 6</td>
<td>&lt;0.001*</td>
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<tr>
<td>$FEV_1$/FVC, Z-score</td>
<td>-0.51 ± 0.68</td>
<td>-2.07 ± 0.69</td>
<td>&lt;0.001*</td>
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<tr>
<td>TLC, liters</td>
<td>7.07 ± 1.59</td>
<td>6.35 ± 1.24</td>
<td>0.182</td>
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<tr>
<td>TLC, %</td>
<td>107 ± 14</td>
<td>106 ± 18</td>
<td>0.912</td>
</tr>
<tr>
<td>RV, liters</td>
<td>2.39 ± 0.66</td>
<td>2.41 ± 0.83</td>
<td>0.926</td>
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<tr>
<td>RV, %</td>
<td>106 ± 27</td>
<td>114 ± 39</td>
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<tr>
<td>$V_A$, liters</td>
<td>0.79 ± 0.37</td>
<td>0.81 ± 0.19</td>
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<td>$V_A$, %</td>
<td>0.45 ± 5</td>
<td>15 ± 4</td>
<td>0.119</td>
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<td>DLCO, mL·min⁻¹·mmHg⁻¹</td>
<td>28.4 ± 7.3</td>
<td>18.6 ± 6.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>DLCO adjusted for $V_A$</td>
<td>28.9 ± 6.9</td>
<td>20.0 ± 5.8</td>
<td>0.001*</td>
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<tr>
<td>$V_O_{2peak}$, L/min</td>
<td>2.6 ± 0.7</td>
<td>1.6 ± 0.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>$V_O_{2peak}$, L·kg⁻¹·min⁻¹</td>
<td>3.30 ± 0.95</td>
<td>22.6 ± 5.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>$S_{PO_2}$, rest, %</td>
<td>96.7 ± 3.3</td>
<td>95.8 ± 3.0</td>
<td>0.480</td>
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<tr>
<td>$S_{PO_2}$, peak, %</td>
<td>94.1 ± 3.7</td>
<td>92.6 ± 3.4</td>
<td>0.25</td>
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</table>

Values expressed as means ± SD. COPD, chronic obstructive pulmonary disease; $V_O_{2peak}$, peak $O_2$ consumption; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; $V_A$, tidal volume; $Fb$, breathing frequency; DLCO, diffusing capacity; $V_A$, alveolar volume; $S_{PO_2}$, oxygen pulse saturation. *Significantly different from control group.
was no disease-by-position interaction (P = 0.203) nor work-
load-by-position interaction (P = 0.231). However, a disease-
by-workload interaction was observed (P = 0.028), indicating
that DLCOAdj increased with exercise more in controls than in
mild COPD. Evaluating the 55 W/60 W data, there was no
disease-by-position interaction (P = 0.170) nor work-
load-by-disease interaction (P = 0.921), with no
disease-by-position interaction (P = 0.930). These results
indicate that supine position did not increase DLCOAdj in

Fig. 1. Pulmonary diffusing capacity (DLCO, left) and adjusted DLCO (DLCOAdj, right) responses to upright and supine exercise. Values are reported as means ± SE.
*Main effect of disease state; †main effect of workload; #†workload-by-disease interaction. Alpha was set as P < 0.05 for all outcomes. Completion rates at 55 and
60 W are as follows: control upright = 13, control supine = 12; chronic obstructive pulmonary disease (COPD) upright = 10, COPD supine = 7. Findings demonstrated reduced DLCO and DLCOAdj in mild COPD. Both groups increased DLCO and DLCOAdj with exercise, with the controls demonstrating a greater increase in DLCOAdj with exercise. The supine position did not affect DLCO or DLCOAdj.
either group at rest or during exercise and that the DLCOAdj response to upright and supine exercise is blunted in mild COPD.

**Positional pulmonary capillary blood volume at rest and during exercise.** At baseline, $V_c$ was lower in the mild COPD group compared with the control group ($P < 0.001$). The supine position did not result in an increase in $V_c$ that reached statistical significance (control upright = 63, control supine = 64, COPD upright = 37, COPD supine = 40 mL; main effect $P = 0.073$, Fig. 2). Compared with rest, exercise at 35 W/40 W did increase $V_c$ in both groups (control upright = 62, control supine = 73, COPD upright = 40, COPD supine = 45 mL; $P = 0.024$). There was no disease-by-position interaction ($P = 0.016$), with no work-load-by-position interaction ($P = 0.527$) nor workload-by-position interaction ($P = 0.027$). Evaluating the 55 W/60 W data, the supine position did not affect $V_c$ ($P = 0.378$), with no disease-by-position interaction ($P = 0.755$). These results indicate that supine position did not increase $V_c$ in either group at rest or during exercise.

At baseline, $V_c$ was lower in the mild COPD group compared with the control group ($P < 0.001$). The supine position resulted in an increase in $V_c$ in both groups (control upright = 61, control supine = 65, COPD upright = 37, COPD supine = 42 mL; main effect $P = 0.044$). Exercise at 35 W/40 W increased $V_c$ in both groups (control upright = 61, control supine = 74, COPD upright = 39, COPD supine = 46 mL; $P = 0.016$), with no disease-by-position interaction ($P = 0.527$) nor workload-by-position interaction ($P = 0.027$). Evaluating the 55 W/60 W data, the supine position did not affect $V_c$ ($P = 0.109$), with no disease-by-position interaction ($P = 0.567$). These results indicate that supine position increased $V_c$ Adj similarly in both groups at rest and during exercise.

**Positional membrane diffusing capacity at rest and during exercise.** At baseline, $D_M$ was lower in the mild COPD group compared with the control group ($P < 0.001$). The supine position actually resulted in a decrease in $D_M$ (control upright = 30.3, control supine = 30.7, COPD upright = 23.6, COPD supine = 19.3 mL·min$^{-1}$·mmHg$^{-1}$; main effect $P = 0.015$; Fig. 3). Compared with rest, exercise at 35 W/40 W increased $D_M$ in both groups (control upright = 42.6, control supine = 37.7, COPD upright = 30.8, COPD supine = 26.5 mL·min$^{-1}$·mmHg$^{-1}$; $P < 0.001$). There was no disease-by-position interaction ($P = 0.416$) nor work-load-by-position interaction ($P = 0.240$). Evaluating the 55 W/60 W data, there was no effect of the supine position on $D_M$ ($P = 0.241$), with no disease-by-position interaction ($P = 0.817$). These results indicate that supine position actually decreased $D_M$ similarly in both groups at rest and during exercise.

At baseline, $D_M$ was lower in the mild COPD group compared with the control group ($P < 0.001$). The supine position resulted in a decrease in $D_M$ (control upright = 31.0, control supine = 31.1, COPD upright = 23.3, COPD supine = 19.2 mL·min$^{-1}$·mmHg$^{-1}$; main effect; $P = 0.027$), whereas exercise at 35 W/40 W did increase $D_M$ in both groups (control upright = 41.6, control supine = 38.4, COPD upright = 29.6, COPD supine = 26.8 mL·min$^{-1}$·mmHg$^{-1}$; $P < 0.001$). There was no disease-by-position interaction ($P = 0.395$) nor workload-by-position interaction ($P = 0.583$). Evaluating the 55 W/60 W data, the supine position did not affect $D_M$ ($P = 0.339$), with no disease-by-position interaction ($P = 0.884$). These results indicate that supine position decreased $D_M$ similarly in both groups at rest and during exercise.

**DISCUSSION**

The objective of this study was to examine whether the supine position would normalize the blunted exercise diffusing capacity and pulmonary capillary blood volume responses in mild COPD. Contrary to the original hypothesis, the supine position did not improve diffusing capacity at rest or during exercise in either group. However, the supine position did increase pulmonary capillary blood volume (adjusted for alveolar volume) by a similar magnitude in both mild COPD and control groups, whereas membrane diffusing capacity was actually reduced in both groups. The increase in $V_c$ while supine indicates that patients with mild COPD still retain pulmonary capillary recruitment capacity; however, $V_c$ did not normalize in these patients while supine, suggesting that the
reduction in exercise DLCO and $V_C$ in mild COPD is not fully explained by pulmonary vascular dysfunction.

**Diffusing capacity, capillary blood volume, and the pulmonary microvasculature.** The supine position results in a translocation of blood centrally, while also lowering the vertical distance (hydrostatic column) of the lung. Previous work in healthy participants has demonstrated that the shift from upright to supine position increased resting pulmonary arterial pressure (PAP) and pulmonary arterial wedge pressure by ~3.5 and 4.2 mmHg, respectfully (37), which would increase the amount of zone III conditions within the lung. Consistent with greater capillary recruitment and distention, pulmonary vascular resistance (PVR) is reduced by roughly 25% in health when supine (37). Although the supine position increases recruitment and distention, there is evidence that, with increasing exercise intensity in the supine position, pulmonary capillary recruitment is further augmented (13, 23). Consistent with this previous work, our data demonstrate that $V_C$ and DLCO increased with incremental supine exercise in both healthy controls and mild COPD. Furthermore, the increase in $V_C$ and DLCO in mild COPD was generally proportional to that observed in healthy controls, and unaffected by position.

From the perspective of the pulmonary microvasculature, alveolar-capillary destruction would manifest as a blunted pulmonary capillary blood volume response during upright exercise that would remain blunted during supine exercise despite the increase in perfusion pressure with the supine position. A dysfunctional pulmonary microvasculature, by contrast, may demonstrate a reduced DLCO and $V_C$ response to upright exercise (41), but the increased perfusion pressure with the supine position would facilitate recruitment and distention of an otherwise intact alveolar-capillary system. Therefore, DLCO and $V_C$ would be expected to normalize by lying supine in the setting of pulmonary vascular dysfunction alone. The comparable increase in $V_C$ and DLCO with exercise in both mild COPD and controls in the present study would suggest that the capillary recruitment and distention responses to exercise may be appropriate in mild COPD. However, the observation that the supine position does not normalize DLCO and $V_C$, neither at rest nor during exercise, suggests a component of vascular destruction in mild COPD that cannot be overcome with increased perfusion pressure.

The reduced diffusing capacity at rest and during exercise in patients with mild COPD may have important implications. Recent work has shown that, after accounting for differences in airflow limitation, patients with COPD with a reduced resting DLCO had greater dyspnea, higher $V_E/V_{CO_2}$, and lower peak $V_O_2$ compared with those COPD patients with a preserved resting DLCO (6). This is consistent with our previous work demonstrating that the blunted $V_C$ response to exercise in mild COPD is associated with an elevated exercise $V_E/V_{CO_2}$ (41), and further supported by the reduction in $V_E/V_{CO_2}$ with supine exercise observed in the present study. Additional work has shown that the elevated nadir $V_E/V_{CO_2}$ was associated with a reduced resting DLCO in mild COPD, which in turn was associated with emphysema severity quantified by computed tomography (CT) and a blunted cardiac output response to exercise (20). These results suggest that dysfunction within the pulmonary microcirculation may be an important determinant of ventilatory inefficiency and exercise intolerance.

**Pulmonary arterial pressures in mild COPD.** A reduced resting DLCO is associated with a higher resting PAP in moderate and severe COPD (16). Although pulmonary vascular pressure data have previously been collected during exercise in COPD (14, 32, 45), the amount of data available in mild COPD are extremely limited, requiring extrapolation from more advanced COPD. Patients with moderate COPD have lower resting PVR compared with severe and very severe COPD, and, of these subgroups, only those with moderate COPD show a reduction in PVR with exercise (32). It has been suggested that the $\Delta PAP/\Delta CO$ ratio derived from the hemodynamic response to exercise may better delineate both the presence and severity of an underlying pulmonary vasculopathy (35), with an abnormal increase of mean PAP during exercise defined as a $\Delta PAP/\Delta CO$ response of $>3$ (32).

With respect to vascular dysfunction and damage in COPD, Wright et al. (45) examined the hemodynamic exercise response in patients with mild and moderate COPD with minimal...
vs. moderate emphysema. Despite similar FEV$_1$-to-FVC ratios, those with moderate emphysema had a lower DLCO, and the $\Delta$PAP/ACO response to exercise (calculated from the reported table) in the moderate emphysema group was much greater than in the minimal emphysema group (~6.0 vs. ~3.8 mmHg·L$^{-1}$·min$^{-1}$, respectively). Moreover, the minimal emphysema group demonstrated a reduction in PVR with exercise, whereas the moderate emphysema group showed an increase in PVR with exercise. Thus, despite the lack of available data in mild COPD, emphysematous destruction of pulmonary capillaries at any stage of disease can manifest with an abnormal DLCO and in alterations in PAP and PVR. Although the current study did not obtain pulmonary hemodynamic data, emerging work supports the notion that the pulmonary microcirculation is an important contributor to pulmonary gas exchange abnormalities and exercise intolerance in mild COPD.

The influence of aging on the observed responses to supine exercise. DLCO was not increased by lying supine in either group. Previously, a 26% increase in DLCO from upright to supine positions was observed at rest in young healthy participants (mean age = 25 yr; see Ref. 38), whereas a mean increase of 12% was observed in a group containing older individuals (mean age = 41 yr; see Ref. 17). In the present study, the increase in unadjusted DLCO with lying supine in the control and mild COPD groups was only 2.8 and 2.2%, respectively. Importantly, the magnitude of increase with supine positioning on DLCO and on the DLCO response to exercise appear to be blunted with age (17). Chang et al. (4) found that, while participants $<$40 yr of age had a mean improvement in DLCO of ~15% from upright to supine, the change in the group $>$40 yr of age was also improved although attenuated. Consistent with the resting DLCO response, elderly individuals also show an altered PVR response to exercise; the reduction in PVR with exercise is blunted in individuals $>$50 yr of age compared with those $<$50 yr of age (22). Furthermore, the exercise $\Delta$PAP-to-$\Delta$CO ratio appears to be greater in subjects aged 50–70 yr (2.85 mmHg·L$^{-1}$·min$^{-1}$) compared with individuals aged $<$50 yr (1.06 mmHg·L$^{-1}$·min$^{-1}$) (22). The mean age of our control and mild COPD groups was 64 and 66 yr, respectively, which provides an explanation for the minimal DLCO response to supine positioning in the present study. Combined, these results suggest that aging alone appears to impair exercise DLCO recruitment and/or contribute to pulmonary vascular dysfunction.

The reduction in membrane diffusing capacity with supine positioning observed in the present study was demonstrated in both mild COPD and age-matched controls. It has been hypothesized that age-related arteriosclerotic changes in the pulmonary capillaries could increase the rigidity of these vessels and therefore attenuate the membrane diffusing response to exercise (4). Additionally, supine positioning reduces alveolar volume, which appears to reduce membrane diffusing capacity disproportionately more so than pulmonary capillary blood volume likely because of the effect of the reduction in the surface area available for gas exchange (19). In addition to age-related phenomena, the concomitant increased Vc and reduced $D_M$ response to supine positioning likely explains the lack of change in DLCO with the supine position.

Limitations. This study has several limitations that are worth noting. First, it is possible that the mild COPD group in the present study had at least some degree of emphysema; however, this was not quantified by CT imaging. Quantification of emphysema severity may be important to better understand the vascular recruitment potential in patients with mild COPD. For example, it may allow for delineation of the contribution of vascular dysfunction vs. destruction to ventilatory inefficiency, dyspnea, and exercise intolerance in mild COPD. Second, we did not systematically screen for comorbid resting or exercise-induced pulmonary hypertension in study participants. Previous work has documented a prevalence of precapillary pulmonary hypertension in moderate COPD of only 5–7% (14, 32). Because we included only patients with mild COPD, we would expect the prevalence of pulmonary hypertension to be <5% within our sample. Pulmonary hemodynamic data were not obtained in the present study because of difficulties in obtaining noninvasive pulmonary artery systolic pressure during exercise in COPD. Of note, $V_{\text{E}}/V_{\text{CO}_2}$ decreased during supine exercise, which would suggest a reduction in zone I conditions within the lung and an increase in zone III conditions, consistent with an increase in perfusion pressure. Third, the supine position is well known to reduce lung volumes, relative to the upright position, because of the displacement of abdominal contents toward the diaphragm. Inherent to the design of this study was the acknowledgment that $V_A$ would be reduced when supine and therefore DLCO, and correspondingly $V_C$ and $D_M$, would need to be adjusted for $V_A$ to allow for appropriate comparisons between supine and upright positions. Although DLCO measurement at defined lung volumes during supine exercise has been described previously in young healthy participants (38), this was not feasible in older patients with mild COPD. We therefore relied instead on adjusting DLCO values (and corresponding $V_C$ and $D_M$ values) by measured lung volumes as published previously (19) and as recommended in guidelines (25). Last, in using the multiple $\text{FiO}_2$ technique, five breaths may not have resulted in complete equilibration with each inhaled test gas mixture; however, any degree of under-equilibration would be consistent across positions and would therefore be unlikely to influence the key findings.

Conclusion. In summary, the supine position increased $V_C$ in mild COPD and healthy controls by a similar magnitude, and the supine position did not normalize resting or exercise DLCO and $V_C$ in patients with mild COPD. Collectively, these findings suggest that, although mild COPD patients retain pulmonary capillary recruitment capacity, the persisting reduction in exercise DLCO and $V_C$ in the supine position suggests that pulmonary vascular destruction is a contributing factor to the blunted DLCO and $V_C$ response to exercise.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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**PULMONARY VASCULAR RESPONSES TO SUPINE EXERCISE IN MILD COPD**


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