

Effects of Lung Volume Reduction Surgery on Gas Exchange and Breathing Pattern During Maximum Exercise*

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Background: The National Emphysema Treatment Trial studied lung volume reduction surgery (LVRS) for its effects on gas exchange, breathing pattern, and dyspnea during exercise in severe emphysema.

Methods: Exercise testing was performed at baseline, and 6, 12, and 24 months. Minute ventilation (\dot{V}_E), tidal volume (V_T), carbon dioxide output (\dot{V}_{CO_2}), dyspnea rating, and workload were recorded at rest, 3 min of unloaded pedaling, and maximum exercise. P_{aO_2} , P_{aCO_2} , pH, fraction of expired carbon dioxide, and bicarbonate were also collected in some subjects at these time points and each minute of testing. There were 1,218 patients enrolled in the study (mean [\pm SD] age, 66.6 ± 6.1 years; mean, 61%; mean FEV_1 , 0.77 ± 0.24 L), with 238 patients participating in this substudy (mean age, 66.1 ± 6.8 years; mean, 67%; mean FEV_1 , 0.78 ± 0.25 L).

Results: At 6 months, LVRS patients had higher maximum \dot{V}_E (32.8 vs 29.6 L/min, respectively; $p = 0.001$), \dot{V}_{CO_2} (0.923 vs 0.820 L/min, respectively; $p = 0.0003$), V_T (1.18 vs 1.07 L, respectively; $p = 0.001$), heart rate (124 vs 121 beats/min, respectively; $p = 0.02$), and workload (49.3 vs 45.1 W, respectively; $p = 0.04$), but less breathlessness (as measured by Borg dyspnea scale score) [4.4 vs 5.2, respectively; $p = 0.0001$] and exercise ventilatory limitation (49.5% vs 71.9%, respectively; $p = 0.001$) than medical patients. LVRS patients with upper-lobe emphysema showed a downward shift in P_{aCO_2} vs \dot{V}_{CO_2} ($p = 0.001$). During exercise, LVRS patients breathed slower and deeper at 6 months ($p = 0.01$) and 12 months ($p = 0.006$), with reduced dead space at 6 months ($p = 0.007$) and 24 months ($p = 0.006$). Twelve months after patients underwent LVRS, dyspnea was less in patients with upper-lobe emphysema ($p = 0.001$) and non-upper-lobe emphysema ($p = 0.007$).

Conclusion: During exercise following LVRS, patients with severe emphysema improve carbon dioxide elimination and dead space, breathe slower and deeper, and report less dyspnea.

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Key words: cardiopulmonary exercise; COPD; emphysema

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; LVRS = lung volume reduction surgery; MVV = maximal ventilatory volume; NETT = National Emphysema Treatment Trial; rpm = revolutions per minute; SaO_2 = arterial oxygen saturation; \dot{V}_{CO_2} = carbon dioxide output; \dot{V}_E = minute ventilation; \dot{V}_{EMAX} = maximum minute ventilation; V_T = tidal volume

COPD markedly impairs exercise performance, especially in those with predominantly emphysema. Emphysema causes decreased lung elastic recoil, which increases expiratory airflow resistance and leads to dynamic hyperinflation.^{1–3} During exercise, dynamic hyperinflation progresses rapidly, decreasing chest wall compliance and impairing respiratory muscle func-

tion.^{3–9} Dynamic hyperinflation and an elevated work of breathing precipitate breathlessness, thereby decreasing exercise tolerance and quality of life.^{1,10,11}

Lung volume reduction surgery (LVRS) increases lung elastic recoil¹² and decreases end-expiratory lung volume,^{3,6,13,14} thereby improving lung^{15–18} and respiratory muscle mechanics^{5,7} and overall exercise toler-

ance.^{19–24} However, most of the published reports are uncontrolled, unicenter trials involving small numbers of patients with short-term follow-up.^{3,5,17–19,22,23,25–27}

The National Emphysema Treatment Trial (NETT) represents the most extensively characterized patient cohort with severe emphysema undergoing repeated exercise testing. Here we report the effects of optimal medical therapy plus LVRS vs optimal medical therapy alone on maximum exercise after outpatient rehabilitation and through 2 years postrandomization to treatment. Specifically, we assessed the effects of LVRS vs medical treatment on gas exchange, breathing pattern, presence of exercise limitation, and sensation of dyspnea during exercise.

MATERIALS AND METHODS

The design and methods of NETT have been previously detailed.²⁰ All patients provided written informed consent, and the study was approved by the institutional review board at each center. All 17 NETT centers performed maximum exercise testing at baseline, 6 and 12 months after randomization, and yearly thereafter. Baseline measurements were completed after pulmonary rehabilitation and before randomization, except for DLCO, which was obtained before pulmonary rehabilitation. Five of the 17 centers additionally participated in the exercise substudy. Exercise substudy patients had additional measures collected during maximum exercise testing. There were 1,218 patients randomized in NETT, 608 to LVRS and 610 to medical treatment. Of these patients, 238 also participated in the exercise substudy; 122 were randomized to medical treatment and 116 to LVRS.

Patient Selection

Enrollment criteria for NETT have been previously reported.¹⁵ Exercise substudy participants satisfied NETT main study criteria

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†A list of centers and participants in the National Emphysema Treatment Trial Research Group is located in the Appendix.

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and had no contraindications to exercise testing. Contraindications to exercise testing included unstable angina; lower extremity or back problems that prohibited pedaling; history of syncope, cardiac dysrhythmia, hypoxemia, arterial oxygen saturation (SaO_2) < 80% within 2 min of unloaded cycling despite supplemental oxygen; uncontrolled systemic hypertension; bradycardia (< 50 beats/min), multifocal premature ventricular contractions; inability to coordinate a cycle cadence of > 40 revolutions per minute (rpm); fever; or exacerbation of COPD at test time.

Clinical Assessment

Demographic data and medical history were collected using standardized instruments.²⁰ Pulmonary function testing was performed using American Thoracic Society guidelines.^{28–30} Lung volumes were measured via body plethysmography. Diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single-breath technique. All pulmonary function measures are post-bronchodilator values (except DLCO) and are reported in absolute numbers or as a percentage of normal predicted.^{31–33} The cranio-caudal distribution of emphysema on chest CT scan was classified by radiologists as upper lobe predominant, lower lobe predominant, diffuse, or superior segments of lower lobes predominantly involved; the latter three choices were grouped as non-upper-lobe-predominant.

Cardiopulmonary Exercise Test Setup

All clinics used an electromagnetically braked lower extremity cycle ergometer that had the capacity to provide ramped workloads at 5 W/min, metabolic cart systems capable of analyzing data in 20-s intervals using breath-by-breath analysis or mixing chamber systems, and continuous ECG and pulse oximetry monitoring. Supplemental oxygen (30%) was provided by a high-flow oxygen blender capable of delivering 100 L/min using a flow-by circuit to the inspiratory port of a unidirectional valve (Fig 1).

Measures Collected During Exercise Testing

Measures were collected after 5 min at rest, after 3 min of unloaded pedaling, and at maximum exercise. Measures included SaO_2 , minute ventilation (\dot{V}_E), tidal volume (V_T), carbon dioxide output (\dot{V}_{CO_2}), heart rate, respiratory rate, systolic BP, diastolic BP, and modified Borg scale ratings (scale, 0 to 10)^{34,35} for breathlessness and leg muscle fatigue. Load was reported at maximum exertion. Under the substudy protocol, PaCO_2 , PaO_2 , pH, fraction of expired carbon dioxide, and SaO_2 were also collected after 5 min at rest, after 3 min of unloaded pedaling, after each minute of exertion, and at maximal exercise. Arterial blood samples were timed precisely to expired gas collections and used for dead space calculation.

Exercise Testing Protocol

At least 15 min and no more than 4 h prior to testing, patients received a short-acting inhaled bronchodilator. Before performing any exercise, patients sat for 10 min with a Venturi mask inspiring 30 to 31% oxygen. Patients were then transferred to the cycle ergometer and rested for 5 min prior to beginning pedaling. Patients were then instructed to begin 3 min of unloaded pedaling. Work increments were ramped at 5 W/min in patients with a maximum voluntary ventilation \leq 40 L/min; 10 W/min work increments were used in patients with maximum voluntary ventilation > 40 L/min. During exercise the patient was instructed to maintain a cadence of 40 to 70 rpm. The test ended when the cadence fell below 40 rpm and did not return with exhortation, the patient requested termination, or the technician terminated the test for safety. Maximum

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