Elevated O$_2$ Cost of Ventilation Contributes to Tissue Wasting in COPD*

Edward T. Mannix, PhD; Felice Manfredi, MD; and Mark O. Farber, MD

**Background and objectives:** Thirty to 50% of all COPD patients experience tissue wasting that may be caused by hypermetabolism, but the cause of the perturbed metabolic state is unclear. We hypothesized that the elevated O$_2$ cost of ventilation (O$_2$ COV) may be a contributing factor. All of the data are presented as means ($\pm$ SEM). Ten hypoxemic (a Pa$_O_2$ of 54 $\pm$ 3 mm Hg) stable COPD patients (an FEV$_1$/FVC ratio of 42 $\pm$ 4%) and five healthy control subjects were studied. The patients were divided into two groups based on nutritional status. Group 1 (n = 6) was malnourished (a body mass index [BMI] of 17.6 $\pm$ 0.7 kg/m$^2$), and group 2 (n = 4) was normally nourished (a BMI of 26.0 $\pm$ 3 kg/m$^2$). The O$_2$ COV was determined by measuring the change in the oxygen consumption (V˙$O_2$) and the minute ventilation (V˙$E$) caused by CO$_2$-induced hyperventilation.

**Results and conclusions:** Group 1 had an elevated O$_2$ COV when compared to group 2 and the control group, respectively: 16.4 $\pm$ 1.0 vs 9.7 $\pm$ 1.0 and 2.4 $\pm$ 0.2 mL O$_2$/L of V˙$E$ (p < 0.05). The V˙$O_2$ at rest was higher for group 1 than for group 2 and the control group, respectively: 4.5 $\pm$ 0.3 vs 3.1 $\pm$ 0.5 and 3.4 $\pm$ 0.2 mL/kg/min (p < 0.05). The resting energy expenditure (REE) % predicted for group 1 was also higher than group 2 and the control group, respectively: 125 $\pm$ 3% vs 87 $\pm$ 7% and 97 $\pm$ 2% (p < 0.05). Significant correlations were observed that implicate the increased O$_2$ COV as a cause of tissue wasting: O$_2$ COV vs BMI (r = 0.79; p = 0.007), O$_2$ COV vs REE % predicted (r = 0.66; p = 0.039), and REE % predicted vs BMI (r = -0.83; p = 0.003). The O$_2$ COV was also correlated with lung function: FEV$_1$/FVC vs O$_2$ COV (r = -0.84; p = 0.002). We conclude that in these COPD patients the O$_2$ COV is associated with an increased metabolic rate which, in turn adversely affects the nutritional status. (CHEST 1999; 115:708–713)

**Key words:** emphysema; hypermetabolism; malnutrition

**Abbreviations:** BMI = body mass index; O$_2$ COV = oxygen cost of ventilation; REE = resting energy expenditure; V˙$E$ = minute ventilation; V˙$O_2$ = oxygen consumption

Malnutrition is common among hypoxemic COPD patients, 30 to 50% of whom weigh < 90% of their ideal body weight.$^{1–3}$ Although increased mortality and morbidity have been associated with weight loss in this patient population,$^{1–6}$ the pathophysiology of malnutrition remains unclear.$^7$ Among the likely mechanisms is hypermetabolism (an increased total caloric expenditure) arising from several perturbations, one of which appears to be an increase in the O$_2$ cost of ventilation (O$_2$ COV).$^{1,5}$ When contrasted with normally nourished COPD patients, malnourished COPD patients display an increased O$_2$ COV$^{1,8}$ that is driven by higher airway resistance.$^{9,10}$ Therefore, significant relationships between the variables defining lung function, metabolic rate, and nutritional status should be demonstrable.

We hypothesized that an elevated O$_2$ COV is a contributing factor subtending the hypermetabolic state often seen in COPD, and that this perturbed metabolic state adversely affects nutritional status and contributes to tissue wasting.

**Materials and Methods**

**Patients**

All of the data are presented as means ($\pm$ SEM). Ten male patients with an age of 59.5 $\pm$ 1.5 years old, a body mass index (BMI) of 20.9 $\pm$ 1.6 kg/m$^2$, and stable COPD (an FEV$_1$/FVC ratio of 42.3 $\pm$ 4.1%) as determined by clinical observation, pulmonary function tests, and arterial blood gas data were recruited from the Pulmonary Medicine Clinic of the Veterans
Affairs Medical Center in Indianapolis, IN. The study protocol was approved by the institutional review board of Indiana University and was carried out according to the provisions set forth by the Declaration of Helsinki. Inclusion criteria required a clinical diagnosis of COPD, including an FEV1/FVC ratio of <60%, and the absence of the symptoms and signs of cor pulmonale, congestive heart failure, hyperthyroidism, diabetes, GI disease, neoplasm, and renal or hepatic dysfunction.

The patients were divided into two groups based on nutritional status as determined by the BMI. A normal BMI for adult men ranges from 19.0 to 27.0 kg/m², and grade I protein energy malnutrition for adult men ranges from 17.0 to 18.4 kg/m². All six group 1 patients (aged 57.5 ± 1.7 years old) met the criteria for protein energy malnutrition (a BMI of 17.6 ± 0.7 kg/m²). The four group 2 patients (age of 62.5 ± 1.9 years old) exhibited no evidence of protein energy malnutrition (a BMI of 26.0 ± 3 kg/m²). The pertinent patient data appear in Table 1.

In order to establish the reference values for our laboratory, the O₂ COV was measured in five healthy adult men with mean (±SEM) age of 42.0 ± 5.6 years old who were breathing room air.

Protocols

The data contained herein were collected as part of a previously published manuscript; the present report represents a completely new and novel analysis of these data. The data collection occurred with each patient breathing room air. Briefly stated, the patients reported to the laboratory at 8 AM in the fasted state, and were prepared for the determination of the resting energy expenditure (REE) and the resting O₂ COV. After being weighed, each patient was seated and fitted with electrodes for ECG monitoring of heart rate in V6 by a cardioscope (model 901-MK2; P.K. Morgan) concentrations. Before each test, the analyzers were calibrated using a tank of standard compressed dry gas with a known concentration of 16% O₂, 4% CO₂, and balance N₂. The output signals from all of the analyzers on-line microcomputer (Micro IT; Mitsubishi; Tokyo, Japan) for the involuntary hyperventilation required for the O₂ COV determination. The patients breathed the mixture for a minimum of 7 min, so that a plateau value for the O₂ COV and the V˙e for at least 3 min was evident during the fifth through the seventh min of the maneuver. The O₂ COV (mL O₂/L of V˙e) was calculated as follows:

\[ \text{O}_2 \text{ COV mL O}_2/L \text{ V}_e = \Delta \text{Vol}_2 \text{ mL/min } \times \Delta \text{Ve} \text{ L/min} \]

where \( \Delta \) refers to the difference between the baseline and the hyperventilatory VO₂, and between the baseline and the hyperventilatory Ve. Further details of the method employed in measuring the O₂ COV can be found elsewhere.

Statistics

The data were examined for the normalcy of distribution, and transformations were made where appropriate. Unpaired t tests were utilized to detect the differences among the patient groups. When the intergroup comparisons included the healthy control subjects, t tests with Bonferroni adjustments were performed. The Pearson product moment correlation was used to examine the relationships among the pertinent variables. Significance was noted at the p < 0.05 level for all tests.

Results

A comparison of the two groups of COPD patients using demographic, spirometric, and blood gas data is presented in Table 1. The heights were equivalent in the two patient groups. A greater degree of airflow obstruction was observed in the malnourished group, as indicated by a lower FEV₁ (p = 0.05) and a lower FEV₁/FVC ratio (p = 0.03). The FVC values (p = 0.10) and the PaCO₂ values (p = 0.49) of the patient groups were statistically equivalent, but the magnitude of the differences indicates that physiologic inequities were present, as the malnourished patients had a lower FVC and a higher PaCO₂ than the normally nourished patients. The hypercapnic state of the malnourished COPD group resulted in a significantly lower arterial pH for that group (p = 0.01).

The data describing the O₂ uptake and ventilatory

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**Table 1—Demographic, Spirometric, and Blood Gas Data**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 10)</th>
<th>Group 1 (n = 6)</th>
<th>Group 2 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, m</td>
<td>1.78 ± 0.02</td>
<td>1.76 ± 0.03</td>
<td>1.82 ± 0.01</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.6 ± 5.5</td>
<td>50.0 ± 1.5</td>
<td>86.5 ± 2.7</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.95 ± 0.25</td>
<td>0.58 ± 0.11</td>
<td>1.53 ± 0.49</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.27 ± 0.35</td>
<td>1.81 ± 0.11</td>
<td>2.95 ± 0.76</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>42 ± 4</td>
<td>32 ± 4</td>
<td>49 ± 5</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>54 ± 3</td>
<td>55 ± 4</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>47 ± 3</td>
<td>49 ± 5</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>7.45 ± 0.021</td>
</tr>
</tbody>
</table>

*Data are presented as means ± SEM.

†p < 0.05 between patient groups.
parameters of the two patient groups and the control group are presented in Table 2. The resting $V_\text{o}_2$, expressed in mL/kg/min to standardize these values relative to body mass, was elevated in the malnourished patients ($p = 0.03$) when compared to the group 2 patients and the control group. The REE, expressed as kilocalories expended in 24 h, was not different across the groups because the malnourished patients had a significantly reduced body mass. The REE, however, was significantly elevated in the malnourished patients when expressed as REE/24 h/kg body mass ($p = 0.001$), and as a percent of predicted based on body mass ($p < 0.001$). The $V_e$ was statistically equivalent across the patient groups, but the group 2 patients were hyperventilatory when compared to the healthy control subjects ($p = 0.01$). The $O_2$ COV of each COPD group was increased above that of healthy control subjects, and it was higher in the malnourished patients than in the normally nourished patients. An additional result worthy of note was that the increase in the $V_e$ from baseline, which occurred during the measurement of the $O_2$ COV, was $7.1 \pm 1.9$ L/min for the malnourished patients and $14.9 \pm 5.2$ L/min for the normally nourished patients.

The correlation between the degree of airflow obstruction and the increased $O_2$ COV in the 10 patients studied is shown in Figure 1. The patients with the greatest obstruction to airflow (the lowest $FEV_1/FVC$ ratio) had the highest $O_2$ COV. There was also a significant correlation between the $FEV_1$ and the $O_2$ COV ($r = -0.79; p = 0.007$).

Additional results from correlational analyses are shown in Figure 2. A significant positive relationship is noted between the $O_2$ COV and the REE % predicted. The patients with the highest $O_2$ COV had the highest REE and, thus, the highest metabolic rate. The right panel of this figure represents the significant, inverse relationship between the resting metabolic rate (the REE % predicted) and the BMI. The patients with the highest resting metabolic rate had the lowest BMI.

### Table 2—Metabolic and $O_2$ COV Data*

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 6)</th>
<th>Group 2 (n = 4)</th>
<th>Control Subjects (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_\text{o}_2$, mL/kg/min</td>
<td>4.5 ± 0.3†</td>
<td>3.1 ± 0.5</td>
<td>3.4 ± 0.2</td>
</tr>
<tr>
<td>REE, kcal/24 h</td>
<td>1692 ± 48</td>
<td>1817 ± 176</td>
<td>1704 ± 54</td>
</tr>
<tr>
<td>REE, kcal/kg</td>
<td>31 ± 11</td>
<td>21 ± 2</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>REE, % predicted</td>
<td>125 ± 31</td>
<td>87 ± 7</td>
<td>97 ± 2</td>
</tr>
<tr>
<td>$V_e$, L/min</td>
<td>10.8 ± 0.9</td>
<td>13.6 ± 1.7</td>
<td>8.3 ± 0.6</td>
</tr>
<tr>
<td>$O_2$ COV, mL $O_2/L, V_e$</td>
<td>16.4 ± 1.0</td>
<td>9.7 ± 1.0</td>
<td>2.4 ± 0.2</td>
</tr>
</tbody>
</table>

*Data presented as mean ± SEM.  †p < 0.05 vs group 2 and control subjects.  ‡p < 0.05 vs control subjects.

Additional evidence is presented in Figure 3 supporting the contention that in the patients studied an elevated $O_2$ COV, with its attendant elevated resting metabolic rate, is inversely related to the BMI.

### Discussion

The progressive decline in body mass that often occurs in advanced COPD has dire consequences: decreased respiratory muscle strength and endurance; decreased diaphragmatic size; worsening lung function; predisposition for death by heart failure; and, ultimately, decreased survival rate. A clear understanding of the mechanisms responsible for tissue wasting in COPD is crucial so that strategies can be developed to combat this serious problem.

Donahoe and Rogers state that a unifying hypothesis addressing the mechanism of weight loss in COPD has not been established. Many believe that weight loss in COPD is due to a state of hypermetabolism that creates a negative energy balance and, eventually, weight loss. Hypermetabolism in these patients has been shown to be the result of several factors, including: (1) elevated work of breathing;
(2) increased levels of proinflammatory cytokines\(^2\); (3) medications, including \(\beta\)-agonist and theophylline compounds that could stimulate metabolism\(^2\); and (4) ventilatory muscle inefficiency, resulting in a greater energy demand per amount of work performed.\(^1\) A second hypothesis for weight loss in COPD is an inadequate caloric intake that prevents the patient with hypermetabolism from meeting his energy requirements.\(^2\) A third hypothesis for weight loss in COPD states that tissue oxygenation may be abnormal in COPD,\(^19\) even in those with relatively normal arterial \(\text{O}_2\) content.\(^2\) This abnormality, along with a deficiency of high-energy phosphate molecules within the peripheral and respiratory muscles of COPD patients,\(^2\) may interfere with the adequate delivery of nutrients, resulting in weight loss. Donahoe and Rogers\(^19\) have offered their own hypothesis: a “step-decline” process wherein an initial event, \textit{ie}, a COPD exacerbation, results in hypermetabolism and/or a reduced caloric intake. The subsequent weight loss is accompanied by an incomplete metabolic adaptation, so that the caloric intake may only be sufficient to maintain a new stable, but lower, weight. This process continues as additional COPD exacerbations present themselves, ultimately resulting in a body weight low enough to be classified as protein energy malnutrition.

The results of the present investigation demonstrate the relative hypermetabolism of malnourished COPD patients. The associated strong negative correlations between the REE and the BMI, and between the \(\text{O}_2\) COV and the BMI suggest that the high \(\text{O}_2\) COV of the malnourished COPD patients may be the driving force responsible for the observed increase in metabolic rate. This notion is given added credence when one examines the relationship between the \(\text{O}_2\) COV and the REE in the

\[ r = -0.79 \quad p = 0.007 \]
patient groups. The ratio of the O$_2$ COV of the malnourished patients over the O$_2$ COV of the normally nourished patients equals 1.6. One might expect that if the increase in the O$_2$ COV in the malnourished group is largely responsible for the increase in the REE in that group, then the ratio of the REE between the two groups should be comparable to the O$_2$ COV ratio. Indeed, the ratio of the REE % predicted of the malnourished group over the REE % predicted of the normally nourished group is 1.4, and the ratio of the REE/24 h/kg body mass of the malnourished group vs the REE/24 h/kg body mass of the normally nourished group is 1.5 (see Table 2). These calculations suggest that, at the least, the observed increase in the REE in the malnourished group may indeed be responsible for the increases in their normalized REE indexes.

The data presented confirm the findings of others. Astin and Penman$^9$ reported significant airway obstruction in hypoxemic COPD patients. Donahoe et al$^1$ measured an elevated O$_2$ COV in COPD patients and found that malnourished patients had a higher O$_2$ COV than normally nourished COPD patients and healthy control subjects. They were also able to demonstrate that malnourished COPD patients had an REE that was significantly greater than predicted ($119 \pm 12\%$ of predicted), i.e., the malnourished patients were hypermetabolic. The REE % predicted of our malnourished patients is slightly higher (125% of predicted) than the values reported by Donahoe et al.$^1$ The O$_2$ COV data from our healthy control subjects are comparable to those reported by others. Evison and Cherniack$^{14}$ reported an average O$_2$ COV of 1.9 $\pm$ 0.8 mL O$_2$/L V$_E$, and Donahoe et al$^1$ reported a value of $1.2 \pm 0.2$ mL O$_2$/L V$_E$ for healthy control subjects. The O$_2$ COV of the COPD patients in the present study is similar to that published by Evison and Cherniack,$^{14}$ who published a range of 3.0 to 19.5 mL O$_2$/L of V$_E$, with a mean value of 6.3 $\pm 1.0$ mL O$_2$/L of V$_E$. In that study, a relationship was observed between the disease severity and the level of O$_2$ COV; patients with severe COPD had a higher O$_2$ COV than patients with mild disease. The O$_2$ COV reported in the present investigation for normally nourished patients (9.7 $\pm 1.0$ mL O$_2$/L of V$_E$) and for malnourished COPD patients (16.4 $\pm 1.0$ mL O$_2$/L of V$_E$) is significantly higher than that published by Donahoe et al$^1$ for normally nourished patients (2.6 $\pm 1.1$ mL O$_2$/L of V$_E$) and malnourished COPD patients (4.3 $\pm 1.0$ mL O$_2$/L of V$_E$). The reasons for this apparent discrepancy may be the different methods used to stimulate ventilation (dead space ventilation vs CO$_2$ stimulation) and/or physiologic or pathophysiologic differences in the patients studied.

In our patients, the respiratory VO$_2$ was calculated to be 71% of the total resting VO$_2$ for the malnourished patients, and 50% of the total resting VO$_2$ for the normally nourished group. This does not imply that under resting conditions the volume of O$_2$ necessary to support the respiratory apparatus is two thirds to one half of the total O$_2$ consumed by the body. The method for measuring the O$_2$ COV requires some form of hyperventilation, either by voluntary effort, by dead space expansion, or by chemical stimulation of the respiratory center by CO$_2$ inhalation. In patients with diffuse airflow obstruction, hyperventilation promotes turbulent air flow, increases the already high airway resistance, and, consequently, increases the work of breathing. There is a hyperbolic relationship between the V$_E$ and the O$_2$ COV in these patients, so that the O$_2$ COV becomes progressively greater with a greater V$_E$.29 This is in contrast to healthy subjects in which the O$_2$ COV remains constant over a much wider range of the V$_E$.1,14,26,27 It is critical to note that the change in the V$_E$ that occurred during the O$_2$ COV measurement of the malnourished patients (those with the highest O$_2$ COV) was only 48% of the increase in the V$_E$ observed in the normally nourished patients. Clearly, the higher O$_2$ COV of the malnourished group was not a result of a greater degree of hyperventilation in that group.

We conclude that the elevated O$_2$ COV often seen in COPD patients is a significant factor in the weight loss that often accompanies this disease process. We were able to draw this conclusion from a series of statistically significant relationships that linked poor lung function with an increased O$_2$ COV, an increased O$_2$ COV with a state of hypermetabolism, and the hypermetabolic state with reductions in BMI.

**References**


16 Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 1982; 126:5–8


