Effects of Lung Volume Reduction Surgery for Emphysema on Oxygen Cost of Breathing*

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Background: Patients with severe pulmonary emphysema have a greatly increased oxygen cost of breathing (O₂ cost), and this is the cause of serious malnutrition, or respiratory cachexia, in such patients.

Study objectives: To clarify the effect of lung volume reduction surgery (LVRS) on respiratory function and the nutritional state of these patients through a reduction in the O₂ cost of the respiratory muscles.

Design: Prospective cohort study.

Setting, patients, and interventions: Twenty-three patients who underwent LVRS in Tohoku University Hospital.

Measurements: Pulmonary function and O₂ cost were measured perioperatively by utilizing a method of continuous dead space. In addition, we calculated the proportion of oxygen consumption (V˙O₂) of respiratory muscles to total V˙O₂ (%V˙O₂resp) from the measured energy expenditure and the predicted values.

Results: FEV₁ and arterial oxygen pressure increased after surgery while lung volume and dyspnea decreased (p < 0.01), and O₂ cost was also reduced from 0.044 to 0.026 log(mL/min)/(L/min) [p < 0.001]. Moreover, the change in O₂ cost had a strong negative correlation with that of FEV₁ (r = -0.70, p < 0.001), and a moderate positive correlation with that of the ratio of residual volume to total lung capacity (r = 0.54, p < 0.01). %V˙O₂resp was 23.1% at rest and 55.5% at maximal ventilation. LVRS reduced %V˙O₂resp at maximal ventilation to 49.0% (p < 0.05), but %V˙O₂resp at rest did not decrease after surgery.

Conclusions: LVRS reduces energy expenditure of respiratory muscles especially during exercise by decreasing small airway obstruction and hyperinflated lung volume. This may reverse the malnourished state in end-stage emphysema.

Key words: lung volume reduction surgery; oxygen cost of breathing; pulmonary emphysema; respiratory muscles

The general treatment for patients with pulmonary emphysema has included cessation of smoking, bronchodilating drugs, oxygen inhalation, and respiratory rehabilitation. Some evidence indicates that aggressive smoking intervention programs reduce the age-related decline in FEV₁,¹ and long-term domiciliary oxygen therapy in patients with chronic hypoxia prolongs the survival period.² Moreover, long-term outpatient rehabilitation improves dyspnea, exercise performance, and quality of life, and these effects last for a period of 2 years.³ Nevertheless, because emphysema is a progressive and nonreversible disease, these therapies may become increasingly ineffective as the disease progresses.

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Because many seriously ill patients with pulmonary emphysema have severe dyspnea, they have a tendency to fall into a state of malnutrition called respiratory cachexia. It has been reported that low body weight in patients is an independent predictor of increased mortality. In addition, oxygen consumption ($V_{\text{O}_2}$) of respiratory muscles in patients with COPD is higher than that found in normal subjects, so these patients can more easily fall into a malnourished state due to the enormous energy expenditure involved in breathing (Fig 1, left, A).

Lung transplantation is still considered a radical treatment for emphysema; however, some of the difficulties with this method include the small number of donated organs and the difficulty in preventing infections resulting from immunosuppression. However, lung volume reduction surgery (LVRS) has spread globally as a palliative surgical treatment for severe emphysema. Not only are there few articles about improvement in the nutritional state of patients after surgery, but no reports have been published about changes in the oxygen cost of breathing ($O_2$ cost) after LVRS. We hypothesized that the decrement of $O_2$ cost may relate to an improvement in pulmonary function after LVRS, and the changes in $O_2$ cost may improve the state of malnutrition (Fig 1, right, B). In the present study, we measured $O_2$ cost before and 3 months after LVRS, and propose to clarify the correlation between $O_2$ cost and various factors that include lung function tests in patients with pulmonary emphysema.

**Materials and Methods**

**Patients and Surgical Techniques**

Twenty-three patients who fulfilled the previously published inclusion and exclusion criteria for LVRS were selected in this study. Patients with giant bullae were excluded. To prevent air leakage, the Endo linear stapling device (Endo-GIAII; U.S. Surgical; Norwalk, CT), reinforced with a felt-like bioabsorbable prosthesis, was used to excise relatively large target areas that were selected according to preoperative diagnostic studies. All procedures were performed by thoracoscopy. A pulmonary rehabilitation program that included exercise and instruction on breathing patterns was conducted for approximately 1 month prior to surgery, depending on the condition of the patient. Informed consent was obtained from all patients entered into the study.

**Data Collection**

Anthropometrics, spirometry (Fudac-70S; Fukuda Denshi; Tokyo, Japan), body plethysmography (Gould 2800J; Gould; Dayton, OH), exercise performance test by treadmill (Aerobic Processor; NEC-Sanei; Tokyo, Japan; and Model DC-103; Tanabe Seishindo; Tokyo, Japan), resting room-air arterial blood gas analysis (Model 213; Instrumentation Laboratories; Lexington, MA), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) ([Vitalpower KH-101; Chest; Tokyo, Japan; Fletcher-Hugh-Jones (F-H-J) score. and $O_2$ cost were measured preoperatively and 3 months postoperatively. Spirometry

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21995/)  
**Figure 1.** Drawings of a thorax in a patient with severe emphysema before and after LVRS. **Left, A:** Before undergoing LVRS, patients had barrel chests resulting from hyperinflated lungs and had to breathe with their accessory respiratory muscles because of diaphragmatic limitations. Thus, they easily fell into a malnourished state due to the enormous energy expenditure involved in breathing. **Right, B:** After LVRS, patients were able to breathe normally because of the improvement in diaphragm and chest wall motion; therefore, their state of malnutrition improved as a result of the decrement in $O_2$ cost.
and lung volumes were expressed as percentage of predicted values, using the formulas of Baldwin et al16 for vital capacity (VC), Berglund et al17 for FEV1, and Nishida et al18 for lung volumes.

O2 cost was measured by the method of Takishima et al19 of using a device for loading continuously extended expiratory dead space. The apparatus consisted of a constant part, an expandable dead space section, and an VO2-measurement part. The expandable dead space was made up of a piece of corrugated plastic tubing with one end of the tube connected to the constant part; the other end, free to move, was pulled at a constant rate (approximately 100 mL/min). The movable end of this expiratory dead space was connected to a pair of flexible tubes, a 40-L/min fan in one arm to circulate in the section for measuring VO2, and a soda lime box in the other arm to absorb carbon dioxide. The total VO2 was measured per minute by the decrease in volume of a 9-L Collins spirometer (Warren E. Collins; Braintree, MA) initially filled with 100% oxygen. Minute ventilation (Ve liters per minute) was construed as 12 times the expired volume that accumulated every 5 s. Measurements were obtained while the patients were in a sitting position, and the rib cage and abdomen were fitted with belts of an inductance plethysmograph. The expandable dead space was held at minimal volume for 3 min to allow the patients to reach a quasi-steady state. They were not allowed to observe the dead space expansion. To prevent dynamic hyperinflation during measurement, the patients were asked to maintain their control functional residual capacity (FRC) by matching their rib cage and abdominal displacement signals at end-expiration to the isovolume FRC control line on the oscilloscope. They were instructed to breathe continuously with this increasing dead space until they reached their highest level of tolerance.

Data Analysis of O2 cost

In the present study, we assumed that metabolic VO2 was constant during the measurement, and defined total VO2 (milliliters per minute) as the summation of metabolic VO2 and that of respiratory muscle VO2 (VO2resp). Therefore, the increment of total VO2 would reflect the increment of VO2resp. The paired points of total VO2 and Ve were obtained each minute for a total of five or more plotted on the semilog chart. Since the logarithm of total VO2 was found to be approximately linearly related to Ve, we characterized the O2 cost by the slope of the semilog regression line. Linear regression analysis was performed by the least-squares method. The slope of each regression line was expressed as dlog total VO2/Ve (log[milliliters per minute]/liters per minute). In addition, the measured energy expenditure (EEmeas, kilocalories [kcal] per day) was calculated from the formula of Weir20 using both resting and maximal VO2 (VO2max):

\[
\text{EEmeas} = (3.94 \times \text{VO2} + 1.10 \times R \times \text{VO2}) \times 1.44,
\]

where R = respiratory exchange ratio.

Resting VO2 was estimated as the amount during first 1 min of O2 cost measurement that we did not add dead space, and VO2max measured by the O2 cost test was estimated as the amount of the last 1 min with maximal ventilation. We assumed 0.8 as the value of the respiratory exchange ratio. Predicted resting energy expenditure (REEpred, kcal/d) was calculated from the formula of Benedict:21

\[
\text{REEpred} = 66.47 + 13.75 \times \text{weight (kilograms)} + 5.03 \times \text{height (centimeters)} - 6.76 \times \text{age (years)};
\]

for men, REEpred = 655.10 + 9.46 weight (kilograms) + 1.85 height (centimeters) - 4.68 age (years);

We calculated the proportion of VO2resp to total VO2 from following formula:

\[
\% \text{VO2resp} = \left( \frac{\text{EEmeas} - 0.98 \times \text{REEpred}}{\text{EEmeas}} \right) \times 100
\]

In this formula, resting VO2resp in normal subjects was assumed at 2%.

Statistical Analysis

Data are expressed as mean ± SD. Paired t tests were used to compare perioperative changes, and the F-H-J score was only compared by Wilcoxon signed-rank test. The Pearson correlation coefficient test and stepwise regression analysis were used to analyze the correlation between O2 cost and other parameters; p < 0.05 indicated statistical significance. All analyses were performed with standard statistical software (StatView 5.0; SAS Institute; Cary, NC).

RESULTS

Characteristics of 23 Patients

The average patient age at operation was 67.3 ± 7.2 years, and all but one patient were male. The average duration of smoking was 55.1 ± 30.3 pack-years. The one female patient, 45 years old, although a nonsmoker, was not α1-antitrypsin deficient. Fifteen patients underwent unilateral operations, and 8 patients underwent bilateral operations.

Preoperative pulmonary parameters are shown in Table 1. FEV1 had very low value, and severe hyperinflation was observed. The values for strength of respiratory muscles represented by MIP and MEP, and exercise performance represented by VO2max measured by the treadmill test were also low. Malnutrition is expressed by the low body mass index (BMI).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before LVRS</th>
<th>3 mo After LVRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2 cost, log(mL/min)/(L/min)</td>
<td>0.044 (0.025)</td>
<td>0.026 (0.019)†</td>
</tr>
<tr>
<td>VC, % predicted</td>
<td>79.7 (18.8)</td>
<td>81.4 (15.5)</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>35.3 (13.0)</td>
<td>46.9 (21.4)†</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>67.6 (9.48)</td>
<td>75.2 (5.30)†</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>43.1 (7.84)</td>
<td>40.5 (4.83)</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>239 (49.9)</td>
<td>196 (37.9)†</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>63.9 (8.36)</td>
<td>58.7 (9.16)†</td>
</tr>
<tr>
<td>MIP, cm H2O</td>
<td>−61.4 (21.1)</td>
<td>−63.1 (19.4)‡</td>
</tr>
<tr>
<td>MEP, cm H2O</td>
<td>75.7 (17.6)</td>
<td>80.4 (27.2)</td>
</tr>
<tr>
<td>VO2max, mL/min/kg§</td>
<td>14.2 (3.78)</td>
<td>17.3 (4.68)‡</td>
</tr>
<tr>
<td>BMI</td>
<td>18.8 (2.19)</td>
<td>19.4 (2.73)‡</td>
</tr>
<tr>
<td>F-H-J score</td>
<td>3.57 (0.73)</td>
<td>3.04 (0.88)†</td>
</tr>
</tbody>
</table>

Table 1—Pulmonary Function Test Results Before and After LVRS (n = 23)*

*Data are expressed as mean (SD);
†p < 0.05.
‡p < 0.001.
§Measured by treadmill test for exercise performance.
Results of Pulmonary Function and O₂ cost After LVRS

All patients were able to complete their O₂ cost measurements, and their fatigue level after performing these measurements was low. The mean values for FEV₁, Pao₂, residual volume (RV), the ratio of RV to total lung capacity (TLC), V̇o₂max, BMI, and F-H-J scores improved significantly after LVRS (Table 1). However, VC, MIP, and MEP did not show significant improvements. Although O₂ cost was decreased in 18 patients and increased in 5 patients after LVRS, the mean values of all patients significantly decreased (from 0.044 ± 0.025 log(mL/min)/(L/min) vs 0.026 ± 0.018 log(mL/min)/(L/min); p < 0.001; Fig 2).

Correlation Between O₂ Cost and Other Variables

Δ expresses the percentage change for each variable. ΔO₂ cost showed a strong negative correlation with ΔFEV₁ (r = −0.70, p < 0.001) and a moderate positive correlation with RV (r = 0.52, p < 0.05) and with RV/TLC (r = 0.54, p < 0.01). ΔO₂ cost had no correlation with MIP, MEP, and BMI (ie, nutritional parameters) [Table 2]. With all of the Δ parameters, although only RV was excluded because of significant correlation with RV/TLC, we obtained the following stepwise regression equation:

$$ \Delta O_2 \text{ cost} = -0.54 \times FEV_1 + 1.07 \times RV/TLC - 3.75 $$

with multiple correlation coefficient = 0.81 (p < 0.001). However, preoperative anthropometrics and pulmonary function had no correlation with O₂ cost (Table 2).

V̇o₂resp

At rest, the values for EEmeas and REEpred were nearly the same preoperatively and postoperatively. Although patients had lower values of REEpred relative to healthy subjects because of lower body weight, they were consuming 23% of total VO₂ in their respiratory muscles and values for %VO₂resp did not decrease after LVRS (Table 3). However, at maximal ventilation, EEmeas decreased significantly after LVRS. Values for %VO₂resp were extremely high, but also decreased significantly from 55.5 to 49.0% (p < 0.05).

| Table 2—Correlation Coefficient Between ΔO₂ cost and Other Variables* |
|--------------------------|--------------------------|
| Variables                | Δ                        | Preoperative Variables |
| VC                       | −0.38                    | 0.41                    |
| FEV₁                     | −0.70†                   | 0.26                    |
| Pao₂                     | −0.41                    | 0.38                    |
| PacO₂                    | 0.36                     | −0.38                   |
| RV                       | 0.52†                    | −0.18                   |
| RV/TLC                   | 0.54†                    | −0.41                   |
| MIP                      | −0.27                    | 0.15                    |
| MEP                      | −0.33                    | −0.08                   |
| V̇o₂max                  | −0.43                    | 0.42                    |
| Age                      | −0.31                    |                         |
| Height                   | 0.30                     |                         |
| BMI                      | −0.29                    | 0.25                    |
| F-H-J score              | −0.40                    |                         |
| Pack-years               | −0.18                    |                         |

*Δ expresses percentage change for each variable.

| Table 3—VO₂resp* |
|------------------|------------------|
|                  | At Rest          | At Maximal Ventilation |
|                  | Before LVRS  | 3 mo After LVRS | Before LVRS  | 3 mo After LVRS |
| EEmeas, kcal/d   | 1,437.6       | 1,453.8         | 2,479.5       | 2,231.1†       |
| REEpred, kcal/d  | 1,095.5       | 1,115.7         | 1,095.5       | 1,115.7         |
| %VO₂resp, %      | 23.1           | 22.4            | 55.5          | 49.0†           |

*EEmeas was calculated from the equation of Weir.²⁰ REEpred was calculated from the equation of Benedict.²¹

†p < 0.05, compared with the value of pre-LVRS at maximal ventilation.
**DISCUSSION**

O$_2$ cost is known to increase with age\textsuperscript{19} and is greater in patients with COPD than in normal subjects.\textsuperscript{5–8} Shindoh et al\textsuperscript{6} showed that O$_2$ cost in patients with COPD was 2.8 times higher than that in age-matched normal subjects. Although the degree of COPD was moderate (F-H-J score 2 to 3) in this report, our patients had more severe emphysema (F-H-J score 3 to 5), and their values for O$_2$ cost were much higher (1.8 times) than for patients with moderate COPD, and 4.5 times higher than that for normal subjects. In our study, O$_2$ cost decreased approximately 40% to a level similar to those in patients with moderate COPD with improvement of pulmonary function after LVRS (Table 1, Fig 2), but still higher than those of normal subjects.

Between O$_2$ cost and other parameters, FEV$_1$ had a strong negative correlation (Table 2). One of the mechanisms for increased O$_2$ cost in emphysema may be the increment of respiratory workload caused by increments of small airway resistance and dynamic hyperinflation during exercise; however, LVRS improves lung elastic recoil and reduces airway resistance,\textsuperscript{21} and reduces the respiratory workload and finally increases FEV$_1$ and decreases O$_2$ cost. Indeed in our study, FEV$_1$ increased approximately 33% after surgery, and FEV$_1$ was one of the effective independent variables according to the stepwise regression analysis.

Hyperinflation of the lung is also thought to be one of the reasons for increased O$_2$ cost.\textsuperscript{5} Collet and Engle\textsuperscript{24} reported that when normal subjects increased FRC to 37% of inspiratory capacity, the O$_2$ cost was significantly increased by 41% from baseline levels. Moreover, in the dynamic MRI study, the diaphragm and chest wall motion that had been regionally impaired by hyperinflated lungs improved their mechanics after LVRS.\textsuperscript{25} Ninane et al\textsuperscript{26} also reported that patients with severe chronic airflow obstruction contract, although breathing at rest, their abdominal muscles during expiration. From these reports, it can be hypothesized that hyperinflation may force accessory respiratory muscles to work as a result of motion limitation of the diaphragm and rib cage muscles, and may cause an increase in the overall mechanical workload of the respiratory muscles. In our study, the change in RV and RV/TLC had significant positive correlations with O$_2$ cost (Table 2), and RV/TLC was also the effective independent variable in the stepwise analysis. We could not predict postoperative decrement of O$_2$ cost because O$_2$ cost had no correlation with any preoperative parameters (Table 2); therefore, if we can use LVRS to reduce the state of hyperinflation, this proves that LVRS is an effective treatment to reduce O$_2$ cost and improve lung function in patients with severe emphysema.

Although Donahoe et al\textsuperscript{7} reported that levels of resting energy expenditure and O$_2$ cost were significantly elevated in malnourished patients with COPD (< 90% ideal body weight) relative to the normally nourished group (> 90% ideal body weight), O$_2$ cost had no correlation with respiratory muscle strength (MIP and MEP) and body weight (BMI) in this study. However, the improvement of these nutritional factors shows a phase lag with respect to the improvement of lung function,\textsuperscript{27} and these factors usually reach a peak level approximately 6 to 12 months after LVRS. In fact, Lahrmann et al\textsuperscript{28} reported that improvements in respiratory mechanics and lung function occurred as early as 1 month after LVRS, whereas the development of improvement in remodeled respiratory muscle function (ie, diaphragmatic strength and central diaphragmatic drive) took a significantly longer time. They also argued that in the early postoperative period after LVRS, the patients were still in the recovery period, and the improvement in diaphragm function occurred 6 months after LVRS. In addition, although we did not present the results in this article, O$_2$ cost had a significant negative correlation with BMI at 12 months in 18 patients (5 patients were excluded because a year had not passed since they underwent LVRS). Therefore, we concluded that the decrement of O$_2$ cost may result in the improvement of nutritional state, not within the early postoperative period but approximately 6 to 12 months after LVRS.

In addition, it is known that normal subjects consume 1 to 2% at rest and approximately 30% at maximal ventilation of their resting energy expenditure in their respiratory muscles. However, malnourished patients with COPD consume approximately 20% even when at rest.\textsuperscript{7} This value is nearly identical to that in our study (Table 3) but, contrary to our expectations, did not decrease after LVRS. At maximal ventilation, our patients were consuming 55.5% in their respiratory muscles, but this amount decreased significantly after LVRS. We concluded that the respiratory muscles of patients with severe emphysema consume more oxygen than those of normal subjects despite their low REEpred, and that LVRS improves O$_2$ cost during exercise rather than at rest.

Severe malnutrition in end-stage emphysema consists of not only “high energy expenditure” represented by O$_2$ cost but “low energy production” caused by the small amount of oral intake due to breathlessness or exercise limitation, so the balance of the total energy metabolism is inclined to be.
extremely negative. We conclude that decrement of \( O_2 \) cost after LVRS may change the energy balance into a positive state, and improve the malnourished state of patients with end-stage emphysema.

REFERENCES